Southern Clinics of Istanbul Eurasia

Journal Abbreviation: South Clin Ist Euras

Volume 37 | Issue 3 | October 2026

KARE MEDYA

ISSN 2587-0998
www.scie.online

Southern Clinics of Istanbul Eurasia

EDITOR-IN-CHIEF

Hasan Fehmi KÜÇÜK
Department of Chest Surgery, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye

EDITORS

Gaye FİLİNTE
Department of Plastic and Reconstructive Surgery, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkiye

Elif ARI BAKIR
Department of Nephrology, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkiye

Özlem SEZEN
Department of Anesthesiology and Reanimation, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye

Yasin TOSUN
Department of General Surgery, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkiye

ASSOCIATE EDITORS

Nesrin KIRAL
Department of Pulmonology, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkiye

Banu ELER ÇEVİK
Department of Anesthesiology and Reanimation, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkiye

Banu ATALAY ERDOĞAN
Department of Otorhinolaryngology, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkiye

Bülent GÜÇLÜ
Department of Neurosurgery, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkiye

Hatice ODABAŞ
Department of Medical Oncology, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkiye

Seydahmet AKIN
Department of Internal Medicine, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkiye

Engin ECEVİZ
Department of Orthopedics and Traumatology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye

Feyza ESEN
Department of Pediatric Emergency Medicine, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkiye

Ahmet Kasım KILIÇ
Department of Neurology, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkiye

Tahsin Batuhan AYDOĞAN
Department of Urology, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkiye

Neslihan BÜYÜKMURAT
Deputy Chief Physician, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkiye

PUBLISHING MANAGER

Özlem SEZEN
Department of Anesthesiology and Reanimation, Kartal Dr. Lutfi Kırdar City Hospital, İstanbul, Türkiye

Statistics

Specialist Dr. Ali Cankut TATLIPARMAK

Publisher

Kare Publishing

Contact: Canan KIRÇİÇEK KARATAŞ
Kartal Dr. Lütfi Kırdar Şehir Hastanesi, Denizer Cad., No: 1, 34865 Cevizli, İstanbul
Phone: +90-216-441 39 00 (23311) Phone 2: +90-216-458 30 00 (23311)
e-mail: info@scie.online, editor@scie.online

Owned by on behalf of the Director of University of Medical Sciences Kartal Dr. Lütfi Kırdar Health Practice and Research Center, İstanbul: Hasan Fehmi KÜÇÜK | Executive Editor: Hasan FEHMİ KÜÇÜK | Publication Type: Periodical | Printed: Yıldırım Matbaacılık +90 212 629 80 37 | Printing Date: October 2026 | Circulation: 50

Southern Clinics of Istanbul Eurasia

ADVISORY BOARD

Altuğ KOŞAR

Department of Thoracic Surgery, Maltepe University Faculty of Medicine, İstanbul

Asıf YILDIRIM

Department of Urology, Istanbul Medeniyet University Göztepe Dr. Süleyman Yalçın City Hospital Urology Clinic, Istanbul, Türkiye

Aslı TUNCER

Department of Neurology, Hacettepe University Faculty of Medicine, Ankara, Türkiye

Ayten SARAÇOĞLU

Department of Anesthesiology and Reanimation, Marmara University Pendik Training and Resarch Hospital, İstanbul

Begüm AYDOĞAN MATHYK

University of South Florida, Obstetrics and Gynecology Department, USA

Canan CERAN ÖZCAN

Department of Pediatric Surgery, Hamidiye International Faculty of Medicine, İstanbul

Daniela GODOROJA

Department of Anesthesiology and Reanimation,University of Medicine and Pharmacy Carol Davila, Bucharest, Romania

Derman BAŞARAN

Department of Obstetrics and Gynecology, Hacettepe University Faculty of Medicine, Gynecologic Oncology, Ankara, Türkiye

Eda DERLE

Department of Neurology, Başkent University Faculty of Medicine, Ankara, Türkiye

Gürdal ŞAHİN

Department of Clinical Sciences, Lund University, Lund, Sweden

Hülya ILIKSU GÖZÜ

Department of Internal Medicine, Marmara University Faculty of Medicine Hospital, İstanbul

İlhan İNCİ

Deaprtment of Thoracic Surgery, University of Zurich, Switzerland

İlknur AKTAŞ

Department of Physical Theraphy and Rehabilitation, Fatih Sultan Mehmet Training and Research Hospital, İstanbul

Kaan GİDEROĞLU

Department of Plastic and Reconstructive Surgery, Taksim Training and Research Hospital İstanbul

Kemal Tolga SARAÇOĞLU

Department of Anesthesiology, University of Florida, UF Health, Jacksonville, USA

Marc SINDOU

Department of Neurosurgery, University of Lyon, Lyon, France

Massimiliano SORBELLO

Department of Anaesthesia and Intensive Care, Azienda Ospedaliero - Universitaria Policlinico - Vittorio Emanuele, Catania, Italy

Mehmet VELİDEDEOĞLU

Department of General Surgery, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul

Merih ALTINTAŞ

Department of Psychiatry, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul

Recep DEMİRHAN

Department of Chest Surgery, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul

Samim EMET

Department of Cardiology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Türkiye

Selin Gamze SÜMEN

Department of Underwater and Hyperbaric Medicine, Kartal Dr. Lütfi Kırdar CityHospital, İstanbul

Serdar CÖMERT

Department of Neonatology, İstanbul Training and Research Hospital, İstanbul

Serdar CÖMERT

Department of Neonatology, İstanbul Training and Research Hospital, İstanbul

Şule KARABULUT GÜL

Radiation Oncology Clinic, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul

Tayfun AKÖZ

Department of Plastic and Reconstructive Surgery, Maltepe University Faculty of Medicine, İstanbul

Tomasz GASZYNSKİ

Department of Anesthesiology and Reanimation, Medical University of Lodz, Lodz, Poland

Southern Clinics of Istanbul Eurasia

AIMS AND SCOPE

Southern Clinics of Istanbul Eurasia - SCIE (formerly Kartal Eğitim ve Araştırma Hastanesi Tıp Dergisi / Medical Journal of Kartal Training and Research Hospital) is the scientific open access publication of University of Health Sciences, Kartal Dr. Lütfi Kırdar City Hospital (the content may be accessed free of charge through the web site www.scie.online). Four issues are released every year in March, June, September, and December. The language of publication is English.

The aim of the journal is to publish high level clinical and experimental studies conducted in all medical branches, reviews comprising the latest research findings, reports on rare and educational cases, and letters to the editor.

The journal observes a double-blinded, peer-review process with external and independent reviewers in the evaluation and approval of manuscripts for publication.

The target population of the journal includes specialists in all medical branches, academicians, and relevant health care professionals.

Publication policy and editorial processes follow the guidelines of the International Committee of Medical Journal Editors, the World Association of Medical Editors, the Council of Science Editors, the European Association of Science Editors, and the Committee on Publication Ethics.

SCIE is indexed in the TUBITAK ULAKBIM TR Index, EBSCO, GALE, ProQuest, DOAJ, CABI, Scope Database, MIAR, Türk Medline, WorldCat and Türkiye Citation Index. The journal is financially supported by University of Health Sciences Kartal Dr. Lütfi Kırdar City Hospital.

Kartal Dr. Lütfi Kırdar City Hospital is the sole copyright holder of the name and brand of the journal and all content. Any part of the content may be quoted only by providing a reference to the journal. For all other utilizations, permission should be obtained from the editorial office.

Editor: Hasan Fehmi KÜÇÜK
Address: Department of General Surgery, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkiye
Phone: +90-216-441 39 00 (23311)
E-mail: editor@scie.online

Southern Clinics of Istanbul Eurasia

INSTRUCTIONS FOR AUTHORS

About the Journal

Southern Clinics of Istanbul Eurasia - SCIE (formerly Kartal Eğitim ve Araştırma Hastanesi Tıp Dergisi - The Medical Journal of Kartal Training and Research Hospital) is published four issue in English by the Kartal Dr. Lütfi Kırdar City Hospital, and is a peer reviewed general medical journal for all physicians, doctors, medical researchers, and health workers. The journal reports the advances and progress in current medical sciences and technology. The journal covers basic and clinical studies in medicine. Articles of clinical interest and implications will be given preference.

Contributions may be in the form of clinical and basic research articles, case reports, personal clinical and technical notes, and letters to the Editor. The Journal also publishes brief reports on original studies or evaluations, book reviews, and proceedings of scientific meetings. The Editor-in-Chief may request from the authors additional data, information, or complementary material concerning the manuscripts, and the authors must comply with such requests.

Manuscripts should be prepared in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals regularly updated by the International Committee of Medical Journal Editors, available at http:// www.icmje.org.

Ethics

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and National Information Standards Organization (NISO).

All manuscripts presenting data obtained from research involving human subjects must include a statement that the written informed consent of the participants was obtained and that the study was approved by an institutional review board or an equivalent body. This institutional approval should be submitted with the manuscript. Authors of case reports must submit the written informed consent of the subject(s) of the report or of the patient's legal representatives for the publication of the manuscript.

All studies should be carried out in accordance with the World Medical Association Declaration of Helsinki, covering the latest revision date. Patient confidentiality must be protected according to the universally accepted guidelines and rules. Manuscripts reporting the results of experimental studies on animals must include a statement that the study protocol was approved by the animal ethics committee of the institution and that the study was conducted in accordance with the internationally accepted guidelines, including the Universal Declaration of Animal Rights, European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, Principles of Laboratory Animal Science, and the Handbook for the Care and Utilization of Laboratory Animals. The authors are strongly requested to send the approval of the ethics committee together with the manuscript. In addition, manuscripts on human and animal studies should describe procedures indicating the steps taken to eliminate pain and suffering.

Submission and peer reviewing

The official language of the Journal is English. Following an initial evaluation and elimination for sufficient priority, manuscripts are subject to blind peer review by at least two reviewers. The Editor, who judges and analyzes the entire review process, reaches a final decision to accept or reject a manuscript, or to recommend a revision. The Editor has the right to reject a revised manuscript.

Copyright - Authors' approval - Conflict of interest

The authors should disclose all issues concerning financial relationship, conflict of interest, and competing interest that may potentially influence the results of the research or scientific judgement. All financial contributions or sponsorship, financial relations, and areas of conflict of interest should be clearly explained in a separate letter to the editor at the time of submission, with full assurance that any related document will be submitted to the Journal when requested.

Manuscripts should be sent with the Copyright-Authors' Approval-Conflict of Interest Letter signed by the author(s). A copy of this letter can be found at web site. Manuscripts will not be accepted for evaluation until the receipt of this document by the Journal.

The Editorial Office inspects all submitted manuscripts concerning plagiarism and duplication. If an ethical problem is detected, the editorial office will act according to the COPE guidelines.

Submitting a manuscript

SCIE accepts only on-line submission via the official web site (please click, http://www.scie.online/en/?s=online_submission) and refuses printed manuscript submissions by mail. All submissions are made by the on-line submission system called Journal Agent, by clicking the icon "Online manuscript submission" at the above mentioned web site homepage. The system includes directions at each step but for further information you may visit the web site.

Important notice

Before the corresponding author submits the manuscript, all authors must obtain ORCİD ID number and provide it to the corresponding author.

Manuscript preparation

The author(s) must declare that they were involved in at least 3 of the 5 stages of the study stated in the "acknowledgement of authorship and transfer of copyright agreement" as "designing the study", "collecting the data", "analyzing the data", "writing the manuscript" and "confirming the accuracy of the data and the analyses". Those who do not fulfill this prerequisite should not be stated as an author.

The number of authors should not exceed 6 for clinical, basic and experimental studies, 4 for case reports and technical notes, and 3 for letters to the editor and reviews. In multi-center or multi-discipline studies, each author's contribution regarding the 5 stages mentioned above should be stated clearly. For this kind of multi-center or multi-discipline studies with excessive number of authors, the editor has the right to request that the number of authors be reduced.

Southern Clinics of Istanbul Eurasia

Manuscripts should be designed in the following order: title page, abstract, main text, references, and tables, with each typeset on a separate page.

Title page: This page should only include the title of the manuscript, which should be carefully chosen to better reflect the contents of the study. Author names should not appear in the title and subsequent pages.

Abstract: It should not exceed 300 words. Abstracts should be structured in four paragraphs using the following subtitles: Objectives, Methods, Results, and Conclusion. Abstracts of case reports should be unstructured.

Main text: The body consists of Introduction, Patients/Materials and methods, Results, and Discussion. Use "Patients and methods" for clinical studies, and "Materials and methods" for animal and laboratory studies.

The Introduction section clearly states the purpose of the manuscript and includes a brief summary of the most relevant literature.

The Patients/Materials and Methods section describes the study population and the study design, with adequate information on the techniques, materials, and methods used. A clear description of the statistical methods should also be given.

The Results section should provide a detailed report on the findings of the study. Data should be concisely presented, preferably in tables or illustrations, which should not exceed the page layout of the Journal.

The Discussion section should mainly rely on the conclusions derived from the results of the study, with relevant citations from the most recent research.

Letter to the Editor: Letters to the editor should not exceed 350 words.

References: References should be numbered in the order in which they are mentioned in the text. Only published articles or articles in press can be used in references. Unpublished data or personal communications should not be used. The style should conform to the standards described in detail in "Citing Medicine-The NLM Style Guide for Authors, Editors, and Publishers" (http://www.nlm.nih.gov/citingmedicine), which is recommended in the most recent update of "Uniform Requirements for Manuscripts Submitted to Biomedical Journals". A brief presentation of these standards can also be found at http://www.nlm.nih.gov/bsd/uniform_requirements.html. Journal titles should be abbreviated according to the Index Medicus. The Journal's title is abbreviated as "South Clin Ist Euras".

The style and punctuation should follow the formats outlined below:

Standard journal article:

Napolitano LM, Corwin HL. Efficacy of red blood cell transfusion in the critically ill. Crit Care Clin 2004;20:255-68.

All authors if six or fewer should be listed; otherwise, the first six and "et al." should be written.

Epub ahead of print Articles:

Rupprecht H, Heppner HJ, Wohlfart K, Türkoglu A. The geriatric polytrauma: Risk profile and prognostic factors. Ulus Travma Acil Cerrahi Derg 2017 Jan 05. doi: 10.5505/tjtes.2016.77177. [Epub ahead of print].

Personal author(s):

Enzingerz FM, Weiss SW. Soft tissue tumors. St. Louis: Mosby; 1995. p. 27-50.

Editor(s), compiler(s) as author:

Günal İ, Barton NJ, Çallı İ, editors. Current management of scaphoid fractures. Twenty questions answered. London: The Royal Society of Medicine Press; 2002.

Chapter in a book:

Henick DK, Kennedy DW. Fungal sinusitis. In: Stankiewicz JA, editor. Advanced endoscopic sinus surgery. St Louis: Mosby; 1995. p. 69-80.

Conference paper:

Kouzelis A, Matzaroglou C, Kravvas A, Mylonas S, Megas P, Gliatis J. Anterior cruciate ligament reconstruction: patellar tendon autogaft versus four strand hamstring tendon. In: Proceedings of the 9th Turkish Sports Traumatology, Arthroscopy and Knee Surgery Congress; 2008 Oct 14-18; İstanbul, Türkiye. p. 223. Unpublished conference papers should not be used in the reference list.

Direct use of references is strongly recommended and the authors may be asked to provide the first and last pages of certain references. Publication of the manuscript will be suspended until this request is fulfilled by the author(s).

Figures and tables

All illustrations (photographs, graphics, and drawings) accompanying the manuscript should be referred to as "figure". All figures should be numbered consecutively and mentioned in the text. Figure legends should be added at the end of the text as a separate section. Each figure should be prepared as a separate digital file in "jpeg" format, with a minimum of 9×13 cm and at 300 dpi or better resolution.

All illustrations should be original. Illustrations published elsewhere should be submitted with the written permission of the original copyright holder.

For recognizable photographs of human subjects, written permission signed by the patient or his/her legal representative should be submitted; otherwise, patient names or eyes must be blocked out to prevent identification. Microscopic photographs should include information on staining and magnification.

Upon the author's request, color prints will be considered for publication; however, the authors are responsible for the extra cost of printing color illustrations. Each table should be prepared on a separate page, either at the end of the text file or as a separate supplementary file, with table heading on top of the table. Table heading should be added to the main text file on a separate page when a table is submitted as a supplementary file.

Checklist

Covering letter

- Signed by all contributors
- Previous publication / presentations mentioned

Southern Clinics of Istanbul Eurasia

Source of funding mentioned

Conflicts of interest disclosed

ORCİD ID number of all contributors

Authors

Last name and given name provided along with Middle name initials (where applicable)

Author for correspondence, with e-mail address provided

Number of contributors restricted as per the instructions

Identity not revealed in paper except title page (e.g. name of the institute in Methods, citing previous study as 'our study', names on figure labels, name of institute in photographs, etc.)

Presentation and format

Double spacing

Margins 2 cm from all four sides

Page numbers included at bottom

Title page contains all the desired information

Abstract page contains the full title of the manuscript

Abstract provided (structured abstract of 300 words for original articles, meta analysis (Backgroud, Methods, Results, Conclusions) and review articles (Objective, Data sources, Study selection, Results, Conclusions)

Key words provided (three or no more than 6 words) Introduction should be short and arresting. State the purpose of the article and summarize the rationale for the study or observation. Give only strictly pertinent references

The references cited in the text should be after punctuation marks

References according to the journal's instructions, punctuation marks checked

Language and grammar

Uniformly American English

Write the full term for each abbreviation at its first use in the title, abstract, keywords and text separately unless it is a standard unit of measure. Numerals from 1 to 10 spelt out

Numerals at the beginning of the sentence spelt out

Check the manuscript for spelling, grammar and punctuation errors

If a brand name is cited, supply the manufacturer's name and address (city and state/country).

Species names should be in italics

Tables and figures

No repetition of data in tables and graphs and in text

Actual numbers from which graphs drawn, provided

Figures necessary and of high quality (colour)

Table and figure numbers in Arabic letters (not Roman)

Labels pasted on back of the photographs (no names written)

Patients' privacy maintained (if not permission taken)

Credit note for borrowed figures/tables provided

Write the full term for each abbreviation used in the table as a footnote

Editor: Hasan Fehmi KÜÇÜK
Address: Kartal Dr. Lütfi Kırdar Şehir Hastanesi, Denizer Cad., No: 1, 34865 Cevizli, İstanbul
Phone: +90-216-441 39 00 (23311)
E-mail: info@scie.online, editor@scie.online

Publisher: KARE Publishing - KARE Medya
Address: Göztepe Mah., Fahrettin Kerim Gökay Cad., No: 200, Da: 2, Göztepe, Kadıköy, İstanbul
Phone: +90-216-550 61 11
Fax: +90-216-550 61 12
E-mail: kare@karepb.com

Southern Clinics of Istanbul Eurasia

CONTENTS

Volume 37 Issue 3 Year 2026

ORIGINAL ARTICLES

207 Effects of transauricular vagus nerve stimulation on cardiac and pulmonary injury in a rat hepatic ischemia–reperfusion model
Demirtas C, Genç MS, Erguven P, Sevgin K, Gokce M, Güler EM, Beyaztaş H, Ahmet Mazlum F, Güleç B

216 Learning curve and early surgical performance of vnotes hysterectomy: a retrospective single surgeon cohort study
Erkmen AD, Arkan K, Çavuşoğlu Çolak G, Halisçelik MA, Adıgüzel Ö, Çakar Yılmaz K, Birol İlter P, Oglak SC

224 Association between vitamin d status and lower respiratory tract infection in children under five years of age
Haykır N, Akın Y, Tutar E

230 Mammographic subcutaneous fat thickness reflects systemic adiposity rather than tumor biology in invasive ductal carcinoma: a retrospective analysis
Gümüştekin B, Teke E

239 The comparison of myocardial dysfunction using speckle tracking echocardiography in resistive and non-resistive familial mediterranean fever patients
Ozkerim U, Kocaayan H, Gucenmez S, Akar S

249 Patient-reported satisfaction and symptom improvement following holmium laser enucleation of the prostate: results from a postoperative telephone survey
Kayalı Y, Aydogan TB, Torun A, Soleimanpour A, Ghasemzadeh A, Eryildirim B

257 retrospectıve analysis of candida auris colonization and infections in the intensive care unit
Şıvğın Til S, Yıldız B, Tükenmez T, Bombacı E

265 Maternal risk factors for term antepartum stillbirth: a 10-year registry-based case–control study
Temoçin RB, Yıldız P, Mat E, Kahyaoglu B, Yıldız G

273 Evaluating smoking-related systemic inflammation through hematological indices: a cross-sectional study
Eryılmaz M, Keskinel I, Türkeli L

279 Impact of breastfeeding on body mass index
Cankır N, Çağ Y, Köle MT, Adak A, Akın Y

286 Surgical outcomes and prognostic factors of pulmonary pleomorphic carcinoma
Cimenoglu B, Ozdemir A, Buz M, Ozlu FT, Dogruyol T, Demirhan R

294 Comparison of efficacy and safety of three chemoradiotherapy regimens in elderly patients with inoperable stage III non-small cell lung cancer
Özdemir P, Özdemir E, Yadigar S, Özdemir E

301 The effect of mismatch between lumbar lordosis and pelvic incidence on prevalence, quality of life, and disability in patients with chronic low back pain
Çalkın Korkmaz M, Oncel A, Bucak ÖF, Tolu S

306 Digital rectal examination-based estimation of prostate volume using posterior surface area: a prospective methodological and reproducibility study
Sevinç AH, Hanci B, Tarhan F

313 Cordocentesis for Rapid Cytogenetic Diagnosis: A Retrospective Cohort Study of 160 Cases Cytogenetic Diagnosis by Cordocentesis: Retrospective Analysis
Sağlam Purut C, Tuncer Can S, Torun R, Sever B, Purut YE, Kutbay YB, Kırbıyık Ö, Özer M, Şahingöz Yıldırım AG

319 Vitamin D Prophylaxis and Changes in Kidney Stone Number and Size in Children: A Prospective Ultrasound-Based Study
Gürpınar B, Yavaş Aksu B, Yürük Yıldırım Z, Çalışkan E, Bayramoğlu Z, Gökçay G, Yılmaz A

CASE REPORT

328 Two-Stage Reconstruction of a Scalp Defect with Exposed Bone Using a Biodegradable Temporizing Dermal Matrix
Ofluoğlu AC, Yaraşır MM, Çiçek Ç, Filinte G

ORIGINAL ARTICLE

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.47354

Effects of Transauricular Vagus Nerve Stimulation on Cardiac and Pulmonary Injury in a Rat Hepatic Ischemia–Reperfusion Model

Cumaali Demirtas,[1] Mahmut Salih Genç,[2] Pelin Erguven,[3] Kubra Sevgin,[3] Mustafa Gokce,[4] Eray Metin Güler,[5] Hakan Beyaztaş,[5] Ahmet Furkan Mazlum,[2] Bülent Güleç[2]

[1]University of Health Sciences, Hamidiye Health Sciences Institute, Istanbul, Türkiye
[2]University of Health Sciences, Sultan II. Abdulhamid Training and Research Hospital General Surgery Clinic, Istanbul, Türkiye
[3]Department of Histology and Embryology, University of Health Sciences, Hamidiye International Faculty of Medicine, Istanbul, Türkiye
[4]Department of Pharmacology, Istanbul University-Cerrahpasa, Faculty of Pharmacy, Istanbul, Türkiye
[5]University of Health Sciences, Hamidiye Faculty of Medicine, Department of Biochemistry, Istanbul, Türkiye

Address for correspondence:
Cumaali Demirtas, University of Health Sciences, Hamidiye Health Sciences Institute, Istanbul, Türkiye
E-mail: cumaali.demirtas@sbu.edu.tr

Received: 29.04.2026
Accepted: 17.05.2026
Published: 29.09.2026

Abstract

Objective: Liver ischemia–reperfusion (I/R) injury, commonly occurring in trauma, organ transplantation, major hepatic surgery, and shock, not only impairs hepatic function but also induces dysfunction in distant organs such as the kidneys, lungs, and heart, leading to increased morbidity and mortality. This study investigated whether non-invasive transauricular vagus nerve stimulation (tVNS) could mitigate cardiac and pulmonary injury in a rat hepatic I/R model.

Methods: Twenty-one male Sprague–Dawley rats were randomly assigned to three groups (n=7 each): Control (laparotomy only), I/R (1 h hepatic ischemia + 3 h reperfusion), and I/R+tVNS (1 h ischemia + 3 h reperfusion with concurrent tVNS). At the end of reperfusion, cardiac and pulmonary tissues were harvested for biochemical analysis.

Results: tVNS reduced oxidative stress and inflammatory responses in both organs. In cardiac tissue, the I/R+tVNS group demonstrated significantly higher total antioxidant status (TAS) and lower total oxidant status (TOS), oxidative stress index (OSI), interleukin-1β (IL-1β), and hypoxia-inducible factor-1α (HIF-1α) compared with the I/R group. In pulmonary tissue, OSI and IL-1β levels were significantly decreased by tVNS, while HIF-1α showed a downward trend without statistical significance.

Conclusions: Non-invasive tVNS effectively alleviated oxidative stress and enhanced antioxidant capacity in the heart and lungs following hepatic I/R. These results suggest that tVNS confers cardiopulmonary protection against hepatic I/R injury, likely through modulation of inflammatory cytokine responses and reinforcement of antioxidant defences.

Keywords: Ischemia–reperfusion injury; vagus nerve stimulation; oxidative stress; inflammation; heart; lung; rat.

Introduction

Liver ischemia–reperfusion (I/R) injury is a common pathophysiological condition encountered in trauma, liver transplantation, major hepatic resections, and haemorrhagic shock, all of which carry high morbidity and mortality risks. Inter-

How to cite this article: *Demirtas C, Genç MS, Erguven P, Sevgin K, Gokce M, Güler EM, Beyaztaş H, Ahmet Mazlum F, Güleç B. Effects of transauricular vagus nerve stimulation on cardiac and pulmonary injury in a rat hepatic ischemia–reperfusion model. South. Clin. Ist. Euras. 2026;37(3):207-215.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Copyright@Author(s)

ruption or reduction of hepatic blood flow results in hypoxia and nutrient deprivation, leading to hepatocellular damage. Restoration of circulation (reperfusion) paradoxically exacerbates the injury by inducing an excessive inflammatory response and a burst of reactive oxygen species (ROS). [1] As a result, hepatic I/R not only impairs liver function but can also trigger secondary injury in distant organs such as the kidney, lung, and heart, contributing to multi-organ dysfunction.[2,3] Both ischemia itself and the reperfusion-induced oxidative burst play central roles in this pathogenesis.

Vagus nerve stimulation (VNS) is an established therapy for refractory epilepsy, severe depression, and certain headache disorders. In recent years, increasing evidence has shown that VNS provides benefits in cardiovascular and inflammatory diseases, including heart failure, obesity, and sepsis.[4,5] These effects are mediated through the vagus nerve's ability to regulate immune responses, a mechanism known as the "inflammatory reflex" or cholinergic anti-inflammatory pathway. Activation of vagal afferents initiates central reflexes that suppress pro-inflammatory cytokine release via efferent signalling to immune cells. Consequently, VNS has been shown to significantly reduce pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α), restoring immune balance in both preclinical and clinical studies.[5,6] This neuroimmune modulation has demonstrated protective effects in various I/R models, improving outcomes in affected organs.[7–9]

Previous studies have reported that VNS can attenuate I/R injury in several organs. In hepatic I/R, invasive VNS delivered through surgically implanted electrodes on the cervical or abdominal vagus nerve was shown to protect the liver and reduce remote organ injury.[10,11] However, invasive methods may lead to complications such as cardiac arrhythmias, asystole, hematoma, infection, vocal cord paralysis, and respiratory distress.[12–14] These risks have accelerated the search for non-invasive alternatives.

One such approach is transcutaneous auricular vagus nerve stimulation (tVNS), which targets the auricular branch of the vagus nerve accessible at the ear. This branch projects to the nucleus tractus solitarius in the brainstem, enabling modulation of autonomic activity. tVNS increases parasympathetic tone while suppressing sympathetic output, exerting effects through sympatho-inhibitory mechanisms. Owing to its non-invasive nature, tVNS has gained considerable attention as a potential therapy for neurological, cardiovascular, and inflammatory disorders. Early clinical studies suggest that tVNS is safe, well tolerated, and effective in modulating autonomic and immune functions.[5,15–17]

Despite these promising findings, most research on vagal stimulation in I/R has involved invasive techniques or has focused primarily on the ischemic organ itself. There is limited evidence on whether non-invasive vagal stimulation can mitigate secondary organ injury induced by hepatic I/R. In particular, its impact on cardiac and pulmonary injury remains unexplored.

We hypothesized that augmenting vagal activity via tVNS during hepatic reperfusion would reduce systemic inflammation and oxidative stress, thereby protecting the heart and lungs. To test this, we established a rat model of partial hepatic I/R and evaluated the effects of concurrent tVNS on biochemical markers of oxidative stress, inflammation, and cellular hypoxia in cardiac and pulmonary tissues. The aim of this study was to assess tVNS as a novel, non-invasive approach for limiting hepatic I/R-associated remote organ injury.

To date, most research on vagal stimulation in I/R injury has involved invasive stimulation methods or has focused on protection of the primary ischemic organ. There is a paucity of data on whether non-invasive vagus nerve stimulation can mitigate I/R-induced remote organ injury. In particular, the effect of tVNS on secondary cardiac and pulmonary damage resulting from hepatic I/R has not been previously examined. We hypothesized that augmenting vagal activity via tVNS during hepatic reperfusion would dampen systemic inflammation and oxidative stress, thereby protecting the heart and lungs from I/R-induced injury. In this study, we established a rat model of partial hepatic ischemia–reperfusion and investigated the impact of concurrent tVNS on biochemical markers of oxidative stress, inflammation, and cellular hypoxia in the heart and lungs. Our aim was to evaluate tVNS as a novel, non-invasive strategy to reduce hepatic I/R-mediated secondary organ damage.

Materials and Methods

Animal Model and Ethical Approval

Experiments were conducted on adult male Sprague–Dawley rats (200–230 g). Animals were housed under

standard laboratory conditions (12-h light/dark cycle, ambient temperature 20–22 °C) with free access to chow and water. All animals were acclimatized prior to the study. Experimental procedures complied with the European Parliament Directive 2010/63/EU on the Protection of Animals Used for Scientific Purposes (22 September 2010). The protocol was approved by the Local Ethics Committee for Animal Experiments of the University of Health Sciences (Approval date: 16.10.2024; No. 06/02).

Experimental Groups and Surgical Procedure

Following a 12-h overnight fast, rats were anesthetized via intraperitoneal injection of ketamine hydrochloride (80 mg/kg) and xylazine (10 mg/kg). Under general anaesthesia, a midline laparotomy was performed to induce partial hepatic ischemia. Rats were randomly allocated into three groups (n=7 each):

- **Control group:** Sham laparotomy only, without hepatic ischemia–reperfusion (I/R) or vagus nerve stimulation. Heart and lung tissues were harvested after the equivalent operative duration.
- **I/R group:** Partial hepatic ischemia was induced by occlusion of the portal triad (hepatic artery, portal vein, bile duct) supplying the left lateral and median lobes (~70% of liver mass) using a non-traumatic microvascular clamp. The right and caudate lobes were left perfused to prevent mesenteric congestion. Ischemia lasted 1 h, followed by 3 h of reperfusion. At the end of reperfusion, heart and lung tissues were collected, and rats were euthanized by cardiac puncture exsanguination.
- **I/R + tVNS group:** The ischemia protocol was identical to the I/R group. During the entire 3-h reperfusion period, transauricular vagus nerve stimulation (tVNS) was applied. At the end of reperfusion, tissues were harvested and animals were sacrificed.

All procedures were performed under aseptic conditions. Depth of anaesthesia was continuously monitored, and supplemental doses were administered if required. Body temperature was maintained using a warming pad. At study termination, humane euthanasia was achieved with deep anaesthesia followed by cardiac puncture.

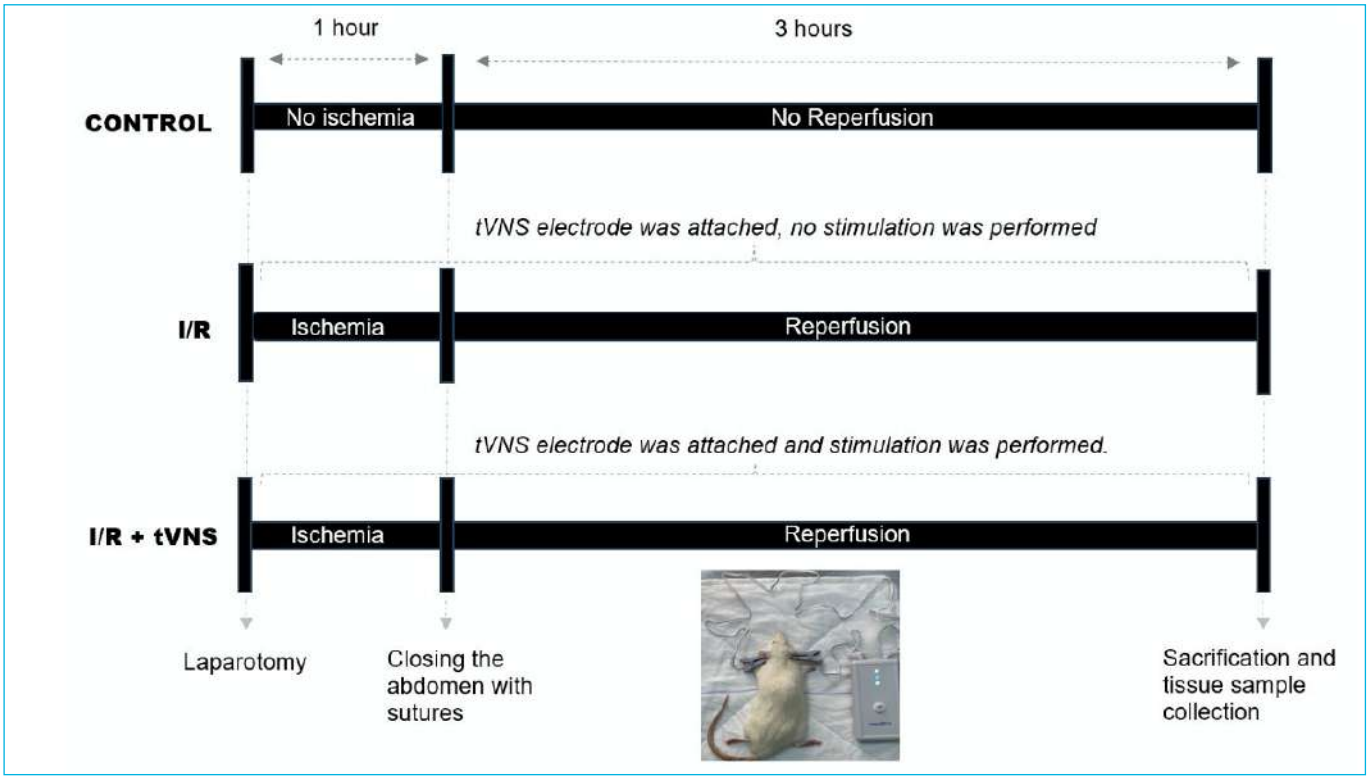

Figure 1. Experimental design. The control group underwent only laparotomy, without ischemia and reperfusion (I/R). The I/R group underwent laparotomy followed by 1 hour of ischemia and 3 hours of reperfusion. In both the control and I/R groups, Vagostim device electrodes were placed on the ears of the animals, but no vagal stimulation was applied. In the I/R+tVNS group, laparotomy and 1 hour of ischemia were performed. Following ischemia, vagal stimulation was applied using the Vagostim device simultaneously with 3 hours of reperfusion.

Transauricular Vagus Nerve Stimulation Protocol

tVNS was applied using the Vagustim® device (Tervigua, Istanbul, Türkiye), a CE-certified stimulator for small animals. Clip electrodes were positioned on the tragus region of both ears, targeting the auricular branch of the vagus nerve. Stimulation parameters were: 30-s ON / 30-s OFF cycles for 3 h, 1 mA current, 500 μs pulse width, 20 Hz frequency, and 5 V output. These parameters were selected based on previous rodent tVNS studies to ensure effective vagal activation without tissue damage. No stimulation was delivered to the Control or I/R groups (Fig. 1).

Tissue Collection and Biochemical Analyses

After reperfusion, cardiac and pulmonary tissues were immediately excised and placed on ice. Samples from the left ventricular myocardium (heart) and right lung were rinsed in cold phosphate-buffered saline (PBS) to remove blood. Each sample (~100 mg) was homogenized (1:10 w/v) in ice-cold PBS using a bead-based homogenizer and centrifuged at 10,000 × g for 30 min at +4 °C. Supernatants were collected for biochemical assays. Protein concentrations were determined by the Bradford method, and all measurements were normalized to total protein.

• **Total Antioxidant Status (TAS) and Total Oxidant Status (TOS):** assessed spectrophotometrically by automated methods.[18,19] The Oxidative Stress Index (OSI) was calculated as the ratio of TOS to TAS (μmol H_2O_2 equivalent/L for TOS; μmol Trolox equivalent/L for TAS).

• **Interleukin-1□ (IL-1□) and Hypoxia-Inducible Factor-1□ (HIF-1□):** quantified using commercial ELISA kits (BTLab, China; Elabscience, USA). Absorbance was read using a microplate reader (Synergy-HTX, Biotek, USA).

Statistical Analysis

Data were analysed with SPSS v22 (IBM, Armonk, NY, USA). Results are expressed as mean ± standard deviation (SD). Data distribution was evaluated by the Shapiro–Wilk test. Since several parameters showed non-normal distribution, non-parametric methods were applied.

• **Overall group comparisons:** Kruskal–Wallis test

• **Pairwise comparisons:** Mann–Whitney U test (Control vs I/R; I/R vs I/R+tVNS)

A Bonferroni correction was applied to adjust for multiple testing. A two-tailed $p<0.05$ was considered statistically significant. Graphs were generated to illustrate group differences, with error bars representing SD.

Results

Oxidative Stress and Antioxidant Status

In both cardiac and pulmonary tissues, Total Oxidant Status (TOS) levels were significantly elevated in the I/R

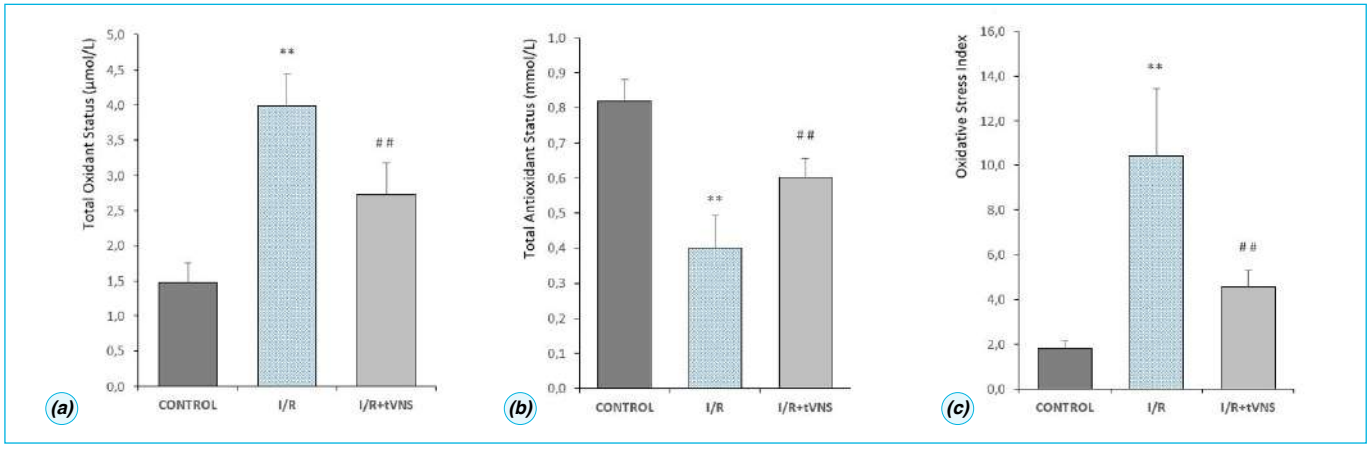

Figure 2. Cardiac oxidative stress values. **(a)** TOS levels were significantly higher in the I/R group compared to the control group and were significantly reduced in the I/R+tVNS group compared to the I/R group. **(b)** In cardiac tissue samples, TAS levels were significantly decreased in the I/R group compared to the control group, while TAS levels in the I/R+tVNS group were significantly increased compared to the I/R group. **(c)** OSI levels in the I/R group were significantly higher than in the control group, whereas OSI levels in the I/R+tVNS group were significantly lower compared to the I/R group. TAS: Total Antioxidant Status; TOS: Total Oxidant Status; OSI: Oxidative Stress Index. Note: Control group (n=7); I/R group (n=7); I/R+tVNS group (n=7). (**=p<0.01 vs. control group; ##=p<0.01 vs. I/R group).

group compared with controls ($p<0.01$), confirming a pronounced oxidative burden induced by hepatic I/R. In the I/R+tVNS group, cardiac TOS levels were markedly reduced compared with the I/R group ($p<0.01$), indicating that vagal stimulation effectively limited oxidant accumulation (Fig. 2; Fig. 3). Although a similar downward trend was observed in pulmonary tissues, the reduction did not reach statistical significance (Fig. 2A, Fig. 3A).

Total Antioxidant Status (TAS) levels were significantly decreased in both cardiac and pulmonary tissues of the I/R group relative to controls ($p<0.01$), reflecting compromised antioxidant defences during hepatic I/R. Treatment with tVNS restored TAS levels, with significant increases observed in the heart ($p<0.01$) and lungs ($p<0.05$) compared with the I/R group (Fig. 2B; Fig. 3B).

As a result of these opposing changes, the Oxidative Stress Index (OSI; TOS/TAS ratio) was significantly elevated in cardiac and pulmonary tissues of the I/R group compared with controls ($p<0.01$). Administration of tVNS led to a pronounced reduction in OSI, with statistical significance achieved in both the heart ($p<0.01$) and lungs ($p<0.05$) relative to the I/R group (Fig. 2C; Fig. 3C). Collectively, these findings demonstrate that tVNS not only suppressed oxidant generation but also enhanced antioxidant defence, thereby rebalancing redox homeostasis.

Inflammatory Cytokine Response

Interleukin-1β (IL-1β) levels were markedly elevated in both cardiac and pulmonary tissues of the I/R group compared with controls ($p<0.01$), indicating a strong pro-inflammatory response triggered by hepatic I/R. In contrast, the I/R+tVNS group exhibited significantly lower IL-1β levels, with reductions observed in cardiac ($p<0.05$) and pulmonary ($p<0.01$) tissues relative to the I/R group (Fig. 4; Fig. 5). This suppression of IL-1β suggests that tVNS effectively attenuates systemic inflammation associated with reperfusion injury.

Hypoxia-Related Marker

Hypoxia-Inducible Factor-1α (HIF-1α) expression was significantly elevated in both cardiac and pulmonary tissues of the I/R group compared with controls ($p<0.001$), reflecting the hypoxic and inflammatory stress caused by I/R. In the I/R+tVNS group, HIF-1α levels in the heart were significantly reduced compared with the I/R group ($p<0.001$), suggesting that tVNS ameliorated myocardial hypoxic stress. Although pulmonary HIF-1α levels also showed a decreasing trend, the difference was not statistically significant (Fig. 4; Fig. 5). This organ-specific effect indicates that the cardioprotective impact of tVNS on hypoxia may be more pronounced than its effect on pulmonary tissues within the early reperfusion period.

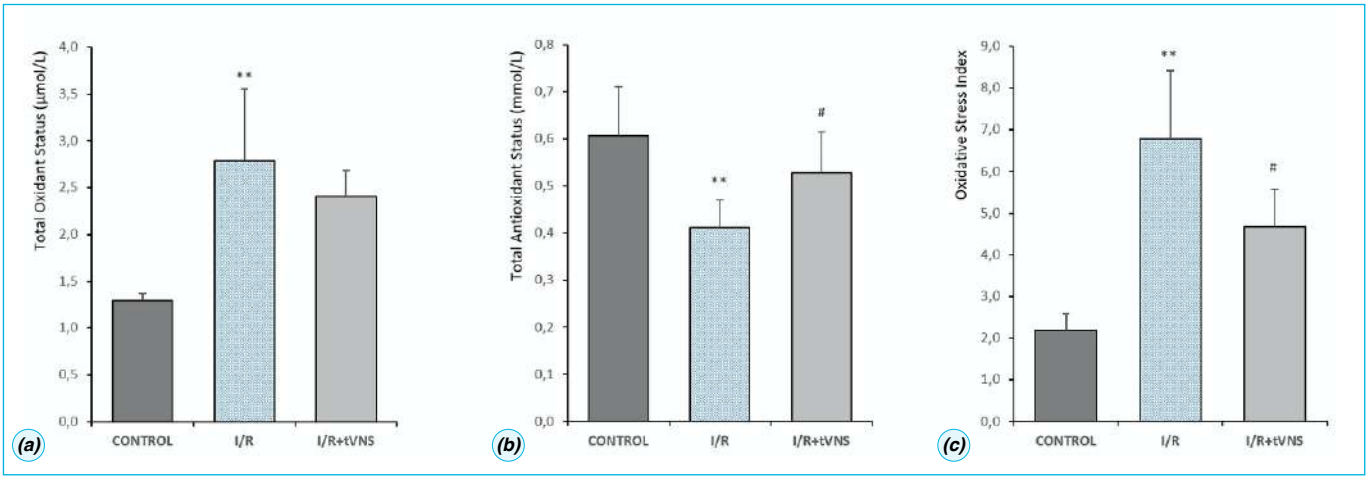

Figure 3. Pulmonary oxidative stress values. **(a)** TOS levels were significantly higher in the I/R group compared to the control group. Although TOS levels in the I/R+tVNS group were lower than in the I/R group, the difference was not statistically significant. **(b)** In lung tissue samples, TAS levels were significantly decreased in the I/R group compared to the control group, while TAS levels in the I/R+tVNS group were significantly increased. **(c)** OSI levels in the I/R group were significantly higher than in the control group, whereas OSI levels in the I/R+tVNS group were significantly lower than in the I/R group. TAS: Total Antioxidant Status; TOS: Total Oxidant Status; OSI: Oxidative Stress Index. Note: Control group (n=7); I/R group (n=7); I/R+tVNS group (n=7). (**=p<0.01 vs. control group; #=p<0.05 vs. I/R group).

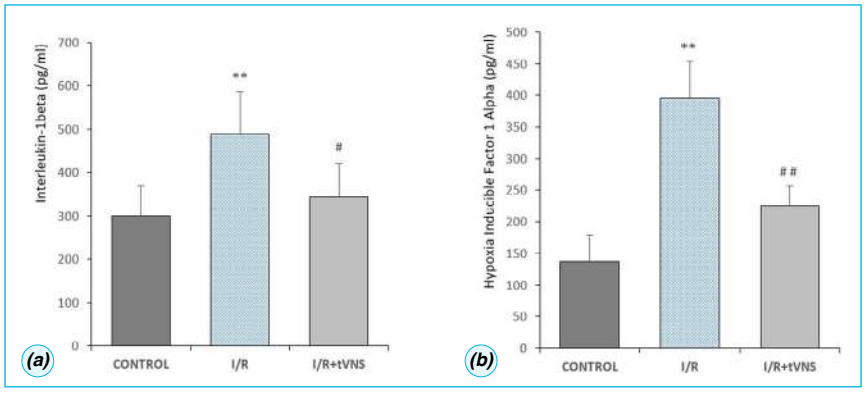

Figure 4. Cardiac inflammatory cytokine levels and HIF-1α values. **(a)** IL-1β levels in cardiac tissue samples of the I/R group were significantly higher than those of the control group. IL-1β levels in the I/R+tVNS group were significantly reduced compared to the I/R group. **(b)** HIF-1α levels were significantly increased in the I/R group compared to the control group, while HIF-1α levels in the I/R+tVNS group were significantly decreased compared to the I/R group. Note: Control group (n=7); I/R group (n=7); I/R+tVNS group (n=7). (**=p<0.01 vs. control group; #=p<0.05, ##=p<0.01 vs. I/R group)

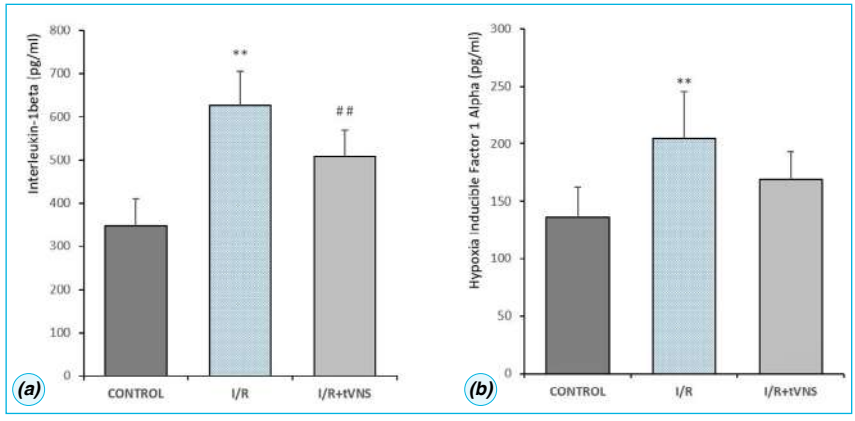

Figure 5. Pulmonary inflammatory cytokine levels and HIF-1α values. **(a)** IL-1β levels in the I/R group were significantly higher than in the control group, while IL-1β levels in the I/R+tVNS group were significantly lower compared to the I/R group. **(b)** HIF-1α levels were significantly higher in the I/R group compared to the control group; however, HIF-1α levels in the I/R+tVNS group did not differ significantly from the I/R group. Note: Control group (n=7); I/R group (n=7); I/R+tVNS group (n=7). (**=p<0.01 vs. control group; ##=p<0.01 vs. I/R group).

Discussion

The findings of this study demonstrate that transauricular vagus nerve stimulation significantly modulated oxidative stress, inflammation, and hypoxia-related responses in cardiac and pulmonary tissues during hepatic ischemia–reperfusion. Hepatic ischemia–reperfusion is known to cause not only direct hepatic injury but also severe dysfunction in distant organs. In our study, the application of transauricular vagus nerve stimulation reduced total oxidant status, enhanced total antioxidant status, and consequently lowered the oxidative stress index in both heart and lung tissues. This observation is in agreement with previous reports indicating that vagus nerve stimulation can restore redox balance toward antioxidation in ischemia–reperfusion injury models.[20]

From a mechanistic perspective, vagus nerve stimulation has been shown to activate endogenous antioxidant pathways. Zhang and colleagues reported that invasive vagus nerve stimulation activated the Nrf2/HO-1 cytoprotective pathway in a hepatic ischemia–reperfusion model, thereby reducing hepatic injury.[1] Deng and colleagues observed increased Nrf2 and HO-1 expression in the kidney and suppression of oxidative stress following

vagus nerve stimulation during hepatic ischemia–reperfusion.[10] Similarly, Xin and colleagues demonstrated an upregulation of SIRT1 in skeletal muscle, which correlated with reduced oxidative damage and apoptosis.[21] In our study, transauricular vagus nerve stimulation appeared to enhance antioxidant defence systems in both the heart and lungs, possibly through activation of glutathione and superoxide dismutase pathways. A recent study further supports this mechanism, showing that vagus nerve stimulation during reperfusion enhanced myocardial expression of glutathione peroxidase (GPX4) and SLC7A11, both of which are critical for the prevention of lipid peroxidation and ferroptotic cell death.[1] The increase in total antioxidant status and the decrease in oxidative stress index observed in our study are consistent with these reports.

Inflammation plays a central role in ischemia–reperfusion injury. Pro-inflammatory cytokines, particularly interleukin-1 beta, promote leukocyte infiltration and amplify inflammatory cascades.[22] In our study, hepatic ischemia–reperfusion markedly increased interleukin-1 beta levels in both cardiac and pulmonary tissues, whereas transauricular vagus nerve stimulation significantly reduced this elevation. These results indicate activation of the cholinergic anti-inflammatory pathway by vagal stimulation. Previous experimental and clinical studies have also demonstrated that vagus nerve stimulation decreases circulating interleukin-1 beta and tumor necrosis factor alpha.[1,5,6,20-23] Caravaca and colleagues showed that vagus nerve stimulation not only suppressed pro-inflammatory cytokines but also promoted the resolution of inflammation by enhancing specialized lipid mediators.[24] Our results are in line with these observations, suggesting that transauricular vagus nerve stimulation mitigates the inflammatory burden in distant organs.

Hypoxia-inducible factor-1 alpha is a key transcription factor in cellular adaptation to hypoxia, but its persistent activation during ischemia–reperfusion contributes to pathological changes. In our study, hepatic ischemia–reperfusion significantly increased hypoxia-inducible factor-1 alpha expression in both the heart and lungs. Interestingly, transauricular vagus nerve stimulation significantly reduced hypoxia-inducible factor-1 alpha levels in the heart but did not show a statistically significant effect in the lungs. This discrepancy may reflect organ-specific pathophysiological responses. The heart is highly sensitive to oxidative stress and energy depletion during reperfusion; therefore, vagal stimulation may improve myocardial oxygen utilization and microcirculation, thereby limiting hypoxia-inducible factor-1 alpha stabilization.[25,26] In contrast, lung injury following hepatic ischemia–reperfusion is predominantly mediated by leukocyte sequestration, neutrophil elastase, and toxic mediator release in the pulmonary vasculature.[27] Although transauricular vagus nerve stimulation attenuated interleukin-1 beta levels in the lung, it may not have been sufficient to prevent transient pulmonary hypoxia during the early reperfusion phase. Moreover, the three-hour reperfusion window used in this study may not have been long enough to detect a measurable decrease in pulmonary hypoxia-inducible factor-1 alpha protein. Longer reperfusion periods or different stimulation protocols might be required to reveal a significant effect.

The clinical implications of our findings are noteworthy. Invasive vagus nerve stimulation is associated with complications such as arrhythmias, infection, hematoma, and vocal cord paralysis.[12–14] In contrast, transauricular vagus nerve stimulation is non-invasive, safe, and easy to apply. Recent clinical studies have reported favourable effects of transauricular vagus nerve stimulation on both autonomic nervous system activity and immune parameters.[15–17] Therefore, this approach may serve as an adjunctive protective therapy in clinical settings with high risk of multi-organ injury, including liver surgery, transplantation, or hypovolemic shock.

This study has several limitations. First, the small sample size may have reduced statistical power. Second, only one stimulation protocol was applied; alternative frequencies, intensities, and durations may yield different outcomes, particularly in the lungs. Third, the biochemical analyses were limited to total oxidant status, total antioxidant status, interleukin-1 beta, and hypoxia-inducible factor-1 alpha; the addition of other biomarkers such as malondialdehyde, superoxide dismutase, catalase, and anti-inflammatory cytokines would provide a more comprehensive picture. Fourth, histological evaluation was not performed with blinded scoring and lacked immunohistochemical confirmation. Finally, experiments were carried out in healthy rats, whereas human patients often have comorbidities such as hepatic steatosis, diabetes, or cardiovascular disease, which could influence the response to vagus nerve stimulation.

Future studies should investigate different stimulation protocols, broader biomarker panels, histological and

immunohistochemical validation, as well as functional outcomes such as cardiac contractility and pulmonary gas exchange. Moreover, studies in clinically relevant models that include comorbid conditions are essential for translation. Such efforts will help clarify the potential of transauricular vagus nerve stimulation as a clinically applicable strategy for multi-organ protection during ischemia–reperfusion injury.

Conclusion

This study shows that tVNS protects the heart and lungs in hepatic I/R by reducing oxidative stress, preserving antioxidant capacity, lowering IL-1β, and modulating HIF-1α, especially in the myocardium. These findings support non-invasive neuromodulation as a potential strategy for multi-organ protection, warranting further research to optimize protocols and confirm clinical efficacy.

Acknowledgment: This study was conducted on the heart and lungs obtained after a liver/ischemia-reperfusion model was created within the scope of the project titled "The effect of non-invasive transauricular vagal stimulation on hepatic ischemia/reperfusion injury" and numbered 2020/092 (Dr. Mahmut Salih Genç's medical specialization thesis), supported by the Scientific Research Projects Coordination Office of the University of Health Sciences.

Ethics Committee Approval: The protocol was approved by the Local Ethics Committee for Animal Experiments of the University of Health Sciences (Date: 16/10/2024, No: 06/02).

Peer-review: Externally peer-reviewed.

Informed Consent: Not applicable.

Author Contribution: Concept: C.D., M.S.G., E.M.G., A.F.M., B.G.; Design: C.D., M.S.G., K.S., E.M.G., A.F.M., B.G.; Supervision: M.S.G., A.F.M., B.G., C.D.; Materials: P.E., K.S., E.M.G.; Data collection &/or processing: C.D., M.S.G., P.E., K.S., E.M.G., H.B., A.F.M.; Analysis and/or interpretation: P.E., K.S., M.G., H.B.; Literature search: M.S.G., M.G., H.B., A.F.M., B.G.; Writing: M.G., C.D., P.E., K.S., E.M.G.; Critical review: C.D., M.G., E.M.G., B.G.

Conflict of Interest: The authors declare that they have no conflicts of interest related to this study.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Zhang P, Qin Y, Wang H, Wang J. Vagus nerve stimulation alleviates myocardial injury following hepatic ischemia-reperfusion in rats by inhibiting ferroptosis via the activation of the SLC7A11/GPX4 axis. Eur J Med Res 2025;30:162. [CrossRef]
2. Jang JH, Kang KJ, Kang Y, Lee IS, Graf R, Clavien PA. Ischemic preconditioning and intermittent clamping confer protection against ischemic injury in the cirrhotic mouse liver. Liver Transpl 2008;14:980–8. [CrossRef]
3. Pantazi E, Bejaoui M, Folch-Puy E, Adam R, Roselló-Catafau J. Advances in treatment strategies for ischemia reperfusion injury. Expert Opin Pharmacother 2016;17:169–79. [CrossRef]
4. Jensen KJ, Alpini G, Glaser S. Hepatic nervous system and neurobiology of the liver. Compr Physiol 2013;3:655–65. [CrossRef]
5. Fang YT, Lin YT, Tseng WL, Tseng P, Hua GL, Chao YJ, et al. Neuroimmunomodulation of vagus nerve stimulation and the therapeutic implications. Front Aging Neurosci 2023;15:1173987. [CrossRef]
6. Wu Z, Zhang X, Cai T, Li Y, Guo X, Zhao X, et al. Transcutaneous auricular vagus nerve stimulation reduces cytokine production in sepsis: An open double-blind, sham-controlled, pilot study. Brain Stimul 2023;16:507–14. [CrossRef]
7. Rawat JK, Roy S, Singh M, Guatam S, Yadav RK, Ansari MN, et al. Transcutaneous vagus nerve stimulation regulates the cholinergic anti-inflammatory pathway to counteract 1, 2-dimethylhydrazine induced colon carcinogenesis in albino Wistar rats. Front Pharmacol 2019;10:353. [CrossRef]
8. Kong J, Fang J, Park J, Li S, Rong P. Treating depression with transcutaneous auricular vagus nerve stimulation: State of the art and future perspectives. Front Psychiatry 2018;9:20. [CrossRef]
9. Cheng J, Shen H, Chowdhury R, Abdi T, Selaru F, Chen JDZ. Potential of electrical neuromodulation for inflammatory bowel disease. Inflamm Bowel Dis 2020;26:1119–30. [CrossRef]
10. Deng S, Zhang Y, Xin Y, Hu X. Vagus nerve stimulation attenuates acute kidney injury induced by hepatic ischemia/reperfusion injury in rats. Sci Rep 2022;12:21662. [CrossRef]
11. Zhang Q, Lai Y, Deng J, Wang M, Wang Z, Wang M, et al. Vagus nerve stimulation attenuates hepatic ischemia/reperfusion injury via the Nrf2/HO-1 pathway. Oxid Med Cell Longev 2019;2019:9549506. [CrossRef]
12. Li J, Zhang Q, Li S, Niu L, Ma J, Wen L, et al. α7nAchR mediates transcutaneous auricular vagus nerve stimulation-induced neuroprotection in a rat model of ischemic stroke by enhancing axonal plasticity. Neurosci Lett 2020;730:135031. [CrossRef]
13. Ma J, Qiao P, Li Q, Wang Y, Zhang L, Yan LJ, et al. Vagus nerve stimulation as a promising adjunctive treatment for ischemic stroke. Neurochem Int 2019;131:104539. [CrossRef]
14. Ben-Menachem E, Revesz D, Simon BJ, Silberstein S. Surgically implanted and non-invasive vagus nerve stimulation: A review of efficacy, safety and tolerability. Eur J Neurol 2015;22:1260–8. [CrossRef]
15. Liu FJ, Wu J, Gong LJ, Yang HS, Chen H. Non-invasive vagus nerve stimulation in anti-inflammatory therapy: Mechanistic insights and future perspectives. Front Neurosci 2024;18:1490300. [CrossRef]
16. He W, Jing XH, Zhu B, Zhu XL, Li L, Bai WZ, et al. The auriculovagal afferent pathway and its role in seizure suppression in rats. BMC Neurosci 2013;14:85. [CrossRef]
17. Deuchars SA, Lall VK, Clancy J, Mahadi M, Murray A, Peers L, et al. Mechanisms underpinning sympathetic nervous activity and its modulation using transcutaneous vagus nerve stimulation. Exp Physiol 2018;103:326–31. [CrossRef]
18. Erel O. A novel automated method to measure total antioxidant response against potent free radical reactions. Clin Biochem 2004;37:112–9. [CrossRef]

19. Erel O. A new automated colorimetric method for measuring total oxidant status. Clin Biochem 2005;38:1103–11. [CrossRef]
20. Singh P, Chaudhary M, Kazmi JS, Kuschner CE, Volpe BT, Chaudhuri TD, et al. Vagus nerve stimulation: A targeted approach for reducing tissue-specific ischemic reperfusion injury. Biomed Pharmacother 2025;184:117898. [CrossRef]
21. Xin Y, Zhang Y, Deng S, Hu X. Vagus nerve stimulation attenuates acute skeletal muscle injury induced by hepatic ischemia/reperfusion injury in rats. Front Pharmacol 2022;12:756997. [CrossRef]
22. Al-Qahtani AA, Alhamlan FS, Al-Qahtani AA. Pro-inflammatory and anti-inflammatory interleukins in infectious diseases: A comprehensive review. Trop Med Infect Dis 2024;9:13. [CrossRef]
23. Meneses G, Bautista M, Florentino A, Díaz G, Acero G, Besedovsky H, et al. Electric stimulation of the vagus nerve reduced mouse neuroinflammation induced by lipopolysaccharide. J Inflamm 2016;13:33. [CrossRef]
24. Caravaca AS, Gallina AL, Tarnawski L, Shavva VS, Colas RA, Dalli J, et al. Vagus nerve stimulation promotes resolution of inflammation by a mechanism that involves Alox15 and requires the α7nAChR subunit. Proc Natl Acad Sci U S A 2022;119. [CrossRef]
25. Nastos C, Kalimeris K, Papoutsidakis N, Tasoulis MK, Lykoudis PM, Theodoraki K, et al. Global consequences of liver ischemia/reperfusion injury. Oxid Med Cell Longev 2014;2014:906965. [CrossRef]
26. An W, Kang JS. Effect of metformin on myocardial injury induced by hepatic ischemia-reperfusion in rats. Front Pharmacol 2022;13:822743. [CrossRef]
27. Deng J, Jiang Y, Wang M, Shao L, Deng C. Activation of vagovagal reflex prevents hepatic ischaemia-reperfusion-induced lung injury via anti-inflammatory and antioxidant effects. Exp Physiol 2021;106:2210–22. [CrossRef]

ORIGINAL ARTICLE

Access this article online
Quick Response Code:

Website: www.scie.online
DOI: 10.14744/scie.2026.77047

Learning Curve and Early Surgical Performance of vNOTES Hysterectomy: A Retrospective Single Surgeon Cohort Study

Ali Deniz Erkmen,[1] Kevser Arkan,[1] Gül Çavuşoğlu Çolak,[2] Mesut Ali Halisçelik,[1] Özgür Adıgüzel,[2] Kübra Çakar Yılmaz,[2] Pınar Birol İlter,[3] Süleyman Cemil Oglak[2]

[1]*Department of Obstetrics and Gynecology, Diyarbakir Gazi Yasargil Training and Research Hospital, Division of Gynecologic Oncology, Diyarbakir, Türkiye*
[2]*Department of Obstetrics and Gynecology, Diyarbakir Gazi Yasargil Training and Research Hospital, Diyarbakir, Türkiye*
[3]*Department of Obstetrics and Gynecology, Kutahya City Hospital, Kutahya, Türkiye*

Address for correspondence:
Ali Deniz Erkmen, Department of Obstetrics and Gynecology, Diyarbakir Gazi Yasargil Training and Research Hospital, Division of Gynecologic Oncology, Diyarbakir, Türkiye
E-mail: erkmendnz@gmail.com

Received: 07.01.2026
Accepted: 04.05.2026
Published: 29.09.2026

Abstract

Objective: To evaluate the learning curve of vaginal natural orifice transluminal endoscopic surgery (vNOTES) hysterectomy during early adoption and to assess changes in operative performance and perioperative safety over consecutive cases. Study Design is retrospective observational learning curve analysis. Setting is tertiary referral center for minimally invasive gynecologic surgery. Forty consecutive patients who underwent vNOTES hysterectomy for benign gynecologic indications. vNOTES hysterectomy performed by a single surgeon during the initial implementation period.

Methods: Operative performance was assessed using total operative time, and learning dynamics were evaluated with cumulative summation (CUSUM) analysis.

Results: Mean operative time decreased progressively across sequential quartiles, from 89.3±7.5 minutes in the first 10 cases to 46.2±3.1 minutes in the final 10 cases. CUSUM analysis demonstrated a clear inflection point at approximately the 18th case, indicating transition from early technical adaptation to stabilized operative performance. Minor perioperative complications and conversions occurred only during the early learning phase, with no major complications observed throughout the series.

Conclusions: vNOTES hysterectomy suggests a consistent learning curve pattern during early adoption. Operative efficiency improves progressively, with technical proficiency achieved after a limited number of cases and without compromise in perioperative safety. These findings support structured implementation and objective learning curve assessment during the introduction of vNOTES into minimally invasive gynecologic practice.

Keywords: vNOTES hysterectomy; vaginal natural orifice transluminal endoscopic surgery; learning curve; cumulative summation (CUSUM); minimally invasive gynecologic surgery; operative efficiency.

How to cite this article: *Erkmen AD, Arkan K, Çavuşoğlu Çolak G, Halisçelik MA, Adıgüzel Ö, Çakar Yılmaz K, Birol İlter P, Oglak SC. Learning curve and early surgical performance of vnotes hysterectomy: a retrospective single surgeon cohort study. South. Clin. Ist. Euras. 2026;37(3):216-223.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Copyright@Author(s)

Introduction

Vaginal natural orifice transluminal endoscopic surgery (vNOTES) has emerged as an innovative extension of minimally invasive gynecologic surgery, combining transvaginal access with endoscopic visualization to perform complex pelvic procedures without abdominal incisions.[1] By avoiding abdominal wall trauma, vNOTES has been associated with favorable postoperative recovery profiles in early clinical reports, including reduced pain and rapid mobilization.[2]

Despite these potential advantages, the adoption of vNOTES has remained gradual. Unlike conventional laparoscopy, vNOTES requires surgeons to operate within a transvaginal endoscopic field characterized by reversed visual orientation, limited instrument triangulation, and distinct ergonomic constraints. These technical characteristics necessitate a period of adaptation, making the learning process a critical determinant of both operative performance and patient safety during early implementation.[3]

Learning curve analysis provides an objective framework to evaluate the progression of surgical proficiency over time and to distinguish temporary technical challenges from intrinsic limitations of a procedure. Operative time has been widely used as a surrogate marker of technical maturation in minimally invasive gynecologic surgery, reflecting cumulative improvements in efficiency, coordination, and procedural confidence.[4] Among available analytical methods, cumulative summation (CUSUM) analysis allows sensitive detection of performance trends and identification of inflection points indicating attainment of technical proficiency.[5]

Although several studies have demonstrated the feasibility of vNOTES hysterectomy, structured evaluations of its learning curve remain limited. Existing reports often focus on short-term outcomes or small case series, providing insufficient insight into how operative performance and safety evolve during early experience.[6] A clear understanding of the learning dynamics associated with vNOTES is essential to inform training strategies, patient selection, and safe dissemination of the technique.

The present study aimed to evaluate the learning curve of vNOTES hysterectomy during its early adoption phase in a single-surgeon cohort. By analyzing sequential cases using CUSUM methodology and examining trends in operative efficiency and perioperative safety, we sought to define the trajectory of technical maturation and identify the case number at which procedural proficiency was achieved.

Materials and Methods

This retrospective observational study was designed to evaluate the learning curve associated with vaginal natural orifice transluminal endoscopic surgery (vNOTES) hysterectomy during the early adoption phase of the technique. The primary objective was to assess the progression of operative performance and perioperative safety over consecutive cases, rather than to compare vNOTES with alternative surgical approaches.

The study was conducted at a tertiary referral center with established experience in advanced minimally invasive gynecologic surgery. Introduction of vNOTES at our institution followed a structured implementation process, including standardized instrumentation, predefined surgical steps, and consistent perioperative management protocols. This controlled setting was intended to minimize institutional variability and allow learning related changes to be interpreted primarily as surgeon dependent effects.[7,8]

To ensure internal consistency, all procedures were performed by a single surgeon with extensive prior experience in conventional laparoscopic hysterectomy. This design choice was made deliberately to reduce interoperator variability and to allow sequential changes in operative metrics to reflect true technical adaptation rather than differences in baseline surgical skill.[9]

Ethical approval was obtained from the Clinical Research Ethics Committee of Health Sciences University, Gazi Yaşargil Hospital, Diyarbakir, Türkiye (Approval No: 643; Date: 19/09/2025). All procedures were conducted in accordance with the Declaration of Helsinki. Given the retrospective nature of the study and the use of anonymized patient data, the requirement for written informed consent was waived by the ethics committee.

All consecutive patients who underwent vNOTES hysterectomy for benign gynecologic indications during the study period were screened for eligibility. Cases were included in strict chronological order based on the date of surgery to preserve the temporal structure required for learning curve analysis.[10] Eligible patients were required to be 18 years of age or older, to have undergone

hysterectomy exclusively via the vNOTES approach for benign gynecologic disease, and to have complete demographic, intraoperative, and postoperative data available for analysis. Patients were excluded if there was suspected or histologically confirmed gynecologic malignancy, if concomitant major pelvic reconstructive or anti-incontinence procedures were performed, if surgery was undertaken on an emergency basis, or if perioperative records were incomplete. Importantly, cases requiring conversion to an alternative surgical approach were not excluded and were retained in their original chronological sequence. This approach was adopted to preserve the integrity of the learning curve analysis, as exclusion of technically challenging cases may artificially attenuate early performance trends and lead to underestimation of the true learning process.[11,12]

The study design intentionally focused on a single surgical technique performed by a single surgeon. While this approach limits generalizability, it is widely accepted as an appropriate and methodologically sound strategy for learning curve analysis, particularly during early adoption of novel minimally invasive techniques.[13]

By eliminating variability related to surgeon experience, instrument preference, and operative style, this design allows more precise characterization of technical maturation over time. Importantly, the purpose of this study was not to define universal proficiency thresholds, but rather to describe the trajectory of performance improvement under controlled conditions, providing a reference framework for future training and multi-surgeon studies.

Eligible cases were arranged in strict chronological order and analyzed sequentially. No case stratification or preselection based on uterine size, body mass index, or prior surgical history was performed. This approach was chosen to reflect real-world clinical practice during early technique adoption and to avoid selection bias toward technically favorable cases.[14] CUSUM was calculated using the mean operative time of the entire cohort as the reference value. For each consecutive case, the difference between the individual operative time and the overall mean operative time was cumulatively summed to construct the CUSUM curve. This method allowed objective identification of performance trends and detection of the inflection point corresponding to technical stabilization.

For descriptive analysis, cases were additionally grouped into sequential phases representing early, intermediate, and late experience. These groupings were used solely for interpretive purposes and did not replace the primary continuous learning curve analysis based on cumulative summation methodology. Group comparisons across sequential learning phases were performed using one-way analysis of variance (ANOVA) for normally distributed variables and the Kruskal-Wallis test for non-normally distributed variables. A two-sided p value <0.05 was considered statistically significant.

Several measures were implemented to reduce potential sources of bias inherent to retrospective learning curve studies. Selection bias was minimized by including all consecutive eligible cases without exclusion based on perceived technical difficulty. Performance bias was limited through use of a standardized surgical technique and consistent perioperative management throughout the study period. Detection bias was reduced by predefined outcome measures and uniform data extraction from electronic medical records. Despite these precautions, residual confounding related to unmeasured patient or anatomical factors cannot be fully excluded and is acknowledged as an inherent limitation of retrospective observational designs.[15]

Surgical technique

All vNOTES hysterectomy procedures were performed using a standardized transvaginal endoscopic approach. Patients were placed in the dorsal lithotomy position under general anesthesia, and a uterine manipulator was inserted to facilitate uterine mobilization and delineation of anatomical landmarks. After preparation and draping, a circumferential colpotomy was performed to access the peritoneal cavity through the vaginal route. A dedicated vNOTES access platform was then inserted transvaginally, and pneumoperitoneum was established under direct visualization. A high-definition endoscopic camera and conventional laparoscopic instruments were used throughout the procedure.[16]

Following entry into the peritoneal cavity, systematic inspection of the pelvic anatomy was performed to confirm orientation and identify critical structures. Particular attention was paid to early recognition of the ureters and pelvic sidewall anatomy, as the reversed visual axis inherent to the transvaginal approach requires deliberate spatial reorientation during initial cases. Dissection proceeded in a stepwise fashion, beginning with identification and sealing of the uterine vascular pedicles under endoscopic guidance. Energy devices were used according to surgeon preference to ensure secure hemostasis while minimizing lateral thermal spread.[17]

Mobilization of the uterus was achieved through sequential dissection of the vesicovaginal and rectovaginal planes. The anterior dissection was performed carefully to avoid bladder injury, especially during early cases when depth perception and instrument angulation were still being refined. Posterior dissection followed the natural anatomical planes toward the pouch of Douglas, allowing gradual release of uterine attachments and progressive descent of the specimen. Throughout the procedure, instrument movements were deliberately controlled to reduce external clashing and to maintain ergonomic efficiency within the confined transvaginal working space.[18]

Once complete mobilization was achieved, the uterus was extracted transvaginally. In cases where uterine size limited direct removal, in bag morcellation was performed under endoscopic visualization to ensure tissue containment and maintain oncologic safety principles, despite the benign indication of surgery. Specimen extraction technique was adapted progressively with increasing experience, contributing to improved procedural flow during later cases.[19]

Vaginal cuff closure was performed transvaginally following specimen removal. Closure technique consisted of either interrupted or continuous suturing, depending on intraoperative conditions and surgeon preference. Care was taken to ensure full thickness approximation of the vaginal cuff with adequate tissue incorporation to promote secure healing. As experience accumulated, cuff closure became increasingly efficient, reflecting improved familiarity with transvaginal suturing under endoscopic conditions.[20]

Throughout the learning period, the overall surgical strategy remained unchanged, and no protocol driven modifications were introduced. Minor intraoperative adjustments, such as optimization of pneumoperitoneum pressure and refinement of instrument positioning, were made organically as part of the learning process. These adaptations were considered inherent to technical maturation rather than deviations from the standardized technique and were not protocolized.[21]

Results

A total of 40 consecutive patients who underwent vNOTES hysterectomy for benign gynecologic indications were included in the analysis. All cases were performed in chronological order during the early adoption period of the technique. Baseline demographic and clinical characteristics were homogeneous across the cohort. No statistically significant differences were observed across sequential cases with respect to baseline demographic or clinical variables ($p>0.05$). Mean age, body mass index, parity, uterine weight, history of prior pelvic surgery, and surgical indications did not demonstrate clinically meaningful variation over time, indicating a stable case mix throughout the learning period (Table 1). No preselection or case filtering based on anticipated technical difficulty was applied.

Progressive improvement in operative performance was observed across sequential cases. Mean total operative time decreased steadily as experience accumulated, declining from 86.4 minutes in the earliest cases to 46.5 minutes in the final phase of the series. This reduction was gradual rather than abrupt, reflecting continuous technical adaptation rather than a single stepwise change.

Cumulative summation (CUSUM) analysis of total operative time demonstrated a clear inflection point after approximately the 18th case (Fig. 1). Prior to this point, the CUSUM curve showed an upward trajectory, indicating operative times above the cohort mean. Following the inflection point, the curve plateaued and subsequently declined, consistent with attainment of technical proficiency and stabilization of operative efficiency. The inflection point identified by CUSUM analysis and the corresponding learning phases are summarized in Table 2.

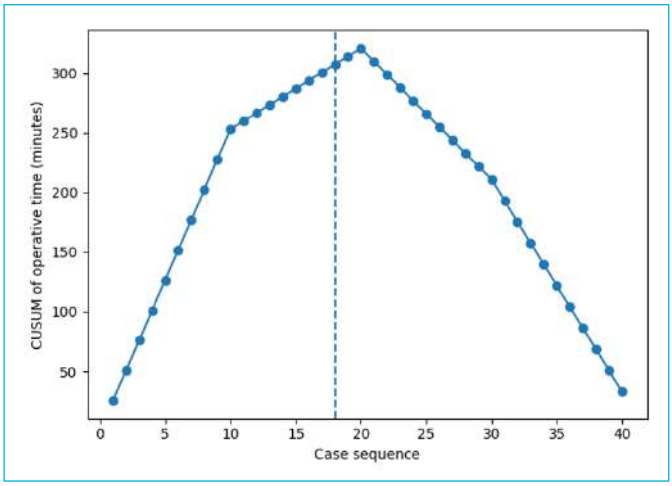

Figure 1. Cumulative summation (CUSUM) analysis of total operative time during the learning process of vNOTES hysterectomy. The vertical dashed line indicates the inflection point at approximately the 18th case, corresponding to the transition from early technical adaptation to stabilized operative performance.

Table 1. Baseline demographic and clinical characteristics of patients undergoing vNOTES hysterectomy

Variable	Overall cohort (n=40)
Age, years	49.1±6.8
Body mass index, kg/m²	27.4±4.1
Parity	3 (0–6)
Prior pelvic surgery, n (%)	14 (35.0%)
Uterine weight, g	182.6±74.3
Surgical indication, n (%)	
Uterine fibroids	22 (55.0%)
Adenomyosis	9 (22.5%)
Abnormal uterine bleeding	6 (15.0%)
Other benign indications	3 (7.5%)

Values are presented as mean ± standard deviation, median (range), or n (%), unless otherwise specified. Baseline characteristics were assessed descriptively to evaluate cohort homogeneity. No preselection based on anticipated technical difficulty was applied.

When cases were stratified into sequential quartiles of 10 cases each for descriptive purposes, a significant downward trend in operative time was observed across learning phases (Table 3). Improvements were evident not only in total operative time but also in procedural flow, with smoother transitions between operative steps and reduced variability in later cases.

Perioperative safety outcomes evolved in parallel with improvements in operative efficiency. Minor intraoperative or postoperative complications were observed exclusively during the earliest phase of experience. These events were self-limited and did not result in prolonged hospitalization or additional surgical intervention. No major complications occurred throughout the series.

Conversion to an alternative surgical approach was rare and occurred only during early cases. No conversions were required after the second quartile, coinciding with the plateau phase identified by CUSUM analysis. Estimated blood loss showed a decreasing trend over time, consistent with improved hemostatic control and refined dissection technique in later cases.

Technical challenges related to spatial orientation and instrument handling were more frequently encountered during the initial learning phase. These difficulties diminished progressively with experience and were minimal in the final quartile. Notably, no procedure-related complications or conversions were observed after technical proficiency had been achieved (Table 4).

Summary of learning-related trends

Overall, vNOTES hysterectomy demonstrated a consistent and observable learning trajectory,characterized by progressive reduction in operative time, stabilization of performance after approximately 18 cases, and concurrent improvement in perioperative safety. Once technical proficiency was achieved, operative outcomes remained consistent with minimal variability across subsequent cases.

Table 2. Learning curve analysis of vNOTES hysterectomy using cumulative summation (CUSUM)

Learning phase	Case range	Mean operative time, min	Technical events	Conversions
Early phase	1-18	78.3±13.4	Frequent minor technical difficulties	1
Proficiency phase	≥19	52.1±8.9	Occasional, self-limited	0

Values are presented as mean ± standard deviation, CUSUM analysis of total operative time identified an inflection point at approximately the 18th case, indicating transition from early technical adaptation to stabilized operative performance.

Table 3. Operative performance metrics across sequential learning phases of vNOTES hysterectomy

Variable	Quartile 1 (Cases 1-10)	Quartile 2 (Cases 11-20)	Quartile 3 (Cases 21-30)	Quartile 4 (Cases 31-40)	p for trend
Total operative time, min	86.4±12.1	71.2±10.4	58.9±8.6	46.5±7.3	<0.001
Estimated blood loss, mL	68.5±24.2	51.3±18.7	39.6±15.4	31.2±12.6	<0.001
Conversion to alternative approach, n (%)	1 (10.0%)	0	0	0	-

Values are presented as mean ± standard deviation or n (%), unless otherwise specified.Trends across sequential learning phases were evaluated using trend analysis in conjunction with cumulative summation methodology. A two-sided p<0.05 was considered statistically significant.

Table 4. Perioperative complications and technical challenges observed during the learning process

	Early phase (Cases 1-18)	Late phase (Cases ≥19)
Minor postoperative complications, n (%)	3 (16.7%)	0
Major complications	0	0
Technical challenges related to visualization or ergonomics	Common	Rare
Procedure-related reintervention	0	0

Minor complications were self-limited and did not require invasive intervention. Complication data were analyzed descriptively due to low event rates.

Discussion

The present study provides a structured evaluation of the learning curve associated with vNOTES hysterectomy during its early adoption phase. By analyzing consecutive cases performed by a single surgeon and applying CUSUM methodology, we were able to characterize the trajectory of technical maturation in terms of operative efficiency and perioperative safety. The findings demonstrate that vNOTES hysterectomy is associated with a measurable and relatively rapid learning process, with stabilization of operative performance after approximately 18 cases.

One of the most relevant observations of this study is the gradual and continuous reduction in operative time rather than an abrupt improvement. This pattern suggests that learning in vNOTES is cumulative and reflects progressive adaptation to the transvaginal endoscopic environment, rather than acquisition of a single isolated technical skill. Similar learning dynamics have been described for other advanced minimally invasive gynecologic procedures, including single port laparoscopy and complex laparoscopic hysterectomy, where proficiency emerges through incremental refinement of spatial orientation, instrument handling, and procedural flow.[22]

CUSUM analysis proved particularly valuable in identifying the transition point between early technical adaptation and performance stabilization. Unlike arbitrary case grouping, CUSUM allows objective detection of inflection points in performance trends and has been increasingly adopted in surgical learning curve research.[23] In the present study, the inflection point identified around the 18th case corresponds with a marked reduction in operative time variability and the absence of further conversions or complications. This convergence of efficiency and safety supports the validity of operative time as a surrogate marker of technical proficiency in vNOTES hysterectomy.

Perioperative safety outcomes evolved in parallel with improvements in operative efficiency. Minor complications and conversions were confined to the earliest cases and diminished as experience accumulated. Importantly, no major complications were observed throughout the series. This finding suggests that early technical challenges encountered during vNOTES adoption are primarily related to adaptation to the surgical approach rather than intrinsic procedural risk. Similar observations have been reported in early experiences with other novel minimally invasive techniques, where complication rates decline as familiarity with ergonomics and anatomical orientation improves.[24]

An innovative aspect of this study lies in its emphasis on qualitative technical maturation in addition to quantitative performance metrics. Early cases were characterized by challenges related to spatial orientation, instrument collision, and maintenance of stable visualization. These issues are inherent to the transvaginal endoscopic approach and reflect the need for cognitive re-mapping of pelvic anatomy rather than deficiencies in fundamental surgical skill. The progressive resolution of these challenges underscores the importance of experiential learning and reinforces the notion that vNOTES proficiency is largely driven by adaptation rather than technical complexity alone.[25]

Patient selection also plays a critical role during the learning phase. In this series, vNOTES hysterectomy was applied to benign indications without preselection based on anticipated technical difficulty. While this approach enhances the real-world relevance of the findings, it also highlights the importance of cautious case selection when vNOTES is introduced into clinical practice. Gradual expansion of indications as experience increases may facilitate safer dissemination of the technique, a strategy that has been recommended for other minimally invasive surgical innovations.[26]

The single-surgeon design represents both a strength and a limitation of this study. Restricting the analysis to one surgeon minimizes variability and allows clearer attribution of performance changes to learning effects. However, this design limits generalizability, as learning curves may differ according to baseline laparoscopic experience, institutional support, and case complexity. Future multicenter and multi-surgeon studies are warranted to determine whether the proficiency threshold observed in this study is reproducible across different practice settings.[27]

Additional limitations include the retrospective design and the relatively modest sample size, which preclude definitive conclusions regarding rare complications and long term outcomes. Patient-reported measures, such as postoperative quality of life and sexual function, were not assessed and represent important areas for future research. Despite these limitations, the present study provides a detailed and methodologically robust characterization of early vNOTES learning dynamics. Additionally, factors such as uterine weight and body mass index may independently influence operative time and surgical complexity, potentially affecting interpretation of learning-related performance trends.

In summary, this study demonstrates that vNOTES hysterectomy is associated with a clear and reproducible learning curve, with technical proficiency achieved after a limited number of cases. Improvements in operative efficiency are accompanied by enhanced procedural safety, suggesting that early technical challenges are transient and manageable. These findings support the structured and cautious adoption of vNOTES hysterectomy in minimally invasive gynecologic practice and provide a framework for future training and implementation strategies.

The principal strength of this study lies in its structured evaluation of the learning curve for vNOTES hysterectomy using consecutive cases and objective CUSUM analysis. Restriction to a single surgeon and a standardized surgical technique minimized variability and allowed performance changes to be attributed primarily to technical maturation. Inclusion of all consecutive cases, without exclusion based on anticipated difficulty, further enhanced the internal validity of the learning curve assessment.

Several limitations should be acknowledged. The retrospective design limits control over unmeasured confounding factors, and the single surgeon, single center setting may restrict generalizability of the findings. The sample size reflects early experience and may be insufficient to capture rare complications. In addition, long-term outcomes and patient reported measures were not evaluated. These limitations highlight the need for future multicenter studies to validate the observed proficiency threshold and to assess broader clinical outcomes.

Conclusion

This study suggests a consistent learning curve for vNOTES hysterectomy during early adoption. Operative efficiency improved progressively, with performance stabilization observed after approximately 18 cases. Early technical challenges diminished with experience without compromising perioperative safety. These findings support structured implementation and careful case selection during initial adoption.

Ethics Committee Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of Health Sciences University, Gazi Yaşargil Hospital (Date: 19/09/2025, No: 643).
Peer-review: Externally peer-reviewed.
Informed Consent: Given the retrospective nature of the study and the use of anonymized patient data, the requirement for written informed consent was waived by the ethics committee
Author Contribution: Concept: A.D.E., K.A.; Design: A.D.E., S.C.O., K.A.; Supervision: G.C.C., K.C.Y., K.A.; Fundings: K.A., A.D.E., O.A.; Materials: A.D.E., M.A.H., O.A..; Data collection &/or processing: K.A., G.C.C., A.D.E.; Analysis and/or interpretation: K.A., P.B.I.; Literature search: A.D.E., M.A.H.; Writing: K.A., S.C.O.; Critical review: K.A., G.C.C., S.C.O.
Conflict of Interest: No conflict of interest was declared by the authors.

References

1. Baekelandt J. Total vaginal NOTES hysterectomy: A new approach to hysterectomy. J Minim Invasive Gynecol 2015;22:1088–94. [CrossRef]
2. Yan B, Miao HX, Wang Y, Xu JM, Lu XQ, He WH, et al. Hysterectomy by transvaginal natural orifice transluminal endoscopic surgery versus transumbilical laparoscopic single-site surgery: A single-center experience from East China. Biomed Res Int 2022;2022:8246761. [CrossRef]
3. Tessier C, Zhang L, Cao CG. Ergonomic considerations in natural orifice translumenal endoscopic surgery (NOTES): A case study. Work 2012;41:4683–8. [CrossRef]
4. Ma J, Yang J, Cheng S, Jin Y, Zhang N, Wang C, et al. The learning curve of laparoendoscopic single-site surgery in benign gynecological diseases. J Invest Surg 2022;35:363–70. [CrossRef]
5. Bolsin S, Colson M. The use of the Cusum technique in the assessment of trainee competence in new procedures. Int J Qual Health

Care 2000;12:433–8. [CrossRef]

6. Hanedan C, Öncü HN, Öztürk N, Ege G, Köksal OK, Korkmaz V. Feasibility of vNOTES hysterectomy in patients with enlarged uteri: A single-center experience. J Turk Ger Gynecol Assoc 2025;26:284–8. [CrossRef]
7. Adamyan LV. Minimally invasive surgery in gynecologic practice. Int J Gynaecol Obstet 2003;82:347–55. [CrossRef]
8. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: Five-year experience. Ann Surg 2009;250:187–96. [CrossRef]
9. Wattiez A, Soriano D, Cohen SB, Nervo P, Canis M, Botchorishvili R, et al. The learning curve of total laparoscopic hysterectomy: Comparative analysis of 1647 cases. J Am Assoc Gynecol Laparosc 2002;9:339–45. [CrossRef]
10. Cook JA, Ramsay CR, Fayers P. Statistical evaluation of learning curve effects in surgical trials. Clin Trials 2004;1:421–7. [CrossRef]
11. Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT. Statistical assessment of the learning curves of health technologies. Health Technol Assess 2001;5:1–79. [CrossRef]
12. Ryu KJ, Suh SW, Kim HW, Lee DH, Yoon Y, et al. Quantitative analysis of a spinal surgeon's learning curve for scoliosis surgery. Bone Joint J 2016;98-B:679–85. [CrossRef]
13. Hopper AN, Jamison MH, Lewis WG. Learning curves in surgical practice. Postgrad Med J 2007;83:777–9. [CrossRef]
14. Paradis C. Bias in surgical research. Ann Surg 2008;248:180–8. [CrossRef]
15. Vickers AJ, Savage CJ, Hruza M, Tuerk I, Koenig P, Martínez-Piñeiro L, et al. The surgical learning curve for laparoscopic radical prostatectomy: A retrospective cohort study. Lancet Oncol 2009;10:475–80. [CrossRef]
16. Temtanakitpaisan T, Wu KY, Huang CY, Jaiswal A, Yen CF, Lee CL. The outcomes of transvaginal NOTES hysterectomy in various uterine sizes. Taiwan J Obstet Gynecol 2018;57:842–5. [CrossRef]
17. Law KS, Abbott JA, Lyons SD. Energy sources for gynecologic laparoscopic surgery: A review of the literature. Obstet Gynecol Surv 2014;69:763–76. [CrossRef]
18. Catanzarite T, Tan-Kim J, Whitcomb EL, Menefee S. Ergonomics in surgery: A review. Female Pelvic Med Reconstr Surg 2018;24:1–12. [CrossRef]
19. Quian A, Mercier AM, Lam C, Wenham RM, Chon HS, Shahzad MM, et al. Specimen extraction techniques utilized in minimally invasive surgery for uterine cancer and an enlarged uterus: A quality assurance study. J Robot Surg 2025;19:580. [CrossRef]
20. Tsafrir Z, Palmer M, Dahlman M, Nawfal AK, Aoun J, Taylor A, et al. Long-term outcomes for different vaginal cuff closure techniques in robotic-assisted laparoscopic hysterectomy: A randomized controlled trial. Eur J Obstet Gynecol Reprod Biol 2017;210:7–12. [CrossRef]
21. Kasparian AC, Martinez AC, JoverClos RJ, Chércoles RA. Evaluation of technical skills in surgical training. Rev Fac Cien Med Univ Nac Cordoba 2014;71:97–104. Article in Spanish. [CrossRef]
22. Ross SB, Choung E, Teta AF, Colibao L, Luberice K, Paul H, et al. The learning curve of laparoendoscopic single-site (LESS) fundoplication: Definable, short, and safe. JSLS 2013;17:376–84. [CrossRef]
23. Puntambekar S, Shetty T, Puntambekar S, Goel A, Panse M, Sathe R, et al. Learning curve of total laparoscopic hysterectomy for a resident in a high-volume resident training setup. J Obstet Gynaecol India 2022;72:267–73. [CrossRef]
24. Shen CC, Wu MP, Kung FT, Huang FJ, Hsieh CH, Lan KC, et al. Major complications associated with laparoscopic-assisted vaginal hysterectomy: Ten-year experience. J Am Assoc Gynecol Laparosc 2003;10:147–53. [CrossRef]
25. Cardoso SA, Suyambu J, Iqbal J, Cortes Jaimes DC, Amin A, Sikto JT, et al. Exploring the role of simulation training in improving surgical skills among residents: A narrative review. Cureus 2023;15. [CrossRef]
26. Sachdeva AK, Russell TR. Safe introduction of new procedures and emerging technologies in surgery: Education, credentialing, and privileging. Surg Oncol Clin N Am 2007;16:101–14. [CrossRef]
27. Varban OA, Thumma JR, Finks JF, Carlin AM, Ghaferi AA, Dimick JB. Evaluating the effect of surgical skill on outcomes for laparoscopic sleeve gastrectomy: A video-based study. Ann Surg 2021;273:766–71. [CrossRef]

ORIGINAL ARTICLE

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.28445

Association Between Vitamin D Status and Lower Respiratory Tract Infection in Children Under Five Years of Age

Nahide Haykır, Yasemin Akın, Engin Tutar

Abstract

Objective: This study aimed to evaluate serum 25-hydroxyvitamin D [25(OH)D] levels in children aged 0–5 years presenting with lower respiratory tract infection (LRTI) and to investigate the association between vitamin D deficiency and infection severity.

Methods: In this prospective controlled study, a total of 100 children aged 0–5 years were enrolled. The study group consisted of patients diagnosed with LRTI, while the control group included healthy children. Serum 25(OH)D, calcium, phosphorus, alkaline phosphatase (ALP), C-reactive protein (CRP), and complete blood count parameters were measured in all participants. Vitamin D status was classified as severe deficiency, deficiency, insufficiency, or normal. Statistical significance was set at $p<0.05$.

Results: Children diagnosed with LRTI had significantly lower serum 25(OH)D levels compared to the control group ($p<0.001$). CRP and leukocyte levels were significantly higher in the study group ($p<0.001$). A significant association was observed between vitamin D deficiency and frequent infections as well as hospitalization rates. Inflammatory markers were higher in the severe vitamin D deficiency group. Additionally, serum 25(OH)D levels decreased with increasing age ($p<0.001$).

Conclusions: Low serum 25(OH)D levels appear to be associated with increased frequency and severity of lower respiratory tract infections in early childhood. Early detection of vitamin D deficiency and maintenance of appropriate supplementation strategies may represent an important preventive approach to reducing infection burden.

Keywords: Vitamin D deficiency; lower respiratory tract infections; 25-Hydroxyvitamin D.

Introduction

Respiratory tract infections represent one of the most frequent infectious conditions encountered in pediatric populations. Among these, lower respiratory tract infections (LRTIs) continue to constitute a major contributor to global morbidity and mortality, particularly during infancy and early childhood.[1] Data from the World Health Organization (WHO) indicate that lower respiratory tract infections account for over 700,000 deaths each year among children younger who are than five years, corresponding to nearly 2,000 deaths per day, including approximately 190,000 neonatal fatalities. Notably, most of these deaths are regarded as preventable.[2]

Department of Pediatrics, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye

Address for correspondence:
Nahide Haykır, Department of Pediatrics, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye
E-mail: drnahide@gmail.com

Received: 18.02.2026
Accepted: 06.05.2026
Published: 29.09.2026

How to cite this article: *Haykır N, Akın Y, Tutar E. Association between vitamin d status and lower respiratory tract infection in children under five years of age. South. Clin. Ist. Euras. 2026;37(3):224-229.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Copyright@Author(s)

Vitamin D exerts dual biological functions. First, it acts locally within tissues through paracrine and autocrine mechanisms, modulating immune responses in a cytokine-like manner. Second, it functions systemically. acting in the systemic circulation with hormonal effects are biologically active metabolite of vitamin D is 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] is primarily synthesized by monocytes and macrophages and regulates host immune responses to microbial pathogens hrough binding to the vitamin D receptor (VDR).[3] Within the inflammatory microenvironment, sufficient synthesis of $1,25(OH)_2D_3$ promotes interactions with T and B lymphocytes, thereby contributing to the regulation of adaptive immunity.

$1,25(OH)_2D_3$ is recognized as a potent immunomodulator. Recent human studies have shown that the vitamin D–cytokine pathway is essential for antimicrobial peptide production through the monocyte–macrophage system.[3] Early evidence of vitamin D's immunological significance emerged from reports suggesting that decreased serum 25(OH)D concentrations were associated with increased susceptibility to Mycobacterium tuberculosis infection and experienced more severe disease courses.[4]

The $1,25(OH)_2D_3$–VDR complex is regulate the transcription of antimicrobial genes. Consequently, the relationship is serum 25(OH)D levels and susceptibility to various infectious diseases has been extensively investigated. Several studies have reported that upper respiratory tract infections occur more frequently during periods of when serum 25(OH)D levels are low, independent of seasonal variation.[5]

When serum 25(OH)D values fall under 20 ng/mL (50 nmol/L) have been associated with impaired activation of monocyte and macrophage-mediated immune responses. Recent evidence has shown that reduced or insufficient vitamin D levels in children are associated with a greater likelihood of hospitalization and a higher occurrence of LRTIs.[5]

Vitamin D deficiency appears to be linked with a heightened incidence of invasive pneumococcal infections, meningococcal disease, and Group A streptococcal infections, particularly during winter months. Accordingly, pharmacological vitamin D supplementation has been proposed as a potential adjunctive strategy in the management of certain infectious diseases.[6] Indeed, multiple studies have demonstrated that individuals with low vitamin D levels experience respiratory tract infections more frequently.[7]

However, data evaluating the association between vitamin D status and LRTIs in children under five years of age remain limited and inconsistent. Therefore, this study aimed to explore whether serum 25(OH)D status correlates with levels and LRTI in children aged 0–5 years.

Materials and Methods

Study Design and Participants

This investigation utilized a prospective case–control framework and was performed within the Department of Pediatrics, including the Pediatric Outpatient Clinic and Pediatric Emergency Unit of our hospital. Children aged 0–5 years who attended the clinic within the study timeframe were considered for enrollment. Participant recruitment and sample collection were performed between January and June, encompassing both winter and late spring seasons.

Ethical approval was granted by the Institutional Review Board of Dr. Lütfi Kırdar City Hospital (Date: 18/01/2011, No: B104İSM4340029/1009/2), and informed consent was secured in writing from the parents or legal guardians before inclusion in the study.

Participants were divided into two groups: the lower respiratory tract infection (LRTI) group and the healthy (control) group.

LRTI Group

Children aged 0–5 years diagnosed with LRTI based on clinical evaluation and/or respiratory system examination findings were included in the study group. Patients were managed either as outpatients or hospitalized depending on disease severity. Children with concomitant acute or chronic systemic diseases other than LRTI were excluded.

Control Group(CG)

Healthy children aged 0–5 years, matched for age, were enrolled as the control group with no evidence of acute infectious disease or chronic medical conditions at the time of evaluation.

Data Collection

Demographic characteristics, clinical findings, and laboratory parameters were recorded for all participants.

Medical history included regular or irregular vitamin D supplementation, history of recurrent infections, and previous hospitalizations.

Laboratory Measurements

Peripheral venous blood samples were obtained from all participants.Levels of calcium (Ca), phosphorus (P), and alkaline phosphatase (ALP) in serum samples were analyzed using a Roche DP Modular System (Roche Diagnostics, Mannheim, Germany) by a photometric method.

Circulating 25-hydroxyvitamin D [25(OH)D] concentrations were assessed by means of a LIAISON® analyzer (DiaSorin, Italy) via a competitive chemiluminescent immunoassay.

CRP quantification was carried out in serum samples derived from plain collection tubes. Measurements were conducted using a Dimension RXL automated system (Siemens Healthcare Diagnostics, Newark, DE, USA) based on the PETIA methodology and Dade Behring RCRP assay reagents.

Complete blood count parameters, including leukocyte count and differential, were measured from EDTA-anticoagulated blood samples using impedance and optical scatter techniques.

Serum 25(OH)D concentrations were categorized according to internationally accepted pediatric reference thresholds as detailed below: Based on serum 25(OH) D measurements, vitamin D levels were classified into four categories: values below 10 ng/mL were defined as severe deficiency; 10–19 ng/mL as deficiency; 20–29 ng/mL as insufficiency; and levels ≥30 ng/mL as sufficient. . These cut-off values were defined in accordance with established clinical practice guidelines and widely adopted pediatric criteria.

Statistical Analysis

Statistical analyses were performed using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA).

Descriptive statistics were expressed as mean ± standard deviation (SD). Independent samples t-test was used for comparisons between two groups. One-way analysis of variance (ANOVA) with Tukey post hoc test was applied for subgroup analyses. Categorical variables were analyzed using the chi-square test, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated where appropriate.

A p-value <0.05 was considered statistically significant.

A post-hoc power analysis based on the primary outcome variable (serum 25(OH)D levels) demonstrated that the study had a statistical power exceeding 80% at an alpha level of 0.05, indicating adequate sample size to detect clinically meaningful differences between groups.

Results

The proportion of female participants was 34% in the LRTI group and 46% in the control group. No statistically meaningful differences were identified between groups regarding age or sex characteristics (p>0.05).

The mean age was 34.0±30.0 months in the study group and 29.7±26.8 months in the CG (p=0.453).

The LRTI group exhibited significantly reduced mean serum calcium levels compared with the control group. (9.8±0.6 mg/dL vs. 10.4±0.6 mg/dL, p<0.001). Similarly, mean serum 25(OH)D levels were markedly lower in the study group (18.4±11.2 ng/mL) than control group (27.8±13.2 ng/mL), demonstrating a highly significant difference (p<0.001).

A statistically significant decrease in serum phosphorus values was observed among participants in the LRTI group (p=0.018), whereas no significant difference was observed in alkaline phosphatase (ALP) levels between groups (p=0.508). Leukocyte counts and CRP levels were significantly higher in the study group compared with controls (both p<0.001) (Table 1). Independent samples t-test was applied for continuous variables, and p<0.05 was considered statistically significant.

The overall prevalence of vitamin D deficiency was 94% (n=47) in the study group and 78% (n=39) in the control group. Severe deficiency and deficiency categories were significantly more frequent in the LRTI group (p=0.013 and p=0.048, respectively). Total vitamin D deficiency was significantly associated with LRTI (OR: 5.91; 95% CI: 1.25–28.24; p=0.044) A multivariate logistic regression model adjusting for age and sex was performed. (Table 2).

A history of recurrent infections was reported in 92% (n=46) of the study group and 30% (n=15) of controls, representing a highly significant difference (p<0.001). The risk of recurrent infections was 26.8-fold higher in the LRTI group (OR: 26.8; 95% CI: 8.2–88.0).

Table 1. Comparison of biochemical and ınfection parameters between the study and control groups

Parameter	Study Group (Mean±SD)	Control Group (Mean±SD)	t	p value
Calcium (mg/dL)	9.8±0.6	10.4±0.6	-5.12	<0.001
Vitamin D (ng/mL)	18.4±11.2	27.8±13.2	-3.85	<0.001
Phosphorus (mg/dL)	5.1±0.9	5.5±0.7	-2.41	0.018
ALP (IU/L)	217.3±61.3	207.9±79.2	-0.66	0.508
Leukocyte (mm^3)	9.84±0.62	4.06±0.24	8.32	<0.001
CRP (mg/L)	10.9±0.3	1.24±0.43	-8.85	<0.001

Independent samples t-test was applied. Statistical significance was set at p<0.05.

Table 2. Distribution of vitamin D levels and comparison between study and control groups

Vitamin D Level	Study Group n (%)	Control Group n (%)	OR	95% CI	p value
Severe vitamin D deficiency	13 (26%)	5 (10%)	9.53	1.85–49.22	0.013
Vitamin D deficiency	16 (32%)	11 (22%)	5.33	1.20–23.66	0.048
Vitamin D insufficiency	18 (36%)	23 (46%)	2.87	0.70–11.85	0.240
Total vitamin D deficiency	47 (94%)	39 (78%)	5.91	1.25–28.24	0.044

OR: Odds Ratio; CI: Confidence Interval. Chi-square test was applied. Statistical significance was set at p<0.05.

Table 3. Distribution of vitamin D levels by age and frequency when both groups were analyzed together

	Severe Vitamin D Deficiency	Vitamin D Deficiency	Vitamin D (Insufficiency) Deficiency	Normal	p
Age (months)	48.0±30.7	43.3±28.3	21.6±22.9	19.0±23.3	p<0.001
Cases	18%	27%	41%	14%	

A history of hospitalization was absent in the control group but present in 64% (n=32) of the study group (p<0.001). The odds of hospitalization were markedly increased in the LRTI group (OR: 177.43; 95% CI: 10.32–349.3). Due to zero hospitalization events in the control group, the OR estimate may be inflated and should be interpreted cautiously.

When both groups were analyzed collectively, an inverse relationship between vitamin D levels and age was observed. The mean age was highest in the severe vitamin D deficiency group (48.0±30.7 months) and lowest in the normal vitamin D group (19.0±23.3 months), with a statistically significant difference among groups (p<0.001) (Table 3).

The distribution of recurrent infections differed significantly across vitamin D deficiency groups (p<0.001). Furthermore, CRP levels were significantly higher in the severe and moderate vitamin D deficiency groups compared with the insufficiency and groups of normal (p<0.05) (Table 4).

Discussion

This study, designed as a prospective case–control analysis. A significant decrease in serum 25(OH)D levels was observed among children with LRTI compared with healthy controls. The prevalence of severe and overall was substantially higher in the LRTI cohort. Notably, low vitamin D levels correlated with increased likelihood of LRTI, recurrent infectious episodes, and hospitalization, suggesting that suboptimal vitamin D status may be linked to both vulnerability and severity of illness.

Vitamin D plays a central role in both innate and adaptive immunity. The active metabolite $1,25(OH)_2D_3$ regulates antimicrobial gene transcription through interac-

Table 4. Distribution of diagnosis, vitamin D supplementation, and ınfection characteristics by vitamin D level

	Severe Vitamin D Deficiency		Vitamin D Deficiency (Insufficiency)		Vitamin D Deficiency		Normal		
Diagnosis									
Pneumonia	12	66.7%	12	44.4%	14	34.1%	2	14.3%	
Bronchiolitis	1	5.6%	4	14.8%	4	9.8%	1	7.1%	p=0.064
Control group	5	27.8%	11	40.7%	23	56.1%	11	78.6%	
Vitamin D Supplementation									
Regular	4	22.2%	4	14.8%	15	36.6%	11	78.6%	
Irregular	7	38.9%	19	70.4%	24	58.5%	3	21.4%	p<0.001
None	7	38.9%	4	14.8%	2	4.9%	0	0.0%	
Recurrent Infection									
Yes	17	94.4%	21	77.8%	21	51.2%	2	14.3%	
No	1	5.6%	6	22.2%	20	48.8%	12	85.7%	p<0.001
Hospitalization									
Yes	7	38.9%	8	29.6%	14	34.1%	3	21.4%	
No	11	61.1%	19	70.4%	27	65.9%	11	78.6%	p=0.737

tion with the VDR, leading to increased antimicrobial peptide production within the monocyte–macrophage system.[8] Experimental and clinical data have demonstrated that insufficient 25(OH)D concentrations in serum are connected with impaired immune activation and increased vulnerability to infectious diseases, including Mycobacterium tuberculosis.[9] Serum levels 20 ng/mL have been linked to suboptimal monocyte and macrophage responses,[10] which may explain the higher infection burden observed in vitamin D–deficient children in our cohort.

The current data corroborate existing literature demonstrating epidemiological and clinical studies demonstrating an correlation between vitamin D-deficiency and respiratory tract infections. Several investigations have reported increased frequency of upper and lower respiratory tract infections in individuals with low 25(OH)D concentrations.[10-12] Furthermore, vitamin D deficiency has been linked to invasive pneumococcal and meningococcal infections, particularly during winter months.[11] The significantly higher CRP levels observed in children with severe and moderate vitamin D deficiency in our study further support the hypothesis that inadequate vitamin D status may be associated with heightened inflammatory responses. An evident association emerged between deficient vitamin D status and hospitalization in our cohort aligns with reports suggesting that reduced serum 25(OH)D concentrations may be associated with a higher incidence of LRTI. disease severity.[11] However, the markedly elevated odds ratio for hospitalization should be interpreted cautiously, as no hospitalization occurred in the control group, which may have amplified the calculated risk estimate.

A negative correlation was observed between age and circulating 25(OH)D levels. was also identified. Older children demonstrated lower vitamin D levels, potentially reflecting reduced supplementation after infancy and decreased sunlight exposure. Similar observations have been reported in previous pediatric studies,[12] highlighting the importance of sustained vitamin D monitoring beyond the first year of life.[13]

The study design entails certain limitations; notably, the small cohort size reduced the statistical power to perform multivariate logistic regression analyses addressing confounding factors The study did not include a standardized measurement of seasonal fluctuations or individual ultraviolet exposure. Third, causality cannot be established due to the observational design. Nevertheless, the prospective structure, clearly defined vitamin D categories, standardized laboratory measurements, and consistent associations across multiple clinical outcomes strengthen the validity of our findings.[14]

In conclusion, Vitamin D deficiency emerged as a frequent finding in this cohort among children with LRTI and was significantly associated with increased infection

frequency and hospitalization. These findings support an increasing number of investigations suggesting that maintaining adequate vitamin D status play a role in reducing susceptibility to respiratory infections in early childhood. Larger, multicenter studies with multivariate modeling are warranted to further clarify the independent contribution of vitamin D to LRTI risk.

Ethics Committee Approval: Ethical approval was granted by the Institutional Review Board of Dr. Lütfi Kırdar City Hospital (Date: 18/01/2011, No: B104İSM4340029/1009/2).
Peer-review: Externally peer-reviewed.
Informed Consent: Written informed consent was secured in writing from the parents or legal guardians before inclusion in the study.
Author Contribution: Concept: N.H.; Design: E.T., N.H.; Supervision: E.T., Y.A.; Fundings: N.H.; Materials: N.H.; Data collection &/or processing: N.H.; Analysis and/or interpretation: N.H.; Literature search: N.H.; Writing: N.H.; Critical review: N.H., E.T., Y.A.
Conflict of Interest: The authors declare no conflict of interest.

References

1. Yılmaz G, Uzel N, Işık N, Uğur S, Aslan S, Badur S. Viral agents and respiratory syncytial virus subgroups in children with acute lower respiratory tract infection. Turk J Infect 2000;14:157–62.
2. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Activation of human TLR 2/1 triggers a vitamin D receptor-dependent antimicrobial response. Science 2006;311:1770–3. [CrossRef]
3. Munger KLM, Zhang SM, O'Reilly E. Vitamin D intake and incidence of multiple sclerosis. Neurology 2004;62:60–5. [CrossRef]
4. Koli K, Keski-Oja J. 1 alpha, 25-dihydroxyvitamin D3 and its analogues down-regulate cell invasion-associated proteases in cultured malignant cells. Cell Growth Differ 2000;11:221–9.
5. Wayse V, Yousafzai A, Mogale K, Filteau S. Association of subclinical vitamin D deficiency with severe acute lower respiratory infection in Indian children under 5 y. Eur J Clin Nutr 2004;58:563–7. [CrossRef]
6. Ginde AA, Mansbach JM, Camargo CA Jr. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch Intern Med 2009;169:384–90. [CrossRef]
7. Cantorna MT. Vitamin D and its role in immunology: Multiple sclerosis, and inflammatory bowel disease. Prog Biophys Mol Biol 2006;92:60–4. [CrossRef]
8. Ozsoylu S, Hasanoglu A. 25-Hydroxycholecalciferol serum levels in breastfed infant. Arch Dis Child 1981;56:318. [CrossRef]
9. Erol M, Isman FK, Kucur M, Hacibekiroglu E. Assessment of vitamin D deficiency in mothers. Turk Pediatr Ars 2007;42:29–32.
10. Gordon CM, Huh SY. Vitamin D deficiency in children and adolescents: Epidemiology, impact and treatment. Rev Endocr Metab Disord 2008;9:161–70. [CrossRef]
11. Yamshchikov AV, Desai NS, Blumberg HM, Ziegler TR, Tangpricha V. Vitamin D for treatment and prevention of infectious diseases: A systematic review of randomized controlled trials. Endocr Pract 2009;15:438–49. [CrossRef]
12. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in school children. Am J Clin Nutr 2010;91:1255–60. [CrossRef]
13. Roth DE, Jones AB. Vitamin D status is not associated with the risk of hospitalization for acute bronchiolitis in early childhood. Can J Public Health 2005;96:443–9.
14. Glerup H, Mikkelson K, Poulsen L, Hass E, Overbeck S, Thomsen J, et al. Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. J Intern Med 2000;247:260–8. [CrossRef]

ORIGINAL ARTICLE

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.36034

Mammographic Subcutaneous Fat Thickness Reflects Systemic Adiposity Rather Than Tumor Biology in Invasive Ductal Carcinoma: A Retrospective Analysis

Burcu Gümüştekin,[1] Emre Teke[2]

Abstract

Objective: Mammographic subcutaneous fat thickness (SFT) has been proposed as a spatially specific surrogate of locoregional adiposity in breast cancer research. This study aimed to evaluate the relationship between mammographically measured SFT and molecular subtypes, Ki-67 proliferation index, hormone receptor expression, and key clinicopathological parameters in patients with invasive ductal carcinoma (IDC).

Methods: This retrospective, cross-sectional, single-center study included 180 female patients who underwent surgical treatment for IDC between October 2023 and January 2026. SFT was measured from standard mammographic images. Molecular subtype classification followed the St. Gallen 2013 Consensus criteria. Statistical analyses included Spearman correlation, Kruskal–Wallis and Mann–Whitney U tests, multivariable linear regression, and receiver operating characteristic (ROC) curve analysis.

Results: SFT showed no statistically significant correlation with Ki-67 (ρ=0.127, p=0.089), tumor size, age, estrogen receptor (ER) percentage, or progesterone receptor (PR) percentage. SFT did not differ significantly across molecular subtypes, BI-RADS density categories, histological grade, or lymph node status. In multivariable linear regression, body mass index (BMI) was the sole independent predictor of SFT (β=0.331, p<0.001; R^2=0.110). BMI differed significantly across molecular subtypes (p=0.024), with the triple-negative (TN) subtype associated with significantly higher BMI than both Luminal A (p=0.021) and Luminal B (p=0.004). A statistically significant linear trend was identified between increasing BI-RADS density category and tumor biological aggressiveness (linear-by-linear association, p=0.046). The area under the ROC curve (AUC) for SFT in predicting Ki-67≥20% was 0.590 (95% CI: 0.458–0.721, p=0.192), and for BMI was 0.417 (95% CI: 0.287–0.547, p=0.227); neither reached statistical significance.

Conclusions: In IDC, mammographic SFT reflects systemic adiposity rather than tumor biology and lacks clinically meaningful discriminatory power as an independent imaging biomarker. The association between the triple-negative subtype and higher BMI supports the role of systemic adiposity in subtype-specific tumor biology.

Keywords: Breast cancer; invasive ductal carcinoma; Ki-67; subcutaneous fat thickness; body mass index.

[1]Department of General Surgery, Gaziantep City Hospital, Gaziantep, Türkiye
[2]Department of General Surgery, İstanbul Şişli Hamidiye Etfal Research and Training Hospital, İstanbul, Türkiye

Address for correspondence:
Burcu Gümüştekin, Department of General Surgery, Gaziantep City Hospital, Gaziantep, Türkiye
E-mail: drburcugumustekin@hotmail.com

Received: 01.04.2026
Accepted: 01.06.2026
Published: 29.09.2026

How to cite this article: *Gümüştekin B, Teke E. Mammographic subcutaneous fat thickness reflects systemic adiposity rather than tumor biology in invasive ductal carcinoma: a retrospective analysis. South. Clin. Ist. Euras. 2026;37(3):230-238*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Copyright@Author(s)

Introduction

Breast cancer is the most frequently diagnosed cancer in women worldwide, with an estimated 2.3 million new cases reported in 2022, representing 11.6% of all newly diagnosed malignancies.[1] Over the past two decades, the clinical management of breast cancer has shifted markedly toward a biology-driven approach. Molecular subtype classification, based on the expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 proliferation index, now underpins treatment selection, prognostic stratification, and follow-up planning.[2,3] This immunohistochemical framework identifies four major subtypes — Luminal A, Luminal B, HER2-enriched, and triple-negative (TN) — each with distinct biological behavior and clinical outcomes.[3]

Mammography remains the cornerstone of breast cancer screening and early detection. In addition to its diagnostic role, mammographic imaging provides information on breast tissue composition. Breast density, classified according to the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS), is an established independent risk factor for breast cancer development.[4,5]

Systemic adiposity, most commonly quantified by body mass index (BMI), has been linked to breast cancer risk and prognosis through multiple biological pathways, including aromatase-mediated estrogen synthesis, adipokine dysregulation, chronic low-grade inflammation, and insulin signaling. However, BMI reflects global adiposity and does not directly account for the regional distribution of adipose tissue within the breast. Mammographic subcutaneous fat thickness (SFT), measurable from standard two-view mammography without additional cost or imaging, has been proposed as a potential imaging-derived adiposity parameter that may reflect locoregional fat distribution.[6–9]

An important conceptual distinction should be drawn between subcutaneous adipose tissue — the superficial fat layer of the breast wall that SFT measures — and peritumoral adipose tissue, the cancer-associated adipocyte compartment immediately surrounding the tumor. These compartments differ in anatomical location, metabolic activity, and biological proximity to the tumor. Adipocytes within the tumor microenvironment undergo cancer-associated reprogramming, including altered leptin and adiponectin secretion, pro-inflammatory cytokine release, and stromal remodeling.[10] Whether a measurement taken at the breast surface can reflect these processes is an open question that motivated the present study.

Despite interest in adiposity as a modulator of tumor biology, data on the association between mammographic SFT and molecular subtype, hormone receptor expression, and Ki-67 remain limited.[11,12] Most published studies have focused on BMI or global mammographic density. The present study was designed to examine, in an exploratory fashion, whether mammographically measured SFT is associated with molecular subtypes, Ki-67, hormone receptor expression, and clinicopathological parameters in a cohort of 180 patients with pathologically confirmed IDC, and whether it provides information beyond what is captured by BMI alone.

Materials and Methods

Study Design and Ethics

This was a retrospective, cross-sectional, single-center observational study conducted at a tertiary referral hospital. The retrospective design was selected given the availability of complete archival mammographic and pathological data; its limitations, including potential selection bias and the inability to establish causal relationships, are discussed below. The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of our institution (Approval Number: 432/2026, Date: 06.02.2026) and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Individual patient informed consent was waived given the retrospective archival nature of the data.

Study Population

Female patients aged 40 years or older who underwent surgical treatment for histopathologically confirmed IDC between October 2023 and January 2026 were evaluated for inclusion. Male patients were excluded owing to anatomical and imaging differences that preclude valid SFT measurement.

Inclusion criteria: (i) histopathologically confirmed IDC; (ii) female sex, aged ≥40 years at the time of diagnosis; (iii) availability of diagnostic mammographic images suitable for BI-RADS density classification and SFT measurement; (iv) complete pathology report including ER,

PR, HER2, Ki-67, and histological grade; (v) documented ultrasonographic tumor size and BMI recorded in the medical chart.

Exclusion criteria: (i) prior ipsilateral or contralateral breast cancer; (ii) evaluation after neoadjuvant chemotherapy; (iii) insufficient image quality for reliable SFT measurement; (iv) incomplete immunohistochemistry precluding molecular subtype classification; (v) inconsistent or missing data in medical records.

Data Collection and Measurement Parameters

All data were collected from the hospital information system (HIS), picture archiving and communication system (PACS), and pathology information system by a single investigator using a standardized protocol. BMI was categorized according to WHO criteria as normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obese (≥30.0 kg/m²).

SFT Measurement

SFT was measured from CC and MLO mammographic views at three standardized anatomical points: (i) 2 cm lateral to the nipple–areola complex; (ii) 45° superior to this point; and (iii) 45° inferior to this point. The mean of these three measurements was recorded as the SFT value.[6] All measurements were performed by a single investigator blinded to pathological results, using measurement tools integrated in the institutional PACS workstation.

Several measurement limitations merit acknowledgment. Mammographic compression variability between examinations may influence absolute SFT values, as compression force affects the apparent thickness of superficial soft tissues; standardized protocols were employed, but inter-examination variability cannot be fully excluded in a retrospective dataset. SFT values derived from mammography also represent a two-dimensional projection of a three-dimensional tissue layer. Additionally, the single-investigator design precludes formal inter-observer reproducibility assessment, which is an acknowledged limitation of mammographic fat measurement. These factors should be considered when interpreting the absolute SFT values reported here and when comparing them with values derived using ultrasound or other modalities.

Molecular Subtype Classification

Mammographic density was classified as Type A through D according to the fifth edition of the ACR BI-RADS lexicon.[13] Histological grade was assigned using the modified Scarff–Bloom–Richardson (Nottingham) grading system as described by Elston and Ellis, with scores of 3–5, 6–7, and 8–9 corresponding to Grades 1, 2, and 3, respectively. ER and PR status and expression levels, HER2 status, Ki-67 proliferation index (%), and lymph node involvement (N0–N3) were recorded from pathology reports.

Molecular subtype assignment was performed according to the St. Gallen 2013 Consensus criteria: Luminal A (ER/PR-positive, HER2-negative, Ki-67<20%); Luminal B/HER2-negative (ER/PR-positive, HER2-negative, Ki-67 ≥20% or PR-negative); HER2-enriched (ER-negative, PR-negative, HER2-positive); and TN (ER-negative, PR-negative, HER2-negative).

TN cases (n=20) were included in descriptive and subgroup analyses. Given the limited subgroup size, findings pertaining to TN patients should be interpreted with caution.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Normality was assessed using the Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation (SD); non-normally distributed data as median (interquartile range [IQR]). Relationships between SFT and continuous variables were assessed using Spearman rank correlation. Group comparisons were performed using the Kruskal–Wallis test (three or more groups) and the Mann–Whitney U test (two groups); post-hoc pairwise comparisons with Bonferroni correction were applied where indicated. Categorical associations were examined using Pearson chi-square or Fisher exact tests. Linear trend analysis was performed using the linear-by-linear association test with Monte Carlo simulation. Multivariable linear regression was used to identify independent predictors of SFT. ROC curve analysis was performed to assess discriminatory performance for predicting high Ki-67 (≥20%). The significance threshold was set at $p<0.05$.

ROC analysis was included as a post-hoc exploratory analysis to quantify the discriminatory capacity of SFT and BMI for Ki-67 classification. It was not pre-specified in the study protocol, and the resulting AUC values are reported descriptively; they should not be interpreted as defining a diagnostic threshold.

Results

Patient Characteristics

The study included 180 female patients with IDC. Mean age was 54.2±10.6 years. Median BMI was 29.0 kg/m² (IQR 25.9–32.0), median SFT was 4.1 mm (IQR 3.1–5.1), median tumor size was 2.2 cm (IQR 1.6–2.9), and median Ki-67 was 10% (IQR 3–18). Among ER-positive cases (n=141), median ER expression was 90% (IQR 82–97); among PR-positive cases (n=137), median PR expression was 80% (IQR 54–100). Full demographic, imaging, and pathological characteristics are presented in Table 1.

Correlation Analysis

Spearman rank correlation analysis revealed no statistically significant association between SFT and Ki-67 (ρ=0.127, p=0.089), tumor size (ρ=0.003, p=0.963), age (ρ=− 0.076, p=0.312), ER expression (ρ=− 0.080, p=0.349), or PR expression (ρ=− 0.167, p=0.051). A moderate and statistically significant positive correlation was observed between SFT and BMI (ρ=0.427, p<0.001).

Table 1. Patient demographics and clinicopathological characteristics (n=180)

Variable	Value / n	% / Format
Age (years)	54.2±10.6	Mean ± SD
BMI (kg/m²)	29.0 (25.9–32.0)	Median (IQR)
SFT (mm)	4.1 (3.1–5.1)	Median (IQR)
Tumor size (cm)	2.2 (1.6–2.9)	Median (IQR)
Ki-67 (%)	10 (3–18)	Median (IQR)
ER expression % (n=141)	90 (82–97)	Median (IQR)
PR expression % (n=137)	80 (54–100)	Median (IQR)
BI-RADS Density Category		
Type A (almost entirely fatty)	8	4.4%
Type B (scattered fibroglandular)	67	37.2%
Type C (heterogeneously dense)	91	50.6%
Type D (extremely dense)	14	7.8%
Histological Grade		
Grade 1	46	25.6%
Grade 2	106	58.9%
Grade 3	28	15.6%
Lymph Node Status		
N0 (node-negative)	55	30.6%
N1	101	56.1%
N2	19	10.6%
N3	5	2.8%
Molecular Subtype		
Luminal A	68	37.8%
Luminal B	42	23.3%
HER2-enriched	50	27.8%
Triple-negative	20	11.1%

BMI: body mass index; SFT: subcutaneous fat thickness; ER: estrogen receptor; PR: progesterone receptor; SD: standard deviation; IQR: interquartile range.

Group Comparisons for SFT

Kruskal–Wallis analysis demonstrated no significant difference in SFT across molecular subtypes (H=1.934, p=0.586), BI-RADS density categories (H=3.220, p=0.359), or histological grade groups (H=3.723, p=0.155). Similarly, no significant difference in SFT was found between node-positive and node-negative patients (Mann–Whitney U=3093, p=0.285).

BMI and Molecular Subtypes

BMI did not correlate significantly with Ki-67 (ρ=− 0.036, p=0.631), tumor size (ρ=− 0.047, p=0.535), age (ρ=0.030, p=0.690), lymph node status (p=0.879), or histological grade (p=0.827). However, BMI differed significantly across molecular subtypes (H=9.440, p=0.024). Post-hoc pairwise comparisons with Bonferroni correction revealed that TN patients had significantly higher BMI than both Luminal A (p=0.021) and Luminal B (p=0.004) patients; no other subtype pairs reached significance. SFT differed significantly across BMI categories (H=26.580, p<0.001), with obese patients having higher SFT than both normal-weight (p<0.001) and overweight patients (p<0.001); the difference between normal-weight and overweight groups did not reach significance (p=0.061).

BI-RADS Density and Molecular Subtypes

The overall association between BI-RADS density categories and molecular subtypes was not statistically significant by Pearson chi-square test (χ^2=11.97, df=9, p=0.215) or Fisher–Freeman–Halton exact test (p=0.305). Linear-by-linear association analysis, however, identified a statistically significant ordinal trend between increasing mammographic density and a shift toward more aggressive molecular subtypes (p=0.046), confirmed by Monte Carlo one-sided probability estimation (p=0.027). Subtype distribution across BI-RADS categories is presented in Table 2.

Multivariable Linear Regression

A multivariable linear regression model with SFT as the dependent variable and age, BMI, tumor size, and Ki-67 as independent variables was statistically significant overall (F=5.420, p<0.001, R^2=0.110). BMI was the sole statistically significant independent predictor of SFT (standardized β=0.331, p<0.001). Age, tumor size, and Ki-67 did not independently predict SFT (all p>0.05). Full results are presented in Table 3.

Table 2. BI-RADS density categories and molecular subtype distribution

Subtype	BI-RADS A (n=8)	BI-RADS B (n=67)	BI-RADS C (n=91)	BI-RADS D (n=14)	Total
Luminal A	4 (50.0%)	26 (38.8%)	33 (36.3%)	5 (35.7%)	68
Luminal B	2 (25.0%)	16 (23.9%)	22 (24.2%)	2 (14.3%)	42
HER2-enriched	1 (12.5%)	16 (23.9%)	28 (30.8%)	5 (35.7%)	50
Triple-negative	1 (12.5%)	9 (13.4%)	8 (8.8%)	2 (14.3%)	20

Table 3. Association of SFT and BMI with clinicopathological variables

Analysis	Test Statistic	Value	p-value
SFT – Continuous Variable Correlations (Spearman)			
SFT ↔ BMI	ρ	0.427	<0.001*
SFT ↔ Ki-67 (%)	ρ	0.127	0.089
SFT ↔ Tumor size	ρ	0.003	0.963
SFT ↔ Age	ρ	–0.076	0.312
SFT ↔ ER (%)	ρ	–0.080	0.349
SFT ↔ PR (%)	ρ	–0.167	0.051
SFT – Categorical Group Comparisons			
SFT ~ Molecular subtypes	Kruskal–Wallis H	1.934	0.586
SFT ~ BI-RADS density	Kruskal–Wallis H	3.220	0.359
SFT ~ Histological grade	Kruskal–Wallis H	3.723	0.155
SFT ~ Lymph node metastasis	Mann–Whitney U	3093	0.285
BMI – Categorical Group Comparisons			
BMI ~ Molecular subtypes	Kruskal–Wallis H	9.440	0.024*
Post-hoc: TN vs. Luminal A	Bonferroni	—	0.021*
Post-hoc: TN vs. Luminal B	Bonferroni	—	0.004*
BMI ~ Lymph node status	Mann–Whitney U	3388.5	0.879
BMI ~ Histological grade	Kruskal–Wallis H	0.380	0.827
Multivariable Linear Regression (Dependent: SFT)			
Overall model – F statistic	F test	5.420	<0.001*
R^2 (variance explained)	—	0.110	—
BMI (standardized β)	Standardized β	0.331	<0.001*
Age	Standardized β	n.s.	>0.05
Tumor size	Standardized β	n.s.	>0.05
Ki-67 (%)	Standardized β	n.s.	>0.05

ρ: Spearman correlation coefficient; β: standardized regression coefficient; TN: triple-negative; n.s.: not significant; *p < 0.05.

ROC Curve Analysis

ROC curve analysis was performed to evaluate discriminatory performance of SFT and BMI for high Ki-67 (≥20%). The AUC for SFT was 0.590 (95% confidence interval [CI]: 0.458–0.721, p=0.192). BMI yielded an AUC of 0.417 (95% CI: 0.287–0.547, p=0.227). Neither reached statistical significance (Table 4; Fig. 1).

Discussion

In this retrospective cohort of 180 patients with histopathologically confirmed IDC, mammographic SFT showed no statistically significant association with any of the tumor-related parameters examined, including molecular subtype, Ki-67 proliferation index, hormone receptor expression, histological grade, or lymph node

Table 4. ROC analysis – Predicting high Ki-67 (≥20%)

Variable	AUC	Std. Error	p-value	95% CI
SFT (mm)	0.590	0.067	0.192	0.458–0.721
BMI (kg/m²)	0.417	0.066	0.227	0.287–0.547

AUC: area under the curve; CI: confidence interval; SFT: subcutaneous fat thickness; BMI: body mass index.

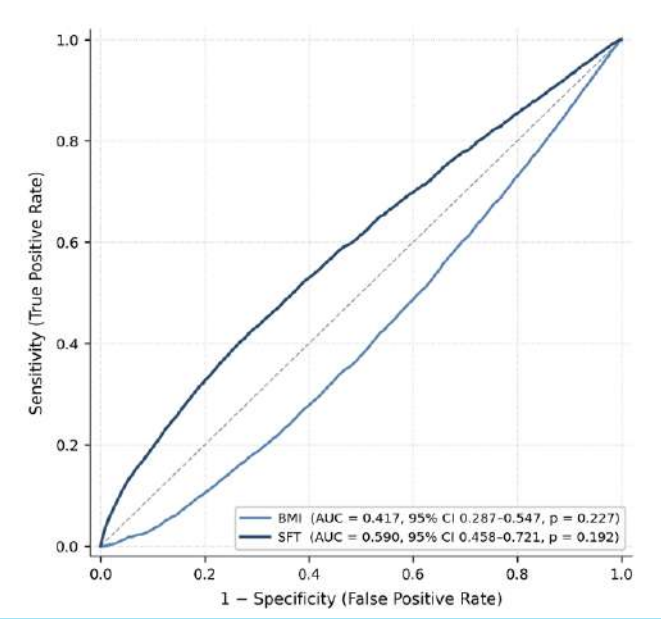

Figure 1. Receiver operating characteristic (ROC) curves for SFT and BMI as predictors of high Ki-67 (≥20%) in 180 patients with invasive ductal carcinoma. SFT:AUC=0.590 (95% CI 0.458–0.721; p=0.192). BMI:AUC=0.417 (95% CI 0.287–0.547; p=0.227). Neither reached statistical significance. The dashed diagonal represents chance-level discrimination (AUC=0.500). AUC, area under the curve; BMI, body mass index; CI, confidence interval; IDC, invasive ductal carcinoma; SFT, subcutaneous fat thickness. *ROC analysis was conducted as a post-hoc, exploratory step and was not pre-specified in the study protocol. The analysis was used descriptively to quantify the absence of discriminatory capacity of SFT and BMI for Ki-67 status; the resulting AUC values do not define a diagnostic threshold. Results are consistent with the primary negative findings of the study.*

status. In multivariable linear regression, BMI was the sole independent predictor of SFT (β=0.331, R^2=0.110), with the overall model explaining approximately 11% of the variance in SFT. These findings suggest that, within this cohort, mammographic SFT may primarily reflect systemic adiposity rather than locoregional adipose–tumor interactions.

The Spearman correlation between SFT and Ki-67 was positive but non-significant (ϱ=0.127, p=0.089). This result differs from that of Wang et al.,[6] whose series of 1,670 patients identified an SFT threshold of 8.65 mm above which Ki-67 was significantly elevated (p=0.004). The discrepancy may reflect differences in population-level adiposity and measurement modality. Our cohort had a median SFT of 4.1 mm, substantially below that threshold, and SFT was derived from mammography rather than ultrasound. A threshold effect is plausible — the relationship between fat accumulation and proliferative activity may only become apparent above a level of subcutaneous fat not reached within the range of SFT values observed in this cohort. The positive direction of the correlation is consistent with this interpretation, though it falls well short of significance. Whether the discrepancy reflects a population-specific threshold, methodological differences, or both remains to be examined in larger, more adipose-diverse cohorts.

The concept of spatial mismatch is relevant to interpreting these results. SFT, as measured mammographically, measures the thickness of the superficial subcutaneous fat layer at fixed anatomical reference points on the breast surface — a location anatomically remote from the tumor and its surrounding stroma. This layer is separated from the glandular parenchyma and deeper adipose compartments by fascial planes and Cooper's ligaments, structures that traverse the breast and create boundaries between anatomically distinct fat compartments. Cancer-associated adipocytes in the peritumoral compartment undergo metabolic reprogramming involving altered adipokine secretion, enhanced lipolytic activity, and direct lipid transfer to tumor cells — processes that are unlikely to be reflected by measurements taken at the superficial breast surface. Bocian-Jastrzębska et al.[14] reported that leptin's pro-tumorigenic effects appear most pronounced within the peritumoral compartment, where local concentrations have been reported to substantially exceed systemic levels. Adiponectin, conversely, appears to be suppressed by cancer-associated adipocytes within the immediate tumor microenvironment. These anatomical and functional differences are consistent with the absence of a significant association between SFT and tumor biology in this dataset, despite its correlation with global adiposity.

Analysis of BI-RADS density categories against molecular subtype distribution showed no statistically significant categorical association (χ^2=11.97, p=0.215). This is consistent with prior literature. Heusinger et al.,[8] in a series of 1,975 cases, reported no significant relationship between mammographic density and Ki-67 (p=0.31). Bai et al.,[15] in a pooled analysis of over 17,000 patients, identified only a non-significant trend toward altered receptor profiles in denser breasts. These findings, taken together, suggest that standard BI-RADS density categorization has limited value for inferring tumor biological phenotype; the system was developed for risk stratification rather than molecular profiling.

Despite the non-significant chi-square result, the linear-by-linear association test identified a statistically significant ordinal gradient between increasing BI-RADS density and a directional shift toward more aggressive molecular subtypes (p=0.046; Monte Carlo one-sided p=0.027). The two tests differ in what they assess: the chi-square test examines group differences in any direction, while the linear-by-linear test captures a directional gradient across ordered categories. The significance of only the latter suggests that any relationship between density and subtype distribution is incremental and directional rather than categorical. Razzaghi et al.[5] noted that BI-RADS categories failed to differentiate basal-like from Luminal A subtypes, partly due to confounding by menopausal status — a variable also unavailable in our dataset. Eriksson et al.[16] proposed that density functions as a subtype-independent risk factor rather than a subtype classifier, a view supported at the meta-analytic level by Antoni et al.[17] Our ordinal trend finding is consistent with this perspective and should be treated as hypothesis-generating.

In our cohort, SFT was moderately correlated with BMI (ϱ=0.427, p<0.001), yet showed no significant association with any tumor biological variable examined. This pattern is consistent with SFT primarily reflecting the systemic fat burden rather than the biological activity of adipose tissue near the tumor. Soguel et al.[18] and Chu et al.[19] have similarly documented the structural dependence of SFT on total body adiposity, and Masala et al.[20] observed a corresponding relationship between BMI and non-dense breast volume in a large postmenopausal cohort. The regression model's limited explanatory power (R^2=0.110) is also worth noting: nearly 90% of the variance in SFT was not explained by BMI, Ki-67, tumor size, and age combined, suggesting that other factors — including menopausal status and individual breast composition — contribute substantially.[7] Future research aiming to connect local adiposity to tumor biology may need to employ modalities capable of directly measuring peritumoral fat, such as dedicated breast magnetic resonance imaging (MRI) or computed tomography (CT)-based tissue segmentation.

BMI was significantly higher in TN cases than in Luminal A (p=0.021) and Luminal B (p=0.004) patients. This should be interpreted cautiously given the small TN subgroup (n=20), but is consistent with existing evidence linking elevated BMI to triple-negative breast cancer, particularly in premenopausal women.[21–24] Proposed mechanisms include chronic inflammation, insulin resistance, sex hormone dysregulation, and subtype-specific signaling through JAK/STAT and PI3K/AKT/mTOR pathways, alongside adipokine dysregulation and stromal remodeling, though the relative contributions of these pathways remain to be established.[25–28] The observation that BMI, rather than SFT, showed a significant association with molecular subtypes in this dataset is consistent with systemic adiposity — rather than locoregional mammographic fat distribution — being the more relevant dimension of adiposity in this context.

ROC analysis was consistent with the absence of meaningful discriminatory performance for either parameter. SFT yielded an AUC of 0.590 (95% CI: 0.458–0.721, p=0.192) for predicting Ki-67 ≥20%, and BMI an AUC of 0.417 (95% CI: 0.287–0.547, p=0.227); neither reached significance. Within this cohort, these findings suggest that SFT and BMI have limited discriminatory capacity for Ki-67 status, and do not appear to offer a practical surrogate for tissue-based proliferative assessment in this cohort. This is consistent with guidance from the International Ki-67 in Breast Cancer Working Group,[30] and with observations by Yerushalmi et al.[31] and Bustreo et al.[32] regarding the limitations of non-tissue Ki-67 surrogates.

The absence of significant associations between SFT and tumor biology, given the anatomical considerations discussed above, remains informative. Studies reporting negative associations with imaging-derived parameters may help clarify the interpretive scope of those measurements and avoid overinterpretation in research contexts. Within the context of this dataset, the current data do not support treating SFT as a surrogate measure for tumor biological characteristics in IDC, though its potential utility in epidemiological studies of systemic adiposity and breast cancer risk is not excluded.

Limitations

Several limitations of this study should be acknowledged. First, the retrospective, single-center design introduces inherent selection bias; patients meeting inclusion criteria may differ systematically from those who did not, and unmeasured confounders cannot be excluded. Second, the overall sample of 180 patients may be sufficient for the primary analyses, but limits the strength of subgroup inferences, particularly for the TN group (n=20); BMI findings in this subgroup should be regarded as exploratory. Third, menopausal status data were unavailable, which is a meaningful gap given the influence of menopausal status on adipose tissue distribution, aromatase activity, adipokine profiles, and mammographic density. Fourth, mammographic compression variability introduces uncertainty in absolute SFT values; standardized protocols were used, but inter-examination variability cannot be fully eliminated in a retrospective dataset. Fifth, the single-investigator design precludes formal inter-observer reliability analysis. Sixth, peritumoral adipose tissue was not directly assessed, which would be required to fully characterize tumor–fat interactions. Seventh, the cross-sectional design precludes causal inference. Prospective studies with peritumoral fat measurement, menopausal stratification, and multi-center design are needed to address these limitations.

Conclusion

In this cohort of 180 patients with IDC, mammographic SFT showed no significant association with any tumor biological parameter examined, including molecular subtype, Ki-67, hormone receptor expression, histological grade, or lymph node status. BMI was the sole predictor of SFT in multivariable analysis. The TN subtype was associated with significantly higher BMI than Luminal A and Luminal B subtypes, a finding consistent with prior literature but in need of confirmation in larger cohorts. A statistically significant ordinal trend between increasing BI-RADS density and molecular subtype distribution was also observed.

Taken together, these results suggest that mammographic SFT may reflect systemic adiposity rather than local tumor biology in IDC. Within the limitations of this retrospective cohort, the present findings do not support its use as a surrogate imaging measure for characterizing tumor biology or Ki-67 status. Reporting the absence of these associations may contribute to defining the appropriate scope of mammographic fat measurements in observational research. Future prospective studies with direct peritumoral fat assessment, menopausal stratification, and multi-center validation would help clarify the role of local adiposity in breast tumor biology.

Ethics Committee Approval: The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of Gaziantep City Hospital (Date: 06.02.2026, No: 432/2026).

Peer-review: Externally peer-reviewed.

Informed Consent: Individual patient informed consent was waived given the retrospective archival nature of the data.

Author Contribution: Concept: B.G.; Design: B.G.; Supervision: E.T.; Materials: B.G.; Data collection &/or processing: E.T.; Analysis and/or interpretation: E.T.; Literature search: B.G.; Writing: B.G.; Critical review: E.T.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74:229-63. [CrossRef]
2. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature 2000;406:747-52. [CrossRef]
3. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, et al. Personalizing the treatment of women with early breast cancer: Highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2013. Ann Oncol 2013;24:2206-23. [CrossRef]
4. Tran TXM, Kim S, Song H, Lee E, Park B. Association of longitudinal mammographic breast density changes with subsequent breast cancer risk. Radiology 2023;306:e220291. [CrossRef]
5. Razzaghi H, Troester MA, Gierach GL, Olshan AF, Yankaskas BC, Millikan RC. Association between mammographic density and basal-like and luminal A breast cancer subtypes. Breast Cancer Res 2013;15:R76. [CrossRef]
6. Wang S, Zhou J, Huang Y, Zheng D, Hou R, Zhou S. BMI and breast subcutaneous fat: Potential indicators for ultrasound diagnosis of breast cancer? J Ultrasound Med 2026;45:599-610. [CrossRef]
7. Maskarinec G, Ciba M, Ju D, Shepherd JA, Ernst T, Wu AH, et al. Association of imaging-based body fat distribution and mammographic density in the Multiethnic Cohort Adiposity Phenotype Study. Cancer Epidemiol Biomarkers Prev 2020;29:352-8. [CrossRef]
8. Heusinger K, Jud SM, Häberle L, Hack CC, Fasching PA, Meier-Meitinger M, et al. Association of mammographic density with the proliferation marker Ki-67 in a cohort of patients with invasive breast cancer. Breast Cancer Res Treat 2012;135:885-92. [CrossRef]
9. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K; International Agency for Research on Cancer Handbook Working Group. Body fatness and cancer - viewpoint of the IARC Working Group. N Engl J Med 2016;375:794-8. [CrossRef]
10. Wu C, Dong S, Huang R, Chen X. Cancer-associated adipocytes and breast cancer: Intertwining in the tumor microenvironment and challenges for cancer therapy. Cancers (Basel) 2023;15:726.

[CrossRef]

11. Mao YW, Zeng HD, Fang Y, Wu XY, Zhang MH, Hu CD, et al. Effect of subcutaneous fat on long-term survival after surgery for stage I-III breast cancer as determined by computed tomography. Front Oncol 2025;15:1506629. [CrossRef]
12. Miao S, Jia H, Huang W, Cheng K, Zhou W, Wang R, et al. Subcutaneous fat predicts bone metastasis in breast cancer: A novel multimodality-based deep learning model. Cancer Biomark 2024;39:171-85. [CrossRef]
13. Sexauer R, Hejduk P, Borkowski K, Ruppert C, Weikert T, Dellas S, et al. Diagnostic accuracy of automated ACR BI-RADS breast density classification using deep convolutional neural networks. Eur Radiol 2023;33:4589-96. [CrossRef]
14. Bocian-Jastrzębska A, Malczewska-Herman A, Kos-Kudła B. Role of leptin and adiponectin in carcinogenesis. Cancers (Basel) 2023;15:4250. [CrossRef]
15. Bai S, Song D, Chen M, Lai X, Xu J, Dong F, et al. The association between mammographic density and breast cancer molecular subtypes: A systematic review and meta-analysis. Clin Radiol 2023;78:622-32. [CrossRef]
16. Eriksson L, Hall P, Czene K, Dos Santos Silva I, McCormack V, Bergh J, et al. Mammographic density and molecular subtypes of breast cancer. Br J Cancer 2012;107:18-23. [CrossRef]
17. Antoni S, Sasco AJ, dos Santos Silva I, McCormack V. Is mammographic density differentially associated with breast cancer according to receptor status? A meta-analysis. Breast Cancer Res Treat 2013;137:337-47. [CrossRef]
18. Soguel L, Durocher F, Tchernof A, Diorio C. Adiposity, breast density, and breast cancer risk: Epidemiological and biological considerations. Eur J Cancer Prev 2017;26:511-20. [CrossRef]
19. Chu A, Sung P, Lee J, Cheun JH, Hwang KT, Lee K, et al. Association of body composition fat parameters and breast density in mammography by menopausal status. Sci Rep 2022;12:22224. [CrossRef]
20. Masala G, Bendinelli B, Caini S, Duroni G, Ermini I, Pastore E, et al. Lifetime changes in body fatness and breast density in postmenopausal women: The FEDRA study. Breast Cancer Res 2023;25:35. [CrossRef]
21. Miracle CE, McCallister CL, Denning KL, Russell R, Allen J, Lawrence L, et al. High BMI is associated with changes in peritumor breast adipose tissue that increase the invasive activity of triple-negative breast cancer cells. Int J Mol Sci 2024;25:10592. [CrossRef]
22. Dauccia C, Bruzzone M, Arecco L, Blondeaux E, Sirico M, Gerosa R, et al. Association between body mass index and risk of breast cancer according to breast cancer subtypes: A systematic review and meta-analysis. Breast 2026;86:104710. [CrossRef]
23. Pierobon M, Frankenfeld CL. Obesity as a risk factor for triple-negative breast cancers: A systematic review and meta-analysis. Breast Cancer Res Treat 2013;137:307-14. [CrossRef]
24. Lohmann AE, Soldera SV, Pimentel I, Ribnikar D, Ennis M, Amir E, et al. Association of obesity with breast cancer outcome in relation to cancer subtypes: A meta-analysis. J Natl Cancer Inst 2021;113:1465-75. [CrossRef]
25. Calle EE, Kaaks R. Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4:579-91. [CrossRef]
26. Dietze EC, Sistrunk C, Miranda-Carboni G, O'Regan R, Seewaldt VL. Triple-negative breast cancer in African-American women: Disparities versus biology. Nat Rev Cancer 2015;15:248-54. [CrossRef]
27. Papakonstantinou E, Piperigkou Z, Karamanos NK, Zolota V. Altered adipokine expression in tumor microenvironment promotes development of triple negative breast cancer. Cancers (Basel) 2022;14:4139. [CrossRef]
28. Huo CW, Chew G, Hill P, Huang D, Ingman W, Hodson L, et al. High mammographic density is associated with an increase in stromal collagen and immune cells within the mammary epithelium. Breast Cancer Res 2015;17:79. [CrossRef]
29. Sturesdotter L, Larsson AM, Zackrisson S, Sartor H. Investigating the prognostic value of mammographic breast density and mammographic tumor appearance in women with invasive breast-cancer: The Malmö Diet and Cancer study. Breast 2023;70:8-17. [CrossRef]
30. Nielsen TO, Leung SCY, Rimm DL, Dodson A, Acs B, Badve S, et al. Assessment of Ki67 in breast cancer: Updated recommendations from the International Ki67 in Breast Cancer Working Group. J Natl Cancer Inst 2021;113:808-19. [CrossRef]
31. Yerushalmi R, Woods R, Ravdin PM, Hayes MM, Gelmon KA. Ki67 in breast cancer: Prognostic and predictive potential. Lancet Oncol 2010;11:174-83. [CrossRef]
32. Bustreo S, Osella-Abate S, Cassoni P, Donadio M, Airoldi M, Pedani F, et al. Optimal Ki67 cut-off for luminal breast cancer prognostic evaluation: A large case series study with a long-term follow-up. Breast Cancer Res Treat 2016;157:363-71. [CrossRef]

ORIGINAL ARTICLE

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.32533

The Comparison of Myocardial Dysfunction Using Speckle Tracking Echocardiography in Resistive and Non-Resistive Familial Mediterranean Fever Patients

Ugur Ozkerim,[1] Hasan Kocaayan,[2] Sercan Gucenmez,[2] Servet Akar[2]

Abstract

Objective: Evidence of subclinical myocardial and pericardial involvement has been described in patients with Familial Mediterranean Fever (FMF), even during clinically inactive periods. However, the potential impact of colchicine resistance on cardiac function has not been fully elucidated. The present study investigated myocardial performance in FMF patients with differing responses to colchicine therapy using speckle-tracking echocardiography.

Methods: This study evaluated 74 patients diagnosed with FMF, including 57 colchicine-responsive and 17 colchicine-resistant individuals, together with 74 age- and sex-matched healthy controls. Participants with established cardiovascular risk factors were excluded. Colchicine resistance was defined by recurrent attacks occurring at least once every three months despite treatment with 2 mg/day or the maximum tolerated dose of colchicine, the requirement for biologic therapy, and/or the presence of amyloidosis, defined as proteinuria ≥500 mg/day on at least two occasions or biopsy-confirmed disease. Demographic, clinical, and laboratory variables were collected using a standardized assessment form. All subjects underwent speckle-tracking echocardiographic evaluation performed by experienced cardiologists who were blinded to clinical information.

Results: No significant differences were observed between colchicine-resistant and colchicine-responsive FMF patients with respect to age, sex distribution, or disease duration ($p>0.05$). Global longitudinal strain (GLS) values were significantly reduced in colchicine-responsive FMF patients compared with healthy controls ($p<0.05$). In contrast, GLS measurements did not differ significantly between colchicine-resistant and colchicine-responsive patient groups ($p>0.05$).

Conclusions: Patients with FMF demonstrate subclinical myocardial dysfunction when compared with healthy individuals. However, resistance to colchicine therapy does not appear to be associated with additional impairment in myocardial strain parameters, suggesting that mechanisms independent of treatment response may contribute to cardiac involvement in FMF.

Keywords: Familial mediterranean fever; colchicine resistance; myocardial dysfunction; speckle tracking echocardiography.

[1]Department of Medical Oncology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye
[2]Department of Rheumatology, Katip Çelebi University, Izmir,Türkiye

Address for correspondence:
Uğur Özkerim, Department of Medical Oncology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye
E-mail: ugur.ozkerim@hotmail.com

Received: 09.01.2026
Accepted: 18.05.2026
Published: 29.09.2026

How to cite this article: *Ozkerim U, Kocaayan H, Gucenmez S, Akar S. The comparison of myocardial dysfunction using speckle tracking echocardiography in resistive and non-resistive familial mediterranean fever patients. South. Clin. Ist. Euras. 2026;37(3):239-248.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Copyright@Author(s)

Introduction

Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory condition inherited in an autosomal recessive pattern and characterized by recurrent, self-limited episodes of fever and serosal inflammation. Clinical manifestations most frequently include abdominal pain, arthralgia, peritonitis, pleuritis, and erysipelas-like erythema.[1] Although inflammatory attacks usually resolve spontaneously within a short time frame, many patients remain asymptomatic between episodes, except for occasional persistence of musculoskeletal complaints.[2] FMF predominantly affects populations originating from the Mediterranean basin, including Turkish, Armenian, Arab, and Jewish communities, and epidemiological data indicate that Türkiye has one of the highest reported prevalence rates worldwide.[3–5]

FMF is caused by pathogenic variants in the MEFV gene located on chromosome 16, which encodes pyrin, a key regulator of innate immune signaling pathways.[6] Multiple disease-associated mutations have been identified, with considerable variability in clinical expression. Among these, the M694V mutation is particularly common in the Turkish population and has been linked to more severe disease phenotypes and heightened inflammatory activity.[7,8] While FMF has traditionally been regarded as a disorder confined to serosal inflammation, accumulating evidence suggests that persistent low-grade inflammation may extend beyond serosal tissues and contribute to multisystem involvement.

Cardiac manifestations of FMF have historically received less attention than abdominal or musculoskeletal features; however, growing evidence indicates that cardiovascular involvement may occur even in the absence of overt symptoms. Pericarditis is the most clearly described cardiac manifestation, although it is observed in only a small proportion of patients.[9] In addition, several studies have reported subclinical myocardial involvement in FMF, potentially driven by ongoing inflammatory activity during clinically quiescent periods.[10,11] These observations highlight the need for sensitive imaging techniques capable of identifying early myocardial dysfunction before the development of clinically apparent disease.

Colchicine remains the cornerstone of FMF management and is highly effective in reducing attack frequency and preventing long-term complications, including amyloidosis, in most patients.[12,13] Nevertheless, a subset of individuals continues to experience recurrent attacks despite receiving the maximum tolerated dose of colchicine, necessitating treatment escalation to biologic agents such as interleukin-1 inhibitors.[14–16] The lack of a universally accepted definition of colchicine resistance poses challenges for both clinical practice and research; however, persistent attacks and sustained inflammatory activity despite optimal therapy are generally considered hallmarks of resistance. These patients may therefore be at increased risk of inflammation-related organ involvement, including potential cardiac dysfunction.

Speckle-tracking echocardiography (STE) is a non-invasive imaging modality that allows detailed evaluation of myocardial deformation and enables detection of subtle functional abnormalities that may not be apparent with conventional echocardiographic methods.[11,17–19] Previous studies have demonstrated alterations in myocardial strain parameters among FMF patients; however, it remains unclear whether colchicine-resistant individuals exhibit more pronounced myocardial involvement compared with colchicine-responsive patients. Addressing this knowledge gap may provide insight into the role of persistent inflammation in early cardiac dysfunction and clarify the potential value of STE for risk stratification in FMF.

Accordingly, the present study aimed to assess subclinical myocardial dysfunction in patients with FMF using speckle-tracking echocardiography and to compare cardiac findings among colchicine-resistant patients, colchicine-responsive patients, and healthy control subjects.

Materials and Methods

Study Population

This study included patients diagnosed with Familial Mediterranean Fever (FMF) according to the internationally accepted Tel-Hashomer criteria who were followed at the Department of Rheumatology. The study cohort comprised patients with colchicine-responsive disease as well as individuals classified as having colchicine-resistant FMF. Colchicine resistance was defined as the occurrence of at least one FMF attack within a three-month period despite treatment with 2 mg/day of colchicine or the maximum tolerated dose.

Patients with FMF-associated amyloidosis—defined as

proteinuria ≥500 mg/day documented on at least two separate measurements or biopsy-confirmed amyloidosis—were also included. In addition, patients receiving biologic therapies due to inadequate response or intolerance to colchicine were enrolled. All FMF patients except those demonstrating an adequate response to colchicine therapy were categorized as having colchicine-resistant disease.

An age- and sex-matched healthy control group was recruited for comparison. Controls consisted of healthy relatives of patients, hospital staff, or individuals evaluated in the cardiology outpatient clinic who demonstrated normal echocardiographic findings and had no clinical evidence of cardiovascular disease.

Exclusion criteria included known coronary artery disease, diabetes mellitus, heart failure, presence of a permanent pacemaker, moderate or severe valvular heart disease, atrial fibrillation, prior cerebrovascular events, acute or chronic renal failure, hepatic failure, or unwillingness to participate in the study.

Sample size estimation was based on previously published data reporting radial global strain values of 0.59±0.24 in FMF patients and 0.83±0.51 in healthy individuals. Assuming a type I error rate of 0.05 and a power of 80% (β=0.20), a minimum of 34 participants per group was calculated to be sufficient.

Ethical approval was obtained from the local institutional Ethics Committee of İzmir Katip Çelebi University on January 17, 2018 (No: 15), and the study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Data Collection and Disease Severity Assessment

Demographic and clinical characteristics of participants were recorded using a structured case report form completed by the attending physician (Appendix 1). Collected data included age, sex, age at FMF diagnosis, duration of treatment, clinical manifestations at disease onset and during follow-up, genetic mutation status, and treatment response.

Disease severity was assessed using the International Severity Scoring System for FMF (ISSF) (Appendix 2). Patients were categorized as having mild (≤2 points), moderate (3–5 points), or severe disease (≥6 points) according to their total ISSF score.

Following completion of data collection, all patients underwent cardiologic evaluation. Myocardial performance was assessed using speckle-tracking strain echocardiography.

Conventional Echocardiographic Evaluation

All participants underwent a comprehensive two-dimensional transthoracic echocardiographic examination, including M-mode imaging, color Doppler, tissue Doppler imaging, and strain analysis. Echocardiographic studies were performed using a commercially available ultrasound system (EPIQ 7C, Philips Medical Imaging, Eindhoven, The Netherlands).

Standard echocardiographic measurements were obtained in accordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Image acquisition and analysis were independently performed by two experienced echocardiographers who were blinded to the clinical data of the participants.

Left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson method. Mitral inflow velocities, including early (E) and late (A) diastolic filling waves, were measured using pulsed-wave Doppler. Tissue Doppler imaging was used to assess systolic (s′), early diastolic (e′), and late diastolic (a′) annular velocities at both the lateral and septal mitral annular sites. Tricuspid regurgitation peak velocity was measured using continuous-wave Doppler from the apical four-chamber view.

Left ventricular diastolic function was evaluated using E velocity, mean E/e′ ratio, left atrial volume, and deceleration time (DT), in accordance with current guideline recommendations.

Speckle-Tracking Strain Analysis

Speckle-tracking echocardiographic analysis was performed using dedicated software (QLAB, MVQ module; Philips). Digital cine loops were acquired at frame rates between 50 and 90 frames per second from apical four-, three-, and two-chamber views for longitudinal strain analysis, as well as from parasternal short-axis views at basal, mid-ventricular, and apical levels for circumferential strain analysis. All measurements were synchronized with the peak of the R wave and averaged over three consecutive cardiac cycles.

For circumferential strain assessment, endocardial borders were manually traced at the basal, mid, and api-

cal short-axis levels. Longitudinal strain measurements were obtained by manually placing reference points at the septal and lateral mitral annuli and the apical endocardium at end-diastole. The software automatically generated a region of interest, which was visually inspected for tracking quality. Manual adjustments were performed when necessary.

Segmental strain curves were automatically generated, and peak systolic strain values were calculated. Global longitudinal strain (GLS) and global circumferential strain (GCS) were defined as the mean of corresponding segmental values. A GLS value of 20% was considered normal in accordance with current guideline recommendations.

Statistical Analysis

Statistical analyses were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. As the data did not demonstrate a normal distribution, non-parametric statistical methods were applied.

Continuous variables were expressed as median values with minimum–maximum ranges, while categorical variables were presented as frequencies and percentages. Comparisons between categorical

variables were conducted using the Chi-square test. Differences among the three study groups were evaluated using the Kruskal–Wallis test.

When a statistically significant difference was identified with the Kruskal–Wallis test, pairwise comparisons were performed using the Mann–Whitney U test with Bonferroni correction. A p-value <0.05 was considered statistically significant, and for multiple comparisons, a corrected p-value <0.017 was accepted as significant.

Results

The study cohort consisted of 74 individuals diagnosed with Familial Mediterranean Fever (FMF) and 74 age- and sex-comparable healthy control subjects, with no significant difference in sex distribution between the groups (p=0.508). Among the FMF patients, 57 (77%) were colchicine-responsive, while 17 were classified as colchicine-resistant. No statistically significant differences were found between the groups in terms of age or sex (Table 1).

There was no significant difference in disease duration between colchicine-resistant and colchicine-responsive FMF patients (resistant: 11 years [1–27 years] vs. non-resistant: 6 years [0–33 years], p=0.133). However, a statistically significant difference in FMF severity scores was observed between the resistant and non-resistant groups (resistant: 4 [2–6] vs. non-resistant: 2 [1–4], p<0.001).

Table 1. Comparison of groups in terms of sex and age

	Colchicine-Responsive FMF (n=57)	Colchicine-Resistant FMF (n=17)	Healthy Controls (n=74)	p-value
Female (n, %)	34 (59.6%)	9 (52.9%)	39 (52.7%)	0.713
Male (n, %)	23 (40.4%)	8 (47.1%)	35 (47.3%)	
Age (years), median (min-max)	35 (18–63)	31 (20–49)	37(22–55)	0.186

Table 2. Laboratory results of FMF patients

	Colchicine-Responsive FMF (n=57)	Colchicine-Resistant FMF (n=17)	All FMF Patients (n=74)
CRP (mg/dL)	0.14 (0.02–3.6)	0.22 (0.02–4.00)	0.13 (0.02–4)
ESR (mm/h)	8 (1–37)	11 (1–38)	8 (1–38)
Urine Protein (mg/dL)	103 (10–289)	152 (75–12897)	113.5 (10–12897)
Serum Creatinine (mg/dL)	0.75 (0.56–1.05)	0.72 (0.62–1.99)	0.75 (0.56–1.99)

CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate.

Table 3. Distribution of demographic characteristics of FMF patients

	Colchicine-Responsive FMF (n=57)	Colchicine-Resistant FMF (n=17)	All FMF Patients (n=74)
Parental Consanguinity - No	53 (93%)	15 (88.2%)	68 (91.9%)
Family History of FMF - Yes	30 (52.6%)	10 (58.8%)	40 (54.1%)
Education Level - Primary School	5 (8.8%)	3 (17.6%)	8 (10.8%)
Education Level - Middle School	1 (1.8%)	1 (5.9%)	2 (2.7%)
Education Level - High School	47 (82.5%)	12 (70.6%)	59 (79.7%)
Education Level - University	4 (7.0%)	1 (5.9%)	5 (6.75%)
Marital Status - Married	33 (57.9%)	13 (76.5%)	46 (62.1%)
Smoking History - Current Smoker	17 (29.8%)	3 (17.6%)	20 (27.0%)
Smoking History - Never Smoked	38 (66.7%)	13 (76.5%)	51 (69%)
Smoking History - Quit	2 (3.5%)	1 (5.9%)	3 (4%)
Employment at Diagnosis - Unemployed	45 (78.9%)	12 (70.6%)	57 (77.1%)
Unemployment Due to Disease - No	54 (94.7%)	14 (82.4%)	68 (91.9%)

Table 4. Distribution of clinical symptoms between colchicine-resistant and colchicine-responsive FMF patients

Symptom	Colchicine-Responsive FMF (n=57)	Colchicine-Resistant FMF (n=17)	All FMF Patients (n=74)
Fever - Yes	54 (94.8%)	16 (94.1%)	70 (94.6%)
Fever - No	3 (5.3%)	1 (5.9%)	4 (5.4%)
Peritonitis - Yes	53 (93.0%)	17 (100%)	70 (94.6%)
Peritonitis - No	4 (7%)	0	4 (5.4%)
Pleuritis - Yes	8 (14%)	5 (29.4%)	13 (17.55%)
Pleuritis - No	49 (86%)	12 (70.6%)	61 (82.45%)
Erythema - Yes	4 (7%)	5 (29.4%)	9 (12.15%)
Erythema - No	53 (93%)	12 (70.6%)	65 (87.85%)
Arthritis - Yes	31 (54.4%)	13 (76.5%)	44 (59.3%)
Arthritis - Never	26 (45.6%)	4 (23.5%)	30 (40.7%)
Prolonged Arthritis - Yes	2 (3.5%)	1 (5.9%)	3 (4.1%)
Prolonged Arthritis - No	55 (96.5%)	16 (94.1%)	71 (95.9%)
Prolonged Febrile Myalgia - Yes	3 (5.3%)	1 (5.9%)	4 (5.4%)
Prolonged Febrile Myalgia - No	54 (94.7%)	16 (94.1%)	70 (94.6%)

Upon evaluation of the laboratory results of FMF patients, all were found to be in an attack-free period; however, acute-phase reactants were found to be significantly higher in colchicine-resistant FMF patients (Table 2).

Evaluation of demographic characteristics showed that most FMF patients did not report parental consanguinity, approximately half had a family history of FMF, the majority were high school graduates and married, were non-smokers, were not employed at the time of diagnosis, and had not experienced disease-related unemployment (Table 3).

Evaluation of clinical symptoms revealed that the majority of both colchicine-responsive and colchicine-resistant FMF patients reported fever, peritonitis, and arthritis. However, most patients did not report pleuritis, erythema, prolonged arthritis, or prolonged febrile myalgia (Table 4).

Genetic evaluation demonstrated that M694V heterozygosity was the most frequent mutation among

Table 5. Genetic mutations in FMF patients

Genetic Mutation	Colchicine -Responsive FMF (n=57)	Colchicine-Resistant FMF (n=17)	All FMF Patients (n=74)
M694V/M694V	9 (15.8%)	12 (70.5%)	21 (28.3%)
M694V/wt	21 (36.8%)	2 (11.8%)	23 (31%)
M694V/E148Q	4 (7%)	0	4 (5.4%)
E148Q/wt	9 (15.8%)	2 (11.8%)	11 (16.2%)
Exon 10/E148Q	1 (1.7%)	0	1 (1.35%)
Exon 10/wt	11 (19.1%)	1 (5.9%)	12 (16.1%)
Other	2 (3.4%)	0	2 (2.7%)

*First allele / second allele, wt: wild type.

Table 6. Comorbid Conditions in FMF Patients

Comorbidity	Colchicine-Responsive FMF (n=57)	Colchicine-Resistant FMF (n=17)	All FMF Patients (n=74)
History of Amyloidosis – Yes	0	6 (35.3%)	6 (8.2%)
History of Amyloidosis - No	57 (100%)	11 (64.7%)	68 (91.8%)
Coexisting Inflammatory Disease - None	52 (91.2%)	16 (94.1%)	68 (91.8%)
Spondyloarthritis	3 (5.3%)	1 (5.9%)	4 (5.4%)
Rheumatoid Arthritis	1 (1.8%)	0	1 (1.4%)
Inflammatory Bowel Disease	1 (1.8%)	0	1 (1.4%)

Table 7. Comparison of echocardiographic findings between all FMF patients and healthy controls

Parameter	FMF (n=74) Median (Min-Max)	Control (n=74) Median (Min-Max)	p-value
LA	31 (23–41)	31 (22–44)	0.507
IVS	9 (1–13)	9 (7–13)	0.024
PW	8 (1–13)	9 (7–12)	<0.001
LVD	43 (35–86)	43 (20–50)	0.751
LVS	26 (18–32)	26 (19–34)	0.468
LVEDV	87 (35–152)	82 (47–143)	0.181
LVESEV	32 (10–75)	35 (21–86)	0.228
EF	63 (40–77)	60 (52–70)	0.425
E	95 (9–148)	93 (57–130)	0.240
A	82 (8–153)	81 (57–120)	0.928
DT	183 (100–303)	161 (100–254)	<0.001
E Lateral	14 (8–29)	14 (8–23)	0.754
A Lateral	11 (5–18)	10 (6–17)	0.893
E Septal	11 (5–20)	11 (5–16)	0.263
A Septal	10 (5–17)	9 (4–23)	0.189
GLS	20 (8–55)	22 (16–33)	<0.001
GCS	21 (10–42)	20 (13–30)	0.617

*p<0.05. LA: Left atrium, IVS: Interventricular septum, PW: Posterior wall, LVD: Left ventricular diastole, LVS: Left ventricular systole, LVEDV: Left ventricular end-diastolic volume, LVESEV: Left ventricular end-systolic volume, EF: Ejection fraction, E: Early diastolic flow,A: Atrial filling, DT: Deceleration time, E Lateral: Early lateral filling, A Lateral: Late lateral filling, E Septal: Early septal filling, A Septal: Late septal filling, GLS: Global Longitudinal Strain, GCS: Global Circumferential Strain.

Table 8. Comparison of echocardiographic findings between colchicine-responsive FMF patients, colchicine-resistant FMF patients, and healthy controls

Parameter	Colchicine-Responsive FMF (n=57) Median (Min-Max)	Colchicine-Resistant FMF (n=17) Median (Min-Max)	Control (n=74) Median (Min-Max)
LA	31 (23–41)	30 (26–35)	31 (22–44)
IVS	8 (1–13)*	10 (5–12)	9 (7–13)
PW	8 (1–13)*	10 (6–12)	9 (7–12)
LVD	43 (35–86)	41 (38–48)	43 (20–50)
LVS	26 (20–32)	24 (18–31)	26 (19–34)
LVEDV	87 (35–152)	92 (36–124)	82 (47–143)
LVESEV	32 (16–75)	34 (10–65)	35 (21–86)
EF 62 (40–77)	64 (46–73)	60 (52–70)	
E 95 (23–148)	98 (9–130)	93 (57–130)	
A 83 (26–153)	79 (8–134)	81 (57–120)	
DT 187 (100–303)*	183 (100–296)	161 (100–254)	
E Lateral	14 (8–29)	13 (10–23)	14 (8–23)
A Lateral	11 (5–18)	10 (7–18)	10 (6–17)
E Septal	11 (6–20)	9 (5–16)	11 (5–16)
A Septal	10 (5–17)	10 (5–17)	9 (4–23)
GLS	20 (8–55)*	20 (15–32)	22 (16–33)
GCS	21 (10–29)	20 (11–42)	20 (13–30)

*Significant difference between colchicine-responsive FMF patients and controls, p<0.05. LA: Left atrium, IVS: Interventricular septum, PW: Posterior wall, LVD: Left ventricular diastole, LVS: Left ventricular systole, LVEDV: Left ventricular end-diastolic volume, LVESEV: Left ventricular end-systolic volume, EF: Ejection fraction, E: Early diastolic flow, A: Atrial filling, DT: Deceleration time, E Lateral: Early lateral filling, A Lateral: Late lateral filling, E Septal: Early septal filling, A Septal: Late septal filling, GLS: Global Longitudinal Strain, GCS: Global Circumferential Strain.

colchicine-responsive patients (36.8%), whereas M694V homozygosity predominated in the colchicine-resistant group (70.5%) (Table 5).

With the exception of one colchicine-responsive FMF patient, all patients—both colchicine-resistant and colchicine-responsive—reported regular use of colchicine therapy. Nevertheless, 55.3% of colchicine-responsive patients and all colchicine-resistant patients reported experiencing attacks despite adherence to regular colchicine treatment. Among the colchicine-resistant patients, 11 were receiving biologic therapy: 10 Were being treated with anakinra and 1 with canakinumab.

Evaluation of comorbidities in FMF patients showed that the majority had no history of amyloidosis, no evidence of renal involvement, and no accompanying inflammatory diseases. The most frequently observed comorbid condition was spondyloarthritis (Table 6).

When all patients diagnosed with FMF (n=74) were compared with healthy controls (n=74) using speckle tracking echocardiography, significant differences were observed between the groups in terms of interventricular septum thickness (IVS), posterior wall thickness (PW), deceleration time (DT), and global longitudinal strain (GLS) (p<0.05, Table 7).

When colchicine-resistant and colchicine-responsive FMF patients were compared with healthy controls, significant differences were found among the groups in terms of interventricular septum thickness (IVS), posterior wall thickness (PW), deceleration time (DT), and global longitudinal strain (GLS) (p<0.05). These differences were found to be statistically significant, specifically between colchicine-responsive FMF patients and healthy controls (p<0.05, Table 8).

Discussion

Although pericardial involvement in Familial Mediterranean Fever (FMF) has been examined in multiple studies during both attack and remission periods, evidence specifically addressing patients with severe disease phenotypes or colchicine resistance remains scarce. In the

present study, myocardial function was evaluated using speckle-tracking echocardiography, an imaging modality capable of identifying subtle myocardial abnormalities with greater sensitivity than conventional echocardiographic techniques.

The results of this study revealed significant differences between FMF patients and healthy controls with respect to interventricular septum thickness, posterior wall thickness, deceleration time, and global longitudinal strain (GLS), supporting the presence of subclinical myocardial involvement in FMF. In contrast, no significant differences were observed between colchicine-resistant and colchicine-responsive FMF patients. These findings suggest that myocardial dysfunction may be related to FMF itself rather than being directly influenced by colchicine responsiveness.

Consistent with existing literature, most colchicine-resistant patients in our cohort were carriers of the M694V homozygous mutation, which has been associated with more severe clinical manifestations. Despite evaluation during attack-free periods, these patients demonstrated higher acute-phase reactant levels as well as increased frequencies of amyloidosis and renal involvement compared with colchicine-responsive patients, indicating the persistence of subclinical inflammation.

Previous studies investigating cardiac involvement in FMF have reported inconsistent results. While some authors have demonstrated myocardial dysfunction, others have failed to identify significant cardiac abnormalities. These discrepancies may be explained by variations in study populations, including differences in age, disease duration, genetic profiles, and the diagnostic sensitivity of the imaging methods used.

In support of our findings, Kalkan et al.[17] reported that strain echocardiography detected myocardial abnormalities in FMF patients that were not evident with tissue Doppler imaging. Conversely, Tavil et al.[20] did not identify significant differences in speckle-tracking parameters between FMF patients and healthy controls but reported diastolic dysfunction using Doppler flow analysis. Similarly, Baysal et al.[21] observed diastolic dysfunction in pediatric FMF patients assessed with Doppler echocardiography, underscoring the limited sensitivity of conventional echocardiographic methods for early myocardial involvement.

Terekeci et al.[22] evaluated young FMF patients during attack and remission phases using tissue Doppler echocardiography and found no significant differences, attributing their findings to the relatively young age of the study population. Given that FMF is a chronic disease with onset typically in childhood, cumulative inflammatory exposure over time may contribute to myocardial alterations that become more apparent in adulthood.

Autonomic dysfunction detected by Holter monitoring has been described primarily in pediatric FMF cohorts, whereas similar findings have not been consistently demonstrated in adults. Nevertheless, Sarı et al.[10] reported evidence of possible subclinical myocardial involvement in young FMF patients without conventional cardiovascular risk factors. In line with this observation, Ceylan et al.[11] demonstrated reduced GLS values in pediatric FMF patients, suggesting that myocardial strain abnormalities may be present even at early stages of the disease.

Arslan et al.[23] assessed pediatric FMF patients using Doppler echocardiography and electrocardiography and reported prolonged isovolumetric contraction and relaxation times together with increased P-wave dispersion, indicating early myocardial and electrical alterations. The more prominent echocardiographic changes observed in our adult cohort may therefore reflect the cumulative effects of long-standing disease.

Chronic inflammatory disorders are known to adversely affect vascular and myocardial function. Subclinical systolic and diastolic dysfunction has been documented in patients with rheumatoid arthritis, systemic lupus erythematosus, and Behçet's disease, even in the absence of overt cardiovascular disease.[24,25] In these conditions, diastolic abnormalities often precede systolic impairment and the development of clinical heart failure,[25–27] with inflammation playing a central role through mechanisms such as endothelial dysfunction, atherogenesis, and myocardial remodeling.

Consistent with these findings, recent studies in patients with spondyloarthritis have reported impaired GLS values compared with healthy controls, particularly in radiographic subtypes, whereas non-radiographic subgroups did not demonstrate significant myocardial involvement. A similar pattern was observed in our study.

Importantly, no significant differences in cardiac parameters were identified between colchicine-resistant FMF patients and healthy controls. This finding may

be related to the limited number of colchicine-resistant patients, which could have reduced statistical power, as well as the potential anti-inflammatory effects of biologic therapies used in this subgroup. The observation that many patients continued to experience attacks despite regular colchicine therapy prior to biologic treatment further emphasizes the role of inflammation control in preventing myocardial involvement.

Conclusion

Assessment of myocardial function in this cohort identified distinct echocardiographic differences between patients with Familial Mediterranean Fever and healthy individuals, consistent with subclinical myocardial involvement. However, colchicine resistance was not associated with additional cardiac impairment when compared with colchicine-responsive disease. These findings suggest that myocardial dysfunction in FMF may be related to the underlying inflammatory disease process rather than treatment responsiveness alone. Awareness of potential cardiac involvement in FMF may therefore contribute to more comprehensive patient evaluation and management.

Ethics Committee Approval: Ethical approval was obtained from the local institutional Ethics Committee of İzmir Kâtip Çelebi University (Date: 30/07/2024, No: 15).
Peer-review: Externally peer-reviewed.
Informed Consent: Not applicable.
Author Contribution: Concept: U.O., S.G.; Design: U.O., S.G.; Supervision: S.A.; Fundings: U.O., H.K.; Materials: U.O., H.K.; Data collection &/or processing: U.O., H.K.; Analysis and/or interpretation: S.G., S.A.; Literature search: U.O.; Writing: U.O.; Critical review: S.A.
Conflict of Interest: The authors declare no conflict of interest.
Funding: The authors declared that this study has received no financial support.

References

1. Çakırca G, Çelik MM. Lipid profile and atherogenic indices and their association with platelet indices in familial Mediterranean fever. Turk Kardiyol Dern Ars 2018;46:184–90. [CrossRef]
2. Düzova A, Özen S. Clinical features and diagnosis of familial mediterranean fever. Turkiye Klinikleri J Int Med Sci 2006;2:12–20.
3. Ozen S, Hoffman HM, Frenkel J, Kastner D. Familial Mediterranean fever (FMF) and beyond: A new horizon. Fourth International Congress on the Systemic Autoinflammatory Diseases held in Bethesda, USA, 6–10 November 2005. Ann Rheum Dis 2006;65:961–4. [CrossRef]
4. Ben-Chetrit E, Touitou I. Familial Mediterranean fever in the world. Arthritis Rheum 2009;61:1447–53. [CrossRef]
5. Özdoğan H. Familial mediterranean fever. Cerrahpasa Med Fac Contin Med Educ Act Rheum Dis 2003;34:63–6.
6. Cantarini L, Rigante D, Brizi MG, Lucherini OM, Sebastiani GD, Vitale A, et al. Clinical and biochemical landmarks in systemic autoinflammatory diseases. Ann Med 2012;44:664–73. [CrossRef]
7. Shinar Y, Obici L, Aksentijevich I, Bennetts B, Austrup F, Ceccherini I, et al; European Molecular Genetics Quality Network. Guidelines for the genetic diagnosis of hereditary recurrent fevers. Ann Rheum Dis 2012;71:1599–605. [CrossRef]
8. Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, et al. Familial Mediterranean fever (FMF) in Turkey: Results of a nationwide multicenter study. Medicine 2005;84:1–11. [CrossRef]
9. Kees S, Langevitz P, Zemer D, Padeh S, Pras M, Livneh A. Attacks of pericarditis as a manifestation of familial Mediterranean fever (FMF). QJM 1997;90:643–7. [CrossRef]
10. Sari I, Arican O, Can G, Akdeniz B, Akar S, Birlik M, et al. Assessment of aortic stiffness and ventricular functions in familial Mediterranean fever. Anadolu Kardiyol Derg 2008;8:271–8.
11. Ceylan Ö, Özgür S, Örün UA, Doğan V, Yılmaz O, Keskin M, et al. Assessment of left ventricular functions with tissue Doppler, strain, and strain rate echocardiography in patients with familial Mediterranean fever. Anatol J Cardiol 2015;15:663–8. [CrossRef]
12. Hentgen V, Grateau G, Stankovic-Stojanovic K, Amselem S, Jéru I. Familial Mediterranean fever in heterozygotes: Are we able to accurately diagnose the disease in very young children? Arthritis Rheum 2013;65:1654–62. [CrossRef]
13. Ben-Zvi I, Krichely-Vachdi T, Feld O, Lidar M, Kivity S, Livneh A. Colchicine-free remission in familial Mediterranean fever: Featuring a unique subset of the disease-a case control study. Orphanet J Rare Dis 2014;9:3. [CrossRef]
14. Samuels J, Ozen S. Familial Mediterranean fever and the other autoinflammatory syndromes: Evaluation of the patient with recurrent fever. Curr Opin Rheumatol 2006;18:108–17. [CrossRef]
15. De Benedetti F, Gattorno M, Anton J, Ben-Chetrit E, Frenkel J, Hoffman HM, et al. Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. N Engl J Med 2018;378:1908–19. [CrossRef]
16. van der Hilst JCh, Moutschen M, Messiaen PE, Lauwerys BR, Vanderschueren S. Efficacy of anti-IL-1 treatment in familial Mediterranean fever: A systematic review of the literature. Biologics 2016;10:75–80. [CrossRef]
17. Kalkan GY, Bayram NA, Erten S, Keles T, Durmaz T, Akcay M, et al. Evaluation of left ventricle function by strain imaging in patients with familial Mediterranean fever. Echocardiography 2010;27:1056–60. [CrossRef]
18. Blessberger H, Binder T. Non-invasive imaging: Two dimensional speckle tracking echocardiography: Basic principles. Heart 2010;96:716–22. [CrossRef]
19. Petersen JW, Nazir TF, Lee L, Garvan CS, Karimi A. Speckle tracking echocardiography-determined measures of global and regional left ventricular function correlate with functional capacity in patients with and without preserved ejection fraction. Cardiovasc Ultrasound 2013;11:20. [CrossRef]
20. Tavil Y, Ureten K, Oztürk MA, Sen N, Kaya MG, Cemri M, et al. The detailed assessment of left and right ventricular functions by tissue Doppler imaging in patients with familial Mediterranean fever. Clin Rheumatol 2008;27:189–94.
21. Baysal T, Peru H, Oran B, Sahin TK, Koksal Y, Karaaslan S. Left

ventricular diastolic function evaluated with tissue Doppler imaging in children with familial Mediterranean fever. Clin Rheumatol 2009;28:23–8. [CrossRef]

22. Terekeci HM, Ulusoy ER, Kucukarslan NM, Nalbant S, Oktenli C. Familial Mediterranean fever attacks do not alter functional and morphologic tissue Doppler echocardiographic parameters. Rheumatol Int 2008;28:1239–43. [CrossRef]
23. Arslan D, Oran B, Yazılıtas F, Peru H, Cimen D, Vatansev H. P-wave duration and dispersion in children with uncomplicated familial Mediterranean fever. Mod Rheumatol. 2013;23:1166–71.
24. Wong M, Toh L, Wilson A, Rowley K, Karschimkus C, Prior D, et al. Reduced arterial elasticity in rheumatoid arthritis and the relationship to vascular disease risk factors and inflammation. Arthritis Rheum 2003;48:81–9. [CrossRef]
25. Selzer F, Sutton-Tyrrell K, Fitzgerald S, Tracy R, Kuller L, Manzi S. Vascular stiffness in women with systemic lupus erythematosus. Hypertension 2001;37:1075–82. [CrossRef]
26. Montecucco C, Gobbi G, Perlini S, Rossi S, Grandi AM, Caporali R, et al. Impaired diastolic function in active rheumatoid arthritis. Relationship with disease duration. Clin Exp Rheumatol 1999;17:407–12.
27. Ozkan M, Emel O, Ozdemir M, Yurdakul S, Koçak H, Ozdoğan H, et al. M-mode, 2-D and Doppler echocardiographic study in 65 patients with Behçet's syndrome. Eur Heart J 1992;13:638–41. [CrossRef]

ORIGINAL ARTICLE

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.88965

Patient-Reported Satisfaction and Symptom Improvement Following Holmium Laser Enucleation of the Prostate: Results from a Postoperative Telephone Survey

Yunus Kayalı,[1] Tahsin Batuhan Aydogan,[1] Alpcan Torun,[1] Ali Soleimanpour,[2] Ata Ghasemzadeh,[2] Bilal Eryildirim[1]

Abstract

Objective: To evaluate patient-reported satisfaction and symptom improvement after holmium laser enucleation of the prostate (HoLEP) in a real-world cohort using a structured postoperative telephone survey.

Methods: This single-center observational follow-up study combined retrospective chart review with a structured telephone questionnaire. All HoLEP procedures performed between January 2023 and January 2026 were screened (n=519). Among 462 contact-eligible patients, 209 provided verbal consent and completed the survey in March 2026. The questionnaire assessed global satisfaction, perceived change in voiding symptoms, willingness to undergo HoLEP again, willingness to recommend the procedure, temporal changes in satisfaction, residual symptoms, symptom-related bother, and need for additional treatment.

Results: Favorable overall satisfaction was reported by 146 patients (69.9%), and 184 (88.0%) reported improvement in voiding complaints. In addition, 149 patients (71.3%) stated that they would choose the same operation again, and 143 (68.4%) would recommend HoLEP to others. Favorable satisfaction increased from 22.0% in the first postoperative week to 68.9% at interview. Urinary incontinence was the most frequent residual complaint (78.0%). Less favorable satisfaction was associated with residual symptoms and additional medication requirement (both $p<0.0001$). Longer follow-up showed a weak association with better satisfaction ($rho=0.269$, $p<0.0001$).

Conclusions: HoLEP was associated with substantial patient-reported symptom improvement and generally favorable postoperative appraisal. However, satisfaction was dynamic and was closely related to residual symptoms, additional treatment, and postoperative recovery over time.

Keywords: Benign prostatic hyperplasia; holmium laser enucleation of the prostate; patient satisfaction; patient-reported outcomes; telephone survey.

[1]Department of Urology, University of Health Sciences, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye.
[2]University of Health Sciences, Hamidiye International Faculty of Medicine, Istanbul, Türkiye

Address for correspondence:
Yunus Kayalı, University of Health Sciences, İstanbul Kartal Dr. Lütfi Kırdar City Hospital, Department of Urology, İstanbul, Türkiye
E-mail: dr.yunuskayali@gmail.com

Received: 16.04.2026
Accepted: 17.06.2026
Published: 29.09.2026

How to cite this article: *Kayalı Y, Aydogan TB, Torun A, Soleimanpour A, Ghasemzadeh A, Eryildirim B. Patient-reported satisfaction and symptom improvement following holmium laser enucleation of the prostate: results from a postoperative telephone survey. South. Clin. Ist. Euras. 2026;37(3):249-256.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Copyright@Author(s)

Introduction

Benign prostatic hyperplasia (BPH) is a major cause of lower urinary tract symptoms (LUTS) in aging men and can substantially impair daily function and quality of life. When medical therapy is insufficient or complications of bladder outlet obstruction develop, surgery is often required. Holmium laser enucleation of the prostate (HoLEP) is an established surgical option for men with LUTS secondary to BPH and provides durable functional improvement.[1]

Because BPH surgery is intended to relieve symptoms and improve quality of life, HoLEP should not be judged only by objective perioperative or functional outcomes. Patient satisfaction, willingness to undergo the procedure again, and other patient-reported outcomes are also important. Lee et al.[2] reported that postoperative dissatisfaction after HoLEP was mainly related to urinary incontinence, whereas Cho et al.[3] showed that postoperative appraisal changes over time and is associated with perceived treatment goal achievement.

More recent questionnaire-based studies have described generally favorable medium-term patient-reported outcomes after HoLEP.[4,5] This perspective is especially relevant when counseling patients about postoperative expectations. Although HoLEP does not appear to impair overall sexual function at the population level, ejaculatory changes remain clinically relevant for many patients.[6-8] In addition, information-seeking behavior and the quality of preoperative information may influence postoperative satisfaction and decision appraisal.[9] A recent review emphasized that patient-reported outcomes remain incompletely and inconsistently reported in the HoLEP literature.[10]

The present study evaluated postoperative satisfaction after HoLEP in a real-world cohort using a structured telephone questionnaire. In addition to global satisfaction, the survey assessed perceived improvement in voiding symptoms, willingness to undergo HoLEP again, willingness to recommend the procedure, temporal changes in satisfaction, residual symptoms, symptom-related bother, and the need for additional treatment.

Materials and Methods

Study design and patient selection

This single-center observational follow-up study combined retrospective chart abstraction with a structured postoperative telephone survey. All HoLEP procedures performed between January 2023 and January 2026 were screened from institutional operative records (n=519). Because telephone follow-up was integral to the study design, only patients with available contact information were considered contact-eligible (n=462). All contact-eligible patients were approached in March 2026 using a prespecified interview script and questionnaire. Of these patients, 209 provided verbal consent and completed the survey, yielding a response rate of 45.2% among contact-eligible patients and 40.3% relative to the screened cohort.

Because the study was designed as a fixed-cohort survey of all contact-eligible patients operated on within a predefined institutional period, no formal sample size calculation was performed. No post hoc exclusions based on age, prostate size, comorbidity burden, or perioperative characteristics were applied after questionnaire completion. The unit of analysis was the individual respondent, and the final analytic dataset contained one record per participating patient.

Questionnaire and study variables

The study questionnaire had two components. The first was completed from hospital and operative records and included age, operation date, interview date, postoperative interval in months, comorbidities, preoperative prostate-specific antigen (PSA), prostate volume, preoperative urinary retention, previous BPH surgery, enucleated tissue weight, and operative time. The second component was administered by telephone and assessed overall satisfaction with HoLEP (S1), perceived change in voiding symptoms (S2), willingness to undergo the same operation again (S3), willingness to recommend HoLEP to a relative or acquaintance with similar symptoms (S4), first source of information about HoLEP (S5), satisfaction at predefined postoperative time points (S6), current or recent postoperative symptom burden (S7), symptom-related bother on a 0-10 numerical rating scale (S8), need for postoperative medication or additional treatment (S9), educational level (S10), and occupation (S11).

Items S1-S4 were coded on 5-point ordinal scales, with lower scores indicating more favorable responses. For prespecified summary analyses, favorable overall satisfaction was defined as S1=1-2, perceived improvement in voiding complaints as S2=1-3, willingness to undergo the same operation again as S3=1-2, and willingness to

Table 1. Principal study domains, questionnaire items, operational definitions, and analytical roles

Domain	Variables / items	Coding or operational definition	Analytical role
Source cohort	Screened surgical population	All HoLEP procedures performed between January 2023 and January 2026 were screened from operative records (n=519).	Defines the denominator for overall cohort ascertainment.
Contact eligibility	Telephone contact information	Patients with available telephone contact information were considered contact-eligible (n=462).	Defines the survey-eligible source population.
Analytic cohort	Completed survey	Patients who provided verbal consent and completed the telephone questionnaire in March 2026 (n=209).	Final population used for descriptive and inferential analyses.
Primary satisfaction outcomes	S1-S4	Five-level ordinal items; lower scores indicate more favorable responses. Favorable summaries were prespecified as S1=1-2, S2=1-3, S3=1-2, and S4=1-2.	Main descriptive endpoints.
Longitudinal satisfaction	S6	Ordinal satisfaction at week 1, month 1, month 3, month 6, month 12, and interview. "U" denotes a structurally inapplicable time point not yet reached.	Within-patient time-course analysis.
Current symptoms	S7	Multiple-response item decomposed into separate binary indicators for none, incontinence, dysuria, hematuria, sexual/ejaculatory change, and weak/intermittent stream.	Descriptive symptom prevalence and subgroup analyses.
Symptom burden	S8	Numerical bother score from 0 to 10. If no symptom was reported in S7 and S8 was blank, the score was set to 0 by deterministic rule.	Quantifies current symptom-related bother.
Retreatment after surgery	S9	1=no treatment, 2=medication, 3=additional procedure, 4=both. Nonstandard entries were normalized before analysis.	Postoperative management endpoint.
Baseline covariates	Age, follow-up interval, comorbidities, PSA, prostate volume, urinary retention, previous BPH surgery, enucleated tissue weight, operative time	Continuous or categorical variables abstracted from hospital and operative records; comorbidities coded as separate binary indicators.	Descriptive profiling and covariate exploration.

recommend HoLEP as S4=1-2. For S6, the same coding was used at postoperative week 1, month 1, month 3, month 6, month 12, and interview; lower values again indicated greater satisfaction, whereas "U" denoted a structurally inapplicable time point not yet reached. The multiple-response symptom item (S7) was decomposed into separate binary symptom indicators for analysis. No composite questionnaire score was calculated. The principal study domains and analytical roles are summarized in Table 1.

Data handling

Interview data were entered into Microsoft Excel and transferred to the analytical dataset for cleaning and analysis. Values coded as "X" or "x" were treated as missing. Responses outside allowable categories were recoded as missing. For S7, records in which "none" was selected together with one or more symptoms were considered logically inconsistent; in these cases, symptom-specific responses were retained and "none" was removed. When S7 indicated no current symptom and S8 was blank, S8 was assigned a value of 0 by deterministic rule. For the longitudinal satisfaction item (S6), struc-

Table 2. Baseline demographic and perioperative characteristics of the study cohort

Characteristic	Value
Demographic characteristics	
Patients included in the completed analytic dataset	209
Age, years	63.0 (59.0-70.0)
Postoperative follow-up interval at interview, months	10.0 (5.0-22.0)
Preoperative and perioperative variables	
Prostate-specific antigen, ng/mL	4.1 (1.7-7.0)
Prostate volume, mL	80.0 (61.0-110.0)
Enucleated tissue weight, g	49.3 (42.4-56.0)
Operative time, min	60.0 (46.0-90.0)
Comorbidities	
Hypertension	89 (42.6%)
Diabetes mellitus	47 (22.5%)
Coronary artery disease	23 (11.0%)
Cerebrovascular disease	4 (1.9%)
Other clinical history	
Preoperative urinary retention	71 (34.0%)
Previous benign prostatic hyperplasia surgery	1 (0.5%)

Data are presented as median (interquartile range) or number (%).

Table 3. Distribution of questionnaire responses for global outcomes, treatment preference, awareness source, retreatment, and educational attainment

Questionnaire item	Response option	n (%)
S1. Overall satisfaction with the outcome of HoLEP	Very satisfied	28 (13.4%)
	Satisfied	118 (56.5%)
	Neutral	45 (21.5%)
	Dissatisfied	14 (6.7%)
	Very dissatisfied	4 (1.9%)
S2. Overall change in voiding complaints after surgery	Completely resolved	31 (14.8%)
	Markedly improved	106 (50.7%)
	Slightly improved	47 (22.5%)
	No change	18 (8.6%)
	Worsened	7 (3.3%)
S3. Would choose the same operation again	Definitely yes	37 (17.7%)
	Yes	112 (53.6%)
	Unsure	42 (20.1%)
	No	16 (7.7%)
	Definitely no	2 (1.0%)
S4. Would recommend HoLEP to a relative with similar complaints	Definitely yes	39 (18.7%)
	Yes	104 (49.8%)
	Unsure	35 (16.7%)
	No	30 (14.4%)
	Definitely no	1 (0.5%)
S5. First source of information about HoLEP	Physician/healthcare professional	173 (82.8%)
	Family/friend recommendation	27 (12.9%)
	Internet/social media	6 (2.9%)
	Another patient's experience	3 (1.4%)
S9. Need for additional treatment after surgery	No	125 (59.8%)
	Yes - medication	84 (40.2%)
	Yes - additional procedure	0 (0.0%)
	Yes - both	0 (0.0%)
S10. Educational attainment	Illiterate	50 (23.9%)
	Literate without formal schooling	20 (9.6%)
	Primary school	73 (34.9%)
	Middle school	27 (12.9%)
	High school	22 (10.5%)
	University	15 (7.2%)
	Postgraduate education	2 (1.0%)

tural inapplicability was distinguished from ordinary missingness. If the telephone interview occurred before the third-, sixth-, or twelfth-month time point, the corresponding S6 response was coded as "U" and excluded from imputation and time point-specific denominators. Residual missing or invalid values in applicable structured variables were completed using multivariable k-nearest neighbor imputation. Primary descriptive endpoints were recalculated before and after imputation to confirm that missing-data completion did not materially alter the main findings.

Statistical analysis

Data were analyzed with IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as median and interquartile range (IQR), and categorical variables as number and

Table 4. Residual or recently prominent postoperative symptom profile and symptom-related bother

Variable	Value
No residual or recently prominent symptom	30 (14.4%)
Any residual or recently prominent symptom	179 (85.6%)
Urinary incontinence	163 (78.0%)
Dysuria	31 (14.8%)
Hematuria	12 (5.7%)
Retrograde ejaculation or sexual change	76 (36.4%)
Weak or intermittent stream	3 (1.4%)
Bother score (S8), full cohort	2.0 (1.0-4.0)
Bother score (S8), symptomatic subgroup	3.0 (2.0-4.0)

Data are presented as median (interquartile range) or number (%). Data are presented as number (%) or median (interquartile range). Multiple responses were permitted for symptom categories; therefore, percentages exceed 100%.

percentage. For the multiple-response symptom item, each symptom category was summarized using the full cohort as the denominator; therefore, percentages could exceed 100%.

The prespecified primary descriptive endpoints were favorable overall satisfaction, subjective improvement in voiding complaints, willingness to undergo HoLEP again, and willingness to recommend the procedure. Associations between ordinal satisfaction scores and binary grouping variables were assessed with the Mann-Whitney U test. Within-patient changes in longitudinal satisfaction were assessed with the Wilcoxon signed-rank test. Correlations between satisfaction scores and continuous variables were examined using Spearman's rank correlation coefficient. Associations between categorical variables were analyzed with the chi-square test or Fisher's exact test, as appropriate. All tests were two-sided, and $p<0.05$ was considered statistically significant. No adjustment for multiple comparisons was applied.

Ethics

This study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the Institutional Scientific Research Ethics Committee (January 27, 2026; decision no: 2026/010.99/24/17). Verbal informed consent was obtained from all participants before the telephone interview.

Results

Among 519 screened HoLEP procedures, 462 patients were contact-eligible and 209 completed the survey. Baseline demographic and perioperative characteristics are presented in Table 2.

Overall satisfaction was favorable in 146 patients (69.9%), including 28 (13.4%) who were very satisfied and 118 (56.5%) who were satisfied. Improvement in voiding complaints was reported by 184 patients (88.0%): 31 (14.8%) described complete resolution, 106 (50.7%) marked improvement, and 47 (22.5%) slight improvement. In addition, 149 patients (71.3%) stated that they would undergo the same operation again, and 143 (68.4%) would recommend HoLEP to a relative with similar complaints. HoLEP was first learned from a physician or other healthcare professional by 173 patients (82.8%). Detailed questionnaire distributions are shown in Table 3.

Thirty patients (14.4%) reported no residual or recently prominent symptom, whereas 179 (85.6%) reported at least one. Urinary incontinence was the most frequent complaint (163 patients, 78.0%), followed by retrograde ejaculation or sexual change (76, 36.4%), dysuria (31, 14.8%), hematuria (12, 5.7%), and weak or intermittent stream (3, 1.4%). Because multiple responses were permitted, percentages exceed 100%. The median bother score was 2.0 (IQR, 1.0-4.0) in the full cohort and 3.0 (IQR, 2.0-4.0) among symptomatic patients (Table 4).

Satisfaction became more favorable over time. Favorable satisfaction increased from 46 patients (22.0%) in the first postoperative week to 101 (48.3%) at 1 month, 124 (62.3%) at 3 months, 105 (62.1%) at 6 months, and 70 (60.3%) at

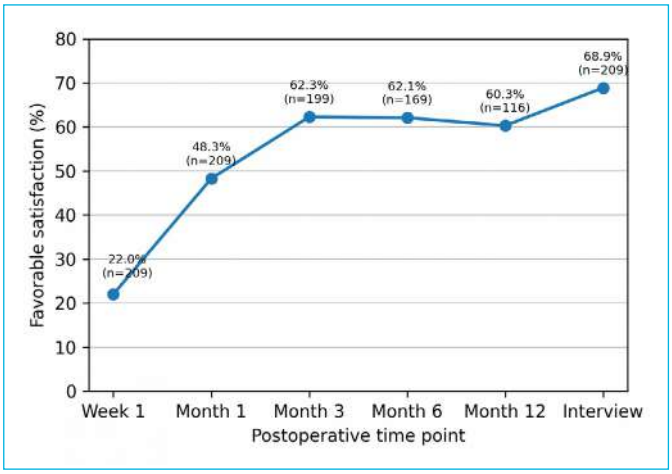

Figure 1. Temporal change in favorable satisfaction after HoLEP.
Values indicate the proportion of patients rating satisfaction as very satisfied or satisfied at each postoperative time point. The n values on the horizontal axis denote the valid number of observations at each time point.

Table 6. Comparative and correlational analyses related to overall satisfaction

Comparison	Statistical test	Summary	p value
Overall satisfaction score vs any residual symptom	Mann-Whitney U	Less favorable score distribution in symptomatic patients	<0.0001
Overall satisfaction score vs additional treatment requirement	Mann-Whitney U	No additional treatment median=2.0 vs medication-required median=3.0	<0.0001
First postoperative week vs interview satisfaction	Wilcoxon signed-rank	First week median=3.0 vs interview median=2.0	<0.0001
Age vs overall satisfaction score	Spearman correlation	rho=0.083	0.233
Follow-up interval vs overall satisfaction score	Spearman correlation	rho=0.269	<0.0001
Favorable overall satisfaction (S1 score 1-2) vs any residual symptom	Chi-square	96.7% vs 65.4% favorable satisfaction	0.0012

Lower scores indicate greater satisfaction for the overall satisfaction item.

12 months among patients who had reached those time points. At interview, 144 patients (68.9%) reported favorable satisfaction. The median satisfaction score improved from 3 in the first postoperative week to 2 from month 3 onward and remained 2 at interview (Table 5; Fig. 1).

Overall satisfaction was significantly associated with residual symptoms and additional treatment. Favorable satisfaction was more common in symptom-free than symptomatic patients (96.7% vs 65.4%; chi-square p=0.0012). Satisfaction scores were less favorable in patients reporting any residual symptom (Mann-Whitney U, p<0.0001) and in those requiring additional medication (median score, 3.0 vs 2.0; Mann-Whitney U, p<0.0001). In paired analysis, satisfaction at interview was significantly better than during the first postoperative week (Wilcoxon signed-rank, p<0.0001). Age was not significantly correlated with overall satisfaction (Spearman rho=0.083, p=0.233), whereas longer follow-up showed a weak but significant association with better satisfaction (Spearman rho=0.269, p<0.0001) (Table 6).

Discussion

In this real-world telephone survey, most patients reported favorable postoperative appraisal after HoLEP, substantial improvement in voiding complaints, and willingness to undergo the same operation again or recommend it to others. However, satisfaction was not static. It improved after the early postoperative period and was less favorable in patients with residual symptoms or additional medication requirements. This overall pattern is consistent with prior HoLEP studies that linked dissatisfaction to incontinence and showed that patient appraisal evolves during follow-up.[2-5]

The temporal pattern of recovery is one of the most clinically relevant findings of the study. Favorable satisfaction increased from 22.0% in the first postoperative week to 68.9% at interview (Fig. 1), and the median satisfaction score improved from 3 to 2 over the same interval (Table 5). This pattern suggests that early postoperative perception may underestimate the eventual patient appraisal of HoLEP. The early postoperative period is likely influenced by transient leakage, dysuria, urgency, irritative symptoms, and adjustment to altered voiding function, whereas later assessments better reflect sustained relief of obstruction. This interpretation is consistent with prior serial HoLEP data.[3]

Residual symptoms appeared to be central to postoperative dissatisfaction. Incontinence was the most frequently reported current or recently prominent complaint and was strongly associated with less favorable satisfaction. This observation is aligned with the study by Lee et al.,[2] in which postoperative urinary incontinence was a leading driver of dissatisfaction. At the same time, the median bother score remained low in the overall cohort, suggesting that symptom prevalence and symptom burden should not be considered interchangeable. Because our questionnaire used a broad patient-reported symptom domain rather than a strict pad-based continence definition, the observed prevalence should be interpreted cautiously.

Additional postoperative medication was also associated with less favorable satisfaction. This finding does not necessarily indicate surgical failure, but it may reduce the perceived completeness of symptom relief and therefore influence whether patients would recommend the procedure to others. The sexual and ejaculatory domain should also be considered when interpreting global satisfaction. More than one-third of respondents reported retrograde ejaculation or sexual change. Previous studies suggest that although HoLEP does not usually worsen overall erectile function, ejaculatory changes may still influence orgasmic experience and postoperative bother in selected patients.[6-8] Therefore, the patient experience after HoLEP should be interpreted as a balance between urinary benefit and treatment-related trade-offs rather than as a purely voiding outcome.

The finding that most patients first learned about HoLEP from a physician or other healthcare professional also has practical relevance. It suggests that counseling quality may substantially shape expectations before surgery. This interpretation is consistent with previous work showing that information-seeking behavior and the quality of preoperative information are associated with later satisfaction and decision appraisal.[9]

The present study has several strengths. It evaluates clinically meaningful patient-reported domains that are not fully captured by surgeon-reported perioperative measures, and it examines satisfaction as a trajectory across multiple postoperative time points rather than as a single static endpoint. It also provides pragmatic real-world data from a broad postoperative cohort. However, the retrospective telephone-based design introduces the possibility of recall bias, especially for time-specific satisfaction ratings. The response rate raises the possibility of nonresponse bias. In addition, the questionnaire was developed for this study and was not a validated patient-reported outcome instrument, which limits direct comparison with studies using standardized measures. Finally, some variables required prespecified cleaning and imputation; although primary descriptive endpoints were stable before and after imputation, residual measurement error cannot be excluded. These issues support recent calls for broader and more standardized reporting of patient-reported outcomes in HoLEP research.[10]

Finally, the clinical value of telephone-based follow-up may extend beyond the assessment of satisfaction and patient-reported symptom improvement. Glienke et al.[11] recently evaluated long-term urethral and bladder neck strictures after HoLEP in a large patient series and incorporated telephone follow-up into postoperative outcome ascertainment. Their findings highlight that persistent or recurrent voiding complaints after HoLEP may occasionally reflect late anatomical obstruction and that structured telephone contact may help identify patients who require further clinical evaluation. In the present cohort, weak or intermittent urinary stream was uncommon, and no patient reported undergoing an additional postoperative procedure. Nevertheless, because objective uroflowmetry, postvoid residual measurement, and cystoscopic assessment were not included in the present survey protocol, clinically silent or unrecognized infravesical obstruction could not be excluded. Telephone follow-up should therefore be regarded as a pragmatic screening and patient-reported outcome tool rather than a substitute for objective urological evaluation in patients with persistent or recurrent symptoms.

Conclusion

HoLEP was associated with substantial patient-reported improvement in voiding symptoms and generally favorable postoperative appraisal in this real-world cohort. Satisfaction improved over time and was closely related to residual symptoms and additional treatment requirements. These findings support careful perioperative counseling and more standardized longitudinal assessment of patient-reported outcomes after HoLEP.

Ethics Committee Approval: Ethics approval was obtained from the Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethics Committee (Date: 27/01/2026, No: 2026/010.99/24/17).
Peer-review: Externally peer-reviewed.
Informed Consent: Verbal informed consent was obtained from all participants before the telephone interview.
Author Contribution: Concept: Y.K., T.B.A., B.E.; Design: Y.K., T.B.A., B.E.; Supervision: Y.K., T.B.A., B.E.; Data collection &/or processing: Y.K., A.T., A.S., A.G.; Analysis and/or interpretation: Y.K., A.T., A.S., A.G.; Literature search: Y.K., A.T., A.S., A.G.; Writing: Y.K.; Critical review: Y.K., T.B.A., B.E.
Conflict of Interest: No conflict of interest was declared by the authors.
Funding: The authors declared that this study has received no financial support.

References

1. Large T, Krambeck AE. Evidence-based outcomes of holmium laser enucleation of the prostate. Curr Opin Urol 2018;28:301–8. [CrossRef]

2. Lee YJ, Oh SA, Kim SH, Oh SJ. Patient satisfaction after holmium laser enucleation of the prostate (HoLEP): A prospective cohort study. PLoS One 2017;12:e0182230. [CrossRef]
3. Cho MC, Kim JK, Ha SB, Ku JH, Paick JS. Self-assessed goal achievement (SAGA) after holmium laser enucleation of the prostate (HoLEP): Association with patients' postoperative satisfaction. PLoS One 2018;13:e0203825. [CrossRef]
4. Kanne M, Beutel H, Krediet J, Kossler R, Kittner B, Schmuck N, et al. Quality of life and outcome after holmium laser enucleation of the prostate (HoLEP). Aktuelle Urol 2023;54:24–9. [CrossRef]
5. Schumacher S, Marghawal D, Brunken C, Herzberg J. Patient reported outcome and quality of life measured by a simple questionnaire in patients with symptomatic benign prostate hyperplasia treated by holmium laser enucleation of the prostate (HoLEP). Front Surg 2024;11:1358701. [CrossRef]
6. Kim SH, Yang HK, Lee HE, Paick JS, Oh SJ. HoLEP does not affect the overall sexual function of BPH patients: A prospective study. Asian J Androl 2014;16:873–7. [CrossRef]
7. Kim JK, Cho MC, Son H, Ku JH, Oh SJ, Paick JS. Patient perception of ejaculatory volume reduction after holmium laser enucleation of the prostate (HoLEP). Urology 2017;99:142–7. [CrossRef]
8. Gild P, Dahlem R, Pompe RS, Soave A, Vetterlein MW, Ludwig TA, et al. Retrograde ejaculation after holmium laser enucleation of the prostate (HoLEP): Impact on sexual function and evaluation of patient bother using validated questionnaires. Andrology 2020;8:1779–86. [CrossRef]
9. Abdul-Muhsin H, Tyson M, Raghu S, Humphreys M. The informed patient: An analysis of information seeking behavior and surgical outcomes among men with benign prostatic hyperplasia. Am J Mens Health 2017;11:147–53. [CrossRef]
10. Hines L, Mali K, Campbell T, Jain R, Quarrier SO. Advancing holmium laser enucleation of the prostate outcomes reporting: an assessment of patient-reported outcomes in the literature. Urology 2024;187:147–53. [CrossRef]
11. Glienke M, Sigle A, Himmelsbach R, von Bargen MF, Schoenthaler M, Özkan A, et al. Holmium laser enucleation of the prostate and strictures: long-term outcomes, stricture characteristics, and risk factors. World J Urol 2025;43:419. [CrossRef]

ORIGINAL INVESTIGATION

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.84565

Retrospective Analysis of Candida Auris Colonization and Infections in The Intensive Care Unit

Sultan Şıvğın Til, Betül Yıldız, Görkem Tükenmez, Elif Bombacı

Abstract

Objective: Candida auris (*C. auris*) is an emerging multidrug-resistant yeast associated with healthcare-associated outbreaks, particularly in intensive care units (ICUs), and is linked to high mortality. This study aimed to evaluate the incidence of *C. auris* colonization and infection, clinical outcomes, and risk factors in ICU patients at a tertiary hospital in Türkiye.

Methods: This retrospective single-center study was conducted at Kartal Dr. Lütfi Kırdar City Hospital (Istanbul, Türkiye) between March 1 and August 31, 2025. Weekly surveillance screening was performed using combined axilla and groin swabs. Clinical specimens were collected in suspected infections. Identification was performed by MALDI-TOF MS. Demographic and clinical variables were analyzed, and logistic regression was used to identify predictors of 30-day mortality.

Results: A total of 38 ICU patients with *C. auris* detection were included. The mean age was 68.8±15.4 years, and 55.3% were male. Colonization was detected in 60.5% of patients, while 39.5% had infection. The overall incidence of *C. auris* was 1.6%. Bloodstream infection was the most common infection type (31.6%). The overall 30-day mortality rate was 55.3%. Azole resistance was observed in 80.0% of isolates, amphotericin B resistance in 73.3%, and echinocandin resistance in 13.3%. In multivariable analysis, mechanical ventilation was independently associated with 30-day mortality (OR=19.27,95% CI:1.02–363.48; p=0.04).

Conclusions: *C. auris* infections have become a serious threat in ICUs in recent years. The mortality rate is quite high in this study. Advanced age, high comorbidity scores, mechanical ventilation, central venous catheterization, and broad-spectrum antibiotic use were highlighted as risk factors for *C. auris*. From a cost-effectiveness perspective, early diagnosis of high-risk patients and targeted preventive strategies may be more appropriate than routine weekly *C. auris* screening. Early detection of *C. auris*, implementation of contact isolation, strengthening of environmental disinfection, and review of antifungal treatment strategies are critical in controlling this infection.

Keywords: Candida auris; candida auris incidence; candida auris colonization.

Department of Anesthesiology and Reanimation, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye

Address for correspondence:
Sultan Şıvğın Til,
Department of Anesthesiology And Reanimation, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye
E-mail:
su.svgn@hotmail.com

Received: 24.02.2026
Accepted: 06.05.2026
Published: 29.09.2026

Introduction

Candida auris (*C. auris*) is a recently emerged multidrug-resistant yeast, first isolated in 2009 from the external auditory canal of a patient in Japan.[1] It is capable of colonizing multiple anatomical sites, including the skin, axillae, nares,

How to cite this article: *Şıvğın Til S, Yıldız B, Tükenmez T, Bombacı E. Retrospectıve analysis of candida auris colonization and infections in the intensive care unit. South. Clin. Ist. Euras. 2026;37(3):257-264.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Copyright@Author(s)

and groin, and is primarily transmitted through direct contact. Importantly, *C. auris* can persist on inanimate surfaces for more than seven days, facilitating nosocomial transmission and prolonged environmental contamination.[2]

The growing global burden of *C. auris* has drawn considerable attention, largely due to challenges in accurate microbiological identification and its wide spectrum of clinical manifestations. Among these, bloodstream infections represent the most severe form, with mortality rates reported to reach up to 40%.[3,4] A major challenge in the management of *C. auris* infections is its unfavorable antifungal susceptibility profile. Approximately 90% of isolates are resistant to fluconazole, 35% to amphotericin B, and over 40% exhibit resistance to two or more antifungal classes.[5,6] This multidrug resistance significantly complicates the treatment of invasive infections, particularly candidemia, and contributes to high mortality rates.[6] Overall mortality associated with *C. auris* ranges from 30% to 60%, especially among critically ill patients.[7,8]

Accordingly, the Centers for Disease Control and Prevention (CDC) has classified *C. auris* among critical priority pathogens, underscoring the urgent need for effective infection prevention strategies and antifungal stewardship programs.[9] Recent outbreaks worldwide have further highlighted its substantial potential for healthcare-associated transmission. However, most available epidemiological data derive from outbreak investigations or passive surveillance systems, with incidence rates varying widely, ranging from 5–10% to as high as 40%.[10,11]

According to a 2024 report by the European Centre for Disease Prevention and Control (ECDC), the first case of *C. auris* in Türkiye was reported in 2020. Since then, the number of cases has increased rapidly, with a total of 114 cases reported between 2013 and 2023.[12]

A comprehensive understanding of the epidemiological characteristics and risk factors associated with *C. auris* is essential to inform targeted preventive strategies. Therefore, this study was designed to determine the incidence of *C. auris* colonization and infection in the intensive care units (ICUs) of our hospital, evaluate clinical outcomes, and identify associated risk factors.

Materials and Methods

Study Design and Setting

This retrospective, single-center study was conducted at a tertiary care teaching hospital in Istanbul, Türkiye. The study period spanned from March 1, 2025, to August 31, 2025 and conducted according to Declaration of Helsinki. Ethical approval was obtained from the Institutional Scientific Research Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (Date: 29/09/2025, No: 2025/010.99/20/16).

Patient data were retrieved from the hospital's electronic medical records system.

Infection Control Protocol and Screening Strategy

Following an increase in *C. auris* cases in our institution, an infection prevention and control protocol was implemented. This protocol included weekly surveillance screening using swab specimens and strict contact isolation precautions.

In accordance with this protocol, ICU patients underwent weekly screening for skin colonization using combined axilla and groin swabs. For patients with clinical signs or symptoms of infection, culture specimens were obtained from blood, urine, wounds, and tracheal aspirates.

Patient Population

The hospital has a total of 121 ICU beds, including 95 tertiary-level and 26 secondary-level beds. All ICU patients with *C. auris* detected either as a pathogen in clinical specimens (blood, urine, wound, or tracheal aspirate cultures) or as colonization in screening swab samples were included.

Repeated isolates from the same patient were excluded, and only the first isolate was included in the analysis.

Definitions

Colonization was defined as the isolation of *C. auris* from combined axilla and groin screening swabs in the absence of clinical signs or symptoms of infection.

Infection was defined as the isolation of *C. auris* from urine, wound, or tracheal aspirate cultures and/or from at least one blood culture.

Microbiological Identification and Antifungal Susceptibility Testing

For colonization screening, combined swab samples were collected from the axillary and inguinal regions using a single swab. Sampling was performed sequentially, first from the axilla and then from the groin, and swabs were transported in Stuart transport medium.

Samples were inoculated onto chromogenic Candida agar (bioMérieux, France). Yeast colonies were identi-

fied to the species level using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS; bioMérieux, France). Plates were evaluated at 48 and 72 hours of incubation, and newly grown colonies were processed similarly.

Data Collection

The following variables were collected: Age, sex, comorbidities, history of nursing home residence, hospitalization within the previous 6 months, abdominal surgery within the last 30 days, prior antibiotic and antifungal use, steroid and immunosuppressive therapy, neutropenia prior to *C. auris* detection, co-isolation of other microorganisms, mechanical ventilation, central venous catheter use, total parenteral nutrition, continuous renal replacement therapy, colonization or infection status, site of infection, antifungal susceptibility profiles, antifungal treatments, ICU length of stay, total hospital length of stay, and 30-day mortality following *C. auris* detection.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Shapiro–Wilk test and graphical methods (histograms and Q–Q plots).

Normally distributed variables were expressed as mean ± standard deviation (SD), while non-normally distributed variables were reported as median and interquartile range (IQR). Categorical variables were presented as frequencies and percentages.

For group comparisons, Student's t-test or the Mann–Whitney U test was used for continuous variables, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test.

To identify independent predictors of 30-day mortality, logistic regression analysis was performed. Variables with $p<0.20$ in univariate analysis, along with clinically relevant factors, were included in the multivariable model. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). A two-sided p-value <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

A total of 38 patients were included in the analysis. The mean age was 68.8±15.4 years, and 55.3% were male. The most frequently observed comorbidities were diabetes mellitus (28.9%), solid malignancy (39.5%), and myocardial infarction (15.8%). The median Charlson Comorbidity Index (CCI) score was 5.5 (IQR: 3.0) (Table 1).

Treatment Characteristics and Clinical Course

Most patients (97.4%) received β-lactam antibiotics prior to *C. auris* detection. Azole exposure was present in 21.1%, steroid use in 44.7%, and echinocandin exposure in 7.9% of patients. Mechanical ventilation was required in 86.8% of patients, central venous catheter use was observed in 78.9%, and total parenteral nutrition was administered in 42.1%.

A total of 2360 patients were admitted to all intensive care units during the study period. The overall incidence of *C. auris* was 1.6%. When colonized and infected patients were evaluated separately, the incidence of colonization with *C. auris* was found to be 0.97%, and the incidence of *C. auris* infection was 0.63%. Infection developed in 17% (n=4) of the 23 colonized patients.

The median ICU length of stay was 25.5 days (IQR: 20), while the median total hospital length of stay was 36.5 days (IQR: 36). The overall 30-day mortality rate was 55.3%. The 30-day mortality rate was found to be 43% for colonized patients and 73% for infected patients. At the end of the study period, 26.3% of patients remained hospitalized in the ICU (Table 2).

Table 1. Demographic and clinical characteristics of the study population

Variables	Data (n=38)
Age, years, mean ± SD	68.8±15.4
Sex, n (%)	
Male	21 (55.3)
Female	17 (44.7)
DM, n (%)	11 (28.9)
COPD, n (%)	4 (10.5)
CKD, n (%)	4 (10.5)
MI, n (%)	6 (15.8)
Solid malignancy, n (%)	15 (39.5)
Hematological malignancy, n (%)	2 (5.3)
Nursing home residence, n (%)	4 (10.5)
Hospitalization within the last 6 months, n (%)	27 (71.1)
Abdominal surgery within the last 30 days, n (%)	6 (15.8)
CCI, median (IQR)	5.5 (3.0)

SD: Standard deviation; IQR: Interquartile range; DM: Diabetes Mellitus; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; MI: Myocardial infarction; CCI:Charlson Comorbidity Index.

Table 2. Medications and ICU-related clinical characteristics prior to detection of *C.auris*

Variables	Data (n=38)
β-lactam antibiotics, n (%)	37 (97.4)
Quinolones, n (%)	2 (5.3)
Polymyxins, n (%)	5 (13.2)
Azoles, n (%)	8 (21.1)
Amphotericin B, n (%)	1 (2.6)
Echinocandins, n (%)	3 (7.9)
Steroid use, n (%)	17 (44.7)
Immunosuppressive therapy, n (%)	3 (7.9)
Neutropenia, n (%)	2 (5.3)
MV, n (%)	33 (86.8)
CRRT, n (%)	3 (7.9)
CVC, n (%)	30 (78.9)
PN, n (%)	16 (42.1)
ICU length of stay, days, median (IQR)	25.5 (20)
Total hospital length of stay, days, median (IQR)	36.5 (36.0)
Overall incidence of C. auris n (%)	38 (1.6)
The incidence of C. auris colonization n (%)	23 (0.97)
The incidence of C. auris infection	15 (0.63)
30-day mortality, n (%)	21 (55.3)
30-day mortality of C. auris colonization	10 (43)
30-day mortality of C. auris infection	11 (73)
Patient status at study end, n (%)	
Discharged	7 (18.4)
Ex	21 (55.3)
Still hospitalized in ICU	10 (26.3)

MV: Mechanical ventilation; CRRT: Continuous renal replacement therapy; CVC: Central venous catheter; PN: Parenteral nutrition; ICU: Intensive care unit; IQR: Interquartile range; Ex: Exitus.

Table 3. Microbiological findings and antifungal susceptibility results

Variables	Data (n=38)
Microorganisms other than C.auris, n (%)	24 (63.2)
C. auris status, n (%)	
Colonization	23 (60.5)
Infection	15 (39.5)
Site of isolation, n (%)	
Colonization screening swab	23 (60.5)
Urine culture	3 (7.9)
Blood culture	12 (31.6)
Antifungal treatment, n (%)	12 (31.6)
Caspofungin	11 (91.7)
Fluconazole	1 (8.3)
Duration of antifungal therapy, days, mean ± SD	16.0±11.6
Azole resistance, n (%)*	12 (80.0)
Amphotericin B resistance, n (%)*	11 (73.3)
Echinocandin resistance, n (%)*	2 (13.3)

*Resistance analysis was performed among patients enfected with *C. auris*. SD: Standard deviation.

Microbiological Findings

Growth of microorganisms other than *C. auris* was detected in 63.2% of patients. Among all cases, 60.5% were classified as colonization and 39.5% as infection. Among infected patients, the most frequent site of isolation was blood culture (31.6%).

Among patients who received antifungal treatment, 91.7% were treated with caspofungin and 8.3% with fluconazole. The mean duration of antifungal therapy was 16.0±11.6 days. Resistance rates were highest against azoles (80.0%), followed by amphotericin B (73.3%). Echinocandin resistance was detected in two patients (13.3%) (Table 3).

Factors Associated With 30-Day Mortality

When patients with and without 30-day mortality were compared, the mortality group had a higher mean age (72.8±14.0 years vs. 63.8±16.0 years; p=0.07). The median CCI score was significantly higher among patients who died [6 (IQR: 3) vs. 4 (IQR: 5); p=0.02] (Table 4).

Regarding clinical variables, hospitalization within the previous 6 months (81.0% vs. 58.8%; p=0.135) and mechanical ventilation use (95.2% vs. 76.5%; p=0.152) were more frequent in the mortality group, although these differences did not reach statistical significance. Similarly, *C. auris* infection was more common among patients who died (47.6% vs. 29.4%; p=0.254), but the difference was not statistically significant.

In microbiological evaluation, blood culture positivity was higher in the mortality group (33.3% vs. 23.5%; p=0.213); however, no significant association was found between mortality and infection type or site. Antifungal treatment initiation was more frequent in the mortality group (38.1% vs. 23.5%; p=0.337), likely reflecting increased disease severity. Antifungal resistance rates were similarly high in both groups (azole resistance 80%, amphotericin B resistance 70–80%, echinocandin resistance 10–20) and did not significantly differ between groups (p>0.05) (Table 4).

Logistic Regression Analysis

In multivariable logistic regression analysis, mechanical ventilation was independently associated with 30-day mortality (OR=19.27, 95% CI: 1.02–363.48, p=0.04). Other

Table 4. Comparison of patients with and without 30-day mortality

Variables	Survivors (n=17)	Non-survivors (n=21)	p-value
Age, years, mean ± SD	63.8±16.0	72.8±14.0	0.07
Sex, n (%)			0.796
Male	9 (52.9)	12 (57.1)	
Female	8 (47.1)	9 (42.9)	
Nursing home residence, n (%)	2 (11.8)	2 (9.5)	1.000
Hospitalization within the last 6 months, n (%)	10 (58.8)	17 (81.0)	0.135
Abdominal surgery within the last 30 days, n (%)	2 (11.8)	4 (19.0)	0.540
CCI, median (IQR)	4 (5)	6 (3)	0.02
Immunosuppressive therapy, n (%)	1 (5.9)	2 (9.5)	1.000
Neutropenia, n (%)	1 (5.9)	1 (4.8)	1.000
MV, n (%)	13 (76.5)	20 (95.2)	0.152
CRRT, n (%)	1 (5.9)	2 (9.5)	1.000
Growth of microorganisms other than C. auris, n (%)	12 (70.6)	12 (57.1)	0.393
C. auris status, n (%)			0.254
Colonization	12 (70.6)	11 (52.4)	
Infection	5 (29.4)	10 (47.6)	
Site of isolation, n (%)			0.213
Colonization screening swab	12 (70.6)	11 (52.4)	
Urine culture	0 (0)	3 (14.3)	
Blood culture	4 (23.5)	7 (33.3)	
Catheter culture	1 (5.9)	0 (0)	
Antifungal treatment administered, n (%)	4 (23.5)	8 (38.1)	0.337
Azole resistance, n (%)*	4 (80.0)	8 (80.0)	1.000
Amphotericin B resistance, n (%)*	4 (80.0)	7 (70.0)	1.000
Echinocandin resistance, n (%)*	1 (20.0)	1 (10.0)	1.000

*Resistance analysis was performed among patients with *C. auris* infection. SD: Standard deviation; CCI: Charlson Comorbidity Index; IQR: Interquartile range; MV: Mechanical ventilation; CRRT: Continuous renal replacement therapy.

Table 5. Multivariable logistic regression analysis for predictors of 30-day mortality

Variables	OR	95% CI	p-value
Age (per 1-year increase)	1.036	0.980–1.094	0.211
Hospitalization within the last 6 months	3.849	0.540–27.440	0.179
CCI (per 1-point increase)	1.210	0.886–1.653	0.231
MV	19.267	1.021–363.482	0.04
C. auris colonization (vs infection)	0.327	0.050–2.145	0.244

OR: Odds ratio; CI: Confidence interval; CCI: Charlson comorbidity index; MV: Mechanical ventilation.

variables, including age, CCI score, hospitalization history, and *C. auris* status, were not independently associated with mortality (Table 5).

Discussion

In this retrospective study, we evaluated the clinical characteristics and outcomes of ICU patients with *C. auris* colonization and/or infection in a single tertiary care center in Istanbul, Türkiye. Consistent with global trends, an increasing number of *C. auris* cases has been observed in our institution. In response, routine surveillance screening was implemented to facilitate early detection of colonized patients and timely initiation of

infection control measures. In the present analysis, patients identified through active surveillance (colonized) and those diagnosed through clinical cultures (infected) were evaluated together.

Among the 38 patients included, 60.5% were colonized and 39.5% were infected. Candidemia was the most common type of infection, followed by urinary tract infections. Compared with previous reports, the spectrum of infection types observed in our cohort was relatively narrow,[13,14] which may be related to the limited duration of the retrospective study period.

Mortality rates associated with *C. auris* candidemia have been reported to range from 30% to 70%,[5,14–16] with most studies focusing on in-hospital mortality. In our cohort, the overall 30-day mortality rate among both colonized and infected patients was 55.3%, exceeding rates reported in studies from Italy and Spain (27% and 23.4%, respectively).[17,18] When colonized and infected patients were evaluated separately, the incidence of colonization with *C. auris* was found to be 0.97%, and the incidence of *C. auris* infection was 0.63% in our study.

The mean age of the cohort was 68.8 years, and 55.3% were male. Although not statistically significant, patients who died were older, in line with previous studies identifying advanced age and male sex as common risk factors.[17,19] The most frequent comorbidities in our cohort were diabetes mellitus, solid malignancy, and prior myocardial infarction. Diabetes mellitus has consistently been reported as a major risk factor,[14,19] whereas a recent systematic meta-analysis identified hypertension as the most prevalent comorbidity.[20]

A previous study evaluating predictors of candidemia among *C. auris*-colonized patients identified central venous catheterization, arterial catheterization, total parenteral nutrition, diabetes mellitus, chronic kidney disease, continuous renal replacement therapy, and mechanical ventilation as independent risk factors.[21] Although subgroup analyses were limited by the small sample size in our study, most patients had a history of prior hospitalization, mechanical ventilation, central venous catheterization, and total parenteral nutrition. While prior hospitalization and mechanical ventilation were more frequent among non-survivors, these differences did not reach statistical significance. However, in multivariable regression analysis, mechanical ventilation emerged as an independent predictor of mortality.

In our cohort, 63.2% of patients had concomitant growth of microorganisms other than *C. auris*, and 97.4% had received β-lactam antibiotics. These findings support the role of broad-spectrum antibiotic exposure as a key risk factor for *C. auris* colonization and infection, consistent with previous studies.[17]

The high prevalence of antifungal resistance among *C. auris* isolates remains a major clinical concern. In our study, resistance was most commonly observed to fluconazole (80.0%), followed by amphotericin B (73.3%), while echinocandin resistance was detected in 13.3% of isolates. Similarly, a large retrospective meta-analysis (2009–2020) reported resistance rates of 79.6% for fluconazole, 34.8% for amphotericin B, and 23.3% for voriconazole among 544 isolates.[19] Several studies have reported fluconazole resistance rates approaching 100%, suggesting that it should not be used empirically.[13,17] Although earlier reports indicated no resistance to echinocandins,[13,14] emerging resistance has increasingly been documented, including in our cohort.[17,22] Moreover, multidrug-resistant *C. auris* strains are being reported with increasing frequency.[19,22] Current guidelines recommend echinocandins as first-line therapy;[23] however, rising resistance to this class may further compromise clinical outcomes. Therefore, the development of novel antifungal agents effective against resistant strains remains a critical need.[19]

Both the CDC and ECDC have issued comprehensive recommendations for the management of *C. auris* cases and outbreaks.[24] Additionally, the World Health Organization (WHO) launched the Global Antimicrobial Resistance Surveillance System (GLASS) in 2016.[25] Given that outbreaks may follow exponential increases in case numbers,[22] strict infection prevention and control measures are essential. Contact precautions, active surveillance screening, and cohorting of colonized patients play a central role in preventing transmission. Hand hygiene remains the most effective intervention. Furthermore, appropriate disinfection of medical equipment and early removal of unnecessary invasive devices, such as central venous catheters, are key components of prevention strategies.

In line with these principles, weekly surveillance screening was implemented for all ICU patients in our institution due to the rising incidence of *C. auris*. In addition, targeted environmental cleaning protocols were established. Despite the availability of single-patient ICU

rooms and adherence to appropriate treatment strategies, mortality remained high, underscoring the importance of prioritizing prevention.

However, the incidence of *C. auris* we found in our study was 1.6%. From a cost-effectiveness perspective, screening patients with risk factors may be more appropriate than weekly routine screenings.

The findings of this study highlight key risk factors associated with *C. auris* colonization and infection and support the implementation of targeted screening strategies in high-risk ICU populations. Future prospective, multicenter studies are needed to better elucidate transmission dynamics, host–pathogen interactions, and the impact of early antifungal therapy on clinical outcomes.

The main limitations of this study include its retrospective design and relatively small sample size, which may have limited the statistical power of some analyses.

Conclusion

In conclusion, *C. auris* represents a significant clinical challenge due to its multidrug-resistant profile and its association with high mortality, particularly among critically ill patients. In our cohort, a high mortality rate and frequent exposure to known risk factors, such as mechanical ventilation and broad-spectrum antibiotic use, underscore the clinical impact of this pathogen in ICU settings.

Infection prevention and control measures remain the most effective strategies to limit the spread of *C. auris*. Strict adherence to hand hygiene, contact precautions, active surveillance for early identification of colonized patients, and cohorting strategies are essential components of outbreak prevention. Instead of routine screening for *C. auris*, from a cost-effectiveness perspective, early identification of high-risk patients and implementation of targeted preventive strategies are critical to improving clinical outcomes.

Ethics Committee Approval: Ethical approval was obtained from the Institutional Scientific Research Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (Date: 29/09/2025, No: 2025/010.99/20/16).
Peer-review: Externally peer-reviewed.
Informed Consent: Not applicable.
Author Contribution: Concept: S.S.T., E.B., B.Y.U.; Design: S.S.T., E.B., B.Y.U.; Supervision: S.S.T., B.Y.U.; Fundings: S.S.T., G.T.; Materials: S.S.T., G.T.; Data collection &/or processing: S.S.T., G.T.; Analysis and/or interpretation: S.S.T., E.B., B.Y.U.; Literature search: S.S.T., G.T.; Writing: S.S.T., E.B.; Critical review: S.S.T., E.B.
Conflict of Interest: The authors declare no conflict of interest.

References

1. Satoh K, Makimura K, Hasumi Y, Nishiyama Y, Uchida K, Yamaguchi H. Candida auris sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital. Microbiol Immunol 2009;53:41–4. [CrossRef]
2. Biswal M, Rudramurthy SM, Jain N, Shamanth AS, Sharma D, Jain K, et al. Controlling a possible outbreak of Candida auris infection: Lessons learnt from multiple interventions. J Hosp Infect 2017;97:363–70. [CrossRef]
3. Abastabar M, Haghani I, Ahangarkani F, Sadegh Rezai M, Taghizadeh Armaki M, Roodgari S, et al. Candida auris otomycosis in Iran and review of recent literature. Mycoses 2019;62:101–5. [CrossRef]
4. Mirhendi H, Charsizadeh A, Aboutalebian S, Mohammadpour M, Nikmanesh B, Groot T, et al. South Asian (Clade I) Candida auris meningitis in a paediatric patient in Iran with a review of the literature. Mycoses 2022;65:134–9. [CrossRef]
5. Lockhart SR, Etienne KA, Vallabhaneni S, Farooqi J, Chowdhary A, Govender NP, et al. Simultaneous emergence of multidrug-resistant Candida auris on 3 continents confirmed by whole genome sequencing and epidemiological analyses. Clin Infect Dis 2017;64:134–40. [CrossRef]
6. Eyre DW, Sheppard AE, Madder H, Moir I, Moroney R, Quan TP, et al. A Candida auris outbreak and its control in an intensive care setting. N Engl J Med 2018;379:1322–31. [CrossRef]
7. Alagha R, Sharaf A, Abdulkhaleq H, Acunin R, Saeed N. Mortality and associated risk factors in patients with Candida auris: Insights from a tertiary care hospital in Bahrain. Cureus 2024;16. [CrossRef]
8. Alvarez-Moreno CA, Morales-López S, Rodriguez GJ, Rodriguez JY, Robert E, Picot C, et al. The mortality attributable to candidemia in *C. auris* is higher than that in other Candida species: Myth or reality? J Fungi 2023;9:430. [CrossRef]
9. Unni Kumaran S, Rajagopal L, Gunasekaran M. Sensitivity assessment of optimal control strategies and cost-effectiveness analysis of a novel Candida auris environmental transmission model in intensive care facilities. J Theor Biol 2024;595:111931. [CrossRef]
10. Shastri PS, Shankarnarayan SA, Oberoi J, Rudramurthy SM, Wattal C, Chakrabarti A. Candida auris candidaemia in an intensive care unit – Prospective observational study to evaluate epidemiology, risk factors, and outcome. J Crit Care 2020;57:42–8. [CrossRef]
11. Ferrer Gómez C, Solís Albamonte P, Delgado Navarro C, Salvador García C, Tormo Palop N, Andrés Ibáñez JA. Analysis of Candida auris candidemia cases in an intensive care unit of a tertiary hospital. Rev Esp Anestesiol Reanim 2021;68:431–6. [CrossRef]
12. European Centre for Disease Prevention and Control. Survey on the epidemiological situation, laboratory capacity and preparedness for Candidozyma (Candida) auris, 2024. Stockholm: ECDC; 2025.
13. Sayeed MA, Farooqi J, Jabeen K, Awan S, Mahmood SF. Clinical spectrum and factors impacting outcome of Candida auris: A single center study from Pakistan. BMC Infect Dis 2019;19:384.

[CrossRef]

14. Kaki R. Risk factors and mortality of the newly emerging Candida auris in a university hospital in Saudi Arabia. Mycology 2023;14:256–63. [CrossRef]
15. Cortegiani A, Misseri G, Fasciana T, Giammanco A, Giarratano A, Chowdhary A. Epidemiology, clinical characteristics, resistance, and treatment of infections by Candida auris. J Intensive Care 2018;6:69. [CrossRef]
16. Chakrabarti A, Sood P, Rudramurthy SM, Chen S, Kaur H, Capoor M, et al. Incidence, characteristics and outcome of ICU-acquired candidemia in India. Intensive Care Med 2015;41:285–95. [CrossRef]
17. Briano F, Magnasco L, Sepulcri C, Dettori S, Dentone C, Mikulska M, et al. Candida auris candidemia in critically ill, colonized patients: Cumulative incidence and risk factors. Infect Dis Ther 2022;11:1149–60. [CrossRef]
18. Mulet Bayona JV, Tormo Palop N, Salvador García C, Rodríguez PH, López de Medrano VA, Gómez CF, et al. Characteristics and management of candidaemia episodes in an established Candida auris outbreak. Antibiotics 2020;9:558. [CrossRef]
19. Hu S, Zhu F, Jiang W, Wang Y, Quan Y, Zhang G, et al. Retrospective analysis of the clinical characteristics of Candida auris infection worldwide from 2009 to 2020. Front Microbiol 2021;12:658329. [CrossRef]
20. Vaseghi N, Sharifisooraki J, Khodadadi H, Nami S, Safari F, Ahangarkani F, et al. Global prevalence and subgroup analyses of coronavirus disease (COVID-19) associated Candida auris infections (CACa): A systematic review and meta-analysis. Mycoses 2022;65:683–703. [CrossRef]
21. Garcia-Bustos V, Salavert M, Ruiz-Gaitán AC, Cabañero-Navalon MD, Sigona-Giangreco IA, Pemán J. A clinical predictive model of candidaemia by Candida auris in previously colonized critically ill patients. Clin Microbiol Infect 2020;26:1507–13. [CrossRef]
22. Cortegiani A, Misseri G, Giarratano A, Bassetti M, Eyre D. The global challenge of Candida auris in the intensive care unit. Crit Care 2019;23:150. [CrossRef]
23. Kordalewska M, Lee A, Park S, Berrio I, Chowdhary A, Zhao Y, et al. Understanding echinocandin resistance in the emerging pathogen Candida auris. Antimicrob Agents Chemother 2018;62:e00238-18. [CrossRef]
24. European Centre for Disease Prevention and Control. Candida auris in healthcare settings – Europe – First update, 23 April 2018. Stockholm: ECDC; 2018.
25. World Health Organization. Global antimicrobial resistance and use surveillance system (GLASS). Available at: https://www.who.int/initiatives/glass. Accessed Sep 9, 2026.

ORIGINAL ARTICLE

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.92668

Maternal Risk Factors for Term Antepartum Stillbirth: A 10-Year Registry-Based Case–Control Study

Rezzan Berna Temoçin,[1] Pınar Yıldız,[2] Emre Mat,[1] Beyzanur Kahyaoglu,[3] Gazi Yıldız[1]

Abstract

Objective: To identify independent maternal risk factors associated with term antepartum stillbirth and to evaluate incidence patterns in a tertiary referral setting.

Methods: This retrospective case–control study was conducted at a tertiary referral center in Türkiye. Singleton term pregnancies between 37+0 and 41+6 weeks of gestation were included. Cases comprised 70 women with term antepartum stillbirth confirmed prior to labor onset, and 282 term live births served as controls. Maternal sociodemographic, obstetric, and clinical variables were analyzed using univariable logistic regression, followed by a prespecified multivariable model including maternal age, obesity, HDP, smoking during pregnancy, and diabetes in pregnancy.

Results: The incidence of term antepartum stillbirth ranged from 2.1 to 2.7 per 1,000 term births and remained stable over time. In univariable analyses, advanced maternal age, low educational attainment, unemployment, smoking, obesity,HDP, and a history of stillbirth were associated with increased odds of term antepartum stillbirth. In the adjusted model, maternal age ≥35 years (aOR 3.01; 95% CI 1.64–5.52), obesity (aOR 1.74; 95% CI 1.02–2.96), HDP (aOR 2.48; 95% CI 1.34–4.61), and smoking during pregnancy (aOR 1.86; 95% CI 1.01–3.44) remained independently associated, whereas diabetes in pregnancy was not. Small for gestational age (SGA) and placental abruption showed strong univariable associations but were excluded from multivariable models due to potential intermediary effects.

Conclusions: Term antepartum stillbirth is uncommon but strongly associated with identifiable maternal risk factors, underscoring the need for individualized risk stratification in late gestation.

Keywords: Term antepartum stillbirth; maternal risk factors; advanced maternal age; hypertensive disorders of pregnancy; obesity.

[1]Department of Obstetrics and Gynecology, Kartal Dr. Lütfi Kırdar City Hospital, Assisted Reproductive Technologies (IVF) Unit, Istanbul
[2]Department of Perinatology, Umraniye Training and Research Hospital, Istanbul, Türkiye
[3]Department of Obstetrics and Gynecology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye

Address for correspondence:
Rezzan Berna Temoçin, Department of Obstetrics and Gynecology, Kartal Dr. Lütfi Kırdar City Hospital, Assisted Reproductive Technologies (IVF) Unit, Istanbul, Türkiye
E-mail: r.bernabaki@hotmail.com

Received: 10.02.2026
Accepted: 21.04.2026
Published: 29.09.2026

Introduction

Stillbirth remains one of the most devastating adverse pregnancy outcomes in contemporary obstetrics, with profound psychological, social, and economic implications for families and healthcare systems worldwide.[1,2] While global efforts have traditionally focused on preterm losses, term stillbirth represents a persis-

How to cite this article: *Temoçin RB, Yıldız P, Mat E, Kahyaoglu B, Yıldız G. Maternal risk factors for term antepartum stillbirth: a 10-year registry-based case–control study. South. Clin. Ist. Euras. 2026;37(3):265-272.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.
Copyright@Author(s)

tent and clinically challenging burden, accounting for a substantial proportion of fetal deaths in otherwise uncomplicated pregnancies.[3,4] In high-income countries, term stillbirth rates have plateaued at approximately 3–4 per 1,000 births, as reflected in recent United States population-based audits.[5–7] Although these figures encompass both antepartum and intrapartum events, the antepartum component alone constitutes a clinically meaningful residual risk, underscoring the limitations of conventional "low-risk" classification at term. However, data specifically addressing maternal risk factors for term antepartum stillbirth in tertiary referral settings in Türkiye remain limited, despite improved access to specialized obstetric care.[8,9]

The etiology of stillbirth is notoriously complex, involving a synergistic interplay between maternal predispositions, environmental stressors, pregnancy-related factors and placental complications.[9,10] Current evidence suggests that a substantial proportion of cases remain "unexplained" even after comprehensive clinical and pathologic evaluation.[2,11] Nevertheless, recent epidemiological data emphasize that identifiable risk factors, including advanced maternal age, maternal obesity, and hypertensive disorders of pregnancy (HDP), significantly elevate the likelihood of late-gestation fetal demise.[6,10,12]

Beyond purely clinical parameters, social determinants of health—specifically socioeconomic deprivation and limited educational attainment—have emerged as critical frontiers in risk assessment.[3,13] While racial disparities are extensively documented in Western literature,[6,7] in the Mediterranean and Middle Eastern regions, factors such as maternal health literacy, regional socioeconomic inequities, and varying access to specialized antenatal care play a more prominent role in risk stratification.[13,14]

Preventing term antepartum stillbirth remains challenging due to difficulties in distinguishing fetuses at increased risk within an otherwise low-risk obstetric population.[12] While elective delivery at 39 weeks may lower stillbirth incidence, individualized risk stratification is essential to minimize avoidable neonatal morbidity.[14-16] In this study, maternal risk factors associated with term antepartum stillbirth are analyzed in a tertiary care cohort using multivariable logistic regression, aiming to delineate independent predictors and inform evidence-based considerations for delivery timing.

Materials and Methods

Study Design and Ethical Approval

This retrospective case-control study was conducted at a major tertiary referral center in Istanbul, Türkiye. The study protocol was designed in accordance with the ethical principles of the Declaration of Helsinki and received formal approval from the local Clinical Research Ethics Committee (Date: 26.05.2021, Decision No: 2021/514/202/18).[17] Due to the retrospective nature of the study and the use of de-identified data, the requirement for individual informed consent was waived by the institutional ethics committee.

Study Population and Eligibility Criteria

This retrospective case–control study was conducted using an institutional perinatal database capturing all deliveries at a tertiary referral center between January 2010 and December 2020. The database included comprehensive records of live births and stillbirths occurring within the institution. For the present analysis, the analytic cohort was restricted to singleton term pregnancies (37+0 to 41+6 completed weeks of gestation) to evaluate maternal risk factors associated with term antepartum stillbirth and to minimize etiologic heterogeneity related to prematurity. Pregnancies complicated by multiple gestations, major structural congenital anomalies, or known chromosomal abnormalities were excluded. Additional exclusions included intrapartum fetal deaths to avoid confounding by acute labor-related events and all preterm deliveries or fetal losses occurring before 37+0 weeks of gestation. Gestational age was determined primarily by first-trimester ultrasonographic crown–rump length measurements; when unavailable, dating was assigned based on the earliest reliable ultrasonographic examination according to institutional protocols.[18]

Case and Control Selection

During the study period, 75 term stillbirths were identified. After prespecified eligibility assessment, five cases were excluded due to major structural congenital anomalies, confirmed chromosomal abnormalities, indeterminate timing of fetal death, or critical missing data. The final case group therefore comprised 70 women with singleton term pregnancies complicated by antepartum stillbirth, defined as intrauterine fetal demise confirmed by the absence of fetal cardiac activity on ultrasonography prior to labor onset. For control selection, 300 singleton term live births were initially identified from the institutional delivery registry. The same prespecified el-

igibility criteria were applied to the control population. Following exclusion of deliveries with major congenital anomalies or incomplete core data, the final control group included 282 women who delivered healthy live-born infants at term, yielding an approximate 1:4 case–control ratio.

Controls were selected using a computerized registry-based sampling approach from the institutional delivery database during the same calendar years as cases to ensure a comparable source population and minimize time-related differences in care and data capture. No individual (pairwise) matching was performed. Given the observed difference in maternal age between groups, age was prespecified as an adjustment variable and included in regression analyses to control for confounding and improve precision.

Data Collection and Clinical Definitions

Maternal sociodemographic characteristics, obstetric history, and relevant clinical variables were extracted from electronic medical records and the institutional perinatal database. Maternal comorbidities and clinical conditions were defined according to internationally accepted guidelines. HDP included preeclampsia, eclampsia, gestational hypertension, and chronic hypertension, defined according to the American College of Obstetricians and Gynecologists criteria.[19] Diabetes in pregnancy encompassed pregestational diabetes mellitus and gestational diabetes mellitus, diagnosed in accordance with institutional screening protocols.[20] Maternal body mass index was calculated using pre-pregnancy measurements and categorized as normal weight, overweight, or obese according to standard definitions.[21] SGA was defined as birth weight below the 10th percentile for gestational age and fetal sex based on INTERGROWTH-21st standards.[22]

Sociodemographic variables included maternal educational attainment and employment status. Obstetric variables comprised parity, prior cesarean delivery, previous adverse pregnancy outcomes, smoking during pregnancy, parental consanguinity, and conception via assisted reproductive technologies. Fetal characteristics recorded at delivery included fetal sex, birth weight, presentation, and major placental complications, specifically placental abruption and placenta previa.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation following assessment of distributional assumptions, and categorical variables as frequencies and percentages. Associations between candidate risk factors and term antepartum stillbirth were evaluated using logistic regression. Univariable models were first fitted to estimate crude odds ratios (ORs) and 95% confidence intervals (CIs). A multivariable logistic regression model was constructed a priori based on clinical relevance and biological plausibility. Maternal age, obesity, HDP, smoking during pregnancy, and diabetes in pregnancy were included as covariates to address potential confounding. Multicollinearity was assessed using variance inflation factors, and model fit was evaluated with the Hosmer–Lemeshow test. All tests were two-sided, with $p<0.05$ considered statistically significant.

Results

Temporal distribution and incidence of term antepartum stillbirths

Between 2010 and 2020, 70 term antepartum stillbirths were identified among 28,183 term births. The standardized incidence remained relatively stable over the study period, ranging from 2.1 to 2.7 per 1,000 term births, with no evidence of temporal clustering or consistent longitudinal trends.

Baseline maternal, pregnancy, and fetal characteristics

Baseline maternal, pregnancy-related, and fetal characteristics for term antepartum stillbirths (n=70) and term live births (n=282) are summarized descriptively in Table 1.

Maternal sociodemographic and clinical factors: Univariable associations

Univariable logistic regression results for maternal sociodemographic and clinical factors are presented in Table 2. Maternal age ≥35 years was associated with higher odds of term antepartum stillbirth (OR 3.48; 95% CI 1.98–6.11; $p<0.001$). Low educational attainment was associated with increased odds (OR 2.82; 95% CI 1.63–4.89; $p<0.001$), as was unemployment (OR 2.30; 95% CI 1.29–4.10; $p=0.005$). Smoking during pregnancy was associated with increased odds (OR 2.29; 95% CI 1.15–4.54; $p=0.016$), and obesity (BMI ≥30 kg/m²) showed an elevated odds ratio (OR 1.86; 95% CI 1.02–3.39; $p=0.043$). A history of stillbirth was also associated with increased odds (OR 3.54; 95% CI 1.05–11.95; $p=0.047$). HDP were associated with higher odds of term antepartum stillbirth (OR 3.05; 95% CI 1.52–6.09; $p=0.001$). Parental con-

Table 1. Baseline maternal, pregnancy, and fetal characteristics of term antepartum stillbirths and term live births

Variable	Term Stillbirth (n=70)	Term Live Birth (n=282)
Maternal age (years), mean ± SD	31.12±7.07	30.16±6.87
Maternal age categories, n (%)		
<20 years	4 (5.71)	9 (3.19)
20–34 years	36 (51.43)	223 (79.08)
≥35 years	30 (42.86)	50 (17.73)
Body mass index (kg/m²), mean ± SD	28.96±4.82	27.18±4.45
BMI categories, n (%)		
Normal BMI	22 (31.42)	140 (49.65)
Overweight	28 (40.00)	92 (32.62)
Obesity	20 (28.58)	50 (17.73)
Parity categories, n (%)		
Nulliparous (0)	15 (21.43)	73 (25.89)
Multiparous (1–4)	33 (47.14)	150 (53.19)
Grand multiparous (≥5)	22 (31.43)	59 (20.92)
Pregnancy history and maternal comorbidities, n (%)		
No antenatal care, n (%)	18 (25.72)	49 (17.38)
Smoking during pregnancy, n (%)	15 (21.42)	30 (10.64)
Parental consanguinity, n (%)	8 (11.42)	16 (5.67)
History of stillbirth, n (%)	5 (7.14)	6 (2.13)
Recurrent pregnancy loss, n (%)	3 (4.28)	3 (1.06)
Prior cesarean delivery, n (%)	13 (18.57)	34 (12.06)
Assisted reproduction (IVF/ICSI), n (%)	3 (4.28)	15 (5.32)
Hypertensive disorders of pregnancy, n (%)	16 (22.85)	25 (8.87)
Diabetes in pregnancy, n (%)	7 (10.00)	16 (5.67)
Suspected chorioamnionitis (clinical), n (%)	2 (2.86)	2 (0.71)
Placenta previa, n (%)	1 (1.43)	2 (0.71)
Placental abruption, n (%)	7 (10.00)	2 (0.71)
Education, n (%)		
Primary or less	42 (60.00)	98 (34.75)
Higher education	5 (7.14)	63 (22.34)
Unemployed, n (%)	51 (72.86)	152 (53.90)
Gestational age (weeks), mean ± SD	38.84±1.52	39.40±1.25
Birth weight (g), mean ± SD	3001±659	3208±498
Small for gestational age (SGA), n (%)	20 (28.57)	16 (5.67)
Male fetus, n (%)	45 (64.29)	146 (51.77)
Malpresentation, n (%)	6 (8.57)	9 (3.19)

Data are presented as mean ± standard deviation or as number (percentage), as appropriate. This table provides a descriptive overview of maternal sociodemographic features, obstetric history, pregnancy characteristics, and fetal characteristics in term antepartum stillbirths and term live births. No statistical comparisons or effect estimates are presented in this table, as its purpose is to describe baseline distributions rather than to infer associations.

sanguinity (p=0.079), grand multiparity (p=0.092), no antenatal care (p=0.112), and diabetes in pregnancy (OR 1.85; 95% CI 0.73–4.68; p=0.185) did not reach statistical significance in univariable analysis.

Pregnancy-related and fetal factors: Univariable associations

Pregnancy-related and fetal factors are shown in Table 3. SGA was strongly associated with term antepartum stillbirth (OR 6.65; 95% CI 3.23–13.71; p<0.001). Placental

Table 2. Maternal sociodemographic and clinical risk factors associated with term antepartum stillbirth

Variable (risk category vs reference)	Term Stillbirth (n=70)	Term Live Birth	Crude OR (n=282)	95% CI	p-value
Maternal age ≥35 years (vs <35 years)	30 (42.86%)	50 (17.73%)	3.48	1.98–6.11	<0.001
Low education (vs secondary or higher education)	42 (60.00%)	98 (34.75%)	2.82	1.63–4.89	<0.001
Unemployed (vs employed)	51 (72.86%)	152 (53.90%)	2.30	1.29–4.10	0.005
Smoking during pregnancy (yes vs no)	15 (21.42%)	30 (10.64%)	2.29	1.15–4.54	0.016
Parental consanguinity (yes vs no)	8 (11.42%)	16 (5.67%)	2.14	0.88–5.23	0.079
Obesity (BMI ≥30 vs <30 kg/m²)	20 (28.57%)	50 (17.73%)	1.86	1.02–3.39	0.043
Grand multiparity (≥5) (≥5 vs <5)	22 (31.43%)	59 (20.92%)	1.69	0.91–3.14	0.092
No antenatal care (yes vs no)	18 (25.72%)	49 (17.38%)	1.65	0.89–3.05	0.112
History of stillbirth (yes vs no)	5 (7.14%)	6 (2.13%)	3.54	1.05–11.95	0.047
Hypertensive disorders of pregnancy (yes vs no)	16 (22.85%)	25 (8.87%)	3.05	1.52–6.09	0.001
Diabetes in pregnancy (yes vs no)	7 (10.00%)	16 (5.67%)	1.85	0.73–4.68	0.185

Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using univariable logistic regression. Each variable was analyzed separately, comparing the predefined risk category with the indicated reference group. Variables were selected based on clinical relevance and prior literature on antepartum stillbirth. This table presents unadjusted associations and does not account for potential confounding.

Table 3. Pregnancy-related and fetal risk factors and crude associations with term antepartum stillbirth

Variable (risk category vs reference)	Term Stillbirth (n=70)	Term Live Birth (n=282)	Crude OR	95% CI	p-value
Gestational age (weeks), mean ± SD	38.84±1.52	39.40±1.25	—	—	0.005
Birth weight (g), mean ± SD	3001±659	3208±498	—	—	0.016
Male fetus (vs female)	45 (64.29%)	146 (51.77%)	1.68	0.98–2.88	0.060
Malpresentation (vs cephalic)	6 (8.57%)	9 (3.19%)	2.84	0.98–8.28	0.089
Small for gestational age (SGA) (yes vs no)	20 (28.57%)	16 (5.67%)	6.65	3.23–13.71	<0.001
Placental abruption (yes vs no)	7 (10.00%)	2 (0.71%)	15.56	3.15–76.60	<0.001

Continuous variables are presented as mean ± standard deviation and were compared between groups using appropriate parametric or non-parametric tests; odds ratios were not estimated for these variables. Categorical variables are presented with crude odds ratios (ORs) and 95% confidence intervals (CIs), derived from univariable logistic regression. Mode of delivery was not included as a risk factor due to the potential for indication bias and reverse causality in case–control comparisons. Small for gestational age (SGA) was defined as birth weight below the 10th percentile according to the applied growth standard.

abruption was also markedly more frequent among stillbirths and was associated with substantially increased odds (OR 15.56; 95% CI 3.15–76.60; p<0.001).

Multivariable logistic regression analysis

Multivariable logistic regression results are presented in Table 4. In the prespecified adjusted model, maternal age ≥35 years remained independently associated with term antepartum stillbirth (aOR 3.01; 95% CI 1.64–5.52; p<0.001). Obesity was independently associated with increased odds (aOR 1.74; 95% CI 1.02–2.96; p=0.041), as were HDP (aOR 2.48; 95% CI 1.34–4.61; p=0.004) and smoking during pregnancy (aOR 1.86; 95% CI 1.01–3.44; p=0.046). Diabetes in pregnancy, retained as an a priori covariate, was not independently associated with term antepartum stillbirth in the adjusted model (aOR 1.21; 95% CI 0.61–2.41; p=0.58).

Table 4. Multivariable logistic regression analysis of risk factors for term antepartum stillbirth

Variable	Adjusted OR (aOR)	95% Confidence Interval	p-value
Maternal age ≥35 years	3.01	1.64–5.52	<0.001
Obesity (BMI ≥30 kg/m²)	1.74	1.02–2.96	0.041
Hypertensive disorders of pregnancy	2.48	1.34–4.61	0.004
Smoking during pregnancy	1.86	1.01–3.44	0.046
Diabetes in pregnancy (a priori covariate)	1.21	0.61–2.41	0.580

Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were obtained from a prespecified multivariable logistic regression model including core maternal clinical covariates. Maternal age ≥35 years, obesity, hypertensive disorders of pregnancy, and smoking during pregnancy were selected based on biological plausibility and univariable associations. Diabetes in pregnancy was retained in the model as an a priori clinically relevant covariate, regardless of statistical significance. Socioeconomic variables were not included in the multivariable model to avoid overadjustment and collinearity with clinical factors.

Discussion

In this study, the incidence of term antepartum stillbirth remained low and relatively stable over time; however, it was found to be significantly associated with the accumulation of maternal and pregnancy-related risk factors. Advanced maternal age, obesity, cigarette smoking during pregnancy, and HDP emerged as independent maternal risk factors, while SGA status and placental abruption were identified as the clinical findings most strongly associated with term antepartum fetal loss. When considered collectively, these findings suggest that term antepartum stillbirth reflects a cumulative process in which increasing maternal risk burden converges with fetal vulnerability during the final weeks of gestation, rather than an isolated acute event.

The institutional incidence of term antepartum stillbirth was 2.38 per 1,000 term births, a rate comparable to those reported in high-income countries for pregnancies between 37 and 42 weeks of gestation.[7] The finding that term antepartum stillbirths accounted for approximately one-third of all stillbirths underscores that late-term gestation remains a clinically vulnerable period. The relative stability of incidence over time further suggests that these losses are more likely attributable to cumulative maternal or placental-mediated pathophysiological processes rather than acute and preventable intrapartum events.[4,23]

Advanced maternal age (≥35 years) remained a strong and independent predictor in our cohort, consistent with the global literature reporting a persistent excess risk even after adjustment for medical and obstetric conditions more prevalent in older pregnancies. This association is in line with evidence linking advanced maternal age to reduced vascular and placental reserve in late gestation, when fetal metabolic demands peak. Our findings demonstrate that the risk attributable to advanced maternal age persists even under tertiary-level surveillance and in term pregnancies, supporting the consideration of this age group as a distinct risk phenotype independent of comorbidities.[24,25]

This finding is consistent with the extensive literature reporting an increased risk of stillbirth associated with HDP in both low- and high-income countries and indicates that this association retains clinical relevance at term.[26] In particular, it has been previously demonstrated that the risk of fetal loss is not fully eliminated despite appropriate surveillance and treatment in the presence of HDP, including chronic hypertension, gestational hypertension, and the preeclampsia spectrum. In our study, conducted at a tertiary referral center, the persistence of antepartum fetal loss risk among pregnancies complicated by hypertensive disorders despite reaching term supports the need to individualize delivery timing in this population based on maternal risk profiles rather than relying solely on standard gestational age thresholds.[27]

Maternal obesity was identified as an independent risk factor for term antepartum fetal death in our cohort. This finding is consistent with previous studies demonstrating that the association persists after adjustment for comorbidities such as hypertension and diabetes.[27,28] These results suggest that term pregnancies complicated by obesity should not be considered uniformly low risk.[28]

Active cigarette smoking during pregnancy was independently associated with term antepartum stillbirth in our cohort, consistent with prior epidemiological and meta-analytic evidence.[29] A dose–response relationship between tobacco exposure and stillbirth risk has been

well established, including at term.[30] These findings support the role of smoking as a clinically significant and modifiable risk factor with direct relevance for perinatal risk stratification and prevention.[27]

Although diabetes in pregnancy has been linked to an increased risk of term stillbirth in prior studies, it was not identified as an independent risk factor in our cohort in either univariable or multivariable analyses.[27] This suggests that the associated risk may be more closely related to glycemic control and overall metabolic burden, including obesity and vascular comorbidities, rather than the diagnosis itself.[31] Accordingly, perinatal risk at term may be better reflected by an integrated metabolic profile than by diabetes status alone.[27,31]

SGA status and placental abruption were prominent findings associated with term antepartum stillbirth. Although abruption is relatively rare, it carries a high risk of fetal death when present.[23] In contrast, SGA is frequently observed in association with stillbirth but is generally considered a contributory condition rather than a direct cause.[32] Therefore, these variables were not included in multivariable analyses due to potential reverse causality and were interpreted descriptively.

A history of prior stillbirth was significantly associated with term antepartum fetal loss in univariable analysis. This finding suggests that a previous stillbirth should not be regarded solely as a risk marker confined to preterm losses, but may reflect a persistent maternal risk profile that remains relevant even in pregnancies reaching term gestation.[33] Our results indicate that a history of stillbirth constitutes a clinically meaningful risk indicator that warrants careful consideration in the management and surveillance of term pregnancies.

Lower educational attainment and unemployment were associated with term antepartum stillbirth in univariable analyses, consistent with evidence linking socioeconomic disadvantage to stillbirth risk through reduced quality of antenatal care and accumulation of maternal risk factors.[34,35] However, these variables were not independent predictors in multivariable models, suggesting that their effects reflect underlying clinical risk profiles rather than direct causality. Similarly, although parental consanguinity, grand multiparity, and inadequate antenatal care were not statistically significant, their higher prevalence in the stillbirth group may indicate a broader high-risk context shaped by combined genetic and sociodemographic influences rather than isolated causal factors.[28,36]

This study includes a clinically homogeneous cohort of singleton term antepartum stillbirths over an 11-year period at a tertiary center. The use of contemporaneous controls and a predefined multivariable model strengthens the evaluation of independent maternal risk factors. However, the retrospective design may allow residual confounding and misclassification. Limited data on HDP and diabetes subtypes, absence of serial fetal biometry and Doppler assessments, and the single-center setting may restrict detailed risk stratification and generalizability.

Conclusion

Although term antepartum stillbirth is a relatively rare event, this study demonstrates a strong association with identifiable maternal risk factors, including advanced maternal age, obesity, cigarette smoking, and HDP. These findings underscore that the routine classification of term pregnancies as uniformly "low risk" is not applicable to all patients and that decisions regarding the timing of delivery should be informed by individualized maternal risk profiles. Further prospective studies are warranted to support the development of targeted surveillance and timing strategies based on the integration of these risk factors.

Ethics Committee Approval: The study protocol received formal approval from the local Clinical Research Ethics Committee of Dr. Lütfi Kırdar City Hospital (Date: 26/05/2021, No: 2021/514/202/18).
Peer-review: Externally peer-reviewed.
Informed Consent: Given the retrospective nature of the study and the use of anonymized routinely collected clinical data, the requirement for written informed consent was waived by the ethics committee.
Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.
Author Contribution: Concept: B.K., M.A., M.B.; Design: B.K., M.A., M.B., S.A.; Supervision: B.K., M.A., M.B., K.G.; Materials: B.K., M.A.; Data collection &/or processing: K.G., M.O., M.A.; Analysis and/or interpretation: B.K., S.A., M.B., M.O.; Literature search: B.K., M.B., K.G., M.O.; Writing: B.K., M.B., S.A.; Critical review: R.B.T., B.K., G.Y., P.Y., E.M.
Conflict of Interest: The authors declare that they have no competing interests.
Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. World Health Organization. Stillbirths. Geneva: World Health Organization; 2020.
2. Korteweg FJ, Gordijn SJ, Timmer A, Erwich JJ, Bergman KA, Bouman K, et al. The Tulip classification of perinatal mortality: Introduction and multidisciplinary inter-rater agreement. BJOG 2006;113:393–401. [CrossRef]
3. Joseph KS, Kinniburgh B, Hutcheon JA, Mehrabadi A, Dahlgren L, Basso M, et al. Rationalizing definitions and procedures for optimizing clinical care and public health in fetal death and stillbirth. Obstet Gynecol 2015;125:784–8. [CrossRef]
4. Lawn J, Shibuya K, Stein C. No cry at birth: Global estimates of intrapartum stillbirths and intrapartum-related neonatal deaths. Bull World Health Organ 2005;83:409–17.
5. Centers for Disease Control and Prevention (CDC). What is stillbirth? Atlanta (GA): CDC; 2022.
6. Gregory ECW, Valenzuela CP, Hoyert DL. Fetal mortality: United States, 2021. Natl Vital Stat Rep Hyattsville (MD): National Center for Health Statistics; 2023. [CrossRef]
7. Gregory ECW, Valenzuela CP, Martin JA. Fetal mortality in the United States: Final 2020–2021 and 2021–provisional 2022. NVSS Vital Statistics Rapid Release, No. 32. Hyattsville (MD): National Center for Health Statistics; 2023.
8. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). Stillbirths: Global, regional, and national estimates and trends. New York: UNICEF; 2023.
9. Hug L, You D, Blencowe H, Mishra A, Wang Z, Fix MJ, et al; UN Inter-agency Group for Child Mortality Estimation and its Core Stillbirth Estimation Group. Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: A systematic assessment. Lancet 2021;398:772–85. [CrossRef]
10. McPherson EW. 3137 fetuses in 33 years: What we have learned from the Wisconsin stillbirth service program. Am J Med Genet A 2021;185:2683–9. [CrossRef]
11. Centers for Disease Control and Prevention (CDC). Data and statistics on stillbirth. Atlanta (GA): CDC; 2024.
12. Silver RM, Varner MW, Reddy U, Goldenberg R, Pinar H, Conway D, et al. Work-up of stillbirth: A review of the evidence. Am J Obstet Gynecol 2007;196:433–44. [CrossRef]
13. Pilliod RA, Dissanayake M, Cheng YW, Caughey AB. Association of widespread adoption of the 39-week rule with overall mortality due to stillbirth and infant death. JAMA Pediatr 2019;173:1180–5. [CrossRef]
14. Atwani R, Saade G, Kawakita T. Impact of the ARRIVE trial on stillbirth rates in nulliparous individuals. Am J Perinatol 2025;42:401–8. [CrossRef]
15. GBD 2021 Global Stillbirths Collaborators. Global, regional, and national stillbirths at 20 weeks' gestation or longer in 204 countries and territories, 1990–2021: Findings from the Global Burden of Disease Study 2021. Lancet 2024;404:1955–88.
16. Di Mario S, Say L, Lincetto O. Risk factors for stillbirth in developing countries: A systematic review of the literature. Sex Transm Dis 2007;34:11–21. [CrossRef]
17. World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA 2013;310:2191–4. [CrossRef]
18. Committee Opinion No. 700: Methods for estimating the due date. Obstet Gynecol 2017;129:e150–4. [CrossRef]
19. ACOG Practice Bulletin No. 202: Gestational hypertension and preeclampsia. Obstet Gynecol 2019;133:1. [CrossRef]
20. American Diabetes Association. 14. Management of diabetes in pregnancy: Standards of medical care in diabetes–2021. Diabetes Care 2021;44:200–10. [CrossRef]
21. WHO. Obesity: Preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894–xii:1–253.
22. Papageorghiou AT, Ohuma EO, Altman DG, Todros T, Cheikh Ismail L, Lambert A, et al; International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for fetal growth based on serial ultrasound measurements: The Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet 2014;384:869–79. Erratum in: Lancet 2014;384:1264. [CrossRef]
23. Fretts RC, Boyd ME, Usher RH, Usher HA. The changing pattern of fetal death, 1961–1988. Obstet Gynecol 1992;79:35–9.
24. Sullivan HK, Sinaiko AD, Fox K, Armstrong JC, Clapp MA, Cohen JL. Stillbirths in the United States. JAMA 2025;334:2033–5. [CrossRef]
25. Fretts RC, Schmittdiel J, McLean FH, Usher RH, Goldman MB. Increased maternal age and the risk of fetal death. N Engl J Med 1995;333:953–7. [CrossRef]
26. Lawn JE, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I, et al; Lancet's Stillbirths Series steering committee. Stillbirths: Where? When? Why? How to make the data count? Lancet 2011;377:1448–63. [CrossRef]
27. Obstetric Care Consensus No. 10. Management of stillbirth. Obstet Gynecol 2020;135–32. Erratum in: Obstet Gynecol 2023;141:1030. [CrossRef]
28. Polnaszek BE, Raghuraman N, Lopez JD, Frolova AL, Wesevich V, Tuuli MG, et al. Neonatal morbidity in the offspring of obese women without hypertension or diabetes. Obstet Gynecol 2018;132:835–41. [CrossRef]
29. Pineles BL, Hsu S, Park E, Samet JM. Systematic review and meta-analyses of perinatal death and maternal exposure to tobacco smoke during pregnancy. Am J Epidemiol 2016;184:87–97. [CrossRef]
30. Varner MW, Silver RM, Rowland Hogue CJ, Willinger M, Parker CB, Thorsten VR, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Stillbirth Collaborative Research Network. Association between stillbirth and illicit drug use and smoking during pregnancy. Obstet Gynecol 2014;123:113–25. [CrossRef]
31. Starikov R, Dudley D, Reddy UM. Stillbirth in the pregnancy complicated by diabetes. Curr Diab Rep 2015;15:11. [CrossRef]
32. Malacova E, Regan A, Nassar N, Raynes-Greenow C, Leonard H, Srinivasjois R, et al. Risk of stillbirth, preterm delivery, and fetal growth restriction following exposure in a previous birth: Systematic review and meta-analysis. BJOG 2018;125:183–92. [CrossRef]
33. Lamont K, Scott NW, Jones GT, Bhattacharya S. Risk of recurrent stillbirth: Systematic review and meta-analysis. BMJ 2015;350:h3080. [CrossRef]
34. Aminu M, Unkels R, Mdegela M, Utz B, Adaji S, van den Broek N. Causes of and factors associated with stillbirth in low- and middle-income countries: A systematic literature review. BJOG 2014;121:141–53. [CrossRef]
35. Di Nallo A, Köksal S. Job loss during pregnancy and the risk of miscarriage and stillbirth. Hum Reprod 2023;38:2259–66. [CrossRef]
36. Kapurubandara S, Melov S, Shalou E, Alahakoon I. Consanguinity and associated perinatal outcomes, including stillbirth. Aust N Z J Obstet Gynaecol 2016;56:599–604. [CrossRef]

ORIGINAL ARTICLE

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.07455

Evaluating Smoking-Related Systemic Inflammation Through Hematological Indices: A Cross-Sectional Study

Müzeyyen Eryılmaz,[1] Ilkay Keskinel,[2] Lara Türkeli[2]

Abstract

Objective: Smoking is a deleterious habit with profound health consequences, often resulting in systemic inflammation that contributes to chronic diseases. We aimed to investigate how different types of exposure (active or passive smoking) affect systemic inflammatory responses, compared to non-smokers.

Methods: This retrospective, single-center study included 306 healthy individuals categorized according to smoking status, with a predominantly female population (253 females and 53 males). Hematologic inflammatory markers, including the systemic immune inflammation index (SII), systemic inflammation response index (SIRI), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) were assessed alongside C-reactive protein (CRP) levels. A CRP level ≥3 mg/L was considered to define systemic inflammation.

Results: Among active smokers, SIRI was the only marker that showed a statistically significant diagnostic value for identifying elevated CRP levels (AUC=0.662, 95% CI:0.522–0.802, p=0.021), whereas the remaining indices were not significant in any group.

The optimal cut-off value for SIRI was 1.50, with a sensitivity of 38.1% and a specificity of 95.8%. In passive smokers and non-smokers there was no significant association was observed between hematologic indices and CRP levels.

Conclusions: SIRI may be a helpful and easily accessible parameter for assessing the inflammatory response in active smokers. Although its discriminatory performance was modest, its derivation from routine complete blood count parameters may support its use as an adjunctive marker in clinical evaluation.

Keywords: Smoking; Systemic Immune Inflammation Index (SII); Systemic Inflammation Response Index (SIRI); Neutrophil/Lymphocyte Ratio (NLR); Platelet/Lymphocyte Ratio (PLR); C-Reactive Protein (CRP)

[1]Department of Internal Medicine, University of Health Sciences, Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Türkiye
[2]Department of Chest Diseases, Okan University Faculty of Medicine, Istanbul, Türkiye

Address for correspondence:
Müzeyyen Eryılmaz, University of Health Science, Fatih Sultan Mehmet Training and Research Hospital, Department of Internal Medicine, Ataşehir, Istanbul, Türkiye
E-mail: drmuzeyyeneryilmaz@hotmail.com

Received: 09.01.2026
Accepted: 12.06.2026
Published: 29.09.2026

Introduction

Cigarette smoking continues to be a significant contributor to global morbidity and mortality. It exerts systemic effects by introducing toxic agents, such as nicotine, carbon monoxide, and free radicals that initiate oxidative stress and disrupt immune balance.[1] These agents trigger chronic inflammation, particularly in mucosal systems like the respiratory tract, increasing susceptibility to cardiovascular

How to cite this article: *Eryılmaz M, Keskinel I, Türkeli L. Evaluating smoking-related systemic inflammation through hematological indices: a cross-sectional study. South. Clin. Ist. Euras. 2026;37(3):273-278.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Copyright@Author(s)

disease, cancer, and neurodegenerative disorders.

Recent research highlights the utility of hematological markers for quantifying systemic inflammation. Indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII), and systemic inflammation response index (SIRI) provide accessible metrics derived from standard complete blood counts.[2] These have demonstrated clinical value in conditions ranging from cardiovascular disorders to malignancies.[3-5]

C-reactive protein (CRP), an acute-phase reactant, reflects inflammatory burden and is considered elevated at values ≥3 mg/L, a level commonly associated with cardiometabolic risk.[6-8]

This study aims to evaluate the influence of smoking status on hematological inflammation indices and to determine how well these markers identify CRP-defined systemic inflammation. By doing so, it seeks to clarify the clinical utility of routine blood count-derived indices for the early detection of smoking-related inflammatory responses.

Materials and Methods

This retrospective cross-sectional study involved healthy individuals who visited the internal medicine outpatient clinics of a training and research hospital between January 1, 2023, and July 1, 2024. Participants were included through simple random sampling, provided they met predefined eligibility criteria.

Participants were eligible if they were aged between 18 and 70 years and had no history of chronic illnesses or current treatments that could affect inflammatory markers. The study excluded individuals with conditions such as malignancies, autoimmune disorders, diabetes mellitus, or any acute infections. Also excluded were those using corticosteroids or NSAIDs, pregnant individuals, and those with hematological or biochemical abnormalities or regular alcohol or substance use.

Subjects were grouped based on smoking status: Group I (active smokers), Group II (non-smokers), and Group III (passive smokers). The analysis compared age, gender, and systemic inflammatory markers-SII, SIRI, NLR, PLR, and CRP-across these groups.

The hematological inflammatory indices were calculated using the following formulas:

SII = (Neutrophil count × Platelet count) / Lymphocyte count

SIRI = (Neutrophil count × Monocyte count) / Lymphocyte count

NLR = Neutrophil count / Lymphocyte count

PLR = Platelet count / Lymphocyte count

CRP levels were dichotomized using the threshold of ≥3 mg/L to denote systemic inflammation. Hematological indices were calculated using standard formulas based on neutrophil, lymphocyte, monocyte, and platelet counts derived from routine complete blood counts.

Ethical approval for the study was obtained from a local ethics committee on July 30, 2024. All procedures were performed in accordance with the principles outlined in the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Because the study variables did not follow a normal distribution, non-parametric methods were used. Continuous variables, including age and hematological inflammatory indices (SII, SIRI, NLR, and CRP), were compared among the three smoking-status groups (active smokers, non-smokers, and passive smokers) using the Kruskal-Wallis test. Categorical variables, such as sex distribution and the proportion of with CRP ≥ 3 mg/L, were evaluated using the chi-square test.

To assess the ability of hematological indices to identify systemic inflammation, receiver operating characteristic (ROC) curve analysis was conducted separately for each smoking group. Systemic inflammation was defined as CRP ≥ 3 mg/L, and the area under the curve (AUC) values with corresponding p-values were calculated for SII, SIRI, NLR, and PLR. A p-value <0.05 was considered statistically significant.

Results

In total, 306 participants were enrolled in the study, including 253 females and 53 males. Group I included 93 individuals (67 females, 26 males), Group II comprised 149 (134 females, 15 males), and Group III included 64 participants (52 females, 12 males). Female participants were predominant in all groups. A statistically significant difference in gender distribution was observed among the groups (p=0.002).

Table 1 presents demographic data and hematological marker values. Mean age was comparable across the groups (Group I: 36.4±12.7; Group II: 37.1±13.2; Group III: 34.0±13.5; p=0.224). Mean CRP levels were slightly higher in passive smokers (4.11±8.10 mg/L), but this difference was not statistically significant (p=0.528).

Among the inflammatory indices, SII, SIRI, and NLR did not significantly differ between the groups. However, PLR values showed a statistically significant variation (p<0.001), being higher in passive and non-smokers compared to active smokers

As shown in Table 2, only SIRI demonstrated statistically significant diagnostic value in active smokers, with an AUC of 0.662 (95% CI: 0.522-0.802, p=0.021). ROC analysis identified an optimal SIRI cut-off value of 1.50, yielding a sensitivity of 38.1% and a specificity of 95.8%. Other indices, including SII (p=0.296), NLR (p=0.332), and PLR (p=0.339), failed to show significant discriminatory power in this group.

In non-smokers and passive smokers, none of the markers, SIRI, SII, NLR, or PLR, demonstrated significant diagnostic performance for identifying CRP levels ≥3 mg/L. While SII had the highest AUC value among non-smokers (0.582), it did not achieve statistical significance (p=0.117).

Table 1. Comparison of demographic characteristics and hematological inflammatory markers among the three smoking status groups

Variable	Group I (Active smokers) (n=93)	Group II (Non-smokers) (n=149)	Group III (Passive smokers) (n=64)	p-value
Age (year)	37.0 [25.0–44.0]	38.0 [25.0–46.0]	32.5 [22.8–43.0]	0.224
Gender				0.002
Male, n (%)	26 (28.0)	15 (10.1)	12 (18.8)	
Female, n (%)	67 (72.0)	134 (89.9)	52 (81.2)	
CRP (mg/L)	1.39 [0.60–2.74]	1.32 [0.61–2.67]	1.60 [0.65–3.72]	0.528
SII	461.30 [343.00–619.90]	484.77 [357.89–666.67]	556.54 [379.73–704.80]	0.124
SIRI	0.77 [0.61–1.12]	0.75 [0.51–0.95]	0.75 [0.58–1.20]	0.352
NLR	1.74 [1.37–2.23]	1.81 [1.46–2.41]	1.84 [1.51–2.38]	0.250
PLR	104.09 [82.69–133.33]	124.62 [95.62–156.60]	131.06 [104.82–167.20]	<0.001

Values are presented as median [interquartile range (IQR)] for continuous variables and n (%) for categorical variables. Group comparisons for continuous variables were performed using the Kruskal–Wallis test, while categorical variables were analyzed using the chi-square test. SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; CRP: C-reactive protein.

Table 2. p-values of SII, SIRI, NLR, and PLR by ROC analysis across smoking status group

Group	Marker	AUC	95% CI	p-value	Cut-off	Sensitivity (%)	Specificity (%)
Group I (Active smokers) (n=93)	SII	0.577	0.434–0.720	0.288	–	–	–
SIRI	0.662	0.523–0.802	0.021	1.50	38.1	95.8	
NLR	0.575	0.432–0.718	0.305	–	–	–	
PLR	0.431	0.295–0.567	0.321	–	–	–	
Group II (Non-smokers) (n=149)	SII	0.582	0.471–0.693	0.145	–	–	–
SIRI	0.566	0.455–0.677	0.243	–	–	–	
NLR	0.547	0.436–0.658	0.403	–	–	–	
PLR	0.455	0.348–0.563	0.416	–	–	–	
Group III (Passive smokers) (n=64)	SII	0.468	0.316–0.620	0.682	–	–	–
SIRI	0.511	0.357–0.666	0.885	–	–	–	
NLR	0.477	0.324–0.629	0.765	–	–	–	
PLR	0.438	0.288–0.587	0.414	–	–	–	

Systemic inflammation was defined as CRP ≥3 mg/L. AUC: area under the receiver operating characteristic curve; CI: confidence interval; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; CRP: C-reactive protein. The optimal cut-off was reported only for SIRI in active smokers, as this was the only statistically significant ROC result.

Discussion

This study aimed to evaluate the diagnostic potential of hematological inflammation markers in identifying systemic inflammation-defined by elevated CRP levels-across individuals with varying degrees of smoking exposure. Among the evaluated markers, only SIRI demonstrated statistically significant discriminatory ability in active smokers (AUC=0.662, 95% CI: 0.522-0.802, p=0.021), supporting its potential value as a marker of smoking-related systemic inflammation.

SIRI incorporates neutrophil, monocyte, and lymphocyte counts and may therefore reflect the balance between activation of innate immune responses and suppression of adaptive immunity. Cigarette smoke exposure promotes oxidative stress through the generation of reactive oxygen species, leading to persistent inflammatory signaling and long-term immune dysregulation. Experimental evidence suggests that cigarette smoke may induce trained immunity through metabolic and epigenetic reprogramming of innate immune cells, particularly monocytes and macrophages, resulting in prolonged inflammatory responsiveness.[1] These immune alterations may contribute to increased neutrophil and monocyte activity together with impaired lymphocyte-mediated adaptive responses. Because SIRI simultaneously reflects these hematological changes, it may provide a more comprehensive representation of smoking-related immune dysregulation than indices derived from fewer blood-cell components.

Our findings are consistent with previous studies demonstrating the prognostic and clinical relevance of SIRI in inflammatory and cardiovascular conditions. Cao et al.[3] reported an association between elevated SIRI levels and mortality in patients with heart failure, whereas Gavriilidis and Pawlik demonstrated its prognostic significance following hepatocellular carcinoma surgery.[2] Similarly, Dziedzic et al.[9] highlighted the clinical utility of SIRI in patients with coronary artery disease and acute coronary syndrome. Several of these studies indirectly support a relationship between elevated SIRI levels and enhanced systemic inflammatory activity in smoking-related conditions.

Evidence from Turkish populations further supports the clinical relevance of SIRI as an indicator of systemic inflammatory burden. Yildiz et al.[10] demonstrated associations between SIRI and different coronary artery plaque characteristics, suggesting a potential role in reflecting vascular inflammation. Likewise, Bayraktar and Coşgun reported that elevated SIRI levels were associated with greater coronary artery disease severity in a Turkish cohort.[11] In addition, Bedel et al.[12] demonstrated the prognostic significance of SIRI in patients with heart failure. Although these studies were not specifically designed to evaluate smoking-related inflammation, they support the broader applicability of SIRI across diverse inflammatory conditions and suggest that these associations are also observable in regional populations.

In our cohort, SII, NLR, and PLR did not demonstrate significant discriminatory performance across smoking subgroups, in contrast to SIRI. Although PLR values differed statistically between groups (p<0.001), ROC analysis did not support meaningful clinical utility. These findings suggest that statistically significant differences in hematological indices may not necessarily translate into adequate diagnostic discrimination. One possible explanation is that smoking influences multiple blood-cell components, including platelet-related parameters and lymphocyte counts, which may alter these indices without producing a consistent discriminatory pattern across smoking subgroups.[13]

Another notable observation was the limited performance of inflammatory indices among passive smokers and non-smokers. This finding may reflect the relatively heterogeneous and low-grade nature of systemic inflammation in these populations. Previous studies have shown that chronic low-grade inflammation can be difficult to characterize using a single biomarker because inflammatory and metabolic pathways vary substantially among individuals.[14,15] Elevated hsCRP levels have long been associated with increased cardiovascular risk; however, chronic inflammation is increasingly recognized as a biologically complex and heterogeneous process involving multiple interconnected innate and adaptive immune pathways rather than a single measurable inflammatory axis.[16–18] In addition to cardiovascular disease, elevated hsCRP levels have also been associated with metabolic disorders such as diabetes mellitus and metabolic syndrome.[16] Nevertheless, CRP alone may insufficiently reflect interindividual variability in inflammatory responses and related clinical risk.[17,18] Contemporary evidence further suggests that chronic inflammatory burden is influenced by persistent inflammatory pathways associated with residual inflammatory risk and trained

immunity mechanisms that extend beyond conventional inflammatory biomarkers.[19–21] In this context, composite inflammatory indices and multi-biomarker approaches have increasingly been proposed as more comprehensive methods for assessing systemic inflammatory burden and immune dysregulation than isolated inflammatory measurements alone.[14,18–21]

Taken together, our findings suggest that SIRI may serve as a practical adjunctive marker for identifying smoking-related low-grade systemic inflammation in active smokers. Because SIRI is derived from routinely available complete blood count parameters, it represents a cost-effective and widely accessible inflammatory index with potential applicability in clinical screening and population-level risk assessment strategies. Chronic low-grade inflammation is increasingly recognized as a biologically complex and heterogeneous process involving multiple interconnected innate and adaptive immune pathways, trained immunity mechanisms, and persistent inflammatory pathways associated with residual inflammatory risk.[14–21] In this context, composite inflammatory indices integrating multiple hematological parameters may provide a more comprehensive representation of systemic inflammatory burden and immune dysregulation than isolated inflammatory biomarkers alone.[9–12,14,18–21] Nevertheless, the modest discriminatory performance observed in the present study indicates that SIRI should be interpreted as a complementary rather than standalone diagnostic marker.

Nonetheless, this study has several limitations. First, its retrospective single-center design may limit generalizability. Second, the study population demonstrated a marked gender imbalance, with a predominance of female participants (253 females vs. 53 males), particularly in the non-smoker group. Because hematological parameters and inflammatory responses may vary according to sex, this imbalance may have introduced potential statistical bias and influenced the observed associations. In addition, the absence of long-term follow-up and the inability to account for potentially confounding variables such as dietary habits, psychosocial stress, and subclinical infections may have affected inflammatory marker levels. Future prospective multicenter studies are warranted to determine whether SIRI predicts longitudinal clinical outcomes and whether its diagnostic performance can be enhanced through integration with additional inflammatory mediators such as IL-6 or TNF-α.

Conclusion

SIRI was the only hematological index that demonstrated statistically significant diagnostic value for systemic inflammation in active smokers, suggesting a potential role in evaluating smoking-related inflammatory changes. In contrast, SII, NLR, and PLR did not show significant discriminatory performance. Because SIRI is inexpensive, easily calculated, and derived from routinely available complete blood count parameters, it may represent a practical adjunctive marker for assessing low-grade systemic inflammation in active smokers. However, given its modest discriminatory performance, SIRI should be interpreted as a complementary rather than standalone diagnostic tool. Further large-scale prospective studies are needed to validate these findings and clarify the clinical applicability of SIRI across broader populations and smoking-related inflammatory conditions.

Ethics Committee Approval: Ethical approval for the study was obtained from the Kartal Koşuyolu High Specialization Training and Research Hospital Clinical Research Ethics Committee (Date: 30/07/2024, No: 2024/14/888).
Peer-review: Externally peer-reviewed.
Informed Consent: Not applicable.
Author Contribution: Concept: M.E., I.K.; Design: M.E., I.K., L.T.; Supervision: M.E., I.K., L.T.; Fundings: M.E., I.K., L.T.; Materials: M.E., I.K., L.T.; Data collection &/or processing: M.E., I.K.; Analysis and/or interpretation: I.K., L.T.; Literature search: M.E., I.K., L.T.; Writing: M.E., I.K., L.T.; Critical review: M.E., I.K., L.T.
Conflict of Interest: No conflict of interest was declared by the authors.
Funding: The authors declared that this study has received no financial support.
Availability of data and materials: Patient's data was obtained from hospital data system.

References

1. Saaoud F, Shao Y, Cornwell W, Wang H, Rogers TJ, Yang X. Cigarette smoke modulates inflammation and immunity via reactive oxygen species-regulated trained immunity and trained tolerance mechanisms. Antioxid Redox Signal 2023;38:1041–69. [CrossRef]
2. Gavriilidis P, Pawlik TM. Inflammatory indicators such as systemic immune-inflammation index and systemic inflammation response index as predictors of outcome after hepatocellular carcinoma surgery. Front Surg 2023;10:1212394.
3. Cao H, He J, Xu H, Zhou Z, Song Y. Relationship between systemic immune-inflammation index (SII) and mortality in congestive heart failure patients. Front Cardiovasc Med 2024;11:1282724.
4. Du Y, Lin H, Ma J, Yu L. Association of systemic immune-inflammation index with coronary artery disease in older adults. BMC

Geriatr 2024;24:1–9.

5. Shao J, Xu H, Liang H, Wu Z. Prognostic value of preoperative systemic inflammation response index and systemic immune-inflammation index in NSCLC patients. BMC Pulm Med 2023;23:201.
6. Xu L, Liang C, Zhou Y, Liu Y. Association between hsCRP and risk of major adverse cardiovascular events: A dose–response meta-analysis. J Clin Hypertens 2023;25:616–24.
7. Müller T, Gruber J, Heigl F. hsCRP is associated with prevalence of diabetes, metabolic syndrome and cardiovascular disease. Cardiovasc Diabetol 2022;21:100.
8. Manne S, Simonsen K, Gerke TA. Association between C-reactive protein levels and all-cause mortality: A national health survey. PLoS One 2024;19:e0284562.
9. Dziedzic A, Góralczyk K, Krela-Kaźmierczak I. Systemic inflammatory response index (SIRI) as a novel and promising prognostic marker in patients with coronary artery disease and acute coronary syndrome. Int J Mol Sci 2022;23:9553. [CrossRef]
10. Yildiz C, Yuksel Y, Rakici IT, Katkat F, Ayça B, Turhan Çağlar FN. Assessment of systemic immune-inflammation index and systemic inflammation-response index in different coronary artery plaque types. Angiology 2023;74:536–44. [CrossRef]
11. Bayraktar MF, Coşgun M. Can the systemic immune inflammation index (SII) and the systemic inflammation response index (SIRI) predict the severity of coronary artery disease? Northwest Med J 2024;4:157–62. [CrossRef]
12. Bedel C, Selvi F, Zortuk Ö, Yildiz G, Yavuz YF, Korkut M. Effect of systemic inflammatory response index (SIRI) and systemic immuno-inflammation index (SII) on mortality in heart failure patients. Rev Rom Med Lab 2024;32:149–54. [CrossRef]
13. Pujani M, Chauhan V, Singh K, Rastogi S, Agarwal C, Gera K. The effect and correlation of smoking with platelet indices, neutrophil lymphocyte ratio and platelet lymphocyte ratio. Hematol Transfus Cell Ther 2021;43:424–9. [CrossRef]
14. Pietzner M, Kaul A, Henning AK, Kastenmüller G, Artati A, Lerch MM, et al. Comprehensive metabolic profiling of chronic low-grade inflammation among generally healthy individuals. BMC Med 2017;15:210. [CrossRef]
15. Minihane AM, Vinoy S, Russell WR, et al. Low-grade inflammation, diet composition and health: Current research evidence and its translation. Br J Nutr 2015;114:999–1012. [CrossRef]
16. Denegri A, Boriani G. High sensitivity C-reactive protein (hsCRP) and its implications in cardiovascular outcomes. Curr Pharm Des 2021;27:263–75. [CrossRef]
17. Libby P. The changing landscape of atherosclerosis. Nature 2021;592:524–33. [CrossRef]
18. Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: Moving upstream to identify novel targets for atheroprotection. Circ Res 2016;118:145–56. [CrossRef]
19. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ, et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: A secondary analysis from the CANTOS randomised controlled trial. Lancet 2018;391:319–28. [CrossRef]
20. Netea MG, Domínguez-Andrés J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. Nat Rev Immunol 2020;20:375–88. [CrossRef]
21. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med 2019;25:1822–32. [CrossRef]

ORIGINAL ARTICLE

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.34445

Impact of Breastfeeding on Body Mass Index

Nihal Cankır,[1] Yakup Çağ,[1] Mehmet Tolga Köle,[1] Ayşe Adak,[1] Yasemin Akın[1]

Abstract

Objective: The objective of this research is to assess the correlation between the length of breastfeeding and the Body Mass Index (BMI) of children in the 3-6 age group, as well as to ascertain the impact of early childhood nutrition on the incidence of obesity.

Methods: A questionnaire was administered to the parents of children aged 3-6 who presented to the outpatient clinic, inquiring about demographic characteristics and the children's feeding practices between the ages of 0-2. Anthropometric measurements of the children were also taken.

Results: A total of 399 children took part in the investigation, with 236 being boys. Judging by the Body Mass Index (BMI) metrics, 27% were categorized as underweight, 54% fell within the normal range, 5% were identified as overweight, and 14% were classified as obese. Notably, 8% of the participants had never experienced breastfeeding, 42% had undergone breastfeeding for six months or less, 25% had a breastfeeding duration of 7-23 months, and another 25% had been breastfed for 24 months or more. Despite the variations in breastfeeding duration, no statistically significant disparities were detected in the BMI values ($p>0.05$). Among those who had never been breastfed, 22% were identified as obese. In contrast, only 9% of individuals breastfed for less than six months fell into the obese category, while 16% of those breastfed for 7-23 months and another 16% breastfed for 24 months or more were deemed obese. Interestingly, a statistically significant association emerged between the duration of breastfeeding and the incidence of chronic illnesses ($p<0.05$). A noteworthy 71.4% of children with chronic ailments had been breastfed for six months or less, indicating a potential link between shorter breastfeeding periods and the presence of chronic illnesses in children.

Conclusions: In our study, no relationship was found between the duration of breastfeeding and BMI values. However, children with chronic illnesses were observed to have a shorter duration of breastfeeding.

Keywords: Breast milk; body mass index; child.

Department of Pediatrics, University of HealthScience, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Türkiye

Address for correspondence:
Nihal Cankır, University of Health Science, Kartal Dr. Lutfi Kirdar City Hospital, Department of Pediatrics, Istanbul, Türkiye
E-mail: nihal_comen@hotmail.com

Received: 05.09.2025
Accepted: 06.05.2026
Published: 29.09.2026

Introduction

The feeding style during the first two years of life is of utmost importance for future growth and development. Incorrect feeding practices during this period can lay the foundation for chronic diseases, obesity, and allergic conditions later in life. Breast milk is the most easily digestible, cost-effective, readily available, and natural source of nourishment that

How to cite this article: *Cankır N, Çağ Y, Köle MT, Adak A, Akın Y. Impact of breastfeeding on body mass index. South. Clin. Ist. Euras. 2026;37(3):279-285.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Copyright@Author(s)

meets all the requirements a newborn needs. The global health authority, the World Health Organization (WHO), along with the United Nations International Children's Emergency Fund (UNICEF), advocates for exclusive breastfeeding during the initial 6 months of a child's life, followed by the continuation of breastfeeding alongside the introduction of complementary foods until the child attains the age of 2.

Obesity is defined as an excessive increase in body fat tissue. It is one of the most significant global health issues today, representing a risk factor for various chronic diseases, primarily diabetes and cardiovascular conditions, making it a major public health concern.[1] Studies have shown an increase in the prevalence of childhood overweight and obesity in recent years.[2–4] Early interventions can be helpful in preventing obesity and related health problems. Therefore, identifying preventable risks and modifiable protective factors has become crucial in efforts to prevent obesity.[5]

It is well known that breastfeeding has many benefits for both the mother and the baby.[6] Numerous studies have reported that breastfeeding can protect against childhood obesity.[7,8] It is suggested that hormones found in the content of breast milk, such as leptin, adiponectin, and Insulin-like growth factor-1, regulate the infant's food intake and help prevent the increasing prevalence of obesity.[9]

In this study, our aim was to assess the relationship between the duration of breastfeeding and the BMI (Body Mass Index) of children aged 3-6 years and to determine the impact of early childhood nutrition on the prevalence of obesity.

Materials and Methods

Our prospective study was conducted at the Dr. Lütfi Kırdar City Hospital, Department of Pediatrics, between March 2022 and April 2023. The study was carried out in accordance with the principles of the Helsinki Declaration and received approval from the Dr. Lütfi Kırdar City Hospital Ethics Committee on January 28, 2022, with decision number 2022/514/218/15.

A questionnaire consisting of 12 questions was prepared to gather information from the parents of children aged 3-6 who presented to the outpatient clinic. This questionnaire covered demographic characteristics, as well as the children's feeding practices between the ages of 0-2, whether they received breast milk and for how long, whether they received dietary supplements, any concurrent chronic illnesses, and the family's educational and socioeconomic status.

Table 1. Descriptive statistics of demographic characteristics of individuals

	Statistics
Age, (Month)	46.63±20.99
Gender, n (%)	
Man	236 (59.15)
Woman	163 (40.85)
Height, (Cm)	109.66±8.22
Weight, (Kg)	18.96±4.77
BMI Categorical, n (%)	
Weak	108 (27.07)
Normal	217 (54.39)
Overweight	19 (4.76)
Obese	55 (13.78)
BMI	15.59±2.75
Formula Usage Time, n (%)	
Any	177 (44.36)
6 Months and under	20 (5.01)
7-23 Months	155 (38.85)
24 Months and above	47 (11.78)
Duration of Breast Milk Intake, n (%)	
Any	32 (8.02)
6 Months and under	171 (42.86)
7-23 Months	98 (24.56)
24 Months and above	98 (24.56)
The First 6 Months, n (%)	
Only Breast Milk	245 (61.4)
Just baby food	31 (7.77)
Breast Milk+baby food	123 (30.83)
Mother's level of education, n (%)	
Primary school	110 (27.57)
Secondary school	86 (21.55)
High school	131 (32.83)
University	72 (18.05)
Chronic disease, n (%)	
No	371 (92.98)
Yes	28 (7.02)
The medication he uses constantly, n (%)	
No	392 (98.25)
Yes	7 (1.75)
Total	399 (100)

n: Number of patients, %: Percentage value, average ± standard it is given as a deviation.

After obtaining parental consent, face-to-face interviews

were conducted. The children's anthropometric measurements, including height and weight, were taken at the clinic, and their BMI values were evaluated using the BMI percentile curves for 2-18-year-old boys and girls by Olcay Neyzi.[10] A BMI value below the 5th percentile was categorized as underweight, between the 5th percentile and below the 85th percentile as normal, between the 85th percentile and below the 95th percentile as overweight, and at or above the 95th percentile as obese.[11]

Statistical Analysis

The information was scrutinized employing IBM SPSS Statistics Standard Concurrent User Version 26 (IBM Corp., Armonk, New York, USA). Descriptive statistics were articulated in terms of unit count (n), percentages (%), mean ± standard deviation, and median (minimum-maximum) values. The normality of numerical variable data distribution underwent assessment through the Shapiro-Wilk normality test. In instances where there were more than two categorical variables, one-way analysis of variance (ANOVA) was executed when the data exhibited a normal distribution, whereas the Kruskal-Wallis H Test was utilized when the data deviated from normality. In cases where analysis of variance yielded significant results, the Dunn-Bonferroni test was employed for post-hoc multiple comparisons. The associations among categorical variables were examined using Pearson's chi-square test and Fisher's exact test. A p-value below 0.05 was deemed indicative of statistical significance.

Results

A total of 399 children participated in the study, with an average age of 46.63 months. Among them, 236 were boys, and 163 were girls. Their average height was 109.66 cm, and their average weight was 18.96 kg. Among the children in the study, 108 were underweight, 217 had a normal weight, 19 were overweight, and 55 were obese. 177 children had never used baby formula, 20 had used it for 6 months or less, 155 had used it for 7-23 months, and 47 had used it for 24 months or more (Table 1).

Regarding breastfeeding, 32 children had never received any breast milk, 171 had received breast milk for 6 months or less, 98 had received breast milk for 7-23 months, and 98 had received breast milk for 24 months or more. In the study, 245 children were exclusively breastfed for the first 6 months, 31 were exclusively fed with formula, and 123 were fed with both breast milk and formula in their first 6 months. Among the children, 28 had chronic illnesses, and 7 were on continuous medication.

A statistically significant difference has been observed between the duration of breastfeeding and the presence of chronic disease ($p<0.05$). Among those with chronic diseases, 71.4% (20 individuals) breastfed for 6 months or less, whereas among those without chronic diseases, 50.6% (188 individuals) breastfed for 7 months or more. Increasing the duration of breastfeeding has reduced the incidence of chronic diseases (Table 2; Table 3; Table 4; Table 5; Table 6).

Table 2. Comparison of the duration of breast milk intake and BMI values according to age and gender

	Duration of Breast Milk Intake					
	Any	6 Months >	7-23 Months	24 Months <	Test Statistics	p
Age	45.28±23.27	47.16±20.39	45.2±21.99	47.58±20.45	0.441	0.932€
	50.5 (4-75)	52 (3-71)	51.5 (3-71)	53 (3-71)		
BMI	15.85±3.67	15.35±2.36	15.45±2.46	16.08±3.25	2.514	0.473€
	14.4 (12.1-26.3)	15.1 (11.1-25.2)	15.1 (10.7-23.5)	15.2 (11.1-26.9)		
Gender					3.566	0.312&
Man	22 (0.09)	94 (0.4)	57 (0.24)	63 (0.27)		
Woman	10 (0.06)	77 (0.47)	41 (0.25)	35 (0.21)		
BMI Categorical					9.497	0.393&
Weak	11 (0.1)	43 (0.4)	29 (0.27)	25 (0.23)		
Normal	13 (0.06)	102 (0.47)	50 (0.23)	52 (0.24)		
Overweight	1 (0.05)	10 (0.53)	3 (0.16)	5 (0.26)		
Obese	7 (0.13)	16 (0.29)	16 (0.29)	16 (0.29)		

Numerical variables are given as mean±standard deviation and median (minimum-maximum). £: One-way ANOVA,€ Kruskal-Wallis test: &: Kikare analysis, ŋ: Fisher exact test.

Table 3. Comparison of duration of use of formula with BMI

	Duration of Use of Baby Food					
	Any	6 Months >	7-23 Months	24 Months <	Test Statistics	p
BMI	15.65±2.67	14.91±3.24	15.78±2.85	15.06±2.46	6.468	0.091€
	15.1 (10.7-25.2)	13.9 (11.7-26.9)	15.1 (11.7-26.3)	14.3 (11.1-22.6)		
BMI Categorical						
Weak	47 (0.44)	10 (0.09)	33 (0.31)	18 (0.17)	13.600	0.137&
Normal	98 (0.45)	7 (0.03)	90 (0.41)	22 (0.1)		
Overweight	8 (0.42)	2 (0.11)	7 (0.37)	2 (0.11)		
Obese	24 (0.44)	1 (0.02)	25 (0.45)	5 (0.09)		

Numerical variables are given as mean±standard deviation and median (minimum-maximum). £: One-way ANOVA, € Kruskal-Wallis test: &: Kikare analysis, ŋ: Fisher exact test.

Table 4. Comparison of BMI with nutrition for the first 6 months by age and gender

	The First 6 Months				
	Only Breast Milk	Only Formula	Breast Milk+Formula	Test Statistics	p
Age	46.96±21.13	44.84±23.52	46.43±20.19	0.473	0.790€
	53 (3-71)	50 (4-75)	51 (3-71)		
BMI	15.6±2.72	15.52±3.19	15.6±2.72	0.815	0.665€
	15.1 (10.7-26.9)	14.3 (12.1-25.9)	15.1 (11.1-26.3)		
Gender					
Man	147 (0.62)	21 (0.09)	68 (0.29)	1.781	0.410&
Girl	98 (0.6)	10 (0.06)	55 (0.34)		
BMI Categorical					
Weak	67 (0.62)	11 (0.1)	30 (0.28)	3.619	0.728&
Normal	133 (0.61)	13 (0.06)	71 (0.33)		
Overweight	11 (0.58)	1 (0.05)	7 (0.37)		
Obese	34 (0.62)	6 (0.11)	15 (0.27)		

Numerical variables are given as mean±standard deviation and median (minimum-maximum). £: One-way ANOVA, € Kruskal-Wallis test: &: Kikare analysis, ŋ: Fisher exact test.

Discussion

Breast milk is the optimal source of nutrition for infants, supplying all essential nutrients during the first 6 months of life. Studies conducted in our country indicate a significantly high rate of breastfeeding. According to the results of the 2018 Turkey Demographic and Health Survey, 98.% of mothers initiate breastfeeding after childbirth. On average, infants are breastfed for 16,7 months. [12]

In our study, the percentage of infants receiving breast milk under six months is higher than those receiving breast milk at seven months and beyond. Telatar et al.[13] found that the postnatal breastfeeding rate was 98%, 63% at the fourth month, and 46% at the sixth month. In a study conducted in the United States, the breastfeeding rate was reported as 66% at the start, decreasing to 32.8% at the sixth month.[14] In a study involving 5003 mothers in our country, the rate of exclusive breastfeeding dropped from 97% at birth to 81.5% in the second month and further decreased to 8.7% at the sixth month.[15] Similarly, the Turkey Demographic and Health Survey data for 2013 and 2018 indicate a decline in the percentage of breastfeeding as children age.[16,17] As infants grow older, the decrease in breastfeeding can be attributed to the introduction of complementary foods.

In our study, when examining the BMI values of chil-

Table 5. Comparison of maternal education level by BMI and duration of breast milk intake

	Mother's Educational Level					
	Primary school	Secondary school	High school	University	Test Statistics	p
BMI	15.9±3.01	15.17±2.37	15.48±2.76	15.84±2.7	4.166	0.244€
	15.1 (11.7-26.3)	14.8 (11.1-26.9)	15.1 (10.7-25.2)	15.4 (11.3-25.9)		
BMI Categorical					9.913	0.358&
Weak	30 (0.28)	26 (0.24)	38 (0.35)	14 (0.13)		
Normal	54 (0.25)	51 (0.24)	68 (0.31)	44 (0.2)		
Overweight	8 (0.42)	2 (0.11)	7 (0.37)	2 (0.11)		
Obese	18 (0.33)	7 (0.13)	18 (0.33)	12 (0.22)		
Duration of Breast Milk Intake					8.620	0.473&
Any	10 (0.31)	7 (0.22)	12 (0.38)	3 (0.09)		
6 Months >	49 (0.29)	30 (0.18)	56 (0.33)	36 (0.21)		
7-23 Months	29 (0.3)	27 (0.28)	29 (0.3)	13 (0.13)		
24 Months <	22 (0.22)	22 (0.22)	34 (0.35)	20 (0.2)		

Numerical variables are given as mean±standard deviation and median (minimum-maximum). £: One-way ANOVA , € Kruskal-Wallis test: &: Kikare analysis, ŋ: Fisher exact test

Table 6. Comparison of the duration of breast milk intake and the chronic disease variable

	Duration of Breast Milk Intake					
	Any	6 Months >	7-23 Months	24 Months <	Test Statistics	p
Chronic Disease						
No	32 (%8.6)	151 (%40.7)	94 (%25.3)	94 (%25.3)	10.740	0.013&
There is	0 (0)	20 (%71.4)	4 (%14.3)	4 (%14.3)		

Numerical variables are given as mean±standard deviation and median (minimum-maximum). £: One-way ANOVA, € Kruskal-Wallis test: &: Kikare analysis, ŋ: Fisher exact test.

dren, the majority were found to be within the normal range, with 4% identified as overweight and 13% as obese. A study involving preschool children revealed that 4.9% were mildly overweight and 11.2% were obese.[18] Another study among children aged 6-59 months showed a higher prevalence of normal BMI.[19] As observed in all these studies, the majority of this age group falls within the normal BMI range. This can be attributed to the active nature of children in this age group and their high level of physical activity, as they are often engaged in play.

In our study, it was determined that the duration of breastfeeding does not affect BMI values. Similarly, in a study by Vafa et al.,[20] it was reported that the duration of breastfeeding does not influence BMI values during childhood. Another study, like ours, indicates that breastfeeding does not prevent overweight or obesity.[21] Likewise, a study conducted in China showed that breastfeeding does not prevent overweight or obesity.[22] Some studies have found that breastfeeding is protective against obesity.[23] In a study in Japan from 2001 to 2009, eliminating other factors influencing obesity (gender, physical activity, chronic illness, maternal education, etc.), it was found that breastfeeding protects against obesity.[24] In another study comparing breastfed and non-breastfed babies, a 15% reduction in the frequency of childhood overweight was observed in breastfed babies.[25] Although our study did not yield statistically significant results, the obesity rate in children exclusively breastfed for twenty-four months and above was 15%, while it was 22% in those exclusively formula-fed. As seen, studies questioning the relationship between breastfeeding duration and BMI have produced different results. This can be attributed to factors such as genetics, physical activity, socio-economic status, in addition to the dietary pattern, influencing obesity.

In our study, a decrease in the occurrence of chronic diseases was observed with the duration of breastfeeding. Among the participants, 71% of those with chronic diseases had received breastfeeding for six months or less. Many of these chronic diseases include asthma and seasonal allergic rhinitis. In a study involving young adults aged 18-30, a significantly higher rate of allergic diseases was found in those who received breastfeeding for the first 4 months compared to those who received breastfeeding for 6 months or more.[26] Numerous studies have shown that an extended duration of breastfeeding is associated with a reduction in the risk of acute illnesses, certain chronic diseases, and hospitalization in later periods.[27] Similarly, an increased duration of breastfeeding has been reported to be associated with a decrease in the incidence of obesity, cancer, adult coronary heart disease, allergic conditions, Type 1 diabetes mellitus, and inflammatory bowel disease.[28]

Conclusion

In conclusion, our study did not find a significant relationship between the duration of breastfeeding and BMI values. However, an increase in the duration of breastfeeding was associated with a reduction in the incidence of chronic diseases. We believe that further studies with larger patient groups will shed more light on these matters.

Ethics Committee Approval: The study was granted approval by the Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 28/01/2022, No: 2022/514/218/15).

Peer-review: Externally peer-reviewed.

Informed Consent: Informed consent has been obtained from all participants.

Author Contribution: Concept: N.C., Y.C.; Design: N.C., Y.C.; Supervision: M.T.K., N.C.; Fundings: M.T.K., N.C.; Materials: M.T.K., N.C.; Data collection &/or processing: N.C., A.A.; Analysis and/or interpretation: M.T.K., N.C.; Literature search: N.C.; Writing: N.C.; Critical review: N.C.

Conflict of Interest: The authors declare no competing interests.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability Statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Dirikoc A, Genc B, Ozdemir D, Ogmen BE, Topaloglu O, Ersoy R, et al. Awareness of normal weight, overweight and obese patients about complications, risk factors and prevention of obesity. Endocr Abstr 2021;73:AEP814. [CrossRef]
2. Devaux M, Sassi F. Social inequalities in obesity and overweight in 11 OECD countries. Eur J Public Health 2013;23:464–9. [CrossRef]
3. Wu JF. Childhood obesity: A growing global health hazard extending to adulthood. Pediatr Neonatol 2013;54:71–2. [CrossRef]
4. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384:766–81. [CrossRef]
5. Ma J, Qiao Y, Zhao P, Li W, Katzmarzyk PT, Chaput JP, et al. Breastfeeding and childhood obesity: A 12-country study. Matern Child Nutr 2020;16:e12984. [CrossRef]
6. Gibson LA, Alava MH, Kelly MP, Campbell MJ. The effects of breastfeeding on childhood BMI: A propensity score matching approach. J Public Health 2017;39:e152–60. [CrossRef]
7. Renfrew MJ, Spiby H, D'Souza L, Wallace LM, Dyson L, McCormick F. Rethinking research in breast-feeding: A critique of the evidence base identified in a systematic review of interventions to promote and support breast-feeding. Public Health Nutr 2007;10:726–32. [CrossRef]
8. Rito AI, Buoncristiano M, Spinelli A, Salanave B, Kunešová M, Hejgaard T, et al. Association between characteristics at birth, breastfeeding and obesity in 22 countries: The WHO European childhood obesity surveillance initiative - COSI 2015/2017. Obes Facts 2019;12:226–43. [CrossRef]
9. Savino F, Liguori SA, Fissore MF, Oggero R, et al. Breast milk hormones and their protective effect on obesity. Int J Pediatr Endocrinol 2009:2009:327505. [CrossRef]
10. Neyzi O, Günöz H, Furman A, Bundak R, Gökçay G, Darendeliler F. Reference values for body weight, height, head circumference, and body mass index in Turkish children. Çocuk Sağlığı Hast Derg 2008;51:1–14. [Article in Turkish]
11. WHO Multicentre Growth Reference Study Group. WHO child growth standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization; 2006.
12. Türkiye Nüfus ve Sağlık Araştırmaları. Özet rapor 2018. Ankara: Hacettepe Üniversitesi Nüfus Etütleri Enstitüsü, Sağlık Bakanlığı Ana Çocuk Sağlığı ve Aile Planlaması Genel Müdürlüğü, Devlet Planlama Teşkilatı ve Avrupa Birliği; 2019. p. 141–7.
13. Telatar B, Vitrinel A, Akın Y, Comert S. The rates of breast feeding of infants from a well-child outpatient clinic. Bakırköy Tıp Derg 2008;4:144–7. [Article in Turkish]
14. Ryan AS, Zhou W, Arensberg MB. The effect of employment status on breastfeeding in the United States. Womens Health Issues 2006;16:243–51. [CrossRef]
15. Ünsal H, Atlıhan F, Özkan H, Targan Ş, Hassoy H. The tendency to breastfeed in society and the factors that affect it. Çocuk Sağlığı Hast Derg 2005;48:226–33. [Article in Turkish]
16. Türkiye Nüfus ve Sağlık Araştırmaları 2013. Available at: http://www.hips.hacettepe.edu.tr/tnsa2013/rapor/TNSA_2013_ana_rapor.pdf. Accessed Oct 10, 2020.

17. Türkiye Nüfus ve Sağlık Araştırması 2018. Available at: http://www.hips.hacettepe.edu.tr/tnsa2018/rapor/TNSA2018_ana_Rapor.pdf. Accessed Oct 10, 2020.
18. Çevik C, Ergün S, Karadaş A, Calışkan T, Karadağ N. Overweight and obesity in preschoolers in a region in western Turkey and related factors. Celal Bayar Univ Sağlık Bilim Enst Derg 2019;6:247–52. [CrossRef]
19. Tchoubi S, Sobngwi-Tambekou J, Noubiap JJ, Asangbeh SL, Nkoum BA, Sobngwi E. Prevalence and risk factors of overweight and obesity among children aged 6–59 months in Cameroon: A multistage, stratified cluster sampling nationwide survey. PLoS One 2015;10:e0143215. [CrossRef]
20. Vafa M, Moslehi N, Afshari S, Hossini A, Eshraghian M. Relationship between breastfeeding and obesity in childhood. J Health Popul Nutr 2012;30:303–10. [CrossRef]
21. Hassan NE, El-Masry SA, El Batrawy SR, Khalil A, Ali MM, Al-Tohamy M, et al. Relationship between breast feeding duration and risk of overweight/obesity among Egyptian children. Egypt Pediatr Assoc Gaz 2018;66:9–14. [CrossRef]
22. Jing H, Xu H, Wan J, Yang Y, Ding H, Chen M, et al. Effect of breastfeeding on childhood BMI and obesity: The China Family Panel Studies. Medicine 2014;93:e55. [CrossRef]
23. Grummer-Strawn LM, Mei Z; Centers for Disease Control and Prevention Pediatric Nutrition Surveillance System. Does breastfeeding protect against pediatric overweight? Analysis of longitudinal data from the Centers for Disease Control and Prevention Pediatric Nutrition Surveillance System. Pediatrics 2004;113:e81. [CrossRef]
24. Yamakawa M, Yorifuji T, Inoue S, Kato T, Doi H, et al. Breastfeeding and obesity among schoolchildren: A nationwide longitudinal survey in Japan. JAMA Pediatr 2013;167:919–25. [CrossRef]
25. Weng SF, Redsell SA, Swift JA, Yang M, Glazebrook CP. Systematic review and meta-analyses of risk factors for childhood overweight identifiable during infancy. Arch Dis Child 2012;97:1019–26. [CrossRef]
26. Demir EG, Köse G, Cambaz M, Pehlivanoğlu E. Anne sütü alım süresinin genç erişkinlik döneminde kronik hastalıklara etkisi. In: 8th International Fetal Life to Childhood First 1000 Days Mother-Child-Nutrition Congress; 2021 Mar 18–20; Online, Türkiye.
27. Horta B, Victora C. The long-term effects of breastfeeding: A systematic review. Geneva: World Health Organization; 2013.
28. Victora CG, Bahl R, Barros AJ, França GV, Horton S, Krasevec J, et al. Breastfeeding in the 21st century: Epidemiology, mechanisms, and lifelong effect. Lancet 2016;387:475. [CrossRef]

ORIGINAL ARTICLE

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.37530

Surgical Outcomes and Prognostic Factors of Pulmonary Pleomorphic Carcinoma

Berk Cimenoglu, Attila Ozdemir, Mesut Buz, Fatma Tugba Ozlu, Talha Dogruyol, Recep Demirhan

Abstract

Objective: Pulmonary pleomorphic carcinoma (PPC) is one of the rarest subtypes of non-small cell lung cancer (NSCLC) and is associated with a poor prognosis. Since this tumor is known to be chemoresistant, anatomical resection is considered the primary treatment option, especially in the early stages. Due to its rarity, the number of studies on this subject in the literature is quite limited. In this study, we aimed to investigate the long-term postoperative outcomes of patients operated on for PPC and the factors affecting survival.

Methods: Patients who underwent surgery for lung cancer were retrospectively reviewed. Those with a postoperative histopathological diagnosis of PPE were included. Demographic and clinicopathological characteristics were analyzed, and factors affecting overall survival (OS) and disease-free survival (DFS) were investigated.

Results: A total of 25 patients who underwent surgery for PPC between 2016 and 2025 were included in the study. After excluding surgical mortality, the mean OS was calculated as 54.3±9.9 months, with a 5-year OS rate of 49.6%. Recurrence developed in 13 (52%) patients. The mean DFS was 43.1±9.9 months, and the 5-year DFS rate was 40.9%. Surgical incision analysis reveals the mean OS was 48.2±11.6 months and the 5-year OS rate was 43.8% in patients who underwent thoracotomy. These values were 77.6±12.9 months and 80% in patients who underwent VATS, respectively (p=0.048). A statistically significant relationship was found between stage and survival (p=0.042). Although not reaching statistical significance, the presence of spread-through air spaces (STAS), perineural invasion, and vascular invasion was associated with poorer prognosis.

Conclusions: In our study, the prognostic factors that had a statistically significant effect on survival in PPC were the use of minimally invasive surgery and the stage of the disease. Invasion-related parameters such as STAS, perineural invasion, and vascular invasion were also found to negatively affect survival, although they did not reach statistical significance.

Keywords: Pleomorphic carcinoma; lung cancer; resection.

Department of Thoracic Surgery, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Türkiye

Address for correspondence:
Berk Cimenoglu, Department of Thoracic Surgery, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Türkiye
E-mail: berkcimenoglu@hotmail.com

Received: 07.05.2026
Accepted: 18.05.2026
Published: 29.09.2026

Introduction

Pulmonary pleomorphic carcinoma (PPC) is an extremely rare subtype among all lung cancers.[1] Although PPC can originate from any part of the body, it most commonly arises from the respiratory system. Histopathologically, it must contain at least 10% giant cells or spindle cells. In the 2021 classification of the World Health Organization (WHO), pul-

How to cite this article: *Cimenoglu B, Ozdemir A, Buz M, Ozlu FT, Dogruyol T, Demirhan R. Surgical outcomes and prognostic factors of pulmonary pleomorphic carcinoma. South. Clin. Ist. Euras. 2026;37(3):286-293.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Copyright@Author(s)

monary pleomorphic carcinoma is classified as a subtype of sarcomatoid carcinoma of the lung.[2]

PPC ha been repoted to have a tendency to metastasize early and is associated with a poor prognosis.[3] PPC is most commonly seen in smoker males. The tumor diamater is usually large at the time of diagnosis.[4]

PPC has been reported to have a tendency for early metastasis and is associated with poor prognosis.[3] It is most commonly seen in male smokers, and the tumor size is usually large at the time of diagnosis.[4] The prognosis of PPC is worse than that of non-small cell lung carcinoma (NSCLC). Since PPC is known to be chemoresistant, the primary treatment in the early stages is surgical resection. In localized and early-stage disease, anatomical resection is considered the treatment of choice. Although systemic therapies may be considered in metastatic disease, these tumors have been reported to show high resistance to platinum-based chemotherapy.[5] While some authors recommend adjuvant treatment even in early-stage disease following surgery, it has also been emphasized that the role of systemic therapy in PPC requires further investigation.[6,7]

Since PPC is a very rare subtype of non-small cell lung cancer, the number of studies in the literature on this tumor type is limited, and most of these studies consist of case reports. The aim of this study was to investigate the surgical outcomes and the factors affecting survival in patients who underwent surgery for lung cancer and were diagnosed with pleomorphic carcinoma on final pathological examination during 10 year period.

Materials and Methods

Patients

Patients who underwent surgery for lung cancer in our clinic were retrospectively reviewed. Among these patients, those whose final postoperative pathology report revealed pleomorphic carcinoma were included in the study. Patients who did not undergo surgery for curative treatment and those with insufficient medical records were excluded. This study was approved by the Ethics Committee our Hospital with the approval number 2026/010.99/27/13 (Date: 29.04.2026) and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

Data Collection

The demographic characteristics of the patients included in the study, the surgical treatment performed, invasion parameters, maximum standardized uptake value (SUVmax) on positron emission tomography/computed tomography (PET/CT), administration of adjuvant therapy, stages according to the 9th TNM classification system, overall survival (OS), and disease-free survival (DFS) were evaluated. Lesions located in the inner half of the lung parenchyma were classified as central, whereas those located in the outer half were classified as peripheral. OS and DFS were defined as the time from surgery to death or recurrence, respectively.

Preoperative Period

All patients scheduled for lung cancer surgery underwent preoperative thoracic CT and PET/CT evaluation. Surgical treatment was recommended for patients who had no evidence of mediastinal lymph node or distant metastasis on PET/CT but were suspected of having malignancy in the pulmonary lesion itself. In such cases, wedge resection lesion was initially performed, and anatomical resection was subsequently carried out if malignancy was confirmed on frozen-section examination. In patients with central lesions or tumors larger than 3 cm, transbronchial needle biopsy or transthoracic aspiration biopsy was performed as the primary diagnostic procedure. In patients with tumors measuring 3 cm or larger, invasive mediastinal staging was performed using endobronchial ultrasound (EBUS) or mediastinoscopy. Patients staged as N0–N1 underwent direct surgery. In patients with N2a disease, surgery was planned following neoadjuvant therapy. Surgery was not planned in cases with multistation N2 disease. The cardiopulmonary functions of the patients were evaluated preoperatively by echocardiography and pulmonary function tests.

Surgical Approach

The type of anatomical resection—segmentectomy, lobectomy, bilobectomy, or pneumonectomy—was determined according to tumor location and size. R0 resection was achieved in all patients included in the study. Video-assisted thoracoscopic surgery (VATS) was preferred for small, peripheral tumors, whereas thoracotomy was performed for central and large tumors. In cases with chest wall invasion, en bloc chest wall resection was performed. For accurate staging, mediastinal lymph node dissection was performed during the same surgical session as the anatomical resection.

Postoperative Follow-up

Patients who underwent anatomical resection due to PPC were followed up with thoracic CT every 6 months for the first 2 years and annually for the subsequent 3 years. Patients with tumors larger than 4 cm or those with metastases in mediastinal or hilar lymph nodes were consulted with the medical oncology department for adjuvant therapy. Some of these patients either de-

Table 1. Demographics of the patients, surgical approach, invasion parameters and staging.

Gender		**Mediastinal Staging**	
Male	22 (88%)	Not performed	10 (40%)
Female	3 (12%)	Performed	15 (60%)
Preoperative Biopsy		STAS	
Malignant	11 (44%)	Negative	19 (76%)
Pleomorphic Carcinoma	1 (4%)	Positive	6 (24%)
AdC	3 (12%)	Pleural invasion	
SqCC	1 (4%)	PL0	15 (60%)
Non-diagnostic	6 (24%)	PL1	2 (8%)
Not performed	3 (12%)	PL 2	4 (16%)
Definitive diagnosis		PL 3	4 (16%)
Pleomorphic Carcinoma	9 (36%)	Vascular invasion	
with AdC component	11 (44%)	No	20 (80%)
with SqCC component	5 (20%)	Yes	5 (20%)
Symptoms		Perineural invasion	
Incidental	4 (16%)	No	21 (84%)
Chronic cough	4 (16%)	Yes	4 (16%)
Chest pain	5 (20%)	Lymphatic Invasion	
Hemoptisis	1 (4%)	No	7 (28%)
Fatigue	1 (4%)	Yes	6 (24%)
Shortness of breath	10 (40%)	Not investigated	12 (48%)
Surgery		T Status	
Trisegmentectomy	1 (4%)	T1b	1 (4%)
RUL	12 (48%)	T1c	4 (16%)
RLL	5 (20%)	T2a	6 (24%)
LUL	3 (12%)	T3	7 (28%)
LLL	2 (8%)	T4	7 (28%)
Upper bilobectomy	1 (4%)	N Status	
Left Pneumonectomy	1 (4%)	N0	15 (60%)
Incision		N1	7 (28%)
VATS	6 (24%)	N2a	3 (12%)
Thoracotomy	18 (72%)	Stage	
Conversion	1 (4%)	IA	4 (16%)
Neoadjuvant Treatment		IB	4 (16%)
No	12 (48%)	2A	1 (4%)
Yes	13 (52%)	2B	3 (12%)
Location		3A	13 (52%)
Peripheral	18 (76%)		
Central	7 (28%)		

AdC: Adenocarcinoma, LLL: Left lower lobectomy, LUL: Left upper lobectomy, PL: pleural invasion, RLL: Right lower lobectomy, RML: Right middle lobectomy, RUL: Right upper lobectomy, , SqCC: Squamous cell carcinoma, STAS: Spread through air spaces, VATS: Video-assisted thoracoscopic surgery.

clined adjuvant treatment or were unable to tolerate its oncological side effects. Patients with an indication for adjuvant therapy were followed with thoracic CT every 3 months for the first 2 years after completion of treatment and every 6 months during the subsequent 3 years. In cases where recurrence or metastasis was suspected on thoracic CT, further evaluation was performed with PET/CT. When necessary, repeat biopsy was performed to confirm recurrence or metastatic disease.

Statistical Analysis

Categorical variables were presented as frequencies and percentages. Continuous variables were expressed as mean ± standard deviation and compared using the Student's t-test. OS and DFS were estimated using the Kaplan–Meier method, with statistical differences assessed by the log-rank test. Survival analyses are carried out after excluding operative mortality. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were carried out using SPSS version 26.0 (IBM Corporation, Armonk, NY, USA).

Results

Between January 2016 and December 2025, a total of 1,066 patients underwent anatomical resection for lung cancer at our hospital. Among these patients, 25 (2.34%) were diagnosed with PPC based on the postoperative pathological report.

Table 2. Recurrence sites of patients included in the study

Recurrence Site	
Bone	5 (20%)
Locoregional	4 (16%)
Brain	2 (8%)
Adrenal	2 (8%)
Total	13 (52%)

The demographic characteristics of the patients, surgical approach, invasion parameters, and stage distrubition are presented in Table 1.

The mean age of the patients was 63.4±8.5 years. The mean tumor size was 54.3±23.6 mm. The mean SUVmax uptake on PET/CT was calculated as 15.3±7.7.

Three patients (12%) died within the first 3 months after surgery and were classified as surgical mortality. During the study period, mortality occurred in 14 patients (56%). The mean OS of the study population was 47.9±9.4 months, and the 5-year OS rate was 43.6%. After excluding surgical mortality, the mean OS was 54.3±9.9 months, and the 5-year OS rate was 49.6%. Recurrence developed in 13 patients (52%). The sites of recurrence and metastasis are presented in Table 2. The mean DFS was 43.1±9.9 months, and the 5-year DFS rate was 40.9%.

En bloc chest wall resection was performed in 5 patients (20%) in addition to anatomical lung resection. Sleeve resection was performed in 2 patients (8%) due to tumor location. Two patients (8%) underwent surgical treatment following neoadjuvant therapy.

The effects of STAS on clinicopathological factors and survival are presented in Table 3.

The impact of perineural invasion and vascular invasion on OS and DFS is shown in Table 4.

In patients who underwent thoracotomy, the mean survival was 48.2±11.6 months, and the 5-year OS rate was 43.8%. These values were 77.6±12.9 months and 80%, respectively, in patients who underwent VATS. One patient who required conversion was lost in the 5th postoperative month. The difference between the groups was statistically significant (p=0.048) (Fig. 1). The mean DFS was 43.8±12.4 months in patients who underwent VATS and 42.1±12.4 months in patients who underwent tho-

Table 3. The effects of STAS on clinicopathological factors and survival

	STAS (+)	STAS (-)	p value
Tumor size (mm)	53.0±27.8	54.7±23.0	0.518
SUVMax	14.9±9.3	15.6±7.4	0.504
Mean OS (months)	40.5±17.6	58.7±11.4	
5-year OS	33.3%	56.3%	0.485
Mean DFS (months)	25.8±14.1	50.1±11.8	
5-year DFS	16.7%	52.5%	0.352

Table 4. The effects of perineural invasion and vascular invasion on OS and DFS. DFS: Disease-free survival, OS: Overall survival

	Mean OS (months)	5-year OS	Mean DFS (months)	5-year DFS
Perineural invasion (+)	12.5±5.4	25.0%	11.0±5.8	25.0%
Perineural invasion (-)	59.6±10.9	55.0%	46.9±11.0	44.4%
p value		0.209		0.348
Vascular invasion (+)	53.8±23.6	50.0%	53.0±24.0	25.0%
Vascular invasion (-)	53.3±10.8	49.4%	38.9±10.4	38.3%
p value		0.970		0.570

racotomy, with 5-year DFS rates of 53.3% and 38.2%, respectively (p=0.305).

OS analysis based on stage reveals the mean OS was 83.3±14.3 months in stage I, 72.0±16.5 months in stage II, and 31.1±11.7 months in stage III disease. The 5-year OS rates were 83.3%, 21.7%, and 12.5%, respectively. The difference between the groups was statistically significant (p=0.042) (Fig. 2). Stage – DFS analysis reveals the mean DFS was 56.6±15.9 months in stage I disease, 23.0±12.9 months in stage II disease, and 37.6 months in stage III disease. The 5-year DFS rates were 62.5%, 25.0%, and 33.3%, respectively (p=0.563).

Discussion

PPC is an extremely rare subtype of NSCLC. When the available literature is reviewed, it is evident that the number of patients included in these studies is low, and a significant proportion of the publications consist of case

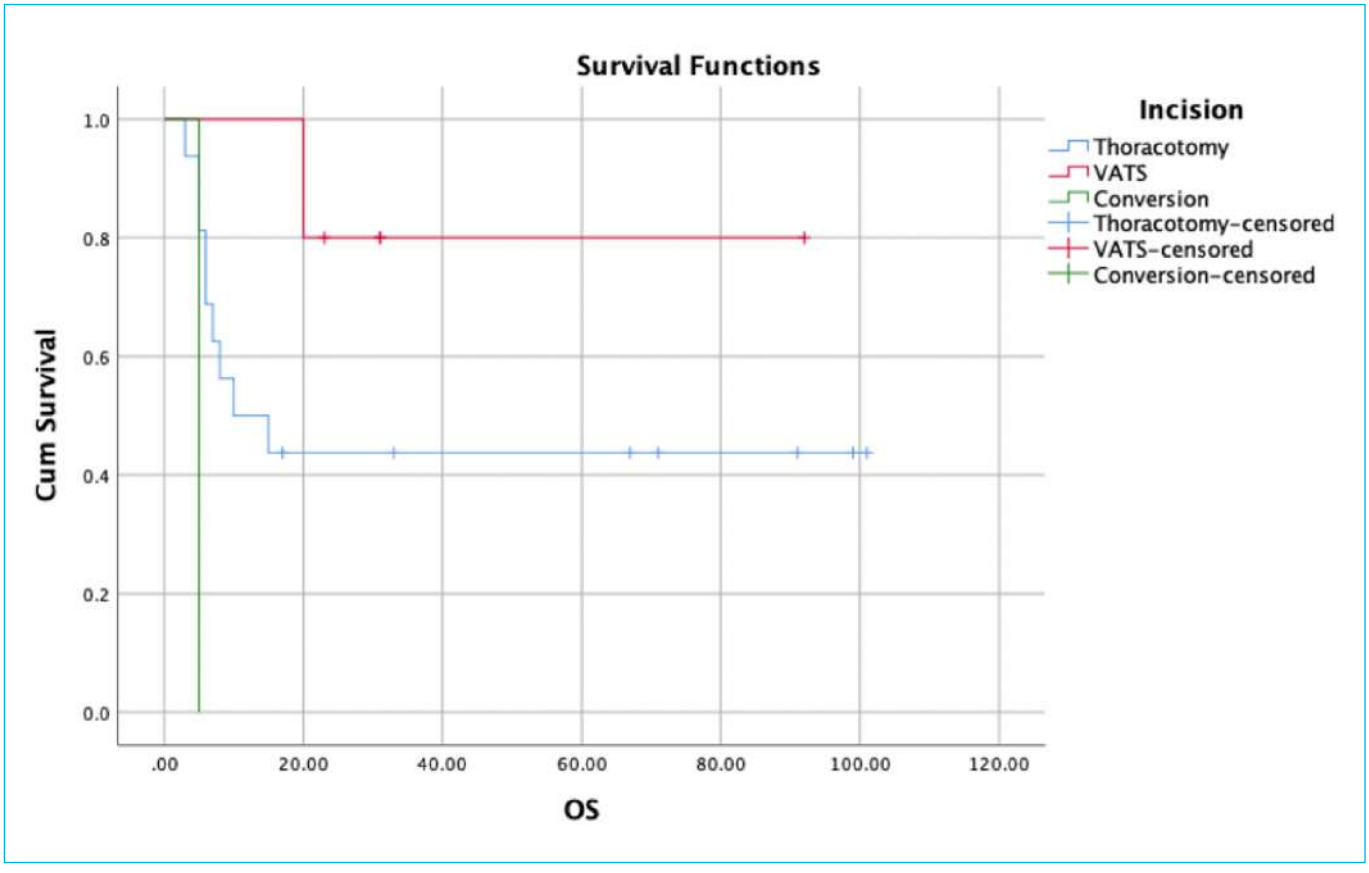

Figure 1. Survival plot of the patients based on surgical invision

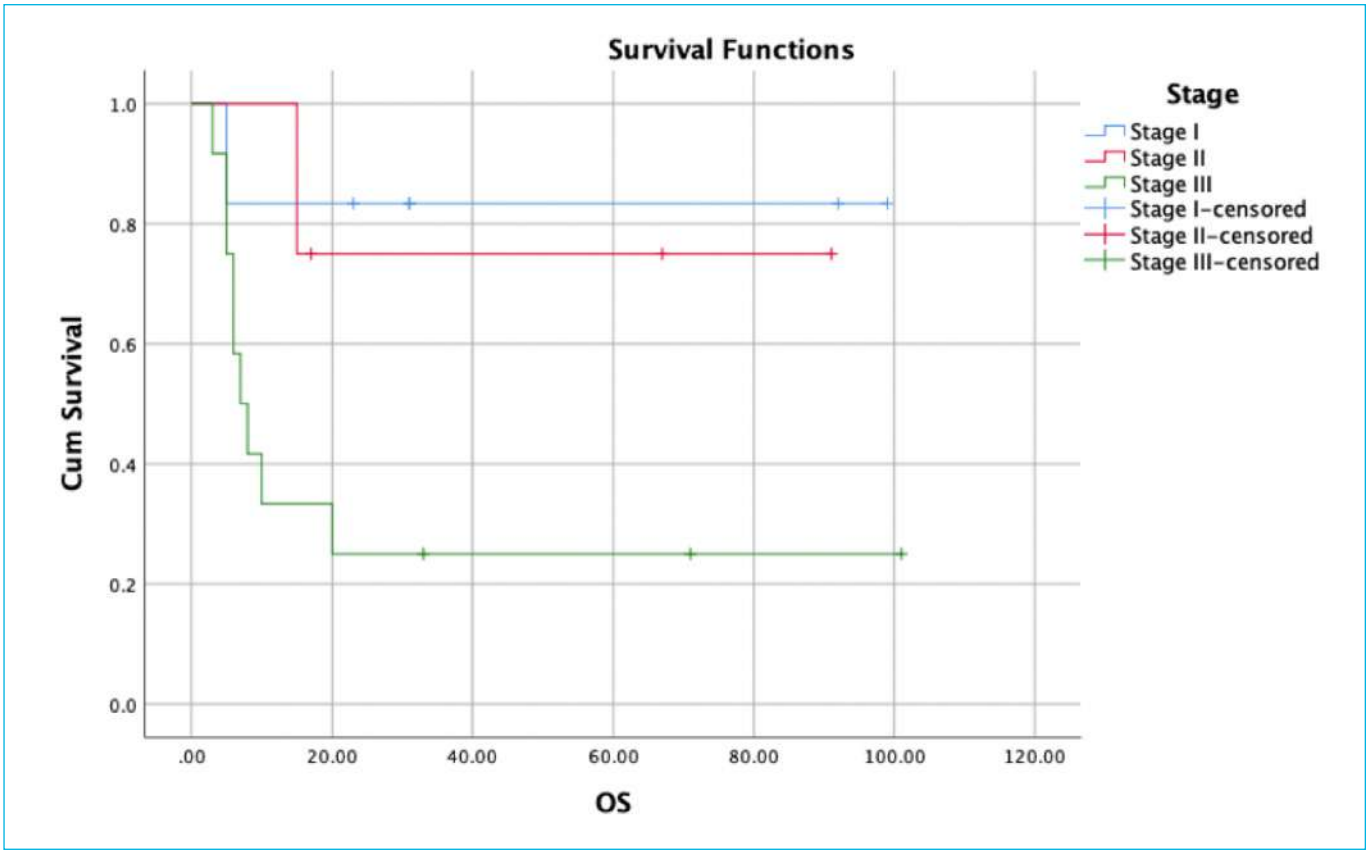

Figure 2. Survival plot of the patients based on stage of the disease.

reports. Therefore, although surgical treatment is considered the primary approach in PPC management, there is no clearly established consensus on an optimal treatment modality. In addition, due to these limitations, prognostic factors affecting survival in these tumors have not been clearly defined. In our study, we evaluated 25 patients with pleomorphic carcinoma who underwent surgery in our clinic over the past 10 years.

In literature, survival in PPC has been reported to be variable. In a study in which the majority of the study population was inoperable, the 5-year OS was reported as 23%.[7] In another study evaluating 17 surgically treated patients, the 3-year and 5-year OS rates were 45.3% and 27.2%, respectively, and the 5-year DFS was reported as 51.0%.[3] In our study, both OS and DFS values were found to be consistent with the literature; however, the OS outcomes were slightly better, which we attribute to close postoperative follow-up. In addition, when survival data from both our study and other published reports on PPC are considered, PPC appears to be associated with poorer survival compared to NSCLC.[8]

First described by Kadota et al.[9] in 2015, STAS is defined as tumor cell clusters or single tumor cells within air spaces beyond the main tumor border. In 2021, the WHO recognized STAS as an invasion pattern and a prognostic factor for adenocarcinomas.[10] In studies on pleomorphic carcinoma, the negative prognostic impact of STAS has also been demonstrated. In a study by Sikora and Langfort, STAS was reported to be a poor prognostic factor for both OS and DFS.[11] In a similar study, STAS was observed in 40% of cases and was shown to be associated with both frequent recurrence and poor prognosis.[12] In our study, consistent with these findings, STAS was associated with poorer OS and DFS; however, this association did not reach statistical significance. In addition to its effect on survival outcomes, we also evaluated the relationship between STAS, SUVmax, and tumor size, and did not find STAS to be a determining factor for SUVmax or tumor size. Beyond STAS, perineural invasion and vascular invasion have also been shown to be associated with poor prognosis in NSCLC.[13,14] Similarly, in our study, we observed that perineural invasion and

vascular invasion were associated with poorer prognosis, although without statistical significance.

PPC has been reported to more frequently present with upper lobe and peripheral localization.[15] For this reason, it may be suitable for minimally invasive surgical approaches. In meta-analyses comparing VATS and thoracotomy, VATS has been shown to be non-inferior to thoracotomy in terms of DFS and OS.[16,17] However, a literature review revealed no study comparing VATS and thoracotomy specifically in PPC. In our study, we found that OS was significantly better in patients who underwent VATS. We believe this may be due to the fact that VATS is more commonly applicable in smaller, peripheral, and earlier-stage tumors. Because PPC tends to show both peripheral growth and a high potential for rapid invasion, chest wall invasion is frequently encountered in these tumors. However, when diagnosed before chest wall invasion occurs, favorable outcomes can be achieved with minimally invasive surgical techniques.

One of the most important prognostic factors in lung cancer is the stage of the disease. This effect appears to be even more pronounced in PPC. The main reason for this is that the most effective treatment modality for this tumor type is surgery, as it shows resistance to oncological therapies. In our study, tumor stage was identified as a statistically significant prognostic factor affecting survival.

Our study has several limitations. One of them is its retrospective design. However, since patient records in our department are maintained in a meticulous manner, the study data were readily accessible. The second limitation is the small sample size. Since PPC is a very rare tumor type, the number of cases in our series is limited, and similarly, studies in the literature on this topic are also characterized by small sample sizes.

Conclusion

PPC is a subtype with a poorer prognosis compared to NSCLC in general. In our study, minimally invasive surgery and disease stage were found to be prognostic factors that had a statistically significant impact on survival in PPC. In addition, invasion parameters such as STAS, perineural invasion, and vascular invasion were also observed to affect survival, although they did not reach statistical significance.

Acknowledgements: Artificial intelligence was utilized solely for writing assistance, grammar correction, and to enhance the clarity and understandability of the manuscript.

Ethics Committee Approval: Ethical approval for the study was obtained from the Ethics Committee of Kartal Dr. Lütfi Kırdar City (Date: 29/04/2026, No: 2026/010.99/27/13).

Peer-review: Externally peer-reviewed.

Informed Consent: Informed consent was obtained from all participants.

Author Contribution: Concept: B.C. F.T.O.; Design: A.O., F.T.O.; Supervision: M.B., T.D.; Materials: M.B., T.D.; Data collection &/or processing: A.O., F.T.O.; Analysis and/or interpretation: B.C.; Literature search: M.B., R.D.; Writing: B.C., R.D.; Critical review: R.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Funding: The authors declared that this study has received no financial support.

References

1. Jeong JH, Seo HJ, Yoon SH, Hong R. Pulmonary pleomorphic carcinoma presenting as undifferentiated non-small cell carcinoma with giant cells: A case report and review of literature. Respir Med Case Rep 2020;31:101225. [CrossRef]
2. WHO Classification of Tumours Editorial Board. WHO classification of tumours. Thoracic tumours. 5th ed. Lyon: IARC Press; 2021.
3. Iijima Y, Nakajima Y, Kinoshita H, Nishimura Y, Iizuka T, Akiyama H, et al. Clinicopathological analysis of 17 surgically resected pulmonary pleomorphic carcinoma cases. Ann Thorac Cardiovasc Surg 2021;27:1–9. [CrossRef]
4. Ito K, Oizumi S, Fukumoto S, Harada M, Ishida T, Fujita Y, et al. Clinical characteristics of pleomorphic carcinoma of the lung. Lung Cancer 2010;68:204–10. [CrossRef]
5. Vieira T, Girard N, Ung M, Monnet I, Cazes A, Bonnette P, et al. Efficacy of first-line chemotherapy in patients with advanced lung sarcomatoid carcinoma. J Thorac Oncol 2013;8:1574–7. [CrossRef]
6. Oyama T, Fujimoto H, Yamamoto M, Onouchi S, Kameyama Y, Nakayama S, et al. Surgical treatment for small bowel metastasis of pleomorphic carcinoma 6 months after pulmonary resection. Kyobu Geka 2012;65:566–9.
7. Chen Z, Liu J, Min L. Clinicopathological characteristics, survival outcomes and prognostic factors in pleomorphic carcinoma: A SEER population-based study. BMC Pulm Med 2022;22:116. [CrossRef]
8. Akcam TI, Tekneci AK, Turhan K, Duman S, Cuhatutar S, Ozkan B, et al. Prognostic value of systemic inflammation markers in early stage non-small cell lung cancer. Sci Rep 2025;15:33886. [CrossRef]
9. Kadota K, Nitadori J, Sima CS, Ujiie H, Rizk NP, Jones DR, et al. Tumour spread through air spaces is an important pattern of invasion and impacts the frequency and location of recurrences after limited resection for small stage I lung adenocarcinomas. J Thorac Oncol 2015;10:806–14. [CrossRef]
10. Lightner-Ferrer C, Burke L. Pathology of lung tumours: WHO 2021 updates and resection status. Diagn Histopathol 2026;32:92–5. [CrossRef]
11. Sikora K, Langfort R. EP06.05-15 STAS and expression of EMT-

markers in surgically resected lung pleomorphic carcinomas. J Thorac Oncol 2023;18:499–500. [CrossRef]

12. Yokoyama S, Murakami T, Tao H, Onoda H, Hara A, Miyazaki R, et al. Tumor spread through air spaces identifies a distinct subgroup with poor prognosis in surgically resected lung pleomorphic carcinoma. Chest 2018;154:838–47. [CrossRef]
13. Liu W, Ren S, Zeng C, Hu Y. Prognostic value of perineural invasion in resected non-small cell lung cancer: A meta-analysis. Heliyon 2023;9:e15266. [CrossRef]
14. Yambayev I, Sullivan T, Rieger-Christ K. Vascular invasion identifies the most aggressive histologic subset of stage I lung adenocarcinoma: Implications for adjuvant therapy. Lung Cancer 2022;171:82–9. [CrossRef]
15. Chen F, Sonobe M, Sato T, Sakai H, Huang CL, Bando T, et al. Clinicopathological characteristics of surgically resected pulmonary pleomorphic carcinoma. Eur J Cardiothorac Surg 2012;41:1037–42. [CrossRef]
16. Harris RA, Law JJ, Hao L, Situ D, Dittberner FA, Bendixen M, et al. Survival outcome of VATS compared with open lobectomy for lung cancer: An individual patient data meta-analysis of randomised trials. Lancet 2026;407:1182–90. [CrossRef]
17. Dittberner FA, Bendixen M, Licht PB. Long-term survival from a randomized controlled trial of lobectomy by video-assisted thoracoscopic surgery versus thoracotomy for early-stage lung cancer. Eur J Cardiothorac Surg 2025;67:ezaf017. [CrossRef]

ORIGINAL INVESTIGATION

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.74547

Comparison of Efficacy and Safety of Three Chemoradiotherapy Regimens in Elderly Patients with Inoperable Stage III Non-Small Cell Lung Cancer

Pınar Özdemir,[1] Erman Özdemir,[2] Serap Yadigar,[1] Erdoğan Özdemir[3]

Abstract

Objective: Concurrent chemoradiotherapy (CRT) is the standard treatment for patients with unresectable stage III non-small cell lung cancer (NSCLC). However, data on its efficacy and safety in elderly populations are limited. This study aimed to evaluate survival outcomes, treatment response, and toxicity profiles of CRT with three different chemotherapy regimens in elderly patients with stage III NSCLC.

Methods: We retrospectively analyzed 75 patients aged ≥65 years with unresectable stage IIIA–IIIB NSCLC who received CRT between October 2006 and October 2014. Patients were treated with one of the following regimens: Carboplatin plus paclitaxel (PC; n=41), cisplatin plus docetaxel (PD; n=21), or cisplatin plus etoposide (PE; n=13). Radiotherapy was administered concurrently in all cases (60 Gy in 30 fractions). Clinical endpoints included overall survival (OS), progression-free survival (PFS), treatment response (per RECIST v1.1), and toxicity (per NCI-CTCAE v4.03).

Results: Median OS was 31.6 months in the PE group, 20.0 months in the PC group, and 13.7 months in the PD group (p=0.322). Median PFS was 19.8, 10.6, and 10.9 months for PE, PC, and PD groups, respectively (p=0.643). Disease control rates—defined as complete response (CR), partial response (PR), and stable disease (SD)—were 92.3% (PE), 75.6% (PC), and 71.4% (PD) (p=0.279). Neuropathy was most common in the PC group (20%), while hematologic toxicities occurred more frequently in the PD group. Chemotherapy discontinuation was significantly higher in patients with Eastern Cooperative Oncology Group (ECOG) performance status of 2 (p=0.012).

Conclusions: In elderly patients with inoperable stage III NSCLC, all three CRT regimens demonstrated acceptable efficacy and safety profiles. Although not statistically significant, the PE regimen was associated with numerically better survival outcomes and higher disease control rates, suggesting it may be a favorable option for selected elderly patients.

Keywords: Elderly patients; non-small cell lung cancer; concurrent chemoradiotherapy; cisplatin-etoposide; toxicity; survival.

[1]Department of Nephrology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye
[2]Department of Nephrology, Pendik State Hospital, Istanbul, Türkiye
[3]Department of Internal Medicine, Fethi Sekin City Hospital, Elazig, Türkiye

Address for correspondence:
Pınar Özdemir, Department of Nephrology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye
E-mail: pinarozdemir23@yahoo.com

Received: 19.05.2026
Accepted: 17.06.2026
Published: 29.09.2026

How to cite this article: *Özdemir P, Özdemir E, Yadigar S, Özdemir E. Comparison of efficacy and safety of three chemoradiotherapy regimens in elderly patients with inoperable stage iii non-small cell lung cancer. South. Clin. Ist. Euras. 2026;37(3):294-300.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Copyright@Author(s)

© 2026 Southern Clinics of Istanbul Eurasia by Kare Media

Introduction

Lung cancer remains the leading cause of cancer-related deaths worldwide, accounting for approximately 1.8 million fatalities annually.[1] Among all lung cancers, non-small cell lung cancer (NSCLC) comprises over 80 % of cases and exhibits a generally poor prognosis, especially when diagnosed at an advanced stage.[2] Stage III NSCLC is a heterogeneous entity, often considered inoperable due to local advancement, but still potentially curable with aggressive multimodality therapy. Concurrent chemoradiotherapy (CRT) has emerged as the standard of care in these patients, offering superior survival outcomes compared to sequential treatment modalities.[3] However, treatment decisions in elderly patients pose unique challenges due to physiological aging, increased comorbidities, and the potential for heightened toxicity.

The median age at diagnosis for NSCLC in developed countries is around 68 years,[4] and a significant proportion of patients with stage III disease fall within the geriatric population. As the global population continues to age, the incidence of NSCLC in elderly patients is expected to rise, prompting a need for more age-inclusive treatment paradigms. Historically, elderly patients have been underrepresented in clinical trials,[5] resulting in a paucity of data regarding the safety and efficacy of standard treatments such as concurrent CRT in this demographic. Moreover, clinicians often face the dilemma of balancing the benefits of aggressive treatment against the risks of toxicity, functional decline, and impaired quality of life.

Geriatrics and Oncology: A Crossroad of Precision Care

Geriatrics, as a medical subspecialty (typically ≥ 65 years), employs a multidisciplinary approach to aging, encompassing physiological, psychological, and social dimensions.[6] The development of geriatrics as a formal discipline has enabled integration of tools like the Comprehensive Geriatric Assessment (CGA), which evaluates functional status, comorbidities, cognition, emotional conditions, nutrition, and social support to guide individualized care plans.[7] In oncology, geriatric principles are crucial, as cancer incidence increases with age. Geriatric oncology—a field at the intersection of these disciplines—aims to tailor treatment decisions based on physiological rather than chronological age. Organizations such as the International Society of Geriatric Oncology (SIOG) and the American Society of Clinical Oncology (ASCO) now strongly recommend integrating geriatric assessments into cancer care to improve outcomes and reduce harm.[8]

Physiological changes associated with aging—such as reduced organ function, altered pharmacokinetics, and diminished marrow reserve—alongside comorbidities render older adults more vulnerable to adverse effects from chemotherapy and radiotherapy.[9] Consequently, there is often a tendency to modify or withhold standard therapy in elderly patients, risking suboptimal cancer control.[10]

Nonetheless, emerging evidence indicates that carefully selected older adults can derive significant benefit from concurrent CRT with manageable toxicity profiles. Several retrospective analyses and population-based studies have demonstrated that age alone should not contraindicate aggressive treatment.[11] Tools such as the CGA and performance scales (ECOG or Karnofsky) help stratify patients by functional reserve and predict tolerance. Elderly patients with good performance status and limited comorbidities may achieve outcomes comparable to their younger counterparts when receiving guideline-concordant therapy.[12]

Advancements in radiotherapy—such as intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and newer chemotherapy regimens have improved treatment precision and tolerability. Supportive care—including nutrition, antiemetics, and granulocyte colony-stimulating factors—further enhances CRT feasibility in older populations.[13]

Despite progress, many questions remain regarding the optimal management of elderly stage III NSCLC patients. This population's heterogeneity demands individualized strategies accounting for physiological age. Robust clinical trials targeting elderly cohorts are needed to establish evidence-based guidelines and refine selection criteria. Moreover, real-world institutional data can further inform treatment outcomes and safety profiles.[14]

In this context, our study evaluates the efficacy and safety of concurrent CRT in elderly patients (aged ≥ 65) with stage III NSCLC. By analyzing treatment responses, survival outcomes, and toxicity profiles, we aim to contribute to geriatric oncology literature and assist clinicians in making informed decisions. With the growing burden of NSCLC in the elderly, such data are critical for optimizing both survival and quality of life.

Materials and Methods

Patient Selection

A retrospective review was conducted on patients aged 65 years or older who were diagnosed with inoperable stage III non-small cell lung cancer (NSCLC) and received concurrent chemoradiotherapy at a tertiary care training and research hospital between October 2006 and October 2014. Histopathologic confirmation of NSCLC was mandatory for inclusion.[15] Patients with stage IIIA or IIIB disease, considered inoperable based on computed tomography (CT) or positron emission tomography (PET) assessments and multidisciplinary evaluation involving radiologists, thoracic surgeons, and both medical and radiation oncologists, were included.[16] Individuals who underwent surgery following neoadjuvant therapy were excluded. Staging was performed according to the seventh edition of the TNM classification system.[17]

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the institutional Scientific Research Ethics Committee (decision number 2025/010.99/17/33, dated June 25, 2025). Owing to the retrospective design of the study, the requirement for written informed consent was waived.

Clinical and demographic data, including age, sex, histologic subtype, performance status (ECOG), chemotherapy protocol, and toxicity profiles, were extracted from institutional records.

Treatment Protocol

All patients received concurrent chemoradiotherapy. Chemotherapy regimens were as follows:

- Cisplatin–Etoposide (PE): Cisplatin at 50 mg/m² on days 1, 8, 29, and 36; etoposide at 50 mg/m² on days 1–5 and 29–33.
- Cisplatin–Docetaxel (PD): Weekly administration of cisplatin 20 mg/m² and docetaxel 20 mg/m².
- Carboplatin–Paclitaxel (PC): Weekly administration of carboplatin (AUC 2) and paclitaxel 45 mg/m².

Radiotherapy was delivered using three-dimensional conformal radiation therapy (3D-CRT) with 6 MV photon beams. A total dose of 60 Gy was administered in 2 Gy fractions per day, five days a week, over six weeks. Radiotherapy was initiated concurrently with chemotherapy on day 1. Target volumes were delineated based on CT or PET imaging. The clinical target volume (CTV) was defined as the gross tumor volume (GTV; the visible tumor on imaging) plus a 1 cm margin; the planning target volume (PTV) included an additional margin of 0.5–1 cm to the CTV.

Toxicity Assessment

Toxicities were evaluated and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.[18] Due to the retrospective nature of the study, only grade 2 or higher adverse events were considered.

Follow-up and Response Evaluation

Patients were monitored every three months during the first two years of post-treatment and at six-month intervals thereafter. Follow-up assessments included physical examination, laboratory analyses, and thoracic CT imaging. Additional imaging was performed if recurrence was suspected. Tumor response was evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[19]

Statistical Analysis

Overall survival (OS) was defined as the duration from initial diagnosis to death or last follow-up. Progression-free survival (PFS) was calculated from the date of diagnosis to either documented disease progression or death from any cause. OS and PFS were estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariate Cox proportional hazards regression was used to determine independent prognostic factors. Differences in toxicity profiles between treatment groups were analyzed using the Chi-square test. Statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). A p-value of less than 0.05 was considered statistically significant.

Results

A total of 75 elderly patients (≥65 years) with an inoperable stage III NSCLC were included in the study. The median age was 69.95 years (range, 65–82), and the majority were male (84%). Patients were treated with one of three chemoradiotherapy regimens: PC (n=41), PD (n=21), or PE (n=13). Demographic and clinical characteristics are summarized in Table 1. The distribution of tumor stages and histologic subtypes is shown in Table 2.

Table 1. Patient characteristics

Chemotherapy Regimen	Number of Patients	Median Age (years)	Age ≥70 (%)	ECOG 0–1 (%)	ECOG 2 (%)
Carboplatin–Paclitaxel (PC)	41	70	56.1	61.0	39.0
Cisplatin–Docetaxel (PD)	21	70	52.4	81.0	19.0
Cisplatin–Etoposide (PE)	13	67	30.8	92.3	7.7

ECOG: Eastern Cooperative Oncology Group.

Survival Outcomes

Median overall survival (OS) was longest in the PE group (31.6 months), followed by the PC group (20.0 months) and the PD group (13.7 months). However, the differences were not statistically significant (p=0.322). Progression-free survival (PFS) showed a similar trend, with medians of 19.8 months (PE), 10.6 months (PC), and 10.9 months (PD), again without statistical significance (p=0.643). The survival data are presented in Table 3 and Kaplan–Meier curves are shown in Figure 1 (OS) and Figure 2 (PFS).

Table 2. Tumor stage and histology

Variable	Total (n=75)
Stage IIIA	39
Stage IIIB	36
Adenocarcinoma	16
Squamous cell carcinoma	45
Other histologies	14

Treatment Response and Toxicity

Disease control rates (CR+PR+SD) were highest in the PE group (92.3%), followed by PC (75.6%) and PD (71.4%) (p=0.279). Grade 3–4 neuropathy was observed most frequently in the PC group (20%). Treatment discontinuation and hospitalization were significantly higher among patients with ECOG performance status of 2 compared to those with ECOG 0–1 (p=0.012 and p=0.030, respectively). Detailed response and toxicity profiles are summarized in Table 4.

Table 3. Survival outcomes

Chemotherapy Regimen	Median OS (months)	95% CI for OS	Median PFS (months)	95% CI for PFS
Carboplatin–Paclitaxel (PC)	20.0	7.53–32.54	10.6	6.03–15.30
Cisplatin–Docetaxel (PD)	13.7	11.54–15.93	10.9	5.67–16.13
Cisplatin–Etoposide (PE)	31.6	13.41–49.86	19.8	14.50–25.10

OS: Overall Survival; PFS: Progression-Free Survival.

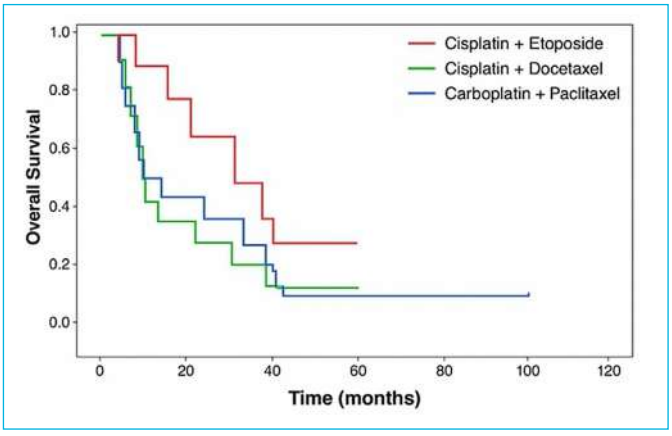

Figure 1. Kaplan–Meier curve for overall survival.

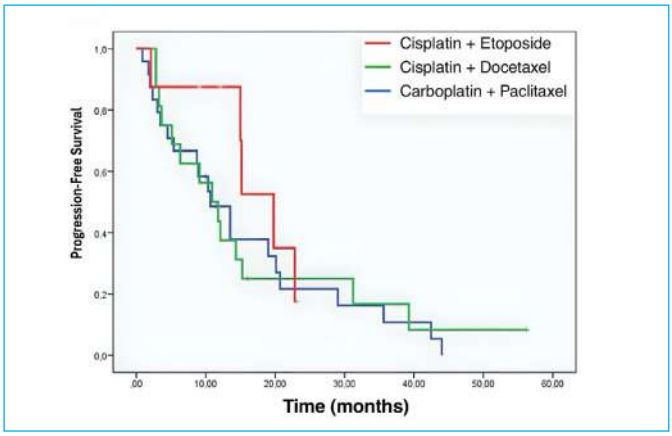

Figure 2. Kaplan–Meier curve for progression-free survival.

Table 4. Treatment response and toxicity

Chemotherapy Regimen	Disease Control Rate (CR+PR+SD)	Severe Neuropathy (%)	Treatment Discontinuation (ECOG 2)
Carboplatin–Paclitaxel (PC)	75.6%	20	Higher
Cisplatin–Docetaxel (PD)	71.4%	Not reported	Higher
Cisplatin–Etoposide (PE)	92.3%	Not reported	Lower

CR: Complete Response; PR: Partial Response; SD: Stable Disease.

Discussion

In this retrospective study, we evaluated and compared three concurrent chemoradiotherapy (CRT) regimens in elderly patients (≥65 years) with inoperable stage III non-small cell lung cancer (NSCLC). Among the treatment arms, the cisplatin–etoposide (PE) regimen demonstrated the most favorable outcomes, with a median overall survival (OS) of 31.6 months and progression-free survival (PFS) of 19.8 months. In contrast, the carboplatin–paclitaxel (PC) and cisplatin–docetaxel (PD) groups yielded OS of 20.0 and 13.7 months, and PFS of 10.6 and 10.9 months, respectively. These findings highlight a potential survival benefit associated with the PE regimen, although the balance between efficacy and tolerability must be carefully considered in elderly populations.

Elderly patients are underrepresented in clinical trials, and treatment decisions in this group are complicated by comorbidities, decreased organ function, and limited performance status. Previous studies such as those by Schild et al.[20] and Belani et al.[21] reported median OS ranging from 17 to 18 months in older patients undergoing CRT, which are lower than those observed in our PE group. In a multinational phase III trial, Ahn et al.[22] demonstrated improved outcomes with concurrent CRT followed by consolidation chemotherapy, reporting OS and PFS of 25.1 and 13.1 months, respectively. Machtay et al.[23] underscored the importance of locoregional control in predicting survival outcomes.

The Atagi study specifically assessed thoracic radiotherapy with or without low-dose carboplatin in elderly patients and found it to be both feasible and clinically beneficial, reinforcing the value of customized regimens in geriatric oncology.[24]

Furthermore, recent data from the LOGIK1902 study by Harada et al.,[12] which investigated weekly carboplatin with concurrent radiotherapy in patients aged ≥75 years, reported a median OS of 25.5 months and PFS of 14.6 months, with only 2.8% experiencing grade 4 hematologic toxicity. Despite the advanced age of the population, these outcomes are comparable to those observed in our cisplatin–etoposide arm, suggesting that a weekly carboplatin-based regimen may offer a safer yet effective alternative in select elderly patients.

In parallel, the RELEVANCE study by Wheatley-Price et al.[25] evaluated real-world outcomes of unresectable stage III NSCLC patients treated with CRT followed by consolidation immune checkpoint inhibitors. Results showed a significant survival benefit, with median OS of 44.6 months and 3-year OS of 56% in the CRT + immunotherapy group, compared to 21.3 months and 32%, respectively, in the CRT-only group. However, in our cohort, consolidation with immune checkpoint inhibitors was not administered because these agents are not yet reimbursed under the national health insurance system in Turkey. This systemic limitation likely contributed to the comparatively lower survival outcomes in our study and highlights a key disparity in access to contemporary standards of care.

Although the PE arm demonstrated promising survival outcomes, these results should be interpreted with caution due to common concerns about increased toxicity from intensive platinum-based regimens in elderly patients. However, in our study, no life-threatening or grade 4 toxicities were observed, and most adverse effects remained within manageable limits.

Limitations

This study's retrospective, single-center design and limited sample size reduce the generalizability of the results. Furthermore, the lack of randomization and potential indication bias in treatment selection represent additional methodological limitations.

Conclusion

Our results demonstrate that concurrent CRT, partic-

ularly the PE regimen, is both feasible and effective in elderly stage III NSCLC patients. Nonetheless, toxicity, frailty, and limited access to immunotherapy remain key concerns. Improved geriatric assessment and broader access to modern therapies are needed to optimize care in this population.

Key Messages

1. In elderly patients with inoperable stage III non-small cell lung cancer, three different concurrent chemoradiotherapy regimens provided similar outcomes in terms of overall and progression-free survival.

2. All treatment arms were tolerated at acceptable levels. Differences in adverse event profiles were observed, but no regimen was associated with significantly higher toxicity leading to treatment discontinuation.

3. This study indicates that selected elderly patients may benefit from concurrent chemoradiotherapy, and regimen choice should be guided by patient comorbidities and performance status rather than age alone.

Ethics Committee Approval: This study was approved by the Scientific Research Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (Date: 25/06/2025, No: 2025/010.99/17/33).
Peer-review: Externally peer-reviewed.
Informed Consent: Owing to the retrospective design of the study, the requirement for written informed consent was waived.
Author Contribution: Concept: P.O., E.O., Ed.O.; Design: P.O., E.O.; Supervision: P.O., E.O., Ed.O.; Fundings: P.O., E.O., S.Y.; Materials: P.O., S.Y.; Data collection &/or processing: P.O., S.Y.; Analysis and/or interpretation: P.O., E.O., Ed.O., S.Y.; Literature search: P.O., Ed.O.; Writing: P.O., E.O.; Critical review: Ed.O., S.Y.
Conflict of Interest: No conflict of interest was declared by the authors.
Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Torre LA, Siegel RL, Jemal A. Lung cancer statistics. Adv Exp Med Biol 2016;893:1–19. [CrossRef]
2. Aupérin A, Le Péchoux C, Rolland E, Curran WJ Jr, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010;28:2181–90. [CrossRef]
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7–33. [CrossRef]
4. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341:2061–7. [CrossRef]
5. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: Clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc 2007;55:780–91. [CrossRef]
6. Wildiers H, Heeren P, Puts M, Topinková E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 2014;32:2595–603. [CrossRef]
7. Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol 2018;36:2326–47. [CrossRef]
8. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: A prospective multicenter study. J Clin Oncol 2011;29:3457–65. [CrossRef]
9. Wedding U, Pientka L, Kiltz U, Klippel H, Höffken K, Kunisch R. Age, severe comorbidity and functional impairment independently contribute to poor survival in cancer patients. J Cancer Res Clin Oncol 2007;133:945–50. [CrossRef]
10. Lilenbaum RC, Cashy J, Hensing TA, Young S, Cella D, et al. Prevalence of poor performance status in lung cancer patients: Implications for research. J Thorac Oncol 2008;3:125–9. [CrossRef]
11. Puts MTE, Hardt J, Monette J, Girre V, Springall E, Alibhai SMH. Use of geriatric assessment for older adults in the oncology setting: A systematic review. J Natl Cancer Inst 2012;104:1133–63. [CrossRef]
12. Harada T, Sasaki T, Ishii H, Takemoto S, Hisamatsu Y, Saito H, et al. A phase II study of weekly carboplatin and concurrent radiotherapy in older adults with locally advanced non-small cell lung cancer (LOGIK1902). Thorac Cancer 2024;15:2128–35. [CrossRef]
13. Extermann M, Aapro M, Bernabei R, et al. Use of comprehensive geriatric assessment in older cancer patients: Recommendations from the task force on CGA of SIOG. Crit Rev Oncol Hematol 2005;55:241–52. [CrossRef]
14. Rubenstein LZ, Stuck AE, Siu AL, Wieland D. Impacts of geriatric evaluation and management programs on defined outcomes: Overview of the evidence. J Am Geriatr Soc 1991;39:8S–16S. [CrossRef]
15. Travis WD, Brambilla E, Riely GJ. New pathologic classification of lung cancer: Relevance for clinical practice and clinical trials. J Clin Oncol 2013;31:992–1001. [CrossRef]
16. Riely GJ, Wood DE, Ettinger DS, Aisner DL, Akerley W, Bauman JR, et al. Non-small cell lung cancer, version 4.2024, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2024;22:249–74. [CrossRef]
17. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: Proposals for revision of the TNM stage groupings in the forthcoming (seventh) edition. J Thorac Oncol 2007;2:706–14. [CrossRef]
18. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Bethesda: U.S. Department of Health and Human Services; 2010
19. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47. [CrossRef]
20. Schild SE, Stella PJ, Geyer SM, Bonner JA, McGinnis WL, Mailliard JA, et al. The outcome of combined-modality therapy for stage III non-small-cell lung cancer in the elderly. J Clin Oncol

2003;21:3201–6. [CrossRef]

21. Belani CP, Wang W, Johnson DH, Wagner H, Schiller J, Veeder M, et al. Phase III study of induction chemotherapy followed by thoracic radiotherapy in unresectable stage IIIA/B non-small-cell lung cancer. J Clin Oncol 2005;23:3760–7. [CrossRef]
22. Ahn JS, Ahn YC, Kim JH, Min YJ, Cho EK, Kim DW, et al. Multinational randomized phase III trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III NSCLC. J Clin Oncol 2015;33:2660–6. [CrossRef]
23. Machtay M, Paulus R, Moughan J, Komaki R, Bradley JE, Choy H, et al. Defining locoregional control and its importance in locally advanced non-small-cell lung carcinoma. J Thorac Oncol 2012;7:716–22. [CrossRef]
24. Atagi S, Kawahara M, Yokoyama A, Okamoto H, Yamamoto N, Ohe Y, et al. Thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with NSCLC: A randomized phase III trial. Lancet Oncol 2012;13:671–8. [CrossRef]
25. Wheatley-Price P, Navani V, Pabani A, Lee A, Cheng S, Cheema P, et al. Real-world survival outcomes and impact of PD-L1 expression among patients with unresectable stage III NSCLC treated with CRT followed by immunotherapy in Canada: The RELEVANCE study. Lung Cancer 2025;204:108583. [CrossRef]

ORIGINAL INVESTIGATION

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.67535

The Effect of Pelvic Incidence–Lumbar Lordosis Mismatch on Quality of Life and Disability in Patients with Chronic Low Back Pain

Merve Çalkın Korkmaz,[1], Adil Oncel,[2] Ömer Faruk Bucak,[3] Sena Tolu[4]

Abstract

Objective: Pelvic incidence–lumbar lordosis (PI–LL) mismatch is considered a marker of sagittal imbalance, but its clinical significance in chronic low back pain remains uncertain. This study aimed to investigate the relationship between spinopelvic alignment and clinical outcomes in patients with chronic low back pain (CLBP).

Methods: In this cross-sectional observational study, 101 patients aged 18 years and older with CLBP (>12 weeks) were included. Spinopelvic parameters, including pelvic incidence (PI) and lumbar lordosis (LL), were measured using standardized standing radiographs. Patients were divided into two groups based on the PI-LL mismatch: PI-LL<10° (normal alignment) and PI-LL ≥10° (mismatch). Visual Analog Scale (VAS), Short Form-36 (SF-36), and Oswestry Disability Index (ODI) scores were compared between the groups.

Results: There were statistically significant differences in PI, LL, and PI-LL between the groups (p=0.026, p<0.001, and p<0.001, respectively). No significant differences were found in ODI, VAS (rest and activity), or SF-36 subdomains, except for general health (p=0.045). Multivariate logistic regression identified general health as a significant predictor of PI-LL mismatch (OR=0.973, p=0.045). BMI showed a statistically significant association (p=0.036).

Conclusions: Spinopelvic mismatch may be associated with higher BMI and lower general health perception, but not with pain or disability scores.

Keywords: Low back pain; chronic pain; disability; quality of life.

[1]*Department of Physical Medicine and Rehabilitation, Kartal Dr. Lutfı Kırdar City Hospital, Istanbul, Türkiye*
[2]*Department of Physical Medicine and Rehabilitation, Nişantaşı University Faculty of Medicine, BHT Clinic Istanbul Tema Hospital, Istanbul, Türkiye*
[3]*Department of Physical Medicine and Rehabilitation, University of Health Sciences, Başakşehir Çam and Sakura City Hospital, Istanbul, Türkiye*
[4]*Department of Physical Medicine and Rehabilitation, Medipol Mega University Hospital, Istanbul, Türkiye*

Address for correspondence:
Merve Çalkın Korkmaz, Department of Physical Medicine and Rehabilitation, Kartal Dr. Lutfı Kırdar City Hospital, Istanbul, Türkiye
E-mail: drmervecalkin@gmail.com

Received: 16.11.2025
Accepted: 01.06.2026
Published: 29.09.2026

Introduction

Chronic low back pain (LBP) is a widespread health problem affecting a significant portion of the global population and resulting in substantial clinical, social, and economic repercussions. It is the primary cause of activity restriction and absenteeism. It puts significant economic impacts on individuals, families, communities, industries, and governments.[1] The risk factors for low back pain are multifaceted, encompassing physical elements, behaviors, psychological influences, and sociodemographic attributes.[2,3] Abnormal spinopelvic parameters have been asso-

How to cite this article: *Çalkın Korkmaz M, Oncel A, Bucak ÖF, Tolu S. The effect of pelvic incidence–lumbar lordosis mismatch on quality of life and disability in patients with chronic low back pain. South. Clin. Ist. Euras. 2026;37(3):301-305.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.
Copyright@Author(s)

ciated with degenerative and isthmic spondylolisthesis, hip osteoarthritis, and related spinal disorders. In patients with deformities, pelvic and spinal parameters deviate from the normative range.[4] The spine, pelvis, hip, and knee function collaboratively to ensure sagittal equilibrium. When the body attains this equilibrium, it utilizes less energy.[5,6] The connection between the pelvis and the spine is referred to as spinopelvic balance. Sagittal balance has three critical parameters: Pelvic incidence (PI), pelvic tilt (PT), and sacral slope (SS). PI is a morphological parameter that remains invariant regardless of pelvic position and posture, and does not alter post-development. The orientation of the pelvis is determined by two positional parameters: PT and SS. The correlation among pelvic incidence, sacral slope, and sagittal curvature, particularly lumbar lordosis, is thoroughly documented in the general population.[6-8]

Maintaining a steady pelvic incidence angle is achievable if the sacral and pelvic inclination angles adjust compensatorily based on the pelvic position.[9] A low pelvic incidence angle correlates with less lumbar lordosis, whereas a high pelvic incidence angle is associated with an increase in lumbar lordosis. This concept is referred to as "spino-pelvic harmony." Boulay et al.[13] presented an equation for forecasting lumbar lordosis in relation to pelvic incidence. Exceeding the confidence limits surpasses the adaptability potential of the spine and pelvis, potentially resulting in pathological postures and loading patterns. Consequently, the prevailing agreement recognizes pelvic incidence as a determinant of the lumbar lordosis necessary for achieving a balanced sagittal posture.[10-14] Numerous risk factors and etiologies of persistent low back pain have been discussed; yet, no correlation with spino-pelvic parameters have been identified to date. Therefore, this study aimed to evaluate the relationship between spinopelvic alignment and clinical outcomes in patients with chronic low back pain.

Materials and Methods

This study was based on a cross-sectional observational study of 101 patients aged 18 years and older with chronic low back pain (>12 weeks) who had anteroposterior and lateral standing radiographs of the lumbar spine. Pelvic incidence and lumbar lordosis measurements were made with the available lumbar radiography. The PI was measured as the angle between a line drawn perpendicular to the sacral endplate at its midpoint and a line drawn from the midpoint of the sacral endplate to the midpoint of the femoral head axis. The LL was the sagittal Cobb angle measured between the superior endplate of L1 and the superior endplate of S1. A physical medicine and rehabilitation specialist made the radiographic measurements, and another specialist repeated them. The concordance (mathematical difference (PI minus LL or PI-LL) between pelvic incidence and lumbar lordosis) was evaluated. Spinopelvic alignment was measured in terms of agreement (mathematical difference) between pelvic incidence and lumbar lordosis (PI - LL). PI-LL<10o was normal, and PI-LL ≥10o was evaluated as a mismatch. Patients were classified into 2 groups. We evaluated the Visual Analog Scale (VAS), Short Form-36 (SF-36), and Oswestry Low Back Pain Disability Questionnaire in the patients included in the study. All scores were juxtaposed between the two groups. We did not include patients with a history of lumbar surgery or low back pain from trauma, inflammatory arthritis, tumors, differences in leg length, scoliosis, neuromuscular diseases, cognitive issues, infections, cauda equina syndrome, or compression fractures of a vertebra.

Results

The study examined the relationship between spinopelvic alignment and various clinical, radiological, and quality of life parameters (Table 1). Table 2 shows statistically significant differences in spinopelvic alignment angles, lumbar lordosis, and pelvic incidence between the two groups (PI-LL<10 and PI-LL≥10) ($p=0.026$, $p<0.001$, and $p<0.001$, respectively). Nevertheless, there was no notable difference in the Oswestry Disability Index, activity pain score, or resting pain score ($p>0.05$ for all). The subscales in Table 3 that did not exhibit statistically significant differences between groups were physical functioning, emotional and physical role difficulties, vitality, mental health, social functioning and pain scores (all $p>0.05$). The overall health score was significantly different between the groups ($p=0.045$). Table 4 shows the results of a statistical analysis that looked for factors related to spinopelvic alignment.

General health score and BMI were significantly associated with PI–LL mismatch, whereas education level was not statistically significant ($p=0.094$). Overall, the model was statistically significant ($\chi 2=12.055$, $p=0.007$) and had a modest explanatory power (Nagelkerke $R2=0.15$).

Table 1. The effect of descriptive characteristics on spinopelvic alignment

Variable	PI–LL<10 (n=37)	PI–LL ≥10 (n=64)	Test Value	p-value
Sex, n (%)			χ^2=0.124	0.724
Male	7 (18.9%)	14 (21.9%)		
Female	30 (81.1%)	50 (78.1%)		
Age (years)			t=-0.055	0.956
Mean ± SD	54.51±9.09	54.63±10.1		
Median (min–max)	55 (40–72)	53.5 (40–77)		
BMI (kg/m²)			t=-2.130	0.036
Mean±SD	28.78±5.09	30.96±4.89		
Median (min–max)	28.7 (16.9–41.6)	31.5 (19.6–45.6)		
Pain Duration (mo)			t=0.183	0.855
Mean ± SD	87.41±90.32	83.78±98.73		
Median (min–max)	54 (1–360)	60 (1–460)		

Bold indicates statistically significant results (p<0.05). Independent samples t-test (t) and Chi-square test (χ^2) were used. Summary statistics are presented as mean ± SD and median (min-max) for continuous variables, and n (%) for categorical variables.

Table 2. Comparison of spinopelvic parameters and pain scores according to spinopelvic alignment

Parameter	PI–LL<10 (n=37)	PI–LL ≥10 (n=64)	Test Value	p-value
Pelvic Incidence	57.61±8.90	62.23±10.45	t=-2.256	0.026
Median (min–max)	56.8 (41.5–74.1)	62.4 (40.7–91)		
Lumbar Lordosis	51.00±8.39	39.76±11.47	t=5.204	<0.001
Median (min–max)	50.6 (33.2–65.9)	40.7 (6.5–68.5)		
PI–LL Mismatch	6.61±2.83	22.47±12.18	t=-7.782	<0.001
Median (min–max)	7.8 (1.1–9.9)	20.7 (10.0–54.5)		
VAS (Rest)	5.16±2.19	4.78±2.26	t=0.826	0.411
Median (min–max)	5 (0–9)	5 (0–9)		
VAS (Activity)	7.73±2.31	7.84±2.28	t=-0.241	0.810
Median (min–max)	8 (1–10)	8 (0–10)		
Oswestry Disability Index	38.18±16.24	38.66±16.83	t=-0.140	0.889
Median (min–max)	37.8 (6–77.7)	37.8 (6.7–71.1)		

Bold indicates statistically significant results (p<0.05). Independent samples t-test was used. Results are presented as mean ± SD and median (min-max).

Table 3. SF-36 quality of life dimensions by spinopelvic alignment

SF-36 Domain	PI–LL<10 (n=37)	PI–LL ≥10 (n=64)	Test Value	p-value
Physical Functioning	47.97±22.77	47.19±25.85	t=0.154	0.878
Role Physical	41.08±38.26	29.69±41.76	t=0.879	0.382
Role Emotional	32.42±38.08	34.37±43.23	t=-0.228	0.820
Vitality	36.22±24.19	41.30±20.39	t=-1.126	0.263
Mental Health	53.14±16.52	56.81±15.86	t=-1.106	0.272
Social Functioning	50.00±24.83	51.64±26.42	t=-0.307	0.759
Pain	31.76±20.94	31.41±17.54	t=0.090	0.928
General Health	50.23±17.72	42.57±23.20	t=-2.067	0.045

No substantial differences were noted across groups (p>0.05), with the exception of general health (p<0.05). Independent samples t-test was used. Results are presented as mean ± SD and median (min-max).

Table 4. Multivariate logistic regression analysis for factors affecting spinopelvic alignment

Variable	β	SE	Wald	p-value	Exp(β)	95% CI (Lower–Upper)
BMI	0.097	0.046	4.384	0.036	1.102	1.006 – 1.206
Education Level	-0.287	0.172	2.806	0.094	0.750	0.536 – 1.050
General Health	-0.027	0.012	5.550	0.045	0.973	0.951–0.995
Constant	-2.863	1.606	3.177	0.075	0.057	–

χ^2=12.055, df=3, p=0.007. Cox-Snell R^2=0.11, Nagelkerke R^2=0.15. Statistically significant values are bolded (p<0.05). Dependent variable in the logistic regression model was PI–LL mismatch (PI–LL ≥10°).

Discussion

This study looked at how spinopelvic alignment relates to the health outcomes of individuals with chronic low back pain by examining the link between pelvic incidence (PI) and lumbar lordosis (LL). Our findings show that although BMI and general health scores differed significantly between patients with normal spinopelvic alignment (PI-LL<10°) and those with mismatch (PI-LL ≥10°), other demographic and clinical factors, such as age, gender, pain duration, and functional outcomes, were not statistically significantly distinct amongst the groups. The lower BMI found in the normal alignment group corresponds with previous studies indicating a relationship between increased body weight and spinopelvic misalignment. By generating postural compensations and increased mechanical strain on the lumbar spine, obesity could exacerbate the misalignment between PI and LL. Our study indicated that BMI influences spinopelvic alignment by itself, implying that treatment for these patients may need to include weight management. Though the PI and LL values differed greatly between the two groups, the Oswestry Disability Index and the VAS scores for both resting and activity-related pain revealed no notable differences. Emphasizing the difficult character of chronic low back pain, this supports other studies indicating that the alignment of the spine on X-rays does not always correspond straight to the suffering or impairment a person experiences. Previous studies have also reported that there is not always a direct correlation between radiological findings and clinical symptoms. Studies conducted in patients with lumbar spinal stenosis have shown that neuropathic pain and impaired quality of life are more closely associated with BMI and pain-related parameters than with radiological findings.[15] Similarly, in our study, PI–LL mismatch was not found to be associated with pain and disability scores, but was found to be associated with BMI and perceived general health. Compensatory biomechanical mechanisms and the multifactorial nature of chronic low back pain may partially explain the lack of association between radiological mismatch and clinical outcomes. Regarding SF-36 quality of life, only the general health domain was significantly lower in the misaligned group; the other subdomains showed no significant change, suggesting a possible relationship between sagittal imbalance and perceived health status. Its standardized radiographic assessment and evaluation by two independent observers strengthen the reliability of the study. Still, some limits have to be acknowledged. First, the cross-sectional nature of the study precludes causal conclusions. Second, although the sample size was reasonable, larger studies could produce clear findings. Excluding patients with prior spinal surgery or abnormalities could also limit generalizability to more general chronic low back pain groups. Our study finally shows a link between spinopelvic alignment, BMI, and general health status in chronic low back pain patients. Radiological differences did not significantly affect pain and disability outcomes, therefore reinforcing the case for a complete management strategy. Long-term studies are required to investigate the causes and to determine whether treatments aimed at BMI can enhance spinopelvic alignment and health results.

Limitations

Firstly, the study's sample size of 101 patients was adequate; however, bigger multicenter studies may provide greater generalizability. Second, we excluded patients having a history of vertebral fractures, neuromuscular problems, inflammatory diseases, scoliosis, or spinal surgery. This enhancement of internal validity may limit the generalizability of our findings to the broader population of individuals with chronic low back pain who frequently present these comorbidities. Third, radiographic evaluations were performed exclusively in an upright position, without the application of dynamic

or functional imaging techniques. Consequently, it was infeasible to assess potential compensating mechanisms during mobility.

Conclusion

In conclusion, our study looked at how spinopelvic alignment affected clinical and functional outcomes in people with chronic low back pain. Our findings revealed that while other variables like pain and disability scores did not reveal significant variations between the alignment groups, body mass index and general health were closely connected to spinopelvic alignment. These results imply that although radiographic measurements provide considerable knowledge of spinal alignment, they might not fully explain patients' pain and functional status. In the treatment of patients with spinopelvic mismatch, addressing modifiable factors including BMI may be important. Long-term studies to clarify cause-and-effect relationships and the development of particular treatments that enhance alignment as well as patient outcomes should be the emphasis of future studies.

Ethics Committee Approval: The study protocol was approved by the Institutional Ethics Committee of İstanbul Medipol University (Date: 09/06/2023, No: E-10840098-772.02-3652).

Peer-review: Externally peer-reviewed.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Author Contribution: Concept: M.C.K.; Design: O.F.B.; Supervision: S.T.; Fundings: A.O., M.C.K.; Materials: O.F.B.; Data collection &/or processing: S.T., M.C.K.; Analysis and/or interpretation: O.F.B.; Literature search: A.O.; Writing: M.C.K.; Critical review: S.T., M.C.K.

Conflict of Interest: The authors declare no conflict of interest.

Funding: No financial support was received for this study. The authors received no financial support for the research, authorship, and/or publication of this article.

AI Assistance Statement: ChatGPT (OpenAI) was used solely for language refinement. All scientific content was authored and verified by the authors.

References

1. Gündüz OH, Erçalık T. Exercise prescription in chronic low back pain. Turk J Phys Med Rehab 2014;60:25–30. [Article in Turkish] [CrossRef]
2. Biglarian A, Seifi B, Bakhshi E, Mohammad K, Mehdi Rahgozar M, Masoud Karimlou M, et al. Low back pain prevalence and associated factors in Iranian population: Findings from the national health survey. Pain Res Treat 2012;2012:653060. [CrossRef]
3. Bener A, Dafeeah EE, Alnaqbi K. Prevalence and correlates of low back pain in primary care. Asian Spine J. 2014;9:227–36. [CrossRef]
4. Karademir M, Karaveli̇oğlu E, Boyacı MG, Eser O. The importance of the sagittal balance of the spine and spinopelvic parameters. J Turkish Spinal Surg 2014;25:139–48.
5. Jackson RP, Hales C. Congruent spinopelvic alignment. Spine 2000;25:2808–15. [CrossRef]
6. Roussouly P, Pinheiro-Franco JL. Biomechanical analysis of the spino-pelvic organization. Eur Spine J 2011;20:609–18. [CrossRef]
7. Roussouly P, Berthonnaud E, Dimnet J. Geometrical analysis of lumbar lordosis. Rev Chir Orthop 2003;89:632–9.
8. Vaz G, Roussouly P, Berthonnaud E, Dimnet J. Sagittal morphology and equilibrium of pelvis and spine. Eur Spine J 2002;11:80–7. [CrossRef]
9. Mehta VA, Amin A, Omeis I, Gokaslan ZY, Gotfried ON. Implications of spinopelvic alignment. Neurosurgery.2012;70:707–21. [CrossRef]
10. Schwab F, Ashish Patel A, Ungar B, Farcy JP, Lafage V. Adult spinal deformity-standing imbalance. Spine 2010;35:2224–31. [CrossRef]
11. Schwab F, Lafage V, Patel A, Farcy FP. Sagittal plane considerations in adult patients. Spine 2009;34:1828–33. [CrossRef]
12. Duval-Beaupere G, Schmidt C, Cosson P. Barycentremetric study of sagittal shape. Ann Biomed Eng 1992;20:451–62. [CrossRef]
13. Boulay C, Tardieu C, Hecquet J, Benaim C, Mouilleseaux B, Marty C, et al. Sagittal alignment regulated by pelvic incidence. Eur Spine J 2006;15:415–22. [CrossRef]
14. Roussouly P, Gollogly S, Berthonnaud E, Dimnet J. Classification of sagittal alignment. Spine 2005;30:346–53. [CrossRef]
15. Akgün AS, Ağırman M. Neuropathic pain and disability in patients with lumbar spinal stenosis. Turk J Geriatr 2018;21:56–61. [CrossRef]

ORIGINAL ARTICLE

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.12989

Digital Rectal Examination-Based Estimation of Prostate Volume Using Posterior Surface Area: A Prospective Methodological and Reproducibility Study

Ahmet Halil Sevinç, Burcu Hanci, Fatih Tarhan

Abstract

Objective: To develop a novel, standardized, and objective method for estimating prostate volume using digital rectal examination (DRE) and to establish a treatment-oriented grading system.

Methods: A total of 330 men aged ≥45 years scheduled for prostate needle biopsy were prospectively analyzed (Group 1). During DRE, the width, length, and height of the posterior prostate surface were measured using the examiner's pre-measured index finger. Reproducibility was assessed in 63 patients examined independently by two urologists (Group 2). Posterior surface area and volume were calculated using ellipse and ellipsoid formulas. Prostate volume measured by transrectal ultrasonography (TRUS) served as the reference standard. Linear regression analyses were performed to generate prediction equations.

Results: Posterior surface area predicted TRUS-measured prostate volume more strongly than palpable posterior prostate volume, explaining 91% of the variance (R^2=0.909, p<0.0001). No significant interobserver difference was observed (p=0.061), while strong correlation (r=0.733, p<0.0001) and high reliability were demonstrated (ICC=0.821). The proposed grading system showed strong agreement with TRUS-based grading (κ=0.884; 95% CI, 0.846–0.922).

Conclusions: Posterior prostate surface area measured by DRE is a reliable and reproducible approach for estimating prostate volume categories. Further validation of this method using advanced imaging techniques such as magnetic resonance imaging is recommended.

Keywords: Prostate volume; digital rectal examination; ultrasonography; prostate grading; posterior prostate surface area.

Department of Urology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye

Address for correspondence:
Ahmet Halil Sevinç, Department of Urology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye
E-mail: drahmethalilsevinc@gmail.com

Received: 10.06.2026
Accepted: 22.06.2026
Published: 29.09.2026

Introduction

Following the medical history, a physical examination and clinical assessment are essential in order to continue evaluating the patient, determine any necessary additional tests and define treatments. A digital rectal examination (DRE) can be used to assess the size, consistency, tenderness and temperature of the prostate.

Prostate size is an important factor in de-

How to cite this article: *Sevinç AH, Hanci B, Tarhan F. Digital rectal examination-based estimation of prostate volume using posterior surface area: a prospective methodological and reproducibility study. South. Clin. Ist. Euras. 2026;37(3):306-312.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Copyright@Author(s)

termining which surgical techniques are most appropriate for patients. Several methods have been used to estimate prostate volume (PV), including DRE, ultrasonography (US)—either transrectal or suprapubic—computed tomography (CT), and magnetic resonance imaging (MRI). Compared with DRE, transrectal ultrasonography provides a more accurate estimation of prostate weight.[1] However, MRI is the most accurate method for determining PV among these modalities.[2,3]

Although DRE is not very successful at determining prostate volume, it is the cheapest and easiest method to perform, and the most frequently used. However, despite being an established method, it is not standardized. Measurement of prostate volume (PV) with DRE remains based on subjective, empirical information. During a DRE examination, the prostate is typically categorised into grades 1–4 based on its height above the rectum.[4] However, there is no universally accepted terminology for defining prostate size. Therefore, measurement results can vary between physicians. Previous studies have used ball, fruit, circle and finger sizing scales,[5-8] as well as three-dimensional relief models[5,6,8,9] and posterior surface area,[6,10] to determine prostate volume (PV). The general consensus is that the accuracy of prostate volume estimation by DRE improves with experience.[11]

Beyond prostate size, DRE plays a crucial role in differentiating various clinical conditions by evaluating gland consistency, surface characteristics, tenderness, and local temperature changes. Characteristic physical findings may be observed in inflammatory conditions such as chronic prostatitis, chronic pelvic pain syndrome, and prostatic abscess, as well as in benign prostatic hyperplasia and prostate cancer. These findings may also provide guidance for the clinical staging of prostate cancer. Furthermore, muscle tenderness and trigger points can be assessed in patients with chronic pelvic pain. During a brief neurological examination of the lower urinary tract, anal tone, voluntary anal contraction, the anal reflex, and the bulbocavernosus reflex can be evaluated using DRE. However, the lack of standardization in DRE may lead to terminological and measurement-related inconsistencies in the interpretation of examination findings. Even in the era of advanced imaging technologies, we believe that an objective and standardized method capable of producing reproducible results in prostate assessment by DRE is still needed.

Therefore, the aim of this study was to develop a novel standardized method for evaluating prostate gland volume using DRE and to establish a treatment-oriented prostate volume grading system.

Materials and Methods

A total of 337 male patients aged ≥45 years who were referred to the biopsy unit for transrectal ultrasound–guided prostate needle biopsy due to suspected prostate cancer between 1 June 2021 and 1 June 2023 were prospectively enrolled (Group 1). To assess the reproducibility of the method, an additional 63 patients underwent digital rectal examination (DRE) independently performed by two different urologists (Group 2).

Seven patients were excluded because of active urinary tract infection, severe anal pain, anatomical obstruction, anal stricture, anal fistula, acute thrombosed hemorrhoids, other conditions precluding DRE, or high-riding prostates that could not be adequately palpated. Consequently, data from a total of 330 patients were analyzed.

Approval was obtained from the institutional clinical ethics committee prior to study initiation. Written informed consent was obtained from all participants, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

All digital rectal examinations (DREs) in Group 1 were performed by a senior urologist with 30 years of clinical experience. Transrectal ultrasonography (TRUS) measurements of prostate volume (PV) were conducted by another senior urologist.

In Group 2, DREs were independently performed by a junior urologist with 2 years of experience and a senior urologist with 30 years of experience. Both examiners were blinded to each other's measurements.

Prior to the study, the width, length (from the fingertip to the distal, middle, and proximal interphalangeal joints), and height of the researchers' dominant index fingers were measured using a ruler, as illustrated in Fig. 1. Subsequently, prostate size was assessed by digital examination using four different prostate models fabricated from modeling clay (Fig. 1; Fig. 2).

Prior to biopsy, with the patients' bladders emptied, the width, length, and height of the right and left prostate lobes were measured using a finger guide during digital rectal examination (DRE), with the patient in the bent-

over position. Subsequently, prostate width, length, and height were measured by another urologist using a transrectal ultrasonography probe (Mindray DP-9900 PLUS and Mindray 65EC10HA, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China) while the patient was positioned in the lateral decubitus position.

The prostate measurements obtained by digital rectal examination (DRE), together with information on gland consistency, temperature, tenderness, and the presence of any additional pathologies, are presented in Table 1.

Grading of PV was performed in accordance with the recommendations of the European Association of Urology (EAU) guidelines for the medical and surgical treatment of benign prostatic hyperplasia, including alpha-blocker monotherapy, combination medical therapy, and surgical treatments such as resection and enucleation.[12]

Table 1. Patients' digital rectal examination record table

Dimension	Right (cm)	Left (cm)	Total (cm)
Height			
Width (right–left)			
Length (antero-posterior)			
Remarks			

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Prostate volume (PV) measured by transrectal ultrasonography and palpable posterior prostate volume calculated from digital rectal examination measurements were determined using the ellipsoid formula ($\pi/6 \times$ width $\times$ length $\times$ height).[3] In addition, posterior prostate surface area was calculated using the ellipse area formula ($\pi \times$ width$/2 \times$ length$/2$).[5]

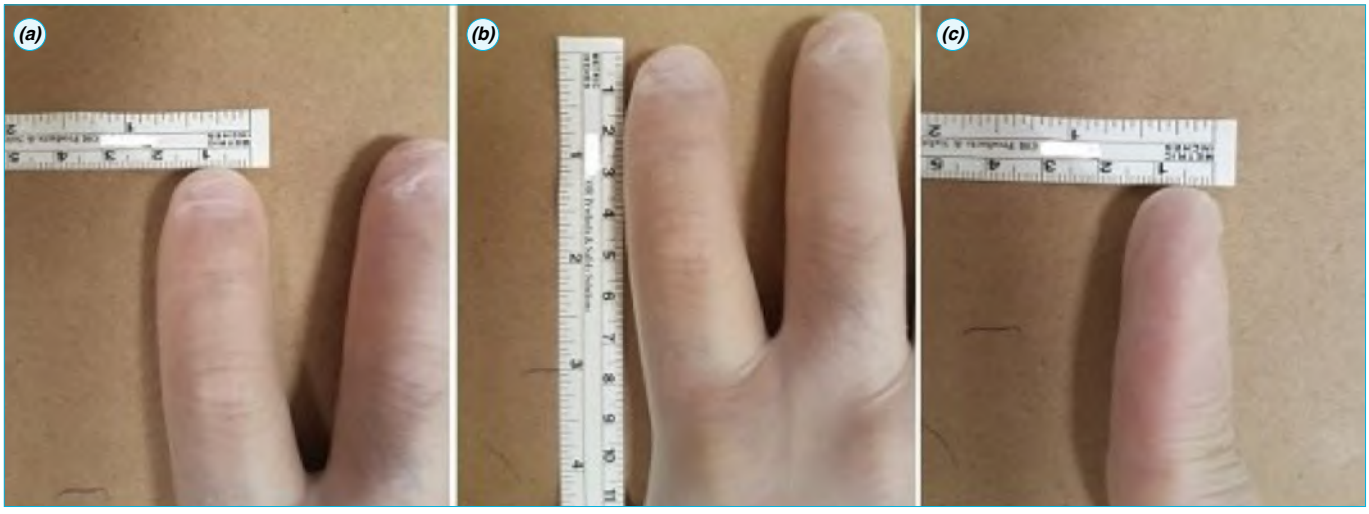

Figure 1. Three-dimensional measurements of the index finger used for digital rectal examination: **(a)** width, **(b)** length, and **(c)** height.

Figure 2. Determination of prostate dimensions by digital rectal examination using an in vitro prostate model: **(a)** width, **(b)** length, and **(c)** height.

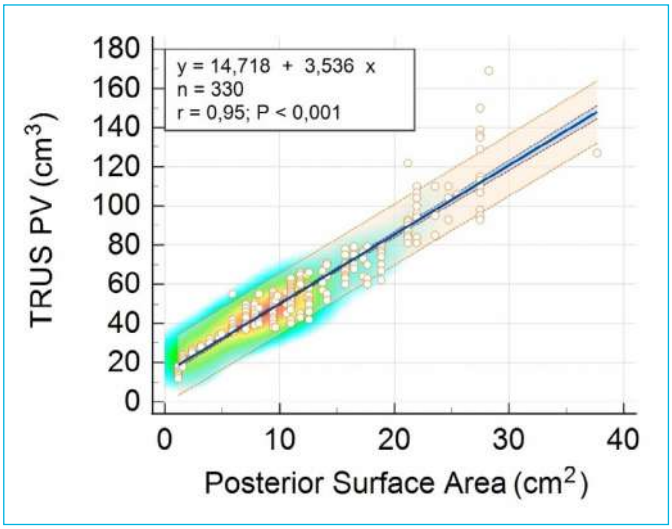

Figure 3. Linear regression analysis between posterior prostate surface area and prostate volume measured by transrectal ultrasonography.

The normality of variable distributions was assessed using the D'Agostino–Pearson test. Comparisons between patient groups were performed using the unpaired t test.

Correlation analysis (Pearson's correlation coefficient) was performed between the measurements obtained by digital rectal examination and those obtained by transrectal ultrasonography. Among the parameters derived from digital measurements (width, height, length, posterior surface area, and palpable posterior prostate volume), those that showed significant correlation with transrectal ultrasonography findings were used to generate prediction formulas by linear regression analysis (Fig. 3).

Comparisons between the measurements obtained by the two investigators were performed using the paired t test. In addition, Pearson's correlation analysis was conducted to evaluate the association between the findings of the two investigators. Agreement between the two observers was further assessed using the intraclass correlation coefficient (ICC). Agreement between prostate volume grading based on TRUS measurements and grading estimated from posterior surface area was evaluated using Cohen's weighted kappa test. For all analyses, a p value <0.05 was considered statistically significant.

Results

The demographic and clinical characteristics of patients in Group 1 and Group 2 are presented in Table 2. No statistically significant differences were observed between the groups for any of the evaluated parameters (p>0.05).

The results of the simple linear regression analyses performed to evaluate the ability of posterior prostate surface area and posterior prostate surface volume to predict prostate volume measured by transrectal ultrasonography (TRUS) are presented in Table 3. The calculated posterior prostate surface area explained 91% of the total variance in TRUS-measured prostate volume (Equation 1), whereas the calculated posterior prostate surface volume explained approximately 72% (Equation 2). As shown in Table 3, the analyses yielded statistically significant models for both parameters. A statistically significant positive association was observed between the calculated surface area and volume and TRUS-measured prostate volume, confirming the predictive value of these calculations for estimating prostate volume.

The correlation and agreement results for the calculated surface area and volume parameters between the investigators are presented in Table 4. No statistically significant difference was observed between the mean values of either parameter (p>0.05). A strong positive correlation was identified between the measurements obtained by the two investigators (p<0.05). In addition, a high level of reliability was demonstrated by the intraclass correlation coefficient (p<0.05). (Table 4).

Table 2. Demographic and clinical characteristics of the patient groups

	Group 1 (n:330)	Group 2 (n: 63)	p*
Age (years)	63.57±0.48	63.84±1.11	0.820
BMI (kg/m²)	27.48±0.23	26.89±0.57	0.315
Total PSA (ng/mL)	47.11±8.17	92.73±37.74	0.067
Prostate volume by TRUS (mL)	52.59±1.43	58.00±3.51	0.134
Posterior prostate surface area (cm²)	10.71±0.39	11.07±0.51	0.501
Palpable posterior prostate volume (cm³)	9.38±0.49	10.19±1.09	0.271

Unpaired t test BMI: Body mass index, PSA: Prostate-specific antigen, TRUS: Transrectal ultrasonography

Table 3. Results of regression analyses between posterior prostate surface area, posterior prostate surface volume, and prostate volume measured by transrectal ultrasonography

Variables	Equation	β	t	p	F	R^2
Estimated PV 1	y=14.718+(3.536 x area)	0.953	57.143	<0.0001	3265	0.909
Estimated PV 2	y=28.730+(2.541x volume)	0.857	30.128	<0.0001	821.2	0.721

PV: Prostate volume.

Table 4. Results of correlation and agreement analyses between investigators

	Investigator 1	Investigator 2	P*	r; R2	P**	ICC	P***
Area (cm^2)	11.07±0.51	11.96±0.68	0.061	0.733; 0.537	<0.0001	0.821	0.0001
Volume (cm^3)	10.19±1.09	11.06±1.35	0.093	0.935; 0.874	<0.0001	0.954	0.0001

Values are presented as mean ± standard error of the mean (SEM). *Paired t test; **Pearson's correlation test; ***intraclass correlation coefficient (ICC).

Table 5. Grading of estimated prostate volume based on calculated posterior prostate surface area

Grade	Posterior prostate surface area (cm^2)	Estimated prostate volume (cm^3)
X*	-	-
1	≤1.6	≤20
2	1.7–5.8	21–35
3	5.9–18.6	36–80
4	≥18.7	≥81

*Not evaluated.

Table 6. Agreement between posterior prostate surface area grading and TRUS prostate volume grading

Area PV (cm^3)	Grade 1	Grade 2	Grade 3	Grade 4	n (%)
Grade 1	18	16	0	0	34 (10.3%)
Grade 2	0	46	0	0	46 (13.9%)
Grade 3	0	0	197	0	197 (59.7%)
Grade 4	0	0	13	40	53 (16.1%)
n (%)	18 (5.5%)	62 (18.8%)	210 (63.6%)	40 (12.1%)	330

TRUS: Transrectal ultrasonography, PV: Prostate volume.

As shown in Table 3, posterior prostate surface area demonstrated superior performance in predicting prostate volume compared with palpable posterior prostate volume; therefore, surface area was selected for prostate size grading. Estimated prostate volume was calculated by substituting the posterior prostate surface area obtained using the ellipse formula into the regression equation. For clinical applicability, estimated prostate volume values and the corresponding grading based on posterior prostate surface area are presented in Table 5.

To standardize and simplify the calculation process, an open-access, spreadsheet calculator was prepared. By entering the prostate width and length measured during DRE in centimeters, the calculator automatically computes the posterior prostate surface area, estimated prostate volume, and the corresponding DRE-based grade. The calculator is available online as the Appendix.

The results of the correlation analysis between prostate volume grading based on posterior prostate surface area and grading based on TRUS-measured prostate volume are presented in Table 6. A strong level of agreement was

observed between the two methods (Cohen's weighted kappa=0.884±0.02; 95% CI: 0.846–0.922). (Table 6).

Discussion

In the present study, posterior prostate surface area demonstrated superior performance compared with palpable posterior prostate volume in predicting prostate volume measured by transrectal ultrasonography. The reproducibility of this method was also found to be high. Furthermore, prostate volume grading based on estimated prostate volume derived from posterior surface area showed a strong correlation with prostate volume grading based on TRUS measurements.

In this study, acknowledging that findings obtained from digital rectal examination cannot directly determine the total prostate volume, we adopted a treatment-oriented grading approach based on estimated prostate volume calculated using a regression equation rather than attempting to directly measure prostate volume.

The use of finger length as a reference during digital rectal examination was previously described by Koulikov et al.[13] However, in their study, finger length was not used to estimate prostate size but rather to measure the distance between the prostate gland and the anal verge. The calculation of posterior prostate surface area using the ellipse formula based on sagittal and transverse dimensions obtained by DRE has previously been reported by Roehrborn et al.[10] and Stone et al.[14] Roehrborn et al.[10] demonstrated that posterior prostate surface area correlates with prostate volume measured by transrectal ultrasonography. Similarly, Stone et al.[14] reported a strong correlation between posterior prostate surface area and TRUS-measured prostate volume.

Although digital rectal examination remains an indispensable component of prostate assessment, its use has been reported to be declining. In a survey conducted among healthcare professionals, DRE was not performed in up to 20% of routine clinical practice, and approximately 60% of respondents reported not feeling sufficiently competent in performing DRE.[4] Due to inadequate training, lack of standardization, and the subjective nature of the technique, DRE is often considered unreliable in clinical practice, which discourages physicians from routinely performing the examination. Three main limiting factors for estimating prostate volume by DRE have been proposed in the literature: limited examiner experience, prostate volumes <30 mL or >50 mL,[15,16] and the lack of standardization of the method.[4] Furthermore, direct assessment of the entire prostate gland by DRE is anatomically not possible, as only the posterior surface adjacent to the rectum can be evaluated.

In the literature, only a limited number of studies have quantitatively evaluated posterior prostate surface area based on findings obtained from digital rectal examination. Roehrborn et al.[6] reported that among several methods used to estimate prostate volume—including writing scales, rings, spheres, platforms, and three-dimensional models—the strongest correlation with TRUS-measured volume was observed with the three-dimensional model approach. In a study by Yanoshak et al.,[9] training with three-dimensional models was shown to improve the accuracy of prostate volume estimation by DRE. In another study, Reis et al.[7] reported that each fingertip area during DRE corresponded to approximately 10 cm^3 of prostate volume and that prostate volume estimation using this method showed a significant correlation with transabdominal ultrasonography measurements.

Yang et al.[8] evaluated factors affecting prostate volume using both digital rectal examination and ultrasonographic measurements. In their study, experienced urologists estimated prostate volume using three-dimensional relief models composed of ball-scale or rubber models. Prostate volume estimates obtained by DRE were reported to show a significant correlation with prostate volume measured by transrectal ultrasonography.

The methods previously proposed for prostate volume assessment by digital rectal examination are neither sufficiently objective nor reproducible and are difficult to standardize. The novel grading system proposed in the present study transforms palpation-based volume and posterior surface area estimation into a more objective and reproducible approach by relating these measurements to the examiner's finger dimensions and introduces a treatment-oriented grading strategy. By supporting the examination with measurable anatomical references, the proposed method reduces observer dependency and provides a high level of agreement regardless of the examiner's level of experience.

This study has several limitations. First, although magnetic resonance imaging provides more accurate assessment of prostate volume, transrectal ultrasonography rather than MRI was used as the reference standard, which represents an important limitation of our study.

Second, the examination system proposed in this study was not compared with other previously described methods, such as ball, fruit, ring, platform, or three-dimensional relief model–based approaches, which constitutes another limitation.

Conclusion

The examination method proposed in this study appears to be a standardized, reliable, and reproducible approach for estimating prostate volume categories. Further studies using advanced imaging techniques, such as magnetic resonance imaging, are required to validate the proposed method and grading system.

Ethics Committee Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (Date: 30/07/2024, No: 12/05/2021).
Peer-review: Externally peer-reviewed.
Informed Consent: Written informed consent was obtained from all participants.
Author Contribution: Concept: A.H.S.; Design: A.H.S., B.H.S., F.T.; Supervision: A.H.S., B.H.S.; Fundings: F.T.; Materials: F.T.; Data collection &/or processing: A.H.S., F.T.; Analysis and/or interpretation: A.H.S., B.H.S., F.T.; Literature search: B.H.S.; Writing: A.H.S.; Critical review: A.H.S., B.H.S., F.T.
Conflict of Interest: The authors declare no conflicts of interest.
Funding: This research received no external funding.
Acknowledgements: The authors thank all patients who participated in this study.

References

1. Loeb S, Han M, Roehl KA, Antenor JA, Catalona WJ. Accuracy of prostate weight estimation by digital rectal examination versus transrectal ultrasonography. J Urol 2005;173:63–5. [CrossRef]
2. Bezinque A, Moriarity A, Farrell C, Peabody H, Noyes SL, Lane BR. Determination of prostate volume: a comparison of contemporary methods. Acad Radiol 2018;25:1582–7. [CrossRef]
3. Christie DRH, Sharpley CF. How accurately can prostate gland imaging measure the prostate gland volume? Results of a systematic review. Prostate Cancer 2019;2019:6932572. [CrossRef]
4. Udeh EI, Dakum NK, Aderibigbe SA, Edeh JA. The utility of digital rectal examination in estimating prostate volume in a rural hospital setting. Niger J Surg 2015;21:111–4. [CrossRef]
5. Roehrborn CG. Accurate determination of prostate size via digital rectal examination and transrectal ultrasound. Urology 1998;51:19–22. [CrossRef]
6. Roehrborn CG, Sech S, Montoya J, Rhodes T, Girman CJ. Interexaminer reliability and validity of a three-dimensional model to assess prostate volume by digital rectal examination. Urology 2001;57:1087–92. [CrossRef]
7. Reis LO, Simão AF, Baracat J, Denardi F, Gugliotta A. Digital rectal examination standardization for inexperienced hands: Teaching medical students. Adv Urol 2013;2013:797096. [CrossRef]
8. Yang TK, Chang CC, Chang HC, Yang HJ, Huang KH. Factors associated with bothersome lower urinary tract symptoms in middle-aged men receiving health checkup. Sci Rep 2019;9:901. [CrossRef]
9. Yanoshak SJ, Roehrborn CG, Girman CJ, Jaffe JS, Ginsberg PC, Harkaway RC. Use of a prostate model to assist in training for digital rectal examination. Urology 2000;55:690–3. [CrossRef]
10. Roehrborn CG, Girman CJ, Rhodes T, Hanson KA, Collins GN, Sech SM, et al. Correlation between prostate size estimated by digital rectal examination and measured by transrectal ultrasound. Urology 1997;49:548–57. [CrossRef]
11. Cheng WC, Ng FC, Chan KC, Cheung YH, Chan WL, Wong SW. Interobserver variation of prostatic volume estimation with digital rectal examination by urological staffs with different experiences. Int Braz J Urol. 2004;30:466–71. [CrossRef]
12. Cornu JN, Gacci M, Hashim H, Herrmann TRW, Malde S, Netsch C, et al. Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS) EAU Guidelines. Presented at the EAU Annual Congress; 2024 Apr; Paris, France. Arnhem (The Netherlands): EAU Guidelines Office.
13. Koulikov D, Mamber A, Fridmans A, Abu Arafeh W, Shenfeld OZ. Why I cannot find the prostate? Behind the subjectivity of rectal exam. ISRN Urol 2012;2012:456821. [CrossRef]
14. Stone BV, Shoag J, Halpern JA, Mittal S, Lewicki P, Golombos DM, et al. Prostate size, nocturia and the digital rectal examination: A cohort study of 30 500 men. BJU Int 2017;119:298–304. [CrossRef]
15. Yamamoto T, Fukuta F, Masumori N. Does digital rectal examination predict prostate volume greater than 30 mL? Int J Urol 2017;24:373–6. [CrossRef]
16. Su MZ, Lenaghan D, Woo HH. Dichotomous estimation of prostate volume: A diagnostic study of the accuracy of the digital rectal examination. World J Mens Health 2013;31:220–5. [CrossRef]

ORIGINAL INVESTIGATION

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.80378

Cordocentesis for Rapid Cytogenetic Diagnosis: A Retrospective Cohort Study of 160 Cases Cytogenetic Diagnosis by Cordocentesis: Retrospective Analysis

Ceren Sağlam Purut,[1] Sevim Tuncer Can,[2] Raziye Torun,[3] Barış Sever,[4] Yunus Emre Purut,[5] Yaşar Bekir Kutbay,[6] Özgür Kırbıyık,[6] Mehmet Özer,[7] Alkım Gülşah Şahingöz Yıldırım[8]

[1]Department of Perinatology, Izmir Ataturk Training and Research Hospital, Izmir, Türkiye
[2]Department of Perinatology, Elazig Fethi Sekin City Hospital, Elazig, Türkiye
[3]Department of Perinatology, Buca Seyfi Demirsoy Training and Research Hospital, Izmir, Türkiye
[4]Department of Perinatology, Dr. Burhan Nalbantoglu State Hospital, Nicosia, Cyprus
[5]Department of Gynecologic Oncology, University of Health Sciences, Izmir Tepecik Training and Research Hospital, Izmir, Türkiye
[6]Department of Medical Genetics, Izmir City Hospital, Izmir, Türkiye
[7]Department of Perinatology, University of Health Sciences, Izmir Tepecik Training and Research Hospital, Izmir, Türkiye
[8]Perinatology, Private Clinic, Izmir, Türkiye

Address for correspondence:
Ceren Sağlam Purut, Department of Perinatology, Izmir Ataturk Training and Research Hospital, Izmir, Türkiye
E-mail: drcerensaglam@yahoo.com

Received: 13.02.2026
Accepted: 04.05.2026
Published: 29.09.2026

Abstract

Objective: It is aimed to evaluate the concordance between quantitative fluorescent polymerase chain reaction (QF-PCR) and conventional cytogenetic analysis in pregnancies undergoing cordocentesis, and to assess indications, diagnostic yield, turnaround time, and the association between maternal age and chromosomal abnormalities.

Methods: This retrospective cohort study included 160 pregnancies that underwent cordocentesis between August 2019 and July 2022 in the Department of Perinatology of a tertiary referral center. Maternal age, indication for procedure, gestational age, QF-PCR results, conventional karyotype findings, and laboratory reporting times were analyzed. Procedure indications were categorized according to ultrasonographic findings, screening test results, and previous prenatal invasive genetic test results.

Results: The most common indication was major ultrasonographic abnormalities (53.1%). QF-PCR demonstrated 100% concordance with cytogenetic analysis for trisomy 21 and trisomy 18. However, among cases reported as normal by QF-PCR, structural chromosomal abnormalities (4.5%) and rare numerical anomalies, including mosaic trisomy 8 and trisomy 9, were detected on conventional karyotyping. The highest rate of abnormal karyotype was observed in the major ultrasonographic findings group (12.9%). Mean turnaround time for conventional cytogenetic results was 11.7±3.5 days. Advanced maternal age was strongly associated with trisomy 21 and trisomy 18.

Conclusions: QF-PCR provides a rapid and reliable preliminary assessment for common aneuploidies in cordocentesis cases; however, conventional cytogenetic analysis remains essential for definitive diagnosis due to its ability to detect structural and rare chromosomal abnormalities. In late-gestation referrals, the relatively short reporting time of fetal blood culture supports cordocentesis as a valuable diagnostic option when timely clinical decision-making is required.

Keywords: Cordocentesis; cytogenetic; rapid karyotyping; QF-PCR; major fetal anomaly.

How to cite this article: *Sağlam Purut C, Tuncer Can S, Torun R, Sever B, Purut YE, Kutbay YB, Kırbıyık Ö, Özer M, Şahingöz Yıldırım AG. Cordocentesis for rapid cytogenetic diagnosis: a retrospective cohort study of 160 cases cytogenetic diagnosis by cordocentesis: retrospective analysis. South. Clin. Ist. Euras. 2026;37(3):313-318.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Copyright@Author(s)

Introduction

The prenatal diagnosis of chromosomal abnormalities is of critical importance for pregnancy management and genetic counseling. Although non-invasive prenatal testing (NIPT) has become increasingly widespread in recent years, invasive prenatal diagnostic procedures continue to play a pivotal role, particularly in the presence of structural anomalies detected on ultrasonography, high-risk screening results, or suspected genetic abnormalities.[1,2]

In the first and second trimesters, chorionic villus sampling (CVS) and amniocentesis constitute the principal invasive diagnostic techniques. However, in selected cases—especially during later gestational weeks, typically after 20 weeks of gestation—fetal blood sampling (cordocentesis) may be preferred to allow rapid karyotypic, and hematologic evaluation.[3]

Cordocentesis is an invasive diagnostic procedure that is preferentially performed in selected cases during advanced gestational weeks, as it enables rapid and reliable fetal karyotype analysis.[3] Following cordocentesis, the initial result is typically obtained through quantitative fluorescent polymerase chain reaction (QF-PCR), which is primarily used for rapid aneuploidy screening. Definitive diagnosis, however, is most commonly established by conventional cell culture and cytogenetic karyotyping.[4,5] Although QF-PCR allows for the prompt detection of common aneuploidies such as trisomies 21, 18, and 13, it has inherent limitations in identifying structural chromosomal abnormalities, mosaic karyotypes, and rare numerical aberrations.[6]

Data in the literature regarding the indications for cordocentesis, the concordance between QF-PCR and culture results, and turnaround times remain limited. Furthermore, the relationship between maternal age and different types of chromosomal abnormalities—particularly within selected patient populations undergoing cordocentesis—has not been sufficiently investigated. The aim of this study was to retrospectively evaluate the indications for cordocentesis, the concordance between QF-PCR and cell culture results, the distribution of results according to indication, turnaround times, and the association between maternal age and chromosomal abnormalities in pregnancies undergoing cordocentesis.

Materials and Methods

Study Design and Patient Selection

This retrospective study was conducted in our department and data from pregnant women who underwent cordocentesis August 2019 and July 2022 were collected retrospectively. The study was conducted in accordance with the principles of the Declaration of Helsinki.

A total of 165 cases with available post-procedural QF-PCR and conventional culture results were initially identified. Five cases were excluded from the analysis: one case in which cordocentesis was performed for single-gene mutation analysis due to a history of spinal muscular atrophy in a previous child, and four cases in which cordocentesis and intrauterine fetal blood transfusion were performed for fetal anemia secondary to Rh alloimmunization. After these exclusions, 160 cases were included in the final analysis.

Data Collection

Maternal age, indication for cordocentesis, gestational age at the time of the procedure, QF-PCR results, conventional cell culture results, and laboratory turnaround times were obtained from the hospital database system.

Cases were categorized according to the indication for cordocentesis as follows:

- Major ultrasonographic finding: presence of major structural fetal malformations detected on ultrasonography.
- Minor ultrasonographic finding: absence of major malformations but presence of soft markers or minor ultrasound findings.
- High risk in combined serum screening: increased risk identified in first- or second-trimester prenatal serum screening tests (double, triple, or quadruple screening tests).
- High risk in NIPT: increased risk result on cell-free fetal DNA testing (non-invasive prenatal testing).
- Early-onset fetal growth restriction (FGR).
- Non-diagnostic previous invasive prenatal test: cases in which earlier chorionic villus sampling (CVS) or amniocentesis performed at earlier gestational weeks failed to yield a definitive diagnosis and confirmation by fetal blood sampling was required.

All included cases represented late referrals, and cordocentesis was performed after 20 weeks of gestation.

In this retrospective analysis, only conventional karyotype results were evaluated. Advanced genetic investigations, including chromosomal microarray analysis, single-gene mutation testing, and exome sequencing, were not included in the scope of the study.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Primarily descriptive statistical methods were applied. As most continuous variables did not demonstrate normal distribution, they were summarized using mean ± standard deviation and median (minimum–maximum) values. Categorical variables were presented as frequencies and percentages. Comparisons of continuous variables between groups were conducted using the Compare Means procedure, and associations between categorical variables were evaluated using cross-tabulations and the chi-square test.

Results

A total of 160 pregnant women were included in the study. The mean maternal age was 29.77±6.87 years, with a median of 29.5 years (range, 17–50). The mean gestational age at the time of cordocentesis was 22.91±2.65 weeks, with a median of 22 weeks (range, 20–32).

When cordocentesis indications were evaluated, the most common indication was major ultrasonographic abnormalities, accounting for 53.12% of cases (n=85). This was followed by minor ultrasonographic findings (23.12%; n=37) and high risk in combined serum screening tests (18.75%; n=30). Less frequent indications included a non-diagnostic previous invasive prenatal test (2.5%; n=4), high risk on NIPT (1.25%; n=2), and early-onset fetal growth restriction (1.25%; n=2).

According to QF-PCR results, 133 cases (83.12%) were reported as normal karyotype. Maternal contamination was detected in 14 cases (8.75%), trisomy 21 in 7 cases (4.37%), and trisomy 18 in 3 cases (1.87%). In two cases (1.25%), definitive results could not be obtained for the sex chromosomes, and in one case (0.62%), a definitive result for chromosome 13 could not be established. Therefore, cytogenetic analysis was required for these three cases (1.87%) to reach a final diagnosis.

Evaluation of conventional cell culture results demonstrated that among the 133 cases reported as normal by QF-PCR, one case (0.75%) had mosaic trisomy 8 and one case (0.75%) had trisomy 9. Structural chromosomal abnormalities were identified in six cases of normal QF-PCR results (4.5%) [46,XX,13p+; chromosome 22p+; 46,XX,t(5;16)(q11.2;q13); 47,XY,+mar; 46,XX,t(X;3)(p11.4;q27); 46,XX,t(3;10)(q23;q26)]. In three cases (2.25%), no result could be obtained due to culture failure. Additionally, in two cases (1.5%) that were interpreted as normal by QF-PCR, no numerical chromosomal abnormality was detected on culture; however, structural evaluation could not be performed due to insufficient banding quality. Overall, 127 cases (95.5%) were reported as normal karyotype on cytogenetic analysis (Table 1).

Table 1. Comparison of QF-PCR and cytogenetic (cell culture) results

	Sitogenetic Results							
			Abnormal Karyotype					
QF-PCR	Normal karyotype	MC*	Trisomy 21	Trisomy 18	Other numeric chromosomal anomaly	Structural chromosomal	Non-diagnostic anomaly	Total
Normal karyotype	120	0	0	0	2	6**	5	133
MC*	4	10	0	0	0	0	0	14
Trisomy 21	0	0	7	0	0	0	0	7
Trisomy 18	0	0	0	3	0	0	0	3
Non- diagnostic	3	0	0	0	0	0	0	3
Total	127	10	7	3	2	6	5	160

*MC, maternal contamination; ** 46,..,t(X;3)(p11.4;q27); 47,XY,+mar; 46,..,t(5;16)(q11.2;q13); chromosome 22p+; (46,..,13p+); (46,..t(3;10)(q23;q26).

Table 2. Distribution of conventional cytogenetic (cell culture) results according to ındication groups

Indication Groups	Sitogenetic Results							
		Abnormal Karyotype						
	Normal karyotype	MC*	Trisomy 21	Trisomy 18	Other numeric chromosomal anomaly	Structural chromosomal	Non-diagnostic anomaly	Total
Major ultrasonographic finding	66	6	2	3	2	4**	2	85
Minor ultrasonographic finding	30	2	1	0	0	1***	3	37
High risk in combined serum screening test	26	2	2	0	0	0	0	30
Non-diagnostic previous prenatal invasive test	3	0	0	0	0	1****	0	4
High risk in NIPT	0	0	2	0	0	0	0	2
Early-onset FGR	2	0	0	0	0	0	0	2
Total	127	10	7	3	2	6	5	160

*MC, maternal contamination; ** 46,..,t(X;3)(p11.4;q27); 47,XY,+mar; 46,..,t(5;16)(q11.2;q13); chromosome 22p+; *** (46,..,13p+); **** (46,..t(3;10)(q23;q26)

Among the 14 cases in which maternal contamination was detected by QF-PCR, four cases (28.6%) were reported as normal karyotype on cytogenetic analysis, whereas the remaining ten cases (71.4%) were again reported as maternal contamination (Table 1).

All seven cases reported as trisomy 21 and all three cases reported as trisomy 18 by QF-PCR were confirmed by cytogenetic analysis, demonstrating 100% concordance. The three cases for which cytogenetic confirmation was recommended due to inconclusive QF-PCR findings were ultimately reported as normal karyotype on culture analysis (Table 1).

The highest rate of abnormal karyotype on conventional cytogenetic analysis was observed in the group with major ultrasonographic findings (12.9%; n=11). In comparison, the rate of abnormal karyotype was 5.4% (n=2) in the minor ultrasonographic findings group and 6.7% (n=2) in the high-risk combined screening group. In the high-risk NIPT group, abnormal karyotype was detected in 100% of cases (n=2) (Table 2). The average turnaround time for conventional cytogenetic results was 11.71±3.5 days (range, 5–22 days).

When analyzed according to gestational age at the time of the procedure, the highest mean gestational age was observed in the early-onset FGR group, with a mean of 26.5±4.95 weeks (range, 23–30 weeks). This was followed by the major ultrasonographic findings group, with a mean gestational age of 23.41±3.04 weeks. The lowest mean gestational age at the time of cordocentesis was observed in the high-risk NIPT group (21±0 weeks).

According to cytogenetic results, comparison of maternal age across karyotype groups demonstrated that the highest mean maternal age was observed in the trisomy 18 group (41.33±3.79 years; range, 37–44), followed by the trisomy 21 group (36.57±4.23 years; range, 30–43). In the normal karyotype group, the mean maternal age was 29.61±6.73 years (range, 17–50). The youngest maternal ages were observed in the trisomy 9 case (19 years) and the mosaic trisomy 8 case (22 years).

Discussion

In the present study, we analyzed the concordance between QF-PCR and conventional cytogenetic (cell culture) results in pregnancies undergoing cordocentesis, as well as procedure indications, distribution of chromosomal abnormalities according to indication, laboratory turnaround times, gestational age at the time of the procedure, and the association between maternal age and chromosomal abnormalities.

The complete concordance observed between QF-PCR and cytogenetic results for trisomy 21 and trisomy 18 further confirms that QF-PCR is a reliable and rapid preliminary diagnostic tool for common aneuploidies.[7,8] However, the detection of structural chromosomal abnormalities and rare numerical aberrations (mosaic

trisomy 8 and trisomy 9) in cases reported as normal by QF-PCR underscores the inherent limitations of this method. As QF-PCR targets specific chromosomes and short tandem repeat (STR) regions, it does not provide definitive diagnosis for structural rearrangements such as marker chromosomes, inversions, or translocations, nor for most mosaic or rare aneuploidies. These findings support the indispensable role of conventional cytogenetic analysis, particularly in cases with major structural anomalies detected on ultrasonography.[4,5,9]

In our cohort, the most common indication for cordocentesis was major ultrasonographic abnormalities, and the highest rate of abnormal karyotype was observed in this group. This finding reinforces the well-established association between structural fetal anomalies and underlying chromosomal pathology. In a study evaluating 620 karyotype analyses, chromosomal abnormalities were detected in 5.8% of fetuses with anomalies and in 13.3% of those with multiple fetal anomalies, that is similar to our study.[10] Although the rates of abnormal karyotype were lower in the minor ultrasonographic findings and high-risk combined screening groups, they remained higher than in the other indication groups. Notably, the high rate of abnormal karyotype among the limited number of cases with high-risk NIPT results highlights the importance of confirming non-invasive screening results with invasive diagnostic testing. The abnormality rate observed in our study is consistent with the detection rates reported in large high-risk NIPT series for the most common trisomies (trisomy 21, 18, and 13).[11]

Evaluation of the association between maternal age and cytogenetic results demonstrated significantly higher mean maternal age in the trisomy 18 and trisomy 21 groups, supporting the well-documented effect of advanced maternal age on chromosomal nondisjunction. Large cohort studies and amniocentesis series have clearly shown a marked increase in the risk of trisomy 21 and trisomy 18 in women aged 35 years and older.[12,13] In contrast, the younger maternal ages observed in cases of mosaic trisomy 8 and trisomy 9 suggest that rare numerical abnormalities may not be as strongly associated with maternal age as classic aneuploidies. Previous studies have reported that mosaic aneuploidies and structural rearrangements are more frequently observed in younger women, whereas common trisomies become increasingly prevalent with advancing maternal age.[14,15]

The mean turnaround time for conventional cell culture was approximately 12 days, and this duration did not vary substantially according to indication, suggesting standardized and predictable laboratory processing. Compared with the literature, this turnaround time appears shorter than that reported for amniotic fluid–based cytogenetic analyses. In one study, the mean interval between diagnostic amniocentesis and definitive results was 23 days, while another series reported a mean incubation period of 17.9 days for amniocentesis samples.[16,17] This shorter reporting time represents a significant clinical advantage, particularly in cases presenting after 20 weeks of gestation, when rapid diagnosis and timely decision-making are crucial, and may confer an advantage over amniocentesis performed at similar gestational ages.

The differences in gestational age at the time of cordocentesis among indication groups likely reflect the timing of clinical suspicion and referral patterns inherent to each condition. Major structural anomalies are typically detected during routine mid-trimester anomaly screening, so referral for prenatal genetic testing generally occurs after the gestational age at which the anomaly scan is performed.[18,19] Although referral for invasive prenatal genetic testing due to a high-risk NIPT result after 20 weeks of gestation may be considered relatively late compared with referrals in earlier trimesters, this group nevertheless constituted the lowest gestational age category within the cordocentesis cohort. This finding may be explained by delayed performance of NIPT or late presentation following receipt of high-risk results. Together, these findings illustrate how the timing of cordocentesis is largely determined by the natural history and screening pathways of the underlying indication.

The retrospective design of the study and the limited number of cases in certain subgroups constitute important limitations that may restrict statistical power. Nevertheless, classification according to indication and the combined evaluation of QF-PCR and cytogenetic results represent notable strengths of the study.

Conclusion

Major ultrasonographic abnormalities which are detected during mid-trimester sonography scan constitute the indication group with the highest likelihood of detecting an abnormal karyotype. Particularly in pregnancies presenting during the second half of gestation, the relatively shorter time required to obtain karyotype re-

sults from fetal blood culture renders cordocentesis an important diagnostic option when timely decision-making is critical.

Although QF-PCR represents a rapid and reliable first-line diagnostic method in cordocentesis cases, particularly for common aneuploidies such as trisomy 21 and trisomy 18; structural chromosomal abnormalities and rare numerical aberrations may still be detected in cases reported as normal by QF-PCR. For this reason, conventional cytogenetic evaluation remains essential for definitive diagnosis.

Ethics Committee Approval: Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of the University of Health Sciences Izmir Tepecik Training and Research Hospital (Date: 05/04/2023, No: 2023/03-17).
Peer-review: Externally peer-reviewed.
Informed Consent: Not required due to the retrospective design of the study.
Author Contribution: Concept: C.S.P., B.S., S.T.C., R.T., Y.B.K., Ö.K., M.Ö., Y.E.P., A.G.Ş.Y.; Design: C.S.P., B.S., S.T.C., R.T., Y.B.K., Ö.K., M.Ö., Y.E.P., A.G.Ş.Y.; Supervision: C.S.P., B.S., S.T.C., R.T., Y.B.K., Ö.K., M.Ö., Y.E.P., A.G.Ş.Y.; Funding: C.S.P., S.T.C.; Materials: C.S.P., R.T., S.T.C., M.Ö., Y.B.K., Ö.K.; Data collection and/or processing: : C.S.P., R.T., S.T.C., B.S., M.Ö.; Analysis and/or interpretation: C.S.P., B.S., Y.B.K., Ö.K.; Literature search: C.S.P., S.T.C.; Writing: C.S.P., Y.E.P., B.S.; Critical review: C.S.P., B.S., S.T.C., R.T., Y.B.K., Ö.K., M.Ö., Y.E.P., A.G.Ş.Y.
Conflict of Interest: None declared.
Funding: The authors declared that this study has received no financial support.
Acknowledgement: This study was presented as an oral presentation with its preliminary findings at the 2nd International Congress of Gynecology and Obstetrics in 2022.

References

1. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics, Committee on Genetics, Society for Maternal-Fetal Medicine. Screening for fetal chromosomal abnormalities: ACOG practice bulletin, number 226. Obstet Gynecol 2020;136–69. [CrossRef]
2. Fortin O, Mulkey SB, Fraser JL. Advancing fetal diagnosis and prognostication using comprehensive prenatal phenotyping and genetic testing. Pediatr Res 2025;97:1269–79. [CrossRef]
3. Sun Y, Zhang P, Zhang N, Rong L, Yu X, Huang X, et al. Cytogenetic analysis of 3387 umbilical cord blood in pregnant women at high risk for chromosomal abnormalities. Mol Cytogenet 2020;13:2. [CrossRef]
4. Masoudzadeh N, Teimourian S. Comparison of quantitative fluorescent polymerase chain reaction and karyotype analysis for prenatal screening of chromosomal aneuploidies in 270 amniotic fluid samples. J Perinat Med 2019;47:631–6. [CrossRef]
5. Skaro V, Projic P, Korac P, Gjergja-Juraski R, Stipoljev F, Vicic A. Antenatal detection of chromosomal abnormalities combining QF-PCR and cytogeneticanalysis. Mol Exp Biol Med 2020;3:34–43. [CrossRef]
6. Chen C, Tang T, Song QL, He YJ, Cai Y. Confusing finding of quantitative fluorescent polymerase chain reaction analysis in invasive prenatal genetic diagnosis: A case report. World J Clin Cases 2023;11:6895–901. [CrossRef]
7. Cirigliano V, Voglino G, Cañadas MP, Marongiu A, Ejarque M, Ordoñez E, et al. Rapid prenatal diagnosis of common chromosome aneuploidies by QF-PCR. Assessment on 18 000 consecutive clinical samples. Mol Hum Reprod 2004;10:839–46. [CrossRef]
8. Nicolini U, Lalatta F, Natacci F, Curcio C, Bui TH. The introduction of QF-PCR in prenatal diagnosis of fetal aneuploidies: Time for reconsideration. Hum Reprod Update 2004;10:541–8. [CrossRef]
9. Łaczmańska I, Gil J, Stembalska A, Makowska I, Kozłowska J, Skiba P, et al. Rapid diagnostics of the most frequent fetal aneuploidies with QF-PCR method – study of 100 cases. Ginekol Pol 2015;86:694–9. [CrossRef]
10. Petrovic B, Joksimovic J, Sljivancanin D, Joksimovic L, Drinic A, Stamenkovic J. Ultrasound markers of chromosome aberrations on routine second trimester screening. Genetika 2022;54:921–31. [CrossRef]
11. Chen Y, Wu X, Li H, Yin Y, Zhang Y. Evaluation of the prenatal diagnostic value of non-invasive prenatal testing for the detection of rare fetal autosomal trisomies: A single center study of 83,842 cases. Sci Rep 2025;15:26254. [CrossRef]
12. Ferguson-Smith MA, Yates JRW. Maternal age specific rates for chromosome aberrations and factors influencing them: Report of a collaborative European study on 52 965 amniocenteses. Prenat Diagn 1984;4:5–44. [CrossRef]
13. Elmerdahl Frederiksen L, Ølgaard SM, Roos L, Petersen OB, Rode L, Hartwig T, et al. Maternal age and the risk of fetal aneuploidy: A nationwide cohort study of more than 500 000 singleton pregnancies in Denmark from 2008 to 2017. Acta Obstet Gynecol Scand 2024;103:351–9. [CrossRef]
14. Ozawa N, Ogawa K, Sasaki A, Mitsui M, Wada S, Sago H. Maternal age, history of miscarriage, and embryonic/fetal size are associated with cytogenetic results of spontaneous early miscarriages. J Assist Reprod Genet 2019;36:749–57. [CrossRef]
15. Pendina AA, Krapivin MI, Chiryaeva OG, Petrova LI, Pashkova EP, Golubeva AV, et al. Chromosomal abnormalities in miscarriages and maternal age: New insights from the study of 7118 cases. Cells 2024;14:8. [CrossRef]
16. Mulcahy MT, Jenkyn J. Prenatal diagnosis. Results of cytogenetic analysis of amniotic fluid cell cultures. Med J Aust 1973;1:979–82. [CrossRef]
17. Zolotukhina TV, Tsvetkova IV. Amniotic fluid cell culture for prenatal diagnosis of some metabolic diseases. Biull Eksp Biol Med 1980;89:354–6. [CrossRef]
18. Edwards L, Hui L. First and second trimester screening for fetal structural anomalies. Semin Fetal Neonatal Med 2018;23:102–11. [CrossRef]
19. Poojari VG, Paladugu S, Vasudeva A, Mundkur A, Pai MV, Kumar P. We need to improve prenatal screening practices in primary obstetric care: A representative data from a fetal medicine unit in coastal Karnataka. J Obstet Gynaecol India 2022;72:19–25. [CrossRef]

ORIGINAL ARTICLE

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.71598

Vitamin D Prophylaxis and Changes in Kidney Stone Number and Size in Children: A Prospective Ultrasound-Based Study

Buşra Gürpınar,[1] Bağdagül Yavaş Aksu,[2] Zeynep Yürük Yıldırım,[2] Emine Çalışkan,[3] Zuhal Bayramoğlu,[3] Gülbin Gökçay[4] Alev Yılmaz[2]

Abstract

Objective: Vitamin D prophylaxis (400 IU/day) is recommended for all children, at least during the first year of life. This prophylaxis is usually ceased in children with nephrolithiasis despite limited evidence. This study aimed to determine whether the cessation of vitamin D prophylaxis affects the number and size of stones in young children with nephrolithiasis.

Methods: This prospective study evaluated children aged<3 years who were referred to a pediatric nephrology center for nephrolithiasis. Renal ultrasonography was performed by a single experienced pediatric radiologist. Twenty-eight children (17 males, 60.7%) with persistent nephrolithiasis were enrolled. Vitamin D prophylaxis was ceased during the first 3 months (P1) and subsequently administered for 3 months (P2). The number and size of stones were assessed using ultrasonography at the end of both periods.

Results: The mean age at the initial ultrasonography was 13.7±10.7 (range, 2.7–39.4) months. Serum creatinine, calcium levels were normal in all patients, and none had vitamin D hypervitaminosis. Metabolic abnormalities were detected in 12 patients (42.9%), most commonly hypercalciuria (n=8), hypocitraturia (n=7). Stone number and size decreased significantly during both P1 and P2. None of the 12 children who were stone-free at the end of P1 developed new stones after vitamin D prophylaxis was reintroduced during P2. Reduction in stone number was more frequent in younger children (p=0.01), whereas no other clinical or laboratory parameters were associated with stone improvement.

Conclusions: Routine cessation of vitamin D prophylaxis may not be necessary in children with nephrolithiasis when close ultrasonographic monitoring is performed.

Keywords: Nephrolithiasis; kidney stones; vitamin D; prophylaxis; ultrasonography; children.

[1]Departments of Pediatrics, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Türkiye
[2]Division of Pediatric Nephrology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Türkiye
[3]Department of Radiology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Türkiye
[4]Department of Social Pediatrics, Istanbul University Institute of Child Health, Istanbul, Türkiye

Address for correspondence:
Busra Gurpinar Tosun, Departments of Pediatrics, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Türkiye
E-mail: gurpinarbusra@gmail.com

Received: 20.08.2026
Accepted: 27.08.2026
Published: 29.09.2026

Introduction

Nephrolithiasis, commonly known as kidney stone disease, is characterized by the formation of calculi within the renal collecting system or urinary tract.[1,2] In recent years, nephrolithiasis has been increasingly recognized among infants and children, posing a significant clinical concern.[3-5] In addition to lifestyle and dietary changes, more frequent use of imaging modalities in children with spe-

How to cite this article: *Gürpınar B, Yavaş Aksu B, Yürük Yıldırım Z, Çalışkan E, Bayramoğlu Z, Gökçay G, Yılmaz A. Vitamin D prophylaxis and changes in kidney stone number and size in children: a prospective ultrasound-based study. South. Clin. Ist. Euras. 2026;37(3):319-327.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.
Copyright@Author(s)

cific or nonspecific symptoms is more effective in this regard.[6,7] Although genetic and anatomical causes are the primary determinants, metabolic factors are also frequently observed in children, with hypercalciuria being the most common metabolic abnormality.[1,8,9] Therefore, the pathophysiology that may cause hypercalciuria has been investigated for ages, and elevated levels of calcitriol have been identified as detrimental to the risk of nephrolithiasis, likely due to a direct increase in urinary calcium excretion.[10-12] This raises longstanding concerns regarding the safety of vitamin D supplementation in children with idiopathic hypercalciuria or nephrolithiasis. However, the relationship between serum 25-hydroxyvitamin D (25OHD) concentration, vitamin D supplementation, and the occurrence of stone events remains to be elucidated.[10]

Vitamin D plays a well-established role in regulating skeletal health and mineral homeostasis.[13] Epidemiological studies have consistently linked low vitamin D levels to an increased risk of numerous common conditions, such as musculoskeletal, metabolic, cardiovascular, cancer-related, autoimmune, and infectious diseases.[14-16] The prevalence of low vitamin D status in childhood is high, with considerable global variability.[17-19] Additionally, maternal vitamin D deficiency is an important cause of vitamin D deficiency in early infancy.[20] Therefore, vitamin D prophylaxis (400 IU per day) is recommended for all infants at least during the first year of life, preferably up to the age of 18 years, to prevent rickets related to vitamin D deficiency. Moreover, vitamin D prophylaxis plays a crucial role in preventing rickets and is associated with a reduced risk of respiratory tract infections.[21-23] This prophylaxis is usually ceased in children with nephrolithiasis despite limited evidence.

This study aimed to determine whether the cessation of vitamin D prophylaxis affects the number or size of stones in children under the age of 3 years with nephrolithiasis.

Materials and Methods

Children aged <3 years with nephrolithiasis who were referred from a pediatric outpatient clinic to the pediatric nephrology division were evaluated. Children with a history of vitamin D hypervitaminosis and/or hypercalcemia were excluded. Hypercalcemia was defined as a serum total calcium level above the age-specific upper reference limit on at least one measurement.[24] Serum 25OHD concentrations were defined as vitamin D deficiency <12 ng/mL (30 nmol/L), insufficiency 12-20 ng/mL (30–50 nmol/L), and hypervitaminosis ≥100 ng/mL (250 nmol/L).[25] All were confirmed by an initial ultrasound (U1) at our center by a single, experienced pediatric radiologist. Twenty-eight patients (17 males, 60.7%) with nephrolithiasis were included in the study. Data on clinical characteristics and urinary excretion results were obtained from the medical records. Serum creatinine levels were normal in all the patients. Vitamin D prophylaxis was ceased in all patients prior to admission to our department. The study was conducted between September and March in Turkey, a period associated with limited sunlight exposure and reduced cutaneous vitamin D synthesis.

All children underwent the same fixed and sequential follow-up. Intervention period 1 (P1) was defined as a three-month vitamin D–free observation period, during which vitamin D prophylaxis was completely ceased in all patients. Throughout P1, families were instructed to avoid all potential sources of vitamin D, including vitamin D-supplemented foods, formulas and multivitamin preparations. Compliance was reinforced through weekly telephone follow-up with the same caregiver. At the end of P1, a second renal ultrasonography (U2) was conducted. Intervention period 2 (P2) was defined as a subsequent three-month period during which all patients received oral vitamin D prophylaxis at a dose of 400 IU/day. This dose corresponds to the standard recommended prophylactic dose for infants and, young children. During P2, the consumption of vitamin D-supplemented foods and multivitamin preparations was not restricted. At the end of this period, a third renal ultrasonography (U3) was conducted. During both study periods, increased water intake and a salt-free diet were recommended for all patients throughout the follow-up period. Potassium citrate was prescribed to 12 patients based on clinical and laboratory findings and was maintained throughout both periods. A flowchart of the study design and within-subject follow-up is shown in Figure 1.

Ultrasound measurements were performed using both an 8 Mhz curved probe and a 14 Mhz flat probe on the same device (Toshiba Aplio 500, Toshiba Medical Systems, Tokyo, Japan) by the same pediatric radiologist who was blinded to the study period and previous ultrasound findings. Patients were evaluated in terms of the structure of the kidney parenchyma, corticomedullary separation, pelvicalyxial system anatomy and variations,

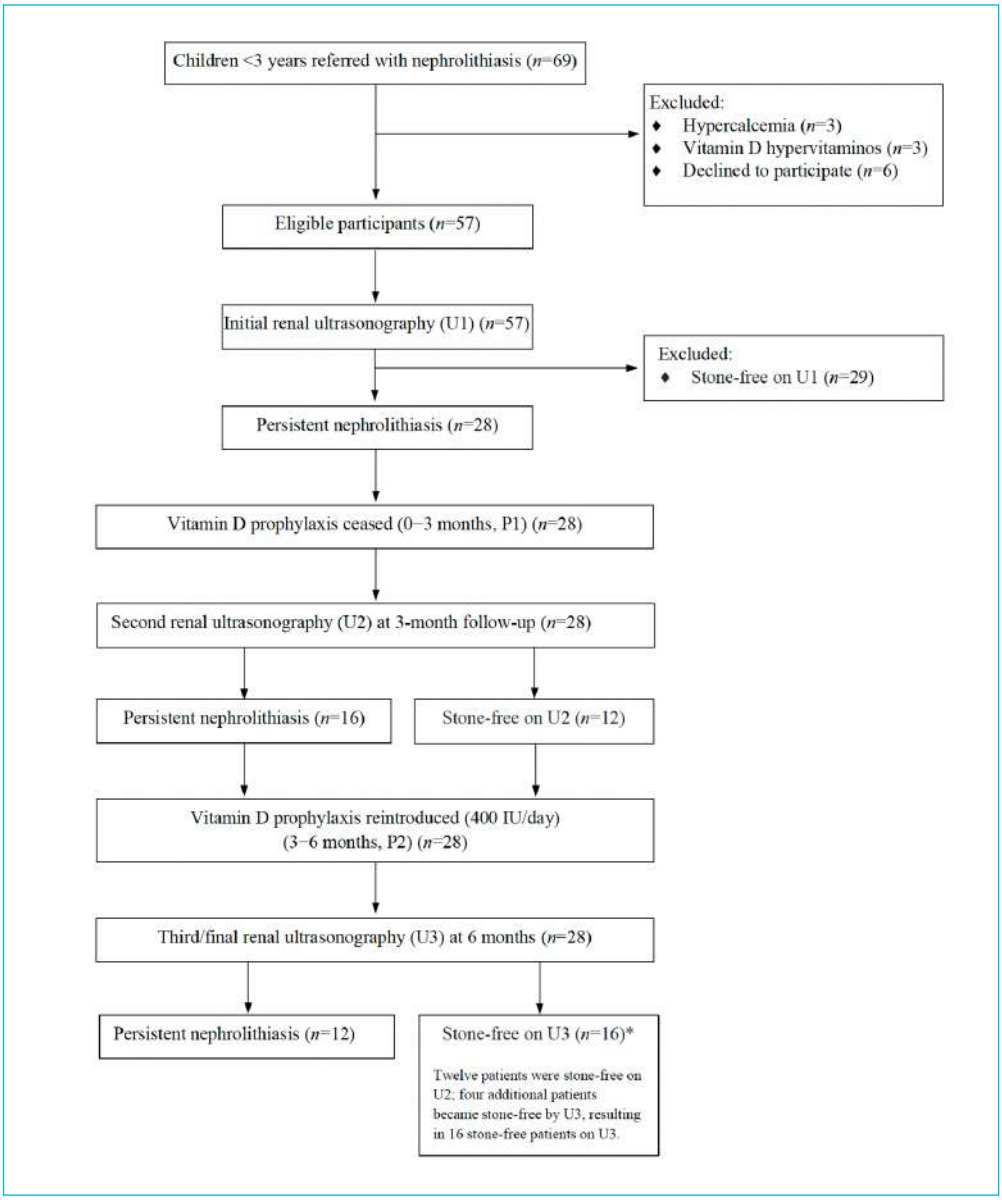

Figure 1. Flow chart of study design and within-subject follow-up.

collector system dilatation, pelvic anteroposterior diameter, bladder wall, and lumen content. The presence of posterior acoustic shadowing on ultrasound and twinkle artifacts on Doppler ultrasound was investigated. In patients with nephrolithiasis, dilatation and calculus were investigated during ureteral tracing. The size and number of stones detected in at least two planes and their locations were documented. The number of stones was calculated as the total number of stones in each kidney. The size of the stones was defined as the maximal stone diameter on ultrasound; in children with bilateral stones, the mean of the maximal diameters from the right and left kidneys was used for analysis. Renal calyceal microlithiasis was defined as hyperechogenic spots less than 3 mm in diameter in the renal calyces.[26] Stone size and number were compared between U1, U2, and U3.

The study was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (No: 2016/724, Date: 13/06/2016). Written informed consent was obtained from the parents or legal guardians of all participants, and all studies were conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Statistical evaluation was performed using GraphPad Prism® V10 software (GraphPad Software Inc., San Diego, California, USA). Data are presented as mean ± SD or median with the range, as appropriate. Normality was assessed using the Kolmogorov-Smirnov test. Between-group comparisons were performed using the Mann-Whitney U test. Longitudinal changes in stone number and maximum stone diameter between U1 and U2 and between U2 and U3 were assessed using the Wilcoxon matched-pairs signed-rank test. Categorical variables were compared using the chi-square or Fisher's exact tests. Statistical significance was set at $P<0.05$.

Results

The mean age at the initial confirmatory ultrasonography (U1) was 13.7±10.7 months (range; 2.7–39.4), at the time of U1. Sixty-two percent of the patients were under 1 year of age. The age distribution of the patients was as follows: <6 months (n=3), 6–18 months (n=18), and >18 months (n=7). The main presenting symptoms were irritability (n=10), vomiting and urinary tract infection (n=5), diaper or urine discoloration (n=4), and poor weight gain (n=2), while eight patients were asymptomatic. A family history of urinary stone disease was present in 46.4% (n=13) of patients. More than half of the patients (n=8, 61.5%) had multiple stones at the time of diagnosis, and the stones were bilaterally located in seven patients. The mean number of stones was 2.4±1.7 (range: 1–8), and the mean size of stones was 4.0±2.4 mm (range: 1–11). Renal calyceal microlithiasis was detected in 42.9% (n=12) of the patients.

Anatomical abnormalities were identified in four patients (14.3%), including vesicoureteral reflux (n=1), ectopic kidney (n=1), and non-obstructive ureteropelvic junction dilatation (n=2). Oral potassium citrate therapy was administered to 42.9% (n=12) of the patients. Urinary tract infection was not observed in any patient during follow-up. Serum urea, creatinine (Cr), calcium (Ca), phosphorus (P), and alkaline phosphatase (ALP) levels were normal in all the patients. Metabolic abnormalities were found in 12 patients (42.9%) (hypercalciuria, n=8; hypocitraturia, n=7; hyperoxaluria, n=3; cystinuria, n=2). Three children had multiple metabolic risk factors. Vitamin D deficiency was observed in three patients (10.7%) and insufficiency in ten (35.7%).

At the end of P1, 12 patients had no remaining stones. The number of stones decreased in 57.1% (n=16) of the children, increased in 10.7% (n=3), and did not change in 32.2% (n=9) of the children. Kidney stone size decreased in 60.7% (n=17) of patients, increased in 14.3% (n=4), and remained unchanged in 25% (n=7). Changes in stone number and size, serum Ca and 25OHD levels, and spot urine Ca/Cr ratio at the end of P1 and P2 are presented in Table 1. Serum 25OHD levels were unchanged, while serum Ca levels and urine Ca/Cr ratios were significantly increased in P2 compared to P1 (p=0.05, p=0.02, p=0.02, respectively).

Eight patients had hypercalciuria at baseline, 75% (n=6) of whom had a positive family history of nephrolithia-

Table 1. Comparison of the period with and without vitamin D prophylaxis

	P1†	P2‡	p
Number of the stone n (%)	Stone Free 12 (42.9)	Stone Free 16 (57.1)*	
	Decrease 16 (57.1)	Decrease 6 (21.4)	0.03
	Increase 3 (10.7)	Increase 0 (0)	
	No change 9 (32.2)	No change 22 (78.6)	
Size of the stone n (%)	Decrease 17 (60.7)	Decrease 12 (42.9)	0.001
	Increase 4 (14.3)	Increase 0 (0)	
	No change 7 (25)	No change 16 (57.1)	
Serum Ca (mg/dL) median (IQR)	10.0 (9.9–10.7)	10.7 (10.5–11.2)	0.02
25OHD (ng/mL)§ median ((IQR)	23.6 (21–40)	31.4 (28–48)	0.05
Spot urine Ca/Cr median (IQR)	0.2 (0.2–0.3)	0.3 (0.2–0.5)	0.02

* Patients who were stone-free at the end of P1 did not develop new stones during P2. † The end of the period without vitamin D prophylaxis (P1). ‡ The end of the period with vitamin D prophylaxis (P2). § 25OHD nmol/L = 2.5× ng/mL.

Table 2. Comparison of periods with and without vitamin D prophylaxis in patients with hypercalciuria (n=8)

	P1†	P2‡
Number of Stone, n		
Decrease	4	5
Increase	0	1
No change	4	2
Size of Stone, n		
Decrease	2	6
Increase	4	1
No change	2	1

†The end of the period without vitamin D prophylaxis (P1). ‡The end of the period with vitamin D prophylaxis (P2).

sis and 50% (n=4) of whom were receiving oral potassium citrate therapy. The baseline mean serum Ca level was 10.4±0.4 mg/dL and the mean 25OHD level was 28.4±17.4 ng/mL. Hypocitraturia was observed in three patients. Changes in the stone number and size in the hypercalciuric subgroup during periods with (P2) and without (P1) vitamin D prophylaxis are presented descriptively in Table 2. In this subgroup, the mean urine Ca/Cr ratio after vitamin D prophylaxis was 0.4±0.3, showing no statistically significant difference compared with the baseline (0.9±0.6, p=0.087).

At U3, 16 of 28 children (57.1%) were stone-free. None

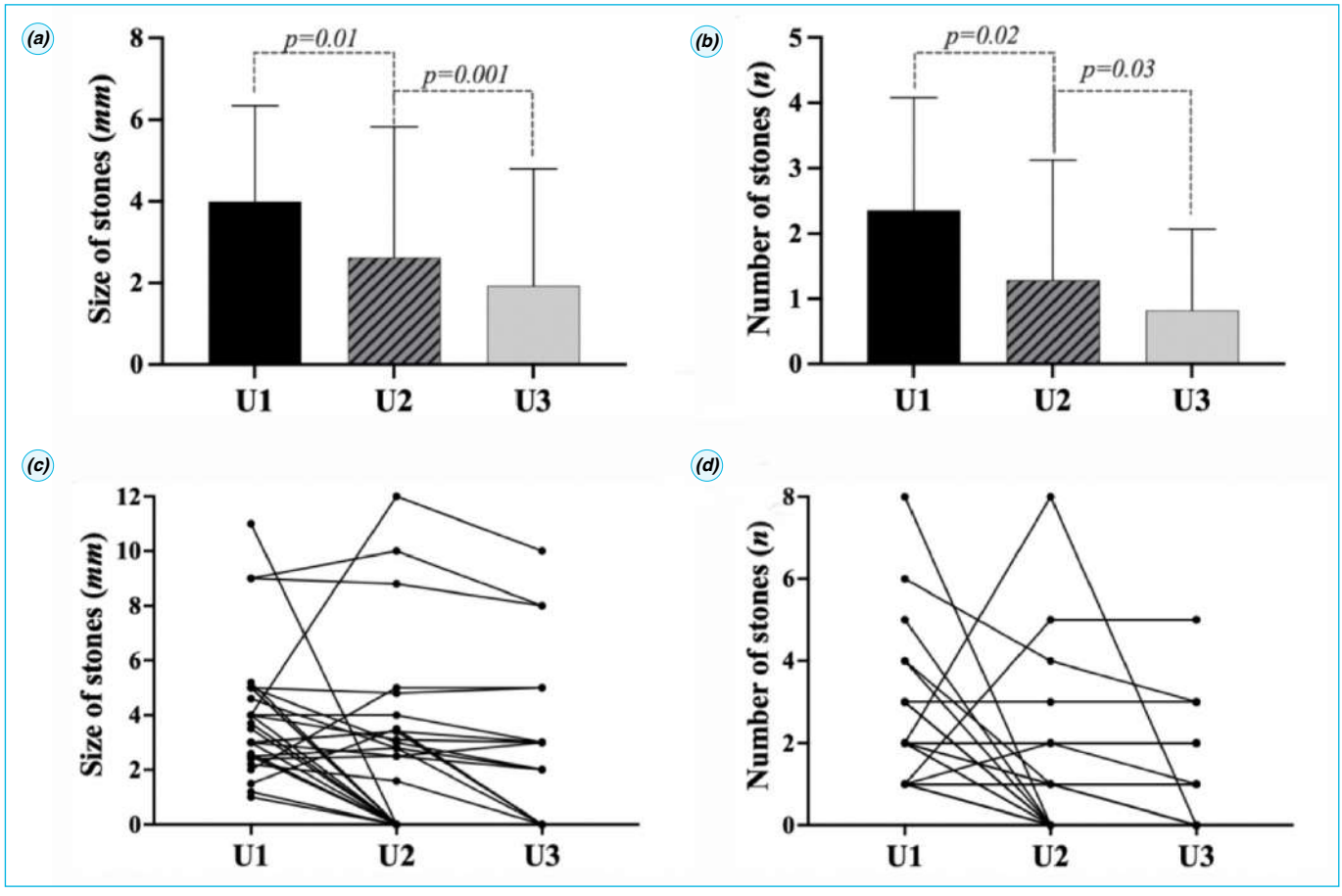

Figure 1. Changes in stone size (a,c) and number (b, d) during patients follow-up. **(a)** U1 represents the initial ultrasound, U2 represents the second ultrasound conducted without vitamin D supplementation for three months, and U3 represents the third ultrasound performed after administering 400 IU/day vitamin D prophylaxis to all patients over a three-month period. **(b)** The total number of stones was counted in both kidneys. The size of the stones was defined as the maximal stone diameter on ultrasound; in children with bilateral stones, the mean of the maximal diameters from the right and left kidneys was used for analysis. **(c)** Figures a and b display the data as mean±SD. Figures c and d show the individual data points. **(d)** The P values in Figure A and B show comparisons between each ultrasound (U1 vs. U2 and U2 vs. U3), calculated using the paired Wilcoxon signed-rank test.

Table 3. Comparison of the patients' clinical and laboratory characteristics with and without decrease the number and size of stones during the study

	Number of Stone			Size of Stone		
	Without decreased n=9	With decreased n=19	p	Without decreased n=5	With decreased n=23	p
Age						
mean±SD months	23.5±6.3	7.2±1.4	0.01[m]	13.3±0.5	7.6±4.2	0.15[m]
Sex						
male/female n	6/3	11/8	0.66 [X²]	4/1	13/10	0.62[X²]
Family history of nephrolitiasis						
Yes/No n	5/4	8/11	0.51[X²]	3/2	10/13	0.50[X²]
Using of potassium citrate						
Yes/No n	4/5	8/11	0.91[X²]	3/2	9/14	0.39[X²]
Hypercalsiuria						
Yes/No n	1/8	7/12	0.16[X²]	2/3	6/17	0.61[X²]
Serum Ca(mg/dL)	10.2	10.5	0.31[m]	10.4	10.5	0.82[m]
median (IQR)	(9.9–10.5)	(10–10.7)		(10.2–10.6)	(9.9–10.7)	
25OHD (ng/mL)§	22.9	34	0.33[m]	45	31.2	0.14[m]
median (IQR)	(21–45)	(29–40)		(35.3–55.4)	(22.9–39.5)	
Spot urine Ca/Cr	0.2	0.3	0.09[m]	0.3	0.2	
median (IQR)	(0.2–0.2)	(0.2–0.4)		(0.2–0.3)	(0.2–0.4)	1.00[m]

§ 25OHD nmol/L = 2.5× ng/mL. m Mann-whitney u test / [X²] Ki-kare test (Fischer test).

of the 12 children who were stone-free at U2 developed new stones during P2. Stone number decreased significantly from U1 to U2 and from U2 to U3 (p=0.02 and p=0.03, respectively). Stone size decreased during both intervals (p=0.01 and p=0.001, respectively). Figure 2 illustrates the changes in the number and size of stones throughout the follow-up period.

When we compared patients with and without a decrease in the number of stones during the study, a decrease in the number of stones was more frequent in younger children (p=0.01), whereas other clinical and laboratory parameters did not differ between the two groups (p>0.05) (Table 3). The clinical and laboratory parameters were similar between the patients with and without decreased stone size during the study period (p>0.05) (Table 3).

Discussion

This prospective sequential ultrasound-based study evaluated the short-term effects of vitamin D prophylaxis on stone dynamics in young children with nephrolithiasis, all of whom resided in the same country and were followed up during the same seasonal period. The short-term ultrasonographic course of nephrolithiasis in young children managed with a fixed vitamin D prophylaxis protocol. Another strength was the use of standardized ultrasonographic assessments by a blinded pediatric radiologist throughout the follow-up period. Of the 57 children referred to our clinic with a previous diagnosis of nephrolithiasis based on ultrasonographic findings, only 28 had confirmed stones when re-evaluated by an experienced pediatric radiologist. This finding highlights the operator-dependent nature of ultrasonography,[27,28] particularly in young children, and supports the reliability of ultrasound assessments in our study.

Hypercalciuria was the most common metabolic abnormality in our cohort, detected in 28.6% of patients, consistent with previous studies .[3,8,29-31] Genetic variants affecting calcium and phosphate metabolism, including CaSR pathway variants, VDR, CYP24A1 and SLC34A1, have been associated with hypercalciuria and early-onset nephrolithiasis.[32-38] It is recommended that vitamin D replacement be administered cautiously and with biochemical monitoring in susceptible individuals, as vitamin D supplementation may increase hypercalciuria or stone burden.[10] Beyond hypercalciuria, hypercalcemia, parathyroid hormone abnormalities, and a strong family

history, including hypercalcemia in relatives, may help guide clinical suspicion for these genetic conditions. In our study, although the genetic etiology was not assessed, none of the patients demonstrated abnormalities in serum Ca, P, ALP, or parathormone (PTH) levels. Milart et al.[11] reported that low-dose vitamin D supplementation in children with idiopathic hypercalciuria increased serum 25OHD levels without increasing calciuria or accelerating stone formation. Similarly, in our hypercalciuric subgroup, the urinary Ca/Cr ratio did not increase significantly after vitamin D prophylaxis was reintroduced, and no consistent ultrasonographic worsening was observed.

The relationship between vitamin D status, urinary calcium excretion, and nephrolithiasis remains complex.[10,39,40] Several studies have proposed a relationship between serum 25OHD levels and urinary calcium excretion,[41-45] whereas others have reported no association with the stone formation or recurrence.[46,47] Malihi et al.[48] showed that prolonged vitamin D supplementation may increase the risk of hypercalcemia and hypercalciuria, although this was not accompanied by an increased risk of kidney stones. Consistent with these findings, our study demonstrated stable serum 25OHD levels, whereas serum Ca and urinary Ca/Cr ratios increased significantly during P2 ($p=0.05$ and $p=0.02$, respectively). Notably, no significant differences in serum Ca or urinary Ca/Cr ratios were observed between patients with and without decreased stone size and number.

In terms of stone size and number over time, our study demonstrated a statistically significant decline in both stone size and stone number over time, and these changes occurred irrespective of vitamin D supplementation. Our findings are consistent with the existing literature, suggesting that maintaining adequate vitamin D status does not necessarily worsen stone burden, particularly in pediatric populations, where vitamin D remains essential for bone health, growth, and immune development.[11,39] The observed improvement may largely reflect the natural history of small, nonobstructive stones in infants and toddlers. High urine output, shorter urinary tracts, increased hydration after diagnosis, salt restriction, and parental awareness may have all contributed to spontaneous stone passage. Renal maturation and improvement in metabolic homeostasis during early childhood may also reduce stone persistence and growth.[49,50] Additionally, the continued use of oral potassium citrate in 12 patients may have contributed to this observed effect.

This study has several limitations. The sample size was small, and the follow-up duration may not have fully captured the long-term recurrence patterns. In addition, genetic testing was not performed, which limits the evaluation of the underlying hereditary causes of nephrolithiasis and hypercalciuria in this young cohort. Although ultrasonography is operator-dependent and may underestimate very small stones compared with computed tomography, it remains the first-line imaging modality in children, and the use of an experienced pediatric radiologist likely reduced misclassification in our study. Generalizability is limited by the single-center design, small sample size, short follow-up, and inclusion of only young children receiving standard-dose vitamin D prophylaxis.Future studies should focus on larger multicenter cohorts with longer follow-up periods and standardized metabolic assessments.

Conclusion

In conclusion, this prospective study demonstrated a statistically significant decline in stone size and number over time during sequential periods of vitamin D discontinuation and prophylaxis. These findings suggest that discontinuation of vitamin D prophylaxis may not be necessary in children with nephrolithiasis. A more individualized and evidence-based approach that balances the risk of kidney stones with the critical role of vitamin D in skeletal health, growth, and development in early childhood is recommended.

Ethics Committee Approval: The study was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (Date: 13/06/2016, No: 2016/724).
Peer-review: Externally peer-reviewed.
Informed Consent: Written informed consent was obtained from the parents or legal guardians of all participants
Author Contribution: Concept: B.G.T., A.Y.; Design: B.G.T., A.Y.; Supervision: G.G., A.Y.; Data collection &/or processing: B.G.T., A.Y., B.Y.A., Z.Y.Y., G.G.; Analysis and/or interpretation: B.G.T., A.Y., B.Y.A., Z.Y.Y., G.G.; Literature search: B.G.T., E.C., Z.B.; Writing: B.G.T., A.Y.; Critical review: B.G.T., A.Y., G.G.
Conflict of Interest: The authors declare no conflicts of interest.
Funding: This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Harvey E, Farhat WA. Renal calculi. Pediatric kidney disease. Springer; 2017. p. 1135–91. [CrossRef]

2. Reusz GS, Hosszu A, Kis E. Evaluation of a child with suspected nephrolithiasis. Curr Opin Pediatr 2020;32:265–72. [CrossRef]
3. Alpay H, Ozen A, Gokce I, Biyikli N. Clinical and metabolic features of urolithiasis and microlithiasis in children. Pediatr Nephrol 2009;24:2203–9. [CrossRef]
4. Güven AG, Koyun M, Baysal YE, Akman S, Alimoglu E, Akbas H, et al. Urolithiasis in the first year of life. Pediatr Nephrol 2010;25:129–34. [CrossRef]
5. Routh JC, Graham DA, Nelson CP. Epidemiological trends in pediatric urolithiasis at United States freestanding pediatric hospitals. J Urol 2010;184:1100–4. [CrossRef]
6. Sas DJ, Hulsey TC, Shatat IF, Orak JK. Increasing incidence of kidney stones in children evaluated in the emergency department. J Pediatr 2010;157:132–7. [CrossRef]
7. Dwyer ME, Krambeck AE, Bergstralh EJ, Milliner DS, Lieske JC, Rule AD. Temporal trends in incidence of kidney stones among children: A 25-year population based study. J Urol 2012;188:247–52. [CrossRef]
8. Demirtas F, Çakar N, Özçakar ZB, Akıncı A, Burgu B, Yalçınkaya F. Risk factors for recurrence in pediatric urinary stone disease. Pediatr Nephrol 2024;39:2105–13. [CrossRef]
9. Sas DJ, Becton LJ, Tutman J, Lindsay LA, Wahlquist AH. Clinical, demographic, and laboratory characteristics of children with nephrolithiasis. Urolithiasis 2016;44:241–6. [CrossRef]
10. Bargagli M, Ferraro PM, Vittori M, Lombardi G, Gambaro G, Somani B. Calcium and vitamin D supplementation and their association with kidney stone disease: A narrative review. Nutrients 2021;13:4363. [CrossRef]
11. Milart J, Lewicka A, Jobs K, Wawrzyniak A, Majder-Łopatka M, Kalicki B. Effect of vitamin D treatment on dynamics of stones formation in the urinary tract and bone density in children with idiopathic hypercalciuria. Nutrients 2020;12:2521. [CrossRef]
12. Hoppe B, Martin-Higueras C. Inherited conditions resulting in nephrolithiasis. Curr Opin Pediatr 2020;32:273–83. [CrossRef]
13. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81. [CrossRef]
14. Bouillon R, Manousaki D, Rosen C, Trajanoska K, Rivadeneira F, Richards JB. The health effects of vitamin D supplementation: Evidence from human studies. Nat Rev Endocrinol 2022;18:96–110. [CrossRef]
15. Harrison SR, Li D, Jeffery LE, Raza K, Hewison M. Vitamin D, autoimmune disease and rheumatoid arthritis. Calcif Tissue Int 2020;106:58–75. [CrossRef]
16. Latic N, Erben RG. Vitamin D and cardiovascular disease, with emphasis on hypertension, atherosclerosis, and heart failure. Int J Mol Sci 2020;21:6483. [CrossRef]
17. Herrick KA, Storandt RJ, Afful J, Pfeiffer CM, Schleicher RL, Gahche JJ, et al. Vitamin D status in the United States, 2011–2014. Am J Clin Nutr 2019;110:150–7. [CrossRef]
18. Andersen R, Mølgaard C, Skovgaard LT, Brot C, Cashman KD, Chabros E, et al. Teenage girls and elderly women living in northern Europe have low winter vitamin D status. Eur J Clin Nutr 2005;59:533–41. [CrossRef]
19. Cashman KD, Sheehy T, O'Neill CM. Is vitamin D deficiency a public health concern for low middle income countries? A systematic literature review. Eur J Nutr 2019;58:433–53. [CrossRef]
20. Giustina A, Bilezikian JP, Adler RA, Banfi G, Bikle DD, Binkley NC, et al. Consensus statement on vitamin D status assessment and supplementation: Whys, whens, and hows. Endocr Rev 2024;45:625–54. [CrossRef]
21. Kleinman, R.E. and Greer, F.R. (2014) Micronutrients and Macronutrients. In: Pediatric Nutrition, 7th Edition, American Academy of Pediatrics, Committee on Nutrition, Itasca, IL, 357–568.
22. Demay MB, Pittas AG, Bikle DD, Diab DL, Kiely ME, Lazaretti-Castro M, et al. Vitamin D for the prevention of disease: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2024;109:1907–47. [CrossRef]
23. Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics 2008;122:1142–52. [CrossRef]
24. Sperling MA. Sperling pediatric endocrinology E-Book. Amsterdam: Elsevier Health Sciences; 2020.
25. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global consensus recommendations on prevention and management of nutritional rickets. J Clin Endocrinol Metab 2016;101:394–415. [CrossRef]
26. La Manna A, Polito C, Cioce F, De Maria G, Capacchione A, Rocco CE, et al. Calyceal microlithiasis in children: Report on 196 cases. Pediatr Nephrol 1998;12:214–7. [CrossRef]
27. Strohmaier WL. Imaging in pediatric urolithiasis-what's the best choice? Transl Pediatr 2015;4:36–40.
28. Fazel M, Gubari MIM, Yousefifard M, Hosseini M. Ultrasonography in detection of renal calculi in children: A systematic review and meta-analysis. Arch Acad Emerg Med 2019;7:e66.
29. Barata CB, Valete COS. Clinical-epidemiological profile of 106 pediatric pacients with urolithiasis in Rio de Janeiro, Brazil. Rev Paul Pediatr 2018;36:261–7. [CrossRef]
30. Issler N, Dufek S, Kleta R, Bockenhauer D, Smeulders N, Van't Hoff W. Epidemiology of paediatric renal stone disease: A 22-year single centre experience in the UK. BMC Nephrol 2017;18:136. [CrossRef]
31. Bilge I, Yilmaz A, Kayiran SM, Emre S, Kadioglu A, Yekeler E, et al. Clinical importance of renal calyceal microlithiasis in children. Pediatr Int 2013;55:731–6. [CrossRef]
32. Colussi G, Ganon L, Penco S, De Ferrari ME, Ravera F, Querques M, et al. Chronic hypercalcaemia from inactivating mutations of vitamin D 24-hydroxylase (CYP24A1): Implications for mineral metabolism changes in chronic renal failure. Nephrol Dial Transplant 2014;29:636–43. [CrossRef]
33. Liu W, Chen M, Li M, Ma H, Tong S, Lei Y, et al. Vitamin D receptor gene (VDR) polymorphisms and the urolithiasis risk: An updated meta-analysis based on 20 case-control studies. Urolithiasis 2014;42:45–52. [CrossRef]
34. Dinour D, Beckerman P, Ganon L, Tordjman K, Eisenstein Z, Holtzman EJ. Loss-of-function mutations of CYP24A1, the vitamin D 24-hydroxylase gene, cause long-standing hypercalciuric nephrolithiasis and nephrocalcinosis. J Urol 2013;190:552–7. [CrossRef]
35. Xu N, Yang M, Liu J, Li X. Association of vitamin D receptor genetic polymorphisms with nephrolithiasis and end-stage renal disease: A meta-analysis. Transplant Proc 2022;54:1773–80. [CrossRef]
36. Geraghty R, Lovegrove C, Howles S, Sayer JA. Role of genetic testing in kidney stone disease: A narrative review. Curr Urol Rep 2024;25:311–23. [CrossRef]
37. De Paolis E, Scaglione GL, De Bonis M, Minucci A, Capoluongo E. CYP24A1 and SLC34A1 genetic defects associated with idiopathic infantile hypercalcemia: From genotype to phenotype. Clin Chem Lab Med 2019;57:1650–67. [CrossRef]

38. Wang Q, Chen JJ, Wei LY, Ding Y, Liu M, Li WJ, et al. Biallelic and monoallelic pathogenic variants in CYP24A1 and SLC34A1 genes cause idiopathic infantile hypercalcemia. Orphanet J Rare Dis 2024;19:126. [CrossRef]
39. Akinci A, Karaburun MC, Kubilay E, Solak VT, Sanci A, Soygur T, et al. Urinary stone in infants; should vitamin D prophylaxis be stopped? J Pediatr Urol 2024;20:604.e1–6. [CrossRef]
40. Taylor EN, Hoofnagle AN, Curhan GC. Calcium and phosphorus regulatory hormones and risk of incident symptomatic kidney stones. Clin J Am Soc Nephrol 2015;10:667–75. [CrossRef]
41. Fallahzadeh MH, Zare J, Al-Hashemi GH, Derakhshan A, Basiratnia M, Arasteh MM, et al. Elevated serum levels of vitamin D in infants with urolithiasis. Iran J Kidney Dis 2012;6:186–91.
42. Giannini S, Nobile M, Castrignano R, Pati T, Tasca A, Villi G, et al. Possible link between vitamin D and hyperoxaluria in patients with renal stone disease. Clin Sci 1993;84:51–4. [CrossRef]
43. Netelenbos JC, Jongen MJ, van der Vijgh WJ, Lips P, van Ginkel FC. Vitamin D status in urinary calcium stone formation. Arch Intern Med 1985;145:681–4. [CrossRef]
44. Ticinesi A, Nouvenne A, Ferraro PM, Folesani G, Lauretani F, Allegri F, et al. Idiopathic calcium nephrolithiasis and hypovitaminosis D: A case-control study. Urology 2016;87:40–5. [CrossRef]
45. Taheri M, Tavasoli S, Shokrzadeh F, Amiri FB, Basiri A. Effect of vitamin D supplementation on 24-hour urine calcium in patients with calcium urolithiasis and vitamin D deficiency. Int Braz J Urol 2019;45:340–6. [CrossRef]
46. Ganji MR, Shafii Z, Hakemi MS. Vitamin D supplementation and risk of hypercalciuria in stone formers. Iran J Kidney Dis 2019;13:27–31.
47. Ferraro PM, Taylor EN, Gambaro G, Curhan GC. Vitamin D intake and the risk of incident kidney stones. J Urol 2017;197:405–10. [CrossRef]
48. Malihi Z, Wu Z, Stewart AW, Lawes CM, Scragg R. Hypercalcemia, hypercalciuria, and kidney stones in long-term studies of vitamin D supplementation: A systematic review and meta-analysis. Am J Clin Nutr 2016;104:1039–51. [CrossRef]
49. Hodhod A, Moneir WM, Alhams A, Burki T, Jamalalail Y, Almodhen F, et al. Outcome of conservative management of small renal stones in prepubertal children. J Pediatr Urol 2026;22:105536 [CrossRef]
50. Evan AP. Physiopathology and etiology of stone formation in the kidney and the urinary tract. Pediatr Nephrol 2010;25:831–41. [CrossRef]

CASE REPORT

Access this article online
Quick Response Code:

Website:
www.scie.online
DOI:
10.14744/scie.2026.26037

Two-Stage Reconstruction of a Scalp Defect with Exposed Bone Using a Biodegradable Temporizing Dermal Matrix

Azmi Can Ofluoğlu, Mustafa Merih Yaraşır, Çağla Çiçek, Gaye Filinte

Abstract

Scalp tissue defects may arise secondary to trauma or tumor resection. Dermal and epidermal matrices provide an important reconstructive alternative for complex scalp defects with exposed bone by promoting vascularization and granulation tissue formation. Depending on the size of the defect, biodegradable temporizing matrices may be applied either as a two-stage procedure in combination with skin grafting or as a single-stage treatment. A 9-year-old male patient presented with a scalp tissue defect measuring 6 × 8 cm with exposed bone following a motor vehicle accident. After debridement of devitalized tissue at the wound margins, a biodegradable temporizing matrix was applied simultaneously. Weekly follow-up evaluations demonstrated progressive color changes within the matrix. At the end of five weeks, sufficient granulation tissue formation was observed beneath the matrix. The outer layer of the matrix was removed, and a split-thickness skin graft was applied to the wound bed. Biodegradable temporizing matrix application facilitates staged reconstruction of scalp defects, particularly in pediatric patients, without the need for complex surgical procedures. It supports reconstructive planning by enabling sequential use of reconstruction steps and represents a safe and effective adjunct in scalp reconstruction.

Keywords: Biodegradable temporizing matrix; scalp defect; reconstruction.

Introduction

Scalp defects are difficult-to-manage reconstructive defects due to the anatomical characteristics of the scalp and its limited tissue elasticity, and they commonly occur following trauma, tumor resection, or pressure injuries.[1] In scalp defects larger than 3 cm, primary closure is often not feasible, particularly in areas with exposed bone, and inadequate coverage significantly increases the risk of osteomyelitis and chronic wound formation.[2] In recent years, biodegradable temporizing matrices have gained increasing popularity by enhancing vascularization and granulation, thereby expanding reconstructive options for such defects.[3]

The biodegradable temporizing matrix (BTM; NovoSorb®, PolyNovo Ltd., Port Melbourne, Australia) is a fully synthetic polyurethane dermal substitute that functions as an inert scaffold, promoting an-

Department of Plastic, Reconstructive and Aesthetic Surgery, Kartal Dr Lutfi Kirdar City Hospital, Istanbul, Türkiye

Address for correspondence:
Mustafa Merih Yaraşır, Department of Plastic, Reconstructive and Aesthetic Surgery, Kartal Dr Lutfi Kirdar City Hospital, Istanbul, Türkiye
E-mail: merihyarasir@gmail.com

Received: 10.02.2026
Accepted: 04.05.2026
Published: 29.09.2026

How to cite this article: *Ofluoğlu AC, Yaraşır MM, Çiçek Ç, Filinte G. Two-stage reconstruction of a scalp defect with exposed bone using a biodegradable temporizing dermal matrix. South. Clin. Ist. Euras. 2026;37(3):328-331.*

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.
Copyright@Author(s)

giogenesis and granulation tissue formation over wound beds unsuitable for immediate skin grafting, such as those with exposed tendon or bone.[4]

Once sufficient granulation tissue development is achieved, as determined clinically, the outer sealing membrane may be removed. Depending on defect size, BTM can be used either as a two-stage reconstruction in combination with split-thickness skin grafting or as a standalone treatment. In this study, we present a successful reconstruction of a post-traumatic scalp defect using a biodegradable temporizing matrix. BTM offers a safe and effective solution for scalp reconstruction without donor-site morbidity associated with flap surgery.

Case Presentation

A 9-year-old male patient was admitted to our clinic following an in-vehicle traffic accident. Physical examination revealed a scalp defect measuring approximately 6 × 8 cm with exposed bone and associated periosteal loss (Fig. 1). Foreign bodies within the right frontoparietal defect were irrigated and removed, followed by thorough debridement of devitalized tissue. Bacterial tissue cultures obtained from the wound bed before BTM application showed no bacterial growth, and there were no clinical signs of active infection. The biodegradable temporizing matrix was trimmed and shaped according to the defect size and applied in accordance with the manufacturer's instructions, ensuring that the appropriate surface contacted the wound bed.

The silicone sealing membrane was left externally and secured to the surrounding healthy skin using skin staples, ensuring full contact of the matrix with the wound base. Weekly wound assessments were performed (Fig. 2). No signs of hematoma or infection beneath the matrix were observed. At the end of the fifth week, characteristic color changes were noted, and removal of the outer membrane revealed complete coverage of the exposed bone with well-vascularized granulation tissue. A split-thickness skin graft harvested from the right thigh was applied to the wound bed. Postoperative follow-up demonstrated complete graft take without any evidence of graft loss (Fig. 3).

Discussion

Reconstruction of scalp defects is guided by the stepwise application of the reconstructive ladder.[5] The choice of

Figure 1. Scalp defect measuring approximately 6 × 8 cm with exposed bone and associated periosteal loss.

Figure 2. Silicone sealing membrane was left externally and secured to the surrounding healthy skin using skin staples.

Figure 3. Postoperative follow-up demonstrated complete graft take without any evidence of graft loss.

reconstructive method depends on defect size, depth, the presence of periosteal or bone exposure, surrounding tissue laxity, and patient-related factors. Small scalp defects may be managed with primary closure, secondary intention healing, or local flaps; however, larger and more complex defects may require skin grafting, tissue expansion, regional or free flap reconstruction, or staged reconstruction using dermal substitutes.

In extensive defects with exposed bone, flap surgery may be disadvantageous due to prolonged operative time and donor-site morbidity.[1,6] These concerns are particularly relevant in pediatric patients, where donor-site morbidity during growth may result in physical deformities and functional limitations later in life.

Biodegradable temporizing matrix offers an alternative treatment option in high-risk or complex cases due to its low infection rates, ease of application, and capacity for staged reconstruction.[3] Complex avulsion injuries caused by dog bites or mechanical trauma may involve extensive tissue loss that is difficult to reconstruct even with free flaps. In such cases, BTM provides effective wound coverage without donor-site morbidity. Patel et al.[2] reported successful BTM use in a 3-year-old patient with near-total scalp avulsion involving 80% of the scalp and exposed bone, followed by split-thickness skin grafting.

Similarly, Calderbank et al.[4] presented a case series of 13 lesions in 12 patients with post-oncological scalp defects successfully reconstructed using BTM. The number of reports supporting successful use of biodegradable dermal matrices continues to increase. Additionally, several studies indicate that BTM facilitates dermal matrix formation and may reduce the risk of excessive scar formation.[7]

In the present case, BTM use resulted in effective reconstruction within a short time frame. The patient was followed on an outpatient basis between stages, with moist dressings applied to the external surface; no matrix replacement was required. In cases of hematoma or infection beneath the biodegradable layer, removal of the matrix may be necessary. While hematomas may be managed by temporary removal and reapplication after hemostasis, infected matrices infiltrated with purulent material should be removed, followed by debridement and reapplication after antibiotic irrigation.[8]

In hair-bearing scalp regions, the use of BTM and skin grafts may result in alopecia, potentially leading to aesthetic dissatisfaction, particularly in pediatric patients. Secondary reconstruction using tissue expanders or hair transplantation may be considered.[9] Tissue expansion is planned for the present patient. By promoting robust granulation tissue formation and allowing outpatient follow-up, BTM has emerged as an effective and reliable treatment option for scalp defects with exposed bone.[2,3,5]

This case demonstrates that biodegradable temporizing matrix may be an effective and reliable option for staged reconstruction of pediatric scalp defects with exposed bone after adequate debridement and infection control. By supporting the formation of a vascularized neodermis, BTM provided a suitable wound bed for subsequent split-thickness skin grafting. In selected cases where local or free flap options are limited by patient age, defect characteristics, donor-site morbidity, or technical complexity, two-stage reconstruction with BTM may be considered a valuable alternative within the reconstructive algorithm.

Peer-review: Externally peer-reviewed.

Informed Consent: Written informed consents were obtained from patient and his family.

Author Contribution: Concept: A.C.O., M.M.Y.; Design: A.C.O., M.M.Y.; Supervision: G.F.; Fundings: M.M.Y.; Materials: M.M.Y.; Data Collection and/or Processing: A.C.O., M.M.Y.; Analysis and/or Interpretation: A.C.O., M.M.Y.; Literature Search: A.C.O., M.M.Y.; Writing: A.C.O., M.M.Y.; Critical Reviews: G.F., C.C.

Conflict of Interest: None declared.

References

1. Shariatmadari I, Kiely J, Kelemen N. Use of NovoSorb biodegradable temporizing matrix in the management of complex scalp defects. PRS Glob Open 2023;11:e4872. [CrossRef]
2. Patel NK, Tipps JA, Graham EM, Taylor JA, Mendenhall SD, et al. Reconstruction of a near-total scalp avulsion with NovoSorb biodegradable temporizing matrix. PRS Glob Open 2022;10:e4091. [CrossRef]
3. Conway L, Snashall E, Gill P, Harper-Machin A. The use of NovoSorb biodegradable temporizing matrix in head and neck skin cancer reconstruction. J Plast Reconstr Aesthet Surg 2025;78:e1–9.
4. Calderbank T, Turner E, Mohamed M, Kanakopoulos D, Kelemen N. Biodegradable temporizing matrix in post-oncological scalp reconstruction: A case series. Plast Reconstr Surg Glob Open 2025;13:e6497. [CrossRef]
5. Schlottmann F, Obed D, Bingöl AS, März V, Vogt PM, Krezdorn N. Treatment of complex wounds with NovoSorb biodegradable temporizing matrix (BTM): A retrospective analysis of clinical outcomes. J Pers Med 2022;12:2002. [CrossRef]
6. Rajaram R, Zhang M, Premaratne G, Ng S. NovoSorb biodegradable temporizing matrix: history, production and application in reconstructive surgery. Front Bioeng Biotechnol 2024;12:1450973. [CrossRef]
7. Kyriazidis I, Demiri E, Lazaridou A, Pavlidis L, Papas A. NovoSorb biodegradable temporizing matrix (PolyNovo) for aesthetic nasal reconstruction: A case report of rhinophyma resurfacing. Cureus 2025;17:e87678. [CrossRef]
8. Jou C, Cephla KJ. NovoSorb biodegradable temporizing matrix for reconstruction of complex upper-extremity wounds. J Hand Surg Glob 2024;6:614–8. [CrossRef]
9. Kasai Y, Igawa H, Abe N, Sakamoto A, Tsushima A, Narui Y, et al. Successful follicular unit extraction hair transplant for bald area after skin graft. JPRAS Open 2017;13:71–6. [CrossRef]