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- Antifungal resistance in Candida auris clade I
- Temporal changes in LBP management
- A bibliometric analysis of dynamic posterior stabilization
- Podological awareness in ingrown toenails
- Transcutaneous electrical nerve stimulation
- Cardiac myxoma: early outcomes by clinical presentation

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CONTENTS

VOL. 13 • NO. 4 • YEAR 2026

IV **Instructions for the authors**

ORIGINAL ARTICLES

367–374 **Ultrasound-guided percutaneous ventriculoatrial shunt placement in pediatric hydrocephalus: Surgical outcomes and thrombotic complications**

Kendirlioglu BC, Yavuz M, Alioglu H, Arslan G, Aydogmus E

375–386 **Mapping publication trends in oral anticoagulation in atrial fibrillation: A bibliometric and thematic analysis of 11,039 publications (2006–2025)**

Coskun S, Tiyekli E

387–394 **Long-term efficacy of genicular nerve radiofrequency ablation in patients with advanced knee osteoarthritis: A retrospective cohort study**

Gozukizil ST, Altun HI

395–402 **Predictive value of an intraoperative gallbladder scoring system for surgical difficulty and post-operative outcomes in laparoscopic cholecystectomy**

Baskent A, Baskent MF

403–412 **Genomic characterization of antifungal resistance patterns in *Candida auris* clade I: A large-scale analysis of 647 global genomes**

Tosunoglu A, Konyali O, Demirci M

413–420 **Changes in pharmacological management of low back pain: Real-world evidence from a 4-year comparison (2021–2025)**

Yumusakhuylu Y, Erhan B, Basal M, Gungor M, Senyurt BC, Akbulut IH

421–433 **The changing paradigm of spine motion preservation: A bibliometric analysis of dynamic posterior stabilization**

Karalar S, Ozdemir MA

434–440 **Awareness of podological treatment methods and treatment preferences in individuals with ingrown toenails: A cross-sectional study from Turkiye**

Akin Z, Akin O, Hidiroglu S, Tanriover O

441–446 **The effect of the duration of transcutaneous electrical nerve stimulation on pain and functionality in the treatment of lumbar spondylosis**

Dogan YE, Cetin M, Erol E, Ones K

447–454 **Early surgical outcomes of cardiac myxoma resection according to dominant clinical phenotype in adult patients**

Karakaya HC, Ceylan L, Yilmaz R, Yargi M, Ketenci B

CONTENTS

VOL. 13 • NO. 4 • YEAR 2026

455–549 **Comparison of 5-year glycemic outcomes after sleeve gastrectomy and Roux-en-Y gastric bypass in patients with pre-operative dysglycemia**

Tasdelen I, Gunes Y

460–468 **Hemodynamic optimization of a novel single-puncture dual-lumen coaxial catheter for arteriovenous fistula access: A computational fluid dynamics study**

Kocaaslan C

REVIEW

469–504 **Financial venous stasis and thrombosis: A circulatory architecture for frozen capital and high-value care**

Tekesin K

LETTER TO THE EDITOR

505–506 **Beyond nutritional knowledge: Dietary supplement use in preschool children**

Ozer E

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Original Article NEUROSURGERY

Ultrasound-guided percutaneous ventriculoatrial shunt placement in pediatric hydrocephalus: Surgical outcomes and thrombotic complications

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ABSTRACT

OBJECTIVE: Ventriculoatrial shunts (VAS) are increasingly used as a salvage option in pediatric hydrocephalus when ventriculoperitoneal shunts (VPS) fail. Although ultrasound-guided percutaneous techniques facilitate catheter placement and reduce surgical trauma, the incidence and management of thrombotic complications remain insufficiently defined.

METHODS: We retrospectively analyzed eight pediatric patients who underwent ultrasound-guided percutaneous VAS placement between January 2019 and December 2024. Demographic characteristics, etiology of hydrocephalus, operative details, and post-operative complications were evaluated, with a particular focus on thrombotic events.

RESULTS: Patients underwent a mean of 3.8±1.3 VPS revisions before VAS placement. Myelomeningocele was the most common etiology (50%). The mean operative time was 75.6±13.9 min, and the mean intraoperative blood loss was 86.25±43.07 mL. Post-operative complications occurred in 3 patients (37.5%), including thrombotic events in 2 patients (25%) and infection in 1 patient (12.5%). One patient required early shunt removal due to thrombus formation with vegetation, whereas another developed late asymptomatic thrombosis requiring intervention. The internal jugular vein was the most commonly used access site.

CONCLUSION: Ultrasound-guided percutaneous VAS placement is a feasible and minimally invasive alternative in selected pediatric patients. However, thrombotic complications may be more frequent than previously reported and can occur both early and late in the post-operative period. These findings highlight the need for standardized surveillance protocols and further investigation into prophylactic strategies, including antiplatelet therapy.

Keywords: Hydrocephalus; pediatric neurosurgery; percutaneous technique; thrombosis; ventriculoatrial shunt.

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Ventriculoatrial shunts (VAS) were first introduced by Nulsen and Spitz in 1951 as an alternative cerebrospinal fluid (CSF) diversion technique for the treatment of hydrocephalus [1]. Over time, ventriculoperitoneal shunts (VPS) became the preferred treatment modality, largely because they are technically simpler, more effective, and easier to revise distally. Consequently, the use of VAS has declined and has been less frequently reported in the literature, particularly in pediatric populations [2, 3].

Traditional open placement of the atrial catheter requires surgical exploration of the cervical venous system. This approach has been criticized for being time-consuming and for causing scar tissue formation, which may complicate subsequent revisions [4, 5]. Pediatric patients may encounter additional challenges, as repeated in-

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terventions are often required to adjust catheter length during growth and to manage shunt-related complications during long-term follow-up. These limitations have led to the search for less invasive alternatives to conventional open techniques [6, 7].

Percutaneous placement of the atrial catheter, particularly when performed under ultrasound guidance, offers several advantages compared with the traditional open technique, including a relatively shorter operative time, avoidance of cervical dissection, and preservation of venous integrity [5, 8, 9]. Previous studies have demonstrated the technical feasibility of this approach; however, data focusing on procedure-related complications and their post-operative management remain limited [9, 10]. In particular, standardized strategies for the detection, prevention, and management of thrombotic and infectious complications following percutaneous VAS placement are not well defined.

Furthermore, there is currently no consensus regarding optimal strategies for the detection, prevention, and management of thrombotic complications following VAS placement [2]. Although recent studies have suggested a potential role for antiplatelet therapy, such as aspirin, evidence remains limited and largely based on small case series [11].

In this study, we aimed to evaluate the surgical outcomes and complication profile of ultrasound-guided percutaneous VAS placement in pediatric patients with hydrocephalus, with a particular focus on thrombotic complications and post-operative management strategies.

MATERIALS AND METHODS

This retrospective study included all pediatric patients (aged ≤18 years at the time of first VAS placement) who underwent ultrasound-guided percutaneous VAS placement at our institution between January 2019 and December 2024. Patients with <12 months of follow-up were excluded. All procedures were performed by the same multidisciplinary team, consisting of neurosurgeons and anesthesiologists, using an ultrasound-guided percutaneous technique. Venous access was primarily obtained through the internal jugular vein under ultrasound guidance by the anesthesiologist.

Medical and radiological records were retrospectively reviewed to obtain demographic data, etiology of hydrocephalus, surgical history, and indications for VAS implantation. Operative time and estimated intraoperative blood loss were recorded as intraoperative variables. Post-operative complications were categorized as early (within 30 days) or late (after 30 days).

Highlight key points

- Ultrasound-guided percutaneous VAS placement is a feasible alternative in pediatric hydrocephalus when VPS fails
- This technique allows safe catheter placement with reduced surgical invasiveness
- Thrombotic complications may occur both early and late after VAS placement
- A relatively high rate of thrombotic events was observed in this series
- Antiplatelet therapy may have a potential role in preventing thrombotic complications.

The study was approved by the institutional review board of our institution (Decision No: 2024/010.99/10/23, date: November 29, 2024). Informed consent was waived due to the retrospective design of the study and the absence of any identifiable patient information.

Surgical Technique

Venous access was obtained through the right internal jugular vein whenever feasible. In cases where the internal jugular vein was not suitable, the right subclavian vein was used as an alternative. In one patient, due to unsuitable cervical venous access, a transhepatic approach was performed. The hepatic vein was accessed under ultrasound guidance, and the catheter was advanced through the inferior vena cava into the right atrium under fluoroscopic guidance.

For cannulation, the patient's head was turned 30° to the left and placed in a slight Trendelenburg position. The internal jugular vein was identified under ultrasound guidance using a linear probe, with the carotid artery as a landmark. Using the Seldinger technique, a 19 G×70 mm puncture needle was advanced under ultrasound guidance, and venous access was confirmed by blood aspiration. A guidewire (0.27 mm×60 cm) was then advanced into the inferior vena cava, with fluoroscopic confirmation of its position.

Following venous access, the distance between the vein entry site and the atriocaval junction was measured using the guidewire. A No. 8F×14 cm dilator and split sheath introducer were then passed over the wire. The guidewire was subsequently removed. The atrial end of the VAS was inserted into the vein through the sheathed dilator and positioned within the atrium; the sheath was

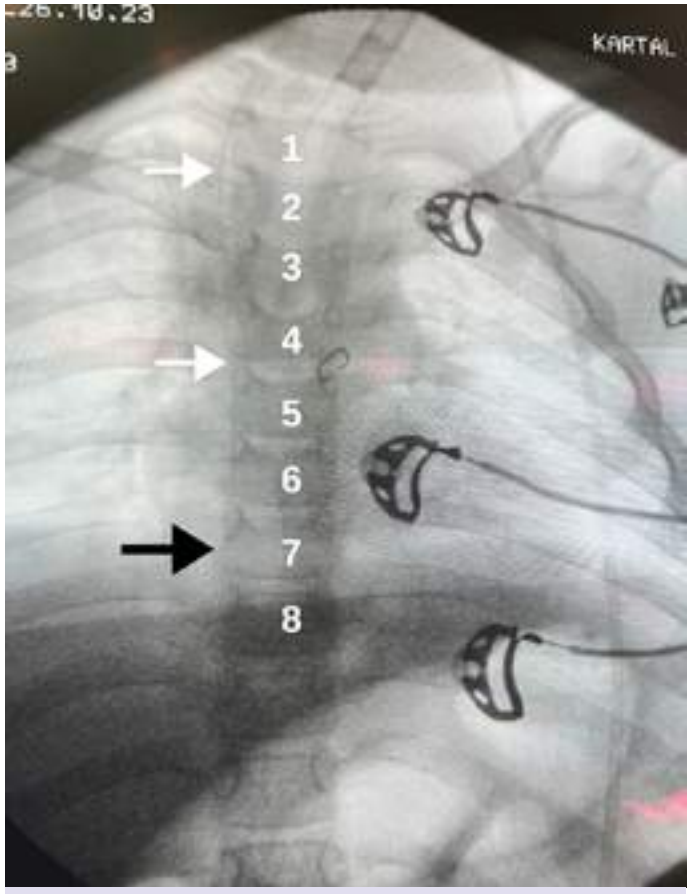

FIGURE 1. Fluoroscopic image demonstrating the position of the distal catheter within the right atrium. The catheter tip is located at the T6–T8 vertebral level, corresponding to the mid-atrium. White arrows indicate the catheter course, and the black arrow marks the catheter tip.

split and removed. The distal catheter was passed into the lower right atrium and flushed with heparinized saline.

Continuous electrocardiographic monitoring was performed by the anesthetist during catheter advancement to detect potential cardiac arrhythmias. Fluoroscopy was used to verify the position of the atrial catheter. The optimal position of the catheter tip was in the mid-atrium, usually located at the T6–T8 vertebral level (Fig. 1). The catheter was then tunneled subcutaneously and connected to the ventricular catheter and shunt valve using standard techniques.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences version 29.0.2.0 (IBM Corp., Armonk, NY, USA). Due to the retrospective design and limited sample size of this study, only descriptive statistics were applied. Continuous variables were reported as mean±standard deviation, together with the corresponding minimum and maximum values, whereas categorical variables were presented as frequencies and percentages.

FIGURE 2. Echocardiographic image demonstrating thrombus formation at the distal end of the ventriculoatrial shunt catheter within the right atrium.

RESULTS

A total of eight pediatric patients were included in the study, with a mean age of 85.6±78.7 months (range: 3 months–18 years). Six patients (75%) were male, and two (25%) were female. Myelomeningocele was the most common etiology of hydrocephalus (50%), followed by congenital hydrocephalus. Other etiologies included intracranial hemorrhage, Chiari malformation type II, and congenital toxoplasmosis. Patients had undergone a mean of 3.8±1.3 VPS revisions before VAS placement (range: 2–6). Pre-operative patient characteristics are summarized in Table 1.

Venous access was obtained through the internal jugular vein in 5 patients (62.5%), the subclavian vein in 2 patients (25%), and via a transhepatic approach in 1 patient (12.5%). The mean estimated intraoperative blood loss was 86.25±43.07 mL, and the mean operative time was 75.6±13.9 min.

Post-operative complications occurred in 3 patients (37.5%). Notably, thrombotic complications were observed in 2 patients (25%), representing the most clinically significant adverse events in this series. One patient developed an early thrombotic complication (post-operative day 15), characterized by thrombus formation with vegetation, necessitating VAS removal and conversion to a VPS. Another patient developed a late asymptomatic thrombotic complication at 6 months (Fig. 2). Despite

Table 1. Pre-operative characteristics of the patients undergoing ventriculoatrial shunt placement

Patient	Sex	Etiology of hydrocephalus	Age at first VPS insertion	Age at first VAS insertion	VPS revisions (n)	Abdominal complications
1	M	Myelomeningocele	1 mo	6 yr	4 (3 VPS, 1 VVS)	Abdominal cyst/ileus
2	F	Congenital	17 d	16 yr	5	Abdominal cyst/peritoneal adhesion
3	M	Congenital toxoplasmosis	1 mo	8 yr	6	Abdominal cyst
4	F	Myelomeningocele	6 d	4 mo	4	Peritoneal adhesion
5	M	Chiari malformation type II	3 d	14 yr	2	Abdominal cyst
6	M	Congenital	1 mo	18 yr	2	Peritoneal adhesion
7	M	Myelomeningocele	1 mo	3 mo	4	Abdominal cyst
8	M	Posthemorrhagic	1 mo	14 mo	4	Peritoneal adhesion

M: Male; F: Female; d: Days; mo: Months; yr: Years; VPS: Ventriculoperitoneal shunt; VAS: Ventriculoatrial shunt; VVS: Ventriculovesical shunt.

Table 2. Perioperative and post-operative outcomes of the patients

Patient	Vein used	Estimated blood loss (mL)	Operative time (min)	Perioperative complications	Early complications (<30 days)	Late complications (>30 days)	Follow-up
1	IJV	50	100	Jugular vein injury/ subcutaneous hematoma	None	Exitus (unrelated to shunt)	14 mo
2	IJV	150	70	None	None	Distal catheter thrombosis	42 mo
3	IJV	100	80	None	None	None	14 mo
4	HV	50	70	None	None	None	13 mo
5	IJV	80	60	None	None	Shunt infection	35 mo
6	SCV	150	75	None	None	None	13 mo
7	IJV	60	90	None	None	None	48 mo
8	SCV	50	60	None	Distal catheter thrombosis and vegetation	Not applicable	15 d

IJV: Internal jugular vein; HV: Hepatic vein; SCV: Subclavian vein; VPS: Ventriculoperitoneal shunt; d: Days; mo: Months.

anticoagulation therapy, thrombus progression was observed, necessitating VAS removal and conversion to a VPS. Due to recurrent abdominal complications, VAS was later reinserted, and follow-up remained uneventful for 32 months under antiplatelet therapy.

One additional patient (12.5%) developed a shunt-related infection during follow-up. Detailed perioperative and post-operative outcomes are presented in Table 2.

The mean follow-up duration was 25.5±15.5 months (range: 13–48 months) among seven patients, as one patient required early VAS removal and was excluded from follow-up analysis. The patient who underwent early shunt removal continues to be followed with a VPS.

DISCUSSION

VAS are associated with a wide range of complications, including infections, thromboembolic events, pulmonary hypertension, and endocarditis [12–14], as well as less common conditions such as immune complex-mediated glomerulonephritis [15]. Despite these risks, VAS

remains an important alternative in patients with VPS failure, particularly in the presence of abdominal complications such as adhesions, pseudocyst formation, or severe peritonitis [16, 17]. The direct interaction between CSF, blood components, and the shunt material may contribute to coagulation activation, thereby increasing the risk of thrombotic complications [18].

In recent years, the development of percutaneous techniques for atrial catheter placement has improved the safety and feasibility of VAS procedures [9, 19, 20]. Ultrasound-guided approaches enable accurate visualization of vascular anatomy and vessel diameter, reducing the risk of complications such as carotid artery puncture and pneumothorax [8]. Compared with conventional open techniques, the percutaneous approach avoids cervical dissection, preserves venous integrity, and is associated with shorter operative times and reduced procedural morbidity [6]. These advantages are particularly relevant in pediatric patients, who often require repeated interventions and long-term shunt dependency.

In addition, hybrid and endovascular-assisted techniques have been described in complex cases with difficult venous access, further expanding the applicability of VAS [4, 21]. Previous studies have reported high technical success rates and favorable outcomes with percutaneous approaches in patients with recurrent VPS dysfunction [22]. However, despite these technical advancements, complication profiles – particularly thrombotic events – remain insufficiently characterized and inconsistently reported in the literature.

Accurate positioning of the distal catheter is critical to minimize shunt dysfunction and cardiopulmonary complications. In our series, the use of ultrasound and fluoroscopic guidance allowed precise catheter placement in all patients, with no procedure-related malposition observed. These findings are in line with previous studies suggesting that imaging-guided techniques can improve the accuracy and safety of catheter placement [23, 24].

Venous cannulation was performed by an anesthesiologist in all cases, emphasizing the importance of a multidisciplinary approach in technically demanding procedures. The involvement of an experienced anesthesiology team may contribute to procedural safety, particularly in pediatric patients with limited vascular access. In addition, routine post-operative cardiological evaluation enabled early detection of potential complications and ensured appropriate catheter positioning during follow-up. Furthermore, the position of the distal catheter within the right atrium was confirmed by echocardiography (Supplementary Video 1).

In one patient, venous access was achieved via a transhepatic approach. Although not routinely used in VAS procedures, this technique has been described as a safe and effective alternative route for central venous access in pediatric patients, particularly when conventional venous pathways are exhausted or not feasible [25]. In our case, the procedure was successfully performed without perioperative complications, supporting its feasibility as a salvage option in selected patients.

Given the limited number of patients in our series, a structured review of previously published case series was performed to contextualize our findings (Table 3) [3, 8, 9, 11, 19, 26–32]. Although several studies have reported on percutaneous VAS placement in pediatric or mixed populations, complication profiles vary considerably across the literature. Iatrogenic carotid artery puncture is among the most frequently reported complications in these series, whereas thrombotic complications are less consistently documented.

Notably, the longest reported follow-up period reached up to 170 months, as described by Udayakumaran and Kumar [11]. However, heterogeneity in follow-up duration and surveillance protocols may contribute to underrecognition of delayed or asymptomatic complications, particularly thrombotic events.

Thromboembolic and cardiopulmonary complications represent some of the most clinically significant concerns associated with VAS. In our series, thrombotic complications were observed in 25% of patients, including both early and late events, highlighting their potential clinical impact.

Previous studies have reported major complications such as pulmonary embolism, pulmonary hypertension, and cor pulmonale, all of which are associated with significant morbidity and mortality. However, their reported prevalence remains below 1% [33–36]. Notably, none of the studies included in Table 3 reported major cardiopulmonary complications such as endocarditis, pulmonary hypertension, or myocardial infarction. This discrepancy may reflect underreporting, as well as the fact that many thromboembolic events remain clinically silent. Furthermore, variability in the definition of complications and inconsistencies in follow-up protocols across studies may contribute to the heterogeneous reporting of adverse events. For this reason, revision rates and causes of shunt dysfunction were not included in our comparative analysis.

Thrombus formation represents a potential complication at any stage following VAS implantation, ranging

Table 3. Summary of published case series on percutaneous ventriculoatrial shunt placement

Authors	Year	Number of patients	Complications	Age (years)	Operative time	Follow-up period
Epstein et al. [26]	1981	8	None	>8 yr	n/a	n/a
Ashker and Fox [19]	1981	3	None	15–28 yr	n/a	n/a
Carol et al. [9]	1986	39	2 carotid punctures	9–74 yr	35–40 min	4 yr
Decq et al. [27]	1995	22	2 carotid punctures	1.5–79 yr	31 min	12 mo
Harrison et al. [28]	1996	2	None	5–72 yr	n/a	2–24 mo
Britz et al. [29]	1998	7	None	6–17 yr	n/a	2–12 mo
Li et al. [30]	2005	17	1 carotid puncture	n/a	60 min	n/a
Slowinski et al. [31]	2006	179	9 carotid punctures; 2 pneumothoraces	14–80 yr	40 min	64 mo
Ellegaard et al. [8]	2007	26	1 infection	5–82 yr	59 min	n/a
Udayakumaran and Kumar [11]	2021	13	None	Pediatric population	n/a	28–170 mo
Oktay et al. [3]	2024	9	1 shunt dysfunction (ventricular catheter-related)	2–15 yr	n/a	14–46 mo
Rollo et al. [32]	2026	13	Lower complication rates (USG vs. OSC), catheter replacement 35.7% (USG) versus 55.5% (OSC)	0.5–14.2	13.36 min	n/a

n/a: Not available; min: Minutes; mo: Months; yr: Years; USG: Ultrasonography.

from the early post-operative period to several years after the procedure. Importantly, patients may remain asymptomatic for prolonged periods, which can delay diagnosis and increase the risk of progression. Therefore, early detection and close surveillance are essential. However, there is currently no consensus regarding optimal strategies for the diagnosis, prevention, or management of thrombotic complications [2, 37]. Recent studies have suggested a potential role for antiplatelet therapy. Udayakumaran and Kumar [11] reported encouraging preliminary results with once-daily low-dose acetylsalicylic acid (5 mg/kg) in pediatric patients with VAS. In contrast, other studies have recommended fixed doses of 75–100 mg for prophylaxis [38].

In our series, one patient developed a late asymptomatic thrombotic complication that progressed despite adequate anticoagulation, necessitating shunt removal. Notably, reimplantation of a VAS under antiplatelet therapy was associated with an uneventful follow-up of 32 months. This observation may point toward a potential role for antiplatelet prophylaxis in selected patients, although the available evidence remains limited.

The reported incidence of infection in VAS ranges from 4.2% to 6.2% [10, 39]. A recent analysis including 52 studies and 2862 patients demonstrated an overall infection rate of approximately 5%, with rates reaching up to 10% in pediatric populations [10]. In our series, the infection rate was 12.5%, which appears slightly higher than previously reported, although this finding may be influenced by the limited sample size.

Several risk factors have been associated with thrombus formation and other complications, including older age, comorbid conditions, extensive catheter manipulation, prior surgical site infection, and prolonged operative time [2]. These factors may partially explain the occurrence of complications in patients with a history of multiple shunt revisions, as observed in our cohort.

The present study has several limitations. First, the relatively small sample size and retrospective design may limit the generalizability of our findings. Second, this was a single-center study, which may introduce selection bias and limit the external validity of the results. In addition, the lack of standardized post-operative surveillance protocols, particularly for the detection of asymptomatic thrombotic events, may have influenced the reported complication rates.

Furthermore, variability in the reporting and definition of complications across previous studies limits direct comparison with the existing literature. Larger, prospective, multicenter studies are needed to characterize complication profiles better and to establish standardized strategies for the prevention and management of thrombotic complications.

Conclusion

VAS remains an important alternative for the management of hydrocephalus in selected cases where VPS is not feasible. Despite the limited experience reported in the literature, percutaneous placement of the atrial catheter can be performed safely and effectively with appropriate planning and a multidisciplinary approach. However, thrombotic complications may be underrecognized and can occur both in the early and late post-operative period. Vigilant post-operative monitoring is essential to enable early detection and management of these events, and further studies are needed to establish standardized surveillance and prophylactic strategies.

Supplementary Video 1: https://youtu.be/l-sf6mticP0

Ethics Committee Approval: This study was approved by The Scientific Research Ethics Committee of Kartal Dr. Lutfi Kirdar City Hospital (Decision no: 2024/010.99/10/23 – 29.11.2024).

Informed Consent: Informed consent was waived due to the retrospective design of the study and the absence of any identifiable patient information.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Authorship Contributions: Concept – BCK, EA; Design – BCK, EA; Supervision – BCK; Materials – MY, HA; Data Collection and/or Processing – MY, HA; Analysis and/or Interpretation – BCK, EA, GA; Literature Search – BCK, EA, GA; Writing – BCK, MY, HA, GA; Critical Reviews – EA.

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Original Article CARDIOLOGY

Mapping publication trends in oral anticoagulation in atrial fibrillation: A bibliometric and thematic analysis of 11,039 publications (2006–2025)

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ABSTRACT

OBJECTIVE: This study aimed to systematically map the intellectual evolution, thematic development, and collaborative patterns of oral anticoagulation research in atrial fibrillation (AF) from 2006 to 2025.

METHODS: This bibliometric study analyzed 11,039 documents indexed in the Web of Science Core Collection (2006–2025) using the Bibliometrix R package (version 4.x) within the R statistical environment (version 4.3.1) for comprehensive science mapping. The analytical workflow comprised descriptive performance analysis, collaboration network analysis, keyword co-occurrence analysis, strategic thematic mapping, and latent Dirichlet allocation (LDA) topic modeling.

RESULTS: Publication output increased exponentially from 2 articles per year (2006) to a peak of 960 per year (2021), with subsequent stabilization that may reflect consolidation of the field. The United States produced the highest number of publications (3636; 32.9%). The RE-LY trial received the most citations (n=8788). Thematic mapping revealed two main research clusters: Motor themes (141 keywords), representing direct oral anticoagulant agents, stroke prevention, and clinical outcomes; and emerging/declining themes (43 keywords), including venous thromboembolism and pharmacokinetics. LDA topic modeling identified nine distinct research domains encompassing real-world data, safety reporting, and implementation guidelines.

CONCLUSION: The bibliometric patterns observed are consistent with a maturing research field, characterized by a gradual shift from efficacy-focused randomized trials toward real-world effectiveness studies, implementation science, and personalized anticoagulation strategies. Future research may benefit from increased emphasis on long-term adherence, health-economic outcomes, and personalized approaches integrating genetic, clinical, and patient-centered factors.

Keywords: Anticoagulants; atrial fibrillation; bibliometrics; periodicals as topic; stroke.

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Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia encountered in clinical practice, affecting more than 59 million individuals worldwide and conferring an approximately five-fold increased risk of ischemic stroke [1]. Thromboembolic risk in AF arises from impaired atrial contractility, blood stasis, and endothelial dysfunction, with thrombus formation occurring predominantly within the left atrial appendage [2]. For decades, Vitamin K antagonists (VKAs), particularly warfarin, constituted the cornerstone of stroke prevention in AF; however, their clinical use has been limited by a narrow therapeutic window, frequent drug–food interactions, and the need for continuous coagulation monitoring [3].

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The introduction of direct oral anticoagulants (DOACs) – beginning with dabigatran (Food and Drug Administration approved 2010), followed by rivaroxaban (2011), apixaban (2012), and edoxaban (2015) – fundamentally reshaped anticoagulation therapy by offering predictable pharmacokinetics, fixed dosing regimens, and comparable or superior efficacy relative to warfarin [4–7]. The terms DOAC and non–VKAs oral anticoagulant (NOAC) are used interchangeably in the literature to denote the same drug class; for consistency, the term DOAC is used throughout this article, except where NOAC appears within an indexed author keyword or an original publication title. Large-scale randomized controlled trials – RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF–TIMI 48 [4–7] – collectively enrolled more than 70,000 patients and established DOACs as first-line agents for stroke prevention in contemporary AF management guidelines [8, 9]. These trials marked a pivotal shift in both clinical practice and research activity, triggering rapid expansion of the literature addressing efficacy, safety, and clinical implementation.

Following the publication of these landmark trials, research emphasis progressively extended beyond randomized efficacy studies toward guideline development, post hoc analyses, real-world effectiveness, and special population studies. This expansion is consistent with the growing clinical adoption of oral anticoagulation in AF, which has progressively extended from controlled trial settings to widespread clinical application. Nevertheless, despite the substantial volume of publications generated over the past two decades, the structural evolution of this research domain – including thematic development, collaborative patterns, and shifting research priorities – has not been comprehensively examined through data-driven computational methodologies.

Bibliometric analysis offers quantitative tools for evaluating scientific production, citation impact, authorship networks, and conceptual relationships within a research field [10]. When combined with thematic mapping approaches, bibliometrics enables the identification of core research themes, emerging topics, and declining areas based on keyword co-occurrence and network structure [11]. Thematic analysis classifies research themes according to their centrality (relevance to the broader field) and density (internal development), positioning them within strategic diagrams that reveal driving forces, niche specializations, and emerging frontiers. Such analyses provide insights that extend beyond traditional narrative reviews by elucidating how knowledge domains evolve over time.

Highlight key points

- This study presents the largest bibliometric dataset to date on oral anticoagulation research in atrial fibrillation, including 11,039 publications from 1,351 journals and 48,486 authors.
- Publication output increased markedly from 2006 to 2021, reflecting the rapid expansion and subsequent maturation of the field.
- Landmark randomized trials and major clinical guidelines, including RE-LY, ARISTOTLE, ROCKET-AF, and the 2020 ESC Guidelines, were the most influential publications.
- The United States led in publication output, while Scandinavian countries showed the highest international collaboration rates and citation impact.
- Thematic analyses showed a shift from efficacy and stroke prevention toward real-world evidence, guideline implementation, and personalized anticoagulation strategies.

The present study aims to systematically map the intellectual evolution – defined as the progression of publication trends, thematic developments, and conceptual shifts – of oral anticoagulation research in AF from 2006 to 2025. Specifically, we sought to (i) characterize temporal publication trends and geographic distribution; (ii) identify highly influential publications, authors, institutions, and journals; (iii) analyze international and author-level collaboration networks; (iv) delineate thematic structures using keyword co-occurrence and strategic thematic mapping; and (v) extract latent research domains through topic modeling. By integrating these complementary objectives, this study provides a comprehensive overview of how AF anticoagulation research has transitioned from foundational clinical trials toward a consolidated, multidisciplinary landscape focused on real-world implementation and personalized care.

MATERIALS AND METHODS

Data Source and Search Strategy

Bibliographic data were retrieved from the Web of Science Core Collection (Clarivate Analytics) on 15 November 2025. A structured Topic Search (TS) strategy was applied, targeting titles, abstracts, author keywords, and Keywords Plus fields. The search query was constructed by combining three conceptual domains: (i) AF –related terms ("atrial fibrillation" OR "auricular fibrillation" OR "AF" OR "AFib"), (ii) thromboembolic and stroke-related outcomes ("stroke" OR "thromboembolism" OR "cerebrovascular"), and (iii) oral anticoagulant agents ("anti-

coagula*" OR "warfarin" OR "vitamin K antagonist" OR "VKA" OR "dabigatran" OR "rivaroxaban" OR "apixaban" OR "edoxaban" OR "DOAC" OR "NOAC").

The complete Boolean query executed in the Web of Science Advanced Search interface was:

> *TS = (("atrial fibrillation" OR "auricular fibrillation" OR "AF" OR "AFib") AND ("stroke" OR "thromboembolism" OR "cerebrovascular") AND ("anticoagula*" OR "warfarin" OR "vitamin K antagonist" OR "VKA" OR "dabigatran" OR "rivaroxaban" OR "apixaban" OR "edoxaban" OR "DOAC" OR "NOAC")) NOT ("pediatric" OR "pediatric" OR "children" OR "valvular")*

To ensure data specificity and to limit irrelevant records potentially introduced by the non-specific abbreviation "AF" (e.g., amniotic fluid, alcohol fraction, or unrelated biochemical indices), the three conceptual blocks were coupled using the strict logical AND operator. Consequently, a record was retrieved only if it simultaneously contained at least one specific AF descriptor, one stroke/thromboembolism outcome term, and one explicit oral anticoagulant agent. This multi-domain logical filter constrained non-specific "AF" matches to the anticoagulation–stroke context and substantially reduced the retrieval of irrelevant records.

The timespan was restricted to 2006–2025 to capture the early developmental phase of DOAC research preceding the publication of pivotal randomized controlled trials, as well as subsequent phases of clinical implementation and real-world investigation. Studies focusing exclusively on pediatric populations or valvular AF were excluded using Boolean NOT operators to ensure clinical homogeneity. All retrieved records were exported in BibTeX format for downstream bibliometric analysis. The search was confined to the Science Citation Index Expanded (SCI-EXPANDED) of the Web of Science Core Collection, and no language or document-type restrictions were applied at the search stage. Because a single database was queried, every record carried a unique Web of Science accession number; the exported dataset therefore contained no within-database duplicate records, and no cross-database deduplication was required. No manual exclusion of records was performed beyond the Boolean NOT criteria specified above, preserving a reproducible, algorithmic workflow. Publications indexed in the most recent years may be partially represented due to indexing delays inherent to the Web of Science database.

Bibliometric Analysis

Bibliometric analyses were conducted using the bibliometrix R package (version 4.x; K-Synth Srl, Naples, Italy) within the R statistical environment (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria) [10]. The Biblioshiny web interface facilitated the interactive exploration and visualization of bibliometric outputs. The analytical workflow comprised five main components: (a) descriptive performance analysis of publication output, citation metrics, and author productivity; (b) collaboration network analysis at author and country levels; (c) conceptual structure analysis based on keyword co-occurrence networks; (d) strategic thematic mapping using centrality and density metrics; and (e) journal productivity assessment based on Bradford's Law. Co-authorship and country collaboration networks were constructed using full counting methods, and network clustering was performed using the Louvain community detection algorithm. Keyword co-occurrence networks were generated from author keywords (DE), applying association strength normalization to reduce bias from highly frequent terms.

Thematic Mapping and Strategic Diagram Analysis

Thematic mapping was performed using the thematicMap() function implemented in the bibliometrix package to identify conceptual structures and their interrelationships within the oral anticoagulation– AF research corpus. Themes were derived from author keyword co-occurrence patterns and positioned on a two-dimensional strategic diagram based on centrality and density measures. Centrality represents the degree of interaction between a theme and other themes within the overall network, reflecting its relevance to the field, whereas density reflects the internal cohesion and developmental maturity of the theme. Based on these parameters, themes were classified into four quadrants: motor themes (high centrality, high density), niche themes (low centrality, high density), emerging or declining themes (low centrality, low density), and basic themes (high centrality, low density). In parallel, a keyword co-occurrence network was constructed to visualize relationships among the 50 most frequent keywords, applying a minimum co-occurrence threshold of three and community detection using the Walktrap algorithm.

Topic Modeling Analysis Latent Dirichlet Allocation (LDA)

LDA, an unsupervised probabilistic generative model, was applied to identify latent thematic structures within

the title and abstract text data of the oral anticoagulation literature related to AF. Before model estimation, textual data were preprocessed by converting all terms to lowercase; removing punctuation, numbers, and common English stop words; and applying sparse-term filtering (removing terms appearing in fewer than 0.5% of documents) to improve the signal-to-noise ratio [11].

The LDA model was implemented using the topicmodels package in R [12]. The optimal number of topics (k) was determined by evaluating candidate models ranging from k=2 to k=20. Model selection relied on standard statistical criteria implemented in the ldatuning package – specifically maximizing the metric of Griffiths and Steyvers [13] while minimizing the metrics of Cao et al., [14] and Arun et al., [15] – evaluated alongside semantic coherence, interpretability, and clinical relevance. These indices converged on an optimal nine-topic solution (k=9), which also exhibited peak semantic coherence and distinct clinical interpretability on qualitative review. Final model estimation was performed using Gibbs sampling with a fixed random seed to ensure full reproducibility, applying the default hyperparameter settings of the topicmodels package (a symmetric document–topic Dirichlet prior of $\alpha=50/k$ and a topic–word prior of $\delta=0.1$) and 2000 sampling iterations. Topic–term probability distributions (β matrix) and document–topic allocations (γ matrix) were extracted to characterize the most representative terms associated with each topic and to summarize thematic prevalence at the field level.

Statistical Analysis

Descriptive statistics were used to summarize publication output, citation metrics, and author productivity. Annual growth rates were calculated as compound annual growth rates (CAGR). Statistical results are reported in accordance with the AMA Manual of Style, 11th edition. p-values are expressed without a leading zero (e.g., p=0.002; p<0.001 for values <0.001); values near 0.05 are reported to three decimal places (e.g., p=0.053). All analyses were performed using the R statistical environment (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria) and the bibliometrix package (version 4.x; K-Synth Srl, Naples, Italy).

Ethical Considerations

This study was based exclusively on publicly available bibliographic metadata obtained from indexed scientific literature. No human participants, patient-level data, or animal experiments were involved. As this is a bibliometric study utilizing only publicly available data, ethics committee approval was not applicable, and informed consent was not required. The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki.

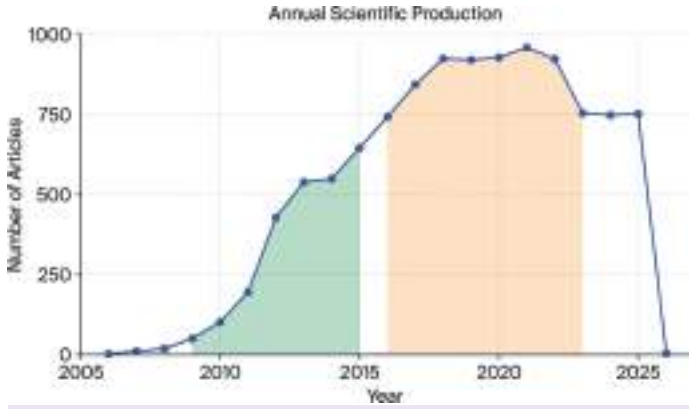

Figure 1. Annual scientific production in oral anticoagulation–AF research (2006–2025). The green shaded area indicates the rapid growth phase (2009–2015), and the orange shaded area represents the plateau phase (2016–2023). The decline in 2024–2025 reflects incomplete database indexing at the time of data retrieval.

RESULTS

General Characteristics of the Dataset

The bibliometric search yielded a total of 11,039 documents published between 2006 and 2025 across 1351 journals (Table 1). The corpus consisted predominantly of original research articles (7391; 66.9%) and review articles (2304; 20.9%), followed by editorial materials (510; 4.6%), letters (179; 1.6%), and other document types 655 (5.9%). A total of 48,486 unique authors contributed to the dataset. The document-per-author ratio was 0.228, corresponding to an average of 4.39 authors per document, whereas the average number of co-author appearances per document was 11.4, reflecting the contribution of large-scale multicenter collaborations. Internationally co-authored publications accounted for 28.15% of the total output.

The average age of the documents was 6.25 years (mean time since publication), indicating that most articles were published around 2018–2019, with a mean citation count of 26.77 citations per document. The overall citation metrics included an H-index of 195, a G-index

Table 1. General characteristics of the bibliometric dataset (Web of Science Core Collection, 2006–2025)

Description	Results
General information	
Timespan	2006–2025
Sources (journals)	1.351
Documents	11.039
Annual growth rate (%)	3.53
Average document age (years)	6.25
Average citations per document	26.77
References	101.838
Citation metrics	
H-index	195
G-index	392
M-index	9.29
Authors	
Total authors	48,486
Documents per author	0.228
Authors per document	4.39
Co-authors per document	11.4
International co-authorships (%)	28.15
Document types	
Articles n (%)	7.391 (66.9)
Reviews	2.304 (20.9)
Editorial material	510 (4.6)
Letters	179 (1.6)
Other types	655 (5.9)
Keywords	
Author keywords (DE)	7.287
Keywords plus (ID)	4.898

DE: Author keywords field (Web of Science); G-index: Cumulative citation impact metric; H-index: Hirsch index (number of papers with ≥H citations); ID: Keywords plus field (Web of Science); M-index: M-quotient (H-index divided by years of academic age).

of 392, and an M-index of 9.29. The dataset contained 7287 author keywords and 4898 Keywords Plus terms, reflecting broad conceptual diversity within the field.

Annual Scientific Production

The annual publication output increased from 2 articles in 2006 to a maximum of 960 articles in 2021 (Fig. 1). Publication growth accelerated markedly after 2009, with sustained high output observed from 2016 onward. The overall annual growth rate was 3.53%. Based on inflection points in the publication trajectory, two distinct phases were identified: a rapid growth phase (2009–2015), defined as the period when annual publication output exhibited CAGR exceeding 20%, temporally coinciding with DOAC regulatory approvals; and a plateau phase (2016–2023), characterized by sustained high output with annual growth rates below 10%, a pattern often associated with consolidation of a research field. During the plateau phase, publication output remained relatively stable, with approximately 870 articles in 2022 and 790 articles in 2023. The publication counts for the most recent years (2024–2025) were lower, consistent with incomplete indexing at the time of data retrieval.

Most-Cited Publications

Table 2 summarizes the 20 most-cited publications in the field of oral anticoagulation in AF. Randomized controlled trials constituted the majority of highly cited documents (15 of 20). The RE-LY trial [4] received the highest number of citations (n=8788), followed by the ARISTOTLE trial [6] (n=6998), the 2020 ESC Guidelines [1] (n=6958), the ROCKET-AF trial [5] (n=6753), and the ENGAGE AF–TIMI 48 trial [7] (n=3964). Six of the top 20 publications were published in the New England Journal of Medicine, and guideline documents accounted for a substantial proportion of highly cited outputs. Notably, several landmark clinical practice guidelines were simultaneously co-published in more than one journal – for example, the 2016 ESC guideline appeared in both the European Heart Journal and Europace, and the 2019 AHA/ACC/HRS focused update appeared in both Circulation and the Journal of the American College of Cardiology – and were therefore indexed as separate records in the Web of Science. These co-published records are retained as listed in Table 2 but represent the same underlying document and should be interpreted accordingly. The comparatively high citation counts of the most recently published (2023–2024) guidelines reflect the rapid citation accrual that is characteristic of major society guidelines rather than indexing or duplication artifacts.

Geographic Distribution and International Collaboration

The United States was the leading contributor, with 3636 publications (32.9%), followed by the United Kingdom (1666), Germany (1432), Italy (1218), and

Table 2. The 20 most-cited publications in oral anticoagulation–atrial fibrillation research (Web of Science Core Collection, 2006–2025)

Rank	First author	Year	Title	Journal	Citations	Study type
1	Connolly et al. [4]	2009	Dabigatran Versus Warfarin in Patients with Atrial Fibrillation	N Engl J Med	8.788	RCT
2	Granger et al. [6]	2011	Apixaban Versus Warfarin in Patients with Atrial Fibrillation	N Engl J Med	6.998	RCT
3	Hindricks et al. [1]	2021	2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation	Eur Heart J	6.958	Guideline
4	Patel et al. [5]	2011	Rivaroxaban Versus Warfarin in Non-valvular Atrial Fibrillation	N Engl J Med	6.753	RCT
5	Giugliano et al. [7]	2013	Edoxaban Versus Warfarin in Patients with Atrial Fibrillation	N Engl J Med	3.964	RCT
6	Ruff et al. [18]	2014	Comparison of Efficacy and Safety of NOACs vs Warfarin in AF: Meta-Analysis	Lancet	3.954	Meta-analysis
7	Kirchhof et al. [9]	2016	2016 ESC Guidelines for the Management of Atrial Fibrillation	Eur Heart J	3.592	Guideline
8	January et al. [8]	2019	2019 AHA/ACC/HRS Focused Update of the 2014 Guideline for Management of AF	Circulation	2.596	Guideline
9	January et al. [8]	2019	2019 AHA/ACC/HRS Focused Update of the 2014 Guideline for Management of AF	J Am Coll Cardiol	2.596	Guideline
10	Schulman et al. [19]	2009	Dabigatran Versus Warfarin in Treatment of Acute Venous Thromboembolism	N Engl J Med	1.982	RCT
11	Connolly et al. [20]	2011	Apixaban in Patients with Atrial Fibrillation	N Engl J Med	1.920	RCT
12	Kirchhof et al. [9]	2016	2016 ESC Guidelines for the Management of AF (Europace)	Europace	1.872	Guideline
13	Steffel et al. [21]	2018	2018 EHRA Practical Guide on NOACs in Patients with AF	Eur Heart J	1.430	Practical guide
14	Holmes et al. [22]	2014	PREVAIL: Watchman LAAC Device vs Long-Term Warfarin in AF	J Am Coll Cardiol	1.374	RCT
15	Joglar et al. [23]	2024	2023 ACC/AHA/ACCP/HRS Guideline for Diagnosis and Management of AF	Circulation	1.254	Guideline
16	Van Gelder et al. [24]	2024	2024 ESC Guidelines for the Management of Atrial Fibrillation	Eur Heart J	1.230	Guideline
17	Camm et al. [25]	2012	2012 Focused Update of the ESC Guidelines for Management of AF	Europace	1.219	Guideline
18	Gibson et al. [26]	2016	Prevention of Bleeding in Patients with AF Undergoing PCI	N Engl J Med	1.214	RCT
19	Kaatz et al. [27]	2015	Definition of Clinically Relevant Non-Major Bleeding in Anticoagulant Studies	J Thromb Haemost	1.127	RCT
20	Van Ryn et al. [28]	2010	Dabigatran Etexilate: Interpretation of Coagulation Assays and Reversal	Thromb Haemost	1.103	Pharmacokinetic

Study types were classified as RCT (randomized controlled trial), guideline, meta-analysis, practical guide, or pharmacokinetic study. ACC: American College of Cardiology; ACCP: American College of Chest Physicians; AF: Atrial fibrillation; AHA: American Heart Association; DOAC: Direct oral anticoagulant; EHRA: European Heart Rhythm Association; ESC: European Society of Cardiology; HRS: Heart Rhythm Society; LAAC: Left atrial appendage closure; NOAC: Non-vitamin K antagonist oral anticoagulant; PCI: Percutaneous coronary intervention; RCT: Randomized controlled trial; VKA: Vitamin K antagonist. Certain landmark guidelines were co-published in more than one journal and are consequently indexed as separate records in the Web of Science (ranks 7 and 12 correspond to the same 2016 ESC guideline; ranks 8 and 9 correspond to the same 2019 AHA/ACC/HRS focused update). These entries are retained as indexed but represent the same underlying document.

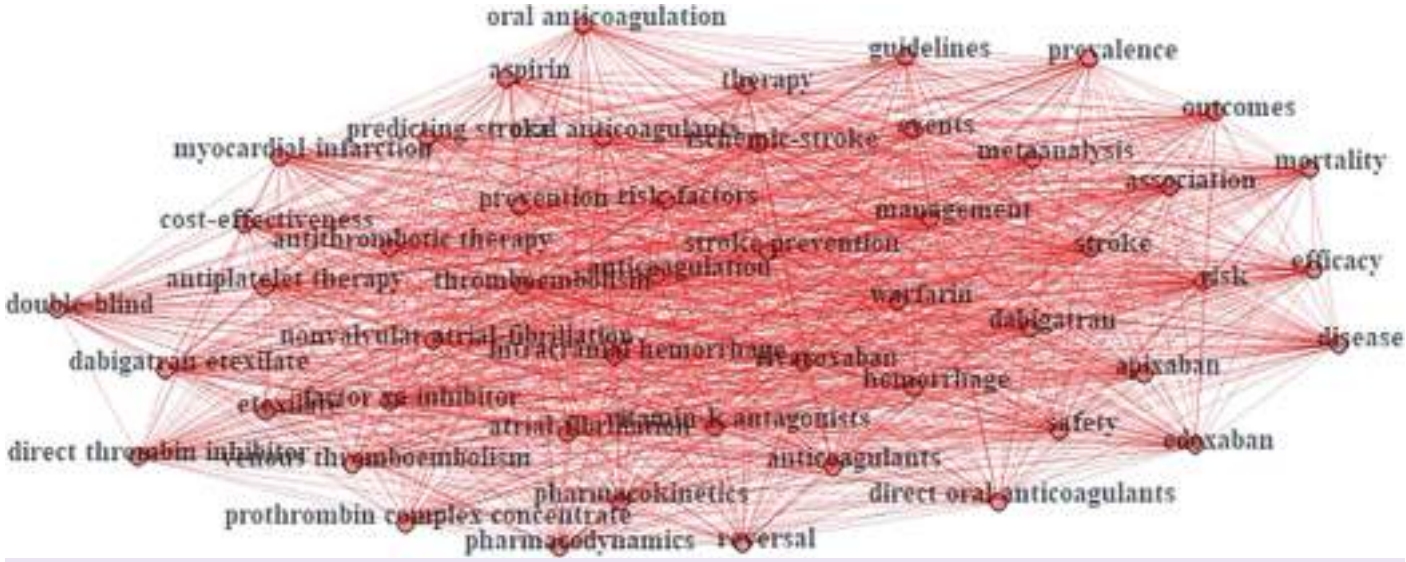

FIGURE 2. Keyword co-occurrence network of the 50 most frequent author keywords (minimum of three co-occurrences). Node size reflects keyword frequency, and edge thickness represents co-occurrence strength. Densely interconnected terms include atrial fibrillation, anticoagulation, stroke, warfarin, and the individual DOAC agents, together with clinical outcome terms such as bleeding, hemorrhage, and mortality.

Canada (1082) (Appendix Table 1). These five countries accounted for 81.8% of total publications. International collaboration rates varied widely across countries, with Denmark (90.2%), Sweden (87.2%), and France (87.2%) exhibiting the highest proportions of multi-country publications. In terms of citation impact, the United States accumulated the highest total number of citations (160,626), whereas Sweden achieved the highest average citations per article (140.7). Country collaboration network analysis revealed a central cluster dominated by the United States and Western European countries, with additional peripheral clusters involving Southern Europe, Eastern Europe, and Asia (Appendix Fig.1).

Leading Authors and Institutions

Author productivity analysis identified the most prolific contributor with 544 publications and a field-specific h-index of 76 (Appendix Table 3). The second- and third-ranked authors had 160 publications (h-index=56) and 156 publications (h-index=62), respectively. The highest average citation counts per article were 321.6, 251.0, and 227.7 for the three most-cited authors. Institutional analysis revealed the leading institution with 889 publications, followed by the second- (694 publications) and third-ranked institutions (576 publications) (Appendix Table 2). The highest citation impact among leading institutions was an average of 137.5 citations per article. Co-authorship network analysis of the top 50 authors revealed three major collaborative clusters corresponding to large clinical trial consortia, with several bridge authors connecting multiple research groups (Appendix Fig. 2).

Journal Analysis

The most productive journals included Circulation (248 articles), the Journal of Thrombosis and Thrombolysis (228), Thrombosis and Haemostasis (191), and the International Journal of Cardiology (185) (Appendix Table 4). The European Heart Journal exhibited the highest citation impact, with an average of 138.8 citations per article. Bradford's Law analysis identified 30 core journals (Zone 1) accounting for 3664 articles (33.2% of total output). These journals spanned cardiology, thrombosis and hemostasis, general clinical medicine, and cerebrovascular research domains.

Keyword Co-Occurrence Network

Keyword co-occurrence analysis of the 50 most frequent author keywords identified three distinct thematic clusters (Fig. 2). The first cluster comprised disease- and classical treatment-related terms, including AF, stroke, anticoagulation, and warfarin. The second cluster consisted of DOAC-specific agent terms such as dabigatran, rivaroxaban, apixaban, edoxaban, and DOACs. The third cluster included clinical outcome-related terms, in-

FIGURE 3. Thematic map (strategic diagram). Research themes are positioned based on centrality (x-axis: relevance to the field) and density (y-axis: theme development). Motor themes (atrial fibrillation, stroke, risk) occupy the upper-right quadrant; basic/transversal themes (anticoagulants, direct oral anticoagulants) lie along the central axis; antithrombotic therapy and aspirin appear as niche-leaning themes; and warfarin, dabigatran, and rivaroxaban occupy the emerging or declining lower-left quadrant.

cluding bleeding, hemorrhage, safety, mortality, and major bleeding. Strong co-occurrence links were observed between AF and stroke, as well as among individual DOAC agents and safety endpoints, reflecting the literature's continued focus on balancing ischemic prevention against hemorrhagic risk.

Thematic Map Analysis

Strategic thematic mapping positioned research themes according to centrality and density measures (Fig. 3). Motor themes, characterized by high centrality (0.215) and high density (1.62), comprised 141 keywords with 50,718 total occurrences and included DOAC agents (warfarin, dabigatran, rivaroxaban, apixaban), stroke prevention, and clinical outcomes (risk, stroke, bleeding, and safety-related terms). The positioning of these themes in the upper-right quadrant indicates that DOAC agents and stroke prevention represent the field's driving research forces. Emerging or declining themes consisted of 43 keywords with 10,860 total occurrences and included pharmacokinetics, venous thromboembolism, and mechanistic concepts in the lower-left quadrant. Additional clusters corresponding to niche themes and basic themes were also identified based on their relative centrality and density positions.

Thematic Evolution

Temporal thematic evolution analysis was performed across five periods defined on the basis of significant milestones in the field rather than equal time intervals: 2006–2015, 2016–2018, 2019–2020, 2021–2023, and 2024–2025 (Fig. 4). The earliest period was dominated by foundational themes of AF, warfarin, and stroke prevention. Through the middle periods (2016–2020), antithrombotic therapy and aspirin appeared alongside the consolidation of AF as the central theme, while procedural concepts such as catheter ablation became increasingly visible, and risk emerged as a persistent dominant node. In the most recent periods (2021–2025), management, risk stratification, and an-

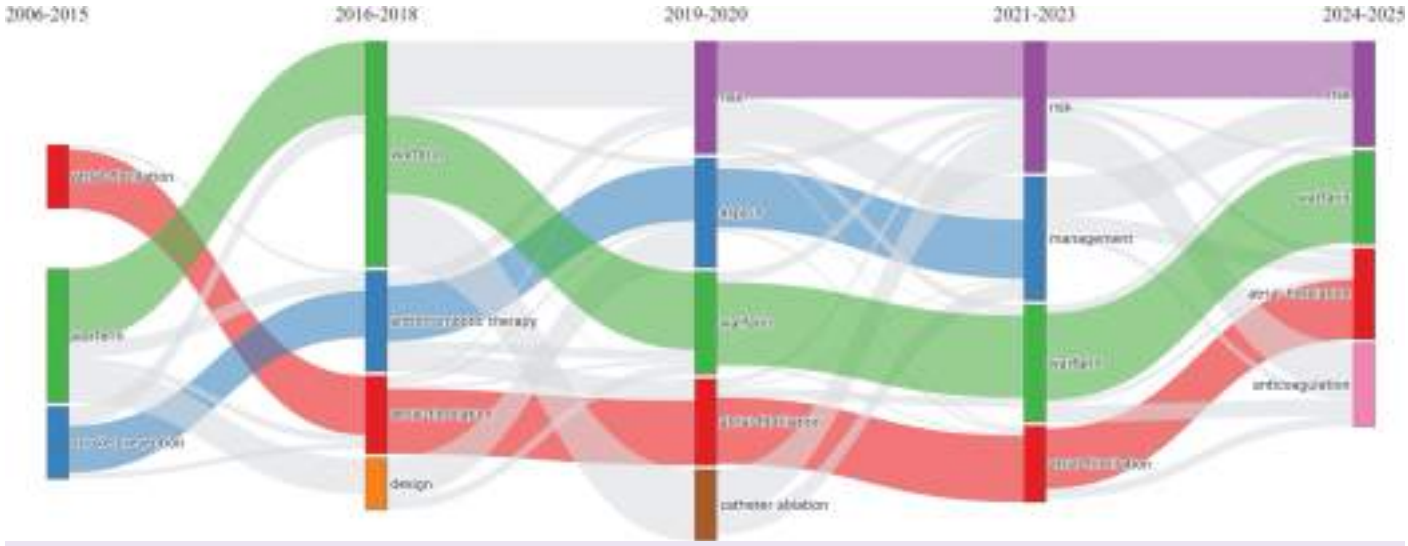

FIGURE 4. Thematic evolution across 5 time periods (2006–2025). Sankey diagram illustrating the temporal evolution of research themes across five periods: 2006–2015, 2016–2018, 2019–2020, 2021–2023, and 2024–2025. Node width represents keyword frequency within each period (wider nodes indicate higher occurrence); connecting flows indicate thematic continuity between consecutive periods, with flow thickness proportional to the strength of thematic linkage.

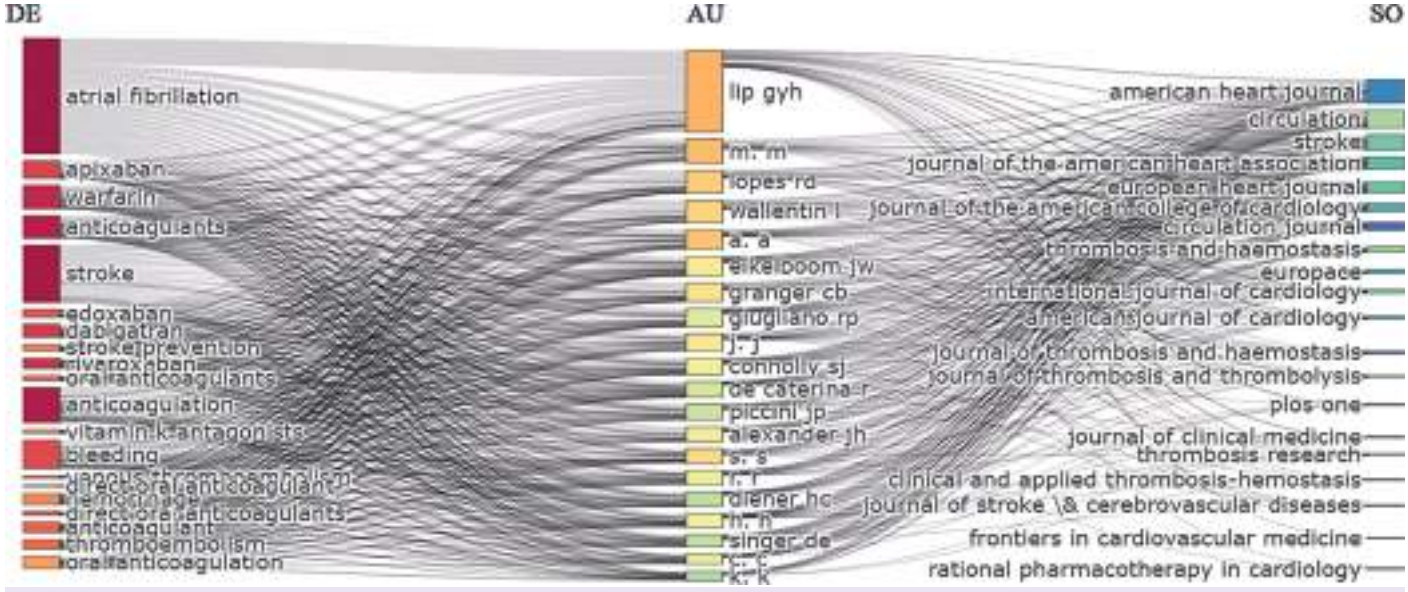

FIGURE 5. Three-field plot: author–keyword–journal relationships. Sankey diagram depicting relationships among the top 20 keywords (left, DE), top 20 authors (center, AU), and top 20 journals (right, SO). Flow width represents the strength of associations based on co-occurrence frequency. The central hub author (Lip GYH) connects multiple keyword clusters to diverse journal outlets, and direct oral anticoagulants-specific keywords demonstrate dual-pathway dissemination through both thrombosis-focused and cardiology-oriented journals.

ticoagulation became increasingly prominent, reflecting a shift toward clinical implementation and patient management rather than agent characterization alone. The overall trajectory illustrates a clear conceptual migration from early stroke-prevention and warfarin-centered models toward AF-specific, management-oriented research.

Author–Keyword–Journal Relationships

The three-field plot illustrating relationships among the top 20 authors, top 20 keywords, and top 20 journals demonstrated that Lip GYH occupied the central hub position, connecting multiple keyword clusters to diverse journal outlets (Fig. 5). DOAC-specific keywords exhibited dual-

pathway dissemination through both thrombosis-focused and cardiology-oriented journals, reflecting the multidisciplinary evolution of anticoagulation research in AF.

Topic Modeling Results LDA

LDA analysis identified nine distinct topics within the corpus (Appendix Table 5): (1) bleeding risk and clinical outcomes, (2) stroke prevention and risk stratification, (3) comparative NOAC versus VKA trials, (4) pharmacology and dosing strategies, (5) guideline-oriented management, (6) antithrombotic therapy and complications, (7) mechanistic studies, (8) venous thromboembolism, and (9) real-world data and prescribing patterns. Topic prevalence analysis demonstrated a relatively uniform distribution across topics, with mean document–topic proportions (γ) ranging tightly between 0.105 and 0.119, indicating that the literature maintains integrated, multi-pronged investigation rather than fragmenting into isolated niches.

DISCUSSION

This bibliometric analysis indicates that research on oral anticoagulation in AF has undergone marked quantitative expansion and thematic diversification over the past two decades. The observed publication trajectory highlights a rapid growth phase between 2009 and 2015, temporally aligned with the publication of pivotal randomized trials and subsequent regulatory approvals of DOACs, followed by a phase of sustained high output suggestive of consolidation within the field. The continued prominence of trial investigators such as Wallentin, Lopes, and Granger in author productivity rankings illustrates the enduring influence of landmark clinical trials and their investigators, who have extended their contributions beyond efficacy trials to post hoc analyses, real-world evidence generation, and guideline development.

Our findings extend and contextualize previous bibliometric work in the anticoagulation field. Earlier bibliometric analyses of AF and anticoagulation, such as those examining NOACs in cardiovascular disease or specific aspects like bleeding complications, typically focused on narrower time windows or specific drug classes. In contrast, the present analysis encompasses the complete DOAC era (2006–2025) and employs an integrated strategic thematic and probabilistic topic-modeling workflow, enabling identification of both established motor themes and emerging research frontiers. While confirming the volume dominance of North American and Western European institutions, our data reveal that international collaboration networks – particularly those involving Scandinavian countries – generate disproportionately high citation impact relative to publication volume. Conversely, the comparatively lower international collaboration profile observed in Japan may reflect region-specific regulatory frameworks, healthcare systems, and prescribing practices. Furthermore, whereas prior bibliometric reviews predominantly relied on citation analysis, our integration of LDA topic modeling maps the steady rise of implementation science, real-world data tracking, and health-systems research as increasingly prominent domains.

Two recent bibliometric analyses published in The Anatolian Journal of Cardiology provide important methodological parallels. Yang et al., [16] conducted a bibliometric investigation of cryoablation for AF (2002–2022) using Web of Science Core Collection data and CiteSpace visualization, identifying the USA as the leading contributor and demonstrating progressive growth in annual publications, consistent with the trajectory observed in the present study. Similarly, Ekenoglu Merdan and Aydogan [17] applied VOSviewer-based keyword mapping to infective endocarditis literature spanning 130 years (1892–2022) through Scopus, confirming that North American and Western European institutions dominate bibliometric output across cardiovascular subspecialties. Both studies highlight the value of periodic bibliometric repetition and keyword visualization in guiding future research priorities – a principle that directly motivated the methodological design of the present work.

The predominance of the four pivotal DOAC trials – RE-LY, ARISTOTLE, ROCKET-AF, and ENGAGE AF–TIMI 48 – among the most highly cited publications underscores the central role of high-level evidence in shaping contemporary anticoagulation practice; these trials established non-inferiority or superiority of DOACs compared with warfarin for stroke prevention in AF while consistently demonstrating favorable safety profiles, particularly with respect to intracranial hemorrhage [4–7, 18]. The concurrent strong citation impact of clinical practice guidelines reflects an emphasis on translating trial-based evidence into standardized clinical decision-making. Strategic mapping positioned real-world effectiveness and guideline-oriented management as highly central but comparatively less dense themes; this suggests substantial relevance to the field alongside opportunities for further methodological refinement, particularly regarding data heterogeneity across diverse healthcare systems. Collectively, these findings indicate a research landscape that has expanded beyond foundational efficacy trials toward

broader clinical, population-based, and health-system-oriented investigations, while maintaining strong integration across pharmacological and clinical domains.

Study Limitations

Several limitations of this study should be acknowledged alongside potential approaches for their mitigation in future research. First, reliance on the Web of Science Core Collection may have resulted in underrepresentation of studies indexed exclusively in other databases such as PubMed or Scopus; future bibliometric analyses could employ multi-database searches with deduplication algorithms to achieve more comprehensive coverage. Second, although no language restrictions were applied, the predominance of English-language publications in the Web of Science Core Collection may limit the visibility of research conducted in non-English-speaking regions; incorporating region-specific databases such as CNKI (China) or LILACS (Latin America) could address this limitation. Third, citation-based metrics do not distinguish between supportive and critical citations and may be influenced by publication age and journal visibility; emerging approaches such as citation context analysis and altmetrics could provide more nuanced assessments of research impact. Fourth, bibliometric indicators reflect research activity and influence rather than clinical efficacy or patient-level outcomes; future studies integrating bibliometric findings with clinical registry data could bridge this gap. Finally, the LDA approach assumes relative independence between topics, which may oversimplify the interconnected nature of research themes within this field; alternative approaches such as structural topic modeling or dynamic topic models could better capture thematic interdependencies and temporal evolution.

Conclusion

This bibliometric and thematic analysis illustrates the progressive evolution of oral anticoagulation research in AF, with a clear shift from efficacy-focused randomized trials toward real-world effectiveness studies, implementation science, and guideline-oriented clinical practice. The literature demonstrates sustained attention to key domains, including bleeding risk assessment, stroke prevention strategies, drug-specific pharmacology, and prescribing patterns across diverse patient populations. Future research may benefit from increased emphasis on long-term adherence, health-economic outcomes across healthcare systems, and personalized anticoagulation approaches integrating genetic, clinical, and patient-centered factors.

Ethics Committee Approval: This study is a bibliometric analysis based exclusively on publicly available bibliographic data and does not involve human participants, animal subjects, or identifiable personal information. Ethics committee approval was not required.

Informed Consent: Informed consent was not required, as this study did not involve human participants.

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Appendix Table 1. Top 20 countries by scientific production (2006–2025)

Country	Articles	SCP	MCP	MCP_ratio	Total citations	TC per article
USA	3636	2090	1546	42.5	160626	44.2
United Kingdom	1666	292	1374	82.5	108514	65.1
Germany	1432	498	934	65.2	100471	70.2
Italy	1218	620	598	49.1	47551	39
Canada	1082	326	756	69.9	79244	73.2
China	1048	692	356	34	41556	39.7
Japan	873	651	222	25	~35531	40.7
Denmark	664	65	599	90.2	37354	56.3
Spain	584	308	276	47.3	34201	58.6
Netherlands	581	135	446	76.8	58082	100
France	546	207	339	87.2	62752	66
Sweden	446	57	389	87.2	62752	140.7
Australia	435	165	270	62.1	46991	108
Switzerland	363	80	283	78	31480	86.7
Korea	314	176	138	43.9	14698	46.8
Belgium	296	49	247	83.4	31763	107.3
Poland	287	129	158	55.1	15128	52.7
Russia	232	178	54	23	17746	~76.5
Austria	227	88	139	61.2	8237	36.3
Greece	225	76	149	66.2	19155	85.1

Geographic distribution of publications showing country name, total publications (TP), single-country publications (SCP), multi-country publications (MCP), MCP ratio (%), total citations (TC), and average citations per article (TC per Article). The United States led productivity with 3,636 publications (32.9% of total), followed by the United Kingdom (1,666 publications, 15.1%) and Germany (1,432 publications, 13.0%). Denmark demonstrated the highest international collaboration ratio (MCP ratio: 90.2%), whereas China showed a relatively lower collaboration ratio (MCP ratio: 34.0%), indicating a higher prevalence of single-country publications. Citation impact varied substantially across countries; the United States exhibited high citation impact, reflecting its central role in global oral anticoagulation research, with additional strong impact observed for several high-income countries (e.g., the United Kingdom and Canada). Data Source: Web of Science Core Collection; Analysis Period: 2006-2025; Minimum threshold: Countries with ≥100 publications.

Appendix Table 2. Top 20 most productive institutions (2006–2025)

Institution	Articles	Total_citations	TC_per_article
Mcmaster Univ	889	79068	88.9
Univ Birmingham	694	61569	88.7
Duke Univ	576	79208	137.5
Aalborg Univ	554	27297	49.3
Harvard Med Sch	507	25849	51.0
Univ Liverpool	477	19103	40.0
Uppsala Univ	449	52422	116.8
Liverpool Heart and Chest Hosp	361	16125	44.7
Univ Toronto	357	15616	43.7
Brigham and Womens Hosp	316	36609	115.9
Natl Cerebral and Cardiovasc Ctr	248	9223	37.2
Chang Gung Univ	236	7661	32.5
Duke Clin Res Inst	234	17897	76.5
Mayo Clin	233	25081	107.6
Heidelberg Univ	222	18011	81.1
Taipei Vet Gen Hosp	220	13323	60.6
Mcgill Univ	208	8231	39.6
Stanford Univ	203	15173	74.7
Capital Med Univ	196	8098	41.3
Univ Michigan	196	12604	64.3

Institutional productivity ranking showing institution name, total articles, total citations, and average citations per article. McMaster University (Canada) emerged as the most productive institution with 889 articles and 79,068 total citations (88.9 citations per article), serving as the coordination center for the ARISTOTLE and RE-LY trials. The University of Birmingham (UK) ranked second with 694 articles and 61,569 citations (88.7 citations per article). Duke University (USA) demonstrated the highest citation impact among top institutions (137.5 citations per article) despite moderate publication volume (576 articles). Data Source: Web of Science institutional affiliations; Analysis method: Full counting (each institution counted once per publication).

Appendix Table 3. Top 20 most productive authors with h-index (2006–2025)

Rank	Authors	Articles	Total_citations	TC_per_article	h_index
1	Lip Gregory Y H	544	33304	61.2	76
2	Lopes Renato D	160	18080	113	56
3	Wallentin Lars	156	30692	196.7	62
4	Granger Christopher B	138	16582	120.2	50
5	Eikelboom John W	124	7767	62.6	44
6	Alexander John H	111	14756	132.9	45
7	Giugliano Robert P	103	12726	123.6	38
8	Singer Daniel E	100	14273	142.7	41
9	Piccini Jonathan P	99	16436	166	46
10	Connolly Stuart J	97	20908	215.5	50
11	Halperin Jonathan L	89	22338	251	38
12	Mahaffey Kenneth W	89	14138	158.9	41
13	De Caterina Raffaele	88	6410	72.8	28
14	Hohnloser Stefan H	85	19355	227.7	38
15	Oldgren Jonas	85	27340	321.6	42
16	Okumura Ken	82	2371	28.9	21
17	Ruff Christian T	82	12735	155.3	36
18	Yamashita Takeshi	82	5846	71.3	19
19	Chao Tze-Fan	79	2882	36.5	26
20	Kirchhof Paulus	78	12819	164.3	31

Author productivity ranking including author name, total articles, total citations, average citations per article, and field-specific h-index calculated exclusively for AF anticoagulation publications. Lip Gregory Y.H. emerged as the most prolific author with 544 articles and h-index of 76, reflecting sustained contributions across stroke risk stratification, bleeding risk assessment, and real-world evidence generation. Lopes Renato D. and Wallentin Lars ranked second and third with 160 and 156 articles respectively, both serving as principal investigators for ARISTOTLE. Data Source: Web of Science author metadata; h-index: Field-specific, computed exclusively for AF anticoagulation corpus.

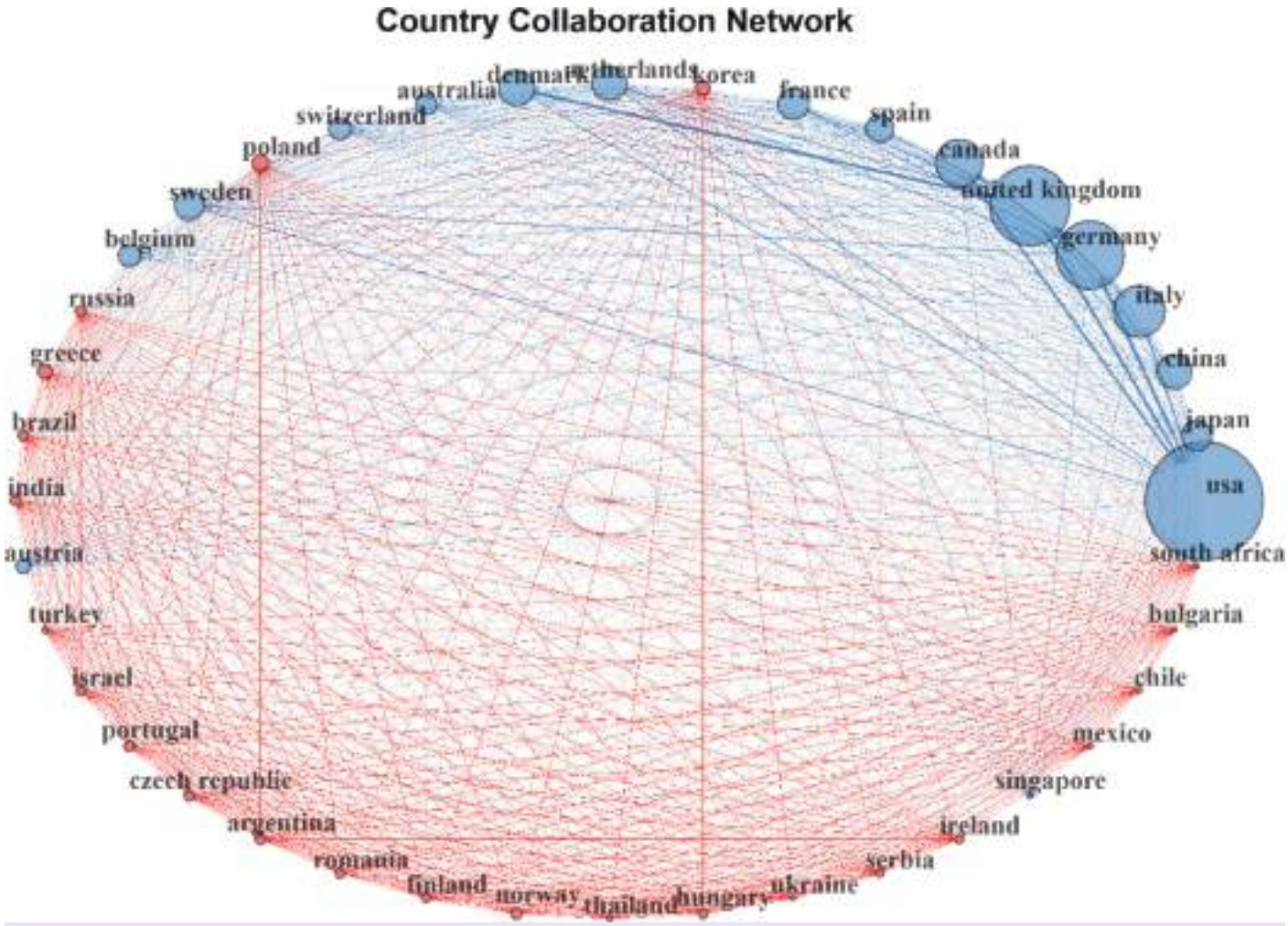
Appendix Table 4. Top 20 most productive journals with impact factor and bradford zone (2006–2025)

Rank	Journal	Articles	Total_citations	TC_per_article	IF_2023	Quartile	Zone
1	Circulation	248	18223	73.5	37.8	Q1	Zone 1
2	Journal of Thrombosis and Thrombolysis	228	3676	16.1	3.4	Q2	Zone 1
3	Thrombosis and Haemostasis	191	11095	58.1	6.7	Q1	Zone 1
4	International Journal of Cardiology	185	3154	17	3.2	Q2	Zone 1
5	Thrombosis Research	177	3013	17	3.7	Q2	Zone 1
6	Stroke	176	6962	39.6	10.2	Q1	Zone 1
7	European Heart Journal	163	22631	138.8	39.3	Q1	Zone 1
8	Journal of the American Heart Association	150	5669	37.8	5.4	Q1	Zone 1
9	Journal of Clinical Medicine	148	1017	6.9	3.9	Q2	Zone 1
10	Journal of the American College of Cardiology	138	14323	103.8	24	Q1	Zone 1
11	Europace	137	9469	69.1	8.4	Q1	Zone 1
12	American Journal of Cardiology	135	3502	25.9	2.5	Q3	Zone 1
13	Plos One	127	2193	17.3	3.7	Q2	Zone 1
14	American Heart Journal	118	5767	48.9	3.7	Q2	Zone 1
15	Journal of Stroke \& Cerebrovascular Diseases	105	1377	13.1	2	Q3	Zone 1
16	Journal of Thrombosis and Haemostasis	99	4345	43.9	6.1	Q1	Zone 1
17	Circulation Journal	98	2778	28.3	3.1	Q2	Zone 1
18	Clinical and Applied Thrombosis-Hemostasis	97	1247	12.9	2.3	Q3	Zone 1
19	Rational Pharmacotherapy in Cardiology	91	83	0.9	0.5	Q4	Zone 1
20	Frontiers in Cardiovascular Medicine	90	667	7.4	3.6	Q2	Zone 1

Journal productivity ranking showing journal name, total articles, total citations, average citations per article, 2023 Impact Factor, quartile classification (Q1-Q4), and Bradford Zone. Circulation published the most articles (248, IF=37.8, Q1, Zone 1), followed by Journal of Thrombosis and Thrombolysis (228, IF=3.4, Q2, Zone 1). Bradford's Law analysis identified 30 journals in Zone 1 (core journals), 296 in Zone 2, and 1,025 in Zone 3 (peripheral journals). All top 20 journals belong to Bradford Zone 1. Data Source: Web of Science; Impact Factors: 2023 Journal Citation Reports; Bradford zones: Calculated by ranking journals by productivity.

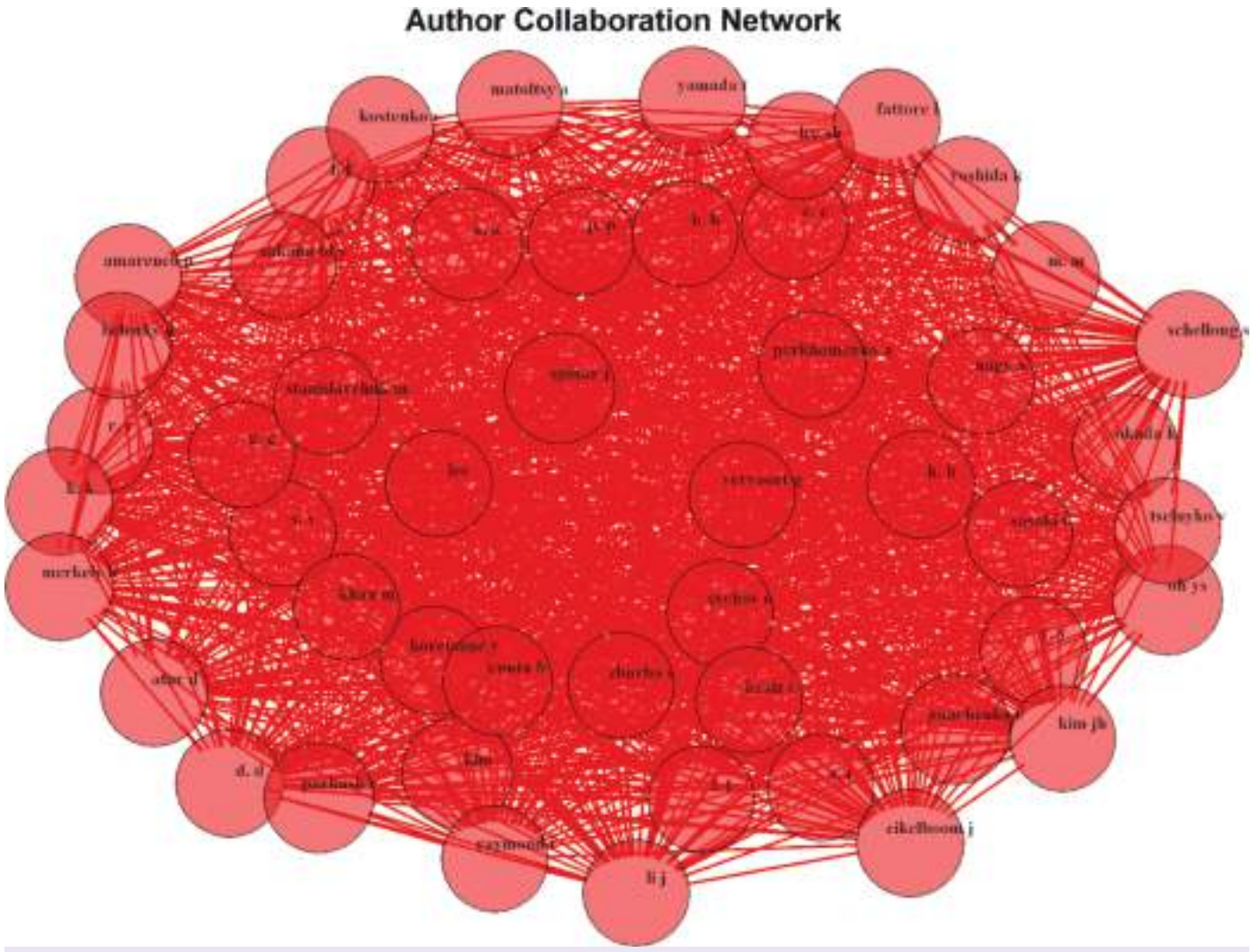
Appendix Table 5. Latent Dirichlet Allocation (LDA)–derived topics and representative keywords

Topic no	Proposed topic label	Top representative keywords	Conceptual interpretation
Topic 1	Bleeding Risk and Clinical Outcomes	bleed, risk, major, outcome, event, mortal	Focuses on major bleeding events, mortality, and adverse clinical outcomes associated with anticoagulant therapy.
Topic 2	Stroke and Atrial Fibrillation Risk Stratification	stroke, atrial, fibril, ischem, renal, prevent	Represents studies on ischemic stroke prevention and risk assessment in patients with atrial fibrillation.
Topic 3	NOAC vs VKA Comparative Safety and Trials	noac, vka, antagonist, trial, safety, vitamin	Encompasses randomized trials and comparative analyses evaluating safety and efficacy of NOACs versus vitamin K antagonists.
Topic 4	DOAC Pharmacology and Dosing Strategies	warfarin, rivaroxaban, apixaban, dabigatran, dose	Covers pharmacological characteristics, dosing strategies, and drug-specific considerations of oral anticoagulants.
Topic 5	Clinical Practice and Guideline-Oriented Management	clinic, manage, practice, recommend, review	Reflects guideline-based recommendations, clinical management strategies, and real-world practice reviews.
Topic 6	Antithrombotic Therapy and Clinical Complications	therapy, antithrombotic, antiplatelet, complication, coronary	Focuses on antithrombotic and antiplatelet therapies, including associated complications and coronary disease contexts.
Topic 7	Mechanisms of Action and Drug Monitoring	factor, dabigatran, inhibitor, drug, monitor	Represents mechanistic studies on anticoagulant drugs, including factor inhibition and therapeutic monitoring.
Topic 8	Oral Anticoagulation in Venous Thromboembolism	oral, doac, thromboembol, venous, treatment	Addresses the use of oral anticoagulants in venous thromboembolism treatment and prevention strategies.
Topic 9	Real-World Data and Prescribing Patterns	age, score, hospital, prescribe, initiate, year	Captures observational studies focusing on prescribing behavior, risk scores, age-related patterns, and real-world data.



Appendix Figure 1. Country collaboration network.

Geographic collaboration network visualization (minimum 5 international collaborations) demonstrating international research partnerships. The network comprises 40 countries with node size proportional to publication volume and edge thickness representing collaboration frequency. Two distinct clusters emerged: Cluster 1 (Blue, Core Group) comprises USA, UK, Germany, Canada, Netherlands, and Denmark with dense transatlantic connections. Cluster 2 (Red, Peripheral Group) includes Turkey, Greece, Brazil, India, and Eastern European countries with more limited intercontinental collaborations. The USA occupies the central hub position serving as the primary bridge between European and Asian research groups. Methodology: bibliometrix R package; Minimum 5 collaborations; Louvain community detection; Fruchterman-Reingold layout



Appendix Figure 2. Co-authorship network (top 50 authors).

Author collaboration network (top 50 authors, minimum 2 joint publications) revealing major trial consortia as organizing structures. Three main clusters identified: Cluster 1 (Lip Gregory Y.H. cluster, Red) focuses on stroke risk stratification and real-world studies. Cluster 2 (ARISTOTLE/Duke cluster, Blue) comprises trial investigators from Duke Clinical Research Institute. Cluster 3 (RE-LY/McMaster cluster, Green) centers at McMaster University. Bridge authors (Connolly SJ, Wallentin L) connect multiple research groups, facilitating cross-trial knowledge transfer. Methodology: bibliometrix; Minimum 2 collaborations; Louvain algorithm; Network metrics: 50 nodes, 187 edges, density 0.153.

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Original Article ALGOLOGY

Long-term efficacy of genicular nerve radiofrequency ablation in patients with advanced knee osteoarthritis: A retrospective cohort study

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ABSTRACT

OBJECTIVE: Conventional treatments for advanced knee osteoarthritis (OA) are often insufficient, and surgery is not always feasible. This retrospective cohort study aimed to evaluate changes in pain, function, and safety over 12 months following ultrasound-guided genicular nerve radiofrequency ablation (GNRFA).

METHODS: We included 44 patients with chronic knee pain unresponsive to conservative treatments for at least 3 months. All patients underwent US-guided radiofrequency ablation of the superomedial, superolateral, and inferomedial genicular nerves. Pain numeric rating scale (NRS) and functional status Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were assessed at baseline, and routinely at 1, 6, and 12 months post-procedure.

RESULTS: Compared to baseline, mean NRS and WOMAC scores decreased significantly at all follow-up points ($p<0.001$). Based on a ≥50% pain reduction threshold (clinical success), 81.8% of patients achieved success at 1 month, and 75.0% maintained it at 6 months. By 12 months, this rate declined to 11.4%. No statistically significant differences in outcomes were observed between radiological grades. A strong positive correlation between NRS and WOMAC scores was observed across all follow-up times. No serious adverse events were reported.

CONCLUSION: US-guided GNRFA was associated with improvements in pain and function, which were most pronounced within the first 6 months in patients with advanced knee OA. However, the marked decline in responder rates at 12 months suggests reduced durability beyond 6 months. These findings suggest that GNRFA may serve as a medium-term management option rather than a permanent solution, and that re-evaluation may be appropriate in patients with recurrent symptoms.

Keywords: Chronic pain; genicular nerves; interventional; knee; osteoarthritis; radiofrequency ablation; treatment outcome; ultrasonography.

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Degenerative osteoarthritis (OA) is the most common cause of chronic knee pain [1]. The global prevalence of knee OA is reported to be 16% in individuals aged 15 and over, and 22.9% in those aged 40 and over [2]. Due to an aging population and rising obesity rates, the number of individuals affected by symptomatic knee OA is projected to increase significantly [3]. The pathogenesis of OA is multifactorial and involves biomechanical, inflammatory, and metabolic processes. These mechanisms contribute to cartilage damage, synovitis, and various subchondral bone abnormalities [4]. This condition, characterized by the progressive degradation of articular cartilage, primarily results in pain, activity limitations, and reduced mobility [5]. Beyond physical impairment, it also restricts social participation and negatively affects overall quality of life [6].

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Management of OA in routine clinical practice generally follows a stepped-care approach. First-line conservative treatments include patient education, physical therapy, weight management, various pharmacological agents, and intra-articular injections with substances such as corticosteroids [7]. In patients with advanced or treatment-resistant disease, total knee arthroplasty (TKA) is often considered as a surgical option. Although randomized controlled trials have demonstrated the superiority of TKA over non-surgical treatment for end-stage knee OA, non-operative management remains an important option for certain patient populations. This group includes individuals with mild-to-moderate symptoms, those who are not surgical candidates due to significant comorbidities, and patients who decline surgical intervention.

Conventional genicular nerve radiofrequency ablation (GNRFA) is one of the interventional procedures used for the symptomatic treatment of eligible patients. The goal of the GNRFA procedure is to partially denervate the anterior knee capsule by creating a thermal lesion, thereby reducing OA-associated pain. The superomedial, superolateral, and inferomedial genicular nerves are the traditional targets for radiofrequency (RF) therapy, based on the initial controlled trial by Choi et al. [8]. Although existing studies have found GNRFA to be effective for pain and function in knee OA, the majority of this research is limited to follow-up periods of 3 or 6 months [9]. Our study aims to demonstrate the effects of GNRFA over a longer follow-up period of 12 months.

Highlight key points

- Ultrasound-guided GNRFA was associated with reduced pain and improved function in advanced knee OA.
- Clinical success was observed in 81.8% of patients at 1 month and 75.0% at 6 months.
- The responder rate declined to 11.4% at 12 months, limiting long-term clinical relevance.
- GNRFA may serve as a medium-term management option, and re-evaluation may be appropriate for recurrent symptoms.

MATERIALS AND METHODS

Study Design and Patients

This retrospective observational cohort study was conducted between January 2022 and January 2023 at the pain management clinic of a training and research hospital. The study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. Written informed consent for the procedure had been obtained from all patients at the time of treatment. Ethical approval for the retrospective review of patient records was obtained from the local Institutional Ethics Committee (No: 89, Date: April 21, 2025). Due to the retrospective nature of the study, ethics approval was obtained after completion of the clinical treatments and before data extraction and analysis. No interventions were performed for research purposes. The research was carried out in compliance with the ethical principles outlined in the Declaration of Helsinki, as revised in 2013.

Patients aged 45 years and older were screened for eligibility. Inclusion criteria were: Knee pain for 3 months or longer due to advanced-stage (Kellgren-Lawrence Grade 3 and 4) knee OA; a numeric rating scale (NRS) score of 5 or higher despite conservative medical and physical therapy; and providing written informed consent. Exclusion criteria included any of the following: Knee injections within the previous 3 months, knee deformity or inflammatory arthritis of other causes, a history of knee arthroplasty, pacemaker or implantable cardioverter defibrillator, lumbar radicular pain, malignancy, psychosis or progressive neurological disease, allergy to study medications, bleeding disorders, or incomplete medical records.

For each included patient, the clinical diagnosis and grade of knee OA were confirmed through physical examination and radiological imaging (magnetic resonance imaging or X-ray).

Procedures

All procedures were performed by physicians specializing in musculoskeletal interventions, using a Toshiba TUS-A300™ ultrasound system (USA) equipped with an 11L4 linear transducer. A Cosman™ RFG-4 RF generator was used for the RF procedures. The interventions were carried out using 60 mm long, 20G Unified™ EchoRF™ hybrid needles, which feature a 5 mm active tip and integrate an electrode, cannula, and injection tube.

A diagnostic block was administered to all three target nerves simultaneously during a single session. Following the blocks, patients were asked to perform provocation maneuvers (e.g., walking, stair climbing) that typically elicited their baseline knee pain. A positive response was defined as a practical pain reduction of ≥50% compared

to their pre-block activity-related pain, occurring within 30–90 min and lasting for at least 2 h. Patients with a positive response to the diagnostic block proceeded to the GNRFA procedure. Both the diagnostic nerve blocks and the GNRFA procedure were performed using the technique described by Merrin and Grimshaw [10].

The patient was placed in the supine position between the physician and the ultrasound equipment. The affected knee was supported by a triangular wedge to maintain approximately 30° of flexion. Using an in-plane technique, the transducer was positioned parallel to the bone shaft to identify the genicular arteries near the periosteum. The superolateral target was at the junction of the lateral epicondyle and the distal femoral shaft; the superomedial target was at the junction of the medial epicondyle and the distal femoral shaft; and the inferomedial target was at the junction of the medial epicondyle and the tibial shaft (Fig. 1). The location of the genicular arteries was confirmed with color Doppler. To facilitate the procedure and improve accuracy, the linear probe was rotated 90° to visualize the genicular arteries longitudinally. The superolateral, superomedial, and inferomedial genicular nerves, which accompany these arteries, were targeted.

The RF needle was gently advanced to the target site. Prior to initiating GNRFA, sensory stimulation was performed at 50 Hz and below 0.6 V to confirm the proximity of the cannula to the sensory nerve. Successful sensory stimulation was confirmed when the patient reported sensory complaints (numbness, tingling, or pain) concordant with their typical knee pain. Subsequently, motor stimulation was performed at 2 Hz and 3 V to ensure the cannula was distant from motor nerve fibers, which was verified by the absence of muscle contractions in the lower extremity.

Once the correct position was verified and appropriate responses were elicited, 1 mL of 1% lidocaine was injected, and thermal RF was applied to each nerve at 80°C for 90 s. This was followed by negative aspiration and the administration of one-third of a mixture containing 1 mL of dexamethasone (4 mg) and 2 mL of 1% lidocaine (1 mL of the mixture per lesion) to the lesion site to reduce the risk of post-procedural neuralgia/neuritis.

All procedures were performed under sterile conditions, and local skin anesthesia was applied before needle insertion. Post-procedure, patients were transferred to a recovery room and monitored for 2 h for any potential complications.

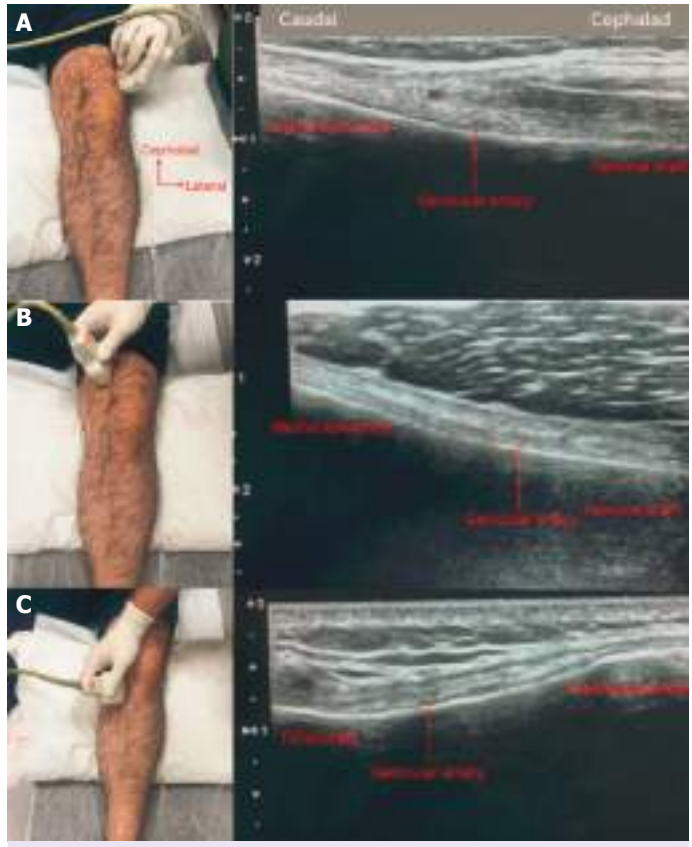

FIGURE 1. Transducer positions and sonoanatomy of genicular nerves. **(A)** Superolateral genicular nerve. **(B)** Superomedial genicular nerve. **(C)** Inferomedial genicular nerve.

One week after the injection, all patients were provided with an exercise booklet to guide their home rehabilitation program. Patients were advised to use 500 mg of paracetamol (up to a maximum of four tablets per day) and/or Naproxen (750 mg) as needed for pain relief. They were instructed not to take any analgesics on the day of or the day before their follow-up assessments, as this could interfere with the clinical outcome measurements.

Outcome Measures

We evaluated all patients for both primary and secondary outcome measures at baseline (pre-injection) and at 1, 6, and 12 months post-injection. The primary outcome measure was the NRS score, while the secondary outcome measures included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores. Any adverse events occurring during the procedure or follow-up visits were documented.

Primary Outcome Measures

Pain intensity was assessed using the 11-point NRS-11, where 0 represents "no pain" and 10 represents "the worst pain imaginable."

Secondary Outcome Measures

The WOMAC is a standardized questionnaire widely used by healthcare professionals to assess the condition of patients with knee and hip OA, including pain, stiffness, and physical function of the joints. It was developed in 1982 by Western Ontario and McMaster Universities. Higher scores indicate worse pain, stiffness, and functional limitations. The WOMAC consists of five items for pain (score range: 0–20), two items for stiffness (score range: 0–8), and 17 items for functional limitation (score range: 0–68). The validity and reliability of the Turkish version have been previously established [11].

Statistical Analyses

Statistical analyses were performed using Statistical Package for the Social Sciences software (version 27, IBM Corp., Chicago, IL, USA). The normality of data distribution was assessed using the Shapiro–Wilk test. As the data were not normally distributed, non-parametric tests were used for the analysis. Descriptive statistics were presented as mean, median, standard deviation, frequency, and percentage. The Wilcoxon signed-rank test was used for pre- and post-procedural comparisons, while the Mann–Whitney U test was used to analyze the difference between two groups. Spearman's correlation coefficient was calculated to assess correlations. Effect sizes (r) for the Wilcoxon signed-rank tests were calculated as $r = |Z|/\sqrt{N}$, where N was defined as the total number of observations contributing to each paired comparison (N=88, i.e., 44 pairs). To evaluate clinical significance at the individual level, clinical success was defined a priori as a ≥50% reduction in the baseline NRS score at the follow-up time points.

RESULTS

A total of 63 patient records were screened for eligibility for the study. After excluding eight patients who met the exclusion criteria, an additional 11 patients were removed due to loss to follow-up. Forty-four patients (n=44) who met the inclusion criteria were included in the final analysis (Fig. 2). An analysis comparing the baseline characteristics (age, sex, and baseline NRS scores) of the 11 patients lost to follow-up with the 44 included patients revealed no significant differences (p>0.05). No significant baseline differences were identified between included and excluded patients.

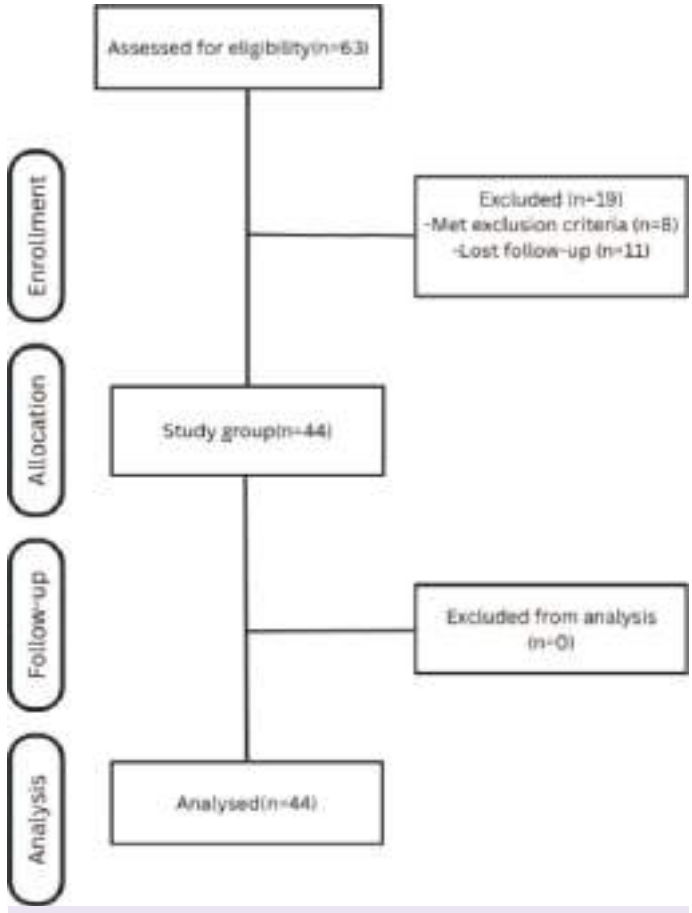

FIGURE 2. Flow diagram of the study.

TABLE 1. Demographic and clinical characteristics (n=44)

	%
Sex	
Woman	72.7
Man	27.3
KL stage	
3	43.2
4	56.8
Side	
Left	22.7
Right	77.3

KL: Kellgren Lawrence.

Table 2. Actual NRS and WOMAC scores at baseline and follow-up time points

Time point	NRS, Mean±SD	NRS, median (IQR)	WOMAC, Mean±SD	WOMAC, median (IQR)
Baseline (T0)	7.1±1.1	7 (6–8)	65.2±5.9	64 (62–70)
1 month (T1)	2.8±1.1	3 (2–3)	26.4±9.9	24 (20–36)
6 months (T2)	3.3±1.0	3 (3–4)	28.6±8.8	28 (24–36)
12 months (T3)	5.1±1.3	5 (4–6)	47.8±11.2	46 (36–56)

Data are presented as Mean±Standard deviation and median with interquartile range. T0=Baseline; T1=1 month; T2=6 months; T3=12 months. IQR: Interquartile range; NRS: Numeric Rating Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; SD: Standard deviation.

Table 3. Pairwise comparisons of changes in NRS and WOMAC scores

Comparison	Mean difference±SD	95% CI of difference	Wilcoxon (Z)	p	Effect size (r)*
NRS					
T0–T1	4.2±1.5	3.76 to 4.64	-5.8	<0.001	0.61 (large)
T0–T2	3.8±1.3	3.42 to 4.18	-5.8	<0.001	0.61 (Large)
T0–T3	1.8±1.4	1.39 to 2.21	-5.2	<0.001	0.55 (large)
T1–T2	-0.4±0.7	-0.61 to -0.19	-3.4	0.001	0.36 (medium)
T1–T3	-2.4±1.7	-2.9 to -1.9	-5.4	<0.001	0.57 (large)
T2–T3	-2.0±1.5	-2.44 to -1.56	-5.3	<0.001	0.56 (large)
WOMAC					
T0–T1	38.9±12.3	35.27 to 42.53	-5.7	<0.001	0.60 (large)
T0–T2	36.6±11	33.35 to 39.85	-5.7	<0.001	0.60 (large)
T0–T3	17.5±13.2	13.60 to 21.40	-5.2	<0.001	0.55 (large)
T1–T2	-2.2±7.2	-4.33 to -0.07	-2.1	0.02	0.22 (small)
T1–T3	-21.3±16.7	-26.23 to -16.37	-5.3	<0.001	0.56 (large)
T2–T3	-19.1±13.9	-23.21 to -14.99	-5.5	<0.001	0.58 (large)

95% CI: 95% Confidence interval. Effect size (r) calculated as $|Z|/\sqrt{N}$ (N=88, i.e., 44 pairs). Interpretation: 0.1=Small; 0.3=Medium; 0.5=Large effect. T0=Baseline; T1=1 Month; T2=6 Months; T3=12 Months. NRS: Numeric Rating Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; SD: Standard deviation.

Of the included patients, 32 (72.7%) were female. Twenty-five patients (56.8%) had Grade 4 OA, and in 34 patients (77.3%), the symptoms were on the right side (Table 1).

Table 2 shows the NRS and WOMAC scores at baseline and follow-up. Both scores decreased significantly at 1, 6, and 12 months compared to baseline ($p<0.001$). Table 3 presents the pairwise comparisons, 95% confidence intervals, and effect sizes. The procedure demonstrated large effect sizes for most pairwise comparisons. Despite this, mean NRS scores began to increase gradually after the 1st month.

Regarding clinical success (≥50% pain reduction), 36 patients (81.8%) met this threshold at 1 month, and 33 (75.0%) met the same criterion at 6 months. By 12 months, only 5 patients (11.4%) still met this criterion.

In patients with Grade 3 knee OA, baseline NRS scores were significantly lower than those in patients with Grade 4 OA ($p<0.05$). Post-procedure, the radiological grade did not create a significant difference in NRS scores ($p>0.05$). No significant difference was found between the radiological grade and WOMAC scores at any time point ($p>0.05$).

No adverse events were observed in patients during the procedure or throughout the follow-up period.

When examining the relationship between NRS and WOMAC scores, a strong positive correlation was observed between NRS and WOMAC scores at baseline (Spearman's ρ=0.822), and this relationship persisted throughout the post-treatment period. At 1 month, ρ was 0.892, at 6 months ρ was 0.896, and at 12 months ρ was 0.973.

DISCUSSION

In this retrospective cohort, we evaluated the safety and efficacy of ultrasound-guided GNRFA in patients with advanced knee OA. Our findings suggest that GNRFA was associated with improvements in pain and function from baseline through the 12-month follow-up. After the initial decline recorded at 1 month, NRS scores showed a subsequent increase at 6 and 12 months. Pain scores increased over time but remained lower than baseline values. The statistically significant increase in pain after the 1st month suggests that the clinical benefit of GNRFA appears to diminish over time rather than representing a permanent solution.

Although mean NRS and WOMAC scores remained statistically lower than baseline at 12 months, only 11.4% of patients maintained a clinically meaningful reduction in pain. This discrepancy highlights the distinction between statistical significance and patient-level clinical benefit, suggesting that the long-term clinical relevance of a single GNRFA procedure may be limited for most patients. Furthermore, these responder rates should be interpreted cautiously, as only patients with a positive diagnostic genicular nerve block proceeded to ablation, which may have enriched the cohort for potential responders. The observed loss of clinical benefit over time may be related to nerve regeneration, although this mechanism was not directly evaluated in the present study. RF energy causes Wallerian degeneration of the axons but largely preserves the nerve's connective tissue sheaths, which theoretically allows the nerve to regenerate [12]. This biological plausibility may partly explain the observed decline in responder rates over time. These findings support the role of GNRFA as a medium-term management option rather than a permanent solution and suggest that re-evaluation may be appropriate in patients with recurrent symptoms around 6 months.

In our study, the baseline NRS scores of patients with Grade 3 knee OA were significantly lower than those of patients with Grade 4. This is consistent with clinical observations and literature findings suggesting that pain intensity increases in the more advanced stages of OA [13]. However, no statistically significant differences were observed in post-procedural NRS scores between patients with Grade 3 and Grade 4 OA. Similar post-procedural outcomes across radiological grades suggest that the observed improvements were not restricted to patients with less advanced disease. These findings indicate that patients with advanced radiographic OA may also experience improvements in pain scores following GNRFA, although confirmation in controlled studies is required.

Another key finding of our study was the high correlation between NRS and WOMAC scores. This relationship supports the notion that the intervention similarly affects both pain intensity and functional limitations, and that these parameters are reliable indicators of a patient's quality of life. The particularly strong correlation of 97.3% at 12 months indicates that long-term pain control and functional improvement proceed in parallel. These findings indicate a close relationship between pain intensity and functional status, which is consistent with other studies in the literature [14].

While studies on GNRFA typically have follow-up periods of 3 or 6 months, the number of studies with a 12-month follow-up, like ours, is limited. While some studies report that the effects of GNRFA diminish after 3 months [15], others have reported sustained efficacy for 12 months or longer [16]. This discrepancy may partly reflect differences in the definitions and thresholds used to define treatment success across studies.

Research into minimally invasive treatments for chronic knee OA has examined the efficacy of various methods beyond GNRFA, such as cryoablation, cooled RF, bipolar RF, and pulsed RF. Some studies have explored GNRFA with different durations and needles, sometimes targeting nerves other than the classic three. The results from these studies are conflicting. The lack of sufficient high-level evidence and the lack of comparative studies against traditional GNRFA indicate the need for further randomized controlled trials. A systematic review and meta-analysis of RCTs comparing cooled, monopolar, or bipolar RFA or cryoneurolysis with sham treatment in adults with symptomatic knee OA concluded that genicular neurolysis, particularly conventional monopolar RF ablation, provides clinically significant pain and functional improvement with a favorable safety profile [17].

In our protocol, a low dose of dexamethasone (4 mg) was administered following the creation of the RF lesion. The primary rationale for this was to minimize the risk of post-procedural neuritis and localized inflammation. While periarticular corticosteroids can provide immediate and short-term analgesia, their duration of action is generally limited to a few weeks. It is highly unlikely that the steroid injection significantly contributed to the sustained analgesic effects observed at the 6- and 12-month follow-ups. Nonetheless, its use represents a minor confounding factor when comparing our long-term outcomes with studies that utilize RF alone.

Our findings also support the safety of GNRFA. Although serious adverse events such as septic arthritis [18], hematoma [19], and third-degree burns [20] have been reported, these are generally limited to case reports. The absence of any serious adverse events in our study, consistent with many others, supports the finding that GNRFA is a safe procedure.

Our study has several important limitations. First, the retrospective observational design and the absence of a control or sham group make it impossible to definitively distinguish the specific effects of GNRFA from placebo effects, regression to the mean, natural symptom fluctuation, or the impact of concomitant treatments like rehabilitation exercises. Second, our sample size was relatively small. Although baseline characteristics did not differ significantly between groups, attrition bias cannot be completely excluded, given that nearly 20% of the initially eligible patients were lost to follow-up. Third, because only patients with a positive diagnostic block proceeded to ablation, the study population was inherently enriched for potential responders. Therefore, the observed responder rates may overestimate treatment outcomes compared with an unselected population of patients with advanced knee OA. In addition, the single-center nature of the study may limit the external validity of the findings. Finally, the routine administration of low-dose dexamethasone after creating the RF lesion represents a minor confounding factor; although its effects are short-lived, it should be considered when comparing our outcomes with studies using RF alone.

Conclusion

In this retrospective cohort, GNRFA was associated with meaningful improvements in pain and function, most prominently in the early post-procedural period, with reduced durability beyond 6 months. These improvements were observed across radiological grades. The decline in responder rates after 6 months suggests that repeat ablation may be necessary in selected patients. GNRFA appears to be a reasonable non-surgical option, particularly for patients at high surgical risk or unwilling to undergo TKA. Confirmation of these findings will require adequately powered randomized sham-controlled studies.

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital (KAEK/2025.04.89 - 21.04.2025).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

Authorship Contributions: Concept – STG, HIA; Design – STG, HIA; Supervision – STG, HIA; Resource – HIA, STG; Materials – HIA; Data Collection and/or Processing – HIA; Analysis and/or Interpretation – STG; Literature Search –STG; Writing – STG; Critical Reviews – HIA, STG.

Peer-review: Externally peer-reviewed.

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ORIGINAL ARTICLE GENERAL SURGERY

Predictive value of an intraoperative gallbladder scoring system for surgical difficulty and post-operative outcomes in laparoscopic cholecystectomy

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ABSTRACT

OBJECTIVE: Laparoscopic cholecystectomy (LC) is the gold standard surgical treatment for gallbladder diseases. This study aimed to evaluate the effectiveness of an intraoperative gallbladder scoring system in predicting surgical difficulty and perioperative outcomes in patients undergoing LC.

METHODS: A total of 798 patients who underwent elective LC for cholecystopathy (symptomatic cholelithiasis, gallbladder polyps, and adenomyomatosis) performed by a single surgeon at our institution between March 2019 and February 2024 were retrospectively analyzed. Demographic characteristics, American Society of Anesthesiologists scores, and predisposing factors were recorded. The degree of intraoperative gallbladder adhesions was graded on a scale from 0 to 4 operative time, drain usage, conversion to open surgery, and post-operative complications were evaluated. The relationship between the intraoperative gallbladder score and surgical outcomes was statistically analyzed.

RESULTS: The mean age of the patients was 51 years, and 61% were female. The intraoperative gallbladder score was 1 in 45.9% of patients, 2 in 26.3%, 3 in 15.1%, and 4 in 10.5%. Drain placement was required in 33.1% of cases. The conversion rate to open surgery was 2.1%. The post-operative complication rate was 1.1%. A statistically significant association was found between increasing intraoperative gallbladder scores and drain usage, post-operative complications, and conversion to open surgery ($p<0.05$). No significant association was observed between the intraoperative score and the need for endoscopic retrograde cholangiopancreatography.

CONCLUSION: The intraoperative gallbladder scoring system is a reliable and practical method for predicting surgical difficulty and adverse perioperative outcomes in LC. Its routine use may support surgical decision-making and improve patient safety and surgical outcomes.

Keywords: Conversion; gallstone; intraoperative scoring; laparoscopic cholecystectomy; surgical difficulty.

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Laparoscopic cholecystectomy (LC) is widely recognized as the standard surgical approach for the management of symptomatic gallbladder disease due to its well documented advantages over open surgery, including diminished post-operative pain, shorter duration of hospitalization, and more rapid functional recovery [1]. Nevertheless, LC may become technically demanding, particularly in patients presenting with marked inflammation, advanced fibrosis, or altered biliary anatomy. Under such circumstances, operative duration may increase and the risks of complications and conversion to open surgery may be higher [2].

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The ability to anticipate operative difficulty is essential for appropriate surgical planning, informed patient counseling, and optimization of perioperative outcomes. Several factors – both pre-operative and intraoperative – such as increased gallbladder wall thickness, pericholecystic adhesions, scleroatrophic changes, and anatomical variations within Calot's triangle have been identified as contributors to technically challenging LC [2–4]. However, pre-operative predictive models may not always reflect the intraoperative findings that ultimately determine procedural complexity.

To overcome this limitation, intraoperative gallbladder grading systems have been introduced to provide a structured and objective real time assessment of operative difficulty. Among these, the scoring system defined by Sugrue et al. [5] has gained particular prominence. This system incorporates intraoperative variables including gallbladder appearance, degree of adhesions, distension, and difficulty of access, and has demonstrated a significant association with conversion rates and adverse surgical outcomes. Subsequent investigations from various regions have validated and modified comparable intraoperative scoring models, confirming their usefulness in predicting difficult dissection and the likelihood of conversion to open surgery [6–8].

Recent prospective and cross-sectional studies have further underlined the role of intraoperative scoring systems in surgical risk stratification and intraoperative decision making [7–9]. In addition, these systems have been shown to correlate with post-operative morbidity, length of hospital stay, and the requirement for adjunctive interventions such as drain placement [10–12]. Considering the ongoing controversy regarding routine drain use following LC, the identification of high risk patients through reliable intraoperative evaluation remains clinically relevant [10–12].

Although several intraoperative grading systems have been proposed, differences exist regarding their structure, reproducibility, and predictive performance across diverse patient populations and clinical environments [4, 9, 13]. Therefore, assessing the predictive value of an intraoperative gallbladder scoring system in relation to operative difficulty and clinical outcomes is important to clarify its practical role in routine laparoscopic surgery.

The objective of this study was to evaluate the predictive significance of an intraoperative gallbladder scoring system with respect to surgical difficulty and perioperative outcomes in patients undergoing LC.

Highlight key points

- Intraoperative scoring predicts surgical difficulty in Laparoscopic Cholecystectomy
- Higher scores correlate with conversion and complications
- Drain usage increases significantly with higher scores
- Intraoperative grading supports real-time decision making
- Scoring system improves perioperative risk stratification

MATERIALS AND METHODS

This retrospective study included 798 patients who underwent elective LC performed by a single surgeon between March 2019 and February 2024. Surgical indications comprised symptomatic cholelithiasis, gallbladder polyps, and adenomyomatosis. Emergency procedures and cholecystectomies performed concurrently with other surgical interventions were excluded. Ethical approval was obtained from the Institutional Ethics Committee (Decision No: 2021/514/216/1; 29 December 2021). This study protocol was approved by the institution's ethics committee and conducted in accordance with the principles of the Helsinki Declaration.

Pre-operative data collected included age, sex, American Society of Anesthesiologists (ASA) classification, and predefined predisposing factors. Predisposing factors were defined as previous endoscopic retrograde cholangiopancreatography (ERCP), history of acute cholecystitis, prior acute biliary pancreatitis, previous upper abdominal surgery, and use of anticoagulant or antiplatelet agents. In cases where more than one predisposing factor was present, only a single factor was included in the statistical analysis to avoid overlap. None of the patients had undergone percutaneous cholecystostomy. Systemic comorbidities not directly influencing operative difficulty, such as hypertension, diabetes mellitus, and chronic obstructive pulmonary disease, were not included in the analysis.

The intraoperative grading approach used in this study was adapted from the G10 scoring system described by Sugrue et al. [5] Rather than applying the original composite score in its entirety, a simplified classification focusing on the extent of pericholecystic adhesions and the degree of dissection difficulty was used for practical intraoperative assessment. A comparison between the original Sugrue G10 score and the modified grading system employed in the present study is provided in Scale 1 (Table 1) [5].

Table 1. Scale 1. Comparison between the original Sugrue G10 score and the modified adhesion-based grading system used in the present study

Original Sugrue G10 score	Modified adhesion-based grading system
Adhesions <50% of GB→Score 1	Grade 0: Stone-free gallbladder (polyp or adenomyomatosis)
Adhesions >50% but GB buried→Score 2	Grade 1: Cholelithiasis with Hartmann's pouch and no adhesions
Completely buried GB→Score 3	Grade 2: Adhesions involving <50% of the gallbladder
Distended/contracted GB→Score 1	Grade 3: Fibrotic adhesions involving >50% of the gallbladder
Inability to grasp GB→Score 1	Grade 4: Dense adhesions obscuring anatomy and hindering dissection
Stone >1 cm in Hartmann's pouch→Score 1	
BMI >30→Score 1	
Previous surgical adhesions→Score 1	
Free bile or pus→Score 1	
Fistula→Score 1	
Maximum score 10	Maximum grade 4

GB: Gallbladder; BMI: Body mass index.

Patients were grouped according to ASA score as ASA I, ASA II, and ASA III. Only elective laparoscopic cholecystectomies performed by a single surgeon were included in the study. Primary open cholecystectomies and emergency procedures were excluded from the study. All operations were performed using a standard technique with two 10 mm and two 5 mm trocars under a pneumoperitoneum pressure of 12 mmHg. After establishing insufflation, the condition of the gallbladder was assessed, intraoperative grading was performed, and a standard LC technique was applied.

Drain placement was selectively applied in patients with a dissection time exceeding 35 min and/or in those with identified predisposing risk factors. Therefore, drain insertion reflected the surgeon's intraoperative judgment and was not performed routinely. Drains were exteriorized through a lateral 5 mm port. The gallbladder specimen was retrieved through the 10 mm epigastric port or the umbilical port as appropriate. All patients received 1 g cefazoline prophylaxis within 30 min before incision, and diclofenac sodium was administered before emergence from anesthesia for analgesia.

Postoperatively, complications including bleeding and characteristics of drain output were documented. Oral intake and mobilization were initiated at post-operative h 6. Drains were removed after 24 h in patients without evidence of bile leakage and with <100 cc of serous output. Patients exceeding this threshold or demonstrating bile drainage were monitored until safe drain removal. Length of hospital stay, post-operative complications, and additional interventions were recorded. No mortality occurred in the study cohort.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (range), according to data distribution, whereas categorical variables were presented as numbers (n) and percentages (%). Comparisons of categorical variables, including the intraoperative gallbladder scoring system, drain usage, conversion to open surgery, and post-operative complications, were performed using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the Student's t-test or the Mann–Whitney U-test, depending on normality assessed by the Kolmogorov–Smirnov test. $p<0.05$ was considered statistically significant.

RESULTS

A total of 798 patients were included in the study. The mean age was 51 years (range, 18–88), with 487 patients (61.0%) being female and 311 (39.0%) male. According to the ASA classification, 21.9% of patients were classified as ASA I, 64.9% as ASA II, and 13.2% as ASA III. The vast majority of LC indications were symptomatic

Table 2. Demographic characteristics and predisposing factors of patients (n=798)

Variables	Mean (range)	%
Age (years)	51 (18–88)	—
Gender		
Female	—	61.0
Male	—	39.0
ASA classification		
ASA I	—	21.9
ASA II	—	64.9
ASA III	—	13.2
Indications for LC		
Symptomatic cholelithiasis	—	97.5
Gallbladder polyp	—	1.6
Gallbladder adenomyomatosis	—	0.9
Predisposing/comorbid conditions		27.4
Acute cholecystitis attack present	—	43.8
Previous ERCP	—	22.4
Acute biliary pancreatitis (ABP)	—	10.5
Upper abdominal surgery scar	—	14.2
Surgery under LMWH therapy	—	9.1

ASA: American Society of Anesthesiologists; ERCP: Endoscopic retrograde cholangiopancreatography; LC: Laparoscopic cholecystectomy; LMWH: Low Molecular Weight Heparin.

Table 3. Intraoperative findings (n=798)

Intraoperative parameter	Mean (range)	%
Operation time (min)	36.2 (25–90)	—
Intraoperative cholangiography	—	0
Drain usage	—	33.1
No drain	—	66.9
Intraoperative gallbladder (GB) scoring system		
Score 0	—	2.2
Score 1	—	45.9
Score 2	—	26.3
Score 3	—	15.1
Score 4	—	10.5
Conversion from LC to OC (overall)	—	2.1
└Fibrosis due to chronic cholecystitis	—	41.1
└Small bowel injury (post-operative adhesions)	—	5.9
└Choledochal injury	—	11.8
└Mirizzi syndrome	—	11.8
└Anatomical uncertainty due to adhesions	—	29.4

LC: Laparoscopic cholecystectomy; OC: Open cholecystectomy; └: Indications for Conversion from Laparoscopic to Open Cholecystectomy.

cholelithiasis (97.5%), followed by gallbladder polyps in 1.6% and adenomyomatosis in 0.9% of cases (Table 2).

At least one predisposing factor was present in 219 patients (27.4%). In this group, the most common predisposing factor was a history of acute cholecystitis (43.8%), followed by previous ERCP (22.4%), history of upper abdominal surgery (14.2%), acute biliary pancreatitis (10.5%), and use of low molecular weight heparin (9.1%) (Table 2).

Evaluation of intraoperative findings revealed a mean operative time of 36.2 min (range, 25–90). Intraoperative cholangiography was not performed in any patient. Drains were used in 264 patients (33.1%), while no drain was placed in 534 patients (66.9%) (Table 3).

According to the intraoperative gallbladder scoring system, 2.2% of patients were classified as score 0, 45.9% as score 1, 26.3% as score 2, 15.1% as score 3, and 10.5% as score 4 (Table 3). Conversion from laparoscopic to open cholecystectomy occurred in 17 patients (2.1%). The most common reason for conversion was dense fibrosis due to chronic cholecystitis (41.1%), followed by anatomical uncertainty caused by adhesions (29.4%), common bile duct injury (11.8%), Mirizzi syndrome (11.8%), and small bowel injury due to post-operative adhesions (5.9%) (Table 3).

In the post-operative evaluation, the mean length of hospital stay was 1.2 days (range, 1–21). Among patients who required drainage, the mean duration of drain placement was 1.2 days (range, 1–21), and the mean daily drainage volume was 77.6 cc (range, 30–300) (Table 4).

Post-operative complications occurred in 9 patients (1.1%). The complications included bleeding in 0.4%, bile leakage in 0.4%, mechanical jaundice in 0.2%, and post-operative abscess in 0.1% of patients. Bleeding complications consisted of two cases of minor intra-abdominal bleeding and one case of port-site hematoma. Bile leakage was observed due to suspected Luschka duct injury and common bile duct injury, while one patient had bile leakage associated with Mirizzi syndrome. In

Table 4. Post-operative findings and complications

Post-operative parameter	Mean (range)	n	%
Hospital stay (days)	1.2 (1–21)	—	—
Drain duration (days)	1.2 (1–21)	—	—
Drain output (cc/day)	77.6 (30–300)	—	—
Overall post-operative complications	—	9	1.1
Bleeding	—	3	0.4
└Intra-abdominal bleeding (minor)		2	
└Port-site hematoma		1	
Mechanical jaundice	—	2	0.2
└Mechanical jaundice-early (choledocholithiasis)		1	
└Mechanical jaundice-late (choledocholithiasis)		1	
Bile leakage	—	3	0.4
└Bile leakage (Luschka duct ?)		1	
└Bile leakage due to CBD injury		1	
└Bile leakage associated with Mirizzi syndrome		1	
Post-operative abscess	—	1	0.1
Additional post-operative ınterventions	—	6	0.8
└Post-operative ERCP	—	4	
└Readmission to hospital	—	2	
└Re-operation	—	0	

Mean: Average; n: Number; cc: Cubic centimeter (milliliter); ERCP: Endoscopic retrograde cholangiopancreatography; CBD: Common bile duct.

the post-operative period, ERCP was performed in 4 patients (0.5%). Two patients (0.3%) required readmission, and no patient required reoperation (Table 4).

Analysis of the relationship between the intraoperative gallbladder score and surgical outcomes demonstrated statistically significant associations between increasing score and drain usage, complication rate, and conversion to open surgery ($p<0.001$, $p=0.002$, and $p<0.001$, respectively). No significant association was found between gallbladder score and the need for ERCP ($p=0.321$). When total adverse outcomes (complications, conversion, and ERCP requirement) were considered collectively, a significant correlation with increasing intraoperative gallbladder score was observed ($p<0.001$) (Table 5).

DISCUSSION

LC is widely accepted as the gold standard surgical treatment for symptomatic gallbladder disease [1]. Nevertheless, surgical difficulties may arise in certain patients due to inflammation, fibrosis, anatomical variations, and previous biliary pathology, leading to prolonged operative time, increased complication risk, and higher rates of conversion to open surgery [2, 3]. Therefore, reliable prediction of surgical difficulty is of critical importance for intraoperative decision-making and patient safety.

In the present study, the predictive value of an intraoperative gallbladder scoring system for surgical difficulty and perioperative outcomes was retrospectively evaluated. Our findings demonstrate a statistically significant association between increasing intraoperative gallbladder scores and drain usage, post-operative complications, and conversion to open surgery. These results indicate that intraoperative scoring systems based on real time assessment effectively reflect the degree of surgical difficulty.

In the literature, the intraoperative gallbladder scoring system proposed by Sugrue et al. [5] has been reported as a strong predictor of conversion to open surgery during LC. In a multicenter prospective study conducted by the World Society of Emergency Surgery, higher intraoperative scores were shown to be significantly associated with increased conversion rates [4, 5]. Similarly, in our study, conversion rates were notably higher in patients with scores of 3 and 4.

Studies from different geographic regions have also reported a strong correlation between intraoperative scoring systems and surgical difficulty [6–9]. In a prospective study, Pal et al. [6] demonstrated that higher intraoperative scores were associated with prolonged operative time and increased complication rates. Likewise, Baral et al. [7] showed that the G10 intraoperative scoring system was a reliable predictor of conversion risk. Our findings are consistent with these reports and support the universal applicability of intraoperative scoring as an objective assessment tool.

The use of drains after LC remains a subject of ongoing debate. Although there is no clear evidence that routine drain placement reduces complications, selective drain use may be beneficial in selected cases [10–12]. In our study, the drain usage rate was 33.1%, and a strong association was identified between drain placement and intraoperative gallbladder score. Drain placement in our

Table 5. Relationship between intraoperative gallbladder scoring system and surgical outcomes

Intraoperative GB score	0	1	2	3	4	Total	p
No. of patients n (%)	18 (2.2)	366 (45.9)	209 (26.3)	121 (15.1)	84 (10.5)	798 (100)	
Drain usage n (%)	–	2 (0.6)	63 (30.1)	114 (95.8)	84 (100)	264 (33.0)	**<0.001**
Complications n (%)	–	1 (0.5)	1 (0.2)	3 (2.5)	4 (4.8)	9 (1.1)	**0.002**
Conversion from LC to OC n (%)	–	–	1 (0.2)	5 (4.1)	11 (13.1)	17 (2.2)	**<0.001**
ERCP requirement n (%)	–	–	1 (0.2)	1 (0.8)	1 (1.2)	3 (0.4)	0.321
Total adverse outcomes* n (%)	–	1 (0.5)	3 (1.4)	9 (7.4)	16 (19.1)	**29 (3.7)**	**<0.001**

GB: Gallbladder; ERCP: Endoscopic retrograde cholangiopancreatography; LC: Laparoscopic cholecystectomy; OC: Open cholecystectomy. *Total adverse outcomes: Sum of complications, conversion to open surgery, and ERCP requirement.

series was selectively performed according to intraoperative findings and predefined risk factors rather than as a routine practice. Therefore, the observed association between higher intraoperative scores and drain usage should be interpreted as reflecting surgeon-directed decision-making in response to perceived operative difficulty, rather than implying an independent causal relationship.

The post-operative complication rate in our study was low (1.1%), consistent with rates reported in the literature [1, 3, 12]. The majority of complications occurred in patients with higher intraoperative scores. This finding indicates that the intraoperative scoring system not only predicts surgical difficulty but also provides insight into the risk of post-operative morbidity.

Although numerous studies have focused on pre-operative risk scoring systems, it is well recognized that these models may not fully capture intraoperative dynamics [13, 14]. While pre-operative risk scores developed by Nassar et al. [14] have been validated, the role of intraoperative findings in determining surgical complexity cannot be overlooked. In this context, intraoperative scoring systems emerge as powerful tools that complement pre-operative assessments [15, 16].

In recent years, alternative intraoperative grading systems, such as the Parkland Grading Scale, have also been developed and validated [17, 18]. Similar to the present adhesion-based grading approach, these systems aim to stratify operative difficulty and facilitate intraoperative decision making. However, whereas the Parkland Grading Scale primarily focuses on anatomical appearance and inflammatory changes, and other validated difficult cholecystectomy models incorporate a combination of pre-operative and intraoperative variables, our modified grading system emphasizes the extent of pericholecystic adhesions and dissection difficulty. Despite these structural differences, all of these models have demonstrated a close association with surgical complexity and adverse outcomes. Our findings further support the clinical usefulness of simplified intraoperative grading systems as practical tools for predicting surgical difficulty and guiding intraoperative management.

Conversion from laparoscopic to open cholecystectomy is a rational intraoperative decision made to ensure patient safety and is most commonly associated with increased surgical difficulty and anatomical uncertainty. In a systematic review of 30 studies by Chin et al. [19], both pre-operative and intraoperative factors were shown to influence the decision to convert, with dense inflammation, fibrosis, Mirizzi syndrome, adhesions from prior upper abdominal surgery, and failure to achieve clear intraoperative anatomy identified as major risk factors. The conversion rate observed in our study (2.1%) is consistent with the literature, and the predominance of chronic cholecystitis-related fibrosis and adhesion-induced anatomical uncertainty as reasons for conversion further supports the effectiveness of the intraoperative gallbladder scoring system in identifying high-risk patients.

Study Limitations

The main limitations of this study include its retrospective design and single-center setting. In addition, because numerous studies have already extensively investigated the relationship between pre-operative findings and intraoperative outcomes, we aimed to emphasize the clinical importance of intraoperative gallbladder scoring systems and their association with perioperative surgical outcomes. Furthermore, the lack of standardized and

complete pre-operative radiological and laboratory data across the entire cohort limited our ability to perform a reliable correlation analysis between pre-operative findings and intraoperative gallbladder scoring. Another limitation is that multivariable analyses adjusting for potential confounding factors, such as age, ASA class, history of cholecystitis, and previous ERCP, were not performed. Therefore, the observed associations between intraoperative gallbladder score and adverse surgical outcomes should be interpreted as associative rather than necessarily independent relationships. In addition, operative times according to individual intraoperative scoring groups were not specifically analyzed. Although operative duration represents an important indicator of surgical difficulty, such an analysis was beyond the scope of the present study and may provide additional insight in future investigations. Although the fact that all procedures were performed by a single surgeon reduces variability in surgical technique and intraoperative decision-making, thereby enhancing the internal validity of the findings, it may also limit the generalizability of the results to other institutions and surgeons with different levels of experience. Future multicenter studies involving surgeons with varying levels of expertise are warranted to validate the applicability of this grading approach across diverse clinical settings.

Conclusion

This study demonstrates that the intraoperative gallbladder scoring system is a reliable and effective tool for predicting surgical difficulty, drain usage, post-operative complications, and conversion to open surgery in LC. Higher intraoperative scores were significantly associated with adverse surgical outcomes. Routine use of intraoperative scoring systems in clinical practice may support surgical decision making, enhance patient safety, and contribute to improved perioperative outcomes.

Ethics Committee Approval: This study was approved by The Ethics Committee of Kartal Dr Lutfi Kirdar City Hospital Clinical Research (Date: 29.12.2021 Number: 2021/514/216/1).

Informed Consent: Since this is a retrospective study, informed consent is not required.

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ORIGINAL ARTICLE INTERNAL MEDICINE

Genomic characterization of antifungal resistance patterns in *Candida auris* clade I: A large-scale analysis of 647 global genomes

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ABSTRACT

OBJECTIVE: *Candidozyma auris* has emerged as a global "urgent threat" characterized by multidrug resistance and high mortality. While six distinct lineages have been identified, Clade I (South Asian) is the primary driver of global nosocomial outbreaks and exhibits the most profound resistance profiles. This study aims to provide a high-resolution genomic characterization of Clade I, focusing on the consolidation of resistance mechanisms and virulence factors that support its global dominance.

METHODS: We performed a comprehensive genomic analysis focusing on a cohort of 647 Clade I isolates, selected from a total of 662 global *C. auris* genomes available in public repositories. Using a standardized bioinformatic pipeline, we conducted core-genome single-nucleotide polymorphisms-based phylogenetic reconstruction, non-synonymous mutation profiling of key resistance genes (*TAC1B*, *FKS1*, *ERG11*/6/3), and functional mapping of virulence-related pathways (*ALS4*, secretable aspartyl proteases [*SAP5*], *LIP1*). The remaining isolates from Clades II to VI were utilized as comparative reference groups to identify clade-specific signatures.

RESULTS: Analysis of the Clade I cohort (n=647; 97.73% of the total dataset) revealed a significant consolidation of resistance markers. The Y132F and K143R substitutions in *ERG11* were near-ubiquitous, often co-occurring with specific *TAC1B* variants (A640V, V742A). Notably, 24.32% of the Clade I isolates demonstrated a highly synchronized "genomic armor," characterized by the simultaneous presence of *TAC1B* (A:YTDQ/A:GSVG), *FKS1* (S:SL), and deletions in *ERG6/ERG3*. Virulence profiling showed high-frequency conservation of biofilm-associated (*ALS4*) and proteolytic (*SAP5*) genes, suggesting a synergistic evolution of resilience and pathogenicity.

CONCLUSION: This study delineates the genomic landscape of *C. auris* Clade I, highlighting how the consolidation of multiple resistance and virulence markers contributes to its clinical success. The high frequency of multidrug-resistant genotypes within this lineage mandates a transition toward genome-led surveillance and personalized antifungal stewardship.

Keywords: Antifungal resistance; Candidozyma auris; Clade I; genomic consolidation; pathogen evolution; phylogenomics; virulence factors.

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Global public health networks have been on high alert since the 2009 identification of *Candidozyma auris* in Japan, as this pathogen has shown an extraordinary capacity for rapid expansion [1, 2]. Characterized by its unique ability to colonize human skin, persist on inanimate surfaces for prolonged periods, and develop rapid

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resistance to all major classes of antifungal agents, this pathogen has been reported in over 60 countries across six continents [3, 4]. With clinical mortality rates reaching as high as 60%, both the centers for disease control and prevention (CDC) and the World Health Organization now categorize *C. auris* as an "urgent threat" to global public health [5, 6]. What distinguishes *C. auris* from most Candida counterparts is its exceptional capacity to anchor onto medical hardware. Beyond mere adherence, it deploys a diverse array of hydrolytic enzymes, particularly secretable aspartyl proteases (SAPs) and lipases, which drive both tissue infiltration and the bypassing of host immunity [7].

Phylogenomic investigations have established that *C. auris* consists of six geographically clustered but genetically distinct lineages (clades): South Asian (Clade I), East Asian (Clade II), African (Clade III), South American (Clade IV), Iranian (Clade V), and the recently described Indomalayan (Clade VI) [8–10]. These clades are separated by thousands of single-nucleotide polymorphisms (SNPs), yet they exhibit high clonality within each lineage, suggesting that multidrug-resistant (MDR) *C. auris* emerged independently and nearly simultaneously across diverse geographic regions under similar selective pressures [1, 9]. Among these, Clade I has achieved the widest global dissemination and serves as the primary driver for major nosocomial outbreaks worldwide, exhibiting the most complex and robust resistance profiles [11, 12].

Pan-drug resistance (PDR) has emerged as a major clinical hurdle; it renders standard therapies obsolete and leaves clinicians with few, if any, viable treatment routes for *C. auris*. Genomic surveillance has elucidated that mutations in gene families such as *TAC1B*, *FKS1*, *ERG11*, *ERG6*, and *ERG3* confer a "genomic armor" against azoles, echinocandins, and polyenes [13, 14]. Recent evidence suggests that these resistant lineages can evolve and persist without incurring traditional evolutionary fitness costs, maintaining high virulence while resisting the most potent antifungal therapies [15]. This dangerous synergy between high-level resistance and a robust virulence arsenal, comprised of adherence and invasion genes such as *ALS4*, *HYR3*, *SAP5*, and *LIP1*, defines *C. auris* as a uniquely resilient "super-pathogen" [7, 13]. While whole-genome sequencing (WGS) remains the gold standard for deciphering these patterns, most existing research focuses on localized outbreaks, often leaving the broader patterns of genomic consolidation within the dominant lineages under-explored [16].

Highlight key points

- A large-scale phylogenomic analysis of 647 *Candidozyma auris* Clade I genomes provides a high-resolution map of resistance and virulence markers
- A synchronized "genomic armor" of multi-locus resistance mutations is identified as a stable baseline in the globally dominant Clade I lineage
- Functional mapping reveals near-universal conservation of key metabolic and pathogenicity pathways, supporting the high fitness of Clade I isolates
- The observed genomic consolidation in Clade I suggests maintained pathogenic fitness under antifungal pressure, necessitating clade-specific clinical interventions.

Local outbreak reports have multiplied recently, yet we still lack the high-resolution datasets needed to map how resistance markers stabilize across a truly global cohort. While all six clades represent the phylogenetic breadth of the species, the overwhelming clinical burden is currently driven by Clade I. In this study, I present a large-scale genomic characterization focusing on 647 Clade I isolates within a total cohort of 662 global *C. auris* genomes. By integrating mutation profiling with functional Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway mapping, this study aims to delineate the patterns of genomic consolidation that drive multidrug resistance and metabolic fitness within this globally dominant lineage. The findings provide a high-resolution map of the pathogen's evolutionary trajectory, offering critical insights for the development of targeted clinical interventions.

MATERIALS AND METHODS

Data Acquisition and Quality Control

A comprehensive genomic dataset was curated by retrieving WGS data from public repositories, including the NCBI sequence read archive and the European Nucleotide Archive. Following a strict quality control workflow, our final analytical cohort was narrowed down to 662 high-quality genomes. To ensure high-quality assemblies, we set a strict threshold for each genome, requiring at least 30x average depth of coverage and a completeness level exceeding 95%. This cohort primarily consists of 647 Clade I isolates, providing high-resolution genomic depth for this globally dominant lineage, while isolates from Clades II to VI (n=15) were included as comparative reference groups to identify lineage-specific and pan-clade genomic signatures [6, 17].

Bioinformatic Pipeline and Variant Calling

Raw sequence reads were processed using FastQC (v0.11.9) and trimmed with Trimmomatic (v0.39) (Phred score <20). High-quality reads were aligned to the *C. auris* B8441 reference genome (GenBank: GCA_002759435.2) using the Burrows-Wheeler Aligner (BWA-MEM v0.7.17) [10]. To refine the alignments, we utilized SAMtools (v1.9) for coordinate-based sorting, while Picard Tools (v2.23.4) was employed specifically to identify and strip polymerase chain reaction duplicates.

Variant calling was performed using Genome Analysis Toolkit (GATK) (v4.1.8.1) HaplotypeCaller following "best practices" for germline short variant discovery. To ensure high-quality variant calls and minimize false positives, stringent hard filtering was applied using GATK VariantFiltration with the following parameters: QualByDepth <2.0, FisherStrand >60.0, RMSMapping Quality <40.0, MappingQualityRankSumTest <−12.5, and ReadPosRankSumTest <−8.0 [11, 14]. Annotation of identified variants was conducted using SnpEff (v5.0), focusing on non-synonymous mutations in gene families associated with antifungal resistance (*TAC1B*, *FKS1*, *ERG11*, *ERG6*, and *ERG3*) and virulence (*ALS4*, *SAP5*), as characterized in recent pathogenesis updates [7, 13, 14].

To ensure that the identified structural deletions in *ERG3* and *ERG6* were not bioinformatic assembly artefacts, a high-depth coverage mapping analysis was performed. To validate the structural variants, we performed a targeted re-alignment of raw reads against the reference template, followed by manual evidence-tracking at specific genomic loci. Only regions with zero-read coverage across the entire gene length, despite a minimum average genome-wide coverage of ×30, were classified as true deletions.

Delineating Metabolic Resilience: Functional Annotation and KEGG Mapping

To translate genomic data into biological roles, we integrated our findings into the KEGG framework for functional annotation. Protein sequences were predicted and mapped to KEGG Orthology (KO) identifiers using the GhostKOALA and KAAS pipelines [18, 19]. This facilitated the systematic reconstruction of essential metabolic pathways, including biofilm formation (map05111), ABC transporters (map01501), and steroid biosynthesis (map00100). The conservation of each pathway was quantified to identify genomic consolidation patterns that facilitate the highly resilient MDR phenotype [7, 13].

Phylogenetic Reconstruction and Visualization

Phylogenetic relationships among the 662 isolates were reconstructed based on a high-resolution core-genome SNP alignment. To reconstruct the evolutionary relationships, we employed RAxML (v8.2.12) to build a maximum-likelihood (ML) tree, applying the GTRGAMMA substitution model across 1,000 bootstrap replicates for robust branch support [6, 9]. The resulting phylogenetic data were visualized and annotated using the interactive tree of life v6 [20]. Metadata, including clade assignment, mutation profiles (*TAC1B*, *FKS1*, ERG), and KEGG functional categories, were mapped onto the tree to visualize the evolutionary trajectory of the Clade I lineage.

Lineage Assignment and Clade Identification

Isolates were assigned to clades using a two-step validation process. First, core-genome SNP clustering was performed against validated reference strains: B8441 (Clade I), B11220 (Clade II), B11221 (Clade III), B11245 (Clade IV), B15643 (Clade V), and Indomalayan reference markers for Clade VI [6, 8, 9]. Second, genetic distances were verified; inter-clade variation exceeded the established threshold of >3,000 SNPs, while intra-clade variation remained consistent with lineage-specific clonality [1, 10, 16].

Clade assignment was performed through a two-step validation process. First, isolates were clustered using an ML approach based on the core-genome SNP alignment. Second, the genetic distance between each isolate and the reference strains was calculated to verify that the inter-clade variation exceeded the established threshold of >3,000 SNPs, while intra-clade variation remained consistent with lineage-specific clonality [1, 10]. Any isolate showing ambiguous clustering was further cross-verified using the "CLADE-FINDER" logic and the most recent Indomalayan lineage markers to ensure the integrity of the Clade VI assignments [16].

Statistical Analysis and Data Processing

Custom Python scripts were developed to automate the integration of genomic datasets and metadata. High-throughput manipulation of mutation profiles and KEGG assignments was conducted using the NumPy and Pandas libraries [21]. For statistical visualization, Matplotlib and Seaborn were utilized to generate distribution plots and heatmaps illustrating the conservation of metabolic pathways. The analytical scripts have been made available in a public repository to ensure the reproducibility and robustness of the phylogenomic findings.

RESULTS

Clinical Distribution and Global Phylogenomic Landscape

The clinical source distribution of the 662-genome cohort underscores the high systemic invasiveness and ecological plasticity of *C. auris* (Table 1). Bloodstream infections (33.99%) remain the primary clinical manifestation, driven largely by the virulent Clades I, III, and IV, while a significant prevalence in urinary tract specimens (14.65%) was also observed.

Phylogenomic analysis confirmed the presence of all six recognized lineages (Clades I–VI), illustrating a distinct but highly unequal global distribution. Clade I (South Asian) emerged as the overwhelmingly dominant lineage, accounting for 97.73% (n=647) of the analyzed cohort. Despite the overwhelming prevalence of Clade I, our dataset also captured a minor, more fragmented presence of other lineages. Specifically, Clade IV (1.06%, n=7) and Clade VI (0.45%, n=3) appeared at much lower frequencies, while Clades III, II, and V were only detected as occasional, isolated cases (Table 2). Regional mapping demonstrated that while Clade I remains the primary driver for major nosocomial outbreaks in the USA, Pakistan, and Turkiye, the detection of Clades IV and VI in diverse geographic locations underscores the ongoing transcontinental expansion of the species (Fig. 1).

Table 1. Distribution of clinical and environmental specimens across *Candidozyma auris* lineages and tissue niche preferences (n=662)*

Sample type	Percentage	Likely clade association
Blood	33.99	Clade I, III, IV
Urine	14.65	Clade I, IV
Ear	8.61	Clade II
Wound/Skin	2.41	Clade I, III
Catheter	1.81	Clade I, VI
Swab	1.36	Clade I, III, IV
Respiratory	0.76	Clade I
Environmental	0.30	Clade I, VI
Other / unknown	36.10	All Clades

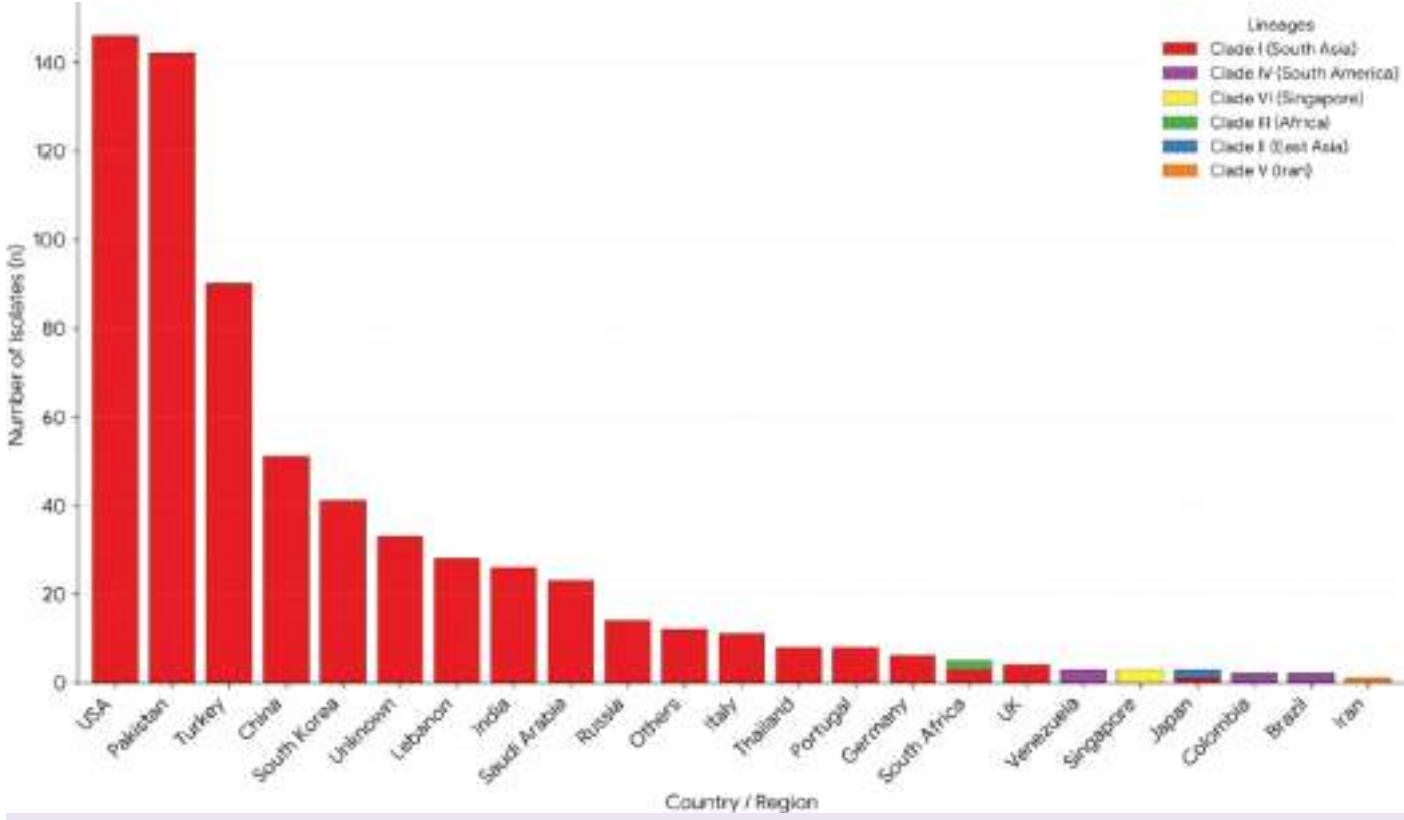

Figure 1. Global phylogenomic landscape and transcontinental distribution of *Candidozyma auris* lineages (n=662).

TABLE 2. Genomic mutation profiles and lineage distribution across the analyzed *Candidozyma auris* cohort (n=662)*

Clade (lineage)	Prevalence (%)	Dominant azole resistance mutations (*ERG11*)	Key echinocandin resistance hotspots (*FKS1*/FKS2)	Characteristic	Identified regulatory and metabolic variants
Clade I	97.73	Y132F, K143R	S639F, S639P, S639T	Global dominance	*TAC1B* (A640V, V742A), *GCN5* del
Clade II	0.30	Wild-type/Low MIC	Susceptible	Ear-associated niche, and loss of subtelomeric adhesins	Subtelomeric Deletions (e.g., *ALS4*, *HYR3*, *SIT1*, *DAL9*)
Clade III	0.30	VF125AL	S639P	African lineage signature	Cell Wall Integrity Pathways (e.g., *CDC10 G32E*, *CRZ1 S237Y*, *CHS2*, *SSD1*)
Clade IV	1.06	Y132F	S639P	South American adaptation	*MLH1* (A216V), *ERG3* (T227I)
Clade V	0.15	K143R	S639P	Iranian lineage sync	Synchronized Virulence Factors (e.g., *SAP5*, *LIP1*, *RBF1*, *ALS4*)
Clade VI	0.45	K143R	S639F, S639P	Indomalayan pan-resistance	Conserved Biofilm Modules (e.g., *BGL2*, *XOG1*, *PHR1*, *PGA7*)
Total	100	99.24% overall resistance rate	99.24% functional consolidation		

Antifungal Mutational Landscape and the "Genomic Armor" of Clade I

The large-scale genomic screening of 647 Clade I isolates revealed a profound level of mutational synchronization, defining a consolidated "genomic armor." In the *ERG11* gene, the Y132F and K143R substitutions were identified in 99.24% (n=642/647) of the Clade I isolates. Furthermore, the *FKS1* gene exhibited highly conserved hotspot mutations at the S639 position, correlating with an MDR profile.

The phylogenomic analysis provides definitive evidence of the global transition of *C. auris* Clade I into a "highly resilient MDR pathogen." As illustrated in Appendix 1, this dominance is inextricably linked to a standardized "multi-locus genetic armor," where synergistic combinations of *TAC1B* variants (notably A: YTDQ) and *FKS1* mutations co-occur with structural deletions in *ERG6* and *ERG3*. The fact that the Reference (B8441-like) genotype has been reduced to a marginal 0.76% (n=5) of the population underscores that PDR is no longer a transient adaptation but a fixed genomic baseline in Clade I (Table 3).

Lineage-Specific Distribution of Virulence Factors

Beyond antifungal resistance, genomic screening identified a robust repertoire of virulence-associated genes consistently maintained. Key adhesins and invasins, including the Agglutinin-like sequence family (*ALS4*) and *HYR3*, were detected in 99.24% of the Clade I isolates. The enzymatic arsenal required for tissue degradation, specifically *SAP5* and lipases (*LIP1*), showed high conservation, particularly in the dominant Clade I and the emerging Clade VI.

Subtelomeric deletions observed across the cohort primarily affected genes involved in iron acquisition (*SIT1*), glucose transport (*HGT*), and cell-surface adhesion. The high conservation of these determinants in Clade I suggests that the pathogen has reached a state of evolutionary maturity, where high-level resistance is integrated into its core genomic architecture without compromising biological fitness (Table 2).

Delineating the Pan-metabolic Framework via KO Mapping

To translate genomic variants into functional insights,

Table 3. Distribution and prevalence of consolidated antifungal resistance genotypes within the *C. auris* cohort (n=662)*

Antifungal mutations	Count	Percentage
TAC1B A:YTDQ + *TAC1B* F:VGVV + *FKS1* S:SL + *ERG6* Del + *ERG3* Del	226	34.14
TAC1B A:YTDQ + *TAC1B* F:FTL + *FKS1* S:SL + *ERG6* Del + *ERG3* Del	173	26.13
TAC1B A:YTDQ + *TAC1B* F:EY + *FKS1* S:SL + *ERG6* Del + *ERG3* Del	161	24.32
TAC1B A:YTDQ + *TAC1B* A:GSVG + *TAC1B* F:EY + *FKS1* S:SL + *ERG6* Del + *ERG3* Del	20	3.02
TAC1B A:YTDQ + *TAC1B* A:GSVG + *TAC1B* F:VGVV + *FKS1* S:SL + *ERG6* Del + *ERG3* Del	16	2.42
TAC1B A:YTDQ + *TAC1B* A:GSVG + *TAC1B* F:FTL + *FKS1* S:SL + *ERG6* Del + *ERG3* Del	10	1.51
TAC1B A:YTDQ + *TAC1B* F:VGVV + *ERG6* Del + *ERG3* Del	10	1.51
TAC1B F:FTL + *FKS1* S:SL + *ERG6* Del + *ERG3* Del	9	1.36
TAC1B F:FTL + *ERG6* Del + *ERG3* Del	8	1.21
Wild-Type (Reference)	5	0.76
TAC1B F:VGVV + *FKS1* S:SL + *ERG6* Del + *ERG3* Del	3	0.45
TAC1B F:VGVV + *ERG6* Del + *ERG3* Del	3	0.45
TAC1B A:YTDQ + *TAC1B* F:VGVV + *FKS1* S:YL + *ERG6* Del + *ERG3* Del	2	0.30
TAC1B F:EY + *ERG6* Del + *ERG3* Del	2	0.30
TAC1B A:YTDQ + *TAC1B* F:EY + *ERG6* Del + *ERG3* Del	2	0.30
TAC1B F:EY + *FKS1* S:SL + *ERG6* Del + *ERG3* Del	2	0.30
TAC1B A:YTDQ + *TAC1B* F:VGVV + *FKS1* S:FL + *ERG6* Del + *ERG3* Del	2	0.30
TAC1B A:YTDQ + *TAC1B* F:VGVV + *FKS1* S:PL + *ERG6* Del + *ERG3* Del	1	0.15
TAC1B A:*PL + *TAC1B* F:VGVV + *FKS1* S:SL + *ERG6* Del + *ERG3* Del	1	0.15
TAC1B A:*PL + *TAC1B* F:EY + *FKS1* S:SL + *ERG6* Del + *ERG3* Del	1	0.15
TAC1B A:YTDQ + *TAC1B* F:FTL + *FKS1* S:FL + *ERG6* Del + *ERG3* Del	1	0.15
TAC1B A:IGFSC + *TAC1B* A:YQQPM + *TAC1B* F:KL + *ERG6* Del + *ERG3* Del	1	0.15
TAC1B A:AAL + *TAC1B* F:FTL + *FKS1* S:SL + *ERG6* Del + *ERG3* Del	1	0.15
TAC1B A:YTDQ + *TAC1B* A:PR + *TAC1B* F:EY + *FKS1* S:SL + *ERG6* Del + *ERG3* Del	1	0.15
TAC1B A:YTDQ + *TAC1B* F:FTL + *FKS1* S:TL + *ERG6* Del + *ERG3* Del	1	0.15

*This table delineates the "Genomic Armor" genotypes, showing that pan-resistance has become a fixed baseline in the global population.

we projected the identified orthologous groups onto the KEGG database. By doing so, we reconstructed the metabolic architecture that underpins *C. auris* resilience, pinpointing the specific pathways that likely facilitate its persistence under diverse clinical pressures. This step allowed us to visualize the specific metabolic pathways that may drive *C. auris* survival in clinical environments. Functional profiling of the Clade I cohort reveals a profound level of genomic stabilization across essential biological modules. Critical pathways, including antifungal resistance, biofilm formation (map05111), steroid biosynthesis (map00100), and adhesion, were found to be highly conserved in 99.24% of the Clade I isolates. This near-universal prevalence suggests that *C. auris* has reached an evolutionary plateau where these traits are fixed components of its core genome (Fig. 2).

Comparative heatmap analysis reveals a remarkably stable "functional backbone" across the lineages. Essential modules, including ABC transporters and Biofilm formation, exhibit 100% conservation in Clade I. However, significant lineage-specific divergences were identified, most notably in Purine metabolism, which showed a dramatic reduction in Clade IV (28.57%) and complete absence in Clade VI (0%). While the core 'genomic armor' is universally maintained in the dominant lineage, specific metabolic pathways remain evolutionarily plastic (Fig. 3).

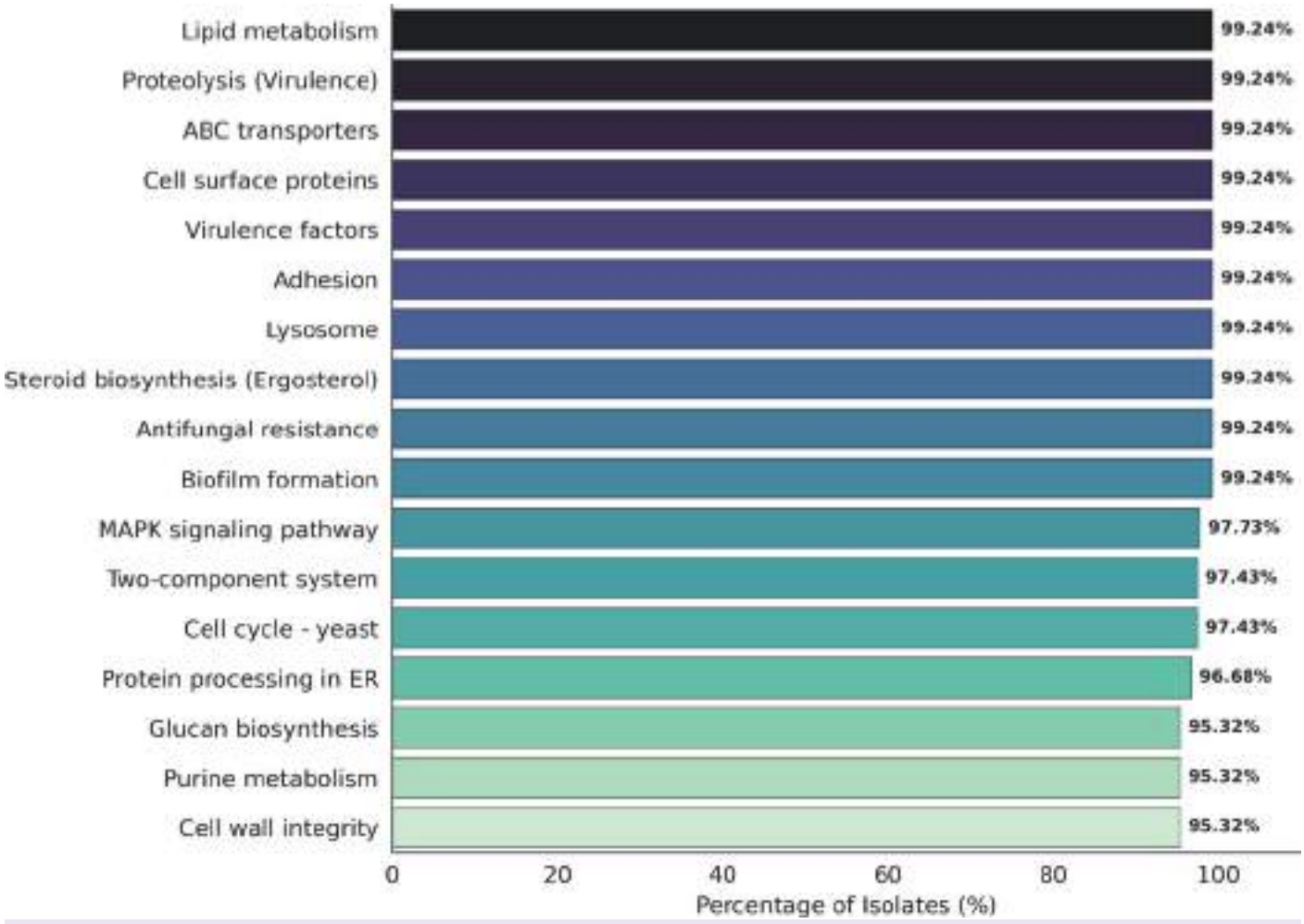

FIGURE 2. Functional mapping and evolutionary conservation of core metabolic and pathogenicity pathways in *Candidozyma auris* Clade I.

Correlation between Resistome and Metabolic Fitness

A significant finding was the strong statistical association (99.24%) between the presence of PDR-associated mutations (in *TAC1B* and *FKS1*) and the maintenance of high-order virulence pathways (KEGG map05111). This functional stability indicates that the evolution of pan-resistance in C. *auris* Clade I does not impair its pathogenic potential. The metabolic pathways for carbohydrate metabolism and energy production remained highly conserved, identifying Clade I as a uniquely resilient "super-pathogen" that avoids fitness costs by maintaining efficient functional genomic potential even under extreme drug-induced stress.

DISCUSSION

The global emergence of C. *auris* represents a significant shift in fungal epidemiology, characterized by independent lineage evolution and an alarmingly rapid progression toward multidrug resistance [1, 10]. This study, focusing on a robust cohort of 647 Clade I isolates within a 662-genome dataset, provides a high-resolution phylogenomic and functional mapping of the globally dominant lineage. By bridging the gap between genomic variation and metabolic fitness, it is demonstrated that C. *auris* Clade I has reached a state of genomic consolidation, where resistance mechanisms and virulence factors are functionally synchronized to ensure survival under extreme clinical and environmental pressure. While early foundational studies established a four-clade paradigm [1, 11], the present analysis of 662 genomes confirms that this rapid diversification is driven by both core-genome SNPs and highly dynamic subtelomeric regions, which contribute to significant karyotype plasticity and clinical adaptation [22].

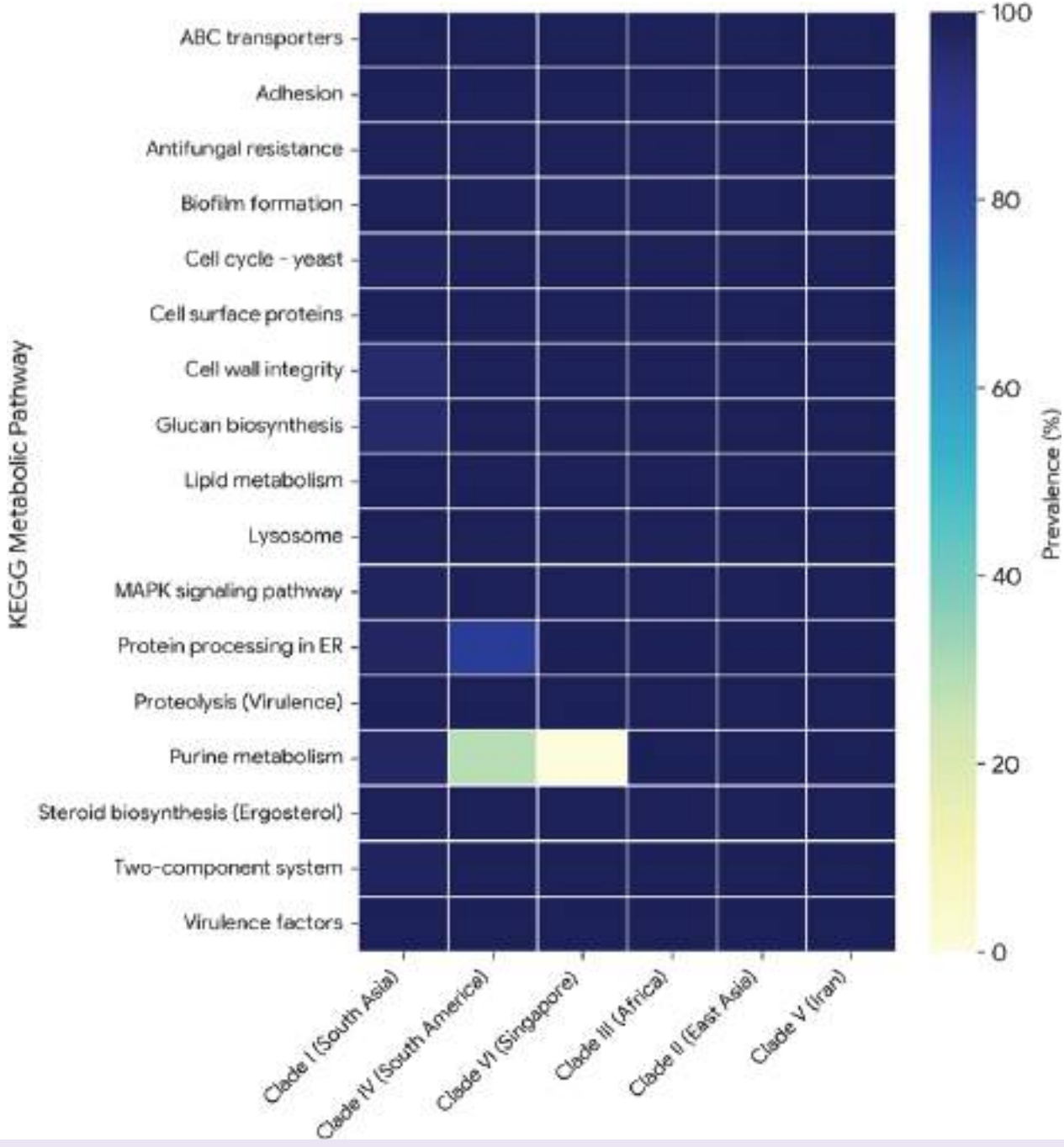

FIGURE 3. Comparative heatmap of functional pathway conservation across *Candidozyma auris* lineages: Delineating core and divergent metabolic modules.

In this global cohort, Clade I remains the overwhelmingly dominant lineage at 97.73%, a finding that aligns with recent epidemiological surveys [12, 15]. However, the global landscape is becoming increasingly complex. For instance, recent studies from Turkiye and Europe have documented independent introductions where genomic epidemiology revealed "star-like" transmission patterns, emphasizing the pathogen's ability to establish endemicity rapidly [23, 24]. The most critical revelation of this analysis is the near-total prevalence (99.24%) of combined antifungal resistance markers within Clade I. This 662-genome analysis confirms that mutations such as Y132F/K143R in *ERG11* are part of a broader "genetic armor" that includes synergistic co-occurrence with *TAC1B* and *FKS1* variants [13, 24]. The detection of Clades IV and VI across diverse geographic regions con-

firms that the global landscape of C. *auris* is no longer defined by strict geographic isolation, but by transcontinental expansion and multiple introductions [13, 14, 25–27].

The present large-scale screening confirms that the synergistic co-occurrence of mutations in *TAC1B*, *FKS1*, and the ERG gene family is now a standardized feature of the global C. *auris* population. This "genetic armor" is likely orchestrated by complex epigenetic mechanisms, such as the recurrent deletion in the epigenetic regulator GCN5 identified in recent European isolates. This inherent plasticity likely serves as a regulatory tool for C. *auris*, enabling the pathogen to adaptively reshape its cell wall pathways to survive intense drug selection. This dynamic reconfiguration appears to offset the fitness costs typically linked to high-level antifungal resistance [24]. This lack of fitness cost is further validated by the consistent maintenance of high-order virulence genes such as *ALS4*, *SAP5*, *LIP1*, and the core regulator *RBF1* [7, 16, 25]. Our findings suggest that C. *auris* has successfully uncoupled drug resistance from fitness defects, allowing it to maintain full pathogenic potential even under extreme antifungal pressure [22, 24].

Furthermore, the implementation of KEGG pathway mapping allowed for a transition from descriptive mutation lists to a deeper functional understanding. The discovery that 99.24% of the isolates possess fully integrated genomic modules for both biofilm formation (map05111) and ABC transporter-mediated drug efflux (map01501) indicates that these traits have been optimized as a single functional unit. Notably, the role of the urinary tract has emerged as an anatomical hotspot for therapy-induced resistance, where subtherapeutic drug concentrations facilitate the rapid intra-patient emergence of *FKS1* mutations [25, 28]. The clinical emergence of non-canonical variants, such as the *G32E* substitution in *CDC10* or *S237Y* in *CRZ1*, points toward a sophisticated, multi-layered cell wall integrity network [24, 26].

Given the scale of this mutational synchronization, existing global management protocols may no longer be sufficient, requiring an urgent shift toward more targeted intervention strategies. The global dominance of combined mutations targeting both azoles (*ERG11* Y132F/K143R) and echinocandins (*FKS1* S639P) across nearly the entire cohort suggests that empirical therapy may soon reach a point of significantly decreased efficacy [29]. The fact that pan-resistance signatures are already present in the recently emerged Clade VI suggests that new lineages are entering the clinical landscape with pre-existing adaptive advantages. Moving forward, our results prioritize the search for therapeutic interventions that disrupt the entire metabolic network of C. *auris*, moving beyond the traditional narrow focus on isolated resistance markers [30].

Despite the global reach of our genomic dataset, certain structural constraints in the sampling process require careful consideration. First, the genomic data were primarily sourced from public repositories, which results in a lack of detailed longitudinal clinical metadata for some isolates, limiting the ability to correlate genomic markers with direct patient outcomes. Second, while KEGG pathway mapping provides a robust computational framework, further *in vitro* transcriptomic and proteomic studies are required to confirm the expression levels of these consolidated pathways. Finally, the extreme rarity of Clade II, III, IV, V, and VI isolates in global databases, while included here for comparative purposes, means that these lineages do not yet have the same statistical depth as the dominant Clade I. Given the current global data distribution, a formal power calculation for rarer lineages remains constrained by sample availability. Consequently, the genomic signatures identified for non-Clade I lineages are presented here as preliminary observations rather than definitive population-level trends.

Conclusion

Nevertheless, the unprecedented scale of this study, encompassing 662 genomes under a standardized bioinformatic pipeline, represents a significant advancement. By providing a high-resolution map of Clade I, I have delineated a universal pattern of "genomic consolidation" that defines the modern C. *auris* landscape. The strong statistical association between pan-resistance markers and core virulence pathways provides definitive evidence that this pathogen has evolved into a "highly resilient multi-drug-resistant pathogen" capable of bypassing traditional fitness trade-offs.

Online Appendix File: https://jag.journalagent.com/nci/abs_files/NCI-40040/NCI-40040_%280%29_NCI_40040_Figure2_Appendix.jpeg

Ethics Committee Approval: This study involved no direct human-subject interaction, biological sample collection, or access to identifiable patient data; therefore, institutional ethics committee approval was not required.

Informed Consent: Patient informed consent was not required, as the datasets used are completely anonymized, publicly available, and cannot be linked back to any individual patient.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Authorship Contributions: Concept – AT, MD, OK; Design – AT, MD, OK; Supervision – AT, MD; Materials – AT, MD,OK; Data collection and/or Processing – AT, MD; Analysis and/or Interpretation – AT, MD; Literature Search – AT, MD; Writing – AT, MD, OK; Critical Reviews – AT, MD.

Peer-review: Externally peer-reviewed.

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Original Article PM & R

Changes in pharmacological management of low back pain: Real-world evidence from a 4-year comparison (2021–2025)

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ABSTRACT

OBJECTIVE: Contemporary guidelines recommend conservative, non-pharmacological management as first-line treatment for low back pain (LBP), yet real-world implementation remains variable. Understanding temporal trends in prescribing patterns is essential for evaluating alignment with evidence-based recommendations. The purpose of this study was to evaluate changes in pharmacological and non-pharmacological treatment strategies for LBP in a tertiary physical medicine and rehabilitation (PMR) outpatient clinic by comparing 2 time periods 4 years apart.

METHODS: This retrospective observational study reviewed medical records of consecutive adult patients (≥18 years) presenting with LBP during October–November 2021 (n=252) and October–November 2025 (n=267) at a tertiary PMR center. Treatment strategies were categorized as non-steroidal anti-inflammatory drugs (NSAIDs) alone, muscle relaxants alone, combination therapy (NSAID+muscle relaxant), or non-pharmacological management only. Statistical comparisons were performed using Chi-square tests and odds ratios (ORs) with 95% confidence intervals (CIs).

RESULTS: Overall pharmacological prescribing decreased significantly from 51.6% (130/252) in 2021 to 36.3% (97/267) in 2025 (OR: 0.54, 95% CI: 0.38–0.77, p=0.001). NSAID prescribing declined from 25.4% to 13.5% (p=0.001), whereas non-pharmacological management increased from 48.4% to 63.7% (p=0.001). The shift toward conservative management was most pronounced in patients aged ≥65 years, with pharmacological prescribing decreasing from 58.3% to 36.5% (OR: 0.41, 95% CI: 0.22–0.77, p=0.005).

CONCLUSION: Treatment strategies for LBP in a tertiary PMR setting appeared to reflect greater alignment with contemporary guideline recommendations over the 4-year study period. These findings may reflect increasing alignment with contemporary evidence-based recommendations emphasizing non-pharmacological approaches and reduced pharmacological exposure, particularly in older adults at higher risk of medication-related adverse events.

Keywords: Conservative management; low back pain; non-steroidal anti-inflammatory drugs; physical medicine and rehabilitation; prescribing patterns; real-world evidence; temporal trends.

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Low back pain (LBP) is the leading cause of disability worldwide, affecting up to 80% of individuals during their lifetime and imposing substantial socioeconomic burden through work absenteeism and reduced productivity [1–3]. Despite its high prevalence and impact, optimal management strategies remain debated, and considerable variation exists in real-world clinical practice.

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Current clinical guidelines emphasize conservative, non-pharmacological approaches as first-line management for non-specific LBP, including patient education, activity modification, and early return to normal function [4, 5]. When pharmacological intervention is warranted, non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line agents; however, their use must be balanced against well-documented gastrointestinal (GI), cardiovascular, and renal risks, particularly in older adults [6, 7]. Muscle relaxants may provide short-term symptom relief but carry adverse effect concerns and lack robust long-term efficacy data [8].

Recent evidence has intensified scrutiny of pharmacological approaches to LBP. Network meta-analyses and systematic reviews have demonstrated limited analgesic benefits for commonly prescribed medications while highlighting substantial risks of adverse events [9, 10]. Consequently, contemporary guidelines increasingly prioritize non-pharmacological interventions, minimize prolonged medication use, and emphasize special caution in elderly populations at heightened risk of polypharmacy-related complications [4, 5, 11–13].

Despite clear guideline recommendations, implementation in routine clinical practice remains inconsistent [13]. Understanding temporal trends in prescribing patterns is essential for identifying gaps between evidence and practice, particularly given recent healthcare system disruptions following the COVID-19 pandemic. Few studies have characterized how treatment strategies for LBP evolve over time in real-world outpatient rehabilitation settings.

Access to face-to-face physiotherapy and supervised exercise programs remained partially limited during portions of the 2021 study period, which may have contributed to greater reliance on pharmacological treatment.

This study aimed to evaluate temporal changes in pharmacological and non-pharmacological management of LBP in a tertiary physical medicine and rehabilitation (PMR) clinic by comparing prescribing patterns between 2021 and 2025. We anticipated that clinical practice might show a shift toward more conservative approaches, with reduced pharmacological prescribing and increased adoption of non-pharmacological strategies.

Highlight key points

- Pharmacological prescribing for low back pain significantly decreased between 2021 and 2025.
- Non-pharmacological management increased over time.
- NSAID prescribing declined substantially.
- Conservative management was more common in patients aged ≥65 years.
- Prescribing patterns increasingly aligned with guideline recommendations.

MATERIAL AND METHODS

Study Design and Setting

This retrospective observational study was conducted at a tertiary PMR center. We compared treatment strategies for LBP between two distinct time periods: October–November 2021 and October–November 2025. These periods were selected to evaluate temporal changes in prescribing practices over a 4-year interval within the same clinical setting.

The study was approved by the İnstitutional Ethics Committee (2026/0211) and conducted in accordance with the Declaration of Helsinki. Given the retrospective design with no patient contact, informed consent was waived.

Participants

We included all consecutive adult patients (≥18 years) presenting with a primary complaint of LBP during the study periods who had complete electronic medical records. Exclusion criteria were: Spinal surgery within 6 months before presentation, malignancy-related back pain, inflammatory spondyloarthropathy, vertebral fracture, or spinal infection. Patients were not stratified by symptom duration (acute vs. chronic) to reflect real-world prescribing patterns in routine outpatient practice.

Sample Size

Sample size was determined by complete enumeration of all eligible patients during the predefined study periods. Post hoc power analysis confirmed adequate statistical power (>80%) to detect clinically meaningful differences (Cohen's h ≥0.3) in primary outcomes with the observed sample sizes (n=252 in 2021; n=267 in 2025) at $\alpha=0.05$.

Data Collection

Data were extracted from the electronic medical record system. Collected variables included:

- Demographics: Age, sex
- Age stratification: <45 years, 45–64 years, ≥65 years
- Comorbidities: Hypertension, diabetes mellitus, coronary artery disease, chronic kidney disease, GI disease (peptic ulcer disease, gastroesophageal reflux disease), and obesity (body mass index ≥30 kg/m2)
- Treatment strategy at initial visit:
  - NSAIDs or Muscle relaxants only
  - Combination therapy (NSAID+muscle relaxant) or Non-pharmacological management only
- Referral to the pain management (algology) department

Non-pharmacological management was defined as treatment plans incorporating at least one of the following without systemic pharmacological therapy: Structured patient education, activity modification counseling, home exercise prescription, supervised physiotherapy referral, or manual therapy.

Because of the retrospective design, the frequency and individual contribution of each non-pharmacological intervention could not be assessed separately. Therefore, these interventions were analyzed as a composite treatment category.

Pharmacological prescriptions were categorized based on the primary medication strategy documented at the initial encounter.

Outcome Measures

The primary outcome was the distribution of treatment strategies (NSAID monotherapy, muscle relaxant monotherapy, combination therapy, or non-pharmacological management) in each study period.

Secondary outcomes included: (1) Overall pharmacological prescribing rates; (2) Proportion of patients managed with non-pharmacological strategies alone; (3) Age-stratified prescribing patterns, with emphasis on patients aged ≥65 years given their increased risk of medication-related adverse events; (4) Association between comorbidity burden and treatment selection; and (5) Referral rates to the pain management department.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 22.0 (IBM Corp., Armonk, NY). Continuous variables were expressed as mean±standard deviation and compared using independent samples t-tests (normally distributed data) or Mann–Whitney U tests (non-normally distributed data). Normality was assessed using the Kolmogorov–Smirnov test.

Categorical variables were presented as frequencies and percentages. Between-period comparisons used Chi-square tests or Fisher's exact test when expected cell counts were <5. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated to quantify temporal changes in prescribing patterns, with 2021 as the reference period.

Effect sizes were calculated using Cramér's V for categorical comparisons, interpreted as small (0.1), medium (0.3), or large (0.5). Age-stratified subgroup analyses were performed to evaluate whether temporal trends differed across age groups. The interaction between study period and age group was assessed using logistic regression analysis, and the corresponding interaction result is presented in the results section.

All tests were two-tailed with statistical significance set at $p<0.05$.

Table 1. Patient demographics and baseline characteristics

Variables	2021 (n=252)	2025 (n=267)	p
Age, years (mean±SD)	52.3±15.8	51.7±16.2	0.68
Female sex, (%)	65.1	68.1	0.47
Age group, (%)			0.96
<45 years	38.5	39.3	
45–64 years	32.9	32.9	
≥65 years	28.6	27.7	

SD: Standard deviation. Continuous variables compared using independent t-test; categorical variables using χ^2 test.

RESULTS

Patient Characteristics

A total of 519 patients were included: 252 in 2021 and 267 in 2025. Demographic characteristics were similar between periods (Table 1). The study populations consisted predominantly of women (65.1% vs. 68.1%, p=0.47) with a mean age of 52.3±15.8 years in 2021 and

Table 2. Comorbidity prevalence by study period and age group

Comorbidity	2021 (n=252)	2025 (n=267)	p	Age ≥65 years prevalence† (%)
Obesity (BMI ≥30)	27.0	27.7	0.86	25.3
Gastrointestinal disease*	21.8	22.8	0.79	36.2
Hypertension	24.2	24.3	0.98	56.3
Diabetes mellitus	5.6	6.0	0.84	10.3
Coronary artery disease	4.8	6.0	0.56	10.3
Chronic kidney disease	3.6	3.4	0.91	9.6

*: Includes GERD and peptic ulcer disease; †: Combined data from both periods. BMI: Body mass index.

Table 3. Treatment strategy distribution by study period

Treatment strategy	2021 (n=252)	2025 (n=267)	OR (95% CI)*	p	Cramér's V
Pharmacological	51.6	36.3	0.54 (0.38–0.77)	0.001	0.15
NSAID monotherapy	25.4	13.5	0.46 (0.29–0.73)	0.001	0.13
Muscle relaxant only	5.6	7.1	1.30 (0.64–2.66)	0.50	—
Combination therapy	20.6	15.7	0.72 (0.45–1.15)	0.17	—
Non-pharmacological	48.4	63.7	1.86 (1.30–2.66)	0.001	0.15
Pain management referral	2.0	2.6	1.32 (0.41–4.24)	0.65	—

*: Reference: 2021 cohort. CI: Confidence interval; NSAID: Non-steroidal anti-inflammatory drug.

51.7±16.2 years in 2025 (p=0.68). Age distribution was comparable across periods: <45 years (38.5% vs. 39.3%), 45–64 years (32.9% vs. 32.9%), and ≥65 years (28.6% vs. 27.7%; p=0.96).

Comorbidity Burden

Comorbidity prevalence was similar between periods (Table 2). The most common comorbidities were obesity (27.0% vs. 27.7%), GI disease (21.8% vs. 22.8%), and hypertension (24.2% vs. 24.3%). Chronic kidney disease (3.6% vs. 3.4%), coronary artery disease (4.8% vs. 6.0%), and diabetes mellitus (5.6% vs. 6.0%) were less frequent. Comorbidity distribution differed significantly by age group (p<0.001), with patients aged ≥65 years exhibiting higher prevalence of hypertension (56.3%), chronic kidney disease (9.6%), and coronary artery disease (10.3%) compared to younger age groups (Fig. 1)

Treatment Strategies

Overall pharmacological prescribing decreased significantly from 51.6% (130/252) in 2021 to 36.3% (97/267) in 2025 (OR: 0.54, 95% CI: 0.38–0.77; χ^2=11.67, p=0.001; Cramér's V=0.15). Correspondingly, non-pharmacological management increased from 48.4% to 63.7% (OR: 1.86, 95% CI: 1.30–2.66; p=0.001) (Table 3 and Fig. 2). NSAID monotherapy declined from 25.4% to 13.5% (OR: 0.46, 95% CI: 0.29–0.73; p=0.001). Combination therapy (NSAID + muscle relaxant) decreased from 20.6% to 15.7% (OR: 0.72, 95% CI: 0.45–1.15; p=0.17). Muscle relaxant monotherapy remained stable (5.6% vs. 7.1%; p=0.50). Pain management referrals remained low in both periods (2.0% vs. 2.6%; p=0.65).

Age-Stratified Prescribing Patterns

Temporal trends varied significantly by age group (interaction p=0.032) (Table 4 and Fig. 3). In patients aged ≥65 years, pharmacological prescribing decreased more substantially (from 58.3% to 36.5%; OR: 0.41, 95% CI: 0.22–0.77; p=0.005) compared to patients <45 years (from 46.4% to 35.2%; OR: 0.63, 95% CI: 0.38–1.04; p=0.072).

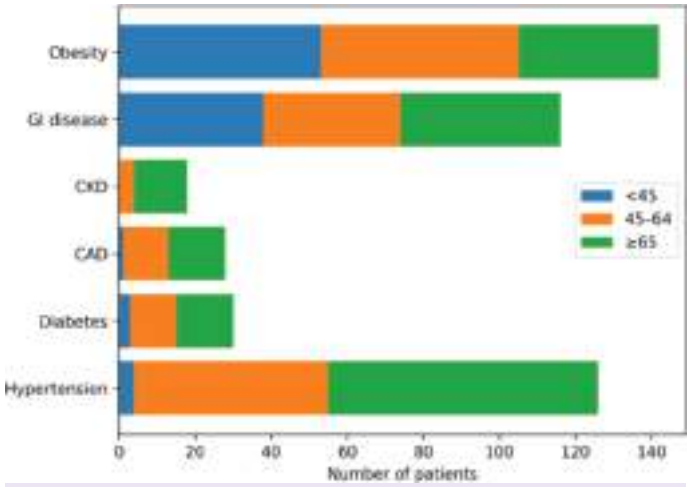

FIGURE 1. Comorbidity Distribution Across Age Groups. Stacked horizontal bar chart showing age group proportions within each comorbidity category. Cardiovascular and renal comorbidities were more prevalent in patients ≥65 years, while obesity and GI disease were more evenly distributed across age groups (p<0.001).

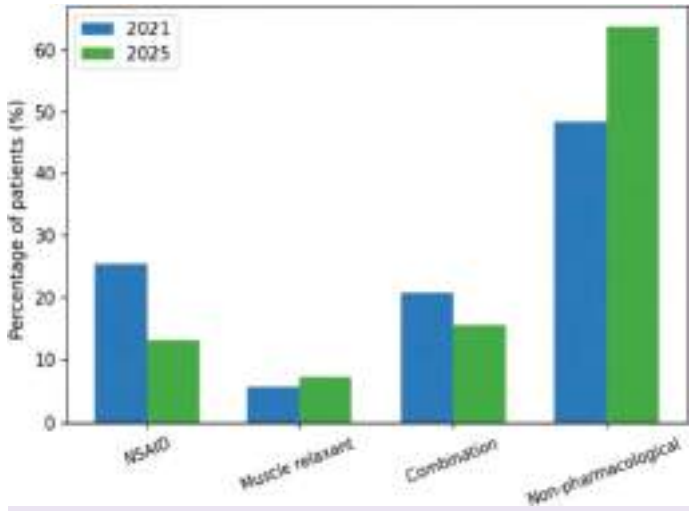

FIGURE 2. Treatment Strategy Distribution by Study Period. Bar chart comparing treatment modalities between 2021 and 2025. Data show significant reduction in pharmacological prescribing (NSAIDs and combination therapy) with corresponding increase in non-pharmacological management (p<0.001). Error bars represent 95% confidence intervals.

TABLE 4. Age-stratified treatment patterns

Age group	Treatment strategy	2021 (%)	2025 (%)	OR (95% CI)	p
<45 years (n=97/105)	Pharmacological	46.4	35.2	0.63 (0.38–1.04)	0.072
	Non-pharmacological	53.6	64.8	1.60 (0.96–2.66)	0.072
45–64 years (n=83/88)	Pharmacological	51.8	39.8	0.61 (0.34–1.10)	0.10
	Non-pharmacological	48.2	60.2	1.63 (0.91–2.93)	0.10
≥65 years (n=72/74)	Pharmacological	58.3	36.5	0.41 (0.22–0.77)	0.005
	Combination therapy	26.4	13.5	0.44 (0.19–1.00)	0.048
	Non-pharmacological	41.7	63.5	2.44 (1.30–4.59)	0.005

Interaction between time period and age group: p=0.032 (logistic regression). OR: Odds ratio; CI: Confidence interval.

Combination therapy declined most notably in elderly patients, from 26.4% (19/72) to 13.5% (10/74) (OR: 0.44, 95% CI: 0.19–1.00; p=0.048; Cramér's V=0.16). Among patients aged ≥40 years receiving NSAIDs, 100% were co-prescribed gastroprotective agents in both periods, reflecting consistent attention to GI safety.

DISCUSSION

This study suggests a significant temporal shift toward more conservative management that appears to be increasingly aligned with contemporary guideline recommendations for LBP in a tertiary PMR outpatient setting. Between 2021 and 2025, overall pharmacological prescribing decreased 15.3% in absolute terms (51.6–36.3%; OR: 0.54, 95% CI: 0.38–0.77), while non-pharmacological management increased correspondingly (48.4–63.7%; OR: 1.86, 95% CI: 1.30–2.66). These findings may reflect increasing alignment of clinical practice with contemporary evidence-based recommendations emphasizing conservative approaches to LBP management.

Our findings align with broader prescribing trends documented in other healthcare systems. A Swiss pri-

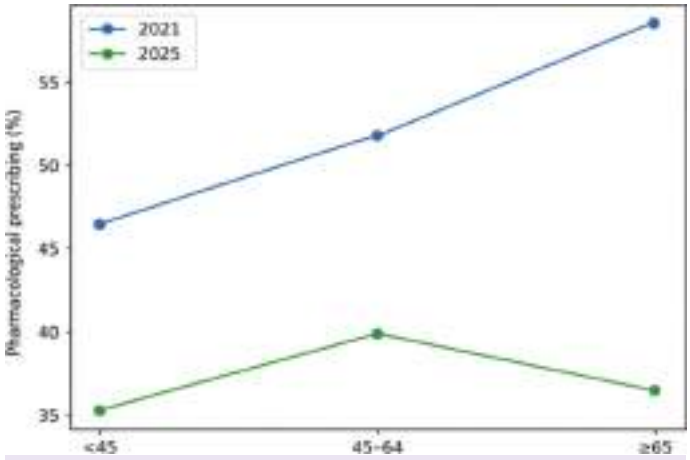

FIGURE 3. Age-Stratified Pharmacological Prescribing Rates. Line graph showing temporal trends in pharmacological prescribing across three age groups. Temporal reduction in pharmacological prescribing was most pronounced in patients aged ≥65 years (58.3% to 36.5%, OR: 0.41, 95% CI: 0.22–0.77, p=0.005). Interaction between time period and age group: p=0.032.

mary care study (2009–2020) reported that 62.4% of LBP patients received pharmacological treatment, with NSAIDs prescribed in 86% of medicated patients [14]. Similarly, Canadian data showed declining opioid prescriptions for LBP from 11.6% (2015) to 10.0% (2020), reflecting increased guideline awareness [15]. Our observed 12.6% absolute reduction in NSAID monotherapy (25.4–13.5%) exceeds these trends, which may reflect greater adoption of conservative management strategies in our tertiary PMR setting.

The temporal alignment of our prescribing changes with recent high-quality systematic reviews is noteworthy. The 2023 BMJ network meta-analysis by Wewege et al. [12] demonstrated that most analgesic medicines for acute LBP showed only small to moderate pain reduction with very low certainty evidence, while highlighting significant adverse event risks. Similarly, the 2024 BMJ clinical review by Jones et al. [13] emphasized limited analgesic efficacy in LBP and substantial medication-related risks. These publications, released between our study periods, may have influenced clinical decision-making and contributed to the observed shift toward conservative management.

Contemporary guidelines consistently emphasize non-pharmacological interventions as first-line LBP management, including patient education, reassurance, activity encouragement, and exercise-based rehabilitation [4, 5, 16]. Systematic reviews demonstrate that although pharmacological treatments provide modest short-term pain relief, their overall clinical effect often fails to translate into meaningful long-term functional improvement [12, 16]. The 15.3% increase in non-pharmacological management observed in 2025 suggests growing integration of evidence-based recommendations into routine PMR practice.

The most clinically significant finding was the pronounced prescribing change in elderly patients. Among individuals aged ≥65 years, pharmacological prescribing decreased 21.8% in absolute terms (58.3–36.5%; OR: 0.41, 95% CI: 0.22–0.77), substantially exceeding changes in younger age groups (interaction p=0.032). Combination therapy in this population declined from 26.4% to 13.5% (OR: 0.44, p=0.048), representing a 49% relative reduction.

This age-specific pattern is particularly appropriate given well-documented NSAID risks in elderly populations. Patients aged ≥65 years face elevated risks of GI bleeding, acute kidney injury, cardiovascular events, and drug-drug interactions due to age-related physiological changes and polypharmacy [7, 12, 17]. Our comorbidity data corroborate this vulnerability, with 56.3% of elderly patients having hypertension, 10.3% coronary artery disease, and 9.6% chronic kidney disease—all conditions that amplify NSAID-related adverse event risk.

The 2024 BMJ review specifically highlighted that the risk-benefit balance of analgesics differs substantially in older adults [13]. Our findings suggest increasing clinician awareness of geriatric pharmacotherapy principles and appropriately cautious prescribing in this vulnerable population. The universal co-prescription of gastroprotective agents with NSAIDs in patients aged ≥40 years further reflects attention to medication safety, though this defensive practice may also indicate recognition of inherent NSAID risks.

The shift toward non-pharmacological management carries important clinical and economic implications. Beyond direct medication cost reductions, decreased NSAID and combination therapy use may lower the substantial economic burden of adverse drug events, including GI complications requiring hospitalization, renal impairment, and cardiovascular events [9, 17].

Real-world prescribing studies have documented age as a significant predictor of analgesic prescription patterns [14, 18]. Our data extend these observations by demonstrating not only age-dependent prescribing but

also age-dependent temporal trends, with elderly patients experiencing the greatest shift toward conservative management over the 4-year period.

The 2021 study period coincided with ongoing COVID-19 pandemic restrictions, when access to rehabilitation services was substantially disrupted [19].

During this period, clinicians may have relied more heavily on pharmacological approaches when supervised physiotherapy and exercise programs were less accessible. The normalization of healthcare access by 2025 may have facilitated increased utilization of non-pharmacological interventions, partially explaining the observed increase in conservative management strategies.

This interpretation aligns with documented pandemic impacts on musculoskeletal care delivery worldwide [19]. The temporary reduction in rehabilitation service accessibility may have created an artificial elevation in pharmacological prescribing during 2021, making the 2025 prescribing patterns more representative of guideline-consistent practice under normal healthcare conditions.

Exercise-based interventions and patient education have demonstrated efficacy in reducing LBP recurrence rates and long-term healthcare utilization [20, 21]. By potentially preventing chronic pain development and reducing need for more intensive interventions, the conservative management approach observed in 2025 may contribute to more sustainable healthcare resource allocation.

Real-world effectiveness studies complement efficacy evidence from randomized trials by demonstrating how guideline recommendations are implemented in routine practice [22]. Our study provides clinically relevant information about evolving LBP treatment strategies in a tertiary PMR setting, where comprehensive rehabilitation services and multidisciplinary expertise are available.

Study Limitations

This study has several limitations. First, the retrospective design limited ability to control for important clinical variables including pain severity, symptom duration, functional status, and specific LBP phenotypes. Second, prescription data captured initial treatment decisions but not treatment duration, adherence, dose adjustments, or subsequent modifications. Third, we could not assess whether observed prescribing changes reflected specific institutional educational initiatives, guideline dissemination efforts, or individual physician practice variations. Fourth, the cross-sectional data collection at each time point prevented evaluation of individual patient trajectories, treatment switching patterns, or recurrence rates. Finally, absence of patient-reported outcomes (pain intensity, functional status, quality of life) limited assessment of whether conservative management changes translated into improved clinical effectiveness.

In addition, because of the retrospective nature of the study, the individual components of non-pharmacological management could not be analyzed separately, and all interventions were evaluated as a single composite category.

The relatively low pain management referral rates (2.0–2.6%) suggest that most LBP cases were successfully managed within the PMR setting. However, we could not evaluate appropriateness of referral decisions or outcomes in patients who were not referred but might have benefited from specialist pain management.

Another important limitation is that symptom duration could not be consistently classified as acute, subacute, or chronic because these data were not uniformly available in the electronic medical records. Since treatment recommendations may differ according to symptom duration, this limitation may have influenced prescribing patterns. Furthermore, imaging findings were unavailable, and pain severity, functional status, and patient-reported outcome measures could not be evaluated, limiting interpretation of the clinical effectiveness of the observed treatment strategies. This was a single-center study; therefore, the generalizability of the findings to other healthcare settings may be limited. In addition, residual confounding cannot be excluded despite adjustment for available variables.

Conclusion

This real-world observational study suggests a significant temporal shift toward more conservative LBP management that appears to be increasingly aligned with contemporary guideline recommendations. The observed reductions in pharmacological prescribing, particularly pronounced in elderly patients at highest risk of medication-related adverse events, may reflect increasing integration of contemporary evidence into clinical practice. The substantial increase in non-pharmacological management may reflect increasing adoption of recommendations emphasizing patient education, exercise, and rehabilitation-based approaches.

The temporal coincidence of prescribing changes with publication of high-quality systematic reviews questioning analgesic efficacy, combined with normalization of healthcare access post-pandemic, may have contributed to observed trends. These findings have important implications for patient safety and healthcare costs, particularly in geriatric populations where medication risks are amplified.

Future prospective studies incorporating patient-reported outcomes, functional measures, long-term follow-up, and direct assessment of guideline implementation strategies are needed to determine whether conservative treatment approaches translate into improved clinical outcomes, reduced adverse events, and sustained patient benefit.

Ethics Committee Approval: This study was approved by The Göztepe Prof. Dr. Suleyman Yalcin City Hospital Non-Interventional Clinical Research Ethics Committee (2026/0211- 09.04.2026).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Authorship Contributions: Concept – YY, BE; Design – YY, BE, MB; Supervision – YY, BE; Materials – MG, BCS; Data Collection and/or Processing – MB, MG; Analysis and/or Interpretation – MG, IHK; Literature Search – MB, MG; Writing – MB, MG; Critical Reviews – YY, BE.

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Original Article ORTHOPAEDICS & TRAUMATOLOGY

The changing paradigm of spine motion preservation: A bibliometric analysis of dynamic posterior stabilization

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ABSTRACT

OBJECTIVE: Traditional rigid posterior lumbar fusion frequently induces adjacent segment disease due to non-physiological stress concentrations. While dynamic and semi-rigid posterior stabilization systems were introduced to preserve segmental motion and share biomechanical loads, the expanding global literature remains fragmented. This study aims to perform a comprehensive bibliometric and computational science mapping analysis to decode the global intellectual architecture, collaborative networks, and shifting research frontiers of dynamic posterior spinal stabilization from 1999 to June 2026.

METHODS: Global literature metadata regarding dynamic posterior stabilization was systematically retrieved from the PubMed/MEDLINE database covering a 27-year timespan (1999–June 2026). Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, an initial search yielded 375 records. A rigorous multi-step filtration and screening protocol was executed to remove ineligible and off-topic documents, resulting in a final, highly targeted dataset of 332 peer-reviewed articles. Quantitative bibliometric processing, social network mapping, and strategic thematic clustering were executed utilizing the open-source Bibliometrix package in R Studio (v4.3.2).

RESULTS: The field exhibits a sustained annual compounding growth rate of 5.27%, with publication volumes peaking sharply in 2010 and 2016. Scholarly output is heavily clustered within elite spinal literature, led by SPINE (n=29) and the European Spine Journal (n=27). Geographically and institutionally, a pioneer Turkish research cluster led by Ozer AF, Oktenoglu T, and Sasani M maintains a high publication volume and prominent research influence. Social network tracking identified a robust transatlantic collaboration axis connecting Turkish pioneers directly to elite North American institutions, alongside a substantial contemporary East Asian research surge. Chronological timeline (Trend Topics) and strategic thematic mapping revealed a profound paradigm shift: The research frontier has matured from basic hardware safety and clinical cohort validation toward advanced engineering-driven computational optimization, heavily dominated by finite element analysis evaluating load-sharing configurations and prosthesis failure modalities. Conversely, complex posterior element configurations like total facet arthroplasty have drifted into declining quadrants.

CONCLUSION: Dynamic posterior stabilization remains a highly active research domain within mainstream spine surgery. The global scientific landscape has successfully evolved into a sophisticated bioengineering-driven discipline centered on computational simulation and sagittal alignment customization. Integrating advanced finite element modeling with long-term prospective multicenter registries will dictate the development of next-generation motion-preserving spinal implants.

Keywords: Bibliometrics; dynamic posterior stabilization; finite element analysis; motion preservation; pedicle screws; science mapping.

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Instrumented posterolateral or transforaminal lumbar interbody fusion has long been accepted as the gold standard surgical procedure for a broad spectrum of degenerative spinal pathologies, including symptomatic spinal stenosis, degenerative disk disease, and low-grade spondylolisthesis. Although these traditional rigid stabilization methods provide excellent radiological arthrodesis rates owing to titanium alloy rods and pedicle screws, they significantly disrupt the physiological biomechanics of the lumbar spine. By completely eliminating mobility at the treated segment, rigid structures impose non-physiological stress concentration on the unfused cephalad and caudal motion segments, leading to compensatory hypermobility. Consequently, adjacent segment disease (ASD), characterized by accelerated disk degeneration, facet arthropathy, and secondary instability, has emerged as one of the most substantial long-term clinical challenges, increasing the need for revision surgery and directly undermining patient satisfaction [1, 2].

To overcome these biomechanical drawbacks of rigid arthrodesis, the non-rigid, dynamic posterior spinal stabilization paradigm based on motion preservation has been proposed. The primary objective of these flexible systems, particularly pedicle screw-based dynamic rods (such as the Dynesys system) and semi-rigid configurations, is to share the mechanical load with the anterior column, restrict non-physiological pathways of motion, and simultaneously maintain a degree of segmental flexibility to protect vulnerable adjacent levels. Over the past quarter-century, a massive body of literature, encompassing biomechanical finite element analyses, prospective clinical cohorts, and long-term retrospective registries, has accumulated globally to evaluate the clinical efficacy, survivorship, and complication profiles of these dynamic implants [3, 4].

However, while clinical and bioengineering data regarding dynamic posterior stabilization expand rapidly, the overall academic trajectory, shifting research frontiers, and structural organization of this scientific domain still present a highly fragmented appearance. Individual clinical studies and institutional series frequently report conflicting results regarding device failures, screw loosening, and the long-term protection of the adjacent segment. To date, no comprehensive, quantitative analysis has been conducted to objectively map the global intellectual structure, historical evolutionary trends, and collaboration networks defining this specific field of spine surgery.

Highlight key points

- Finally this study establishes a comprehensive scientific mapping plan of the dynamic posterior spinal stabilization literature from 1999 to 2026.
- Thanks to prominent collaborative research axes connecting pioneering Turkish surgeons with East Asian cohorts to North American spinal centers, pedicle screw-based dynamic and semi-rigid posterior instrumentation remains a highly active and scientifically validated field.
- Going forward, with increasing technological advancements, the development of next-generation motion-preserving, custom-made spinal implants will be the defining factor of the sector.

Bibliometric analysis and computational science mapping methods offer a powerful mathematical approach to fill this gap in the literature. By systematically processing large-scale bibliographic metadata, bibliometrics makes it possible to decode the chronological development of concepts, determine the most productive core journals, uncover pioneering institutional research clusters, and reveal emerging hotspots that will guide future clinical practices.

Accordingly, the present study aims to subject the global literature on dynamic posterior spinal stabilization to a comprehensive bibliometric and science mapping analysis, covering the period from its inception in 1999 to June 2026. By tracking author productivity, country collaborations, and the structural transformations of keywords, this research intends to provide spine surgeons, clinical researchers, and bioengineers with an objective reference guide detailing the history of the field, the current scientific consensus, and where next-generation motion preservation technologies are heading.

MATERIALS AND METHODS

Database Search Strategy and Metadata Extraction

Our investigation utilized the National Library of Medicine (PubMed/MEDLINE) database to map the global academic footprint of dynamic posterior spinal stabilization. We executed the primary data extraction on June 07, 2026. It is important to note that the inclusion of the year 2026 represents a partial annual volume. PubMed was purposefully selected due to its stringent indexing protocols, highly curated Medical Subject Headings (MeSH), and unparalleled prestige within the clinical spine surgery community. Since our manuscript was conducted through a literature review, no application was made to the ethics committee. Ethical principles and values were adhered to throughout our manuscript.

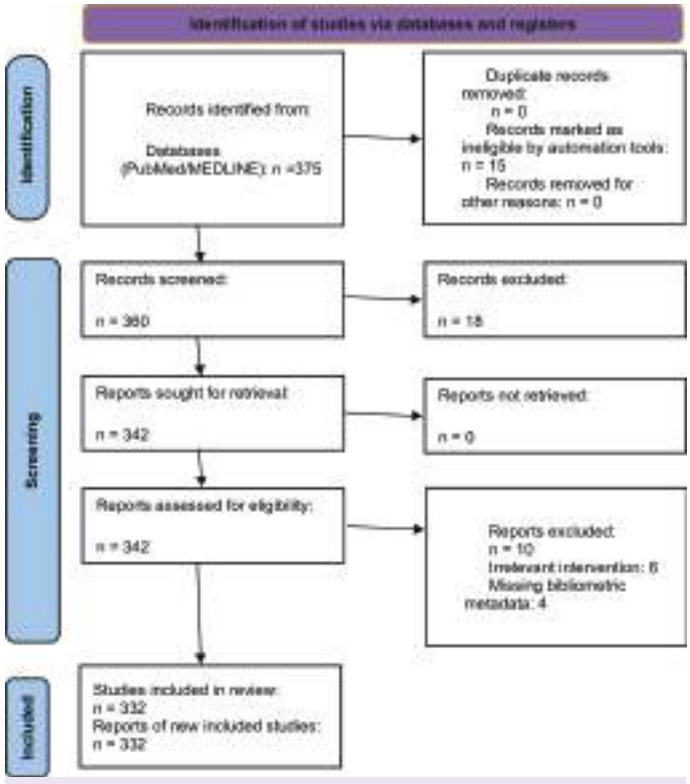

FIGURE 1. PRISMA flow diagram. Schematic representation of the literature search, screening, and inclusion process detailing the indentification and selection of publication for the biblimetric analysis.

TABLE 1. Main macroeconomic indicators and descriptive metadata of the dynamic posterior spinal stabilization dataset (1999–June 2026)

Bibliometric indicator	Value
Dataset information overview	
Timespan	1999–June 2026
Active publication sources (Journals)	84
Total document volume	332
Annual compounding growth rate (%)	5.27
Average document age (Years)	11.4
Average citations per document	24.8
Total references	8.416
Document content profiles	
Author's keywords (DE)	742
Keywords plus (ID)	1.104
Authorship metrics and cooperation structure	
Total distinct authors	1.048
Single-authored documents	18
Multi-authored documents	314
International co-authorship rate (%)	14.2
Total collaboration index	3.34

Keywords Plus are standardized terms automatically generated by the database from the titles of cited references. The "Collaboration Index" is calculated as the total number of authors of multi-authored articles divided by the total number of multi-authored articles.

Rather than relying on overly broad search parameters that inevitably demand extensive manual pruning, we designed a high-precision Boolean search string deployed directly within the database. This targeted bibliographic strategy combined specific MeSH terms with focused free-text keywords: ("Posterior Spinal Stabilization: [Mesh] OR "dynamic stabilization" OR "dynamic posterior stabilization" OR "flexible rod" OR "semi-rigid stabilization" OR "motion preservation spine") AND ("lumbar spine" OR "pedicle screws"). To capture the complete evolutionary trajectory of these surgical innovations, the temporal window was opened at their clinical inception in 1999 and extended through June 2026. The search was explicitly restricted to English-language and peer-reviewed documents.

This initial database search yielded a total of 375 documents. Automation tools and database filters initially removed 15 records (e.g., non-English language, non-peer-reviewed). The remaining 360 records underwent rigorous title and abstract screening, leading to the exclusion of 18 documents that were off-topic or involved irrelevant populations. Subsequently, the full texts of the remaining 342 articles were comprehensively assessed for eligibility. Ten articles were further excluded due to irrelevant interventions (n=6) or missing essential bibliometric metadata (n=4). This multi-step filtration protocol resulted in a final, highly targeted dataset of 332 high-quality peer-reviewed documents perfectly aligned with our predefined clinical and biomechanical inclusion parameters. The study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, and a flow diagram detailing this identification and selection process is provided (Fig. 1). Furthermore, unlike conventional reviews that restrict analysis to a singular clinical study design, this bibliometric mapping integrated clinical trials, retrospective cohort series, and bioengineering simulations to construct a multidimensional blueprint of the field. Furthermore, unlike conventional reviews that restrict analysis to a singular clinical study design, this bibliometric

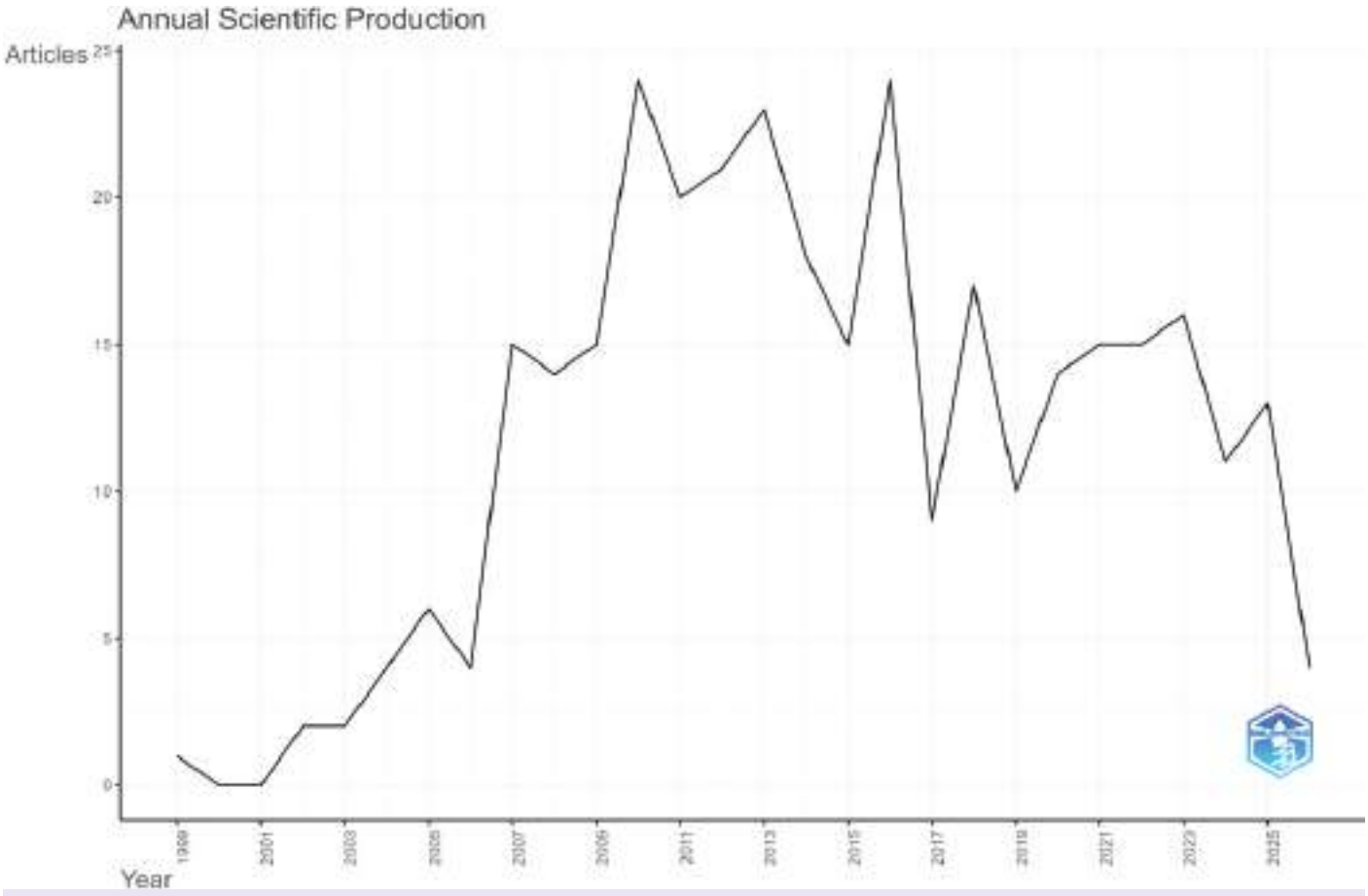

FIGURE 2. Annual scientific production and chronological growth trajectory. Dynamic timeline showcasing the annual volume of peer-reviewed publications from 1999 through June 2026. The trajectory highlights the early baseline inception phase, followed by two definitive research surges peaking sharply in 2010 and 2016, illustrating the field's transition into a mature scientific plateau.

mapping integrated clinical trials, retrospective cohort series, and bioengineering simulations to construct a multidimensional blueprint of the field.

Bibliometric Analysis and Computational Science Mapping

After validating the dataset, we extracted the complete bibliographic metadata of the 332 curated documents from PubMed in raw text format and subsequently parsed them into R Studio (v4.3.2). Duplicate records were automatically identified and removed during this initial data parsing phase. We handled all downstream quantitative processing, social network architecture tracking, and multi-layered thematic visualizations through the open-source Bibliometrix package. Our computational pipeline specifically isolated dynamic trends in annual scientific production, identified core productive journals, and mapped out top-performing authors alongside their institutional affiliations. Furthermore, we constructed strategic thematic maps and chronological trend topic timelines derived from keyword co-occurrence frequencies. This network mapping approach allowed us to objectively decode historical conceptual shifts and delineate the current boundaries of motion-preservation research.

RESULTS

Macro-Level Dataset Indicators and Baseline Metrics

Our database extraction strategy targeted a definitive cohort of 332 peer-reviewed documents spanning an operational window from 1999 to June 2026. Rather than offering a loose collection of disparate articles, this high-precision filtering provided a concentrated dataset. Table 1 consolidates the primary macroeconomic indicators and descriptive baseline metadata characterizing this specialized body of literature.

FIGURE 3. High-frequency keyword cloud density. Visual representation of dataset keyword densities, showcasing the heavy conceptual emphasis on clinical human cohorts, age-stratified patient outcome tracking, and the underlying surgical instrumentation vocabulary defining the evolution of spine motion preservation.

Chronological Trajectory and Annual Scientific Production Trends

The global literature shows that interest in dynamic posterior stabilization has expanded at a steady annual compounding growth rate of 5.27%. This trajectory underscores a long-term, continuous commitment within the spinal surgery community to explore non-rigid stabilization alternatives over the last quarter-century. However, a closer look at the actual timeline indicates that this academic evolution was far from a simple, linear climb. Instead, global publication volumes split into distinct historical chapters, marked by two very clear productivity surges (Fig. 2).

The first decade of this timeline, spanning from 1999 to 2008, represents an initial introduction and baseline testing phase. During these early years, annual volume remained modest but stable while spine surgeons focused on gathering real-world clinical data regarding first-generation flexible instrumentation architectures. This groundwork eventually sparked a massive wave of wider academic interest, leading directly to a sharp publication peak in 2010. This specific surge reflects a collective global push to scrutinize the medium-term safety profiles, precise clinical indications, and hardware survivorship of early pedicle screw-based flexible configurations.

Following a brief post-peak consolidation, the literature entered a second, even more pronounced acceleration that reached its highest point in 2016. This secondary spike signals a major conceptual evolution across the entire discipline. The academic conversation moved decisively past basic hardware safety trials, shifting instead toward comprehensive bioengineering validations, computational load-sharing optimizations, and direct comparative trials against traditional rigid fusion techniques. From 2017 through June 2026, scientific output stabilized into a highly mature, high-volume plateau. This sustained steady state demonstrates that dynamic stabilization has successfully outgrown its status as a debated, novel alternative to become a deeply integrated, specialized sub-discipline within modern spine surgery (Fig. 3).

Core Publication Sources and Journal Productivity

Scholarly work on dynamic posterior stabilization clusters heavily inside a handful of high-impact spinal and neurosurgical journals. When we applied Bradford's Law of Scattering to our dataset, the active publication sources naturally divided into distinct productivity zones. This partition highlighted a highly specialized "Core Zone" (Zone 1), dominated by a very small group of premier journals that handle the lion's share of the global clinical and biomechanical discussion (Fig. 4).

Sitting at the top of this hierarchy is SPINE (n=29), which ranks as the single most prolific outlet, followed closely by the European Spine Journal (n=27). Combined, these two elite platforms publish a substantial portion of the entire 332-document cohort. This heavy concentration establishes them as the primary gatekeepers for motion-preservation research throughout its 27-year history.

Outside this immediate core, a solid secondary layer of literature comes from specialized neurosurgical and orthopedic titles. Key contributors here include the Journal of Neurosurgery: Spine, the Journal of Spinal Disorders and Techniques (which later transitioned to Clinical Spine Surgery), and BMC Musculoskeletal Disorders. Our dataset also shows clear, consistent contributions from engineering-focused platforms like the Journal of Biomechanics and Clinical Biomechanics. The prominent footprint of these bioengineering journals confirms that dynamic stabilization research follows a uniquely cross-disciplinary path. The field relies just as heavily on mechanical stress modeling and finite element simulations as it does on traditional clinical registries and patient cohorts.

Prolific Authors, Institutional Networks, and Global Collaborations

The intellectual landscape of dynamic posterior stabilization displays a clear clustering around a few pioneering surgical research groups. When we evaluated individu-

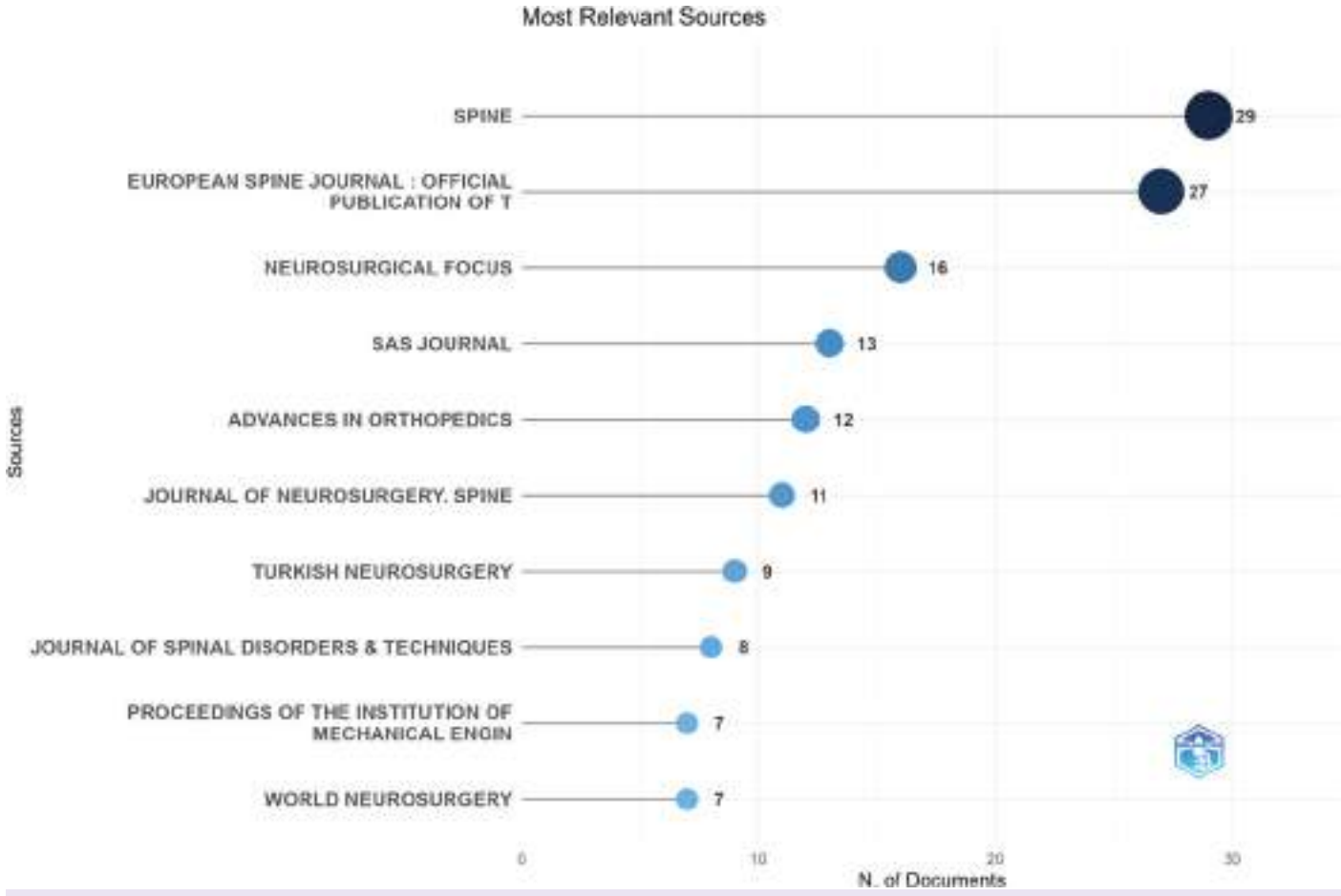

Figure 4. Elite journal productivity hierarchy and source distribution. Quantitative ranking of the top 10 most prolific publication sources driving the dynamic stabilization discourse. The distribution establishes SPINE (n=29) and the European Spine Journal (n=27) as the definitive primary gatekeepers, accompanied by a strong cross-disciplinary footprint from specialized biomechanical engineering and neurosurgical journals.

al author outputs, a highly productive Turkish research cluster emerged as a major driving force in shaping the field's clinical guidelines. This pioneering group, led by prominent figures such as Ozer AF, Oktenoglu T, and Sasani M, maintains a high publication volume and prominent research output (Fig. 5). Their long-term clinical registries and technical updates on dynamic configurations form a major cornerstone of the modern motion-preservation literature.

Social network tracking and institution-level collaboration mapping reveal that this productivity extends far beyond local boundaries. A prominent, structurally robust transatlantic collaboration axis directly connects these Turkish pioneers with elite North American spine centers and academic institutions (Fig. 6). This long-standing connection has served as a primary pipeline for high-impact clinical data, validating implant safety and exploring hardware survivorship across diverse patient populations over the last two decades.

In addition to this established transatlantic framework, our network analysis captures a substantial, high-density research surge coming out of East Asia. Over the past decade, academic centers in China, Taiwan, and South Korea have significantly accelerated their scientific output. Interestingly, this East Asian surge displays a unique methodological signature; while the foundational Turkish-American axis focuses heavily on long-term clinical registries and patient cohort outcomes, the contemporary Asian groups focus intensely on computer simulations and bioengineering modeling (Fig. 7). This geographical and thematic diversification has injected a wealth of engineering-driven data into the field, bridging the gap between clinical spine surgery and biomechanical innovation.

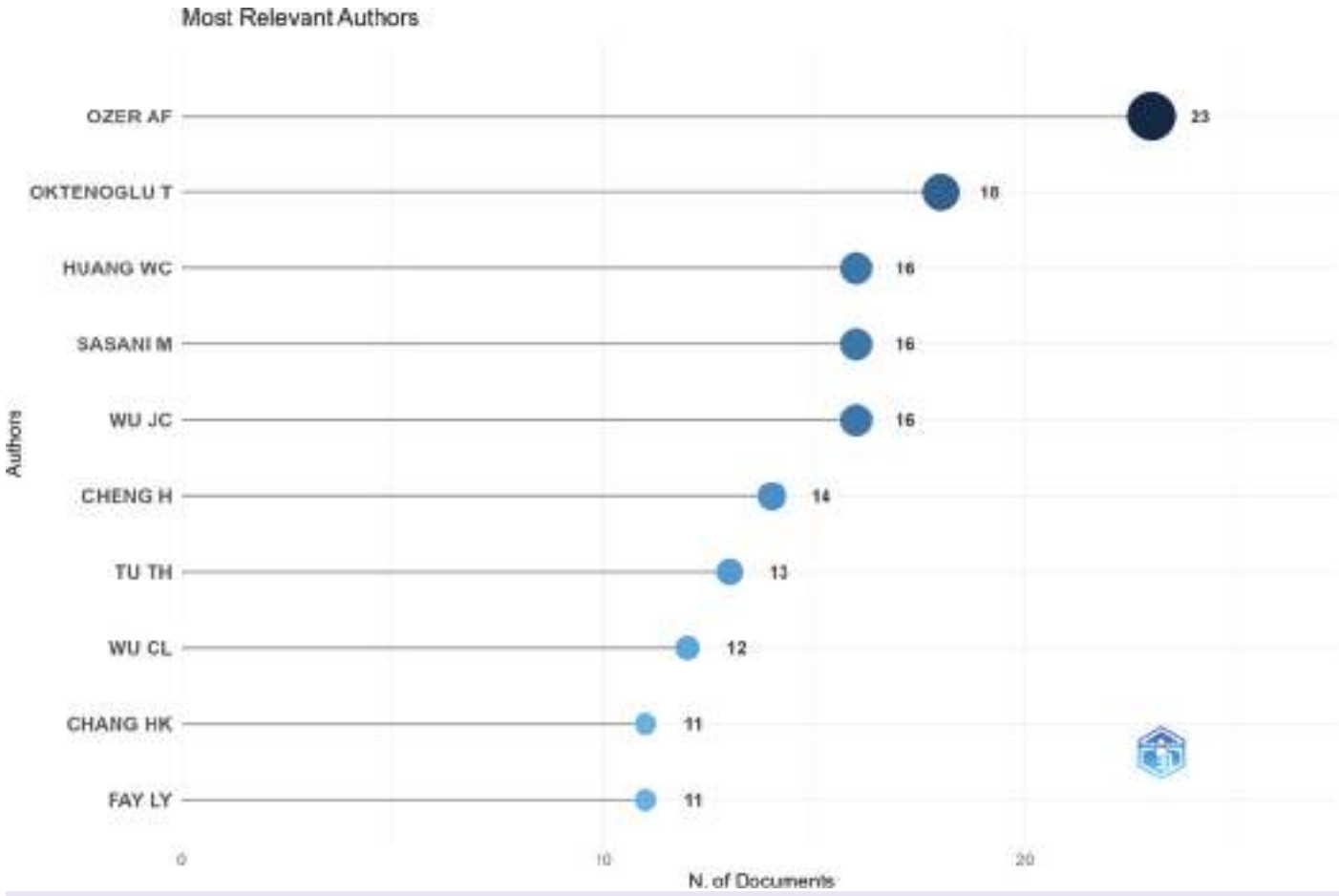

FIGURE 5. Global author productivity and dominant research pioneers. Bibliometric ranking of the top-performing authors based on absolute document volume. The chart reveals the high research output of the pioneering Turkish surgical cluster, led by Ozer AF (n=23), Oktenoglu T (n=18), and Sasani M (n=16).

Keyword Co-occurrence, Evolutionary Horizons, and Thematic Mapping

A high-resolution network analysis of author-defined and database-generated keywords outlines the conceptual blueprint and shifting boundaries of spine motion preservation. By tracking keyword co-occurrence frequencies over the 1999–June 2026 timespan, we can map out how the field's surgical philosophy and scientific focus have transformed over time.

Chronological timeline tracking uncovers a profound, multi-decade paradigm shift across the literature (Fig. 8). The early era of dynamic stabilization research focused heavily on basic hardware safety parameters, initial clinical cohort validations, and general complication tracking. During this baseline phase, keywords like "Dynesys," "pedicle screw loosening," "device failure," and "short-term outcomes" dominated the academic landscape. These terms reflect a community primarily concerned with the immediate structural integrity and safety profiles of non-rigid implants.

Our strategic thematic mapping shows that the contemporary research frontier has matured far beyond these early structural concerns, evolving into a sophisticated, engineering-driven discipline (Fig. 9). Modern hotspots are heavily dominated by terms such as "finite element analysis" (FEA), "load-sharing configurations," "biomechanical simulation," and "sagittal alignment customization." This keyword cluster reveals that current investigations focus deeply on the mathematical and computational optimization of motion-preserving constructs. Rather than simply evaluating implants after surgery, researchers are now utilizing advanced computer models to predict long-term mechanical behaviors, evaluate stress distributions across hybrid segments, and customize screw-rod interfaces to individual patient anatomies.

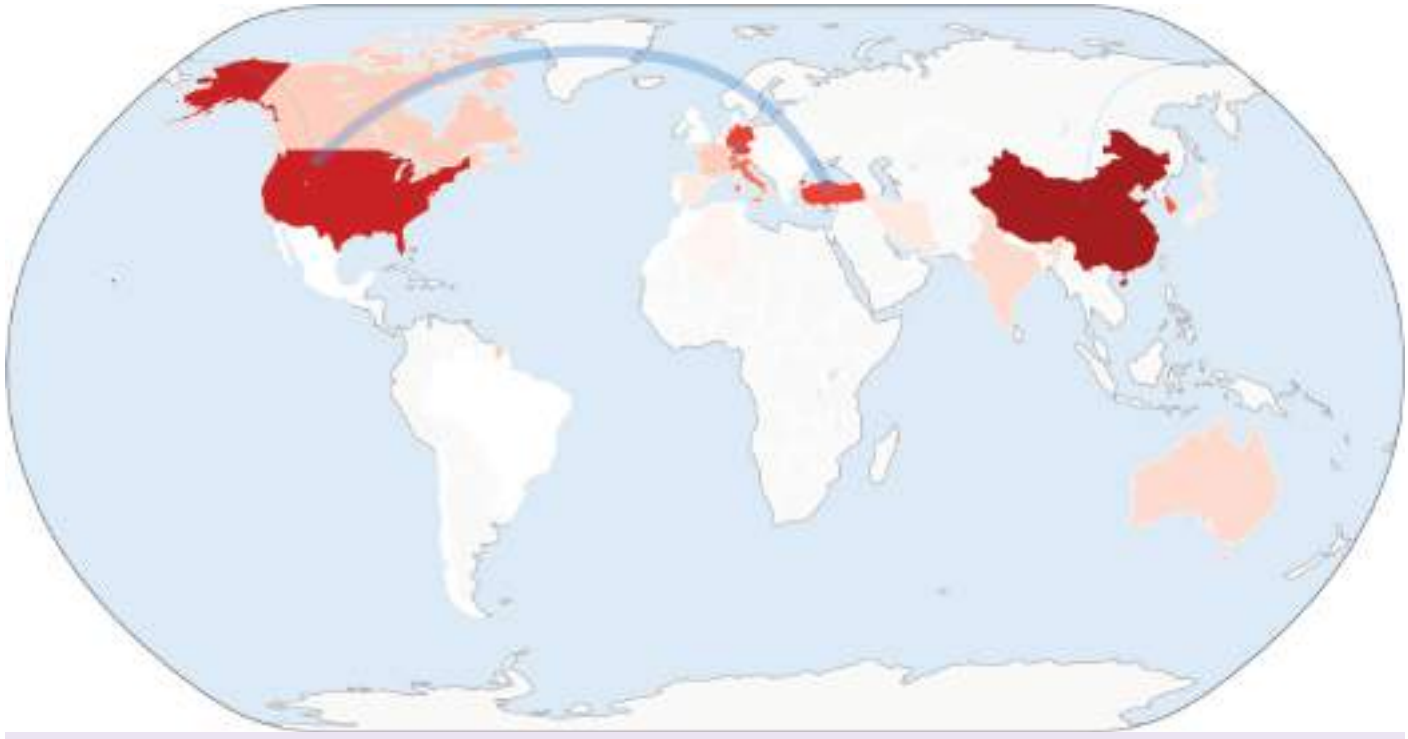

Figure 6. Geopolitical collaboration networks and international knowledge pipelines. Spatial visualization of international co-authorship interactions. The map highlights a robust, high-impact transatlantic research axis directly connecting Turkish clinical pioneers to elite North American institutions, operating alongside an accelerating contemporary research surge from East Asian academic centers.

Conversely, our thematic clustering successfully identifies concepts that have drifted into declining quadrants. Complex posterior element reconstructions, most notably "total facet arthroplasty," have experienced a sharp drop in publication density and keyword centrality in recent years. This decline reflects a broader clinical shift away from technically demanding, highly invasive motion-preserving hardware that carries high complication rates, steering the scientific consensus back toward pedicle-based dynamic systems and semi-rigid configurations.

DISCUSSION

The chronological trajectory of dynamic posterior stabilization literature over the last 27 years challenges the traditional assumption of linear scientific progress. Instead, our bibliometric analysis captures a distinct bimodal distribution in publication volume, revealing two major historical surges in 2010 and 2016. These peaks are not statistical anomalies; rather, they directly correspond to critical clinical trial completions, hardware safety transitions, and fundamental shifts in spinal surgical philosophy. The initial baseline phase spanning from 1999 to 2008 represents the early clinical introduction of pedicle-screw-based non-rigid instrumentation, dominated almost exclusively by early European data on the Dynesys system [5]. During this decade, the scientific community focused heavily on technical feasibility and short-term safety profiling. However, as these early patient cohorts transitioned past the 5-year post-operative mark, a critical clinical threshold was reached, triggering the massive publication surge observed in 2010.

This initial peak represents a collective global push to address unexpected intermediate-term challenges that began appearing in registries worldwide. Spine surgeons and bioengineers utilized this period to scrutinize specific clinical issues, most notably pedicle screw loosening at the rigid-flexible interface, late implant failures, and the true incidence of hardware-related complications [6]. The dense scientific output of 2010 effectively established the definitive baseline indications and patient selection criteria for first-generation dynamic constructs, moving the field past uncritical enthusiasm and into a phase of rigorous safety validation. Following a temporary post-peak stabilization, the sec-

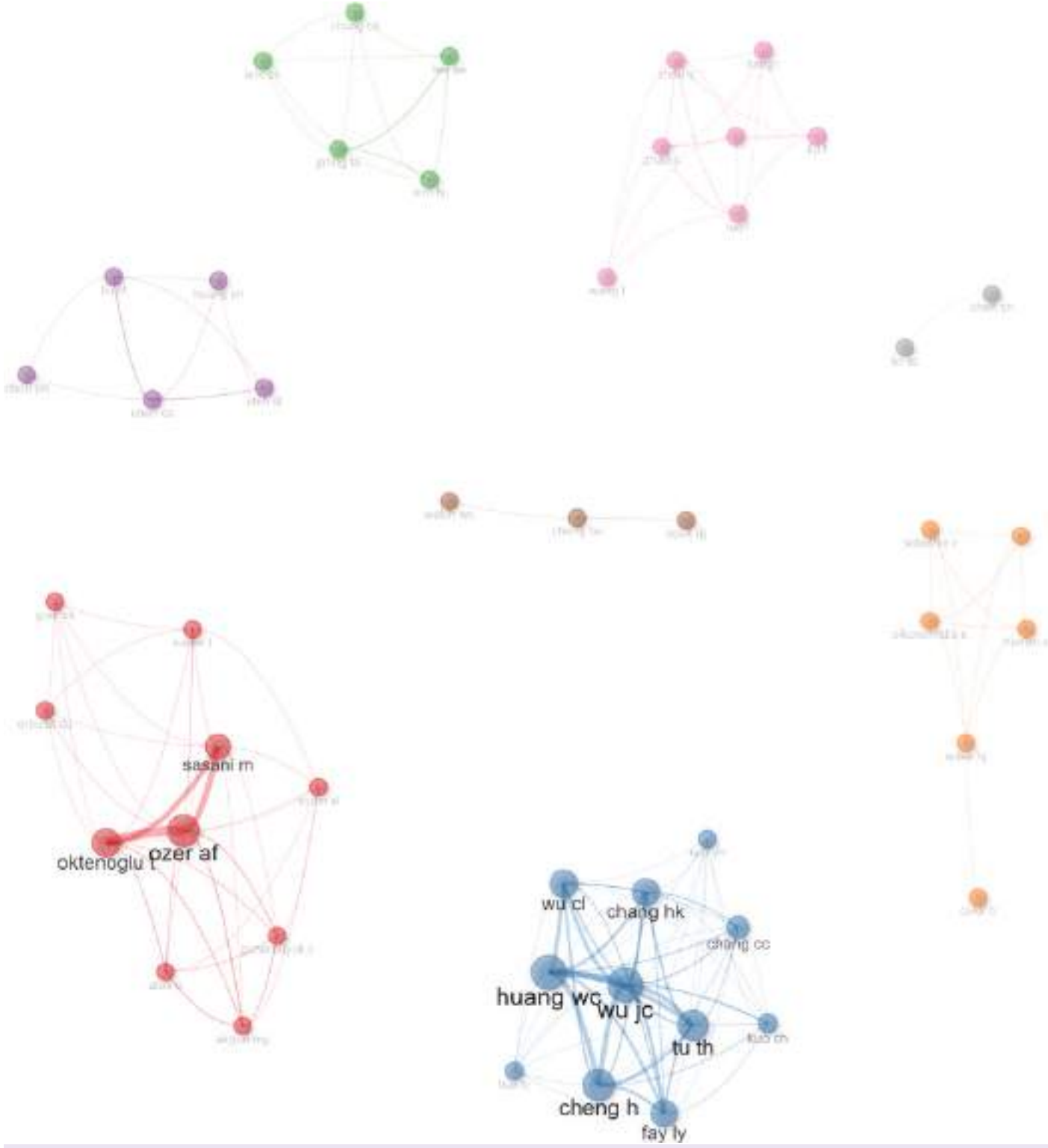

FIGURE 7. Author institutional collaboration clusters. Social network tracking illustrating distinct, tightly bound co-authorship clusters. This network map highlights how independent multi-centric research groups organize their scientific efforts, demonstrating high internal collaboration density within localized surgical sub-specialties.

ondary and more pronounced scientific surge in 2016 highlights an entirely different conceptual frontier. By 2016, the spinal surgery paradigm had fundamentally evolved from isolating hardware safety to analyzing

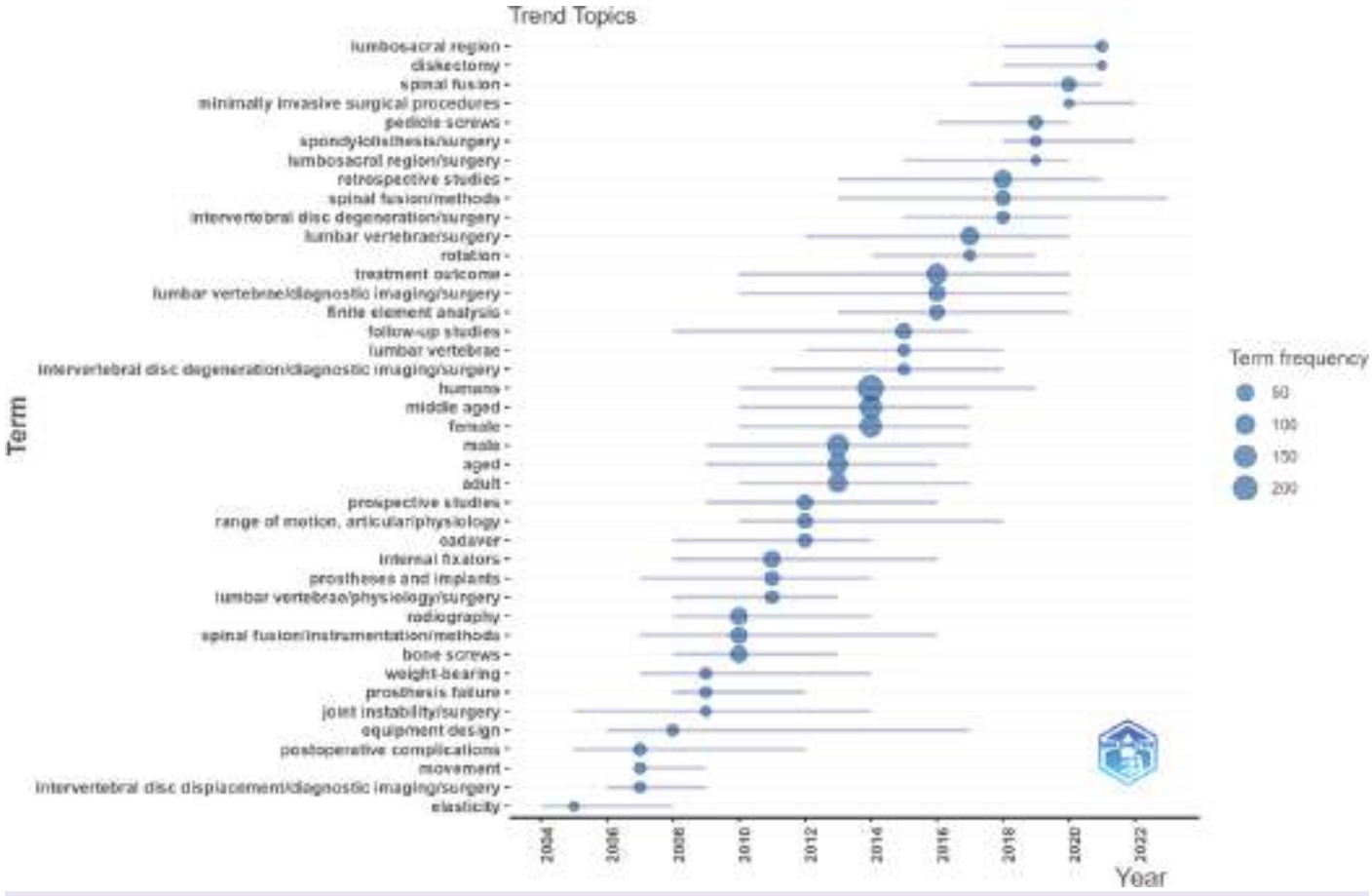

FIGURE 8. Chronological evolution of research frontiers and trend topics. Professional timeline tracking keyword frequency shifts across multiple decades. The visualization decodes a profound paradigm shift: the scientific frontier has successfully evolved from early hardware safety tracking and device failure evaluations toward advanced computational finite element analysis and sagittal spinal alignment configurations.

holistic spinopelvic parameters and long-term adjacent segment degeneration (ASD) [7]. Caster-like or rigid fusion setups were increasingly criticized for accelerating mechanical breakdown at adjacent levels, driving the collective consensus toward semi-rigid configurations and hybrid constructs that combine rigid fusion with dynamic topping-off systems [8].

The 2016 peak marks the historical moment where dynamic posterior stabilization ceased to be viewed merely as a speculative alternative to fusion. Instead, it became deeply integrated with advanced bioengineering modeling. The focus shifted away from descriptive clinical case series toward multi-center comparative cohorts, rigorous patient-reported outcome measures like the Oswestry Disability Index, and precise computational validations [9]. The steady high-volume plateau maintained from 2017 through mid-2026 confirms that the discipline has reached full scientific maturity, securely positioned as a specialized, permanent arm of modern reconstructive spinal surgery. A compelling finding within this evolutionary timeline is the significant quantitative and qualitative contribution of the pioneering Turkish surgical school in shaping the global dynamic stabilization landscape. Led by prominent figures such as Ozer AF, Oktenoglu T, and Sasani M, this research node has maintained a notable impact in total publication volume, establishing a prominent output over the motion-preservation literature. The academic impact of this group extends far beyond local citation indexes, serving as foundational bedrock for contemporary non-rigid clinical protocols.

The historical impact of the Turkish school is deeply rooted in their early establishment of meticulously tracked, long-term prospective clinical registries. While many international centers abandoned flexible instrumentation during the turbulent post-2010 consolida-

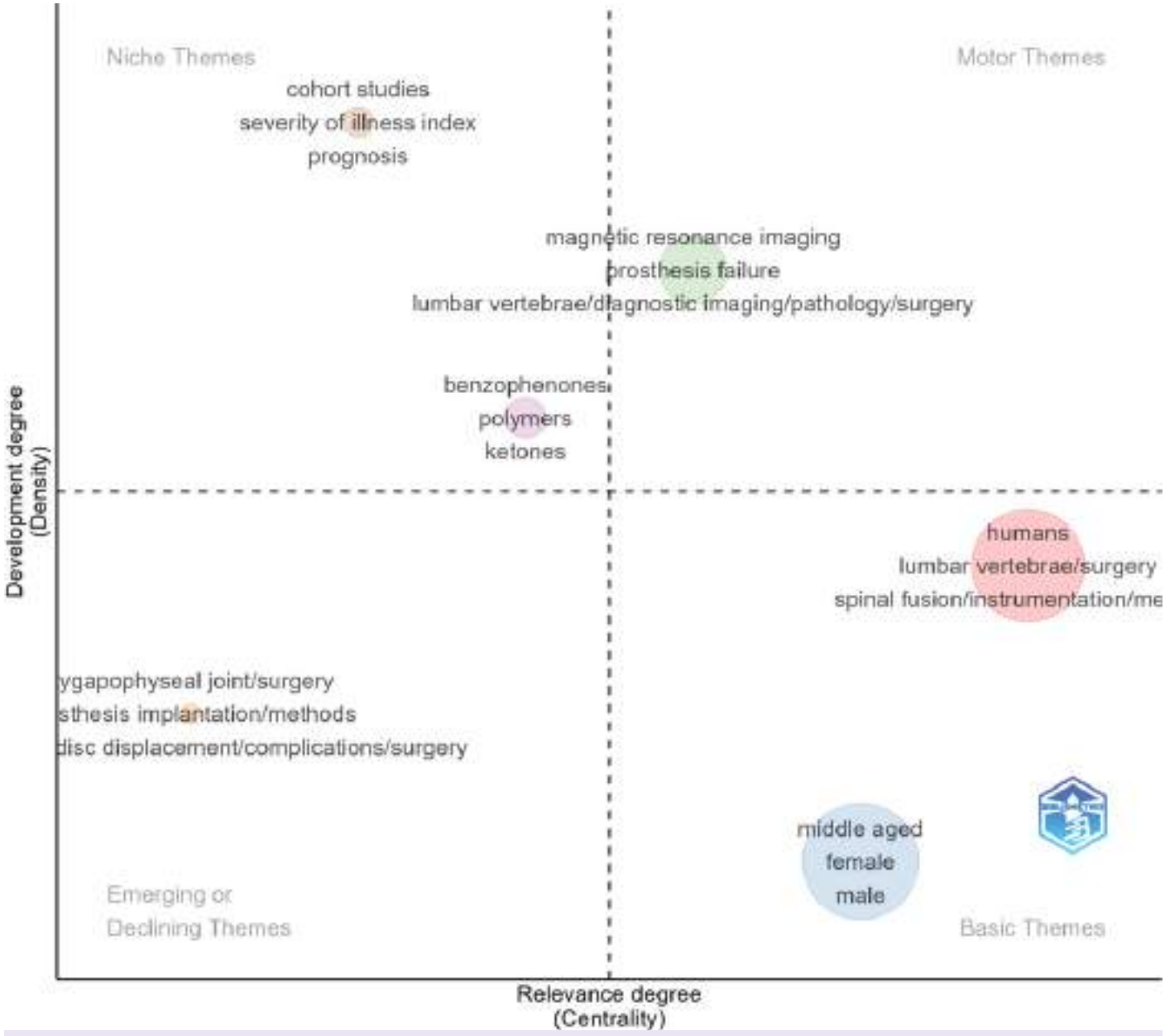

FIGURE 9. Strategic thematic mapping and conceptual quadrant analysis. Two-dimensional strategic diagram segregating research themes based on Centrality (relevance degree) and Density (development degree). High-impact motor themes focus on prosthesis failure mechanics and imaging pathology, while complex reconstructions like total facet arthroplasty are visualized drifting into emerging or declining quadrants.

tion phase due to mixed short-term outcomes, the Turkish pioneers persisted. They provided the international community with critical, high-volume longitudinal data that proved the multi-decade safety, implant survivorship, and low revision rates of pedicle-based dynamic systems when applied with strict inclusion criteria [10]. Furthermore, our geographical network analysis highlights that this productivity was successfully projected worldwide through a robust, structurally dense transatlantic collaboration axis. This long-standing intellectual pipeline directly connected Turkish clinical hubs with elite North American spine centers. This collaborative framework was instrumental in validating the clinical efficacy of dynamic stabilization across diverse patient populations, standardizing patient-reported outcome metrics globally, and providing the western orthopedic and neurosurgical communities with a blueprint for motion-preservation surgery.

While the foundational Turkish-American axis securely anchors the clinical registry and patient cohort data of the literature, our strategic mapping captures a major contemporary shift driven by East Asian academic centers. Over the past decade, a high-density research surge coming out of China, Taiwan, and South Korea has significantly accelerated the field's scientific volume [11, 12]. Crucially, this regional expansion introduces a distinct methodological transformation that marks the modern era of spine research. In contrast to the clinically oriented registries of the Mediterranean and North American pioneers, contemporary East Asian investigators focus intensely on advanced computer simulations, mathematical structural tracking, and bioengineering modeling. This surge has integrated sophisticated FEA directly into the heart of the dynamic stabilization discourse. East Asian research groups have successfully utilized multi-layered computational spine models to map out precise load-sharing configurations, predict the exact mechanical behavior of semi-rigid rods under multi-axial stress, and evaluate the biomechanical performance of hybrid constructs [11, 12]. The clinical translation of these computational findings is critical; modern FEA models directly assist practicing spine surgeons by predicting stress distributions and allowing for the customization of screw-rod interfaces to individual patient alignment before surgery.

This thematic diversification has effectively bridged the historical gap between pure benchtop bioengineering innovation and real-world clinical spine surgery. By providing predictive, mathematical data on stress distributions at the bone-screw interface and across adjacent segments, these modern computational studies have provided a solid mechanical rationale for the long-term clinical successes originally reported by the Turkish surgical cohorts. Consequently, contemporary literature has evolved into a highly balanced, interdisciplinary domain where surgical execution is continuously optimized by computational engineering insight. In sharp contrast to the sustained growth of pedicle-based dynamic systems and computational modeling, our strategic thematic clustering successfully identifies concepts that have drifted into declining quadrants. Most notably, complex posterior element reconstructions, specifically total facet arthroplasty, have experienced a steep drop in publication density, keyword centrality, and overall academic interest over the last decade [13].

This systematic decline reflects a broader, profound clinical consensus shift away from highly invasive, technically demanding motion-preserving hardware. Total facet arthroplasty devices were originally designed to completely replace degenerated posterior structures while maintaining segmental motion. However, long-term clinical tracking revealed prohibitive complication profiles, including high rates of device migration, early component loosening, persistent posterior column pain, and technically catastrophic revision scenarios [14]. The clear marginalization of facet arthroplasty keywords within our strategic mapping documents a collective retreat by the scientific community. The literature demonstrates that researchers and device manufacturers have largely abandoned extensive posterior arch replacements, redirecting the scientific focus back toward pedicle-based dynamic configurations and semi-rigid rod architectures. These systems achieve the desired goals of segment stabilization, load-sharing optimization, and ASD protection without destroying the underlying posterior spinal anatomy, ensuring a safer and more reproducible surgical profile.

Finally, this study has certain methodological limitations that must be acknowledged. The bibliometric analysis was conducted exclusively using the PubMed/MEDLINE database. While PubMed is widely regarded as a rigorous and definitive database for clinical spine surgery literature, the exclusion of other major databases such as Scopus or Web of Science may have resulted in the omission of broader multidisciplinary citation networks and certain bioengineering journals. Future mapping analyses incorporating multiple databases could provide an even more expansive view of the global literature.

Conclusion

This study establishes a comprehensive science mapping blueprint of the dynamic posterior spinal stabilization literature from 1999 to June 2026. The global landscape has successfully transitioned from basic hardware safety reporting to a sophisticated, engineering-driven computational discipline centered on finite element modeling and sagittal balance customization.

Driven by the prominent collaborative research axes connecting Turkish pioneers and East Asian cohorts to North American spine centers, pedicle screw-based dynamic and semi-rigid posterior instrumentation remains a highly active research field. Moving forward, integrating advanced computational simulations with long-term prospective patient registries will dictate the development of next-generation motion-preserving spinal implants.

Ethics Committee Approval: Since our manuscript was conducted through a literature review, no application was made to the ethics committee. Ethical principles and values were adhered to throughout our manuscript.

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Original Article PUBLIC HEALTH

Awareness of podological treatment methods and treatment preferences in individuals with ingrown toenails: A cross-sectional study from Turkiye

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ABSTRACT

OBJECTIVE: Ingrown toenail (onychocryptosis) is a common foot disorder that negatively affects quality of life and may lead to chronic inflammation and recurrence. Public awareness regarding podological treatment methods remains limited. This study aimed to evaluate awareness of podological treatment approaches, treatment preferences, and factors associated with ingrown toenails among adults living in Turkiye.

METHODS: This descriptive cross-sectional study included 1,144 individuals aged 18–60 years between June and October 2023. Data were collected using a 15-item questionnaire administered online. Sociodemographic characteristics, occupational factors, footwear habits, diabetes status, genetic predisposition, podology awareness, treatment preferences, and recurrence rates were evaluated. Statistical analyses were performed using Pearson's Chi-square test.

RESULTS: Chronic ingrown toenails were reported by 15.5% of participants, whereas 42.0% experienced occasional episodes. More than half of the participants (51.7%) had never heard of podology or orthonyxia applications, and only 16.2% had previously undergone treatment at a podology center. Chronic ingrown toenails were significantly associated with female sex, physically demanding occupations, inappropriate footwear use, diabetes, and family history ($p<0.05$). Self-management was the most common treatment preference (34.3%). Recurrence rates were significantly higher following surgical treatment compared with podological orthonyxia applications (67.6% vs. 28.7%, $p<0.001$).

CONCLUSION: Awareness of podological treatment methods in Turkiye remains insufficient. Conservative podological approaches were associated with lower recurrence rates than surgical treatment. Increasing public awareness and expanding access to podological care may contribute to improved management and prevention of ingrown toenails.

Keywords: Conservative treatment; ingrown toenail; onychocryptosis; orthonyxia; podology; public awareness.

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Ingrown toenail (onychocryptosis) is a common foot disorder characterized by penetration of the nail plate into the lateral periungual soft tissue, leading to pain, inflammation, tenderness, and infection [1, 2]. The condition most frequently affects the great toe and may significantly impair daily activities, ambulation, and overall quality of life. If left untreated, chronic inflammation, granulation tissue formation, and secondary infection may develop [1, 2].

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The etiology of ingrown toenails is multifactorial. Improper nail trimming habits, inappropriate footwear, genetic predisposition, trauma, hyperhidrosis, obesity, and diabetes are among the major risk factors [2–5]. In particular, the use of narrow-toed shoes and occupations requiring prolonged standing increase mechanical pressure on the nail plate, thereby facilitating disease development [4, 5].

Clinically, ingrown toenails are evaluated according to different stages. Based on the Heifetz classification, stage I is characterized by mild pain and erythema, stage II includes signs of infection, and stage III presents with granulation tissue and marked inflammation [6–8]. While conservative treatment modalities may provide successful outcomes in the early stages of the disease, advanced cases often require surgical intervention [2, 9].

In recent years, developments in podology have brought conservative podological treatment approaches to the forefront. Podology is a multidisciplinary healthcare field aimed at protecting foot health, preventing foot disorders, and managing these conditions using conservative methods. Orthonyxia techniques, packing applications, kinesio taping systems, and brace-wire applications are widely used in the management of ingrown toenails [10–17]. These methods may reduce the need for surgical intervention in early-stage cases and enable patients to return to daily life more rapidly [18–21].

Although podological practices have shown considerable development in Turkiye in recent years, public awareness regarding these approaches is still thought to be insufficient.

Although numerous studies in the literature have focused on the surgical and conservative treatment of ingrown toenails, studies evaluating public awareness of podological treatment modalities remain limited [2, 9]. Therefore, the present study aimed to evaluate the level of knowledge, treatment preferences, and tendencies regarding podological treatment methods among adults living in Turkiye.

Highlight key points

- Public awareness regarding podological treatment methods and orthonyxia applications remains insufficient in Turkiye.
- Female sex, physically demanding occupations, inappropriate footwear use, diabetes mellitus, and family history were significantly associated with chronic ingrown toenails.
- Self-management was the most commonly preferred treatment approach among individuals with ingrown toenails.
- Recurrence rates were considerably lower following conservative podological orthonyxia applications compared with surgical treatment methods.
- Increasing awareness of podology and expanding access to conservative foot care services may improve the management and prevention of ingrown toenails.

MATERIALS AND METHODS

Study Design and Participants

This descriptive cross-sectional study was designed to evaluate awareness of podological treatment methods and treatment preference tendencies among individuals with ingrown toenail. Ingrown toenail is a common foot health disorder influenced by numerous factors, including age, sex, occupation, footwear habits, genetic predisposition, and overall health status. In addition, access to healthcare services, socioeconomic conditions, and educational background may play significant roles in determining treatment preferences. Within this context, the study assessed the level of knowledge regarding podological treatment methods and approaches to ingrown toenail management among individuals aged 18–60 years living in Turkiye.

Study data were collected between June 15 and October 17, 2023, using an online questionnaire prepared in Google Forms. The survey targeted adults from the general population residing in Turkiye. The survey link was distributed through publicly accessible social media platforms, e-mail, and personal communication networks. Participation was voluntary, and only adults aged 18–60 years residing in Turkiye who were able to read and understand Turkish were eligible to participate. The minimum required sample size for the study was calculated as 1,067 participants, and data collection was terminated after reaching a total of 1,144 participants.

The sample size calculation was based on the 2021 data published by the Turkish Statistical Institute (TURKSTAT). Considering that the population aged 18–60 years in Turkiye was 53,018,176, the sample size was calculated using the formula for known populations. Assuming a 95% confidence interval, a margin of error of 0.03, and p=q=0.50, the minimum sample size was determined to be 1,067 individuals.

Study Variables and Questionnaire

The independent variables in the study included sociodemographic characteristics, occupational features, health

status, and knowledge of podological treatments. Sociodemographic variables included age, sex, educational status, and marital status. Occupational characteristics included physically demanding work, prolonged standing, and the types of footwear used due to occupational conditions. Regarding health status, diabetes and genetic predisposition were evaluated. In addition, participants' awareness of podology practices and podological treatment methods was assessed.

The dependent variables were defined as the presence or absence of a history of ingrown toenail and the health-related behaviors exhibited in cases of ingrown toenail. Participants were asked whether they had experienced ingrown toenails at any point in their lives and whether the condition was chronic or only occasionally recurrent.

Participants' ages were evaluated within the 18–60-year range. Sex was recorded as female or male. Educational status was categorized as primary school, high school or equivalent, associate degree, bachelor's degree, postgraduate degree, and other. Occupational groups were classified as worker, civil servant, self-employed, private sector employee, housewife, retired, student, and unemployed. Marital status was categorized into two groups: Married and single.

Participants were asked separately whether they worked in a physically demanding job and whether they stood for prolonged periods during the day. To evaluate occupational footwear habits, individuals were asked whether they used narrow, tight, or high-heeled shoes that were not suitable for their foot structure. In addition, the use of protective footwear within the scope of occupational health and safety practices was also assessed.

For the evaluation of diabetes status, participants were offered the response options "yes," "no," and "I do not know." The "I do not know" option was included to allow the evaluation of individuals who had not yet been diagnosed but suspected they might have diabetes. To assess genetic predisposition, participants were asked whether any family members or second- or third-degree relatives had a history of ingrown toenails. Response options were arranged as "very common," "rarely," and "none."

To evaluate awareness of podology, participants were asked whether they were familiar with podological practices. To avoid misinterpretation solely due to unfamiliarity with the term "podology," the questionnaire included explanatory examples such as nail brace applications, nail taping methods, tampon applications, and procedures performed using podology devices. In this way, not only terminology recognition but also awareness of practical applications was assessed. Response options were structured as "I have never heard of it before," "I have only heard of it," and "I have previously undergone a procedure at a podology center."

To determine preferred treatment approaches for ingrown toenails, participants were offered the options of self-treatment, pedicure care, application to a podology center, consultation with a physician, or other methods. Thus, the rate of preference for podological practices in society was compared with that for other treatment approaches.

In the final section of the questionnaire, participants were asked to select the statement that best described their ingrown toenail experience. This section included options related to recurrence after surgical intervention, outcomes following podological treatment, successful management using individual methods, or failure to benefit from any treatment approach. In this manner, the outcomes of different treatment approaches were comparatively analyzed.

Statistical Analysis

Statistical analyses of the obtained data were performed using IBM Statistical Package for the Social Sciences Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA). Sociodemographic characteristics, health conditions, and health-related behaviors of the participants were expressed as numbers and percentages for categorical variables and as mean±standard deviation for continuous variables. Associations between ingrown toenails and variables including age, sex, occupation, working conditions, footwear use, diabetes status, genetic predisposition, treatment preferences, and treatment outcomes were analyzed using Pearson's Chi-square test. $p<0.05$ was considered statistically significant.

Ethical Approval

This study was approved by the Institutional Ethics Committee of Marmara University (approval number: 09.2023.815; approval date: June 02, 2023) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants before participation in the study.

Table 1. Sociodemographic characteristics of the participants (n=1144)

Variables	Percentage
Sex	
Female	56.1
Male	43.9
Age groups	
18–25 years	10.9
26–33 years	17.4
34–42 years	27.6
43–51 years	26.6
52–60 years	17.5
Educational status	
Primary school	16.5
High school or equivalent	22.1
Associate degree	18.1
Bachelor's degree	35.1
Postgraduate degree	8.2

Table 2. Prevalence of ingrown toenails and associated factors

Variables	Chronic ITN (%)	Occasional ITN (%)	p
Female sex	17.3	37.8	0.003
Male sex	13.3	47.6	
Physically demanding work	17.3	47.8	0.002
Inappropriate footwear use	14.3	46.9	0.002
Presence of diabetes	24.8	45.9	<0.001
Family history	28.5	54.5	<0.001

ITN: Ingrown toenail. Percentages are calculated within groups. Pearson's Chi-square test was applied.

RESULTS

A total of 1,144 individuals aged 18–60 years were included in the study. Among the participants, 15.5% reported chronic ingrown toenails, 42.0% reported occasional ingrown toenails, and 42.3% reported no history of ingrown toenails.

Sociodemographic Characteristics

The mean age of the participants was 40.6±10.97 years. Of the participants, 56.1% were female, and 43.9% were male. Regarding educational status, 16.5% had a primary school education, 22.1% had graduated from high school or equivalent institutions, 18.1% held an associate degree, 35.1% had a bachelor's degree, and 8.2% had postgraduate education. In terms of marital status, 60.1% were married, and 39.9% were single. Workers, civil servants, and self-employed individuals constituted the majority of the occupational groups (Table 1).

Factors Associated with Ingrown Toenails

A statistically significant association was found between age groups and the presence of ingrown toenails (p<0.001). Chronic ingrown toenails were more common among individuals aged 52–60 years. The prevalence of chronic ingrown toenails was also significantly higher among women compared with men (p=0.003).

In addition, individuals engaged in physically demanding occupations, those using inappropriate footwear, participants diagnosed with diabetes mellitus, and individuals with a family history of ingrown toenails demonstrated significantly higher frequencies of chronic ingrown toenails (p<0.05) (Table 2).

Awareness of Podology

Among the participants, 51.7% reported that they had never previously heard of podology or orthonyxia applications. While 32.1% stated that they had only heard of these approaches, only 16.2% reported having previously undergone a procedure at a podology center.

Awareness of podology was significantly higher among individuals with chronic ingrown toenails. Among participants with chronic ingrown toenails, 44.4% had previously received treatment at a podology center. In contrast, most individuals without a history of ingrown toenails stated that they had never heard of podological applications (p<0.001) (Table 3).

Female participants demonstrated significantly higher awareness levels regarding podological applications compared with male participants (p=0.022).

Treatment Preferences

Self-management was the most commonly preferred treatment approach among participants with ingrown toenails (34.3%). Physician consultation was preferred by 29.5% of participants, while 21.6% preferred pedicure treatment and 14.7% reported that they would apply to a podology center (Table 4).

Table 3. Awareness of podology and orthonyxia

Podology awareness	n	Percentage
Never heard of it	591	51.7
Only heard of it	367	32.1
Previously underwent podology treatment	186	16.2
Podology awareness according to ITN history		
ITN status	Previously underwent podology treatment (%)	
Chronic ITN	44.4	
Occasional ITN	17.5	
No history of ITN	4.8	

P<0.001. Pearson's Chi-square test was applied. ITN: Ingrown toenail.

Table 4. Preferred treatment methods for ingrown toenails (n=1144)

Treatment preference	Percentage
Self-management	34.3
Physician consultation	29.5
Pedicure treatment	21.6
Application to a podology center	14.7

Table 5. Recurrence rates according to treatment methods

Treatment method	No recurrence n (%)	Recurrence n (%)
Surgical treatment	67 (32.4)	140 (67.6)
Orthonyxia/podological treatment	97 (71.3)	39 (28.7)

P<0.001. Pearson's Chi-square test was applied.

Treatment Outcomes and Recurrence Rates

Recurrence rates were significantly higher among individuals who underwent surgical treatment compared with those treated using podological orthonyxia applications. Recurrence was reported in 67.6% of surgically treated participants, whereas the recurrence rate following orthonyxia applications was 28.7%.

The absence of recurrence after podological treatment was observed in 71.3% of participants. In diabetic individuals, recurrence rates after surgical procedures were higher, whereas conservative podological applications were associated with lower recurrence rates ($p<0.001$) (Table 5).

DISCUSSION

Ingrown toenails are a common foot health problem that may occur in all age groups and in both sexes [1–3]. In the present study, health-related behaviors, treatment preferences, and awareness levels regarding podological applications among adults living in Turkiye were evaluated. The findings demonstrated that the level of public knowledge regarding podology and orthonyxia applications remains limited. The fact that more than half of the participants had never previously heard of podological applications suggests that podological services are still insufficiently recognized at the community level.

Conservative treatment methods are known to be effective, particularly in the early stages of ingrown toenails [2, 10, 13, 18, 22]. In stage I and stage II cases, conservative approaches such as orthonyxia applications, education on proper nail trimming, packing techniques, and appropriate footwear selection may reduce the need for surgical intervention [10–17]. Surgical treatment methods become more prominent in advanced-stage disease [23–27]. In our study, the lower recurrence rates observed in podological orthonyxia applications compared with surgical methods support the effectiveness of early conservative treatment approaches.

Only 16.2% of participants in the present study reported having previously undergone treatment at a podology center. Nevertheless, the relatively high preference for orthonyxia treatment among individuals

familiar with podological applications is noteworthy. This finding suggests that increasing awareness of podology may also increase the preference for conservative treatment methods.

Previous studies have generally reported that ingrown toenails are more common among young adults and males [4, 28]. Increased physical activity, excessive sweating, and greater susceptibility to trauma have been proposed as major contributing factors [3, 4]. However, in our study, the prevalence of chronic ingrown toenails was found to be higher among women. This difference may be associated with the use of narrow or inappropriate footwear, cosmetic practices, and lifestyle-related factors. Furthermore, the higher frequency of ingrown toenails observed in the middle-aged population in our study differs from some findings reported in the literature.

Improper footwear use is a well-established risk factor for the development of ingrown toenails [2, 4, 5]. Narrow-toed and unsuitable shoes may exert mechanical pressure on the nail plate, causing the lateral nail fold to become embedded into the surrounding soft tissue [4, 5]. In our study, the significantly higher prevalence of ingrown toenails among individuals wearing inappropriate footwear was consistent with previous literature [4, 5, 28]. Therefore, proper footwear selection appears to play an important role among preventive approaches.

One of the major findings of our study was the relationship between diabetes mellitus and ingrown toenails. Individuals diagnosed with diabetes demonstrated significantly higher rates of chronic ingrown toenails. Foot disorders are more common among diabetic individuals due to circulatory impairment, neuropathy, susceptibility to infection, and delayed wound healing [29–31]. Accordingly, early podological assessment and regular foot care are of considerable importance in diabetic patients.

A strong association was also identified between genetic predisposition and ingrown toenails. The significantly higher prevalence of chronic ingrown toenails among participants with a family history of the condition suggests the contribution of hereditary factors [4]. Since only a limited number of studies in the literature have investigated this relationship, the findings of the present study may provide valuable data for future research.

One of the most important challenges in the treatment of ingrown toenails is recurrence. High recurrence rates have frequently been reported following surgical treatment [23–27]. In our study, the recurrence rate was 67.6% among surgically treated individuals, whereas this rate was 28.7% among individuals treated with orthonyxia applications. These findings indicate that conservative podological applications may represent an effective option, particularly in early-stage cases. In addition, the podological approach contributes not only to treatment itself but also to preventive education regarding proper nail trimming, appropriate footwear selection, and foot hygiene.

This study has several strengths. To the best of our knowledge, it is one of the first studies to evaluate public awareness of podological treatment methods and treatment preferences for ingrown toenails in Turkiye using a large community-based sample. Nevertheless, several limitations should be acknowledged. First, the cross-sectional design precludes causal inferences. Second, the study relied on self-reported data collected through an online questionnaire, which may have introduced recall and selection bias. Third, clinical diagnoses of ingrown toenails were not confirmed by physical examination. Despite these limitations, the large sample size and inclusion of participants from different regions of Turkiye enhance the generalizability of the findings.

Conclusion

This study demonstrated that awareness of podological treatment methods among adults in Turkiye remains insufficient. Although ingrown toenails represent a common health problem, the rate of admission to podology centers was found to be low. The lower recurrence rates observed with conservative orthonyxia applications compared with surgical methods support the effectiveness of podological approaches.

Improper footwear use, diabetes, physically demanding working conditions, and genetic predisposition were identified as important risk factors for ingrown toenails. Expanding podological care services and ensuring early intervention, particularly for diabetic individuals, may play a critical role in preventing serious foot complications.

Increasing public awareness of podology, promoting conservative treatment approaches, and improving multidisciplinary foot health services are recommended. Furthermore, greater integration and visibility of podological applications within the healthcare system, along with support for further research in this field, appear necessary.

Ethics Committee Approval: This study was approved by The Clinical Research Ethics Committee of Marmara University (Approval number: 09.2023.815; Date: 02.06.2023).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Original Article PHYSICAL MEDICINE & REHABILITATION

The effect of the duration of transcutaneous electrical nerve stimulation on pain and functionality in the treatment of lumbar spondylosis

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ABSTRACT

OBJECTIVE: This study aimed to evaluate whether different durations of transcutaneous electrical nerve stimulation (TENS), specifically 20 and 30 min, produce distinct effects on pain and functionality in individuals diagnosed with lumbar spondylosis.

METHODS: A retrospective analysis was conducted involving 42 patients with lumbar spondylosis. Participants were assigned to two treatment groups. In addition to therapeutic ultrasound, superficial heat therapy, and exercise, Group 1 received TENS for 20 min, whereas Group 2 underwent the same treatment protocol with a 30-min TENS application. Pain intensity and functional status were assessed using the visual analog scale (VAS) and the Oswestry disability index (ODI) before treatment initiation and after completion of a 3-week intervention period. Outcomes were analyzed both within and between groups.

RESULTS: Following treatment, both groups exhibited significant reductions in VAS and ODI scores compared with baseline values ($p<0.001$). Comparison of treatment-related improvements revealed no significant differences between groups for either ΔODI or ΔVAS ($p=0.052$ and $p=0.943$, respectively). Although the between-group difference in ΔODI did not reach statistical significance, a moderate effect size favoring the 30-min TENS group was identified (Cohen's $d=0.618$). In contrast, the effect size for ΔVAS was minimal (Cohen's $d=0.022$).

CONCLUSION: The findings indicate that extending TENS application from 20 to 30 min does not provide additional benefits in terms of pain relief or functional recovery in patients with lumbar spondylosis. Given the comparable clinical outcomes, a 20-min TENS protocol may represent a more practical and cost-conscious approach for managing lumbar spondylosis-related low back pain.

Keywords: Low back ache; mechanical low back pain; physical therapy; transcutaneous electrical nerve stimulation.

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Lumbar spondylosis is a degenerative condition affecting the lumbar spine and is characterized by progressive changes involving the intervertebral discs, facet joints, and vertebral structures [1]. As a major source of chronic low back pain (LBP) and functional limitation, it contributes substantially to the global burden on healthcare systems. [2] The underlying mechanisms of lumbar spondylosis are complex and multifactorial, encompassing age-associated degeneration, hereditary influences, and long-term biomechanical stress exerted on the lumbar region [3–6].

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Non-pharmacological treatment strategies play an important role in the management of chronic musculoskeletal disorders, including persistent LBP. Among these approaches, electrical stimulation therapies have gained widespread acceptance due to their non-invasive nature and potential analgesic effects. Transcutaneous electrical nerve stimulation (TENS) remains one of the most extensively utilized electrical stimulation modalities in clinical rehabilitation settings [7–9].

The therapeutic action of TENS is believed to be mediated through modulation of nociceptive transmission at the spinal level as well as stimulation of descending inhibitory pain control mechanisms [7]. The widespread availability, ease of use, and ability for independent application have contributed to its popularity in routine clinical practice. Typically, TENS devices are compact, battery-operated systems designed to deliver electrical stimulation through surface electrodes positioned over or adjacent to the painful region of intact skin [10].

Although TENS has been widely investigated as a treatment option for chronic LBP, uncertainty remains regarding the optimal treatment parameters required to maximize its clinical benefits. Recent evidence syntheses have emphasized the necessity for additional studies exploring the impact of treatment variables such as stimulation intensity, frequency, dosage, and application duration [9]. Accordingly, the present study was designed to compare the clinical effects of 20-min and 30-min TENS sessions on pain intensity and functional status in patients experiencing LBP associated with lumbar spondylosis.

Highlight key points

- This study is, to the best of our knowledge, the first to directly compare 20-min and 30-min TENS application durations in individuals with lumbar spondylosis.
- Increasing the duration of TENS application from 20 to 30 min did not yield statistically superior clinical benefits.
- A 20-min TENS session may offer a more time-efficient and cost-effective option in routine clinical practice.
- These findings may contribute to the optimization of TENS application protocols for patients with lumbar spondylosis.

MATERIALS AND METHODS

This retrospective study included 42 patients with a diagnosis of lumbar spondylosis who were evaluated in the outpatient clinic between January 2023 and October 2025. Only individuals fulfilling the predefined eligibility criteria were enrolled in the analysis.

Eligible participants were men and women between 40 and 70 years of age who experienced LBP attributable to lumbar spondylosis, with or without radiation to the lower extremities, for a duration of at least 3 months. In addition, radiographic confirmation of degenerative lumbar spine changes was required for inclusion. Patients were excluded if they presented with lumbar disc herniation accompanied by neurological findings requiring surgery, pregnancy, spondylolysis, spondylolisthesis, degenerative listhesis, vertebral fractures, osteoporosis, suspected malignant disease, previous spinal surgical procedures, or any diagnosed rheumatologic, neurological, or psychiatric disorder. Individuals with contraindications to TENS treatment, including the presence of a cardiac pacemaker, were also not considered eligible.

This study was approved by the University of Health Sciences Hamidiye Non-Interventional Scientific Research Ethics Committee on August 19, 2025. (Decision number: 2025-16-2). The research was carried out in compliance with the ethical guidelines established by the 1964 Declaration of Helsinki and later updated versions. Written informed consent had been obtained from all patients whose records were retrospectively evaluated.

Treatment Protocol

Based on the treatment protocols documented in their medical records, the patients were divided into two groups. The rehabilitation program in Group 1 consisted of 20 min of TENS combined with therapeutic ultrasound, superficial heat application, and exercise therapy. Group 2 received an identical treatment regimen, with the only difference being a TENS duration of 30 min.

TENS was administered through four self-adhesive electrodes placed bilaterally at spinal levels corresponding to the patient's pain location. Stimulation settings included a pulse frequency ranging from 70 to 100 Hz, a pulse duration of 100 μs, and an intensity adjusted to the maximum level comfortably tolerated by each participant.

In addition to TENS, all patients underwent 20 min of infrared superficial heat therapy, 6 min of therapeutic ultrasound, and 15 min of core stabilization exercises during each treatment session. The rehabilitation program was delivered 5 times weekly for 3 consecutive weeks. Throughout the treatment period, the use of non-steroidal anti-inflammatory medications and other analgesics was prohibited, whereas medications prescribed for coexisting medical conditions were continued without modification.

Table 1. Demographic and clinical characteristics of the study groups

	Group 1 (n=21) Mean±SD (min-max)	Group 2 (n=21) Mean±SD (min-max)	p
Age	52.0±10.1 (40–70)	48.1±8.81 (40–69)	0.186
Gender (%)			
Female	52.4	61.9	0.533
Male	47.6	38.1	
Weight (kg)	76.90±14.00 (55–100)	81.00±16.06 (52–100)	0.333
Height (cm)	171.86±9.45 (157–188)	173.00±9.27 (156–188)	0.694
BMI	25.91±4.89 (17.20–35.20)	27.10±5.46 (18.60–39.50)	0.462
Duration (years)	4.38±2.06 (2–8)	5.24±2.19 (2–9)	0.174
ODI baseline	24.24±3.85	26.48±3.50	0.056
VAS baseline	6.14±1.74	5.95±1.99	0.743

SD: Standard deviation; BMI: Body mass index; ODI: Oswestry disability index; VAS: Visual Analog Scale.

Outcome Assessment

Clinical evaluations were performed before treatment initiation and on completion of the 3-week intervention period.

Assessment of pain was performed with the visual analog scale (VAS). Patients rated their pain at rest and during activity on a numerical continuum ranging from 0 to 10, with higher scores indicating greater pain severity [11].

Functional disability was assessed using the Oswestry disability index (ODI). This questionnaire comprises 10 domains. Each item is scored on a six-point scale from 0 to 5. The ODI percentage score was calculated according to the following formula:

ODI (%) = [Total score/(number of completed items×5)]×100

Higher ODI values indicate greater disability, whereas lower scores reflect better functional performance [12].

Outcome Measures

The primary endpoint of the study was the treatment-related change in VAS score. Changes in ODI score following the intervention were evaluated as the secondary endpoint.

Statistical Analysis

Sample size estimation was performed before data analysis using G*Power software (version 3.1.9.7, Düsseldorf, Germany). Based on a projected moderate effect size (Cohen's d=0.5), a two-sided significance level of 0.05, and a statistical power of 90%, the minimum required sample size was calculated as 40 participants.

All statistical analyses were conducted using the Statistical Package for the Social Sciences version 21.0. Continuous variables were reported as mean±standard deviation or median with interquartile range according to their distribution characteristics, while categorical variables were expressed as counts and percentages.

Distribution normality was assessed using the Shapiro–Wilk test. Comparisons of categorical variables between groups were performed with the Chi-square test. Baseline differences in continuous variables were evaluated using either the independent samples t-test or the Mann–Whitney U-test, depending on data distribution. Changes within each group from baseline to post-treatment were examined using paired samples t-tests. Treatment-related changes (Δ values calculated as post-treatment minus baseline scores) were compared between groups using the independent samples t-test or Mann–Whitney U-test where appropriate. Effect sizes were quantified using Cohen's d statistic. Statistical significance was defined as p-value below 0.05.

RESULTS

No statistically significant differences were identified between the groups regarding demographic characteristics at baseline (Table 1).

Baseline clinical assessments are summarized in Table 1. The two groups demonstrated comparable initial ODI and VAS scores, with no statistically significant differences observed prior to treatment (ODI: p=0.056; VAS: p=0.743).

Table 2. Within-group changes following treatment in Group 1 and Group 2

Group	Baseline, Mean±SD	Post-treatment, Mean±SD	Mean difference (%95 CI)	p	Cohen's d
ODI					
1	24.24±3.85	14.76±2.41	9.48 (7.63, 11.32)	<0.001	2.34
2	26.48±3.50	14.48±1.89	12.00 (10.12, 13.88)	<0.001	2.91
VAS					
1	6.14±1.74	2.76±1.09	3.38 (2.51, 4.25)	<0.001	1.77
2	5.95±1.99	2.62±1.02	3.33 (2.26, 4.40)	<0.001	1.42

SD: Standard deviation; ODI: Oswestry Disability Index; VAS: Visual Analog Scale.

Table 3. Between-group comparison of treatment-induced change

	Group 1, Mean±SD	Group 2, Mean±SD	p	Cohen's d
ΔODI (post-pre)	9.48±4.04	12.00±4.12	0.052	-0.618
ΔVAS (post-pre)	3.38±1.91	3.33±2.35	0.943	0.022

SD: Standard deviation; ODI: Oswestry Disability Index; VAS: Visual Analog Scale.

Evaluation of within-group changes revealed significant clinical improvement following the intervention in both treatment groups. In Group 1, mean ODI and VAS scores were significantly lower after treatment compared with baseline measurements ($p<0.001$ for both comparisons). Similarly, patients in Group 2 experienced significant reductions in both disability and pain scores at the end of the treatment period ($p<0.001$ for both outcomes) (Table 2).

The magnitude of treatment-related improvement was further examined by comparing the changes in ODI and VAS scores between groups. Analysis of ΔODI and ΔVAS values demonstrated no statistically significant differences between the 20-min and 30-min TENS protocols ($p=0.052$ and $p=0.943$, respectively) (Table 3).

Although the between-group comparison for ΔODI did not reach the predefined threshold for statistical significance, the observed effect size favored Group 2 and was within the moderate range (Cohen's $d=0.618$). This finding may indicate a potentially relevant clinical trend toward greater functional improvement with the 30-min TENS protocol. In contrast, the effect size calculated for ΔVAS was negligible (Cohen's $d=0.022$), suggesting that extending TENS duration had little influence on pain reduction outcomes.

DISCUSSION

The present study evaluated whether different TENS application durations influence treatment outcomes in patients with lumbar spondylosis. Although no significant difference was observed between the 20-min and 30-min TENS protocols regarding pain reduction or functional improvement, both treatment approaches resulted in significant improvements compared with baseline values. Furthermore, the reduction in pain scores exceeded the minimum clinically important difference (MCID) threshold in both groups, while the improvement in functional status surpassed the MCID threshold only in the group receiving 30-min TENS sessions. Overall, these findings support previous evidence demonstrating the beneficial effects of TENS on pain control and functional recovery in patients with LBP associated with degenerative lumbar conditions.

Despite the widespread clinical use of TENS, limited evidence is available regarding the optimal duration of treatment sessions in patients with lumbar spondylosis. Therefore, the present study focused specifically on comparing two commonly used application durations. By evaluating the clinical outcomes of 20-min and 30-min TENS protocols under otherwise identical treatment conditions, this study contributes to the ongoing effort to establish more standardized treatment parameters for TENS therapy.

The improvements observed in this study are consistent with the literature. Ezgi Aydın et al. [13] demonstrated significant reductions in pain intensity and disability scores following a treatment program that included 20-

min TENS sessions administered over 15 treatment visits, with no treatment-related adverse effects reported. Similarly, the addition of TENS to conventional kinesitherapy has been associated with meaningful improvements in both pain and functional capacity among individuals with chronic non-specific LBP [14]. In another study, Alizadeh and Ahmadizad [15] compared medical treatment alone, exercise combined with medical treatment, and TENS combined with medical treatment, reporting superior clinical outcomes in the group receiving TENS.

Evidence supporting the analgesic effects of TENS has also been reported in placebo-controlled studies. Dias et al. [16] found that 30-min TENS applications delivered at different stimulation frequencies produced significant pain relief compared with placebo treatment in patients with chronic LBP. Likewise, Elserty et al. [17] observed significant improvements in pain and functional performance after 40-min TENS sessions when compared with exercise alone. Similar findings were reported by Ezema et al. [18], who demonstrated greater pain reduction in patients receiving active TENS than in those receiving sham stimulation. Furthermore, Kibar et al. [19] showed that combining TENS with interferential current therapy resulted in better functional outcomes and reduced activity-related pain compared with interferential current alone, although no superiority was demonstrated over TENS monotherapy. Yaksi et al. [20] also concluded that 30-min TENS treatment was an effective and safe option for short-term pain management in patients with chronic LBP.

Although the between-group comparison of ΔODI did not achieve statistical significance ($p=0.052$), a moderate effect size favoring the 30-min TENS group was observed (Cohen's $d=0.618$). This finding suggests that the absence of statistical significance may be attributable, at least in part, to the relatively small sample size of the present study. Consequently, the possibility of a clinically relevant difference between treatment durations cannot be completely excluded and should be further examined in larger-scale studies.

Previous studies have employed a wide range of TENS treatment durations, highlighting the lack of consensus regarding the optimal application time [13, 18, 20–22]. A recent systematic review concluded that TENS may provide short-term pain relief in individuals with chronic LBP; however, the authors also emphasized the need for additional research investigating the influence of stimulation parameters such as intensity, frequency, dosage, and treatment duration [9]. In the present study, stimulation frequency and treatment dose were kept constant, allowing the isolated evaluation of treatment duration. A review of the available evidence identified a gap in the literature regarding direct comparisons of 20-min and 30-min TENS application periods in patients with lumbar spondylosis-related LBP.

Study Limitations

Only treatment duration was examined, whereas other potentially influential TENS parameters, including stimulation frequency and dosage, were not investigated. Future prospective studies with larger patient populations and varying stimulation protocols are warranted to further optimize and standardize TENS treatment strategies.

Conclusion

The present results demonstrated that extending TENS application from 20 to 30 min did not result in additional benefits in terms of pain reduction or functional improvement among patients with lumbar spondylosis. Given the comparable clinical outcomes observed between the two intervention durations, a 20-min TENS session may represent a more time-efficient and cost-effective treatment option in routine clinical practice. The adoption of shorter treatment sessions may also improve resource utilization and increase patient access to rehabilitation services without compromising therapeutic effectiveness.

Ethics Committee Approval: This study was approved by The University of Health Sciences Hamidiye Non-Interventional Scientific Research Ethics Committee on August 19, 2025. (Decision number: 2025-16-2).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Original Article Cardiovascular Surgery

Early surgical outcomes of cardiac myxoma resection according to dominant clinical phenotype in adult patients

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ABSTRACT

OBJECTIVE: This study aimed to evaluate the early surgical outcomes according to the dominant clinical presentation in adult patients undergoing cardiac myxoma resection.

METHODS: A total of 315 patients who underwent cardiac mass resection procedures in a single center were retrospectively analyzed. After the exclusion criteria were applied, 133 consecutive adult patients who underwent surgical resection of histopathologically confirmed cardiac myxoma between January 2004 and December 2024 in a single center. Patients were categorized into four groups according to their dominant clinical presentation at diagnosis: asymptomatic, cardiac/obstructive, embolic, and constitutional. Baseline characteristics, tumor features, operative variables, and early post-operative outcomes were compared among the groups.

RESULTS: The median age was 63 years, and 63.9% of patients were female. Cardiac/obstructive symptoms represented the most frequent dominant presentation (47.4%). Major early post-operative outcomes were comparable among groups, whereas post-operative atrial fibrillation (AF) and intensive care unit/hospital stay were significantly higher in the cardiac/obstructive group.

CONCLUSION: Dominant clinical presentation was not associated with differences in major early post-operative outcomes following cardiac myxoma resection. Cardiac/obstructive presentation was associated with more post-operative AF and longer recovery.

Keywords: Cardiac myxoma; cardiac surgery; clinical presentation; early post-operative outcome.

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Primary cardiac tumors are rare, and myxomas represent the most common benign primary cardiac tumor in adults [1]. These benign tumors most frequently originate from the interatrial septum, particularly in the left atrium (LA), though they can rarely occur in other cardiac chambers [2]. The tumor's location, size, and structure influence the clinical presentation and are crucial for planning the surgical approach [3]. Although myxomas are benign, they can cause life-threatening hemodynamic and embolic complications.

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These complications may include acute heart failure due to valvular dysfunction or intracardiac obstruction, as well as systemic or pulmonary embolization [4]. Embolization most frequently transpires in the vessels of the central nervous system and may manifest as a stroke or transient ischemic attack [5]. These risks can lead to sudden clinical deterioration or death. Therefore, early diagnosis and prompt surgical intervention are essential.

The clinical presentation of myxoma is highly heterogeneous [6]. Clinical presentation can be categorized into four groups: 1-asymptomatic, 2-cardiac/obstructive symptoms, 3-embolic symptoms, and 4-constitutional symptoms. Cardiac/obstructive symptoms, including dyspnea, chest pain, and palpitations, can mimic other cardiac pathologies [1]. Constitutional symptoms such as fever, fatigue, sweating, and weight loss represent the most insidious form of the disease given the fact that these symptoms may occur in a wide range of other conditions [7]. Given this heterogeneous clinical presentation, evaluating early post-operative outcomes according to dominant presentation phenotype may provide clinically useful information for perioperative risk assessment. The literature on cardiac myxomas offers valuable insights into their clinical spectrum, surgical management, and outcomes. However, in most reports, clinical presentation is reported as part of baseline clinical characterization rather than being used as the primary axis of post-operative outcome analysis [8]. Although presentation-oriented analyses exist, including studies focused on embolic events and series using broader clinical categories such as hemodynamic or systemic manifestations, these approaches do not fully capture the dominant symptom phenotype in relation to early post-operative outcomes [9, 10]. These studies highlight the clinical relevance of presentation at diagnosis, but they do not fully address whether the dominant presenting phenotype is associated with early post-operative outcomes after surgical resection. Therefore, evaluating patients according to dominant clinical presentation may add a clinically oriented perspective to existing anatomical and surgical outcome data.

This study aimed to evaluate baseline characteristics, tumor-related features, operative findings, and early post-operative outcomes according to dominant clinical presentation in adult patients undergoing surgical resection for cardiac myxoma.

Highlight key points

- Cardiac/obstructive symptoms were the most common dominant presentation of cardiac myxoma.
- Major early post-operative outcomes were comparable across dominant clinical presentation phenotypes.
- Cardiac/obstructive presentation was associated with a higher incidence of post-operative atrial fibrillation.
- Patients with cardiac/obstructive symptoms experienced longer intensive care unit and hospital stays.
- Dominant clinical presentation may contribute to perioperative risk stratification despite similar early surgical safety.

MATERIALS AND METHODS

Study Design and Patient Population

This retrospective, single-center, observational cohort study included 133 adult patients with surgically treated, histopathologically confirmed cardiac myxoma between January 2004 and December 2024 at our institution. The study was approved by The Üsküdar University Ethics Committee (Approval number: 61351342/020-126). Demographic, clinical, laboratory, and surgical data were obtained from patient files and the hospital database. The study was conducted in accordance with the Declaration of Helsinki. Among 315 patients who underwent surgical treatment for a cardiac mass, 144 had histopathologically confirmed cardiac myxoma. After application of the exclusion criteria, 133 patients were included in the final analysis. Patients were excluded if they were younger than 18 years at the time of surgery (n=5), had incomplete medical records preventing adequate assessment of clinical or operative variables (n=5), or had undergone previous surgery for recurrent cardiac myxoma (n=1). The flow diagram shows the cohort of the study (Fig. 1).

Pre-operative Work-up and Operative Technique

In the pre-operative assessment, patients' demographic data, clinical profiles, comorbidities, and presenting symptoms were documented. All patients underwent transthoracic echocardiography before surgery. The surgical strategy was then developed based on a comprehensive echocardiographic evaluation, which included assessment of the tumor's location, size, and anatomical relationships to the relevant valve and adjacent structures. Transesophageal echocardiography (TEE) and cardiac computed tomography (CT) or magnetic resonance imaging (MRI) were not routinely performed but only in cases deemed necessary.

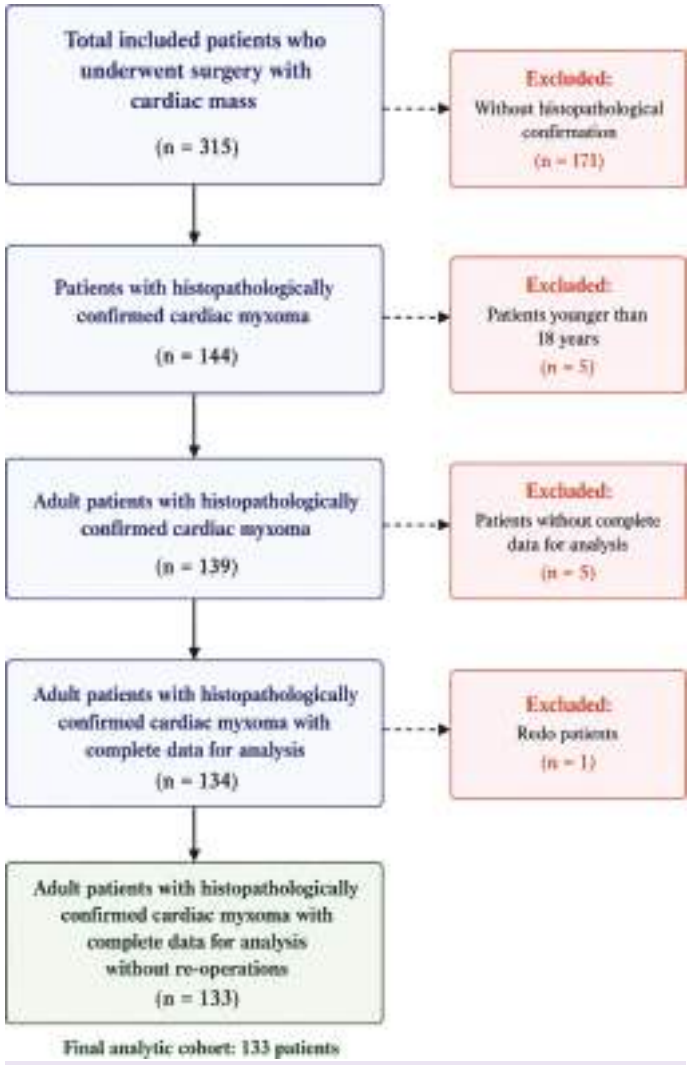

FIGURE 1. Data-flowchart of the study cohort.

Median sternotomy was performed under general anesthesia. Following aortic and bicaval cannulation, cardiopulmonary bypass (CPB) was established. The aorta was cross-clamped, and myocardial arrest was achieved via cardioplegia. Cardiac incisions were individualized considering the tumor location, size, and anatomical relationships. When appropriate, right/left atriotomy, transseptal approach, and right/left ventriculotomy were employed. Tumors attached to the atrial septum were resected en bloc with their base whenever feasible. Interatrial septal resection, if required, was followed by primary closure or patch repair of the resulting defect. In all cases, intraoperative fragmentation was avoided. After tumor excision, concomitant cardiac procedures were performed if needed. Upon weaning from CPB, all patients underwent TEE to confirm absence of residual tumor. The resected tissue was sent to the pathology department for histopathological examination and diagnostic confirmation.

Outcome Measures and Definitions

Early post-operative outcomes were analyzed according to the dominant clinical presentation at diagnosis. Patients were stratified into four mutually exclusive clinical phenotype groups based on the predominant presenting manifestation recorded at diagnosis: 1-asymptomatic, 2-cardiac/obstructive, 3-embolic, and 4-constitutional presentations.

Early post-operative outcomes included 30-day mortality, post-operative atrial fibrillation (AF), post-operative stroke, post-operative pulmonary thromboembolism (PTE), low cardiac output syndrome (LCOS), reoperation for bleeding, permanent pacemaker implantation, length of intensive care unit (ICU) stay, and total hospital stay. Thirty-day mortality was defined as any death occurring within 30 days after surgery or during the index hospitalization. Post-operative AF was defined as new-onset AF occurring during the index hospitalization after surgery; patients with pre-existing AF were excluded from this outcome. Post-operative stroke was defined as any new focal or global neurological deficit, whether transient or permanent, confirmed by clinical assessment and cerebral CT or MRI. Post-operative PTE was defined as a clinically suspected pulmonary thromboembolic event confirmed by appropriate imaging. LCOS was defined as post-operative hemodynamic compromise requiring continuous inotropic support for more than 24 h to maintain adequate systemic perfusion and cardiac output, or the need for mechanical circulatory support, including an intra-aortic balloon pump or extracorporeal membrane oxygenation, in the absence of hypovolemia or other reversible causes.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as median (range), and categorical variables were presented as number (n) and percentage (%). Comparisons among dominant clinical presentation phenotype groups were performed using the Kruskal-Wallis test for continuous variables. Categorical variables were compared using Pearson's Chi-square test or Fisher's exact test, depending on the expected cell counts. All statistical tests were two-sided, and a $p<0.05$ was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the overall cohort are presented in Table 1. The median age was 63 years, and 85 patients were female (63.9%). The most common dominant presentation was cardiac/obstructive symptoms (47.4%), followed by asymptomatic presentation (18.8%), embolic presentation (18.0%), and constitutional symptoms (15.8%). Most tumors were located in the LA (82.0%). Post-operative AF occurred in 21 patients (15.8%), post-operative stroke in 5 patients (3.8%), and 30-day mortality in 5 patients (3.8%).

Baseline and tumor-related characteristics according to dominant symptom group are presented in Table 2. Median age was 59 years in the embolic group, 63 years in the cardiac/obstructive group, 67 years in the constitutional group, and 63 years in the asymptomatic group, with no statistically significant difference among groups (p=0.127). Tumor location, tumor dimensions, pre-operative ejection fraction (EF), prior cardiac surgery, pre-operative AF, and history of other cancer were also similar among the four groups.

Operative characteristics according to dominant symptom group are presented in Table 3. Operative variables did not differ significantly according to dominant symptom group. Median CPB time was 72.5 min in the embolic group, 80 min in the cardiac/obstructive group, 68 min in the constitutional group, and 70 min in the asymptomatic group (p=0.170). The distribution of concomitant procedures was not significantly different between groups (p=0.143).

Early post-operative outcomes were compared across the dominant symptom groups. ICU stay differed significantly among groups, although the median value was 1 day in all groups (p=0.046). Median hospital stay was 8 days in the cardiac/obstructive group, whereas 7 days same in the embolic group and in the constitutional, and 6 days in the asymptomatic group (p=0.043). Post-operative AF was more frequent in the cardiac/obstructive group than in the embolic, constitutional, and asymptomatic groups (25.4% vs. 8.3%, 4.8%, and 8.0%, respectively; p=0.038). Permanent pacemaker implantation, post-operative stroke or PTE, reoperation for bleeding, LCOS, and 30-day mortality were not significantly different among groups. The data regarding these parameters are given in Table 4.

Table 1. Clinical and perioperative characteristics

Characteristic	Value (n=133)
Age	63 (18–92)
Female sex (%)	63.9
HT (%)	45.9
DM (%)	35.3
CAD (%)	30.1
Dominant symptom (%)	
Embolic	18
Cardiac/obstructive	47.4
Constitutional	15.8
Asymptomatic	18.8
Tumor location (%)	
LA	82
RA	11.3
LV	3
LA+RA	2.3
RV	1.5
Tumor size (max. diameter, mm)	35 (12–90)
Pre-operative EF (%)	60 (35–68)
Prior cardiac surgery (%)	31.6
Pre-operative AF	9.8
Other cancer	8.3
CPB time (min)	76 (28–146)
Cross-clamp time (min)	41 (14–111)
Concomitant procedure (%)	
CABG	14.3
Valve	8.3
CABG+Valve	0.8
ICU stay (days)	1 (1–9)
Hospital stay (days)	7 (1–28)
Post-operative AF	21 (15.8)
Permanent pacemaker implantation	8 (6)
Post-operative stroke/PTE	
Stroke	5 (3.8)
PTE	2 (1.5)
Reoperation for bleeding	6 (4.5)
Low cardiac output syndrome	
IABP	3 (2.3)
ECMO	1 (0.8)
30-day mortality	5 (3.8)

Continuous variables are presented as median (range), and categorical variables are presented as n (%). AF: Atrial fibrillation; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CPB: Cardiopulmonary bypass; DM: Diabetes mellitus; ECMO: Extracorporeal membrane oxygenation; EF: Ejection fraction; HT: Hypertension; IABP: Intra-aortic balloon pump; ICU: Intensive care unit; LA: Left atrium; LV: Left ventricle; PTE: Pulmonary thromboembolism; RA: Right atrium; RV: Right ventricle.

TABLE 2. Baseline and tumor characteristics according to dominant symptom groups

Characteristic	Embolic (n=24)	Cardiac/obstructive (n=63)	Constitutional (n=21)	Asymptomatic (n=25)	p
Age	59 (23–78)	63 (18–86)	67 (35–83)	63 (33–92)	0.127☐
Female sex (%)	50	66.7	76.2	60	0.289☐
HT (%)	50	47.6	52.4	32	0.468☐
DM (%)	41.7	34.9	47.6	20	0.223☐
CAD (%)	45.8	30.2	28.6	16	0.157☐
Tumor location (%)					
LA	75	82.5	90.5	80	0.599☐
RA	20.8	9.5	0	16	
LV	4.2	3.2	4.8	0	
LA+RA	0	3.2	0	4	
RV	0	1.6	4.8	0	
Tumor size (mm)	34.5 (15–76)	36 (15–90)	34 (12–69)	36 (12–76)	0.666☐
Pre-operative EF (%)	60 (40–68)	60 (35–65)	60 (35–60)	60 (35–65)	0.101☐
Prior cardiac surgery (%)	20.8	30.2	52.4	28	0.127☐
Pre-operative AF (%)	16.7	11.1	9.5	0	0.259☐
Other cancer (%)	12.5	7.9	4.8	8	0.818☐

Continuous variables are presented as median (range), and categorical variables are presented as n (%). a: Kruskal-Wallis test; b: Pearson Chi-square test; c: Fisher's exact test. P<0.05 was considered statistically significant. AF: Atrial fibrillation; CAD: Coronary artery disease; DM: Diabetes mellitus; EF: Ejection fraction; HT: Hypertension; LA: Left atrium; LV: Left ventricle; RA: Right atrium; RV: Right ventricle

TABLE 3. Operative data according to dominant symptom groups

Characteristic	Embolic (n=24)	Cardiac/obstructive (n=63)	Constitutional (n=21)	Asymptomatic (n=25)	p
CPB time (min)	72.5 (34–146)	80 (28–146)	68 (41–145)	70 (36–132)	0.170[a]
Cross-clamp time (min)	37.5 (15–101)	46 (14–111)	37 (23–94)	39 (15–92)	0.204[a]
Concomitant procedure					0.143[c]
CABG	20.8	19	9.5	0	
Valve	4.2	9.5	14.3	4	
CABG + Valve	0	0	0	4	

Continuous variables are presented as median (range), and categorical variables are presented as n (%). a: Kruskal-Wallis test; c: Fisher's exact test. P<0.05 was considered statistically significant. CABG: Coronary artery bypass grafting; CPB: Cardiopulmonary bypass

DISCUSSION

In this study, we evaluated early post-operative outcomes after surgical resection of cardiac myxoma according to the dominant clinical presentation at diagnosis. Clinical presentation in cardiac myxoma has traditionally been categorized into obstructive or hemodynamic symptoms, embolic events, constitutional manifestations, and asymptomatic or incidental presentation [9, 11]. However, previous studies have mainly used these categories for descriptive clinical characterization rather than for evaluating early post-operative risk [12]. In this context, the present study may provide a clinically practical perspective by focusing on presentation phenotype rather than only on anatomical or surgical variables. The main finding was that dominant presentation groups were

Table 4. Early post-operative outcomes according to dominant symptom groups

Characteristic	Embolic (n=24)	Cardiac/obstructive (n=63)	Constitutional (n=21)	Asymptomatic (n=25)	p
ICU stay (days)	1 (1–6)	1 (1–9)	1 (1–2)	1 (1–5)	**0.046[a]**
Hospital stay (days)	7 (1–27)	8 (5–18)	7 (4–11)	6 (2–28)	**0.043[a]**
Post-operative AF	2 (8.3)	16 (25.4)	1 (4.8)	2 (8)	**0.038[c]**
Permanent pacemaker implantation	2 (8.3)	5 (7.9)	1 (4.8)	0	0.533[c]
Post-operative stroke/PTE					
Stroke	1 (4.2)	1 (1.6)	2 (9.5)	1 (4)	0.544[c]
PTE	0	2 (3.2)	0	0	
Reoperation for bleeding	0	5 (7.9)	0	1 (4)	0.303[c]
Low cardiac output syndrome					
IABP	1 (4.2)	0	2 (9.5)	0	0.151[c]
ECMO	0	1 (1.6)	0	0	
30-day mortality	1 (4.2)	3 (4.8)	0	1 (4)	0.93[c]

Continuous variables are presented as median (range), and categorical variables are presented as n (%). a: Kruskal–Wallis test; c: Fisher's exact test. P<0.05 was considered statistically significant. AF: Atrial fibrillation; ECMO: Extracorporeal membrane oxygenation; IABP: Intra-aortic balloon pump; ICU: Intensive care unit; PTE: Pulmonary thromboembolism.

broadly comparable in terms of baseline, tumor-related, and operative characteristics, and major early adverse outcomes were generally similar among groups. Although embolic presentation is generally considered one of the most clinically concerning manifestations of cardiac myxoma, it did not translate into higher early post-operative mortality or morbidity in our cohort. This finding suggests that a pre-operative embolic event may define the mode of presentation without necessarily indicating a worse early surgical prognosis after resection. Patients presenting with cardiac/obstructive symptoms had a higher rate of post-operative AF and a longer ICU and hospital stays, with statistically significant differences among the groups. These findings suggest that dominant symptom phenotype may not substantially alter early surgical safety after myxoma resection but may still offer useful perioperative information regarding rhythm-related complications and post-operative recovery.

The overall cohort profile was broadly consistent with the classical clinical pattern of cardiac myxoma, in which female predominance, LA location, and cardiac/obstructive symptoms are commonly reported [11, 13]. In the present cohort, women constituted 63.9% of patients, LA tumors accounted for 82.0% of cases, and cardiac/obstructive symptoms were the most frequent dominant presentation. These findings closely parallel the worldwide meta-analysis by Oktaviono et al. [12], which included 8150 patients and reported a female prevalence of 64.3%, LA location in 85.3%, and cardiovascular symptoms as the most common clinical manifestation. However, our cohort differed in terms of age, with a median age of 63 years compared with a mean age of 51 years in the meta-analysis. This difference is clinically relevant because older age may increase perioperative vulnerability and may partly contribute to the higher early mortality observed in our series. In the meta-analysis, early mortality after myxoma surgery was 1.27%, supporting the favorable early outcomes of surgical excision [12]. Similarly, Shah et al. [14] reported a low operative mortality rate of 0.5%. Jiang et al. [15] reported an early in-hospital mortality rate of 0.7%. In this context, the 30-day mortality rate of 3.8% in our cohort was higher than that reported in some large series. Nevertheless, early mortality after myxoma surgery is not uniformly negligible across all cohorts. Nektaria et al. [16] reported an in-hospital mortality rate of 2.8%, whereas Alhasso et al. [17] reported a 30-day mortality rate of 3.75%, with fatal outcomes occurring in the setting of concomitant valve surgery or reoperation. Therefore, the mortality rate in our cohort appears to be higher than some low-mortality series, but comparable to reports involving more complex surgical settings. This difference may be partly explained by the

older age and higher surgical complexity of the present cohort. Prior cardiac surgery was present in 31.6% of patients, and concomitant coronary artery bypass grafting and/or valve procedures were performed in 23.4%. Thus, early mortality in the present cohort should not be interpreted as the risk of isolated myxoma excision alone, but within the broader context of advanced age, redo surgery, concomitant cardiac procedures, and real-world perioperative complexity. All patients in the present cohort underwent surgery via median sternotomy, and no minimally invasive tumor excision was performed. This provides a relatively homogeneous surgical framework for interpreting perioperative outcomes. However, in the contemporary era, minimally invasive approaches are increasingly being applied even to complex cardiac procedures, underscoring that the absence of minimally invasive cases should be considered when positioning our experience within current surgical practice [18].

The most notable phenotype-related difference in early post-operative outcomes was post-operative AF. In our cohort, post-operative AF was more frequent in the cardiac/obstructive group than in the embolic, constitutional, and asymptomatic groups (25.4% vs. 8.3%, 4.8%, and 8.0%, respectively, p=0.038). This finding is clinically relevant because pre-operative AF, EF, CPB time, cross-clamp time, and concomitant procedures were not significantly different among the dominant symptom groups. Therefore, the higher post-operative AF rate in the cardiac/obstructive group may not be explained solely by baseline rhythm status or operative complexity. Sahin et al. [19] identified older age and increased P-wave dispersion as factors associated with post-operative AF, supporting the concept that an underlying atrial substrate may contribute to post-operative rhythm instability. In the present study, cardiac/obstructive presentation may reflect greater pre-operative hemodynamic burden, intermittent mitral inflow obstruction, increased atrial wall stress. These factors, together with perioperative atrial irritability, could predispose to post-operative AF. Although these mechanisms cannot be confirmed without variables such as LA size, pulmonary pressure, or transmitral gradient, the findings suggest that patients presenting with cardiac/obstructive symptoms may require closer post-operative rhythm surveillance despite having similar major early adverse outcomes compared with other presentation groups.

In addition to post-operative AF, ICU stay, and hospital stay differed significantly across dominant symptom groups. Although the median ICU stay was 1 day in all groups, the range was widest in the cardiac/obstructive group (p=0.046). Hospital stay was also longest in the cardiac/obstructive group (p=0.043). Therefore, prolonged post-operative stay in the cardiac/obstructive group may reflect a combination of post-operative AF surveillance, hemodynamic stabilization, symptom-related pre-operative vulnerability, and discharge decision-making rather than an increase in severe post-operative morbidity. This interpretation is consistent with the broader cardiac surgery literature showing that hospital stay is a multifactorial outcome. Ceylan et al. [20] reported that patients with extended hospital stay after cardiac surgery were older, more frequently had coronary artery disease and chronic obstructive pulmonary disease, and had longer CPB time. Although their cohort differs from ours, these findings support the concept that post-operative stay reflects the combined effect of patient profile, operative complexity, and post-operative events. In the present study, CPB time, cross-clamp time, and concomitant procedures were not significantly different among symptom groups, suggesting that the longer ICU and hospital stays in the cardiac/obstructive group may be more closely related to presentation phenotype and post-operative rhythm-related recovery than to operative complexity alone.

This study has several limitations. Its retrospective single-center design, limited sample size, and reliance on medical records may introduce selection bias, limit causal inference, and restrict the generalizability of the findings. Dominant symptom classification was based on available clinical records, and overlap between embolic, cardiac/obstructive, constitutional, and asymptomatic presentations may not have been completely eliminated. Although the overall cohort size was acceptable for a single-center myxoma series, some symptom subgroups were relatively small and unbalanced, limiting statistical power for less frequent outcomes. The number of early adverse events was limited, which restricted the use of robust multivariable adjustment. Late mortality and recurrence were not included in the final analysis because of incomplete follow-up data.

Conclusion

Dominant symptom phenotype was not associated with significant differences in major early adverse outcomes, including 30-day mortality and post-operative stroke or PTE. However, cardiac/obstructive presentation was associated with a higher rate of post-operative AF and

longer ICU and hospital stays. These findings suggest that presentation phenotype may provide clinically useful perioperative information, particularly for anticipating rhythm-related complications and post-operative recovery, without necessarily indicating an increased risk of major early morbidity or mortality. Further studies with larger cohorts, standardized symptom classification, and detailed echocardiographic and hemodynamic data are needed to confirm these observations.

Ethics Committee Approval: This study was approved by The Uskudar University Non-Interventional Research Ethics Committee. (Approval number: 61351342/020-126 – 31.03.2026).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE GENERAL SURGERY

Comparison of 5-year glycemic outcomes after sleeve gastrectomy and Roux-en-Y gastric bypass in patients with pre-operative dysglycemia

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ABSTRACT

OBJECTIVE: The long-term effects of bariatric surgery on glucose metabolism are well established; however, comparative data regarding glycemic outcomes after laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (RNYGB) in patients with pre-operative dysglycemia remain limited. This study aimed to compare 5-year glycemic outcomes following LSG and RNYGB in patients with prediabetes or Type 2 diabetes mellitus.

METHODS: This retrospective cohort study included patients with pre-operative dysglycemia (HbA1c ≥5.7%) who underwent primary LSG or RNYGB between January 2010 and December 2021 at a tertiary referral center and had at least 5 years of follow-up. Demographic characteristics, HbA1c levels, weight loss outcomes, and glycemic status were evaluated. Glycemic status was categorized as diabetes, prediabetes, or normal glycemia according to HbA1c levels.

RESULTS: A total of 142 patients were included, of whom 107 underwent LSG and 35 underwent RNYGB. Baseline HbA1c levels were similar between groups (7.70±1.83% vs. 6.87±1.53%, p=0.619). At 5 years, mean HbA1c was significantly lower in the RNYGB group compared with the LSG group (5.57±0.64% vs. 5.85±0.68%, p=0.033). Total weight loss percentage was greater after RNYGB (28.13±13.79% vs. 24.04±10.72%), although the difference was not statistically significant (p=0.084). Significant improvement in glycemic status was observed following bariatric surgery (p<0.001). At 5 years, normal glycemia was achieved in 44 (41.1%) patients after LSG and 22 (62.9%) patients after RNYGB, whereas persistent diabetes was observed in 10 (9.3%) and 2 (5.7%) patients, respectively.

CONCLUSION: Bariatric surgery resulted in significant long-term improvement in glycemic status among patients with pre-operative dysglycemia. Although both LSG and RNYGB effectively reduced the prevalence of diabetes and prediabetes, RNYGB was associated with lower HbA1c levels and a higher proportion of patients achieving normal glycemia at 5 years. These findings suggest that RNYGB may provide superior long-term glycemic outcomes in patients with obesity-associated dysglycemia.

Keywords: Bariatric surgery; dysglycemia; HbA1c; prediabetes; Roux-en-Y gastric bypass; sleeve gastrectomy; type 2 diabetes mellitus.

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Over the past two decades, bariatric surgery has evolved from a purely weight-loss intervention into an effective metabolic treatment. Landmark randomized trials have demonstrated superior glycemic control and higher rates of diabetes remission following bariatric surgery compared with intensive medical therapy alone. Furthermore, long-term follow-up studies have confirmed the durability of these benefits, with metabolic improvements persisting for up to 10 years after surgery [1, 2].

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The growing evidence supporting metabolic surgery has led to significant changes in international treatment recommendations. Metabolic surgery is now recognized as an effective therapeutic option for patients with obesity and type 2 diabetes mellitus (T2DM) and has been incorporated into treatment algorithms by major international diabetes and surgical societies [3]. More recently, an international consensus statement established standardized definitions for diabetes remission, further emphasizing the role of surgery in the management of obesity-associated dysglycemia [4].

Identification of factors associated with long-term metabolic success after bariatric surgery has become an area of increasing interest. In a previous study from our institution, elevated pre-operative HbA1c levels were associated with less favorable long-term weight loss outcomes, suggesting that pre-operative glycemic burden may influence post-operative results beyond diabetes remission alone [5].

Among currently performed bariatric procedures, laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (RNYGB) are the two most commonly performed operations worldwide. Although both procedures produce substantial weight loss and metabolic improvement, previous comparative studies and meta-analyses have suggested that RNYGB may provide superior diabetes remission and glycemic outcomes compared with LSG [6–8].

Therefore, the aim of the present study was to evaluate long-term glycemic outcomes in patients with pre-operative dysglycemia (HbA1c ≥5.7%) undergoing LSG or RNYGB and to compare post-operative glycemic status and HbA1c levels at 5 years following surgery.

Highlight key points

- Bariatric surgery provided significant long-term improvement in glycemic status in patients with pre-operative dysglycemia.
- Both sleeve gastrectomy and Roux-en-Y gastric bypass effectively reduced diabetes and prediabetes at 5 years.
- Roux-en-Y gastric bypass achieved significantly lower HbA1c levels than sleeve gastrectomy after 5 years.
- Superior glycemic outcomes after Roux-en-Y gastric bypass occurred despite similar long-term weight loss.

MATERIALS AND METHODS

Study Design and Patient Selection

This retrospective cohort study was conducted at a tertiary referral center specializing in bariatric and metabolic surgery. The institutional database was reviewed to identify all patients who underwent primary LSG or RNYGB between January 2010 and December 2021.

Patients were eligible for inclusion if they had a pre-operative HbA1c level of ≥5.7%, indicating prediabetes or T2DM, and had at least 5 years of post-operative follow-up data available. Patients with normal pre-operative glycemic status (HbA1c <5.7%), those who underwent revisional bariatric procedures, patients with incomplete pre-operative metabolic data, and those with <5 years of follow-up were excluded. Fourteen patients who did not continue with the 5-year follow-up and three patients who underwent gastrointestinal surgery were excluded from the study. Patients were evaluated with blood tests during routine check-ups, and vitamin and mineral supplements were prescribed to address any deficiencies.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Scientific Research Ethics Committee of Fatih Sultan Mehmet Training and Research Hospital (approval no: 2026-05; approval date: 30.06.2026).

Data Collection

Demographic, clinical, and laboratory data were extracted from electronic medical records. Collected variables included age, sex, type of bariatric procedure, pre-operative HbA1c levels, and post-operative HbA1c levels at the 5th post-operative year. Weight loss outcomes were assessed using total weight loss percentage (TWL%).

Patients were categorized according to their pre-operative glycemic status as prediabetes (HbA1c 5.7–6.4%) or diabetes mellitus (HbA1c ≥6.5%). At the 5th post-operative year, glycemic status was classified as normal glycemia (HbA1c <5.7%), prediabetes (HbA1c 5.7–6.4%), or diabetes mellitus (HbA1c ≥6.5%).

Outcomes

The primary outcome was glycemic status at 5 years after surgery. Secondary outcomes included changes in HbA1c levels and TWL%.

For patients with pre-operative diabetes mellitus, post-operative glycemic outcomes were further categorized as:

- Complete remission: Transition from diabetes to normal glycemia (HbA1c <5.7%)

TABLE 1. Comparison of LSG and RNYGB groups

Variables	LSG (n=107)	RNYGB (n=35)	p
Age (years)	40.65±9.70	45.20±9.47	0.017
Female sex, (%)	82.2	91.4	0.192
HbA1c pre-operative (%)	7.70±1.83	6.87±1.53	0.619
HbA1c at 5 years (%)	5.85±0.68	5.57±0.64	0.033
TWL (%)	24.04±10.72	28.13±13.79	0.084

LSGL: Laparoscopic sleeve gastrectomy; RNYGB: Roux-en-Y gastric bypass; TWL: Total weight loss.

- Partial remission: Transition from diabetes to prediabetes (HbA1c 5.7–6.4%)
- Persistent diabetes: HbA1c ≥6.5% at 5 years postoperatively.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation, while categorical variables were presented as frequencies and percentages. Comparisons between the LSG and RNYGB groups were performed using the independent samples t-test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables, as appropriate.

A two-sided p<0.05 was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics software (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 142 patients with pre-operative dysglycemia (HbA1c ≥5.7%) and at least 5 years of follow-up were included in the study. Of these, 107 patients underwent LSG and 35 underwent RNYGB.

Baseline characteristics and metabolic outcomes are summarized in Table 1. Patients in the RNYGB group were significantly older than those in the LSG group (45.20±9.47 vs. 40.65±9.70 years, p=0.017). The proportion of female patients was similar between groups (91.4% vs. 82.2%, p=0.192). Pre-operative HbA1c levels did not differ significantly between the two groups (6.87±1.53% vs. 7.70±1.83%, p=0.619). At the 5th post-operative year, mean HbA1c levels were significantly lower in the RNYGB group compared with the LSG group (5.57±0.64% vs. 5.85±0.68%, p=0.033). TWL% was numerically greater after RNYGB than after LSG (28.13±13.79% vs. 24.04±10.72%); the difference did not reach statistical significance (p=0.084).

TABLE 2. Changes in glycemic status from baseline to 5 years after surgery

	Pre-operative	Post-operative 5 years	p
LSG (%) n=107			<0.001
Diabetes	65.4	9.3	
Prediabetes	34.6	49.5	
Normal glycemia	0	41.1	
RNYGB (%) n=35			
Diabetes	54.3	5.7	
Prediabetes	45.7	31.4	
Normal glycemia	0	62.9	

LSG: Laparoscopic sleeve gastrectomy; RNYGB: Roux-en-Y gastric bypass.

Changes in glycemic status between baseline and the 5th post-operative year are presented in Table 2. In the LSG group, 70 patients had pre-operative diabetes, and 37 had pre-operative prediabetes. At 5 years, 44 patients achieved normal glycemia, 53 remained in the prediabetic range, and 10 had persistent diabetes. In the RNYGB group, 19 patients had pre-operative prediabetes, and 16 had pre-operative diabetes. At the 5th post-operative year, 22 patients achieved normal glycemia, 11 remained prediabetic, and only two patients had persistent diabetes.

Overall, bariatric surgery resulted in a significant improvement in glycemic status, with a marked shift from diabetes and prediabetes toward normal glycemia at 5 years postoperatively (p<0.001). The distribution of post-operative glycemic outcomes is illustrated in Figure 1. Patients undergoing RNYGB demonstrated a higher proportion of normal glycemia and a lower proportion of persistent diabetes compared with those undergoing LSG. Notably, the more favorable 5-year glycemic outcomes in the RNYGB group were observed despite the significantly older age of these patients, which would generally be expected to negatively affect long-term glycemic improvement.

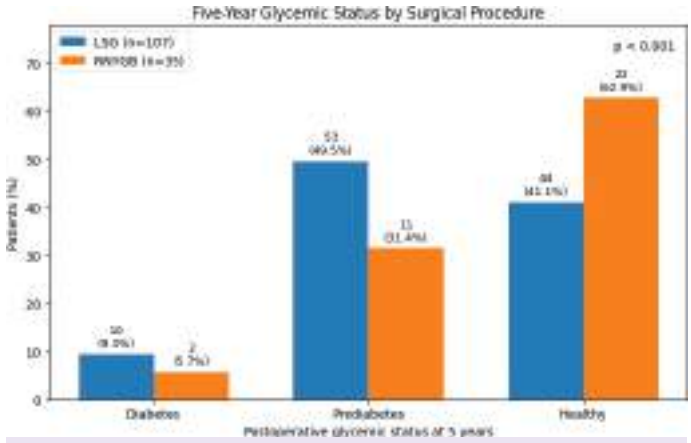

FIGURE 1. Five- year glycemic status by surgical procedure.

DISCUSSION

In the present study, bariatric surgery resulted in significant long-term improvement in glycemic status among patients with pre-operative dysglycemia. Both LSG and RNYGB were associated with a substantial reduction in the burden of diabetes and prediabetes, accompanied by a marked shift toward normal glycemia at 5 years after surgery. Furthermore, patients undergoing RNYGB achieved significantly lower HbA1c levels at long-term follow-up compared with those undergoing LSG.

An important observation in the present study was the favorable outcome among patients with pre-operative prediabetes. The majority of prediabetic patients either achieved normal glycemia or remained within the prediabetic range, while progression to overt diabetes was uncommon. These findings suggest that bariatric surgery may alter the natural history of dysglycemia and potentially prevent progression toward established diabetes. Such observations further support current recommendations advocating earlier metabolic intervention in selected high-risk patients [3, 4].

The comparison between procedures revealed significantly lower HbA1c levels at 5 years among patients undergoing RNYGB. Although both procedures produced substantial metabolic benefits, our findings are in agreement with previous comparative studies suggesting superior glycemic outcomes after gastric bypass procedures. Borgeraas et al. [6] reported higher diabetes remission rates after RNYGB in their meta-analysis, while McTigue et al. [7] and subsequent comparative studies similarly demonstrated more favorable long-term glycemic outcomes following bypass procedures [6–8].

The mechanisms underlying these differences remain incompletely understood but are likely multifactorial. While weight loss is a major contributor to improved insulin sensitivity, bariatric surgery also induces profound metabolic changes independent of weight reduction. Alterations in incretin secretion, gut hormone signaling, bile acid metabolism, intestinal glucose handling, and nutrient delivery have all been implicated in post-operative glycemic improvement [9–12]. These physiological changes are generally more pronounced following RNYGB, potentially explaining the lower HbA1c levels observed in bypass patients despite similar weight loss outcomes.

Interestingly, despite achieving significantly lower HbA1c levels, patients undergoing RNYGB did not experience significantly greater total weight loss than those undergoing LSG. This observation supports the concept that long-term metabolic improvement cannot be explained solely by the magnitude of weight reduction. Previous studies have similarly demonstrated that diabetes remission and glycemic control are influenced by complex metabolic adaptations beyond simple weight loss alone [11–13].

Long-term observational studies have consistently confirmed the durability of metabolic improvements after bariatric surgery. Aminian and colleagues demonstrated sustained metabolic benefits and improved patient-reported outcomes following metabolic surgery, while more recent investigations from large bariatric cohorts have reported durable diabetes remission despite partial weight regain [13, 14]. Similarly, Meira et al. [15] reported persistent diabetes remission beyond 10 years after bariatric surgery in a substantial proportion of patients. The results of the present study are in agreement with these findings and further support the long-term effectiveness of bariatric surgery in patients with dysglycemia.

This study has several limitations. The retrospective design, the relatively small sample size in the bypass group, and potential selection bias may have influenced the results. In addition, differences in post-operative follow-up and medical management may have affected long-term glycemic outcomes. The absence of multivariable adjustment and the relatively small, unequal surgical groups limit causal interpretation of the observed differences. Nevertheless, the study possesses several strengths, including the evaluation of a well-defined dysglycemic population and the availability of long-term follow-up extending to 5 years.

Conclusion

Bariatric surgery resulted in significant long-term improvement in glycemic status among patients with preoperative dysglycemia. Both LSG and RNYGB effectively reduced the burden of diabetes and prediabetes; however, RNYGB was associated with lower HbA1c levels and a greater proportion of patients achieving normal glycemia at 5 years. These findings support the role of metabolic surgery in the management of obesity-related dysglycemia and suggest that RNYGB may provide superior long-term glycemic outcomes in selected patients.

Ethics Committee Approval: This study was approved by The Scientific Research Ethics Committee of Fatih Sultan Mehmet Training and Research Hospital (approval no. 2026-05; approval date: 30.06.2026).

Informed Consent: The requirement for informed consent was waived due to the retrospective study design.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Authorship Contributions: Concept – IT, YG; Design – IT, YG; Supervision – IT, YG; Resource – IT, YG; Materials – IT, YG; Data Collection and/or Processing – IT, YG; Analysis and/or Interpretation – IT, YG; Literature Search – IT, YG; Writing – IT, YG; Critical Reviews – IT, YG.

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Original Article CARDIOVASCULAR SURGERY

Hemodynamic optimization of a novel single-puncture dual-lumen coaxial catheter for arteriovenous fistula access: A computational fluid dynamics study

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ABSTRACT

OBJECTIVE: Arteriovenous fistula (AVF) is the gold standard for hemodialysis access, but traditional dual-needle cannulation is limited by a restricted cannulation area and progressive stenosis; single-puncture systems may reduce these risks if hemodynamics can be optimized to prevent recirculation. This study aimed to design a novel single-puncture dual-lumen coaxial catheter and to evaluate its hemodynamic performance, flow efficiency, and recirculation rate using high-resolution computational fluid dynamics (CFD).

METHODS: In this CFD and design-optimization study, a dual-lumen coaxial catheter with a unique fenestration geometry was designed and analyzed using SolidWorks Flow Simulation at a physiological temperature of 37°C. Boundary conditions included an AVF flow rate of 1000 mL/min and a dialysis pump speed of 300 mL/min. The primary endpoints were flow velocity, shear stress, and recirculation control.

RESULTS: CFD simulation (1,030,641 cells) showed a maximum flow velocity of 12.69 m/s and a peak calculated shear stress of 2,602.45 Pa at the narrowest lumen section; because blood damage depends on both stress magnitude and exposure time, these computational data alone do not establish blood compatibility. Thermodilution analysis yielded a theoretical recirculation rate of 0.007% under the modeled conditions, and flow trajectories showed spatial separation of the venous jet from the arterial intake.

CONCLUSION: Under the modeled steady-state conditions (AVF flow, 1000 mL/min; dialysis pump flow, 300 mL/min), CFD predicted stable separation of the return and aspiration streams and a theoretical recirculation rate of 0.007%. These proof-of-concept findings support further geometric optimization and physical testing; they do not establish clinical safety, efficacy, or superiority over standard dual-needle cannulation.

Keywords: Arteriovenous fistula; computational fluid dynamics; dialysis; hemodialysis catheter; recirculation; single-puncture catheter.

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End-stage renal disease remains a global health challenge requiring long-term renal replacement therapy. While in-center hemodialysis is prevalent, home hemodialysis is increasingly considered to improve patient autonomy and selected outcomes [1, 2]. Reliable vascular access is essential. The autogenous arteriovenous fistula (AVF) is preferred in appropriate patients because of its patency and infection profile compared with grafts or central venous catheters [3–6]. A standard thrice-weekly schedule requires 156 treatment sessions and, with two needle entries per session, approximately 312 routine needle entries per year. Repeated cannulation can contribute to local complications, but this arithmetic puncture count does not establish that a single larger access device causes less net tissue trauma.

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Mechanical puncture trauma contributes to local access complications, whereas AVF stenosis and failure are multifactorial processes in which neointimal hyperplasia and abnormal hemodynamic forces play central roles [7–9]. Limited or difficult cannulation anatomy may require secondary procedures such as basilic vein superficialization or transposition [10–12]. Earlier single-needle techniques reported recirculation and clearance limitations [13, 14], but contemporary systems, including the single-needle single-pump system evaluated by Bieser et al. [15], have demonstrated improved dialysis performance. Thus, modern single-needle therapy should not be characterized solely by the limitations of historical systems.

Advanced catheter geometries may provide simultaneous dual-lumen flow through one access site. Prior computational fluid dynamics (CFD) studies have shown the value of evaluating catheter geometry, flow separation, velocity, and recirculation before physical testing [16–18]. The present study was designed as a computational proof-of-concept to develop a single-puncture coaxial geometry and evaluate its predicted hemodynamic performance at one prespecified AVF flow rate (1000 mL/min) and one dialysis pump flow rate (300 mL/min).

Highlight key points

- A novel single-puncture, dual-lumen coaxial catheter was designed to enable simultaneous arteriovenous fistula aspiration and return through one access site.
- High-resolution CFD simulation predicted a theoretical recirculation rate of only 0.007% under the modeled steady-state conditions (AVF flow 1000 mL/min; dialysis pump flow 300 mL/min).
- Flow trajectories showed spatial separation of the venous return jet from the arterial aspiration zone, supporting the structural flow-separation hypothesis of the coaxial design.
- A localized peak shear stress of 2,602.45 Pa was calculated, but hemolysis safety and clinical blood compatibility were not established by this computational model alone.
- These proof-of-concept findings support further geometric optimization and physical flow-loop, hemolysis, and pre-clinical testing before any claim of clinical benefit over standard dual-needle cannulation.

MATERIALS AND METHODS

Ethical Considerations

This study did not require approval from an institutional ethics committee (Institutional Review Board). It is a purely computational (in silico) engineering analysis; the modeled "arteriovenous fistula" and "vessel" are idealized computational-domain geometries, not tissue from an actual patient. The study did not enroll human participants, use identifiable patient data, involve animal subjects, or include any physical prototype, clinical procedure, or intervention. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Geometric Design

The novel dual-lumen coaxial catheter was modeled in a 3D CAD environment (Shapr3D, Shapr3D Inc., Budapest, Hungary). The inner lumen carries venous return, and the annular outer lumen provides arterial aspiration through side fenestrations (Fig. 1). The modeled intravenous segment is 10.5 cm long with a 7Fr outer profile. Arterial aspiration openings are distributed from 2.1 to 4.5 cm, leaving a 6 cm separation between the most distal aspiration region and the venous return tip. These dimensions were selected through CAD-based geometric iteration to preserve two flow paths and spatially separate aspiration from return; alternative lengths, diameters, and fenestration areas were not evaluated in the present study. In a proposed clinical workflow, not tested here, an access needle would enter the AVF, a guidewire would be advanced through the needle, the needle would be withdrawn, and the catheter would be advanced over the guidewire after appropriate tract preparation (Seldinger technique). This proposed workflow may assist tracking through gently curved anatomy, but it does not eliminate the requirement for a sufficiently long and safely traversable venous segment. No physical prototype, insertion test, or clinical usability study was performed.

CFD Simulation

Hemodynamic performance was evaluated using SolidWorks Flow Simulation (Dassault Systèmes SolidWorks Corp., Waltham, MA, USA). The host environment was modeled as a mature AVF vein. Blood was represented as a Newtonian fluid (density 1050 kg/m^3, dynamic viscosity 0.0035 Pa.s) at 37°C, consistent with simplifications commonly used in catheter CFD studies [18].

Boundary Conditions and Protocol

- AVF flow: Set at 1000 mL/min to replicate a high-flow fistula environment
- Dialysis flow: Constant 300 mL/min for both aspiration and return
- Recirculation quantification: Conducted using a ther-

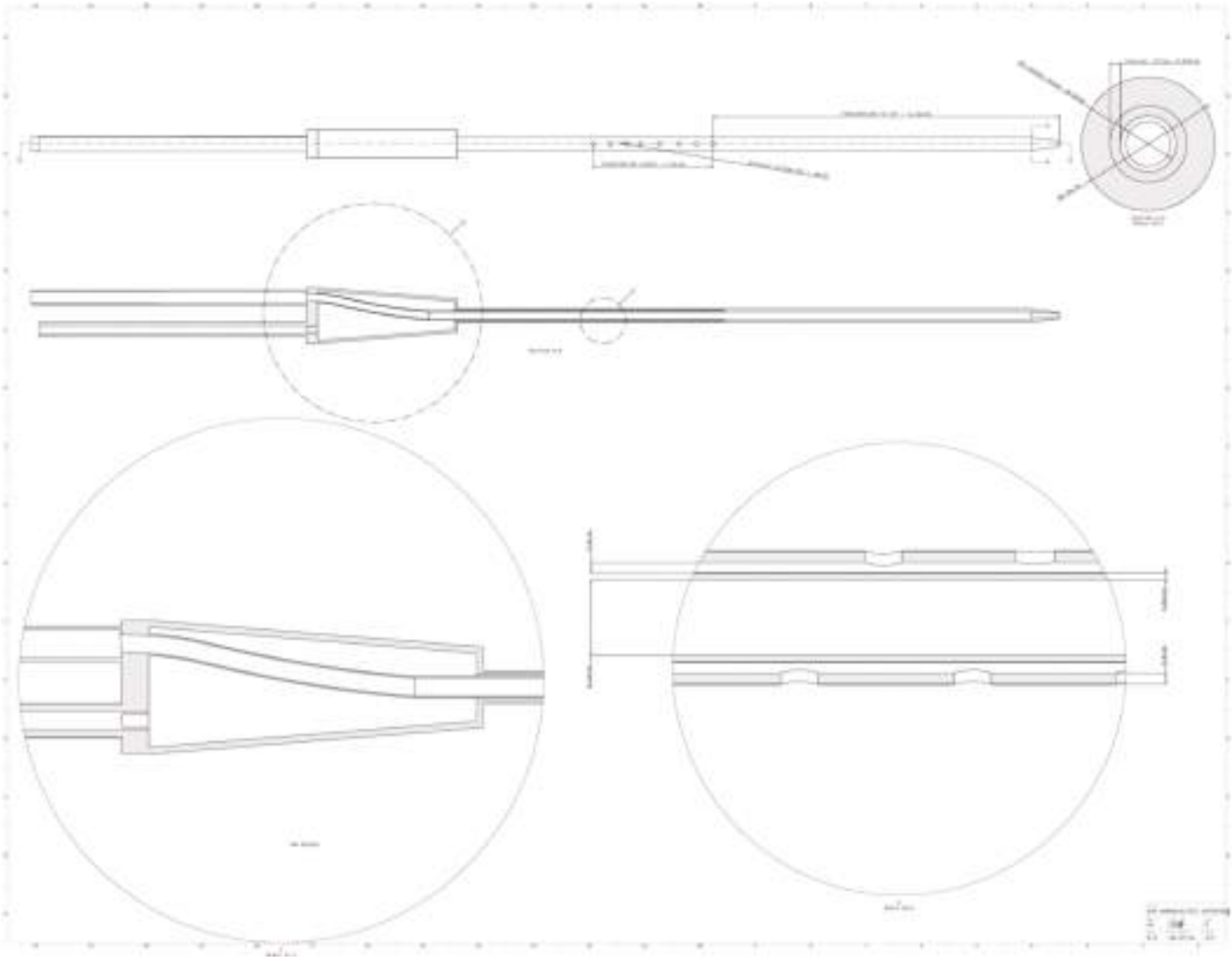

Figure 1. CAD design drawing. The modeled catheter has a coaxial structure with arterial and venous machine connection ports at the proximal hub. The inner lumen carries venous return to the distal tip, while arterial aspiration side holes are positioned between 2.1 and 4.5 cm. A 6 cm separation is maintained between the aspiration region and return tip. The intravenous segment is 10.5 cm long with a 7Fr outer profile. These dimensions represent the computational prototype and were not validated in an insertion study.

mal fluid approach known as the thermodilution technique (35°C venous return vs. 37°C systemic blood)

- Numerical convergence: A high-resolution mesh of 1,030,641 cells (615,959 fluid cells) was utilized. Numerical convergence was achieved at 681 iterations, ensuring stable mass flow and pressure results.

Statistical Analysis

This study reports a single deterministic CFD simulation performed under one prespecified set of boundary conditions, without experimental replicates, comparison groups, or randomization. Accordingly, inferential statistical analysis and hypothesis testing were not applicable; all reported values (flow velocity, shear stress, pressure, and thermodilution-based recirculation rate) are descriptive outputs extracted directly from the CFD solver at numerical convergence.

RESULTS

Numerical Convergence

Convergence was confirmed at 681 iterations. Mass balance was perfectly maintained, with inlet and outlet flow rates remaining constant at 300 mL/min (Fig. 2).

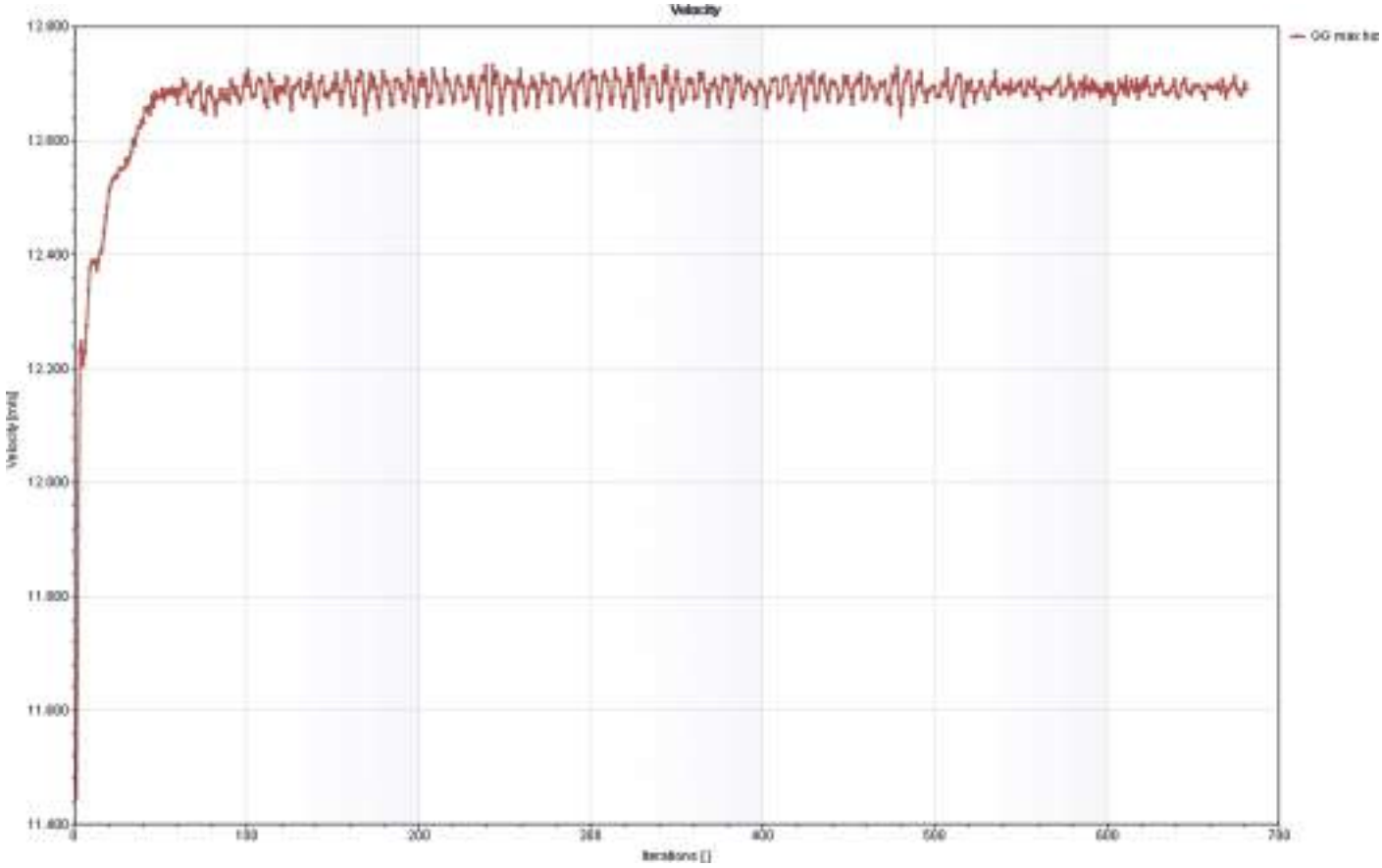

FIGURE 2. Convergence history of maximum flow velocity. The graph demonstrates the iteration history for the maximum velocity during the simulation. Following an initial steep increase, the maximum velocity oscillates within a stable, narrow band starting from approximately the 50th iteration. This stabilization confirms that numerical convergence was successfully achieved over the total 681 iterations.

Hemodynamic Performance

Maximum flow velocity was 12.69 m/s within the catheter lumens (Fig. 3). Flow trajectories showed a linear jet at the venous outlet directed away from the arterial aspiration zone (Fig. 4). The peak calculated shear stress was 2,602.45 Pa at the narrowest lumen section. The model did not calculate a validated exposure-time-based hemolysis index, and no blood damage testing was performed. Accordingly, the biological significance and safety of this localized peak cannot be established from the present simulation and require bench and *in vivo* validation.

Flow trajectories around and within the coaxial catheter were evaluated at a constant AVF flow of 1000 mL/min and a dialysis pump flow of 300 mL/min. The simulation showed spatial separation of the venous return jet from the arterial intake region under this single idealized condition. The model does not represent lower-flow AVFs, physiological vessel compliance, pulsatility, or patient-specific anatomy.

Pressure and Recirculation

A stable pressure difference of approximately 60 mmHg was observed between the modeled vessel and arterial inlet. The reported absolute pressures were 879.14 mmHg for the vessel and 819.59 mmHg for the arterial inlet; after subtracting standard atmospheric pressure (approximately 760 mmHg), the corresponding gauge pressures were approximately 119 mmHg and 60 mmHg. Thermal tracking produced a temperature difference of 0.00014°C at the arterial intake and a theoretical recirculation rate of 0.007% (Fig. 5). These values describe only the specified computational boundary conditions and should not be interpreted as clinical validation.

DISCUSSION

Under the specified computational conditions, the coaxial geometry produced a theoretical recirculation

Figure 3. Internal flow velocity distribution according to pressure change within the catheter lumens. Computational fluid dynamics visualization of the internal hemodynamic profile. The color gradient indicates variations in flow velocity, with a recorded maximum of 12.69 m/s localized at the narrowest cross-sections of the catheter. These high-velocity regions correspond to transient peaks in shear stress (maximum 2,602.45 Pa), characterized by extremely brief erythrocyte transit times.

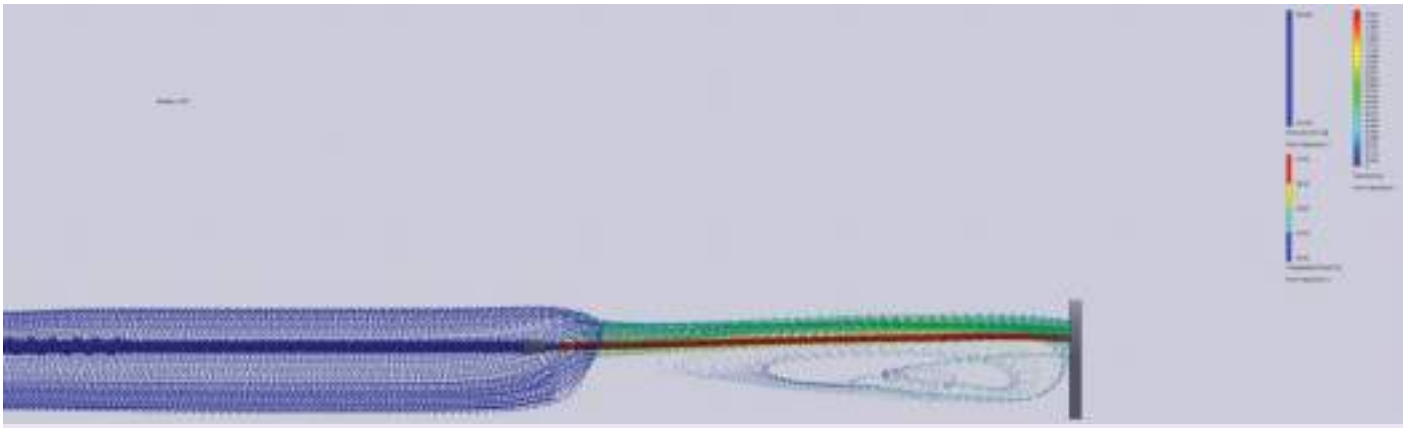

Figure 4. Flow trajectory and streamline visualization at the venous outlet. Computational fluid dynamics visualization of the modeled return-flow dynamics. Streamlines form a jet directed away from the arterial aspiration region. The full-catheter view represents the closed computational domain and is not a clinical implantation schematic.

rate of 0.007% and spatial separation of the return and aspiration streams. Earlier single-needle studies reported recirculation and clearance limitations [13, 14], whereas Bieser et al. [15] demonstrated that a contemporary single-needle system can achieve improved dialysis performance. The present design should therefore be viewed as an alternative engineering approach to flow separation, not as evidence that modern single-needle modalities are generally inadequate.

Prior experimental and computational work on dialysis catheters shows that outlet geometry and lumen configuration can materially affect recirculation and local flow fields [16–20]. Our simulation supports the structural flow-separation hypothesis for this geometry, but it did not measure urea clearance, platelet activation, hemolysis, thrombosis, access patency, pain, or clinical outcomes. Direct comparison with standard dual-needle dialysis or contemporary single-needle systems was not performed.

For a thrice-weekly schedule, two needle entries per treatment correspond to approximately 312 routine entries per year, whereas one entry per treatment would correspond to approximately 156. This is a 50% reduction in the number of entry events, not evidence of a 50% reduction in pain or vascular trauma. The proposed 7Fr profile is larger than standard hemodialysis needles and may increase tract size, bleeding, hematoma, wall injury, hemostasis time, and pseudoaneurysm risk. Whether fewer but larger punctures provide a net clinical benefit must be determined experimentally. Patients with limited cannulation anatomy may be a future target population, but the 10.5 cm intravascular length may itself restrict eligibility [5, 10–12].

Medical-grade polyurethane was selected as a proposed flexible catheter material, but material compliance, trackability, kink resistance, thrombogenicity, and endothelial interaction were not modeled or tested. Surface and material properties can influence device performance

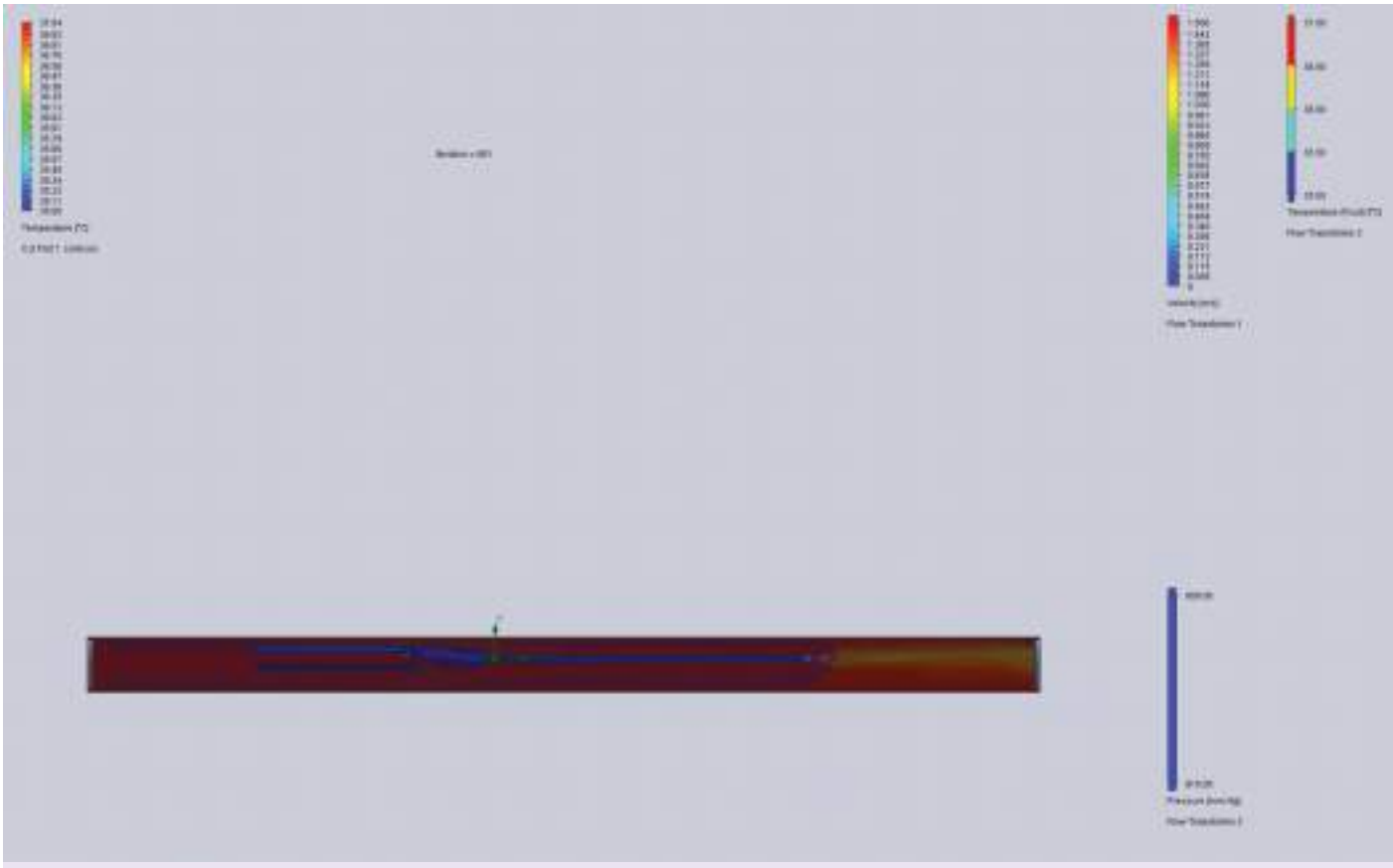

FIGURE 5. Thermal analysis and recirculation evaluation of the coaxial catheter design. Computational fluid dynamics visualization of temperature and pressure in the modeled vessel. Thermal tracking produced a 0.00014°C difference at the arterial intake and a theoretical recirculation rate of 0.007% under the specified boundary conditions. The full-catheter view represents the closed computational domain and is not a clinical implantation schematic.

[21], yet no claim of reduced neointimal hyperplasia or stenosis can be made from the current CFD results. The 7Fr access defect also requires dedicated hemostasis evaluation. Miniaturization, larger aspiration fenestrations, shorter intravascular lengths, and operation at lower pump flow (for example, 200 mL/min) are priorities for future parametric optimization rather than validated features of the present design.

A hemostatic compression device or topical hemostatic material could be evaluated as an adjunct because hemostatic patches and gauze have shown benefit in other procedural settings [22, 23]. However, neither a wristband nor a hemostatic patch was tested in this study, and these adjuncts should not be presented as mitigation of the 7Fr risk without dedicated evidence. Home hemodialysis remains an important care model [1, 2], but frequent self-cannulation with a 7Fr device may create substantial safety and usability concerns. Procedural simplicity does not by itself establish improved access longevity or suitability for home use; such use would require insertion testing, human-factors evaluation, training protocols, and prospective clinical safety data.

Overall, the computational results justify continued engineering evaluation of the coaxial concept. They do not establish clinical efficiency, vessel preservation, reduced pain, reduced intervention rates, or improved quality of life. The next development steps should include parametric CFD, physical flow-loop and hemolysis testing, prototype insertion and trackability studies, pre-clinical evaluation, and only then carefully designed clinical studies.

Clinical Implications

The coaxial concept is a computationally supported engineering hypothesis for separating aspiration and return flow through one access site. AVF failure remains multifactorial; abnormal hemodynamics and neointimal hyperplasia are central mechanisms, while repeated punc-

ture contributes to local access injury [7–9]. The present results do not show that reducing entry count will reduce stenosis, access failure, or endovascular intervention.

Patients with limited usable fistula segments or difficult access anatomy may motivate development of single-site devices [5, 10–12]. However, the proposed device itself requires a 10.5 cm trackable intravascular segment, and no patient-selection criteria have been established. Its feasibility after revision surgery or in patients with obesity must be tested rather than assumed.

Polyurethane may offer flexibility for a catheter platform, and surface characteristics are relevant to device performance [21]. Nevertheless, the present simulation treated the catheter and vessel as fixed geometries and did not test trackability, kinking, endothelial contact, thrombogenicity, or durability. Material-related clinical advantages therefore remain unproven.

Home hemodialysis programs aim to expand patient-centered treatment options [1, 2]. A single access event could simplify one aspect of cannulation, but frequent self-cannulation with a 7Fr device could also increase bleeding, hematoma, and access-loss risk. The current design should not be recommended for home use until size reduction, insertion mechanics, hemostasis, human factors, and repeated-use safety have been evaluated.

No economic analysis was performed. Manufacturing cost, disposables, training, hemostasis resources, complications, and comparative treatment costs must be evaluated before any claim of cost-effectiveness or health-system benefit can be made.

Study Limitations

Despite the high-resolution data provided by the computational models, several critical limitations must be acknowledged to contextualize the findings.

First, this study is a purely computational engineering analysis. The theoretical recirculation rate, velocity field, pressure field, and shear-stress distribution have not been validated in a physical flow loop, by particle image velocimetry, in a hemolysis assay, or in an animal model. No physical prototype or insertion procedure was tested. Clinical implications, including access preservation, pain, bleeding, and patency, must therefore be interpreted as hypotheses rather than demonstrated outcomes.

Second, the boundary conditions were idealized. The simulation assumed steady-state flow and a fully developed velocity profile, without physiological entrance effects or cardiac-cycle pulsatility. Blood was modeled as a Newtonian fluid with constant viscosity, thereby excluding hematocrit-dependent and shear-thinning behavior.

Third, the treatment of transitional and turbulent flow was not compared across alternative turbulence models. Local eddies near the fenestrations may be sensitive to model selection and mesh refinement. Future studies should report Reynolds-number regimes explicitly and perform model-sensitivity and mesh-independence analyses.

Fourth, the host vessel was represented as a rigid cylindrical domain. The model did not include fluid-structure interaction, patient-specific curvature, stenosis, aneurysm, branches, or dynamic wall collapse during aspiration.

Fifth, the 10.5 cm intravascular segment and 6 cm tip-to-fenestration separation require a sufficiently long, safely traversable venous segment. Seldinger insertion may facilitate tracking but does not remove this anatomical requirement. Tortuosity, depth, previous revision surgery, obesity, and limited cannulation zones may impair placement. The full-catheter views in Figure 4 and 5 depict the closed computational domain and are not clinical implantation schematics.

Sixth, only one AVF flow rate (1000 mL/min) and one dialysis pump flow rate (300 mL/min) were tested. Safety and recirculation cannot be extrapolated to lower-flow AVFs. Future work should include parametric CFD and physical testing at clinically relevant AVF flows (for example, 300, 600, and 1000 mL/min), lower pump flow such as 200 mL/min, and alternative catheter diameters, lengths, and fenestration areas.

Finally, the study focused on acute modeled hemodynamics. Peak shear stress was reported without a validated exposure-time-based blood-damage calculation. The model cannot predict hemolysis, platelet activation, thrombosis, infection, biofilm formation, endothelial injury, neointimal hyperplasia, pain, hemostasis, pseudoaneurysm formation, or long-term access patency.

Conclusion

This study developed a novel dual-lumen coaxial catheter geometry and evaluated it in a high-resolution CFD proof-of-concept model. At an AVF flow of 1000 mL/min and a dialysis pump flow of 300 mL/min, the model predicted spatial separation of return and aspiration flow and a theoretical recirculation rate of 0.007%.

The model also calculated a localized peak shear stress of 2,602.45 Pa, but it did not establish hemolysis safety or clinical blood compatibility. A one-entry strategy would reduce the number of routine entry events, but the 7Fr diameter and 10.5 cm intravascular length introduce important bleeding, vessel-injury, trackability, and anatomical feasibility concerns. No conclusion regarding reduced pain, access preservation, suitability for home hemodialysis, or superiority to standard cannulation can be drawn.

Further development should proceed through parametric CFD across clinically relevant AVF and pump flows, geometric miniaturization, physical flow-loop and blood-damage testing, prototype insertion studies, and pre-clinical evaluation. Clinical trials would be required to determine safety, dialysis adequacy, usability, hemostasis, and long-term access outcomes.

Ethics Committee Approval: Not applicable; this is a computational (in silico) engineering simulation study that did not involve human participants, patient data, or animal subjects.

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The author declare that there is no conflict of interest.

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REVIEW GENERAL SURGERY

Financial venous stasis and thrombosis: A circulatory architecture for frozen capital and high-value care

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ABSTRACT

Health systems face a paradox. Aging populations, advanced therapeutics, and long-term needs expand demand for high-value care while large financial stocks coexist with incomplete service coverage and widespread financial hardship. The article examines whether this mismatch reflects a circulatory pathology of capital allocation in care-intensive sectors where biological vulnerability and human dignity are most exposed. This paper uses a structured conceptual synthesis for theory building rather than statistical estimation. It integrates research on precautionary saving, institutional trust, health financing, accreditation, real-world evidence, and programmable financial governance under protocols for source selection, bibliographic verification, and bias control. Interdisciplinary convergence is treated as theoretical triangulation, not empirical proof. The synthesis develops financial venous stasis and thrombosis as a bounded theory-building metaphor. Care cost insecurity is its proposed behavioral hinge. Capital may pool for future security and care assurance as well as yield. When prudent preservation against aging, illness, and care uncertainty scales through institutional routines and risk controls, it may harden into systemic low flow that monetary expansion alone may not resolve. The response is an institutional treatment architecture for financial thrombolysis. It places a clinical core without profit distributions within an auditable, phased centralized finance-to-decentralized finance governance structure supported by accreditation, real-world evidence, and transparent flow protocols. The framework does not claim empirical validation. It is a falsifiable health policy agenda dependent on pilot testing and assessable through clinical outcomes, patient experience, compliance integrity, cash flow durability, equity effects, and transparent social allocation. Its central contribution reframes capital not as a scarce resource to be rationed but as a circulatory medium whose movement may be impaired. It tests whether usable channels can restore circulation and convert defensive preservation into measurable care capacity that protects dignity without penalizing capital.

Keywords: Care–cost insecurity; CeAI; centralized finance; DeAI; decentralized finance; financial thrombolysis; frozen capital; health care financing; institutional trust; precautionary saving; real-world evidence; reverse health silk road.

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INTRODUCTION

Financial Venous Stasis and Thrombosis: The Pathophysiology of Frozen Capital

The Paradox: Freezing Amid Abundance

This study proceeds from a tradition that represents economic activity as regulated circulation and takes the Tableau Économique, written by François Quesnay, who followed Harvey's theory of blood circulation, as its historical point of departure [1, 2]. On this basis, the study translates the deontological duties to diagnose accurately, avoid harm, and intervene only after adequate testing into a conceptual method for examining contemporary macrofinancial congestion. Figure 1 summarizes the manuscript's overarching homeostatic architecture. Figure 2 anchors the historical frame, while the contemporary record supplies the problem.

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At the end of 2024, financial assets in the monitoring sample stood at United States dollar (USD) 503.7 trillion, 6.3% above the previous year, a total that does not identify frozen capital [3]. It covers central banks, banks, public financial institutions, and non-bank financial intermediaries, yet does not reveal if any portion is idle, low-yielding, unencumbered, or suitable for care financing, or if it is already committed elsewhere [3]. Against that limitation, the study examines whether a substantial share of accumulated capital has left productive circulation as aging populations, advanced therapeutics, and long-term care needs enlarge demand for high-value care. Separate records show 4.6 billion people without full essential service coverage in 2023 and 2.1 billion experiencing financial hardship from out-of-pocket health spending in 2022, establishing coexistence but not causation [3, 4].

The inquiry narrows from global capital to health systems and international care corridors, bringing destination, continuity, clinical consequence, and the rules governing movement into a single field of examination [2, 4–6]. Coexistence creates no financing obligation, and the diagnostic task is narrower and harder because it asks how lawfully held resources and recognized need persist with no usable institution joining them, how resource differs from route, and when a route becomes credible, lawful, and usable.

Highlight key points

- This article begins with the coexistence of two immense figures, as total financial assets in the Financial Stability Board monitoring sample reached USD 503.7 trillion at the end of 2024 while approximately 4.6 billion people lacked full access to essential health services in 2023, a juxtaposition that implies no causality but reveals the distance between abundance and unmet care.
- It identifies care cost insecurity arising from illness, old age, long term care, and future dependence on others as the behavioral hinge through which reasonable individual prudence may become low velocity capital at system scale, while treating financial venous stasis and thrombosis as a bounded and falsifiable metaphor for theory building rather than an empirical diagnosis.
- At the heart of the proposed financial thrombolysis architecture stands an independent nonprofit hospital protected from investor influence, while the shared social conscience of the hospital and its phased CeFi to DeFi architecture takes institutional form in a foundation that directs protected resources toward dignified care for older people, support for orphans, poverty alleviation, assistance to people in need, and social and ecological sustainability.
- Governance begins with CeFi, which bears legal responsibility, custody, compliance, and oversight, and only then extends within the same ownership and partnership structure to limited, traceable, and programmable DeFi functions, while independent accreditation and real world evidence make quality observable and financial participation remains wholly separate from clinical authority.
- The Reverse Health Silk Road integrates accredited high value care and cross border financing within an auditable international care corridor that preserves the sovereignty of every state, clinical independence, and protected social allocation, allowing capital to cross borders without ever acquiring authority over care.

The Diagnosis: The Bio-social Framework and the Oxygen Paradox

Financial venous stasis and thrombosis is a bounded theory-building metaphor, not a clinical diagnosis [2]. Capital may move through regulated channels toward productive activity and care capacity, yet pool in defensive reserves, acquire low-velocity inertia, and become less available where vulnerability is exposed. Modern finance treats liquidity as a systemic condition in which market and funding liquidity interact through spirals, and liquidity theory asks when private claims support productive activity and when public provision should complement them [7, 8]. Market freezes, fire sales, contagion, insolvency, and policy intervention belong inside the diagnostic field, so the relevant evidence stays financial and institutional [9].

The biological analogy separates carrier, substrate, and delivery mechanism. Whole blood is a composite transport tissue whose plasma carries proteins, electrolytes, nutrients, lipids, metabolites, hormones, and other solutes, including vitamins [10]. Hemoglobin within erythrocytes carries most oxygen, and endothelial permeability together with microvascular fluid exchange governs delivery across plasma and tissue compartments [11–13]. Within the economic mapping, oxygen represents liquidity. No single biological component represents every economic function. In the economic mapping, glucose represents readily mobilizable energy, amino acids and lipids represent structural or reserve inputs, and vitamins, trace elements, and electrolytes represent indispensable regulatory inputs [10, 11, 13]. Energy, commodities, raw materials, labor, expertise, standards, and other productive inputs form the differentiated substrate layer, and infrastructure for law, payment, settlement, logistics, information, and governance carries them. The mapping clarifies transport and delivery without making biological and financial systems equivalent [2].

FIGURE 1. Homeostasis as the Visual Thesis of the Proposed Architecture. Conceptual overview of the manuscript's overall architecture. Precision medicine and compassionate care, an audited trust anchor, and a distributed value engine converge around homeostasis, connecting clinical integrity, financial circulation, social assurance, environmental continuity, and human dignity. The image presents a normative architectural horizon rather than an empirically validated result (AI- generated illustration, © 2026 ktekesin).

Liquidity provides the capacity to move resources, but institutional trust determines whether people are willing to enter and remain in the channel [6]. Even when a channel appears acceptable, one doubt remains. Is it genuinely credible, or does it merely appear usable? Care makes the answer observable by showing where resources go, whether they arrive on time, whether care continues, and what happens to the patient. Emergency liquidity may make the system appear to breathe again, but if reluctance to commit persists, visible movement is temporary compensation rather than durable recovery [14].

Accreditation and credible governance are hypothesized to lower resistance. The hypothesis also includes lower verification burdens, observable integrity, and credible care assurance, but it is distinct from liquidity support, subsidy, guarantees, and preferential treatment, each of which can preserve activity even when reluctance to commit persists [14–16]. Durable recovery is defined as measurable reductions in care-cost insecurity, institutional opacity, verification burden, and the perceived risk of entrusting resources to the channel. Each indicator is specified before the pilot begins and measured at its respective level, because change in one domain cannot establish change in another.

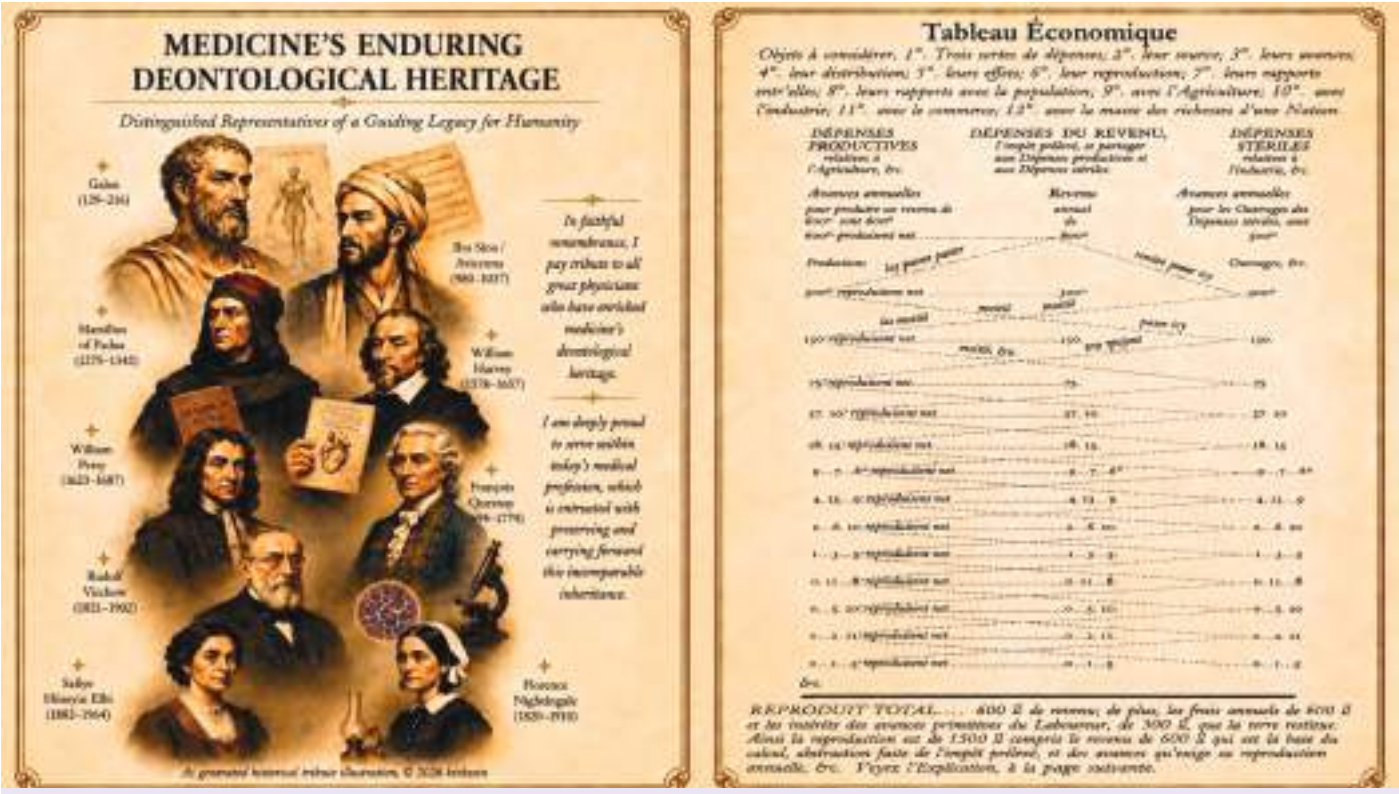


FIGURE 2. Historical point of departure: Medical deontology and Quesnay's Tableau Économique. Historical-conceptual composite linking medicine's deontological inheritance with François Quesnay's Tableau Économique (1759). The left panel represents diagnostic accuracy, avoidance of harm, and disciplined intervention. The right panel represents regulated economic circulation. The juxtaposition marks the study's historical starting point without claiming a literal transfer of blood circulation into economic theory.

Digital tools enter only when they make allocation, responsibility, and destination visible and support programmable rules open to audit [17, 18]. The framework begins with centralized finance (CeFi), and decentralized functions appear later under bounded conditions because distributed execution alone establishes neither decentralization nor legal validity nor accountability [17, 19, 20]. Technology cannot by itself confer validity on the institution that deploys it. Diagnosis must therefore come first.

Within the metaphor, oxygen is delivered and consumed in relation to metabolic demand, not accumulated as an end in itself, but this supplies no literal macroeconomic blueprint and does not imply that every reserve should be released [2, 8, 11]. Purpose gives liquidity its significance as an input that enables the system to remain viable, and the role of this input depends on whether it is mobilized, where it is delivered, and what function it sustains. The question therefore shifts from aggregate quantity to the conditions governing the mobilization, delivery, and trustworthiness of existing resources, and to whether scarcity reflects an allocation problem or an institutional access problem.

Redefining the Economy: Reframing the Axiom of Scarcity

The oxygen analogy does not deny scarce means, physical limits, or contextual differences in essential needs [21]. It asks a narrower question: when capacity exists, can scarcity in health, autonomy, dignity, and care persist because available resources do not reach those needs or cannot be accessed through institutions [22–24]? The supporting traditions illuminate different parts of this distinction and therefore complement rather than replace one another.

Basic human needs have a finite, classifiable, and satiable conceptual core [22, 23, 25]. Although the satisfaction of these needs occurs within material and biophysical limits [26–28], the historical, cultural, technological, and institutional satisfiers through which they are met may vary, diversify, and multiply by context and period [23, 25, 29].

Scarcity may be experienced because existing capacity is inaccessible, immobilized, or institutionally prevented from reaching the functions it could otherwise sustain [24]. Yet each of these mechanisms may proceed independently of the others and without being consciously recognized.

The study frames as a testable problem whether care-related insecurity, institutional access, and low-velocity allocation can be joined without treating evidence from one level as proof at another, while explicitly preserving each level's inferential limits. A reserve manager may satisfy a prudential mandate. A care institution may document a need for which no usable financing channel exists. Both positions may be institutionally defensible [22, 23].

Aggregate abundance grows. Unmet basic need persists. Nothing in this arrangement needs to announce itself as failure. The disturbance lies in the distance between resources that are protected and needs that remain present. What remains to be explained is why that distance persists.

The Missing Link: Care-cost Insecurity and Low-velocity Capital Stasis

The unresolved distance needs a behavioral and institutional mechanism. Care cost insecurity is proposed as the hinge of low-velocity capital stasis, drawing on work that links uncertainty to additional saving and prudence as a distinct response to risk [30, 31]. Social insurance can reduce that motive by absorbing part of worst-case exposure, and uncertain medical expenditure together with longevity risk can influence saving among retired single people [32, 33]. The evidence reaches households and does not establish the motives of corporations, institutions, or sovereign funds. Capital often pools in search of future security and care assurance, not yield maximization alone. If uncertainty related to care enters institutional rules, it may reinforce low-velocity holdings through mandates, liabilities, reserve requirements, routines, and connected portfolios. The cross-level relation is untested. Units and mechanisms must therefore be specified separately for households, institutions, and sovereign actors, and the proposition is open to narrowing or rejection.

The first disturbance is not panic, but prudence becoming universal. A household preserves against illness. An institution preserves against liability. A sovereign fund preserves against demographic exposure. Each act appears responsible in isolation.

Yet when generalized across the system, responsible preservation may become low-velocity stasis. The danger is therefore not only irresponsible speculation, but also the invisible accumulation of safety-seeking behavior. Fragmented decision authority and responsibility for bearing losses can create institutional gaps [34]. Authority to make the decision may be transferred on valid grounds, yet responsibility for the outcome may remain unassigned. No alternative use of the reserve is recorded, and the resource remains in place, while the verified need for care remains unfunded.

The World Health Organization and World Bank [4] document measurable hardship from out-of-pocket health spending among working-age households, whereas De Nardi et al. [33] identify aging, long-term care, and obligations to dependents as distinct precautionary motives. The pilot tests whether these exposures favor liquid reserves with modest returns. Virchow's triad maps stasis to capital that does not reach care, channel integrity to a credible, enforceable allocation route, and coagulation tendency to one actor's withdrawal causing others to wait [35]. Declared trust may diverge from actual allocation. If all three persist, the system may cross a non-linear threshold toward acute crisis [36].

Folkow [15] explains load-induced resistance, Haldane and May [37] show local robustness alongside systemic fragility, and Woods [38] describes declining adaptive capacity. Apparently reasonable defensive restraint can become security-seeking behavior, yet convergence across disciplines does not prove that such insecurity causes capital stasis. It cannot replace empirical validation. The mechanism must remain falsifiable. Drawing on Leland [30] and Kimball [31], the pilot tests whether care cost insecurity accompanies low capital velocity and defensive concentration, then examines a prespecified threshold at household, institutional, and sovereign levels. If the expected pattern is absent, the mechanism must be narrowed or rejected.

The pilot compares a lower-yield, stronger assurance instrument with a higher-yield, weaker assurance alternative and accounts for liquidity support, guarantees, legal privilege, and political direction [8]. Choosing stronger assurance despite its lower return may reveal a divergence between stated yield priorities and actual allocation. That result is insufficient. Clinical performance, patient experience, regulatory compliance, cash flow durability, and equity require separate assessment. The architecture warrants support only if its mechanism survives these tests and rival explanations (Fig. 3).

Contribution and Scope

This study defines a pilot architecture that would direct a bounded share of defensively held capital toward cross-border high-value care infrastructure. Consistent with Eldridge et al. [39], it is not a completed interven-

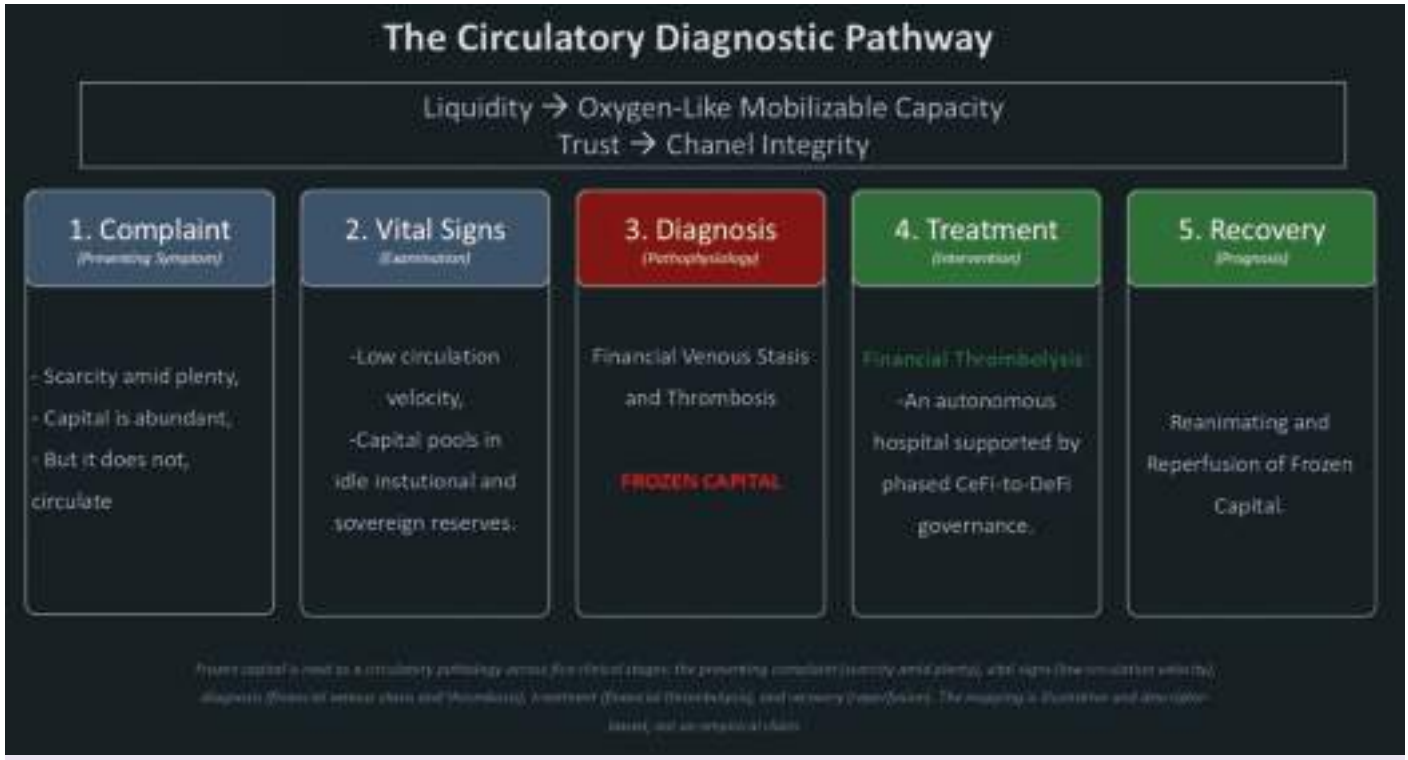


FIGURE 3. The circulatory diagnostic pathway. This explanatory schematic presents the five-stage sequence from complaint and vital signs through diagnosis and treatment to conditional recovery, together with the proposed venous-return loop. Liquidity denotes oxygen-like mobilizable capacity, whereas trust denotes channel integrity. Neither substitutes for the other. The mapping is illustrative and descriptor-based. It is a testable conceptual mechanism, not a literal biological equivalence or completed empirical validation.

tion and its validity depends on pilot findings. It places a non-distributing clinical core within an auditable structure that begins with legally identifiable centralized responsibility and later permits bounded decentralized functions. Financial participation confers no clinical authority. Governance sources define these limits without validating the design [17].

Eligibility, professional judgment, continuity, and public accountability remain outside the financial layer. Independent accreditation and a prespecified evidence plan make quality and performance observable. Observability is not proof. The contribution assigns complementary functions within one architecture to literatures on dynamic capabilities, global value chains, institutional capital, blended finance, accreditation, real-world evidence, and programmable governance, thereby linking low-velocity capital with unmet need [40]. The architecture claims no superiority. Its scope ends if clinical independence, protected allocation, traceability, or continuity cannot be observed and audited under financial pressure, related party arrangements, jurisdictional conflict, or operational failure. The first test is whether the system can operate without interrupting ongoing care. A pilot does not prove benefit. Benefit requires later outcome evaluation.

The Philosophy of Triage and Diagnostic Sufficiency

In a resource-constrained crisis with multiple casualties, treatment accuracy depends on diagnostic accuracy, and clinicians must prioritize fairly by clinical urgency. Yet bedside triage is never an allocation among abstractions. Even when urgency places one patient before another, every priority decision concerns a particular person [41]. The decision maker may change with scale, but benefit, delay, and harm are first lived in one life before becoming aggregate outcomes. The individual remains the unit.

The central question asks whether an inclusive financial treatment architecture can direct capital toward dignity-preserving, socially valuable care without excluding stakeholders or penalizing capital itself. It also examines whether the distance between capacity and care can be reduced without allowing financial claims to determine

FIGURE 4. Virchow's triad as a bounded financial mechanism map. The clinical triad is mapped to three separable financial hypotheses concerning impaired channel integrity, defensive retention characterized by low velocity, and correlated defensive positioning. Joint persistence may indicate a nonlinear threshold. The mapping is a conceptual heuristic, not biological equivalence or empirical proof.

who receives treatment [5]. The patient must remain visible. Only then may success be claimed.

At system level, diagnostic framing defines the problem and locates responsibility, whereas prognostic framing develops a response [42, 43]. Diagnostic sufficiency therefore requires discriminating tests and rival explanations capable of overturning the proposed account. Withdrawal from circulation is the observable sign. The original hypothesis is that defensive allocation may operate as a system-level analog of anxiety, while the bounded test examines institutional obligations, rules, and allocation patterns without assigning psychiatric status to any actor. Monetary conditions, regulation, portfolio mandates, market structure, and geopolitical constraints remain competing or interacting mechanisms. Because a frame can remain useful even when some mechanisms lie beyond its scope, shortcomings in health and economic policy responses justify a structured synthesis that preserves professional judgment and defines the map before empirical evaluation [44].

CONCEPTUAL FRAMEWORK AND PATHOPHYSIOLOGY

Section 1 identified care cost insecurity as a possible link between protected resources and unmet care. Section 2 examines its operation, consistency with long-term patterns, and role in recurrent crises.

The Baseline Pathology and the Paradox

When does a reserve cease to be merely prudent? Uncertainty may strengthen the motive to retain resources [31], whereas medical expenditure and longevity risk can shape saving among single retirees [33]. Firms present a different case. Policy uncertainty may delay investment [45], whereas cash flow risk and financing constraints are associated with higher corporate cash holdings [46]. These mechanisms are not interchangeable. Each level requires separate assessment through mandates, liabilities,

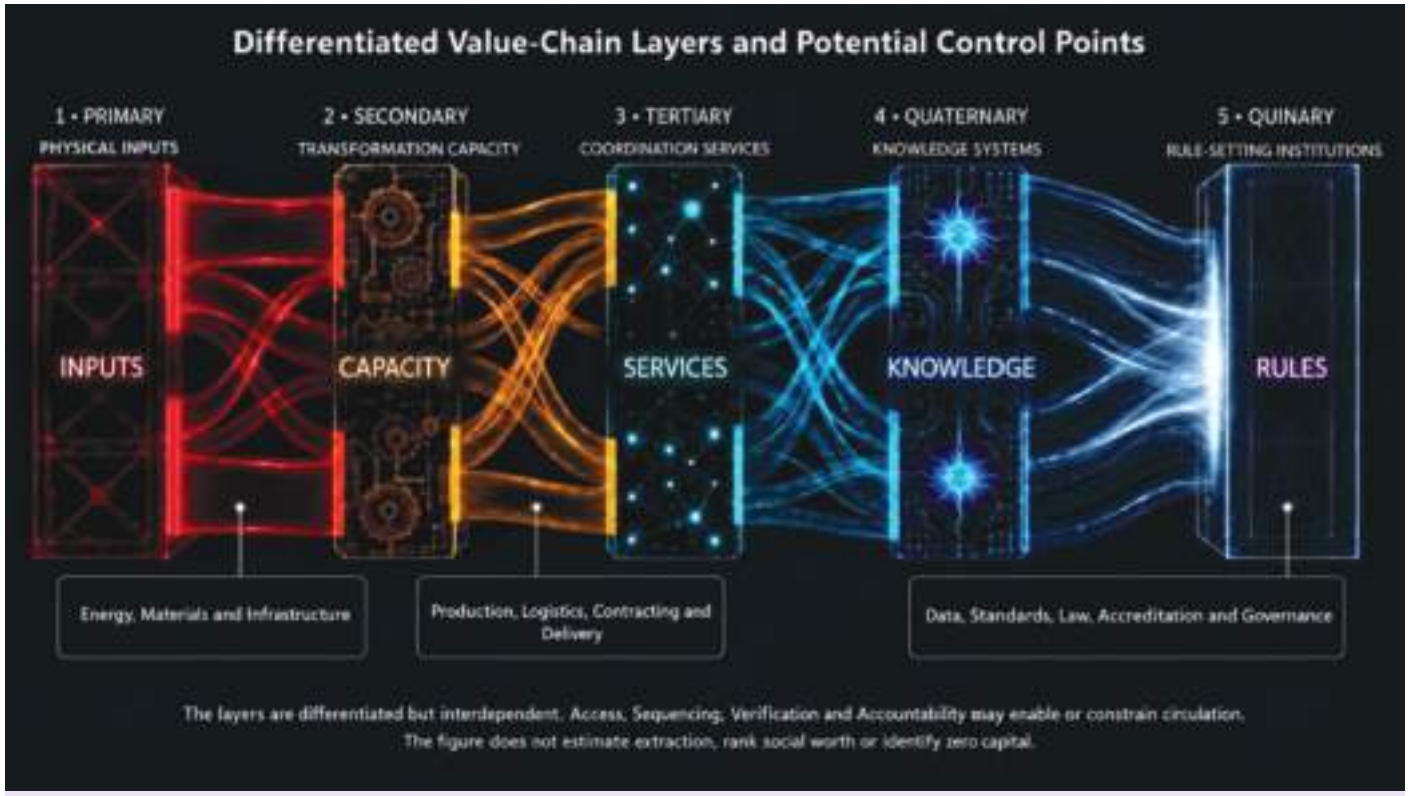


FIGURE 5. Differentiated value chain layers and potential control points. The figure distinguishes physical inputs, transformation capacity, coordination services, knowledge systems, and institutions that set rules. Access, sequencing, verification, and accountability may enable or constrain circulation. The figure does not estimate extraction, rank social worth, or identify frozen capital.

reserve rules, and observed allocations. A separate test must ask whether care obligations induce synchronized defensive holdings.

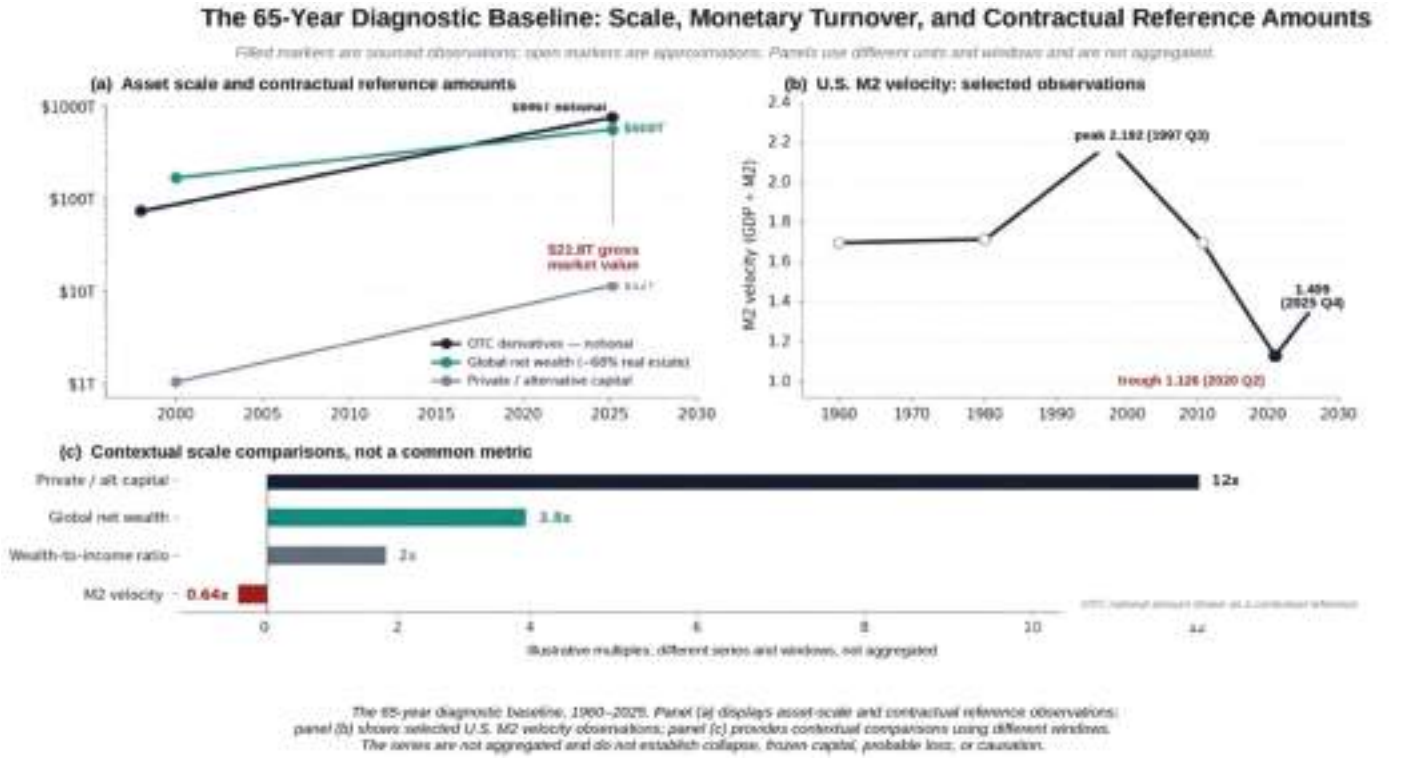
Every actor can behave reasonably in isolation. That is the paradox. When defensive positions become synchronized, aggregate security need not rise, even if no participant intends the common outcome and no single accumulation appears excessive. Productive circulation may still contract. Infrastructural resilience might weaken. Individually prudent decisions can then generate systemic stagnation, a coordination effect that network analysis makes measurable [37].

Virchow's triad explains venous thrombosis through slowed flow, increased coagulation tendency, and endothelial injury, but it is not transferred to finance as a biological law [35]. Here it separates three testable questions. Has the velocity of defensive holdings declined? Has simultaneous restraint formed a connected pattern? Have financial channels lost reliability or functional integrity? Figure 4 presents these hypotheses without suggesting that assets form a literal thrombus or that biological pathology counts as financial evidence.

Withdrawal may reduce effective circulation despite movement. Turnover, emergency liquidity, and guarantees do not establish redeployment of pooled resources or functional recovery. Volume is not decisive. Stasis must be assessed by duration, destination, constraints, alternative use, and functional consequence. Flight to quality together with funding constraints can concentrate resources [7], whereas network dependence and overlapping holdings can transmit disruption as correlated defensive positioning [37]. Weak trust or enforceability can disable routes [47]. Channel integrity remains distinct from liquidity.

The Map of Acceleration Across 65 Years: A Diagnostic Baseline

Long-term macrofinancial indicators map conditions compatible with proposed mechanisms. They do not test causality. Four windows cover US M2 velocity from 1960 to 2025, worldwide net worth from 2000 to 2024, corporate cash holdings in recent decades, and over-the-counter derivatives in June 2025 [48]. Measures are neither added nor treated as frozen capital.



The 65-year diagnostic baseline, 1960–2025. Panel (a) displays asset-scale and contractual reference observations; panel (b) shows selected U.S. M2 velocity observations; panel (c) provides contextual comparisons using different windows. The series are not aggregated and do not establish collapse, frozen capital, probable loss, or causation.

FIGURE 6. The diagnostic baseline across 65 years. The figure juxtaposes observations of asset scale, contractual reference amounts, selected U.S. M2 velocity observations, and contextual comparisons across different units and windows. The series are not aggregated and do not identify frozen or deployable capital, measure probable loss, or establish collapse or causation.

Global net worth rose from about USD 160 trillion in 2000 to nearly USD 600 trillion by late 2024, mostly from valuation, not new investment. US M2 velocity fell from 2.192 in 1997 Q3 to 1.126 in 2020 Q2, then reached 1.409 in 2025 Q4. Series from McKinsey Global Institute [49, 50] and the Federal Reserve Bank of St. Louis [51] establish no causal link. They juxtapose expanding wealth with a different monetary turnover path.

US industrial firms held more cash amid cash flow risk, financing constraints, and changing characteristics [46]. Defensive retention becomes measurable. It proves neither universal causation nor macroeconomic stasis. Figure 5 maps possible control points in information, intellectual property, algorithms, and governance. It estimates no extracted value. Nor does it identify frozen capital. The pattern remains compatible with financialization, secular stagnation, or a global saving glut, but confirms none of them.

Figure 6 compares three measures without aggregation. Asset scale, monetary velocity, and over-the-counter derivatives measure different things, and the USD 846 trillion notional amount is not deployable capital. It records contractual scope. Gross market value of USD 21.8 trillion reflects replacement value [48]. Neither figure proves recovery. Large figures do not show capital is usable or circulation restored. It provides context.

Roman debasement shows that nominal size alone cannot preserve economic function [52]. The late Soviet system retained capacity despite shortages and weak exchange [53]. Appearances can mislead. Resources may not reach need. Control over key networks can restrict choices without making collapse inevitable [54]. These cases do not prove the mechanism. They show that visible scale may diverge from function. The next section tests whether this divergence sustains recurrent crises.

The Behavioral Cycle of Crises and Historical Pathophysiology

Financial stasis is more accurately understood as a recurring behavioral cycle than as a linear sequence of isolated monetary anomalies. During friction, authorities may use guidance, reassurance, and temporary liquidity, but communication can relieve stress without repairing liabilities, incentives, or trust. The ECB's 2012 "whatever it takes" commitment supplied the paradigmatic signal [55], whereas the subsequent OMT

announcements calmed stress in sovereign debt markets before full structural repair was achieved [56]. The words mattered because the institution could act, so the episode demonstrates assurance rather than structural repair [56]. Recurrent crisis histories show the same pattern [57], while credit and leverage can accumulate during apparent stability and surface when financing conditions turn [58].

Bailout expectations and maturity mismatch can alter behavior before a crisis becomes visible [59], as neglected risk accumulates beneath apparently safe arrangements [60] and funding with short maturities magnifies vulnerability [61], with diagnostic expectation errors reinforcing both processes [62]. Protection is not mistaken, but it is incomplete. Safeguards introduced after crises preserve functions and reshape expectations about future losses, but the cycle turns when necessary relief enters renewed risk formation [59–62].

This argument does not require assigning psychiatric diagnoses to states, markets, or societies. Mortality awareness is associated with materialistic responses [63]. Exposure to health costs and longevity risk is associated with saving [33]. Social isolation represents a distinct vulnerability pathway [64]. Similarly, intolerance of uncertainty constitutes another discrete pathway [65]. These mechanisms are not interchangeable. None establishes institutional or sovereign motives, which must be inferred from mandates, liabilities, capital rules, governance routines, and observed allocations.

Mortality awareness can shape subsequent thought and behavior [66]. Experimental exposure has been associated with changes in affective expression [67]. The evidence remains qualified by concern regarding informed consent and procedures for opting out [68]. Observational work examines clustering and longitudinal association [69]. Economic sociology places action within social relations rather than isolated calculation [70]. Together, these literatures identify possible transmission routes.

A parallel threshold logic, whereby small, individually negligible accumulations can, beyond a critical point, precipitate disproportionately large systemic shifts, recurs across complexity science from self-organized criticality [71] to signals that provide early warning of critical transitions [72]. In this sense, anxiety at the individual level does not mechanically become a social illness. Rather, it may be amplified through networks, expectations, and institutional routines into defensive behavior at the system level. This interdisciplinary recurrence is treated as structural correspondence rather than literal identity.

Within the cycle, the conflict turns at a smaller scale. A discrepancy may remain concealed while every participant follows a defensible rule. Credible assurance can reopen contact, but it does not abolish the discrepancy. What has been quieted can return. When loss becomes visible, protective force enters. Without measure, that force can damage the relation. Learning can contain it while rival explanations remain available and failure is recorded. Yet successful rescue can turn knowledge toward institutional preoccupation with itself. The capacity to stabilize becomes evidence, in its own account, that the architecture is already safe. Direction changes when actors accept limits, share authority, and preserve a path by which another party can move without humiliation. No side is erased. A balance becomes possible because the parties return to their functions rather than defeat one another. It remains homeostatic only while contact, measure, restraint, memory, and cooperation remain active. The discrepancy can return. Balance cannot be declared complete.

The Fashoda Crisis shows that credible communication can interrupt escalation [73]. The Cuban Missile Crisis shows that reciprocal restraint can keep retreat possible [74]. Both cases indicate that institutional exit routes can prevent danger from becoming irreversible [75]. They are prognostic warnings rather than predictions that financial disputes will follow the same path, and preventive trust architecture carries their transferable restraint into institutional memory.

Mount Rushmore bears the faces of four presidents, representing the nation's birth through George Washington, growth through Thomas Jefferson, development through Theodore Roosevelt, and preservation through Abraham Lincoln [76]. The memorial is a national tribute and a public work of art. Its honor is not diminished by placing it within a wider human horizon. The National Banking Acts of 1863 and 1864 created a federal chartering framework and supported a more uniform national currency, but later panics exposed unresolved limits [77]. Federal deposit insurance followed in 1933, while the coordinated interventions of 2008 relied on later institutions and emergency authorities [78, 79]. These were separate historical layers, each preserving what could be retained while repairing what experience had shown to be incomplete. To have a leader's face carved into a mountain is an enduring national honor. To serve the cause of world peace and human dignity is greater still, for such service is inscribed not in stone alone but in the conscience of humanity [80–83].

The section ends neither with catastrophe nor with commemoration alone. Defensive preservation can spread through mandates, networks, and expectations, while credible assurance can interrupt the cycle and protective intervention requires measure. Stabilizing success must remain open to examination lest protection become renewed fragility, because homeostasis is recoverable rather than permanent. Section 3 receives these claims for delimitation, comparison, and independent testing, and the historical examples, the threshold between individual and system levels, and temporary balance define the problem methodology must examine rather than the answer it may assume.

METHODOLOGY, SCOPE, AND SOURCE SELECTION

Before empirical testing, this section defines the epistemic status, methodological boundaries, and inference rules of the propositions developed in Section 2. It is a structured conceptual synthesis that develops a testable institutional architecture from established mechanisms and empirical anchors. The propositions were formulated before implementation and observation of outcomes and remain open to feasibility assessment and supervised pilot testing [40, 84–86].

Health sciences, economics, finance, organization theory, and institutional governance enter one analytic frame, while each literature retains its object, measure, evidentiary standard, and limit of inference. Their convergence provides theoretical triangulation, not empirical proof. No discipline surrenders its identity.

Research Design: Theory-Building Integrative Conceptual Synthesis

Precautionary capital preservation, healthcare financing, institutional trust, governance, accreditation, real-world evidence, and programmable financial circulation arise from distinct traditions. The study therefore brings these literatures into functional relation without reducing any one to the terms of another, uses each body of scholarship only for the mechanism it can directly support, and treats no biological, financial, organizational, or technological construct as literally identical across domains.

The synthesis proceeds through four linked operations. It identifies each mechanism's unit of analysis and evidentiary status, maps only functionally comparable relations, records where every analogy stops, and translates the architecture into propositions that a supervised pilot can test or reject. This sequence prevents conceptual integration from becoming evidentiary substitution while rival explanations remain available.

Conceptual work must identify, differentiate, integrate, or reframe constructs and explain why particular theories were selected and what role each performs [84, 86]. Its theoretical contribution depends on the clarity, usefulness, and testability of the relations rather than prior validation, so each concept enters the architecture with its identity and evidentiary boundary intact [40, 87].

Source Selection Protocol

Three criteria guided source selection, namely scholarly validity, conceptual relevance, and verifiability. Priority went to peer-reviewed research and authoritative institutional records. Verified journal quartile status remained a secondary screening signal rather than a proxy for individual study quality [85].

Selection required a direct match between each claim and its source. Each publication was entered only after its object, population, measure, method, and inferential reach were identified.

Citation density followed epistemic function. Independent lines were added when claims crossed disciplines or carried causal or normative weight. Convergence increased theoretical confidence without creating a threshold of truth.

Bibliographic integrity, stable identifiers, data definitions, contextual fit, and assigned function were assessed separately, and no publication carried more than its documented support allowed. Where no source met the criteria, the line remained blank.

Bibliographic Verification and Publication Ethics Protocol

Verification covered relevance and traceability. Journal articles were checked through DOI and publisher records, whereas other source classes used appropriate identifiers and institutional records. Numerical claims also required a definition, observation period, and source location, while an auditable chain linked each claim to the cited work, its stable identity, and the passage, table, figure, or data definition carrying it. A citation entered the evidence layer only when its identity could be traced across independent records. No unresolved record was closed by assumption.

Table 1. Empirical records, model inputs, and interpretive limits for pilot calibration

No.	Source or model input	Measure or epistemic status	Role in pilot calibration	Inference not supported
1	Himmelstein et al. [88] Approximately USD 2,213	Average patient care revenue per patient day in the studied hospital groups	Lower empirical reference point	A per diem tariff specific to targeted high-value care
2	Bolenz et al. [89]	Cost and resource intensity differences across surgical approaches	Surgical resource intensity reference	Daily room revenue or reimbursement
3	Lyman et al. [90]	Total episode cost of CAR T-cell therapy by site of care	High intensity episode cost reference	Flat daily hospital revenue
4	USD 3,700	Falsifiable midrange calibration assumption	Midrange pilot scenario	A published per diem fact
5	Approaching USD 6,700	Falsifiable higher intensity calibration assumption	Upper pilot scenario	A proven revenue level, profit, or investor return
6	Alnakhi et al. [91]	Treatment destinations, specialties, and travel patterns in a defined population	Contextual indicator of existing international care demand	National annual expenditure of USD 2 billion
7	100 operational beds at 60% occupancy	Operational capacity in the pilot scenario	Capacity input for gross operational revenue estimate	Profit, free cash flow, or investor return
8	Foundation allocation before distributable surplus	Untested model proposition	Pilot test of allocation order	An empirically validated allocation sequence

CAR: Chimeric antigen receptor; USD: United States dollar.

A relevant publication remained outside the evidence layer when its identity, metadata, data definition, or publication context could not be verified. Corrections, retractions, and expressions of concern were disclosed at citation and assessed against the specific claim, because neither silent retention nor automatic exclusion was sufficient.

Validity and Bias Control Protocol

Conceptual synthesis can privilege supportive literature while overlooking evidence that limits or contradicts the proposed account [85]. Supportive, limiting, and contradictory evidence were evaluated under the same rule, and evidence that narrowed the framework was retained for the boundary it established. Disagreement was treated as analytical information rather than grounds for exclusion. Independence was assessed across authorship, data, method, disciplinary assumptions, and interpretive function. No volume of convergent citation substituted for direct empirical testing.

The same discipline governed macrofinancial anchors, international care demand, medical travel, and pilot financial assumptions. Deterministic language was replaced by categorical distinctions and falsifiable propositions. The architecture remains theoretically grounded but empirically untested, and each claim ends where evidence marks its boundary without dissolving the shared research question.

Empirical Financial Anchors and Per-Diem Revenue Calibration

Financial anchors calibrate a future pilot. Patient care revenue, hospital operating expense, procedure cost, episode cost, market demand, and model assumptions remain analytically distinct. Table 1 separates empirical records, calibration assumptions, and interpretive limits.

At the lower boundary, the approximate USD 2,213 figure reported by Himmelstein et al. [88] is used strictly as an indicator of average patient care revenue per patient

day. Evidence on robotic surgery and CAR T cell episode costs provides clinical intensity anchors but does not establish per diem hospital revenue [89, 90].

USD 3,700 and values approaching USD 6,700 remain falsifiable calibration assumptions rather than published per diem revenue facts. They define a testable range that observed data must refine or reject.

Alnakhi et al. [91] document treatment destinations, clinical specialties, and repeated overseas travel in a defined population. The source provides contextual support for existing international demand but does not support a national annual expenditure estimate of USD 2 billion, so such regional totals remain excluded unless independently verified.

A pilot calculation based on 100 operational beds, 60% occupancy, and a weighted revenue mix bounded by the literature yields only gross operational revenue. Personnel, technology reinvestment, clinical quality, accreditation, compliance, and other operating obligations must be accounted for before distributable surplus is assessed.

Within the proposed architecture, the foundation allocation is reserved before distributable surplus is assessed. This ordering is specific to the model and remains a pilot proposition. Young et al. [92] document community benefit spending by hospitals exempt from tax but do not validate the proposed sequence, while the allocation remains available without requiring a request or creating any reciprocal obligation for those it serves.

The calibration architecture is tested through observed clinical activity, occupancy, financial categories, operating obligations, and the destination of the reserved allocation. The test asks whether the allocation reaches the particular person it was intended to serve while clinical integrity, accreditation, and financial traceability remain observable. Its assumptions may be measured, corrected, or rejected during pilot implementation. The allocation remains available to those it serves and unavailable as distributable surplus.

SYNTHESIS — INSTITUTIONAL ARCHITECTURE

Section 3 established a bounded, auditable, and falsifiable calibration architecture rather than a financial promise [40]. This section translates the calibration architecture into operational terms. The medical circulatory metaphor serves as a theory-building lens for roles, boundaries, value flows, and scaling conditions. Feasibility and progression are open to testing and rejection [2, 39, 93].

Holistic View of the Architecture

The diagnosis becomes an institutional design that protects the clinical core and prioritizes social allocation by routing low-velocity capital via lawful, auditable channels [2]. Institutional legitimacy lies in fair and enforceable process, not biological resemblance [94].

The social share receives priority; the foundation neither replaces public welfare nor releases the host authority from statutory duties [95]. It creates an auditable obligation tied to named people and purposes, with reasons and enforcement for allocation failures [94]. Clinical and social logics coexist with financial and assurance logics whose boundaries require continuing management [96, 97].

Four layers carry the design, namely an autonomous non-distributing hospital core, a foundation for protected social allocation, a CeFi trust and compliance layer, and a decentralized finance (DeFi) layer linking programmable execution to real assets. Implementation begins with CeFi, and an affiliated DeFi entity may follow under common ownership and partnership. Accountability must always precede distributed execution [17]. Hierarchy does not define the ecosystem. Roles and interfaces do [18, 98, 99].

The hospital is the autonomous clinical core. It carries responsibility for life, clinical value, and dignity, whereas return rights attach only to auditable claims, and capital may enter bounded relations with real assets without gaining authority over treatment, leaving the clinical domain protected from capital domination [100]. Care quality combines safety and privacy with infection control, continuity, and protection of patients and caregivers [101, 102]. Separating patient space from caregiver living and hygiene space is framed as a testable public health design proposition. Accreditation is an external intervention whose effects await testing [103].

The foundation directs the protected social share toward elderly care, children and orphans, poverty alleviation, and socioecological sustainability [104, 105]. Assistance reaches need before dignity is compromised, not after a dignity-eroding proof process [106]. Physicians and nurses, with other care personnel, form the architecture's trust tissue. Compensation and social rights, together with retirement benefits and bounded participation,

support workforce continuity without converting financial participation into clinical authority [107, 108]. Staffing availability separately constrains usable bed capacity and is therefore a structural condition of delivery [109].

The structure differs from public–private partnerships and infrastructure funds because a verifiable layer outside the clinical core finances but does not govern care. Health partnership evidence shows heterogeneity across cost and risk transfer as well as quality and accountability [100]. Coexistence between commercial and social purposes may produce mission tension [96, 110]. The distinction depends on enforceable boundaries irrespective of institutional label.

A human organism develops from one cell through proliferation, differentiation, and fate specification into tens of trillions of cells, although its force here lies in shared origin rather than precision [111, 112]. Moris, Pina, and Martinez Arias [113] show that differentiation does not abolish lineage. The bounded analogy extends this relation to the body's organs. As a shared origin archetype, the image frames humanity as one body differentiated into nations, institutions, classes, cultures, professions, and beliefs [114, 115]. The danger begins not with difference, but when differentiated members behave as strangers.

Institutionally, CeFi is the rooted and accountable body, legally defined, operationally disciplined, and responsible for ownership continuity, governance, and memory. DeFi is a differentiated extension of the same originating code. Zetzsche, Arner, and Buckley [17] show why wider participation and programmable execution remain legitimate only while responsibility, legal validity, and enforceable limits remain visible. Smart contracts may extend programmable coordination [116].

Component Integration and Value Flow

The architecture becomes operational only after its cash flow sequence and legal status are defined and its audit trail established [95]. Audited gross clinical revenue first funds the minimum 5% protected social allocation, after which contractual rights pass through CeFi and authorized execution stays legally subordinate. This order expresses "protect first, generate returns subsequently, then integrate into circulation" and carries the founding statement "Humanity is the art of reaching out to those in need before their dignity is compromised, and of doing so without ever compromising it." Medical deontology supports this boundary [106, 117]. Medicine is the art of humanity, and its infrastructure cannot be treated as a speculative asset.

The 5% allocation is a model parameter and has not been validated as an optimum. Pilot assessment determines legal treatment, accounting base, timing, affordability, clinical continuity, and delivery before social value is claimed. Favorable performance does not permit offsets that delay or reclaim the protected share, while gross revenue and protected allocation stay separate from operating expenditure and contractual rights. Every transfer requires a lawful source and authorized purpose under a decision rule naming the accountable recipient [94, 118].

CeFi and DeFi are complementary within strict role boundaries. CeFi performs identity verification and custody, manages compliance and allocation control, and reports. Potential DeFi gains concern divisibility and traceability under execution governed by rules [119]. Apparent decentralization may conceal reconcentrated control, so the corridor rests on auditability and responsibility grounded in real asset linkage because liquidity alone is insufficient (Fig. 7) [17].

Care entitlement and voluntary asset contribution must remain separate. Contributions from elderly or unaccompanied people and others in vulnerable circumstances are inadmissible as a financing target, a prerequisite for care, or a counterpart to treatment. Autonomy fails when an ethical structure allows vulnerability to become leverage [120]. Contributions require independent legal review, explicit voluntary consent, conflict-free counsel, and reviewable records. Testamentary capacity requires functional assessment specific to the decision [121], while susceptibility to undue influence requires contextual screening [122]. Care comes before wealth, and free will with independent oversight is a condition of admissibility, not procedural decoration [106, 123].

Actor Roles and Governance

Long-horizon sovereign, pension, or institutional investors supply debt-free seed capital, external health quality bodies verify standards, research and data functions assess outcomes, and coordination actors provide legal and operational assurance with financial oversight under transparent investment frameworks [98, 99, 124, 125]. Roles are portable only when each interface has capable actors whose independence and accountability are demonstrable.

Conflicts of interest are disclosed and managed before a contested decision. Related party procurement, transfer pricing, asset valuation, assurance appointments, and

FIGURE 7. Institutional value circulation and reperfusion. The figure presents a conceptual architecture rather than a demonstrated outcome.

role changes require scrutiny, and clinical leaders decide eligibility and treatment, the foundation governs purpose, financial administrators manage claims, independent data and accreditation functions assess evidence, and the designated authority retains legal powers. Explicit decision centers prevent silent recombination of those powers, and no contract, token, vote, or ownership right overrides that separation [107, 126, 127].

Governance follows a polycentric separation of powers so that no single actor can unilaterally control the clinical core or capital allocation, nor can it control the social share. The foundation is the mission lock, and review and proportional response stay independent of operational control [126]. External assurance tests the boundaries without assuming operational authority. Performance alone is not authority, so serious breaches trigger review. Participation can be paused. The power to stop a harmful flow must exist before the pilot begins [93, 94].

Legal and Operational Foundations

Host law governs the legal foundation. The foundation provides enforceable protections and predictable rules supporting credible implementation and capital availability for external finance, and international arbitration, external reporting, and reviewable records can support a regulated, traceable corridor of trust and auditable allocation [128]. Automated execution remains distinct from the underlying legal obligation it purports to execute [119]. Financing traditions converge only through compatible and clinically bounded claims on one identifiable real asset anchor, and any instrument conflicting with patient protection, professional independence, social allocation, or host law is excluded or redesigned [118].

Scaling Architecture

Scaling rejects unchecked commercial growth and proceeds through validation gates. The phased pilot assesses occupancy, revenue per bed, clinical outcomes, patient experience, workforce sustainability, compliance, equity, free cash flow, and cash flow durability, and progression follows prespecified thresholds. Financial performance does not override failure in patient safety, clinical independence, mission integrity, or the protected allocation [39, 93]. Real-world evidence informs evaluation but does not replace prospective validation [129, 130].

The host public authority is not assumed to incur debt or new fiscal burdens because it provides the lawful platform for testing, and low-velocity capital enters through the phased CeFi-to-DeFi layer and foundation oversight, provided the clinical core stays protected. Financing form alone establishes neither value, risk transfer, quality, nor responsible governance, so expanding care capacity without public debt is a pilot question [100]. Adaptation is permitted when local law, clinical regulation, workforce capacity, and evidence preserve the protected purpose [131].

The long-term horizon is a peaceful care and capital corridor toward centers of need, not property acquisition or corridor hegemony. Scaling replicates protected functions at nodes that increase dignity-preserving access, sustain workforce and host system capacity, and maintain auditable circulation. Only a node passing these tests may qualify as a novel homeostatic equilibrium point among the patient, employee, foundation, investor, and host society [132]. Cornelissen [2] requires homeostatic language to remain a bounded metaphor.

SYNTHESIS — CONVERGENCE AND FIELD EVIDENCE

The Function and Boundary of Convergence

Convergence indicates theoretical triangulation and plausibility, not empirical proof. Each field enters only for its task in Section 4. Following Whetten [40], the matrix links adaptation, role complementarity, coordination across borders, funding layers, accreditation, programmable traceability, and value measurement without treating coexistence as whole system efficacy. Thorp [133] distinguishes convergence from consensus, whereas Tambolo and Cevolani [134] show that independent discovery leaves an integrated design unproven. Every transfer therefore requires a named object, a limited task, and an explicit stopping point [2, 40].

Adaptation and Reconfiguration: Dynamic Capabilities

The foundation bears defined responsibility for interpreting changing needs and redirecting resources. Teece [131] describes sensing, seizing, and reconfiguration as enterprise capacities. Research on hybrid organizations shows that adaptation can intensify conflict among purposes [96, 97, 135]. The organizational analog therefore cannot prove that a non-distributing mission foundation will adapt lawfully, equitably, or effectively.

Pilot assessment must distinguish motion from adaptation that preserves mission. Redirection fails when it weakens access, displaces designated groups, or lacks an auditable rationale. Means may change only while reserved treatment and public purposes remain binding, and each choice remains open to review [96, 110]. Survival or speed remains insufficient when reconfiguration conceals unmet need or preserves the organization as its purpose deteriorates [131, 135].

Multi-Actor Arrangement: Ecosystem and Platform Theory

That responsibility is distributed across long-horizon funders, the foundation, accreditation, real-world evidence, CeFi compliance, and the non-distributing clinical core, which remain distinct yet interdependent. Adner [98] maps their positions, activities, links, and interconnections. Each interface identifies exchanged information, retained mandate, acceptance standards, remedies, and the entity able to pause or replace a deficient complementor. Complementarity becomes credible only when decision powers and remedies precede reliance [98, 126].

Portability rests on functional equivalence rather than institutional identity. A role travels only after the receiving actor meets capability, independence, accountability, and interface performance criteria. Local law, clinical regulation, institutional capacity, and pilot findings then determine transferability [126, 135].

International Service Production: Global Value Chains

Care across borders provides the first portability test. Gereffi et al. [124] explain coordination through transaction complexity, codifiability, and supplier capability. In this architecture, advanced care becomes a pathway linking referral, appropriateness assessment, transfer, clinical delivery, data and payment interfaces, discharge, and follow-up.

The contemporary Silk Road is an increasingly consequential structure of connectivity whose commercial promise raises questions of balance, mutual reassurance, and inclusive participation. The Asian Development Bank [136] identifies opportunities for cooperation through the Belt and Road Initiative, the Silk Road Fund, and related initiatives, while warning that weak coordination and harmonization create overlap and competition. Through its Outlook on the Indo-Pacific, ASEAN [137] likewise identifies opportunities and challenges from geopolitical change and calls for dialogue, coop-

eration, openness, transparency, inclusivity, and mutual trust to avoid deeper mistrust, miscalculation, and zero-sum behavior.

The present study introduces the Reverse Health Silk Road. Here, "reverse" denotes health cooperation flowing from West to East as a complementary corridor within wider Silk Road connectivity. The proposed corridor prioritizes accredited care, clinical independence, protected social resources, and shared institutional trust while remaining open to broader commercial integration. Hall et al. [5] show that trust in physicians and medical institutions is measurable. Care across borders requires uninterrupted service and coordinated responsibility across jurisdictions [138, 139].

The corridor extends beyond patient travel through documented handoffs, logistics, data oversight, payment processes, regulatory compliance, and ongoing service. The pilot follows the patient across interfaces instead of counting a completed transaction. Resilience differs across firm, chain, and state levels, but the service adds a patient-level test that may fail despite logistical efficiency [139, 140]. A breakdown in referral, privacy, handoff, discharge, or follow-up overrides financial or operational convenience.

Blended Finance and Health Infrastructure

The corridor is anchored by a non-profit hospital that serves as the non-distributing clinical core and preserves professional independence from investor influence, while a foundation holds the reserved share outside funder claims and investment layers separate risk, capped returns, specified participation terms, and reserved treatment and community uses. Partnership and social enterprise research supports explicit oversight, risk allocation, and accountability, but only conditional coexistence between social mission and financial viability [100, 110].

Distinct ledgers, traceable transfers, predefined terms, and independent review test whether costs or risks have shifted toward the hospital or mission core, while hybrid structures can preserve several objectives even as selective coupling may conceal the governing logic [96, 100, 135].

Clinical decisions, accreditation, empirical integrity, reinvestment, mandatory quality expenditure, and the reserved share remain outside funder authority [100, 110]. The model fails if losses shift toward protected layers while gains or influence concentrate elsewhere, participant entitlements enter professional judgment, or transfers cannot be reconstructed. Jointly beneficial operation remains conditional on pilot findings [141, 142].

Quality Assurance and Accreditation

Ongoing quality assurance belongs to the clinical core. Joint Commission International [101] treats periodic accreditation as a conformity assessment that makes standards and evidence visible. Reviews report heterogeneous effects and knowledge gaps, so certification alone supports no outcome claim [103, 127].

The pilot therefore asks four distinct questions. Does a standard exist? Does the site conform? Does conformity persist in routine work? Do patients experience safer or better care? Certification serves as a condition of participation only when the clinical core retains routine monitoring, improvement, and corrective action because certification establishes neither trust, regulatory approval, investor confidence, nor effectiveness [103, 127].

Breakdown appears when presentation is staged for surveys, metrics are gamed, independence is compromised, standards are poorly localized, or certification diverges from outcomes. Periodic reassessment, internal quality management, corrective action, and outcome assessment by an external reviewer serve different roles. The certificate may open the door. It cannot complete the clinical judgment [101, 103, 127].

Capital Source: Sovereign and Institutional Capital

Sovereign wealth funds, pension funds, and other institutional investors differ in target selection, governance, political exposure, and investment behavior [143, 144]. Liang and Renneboog [145] add sustainability orientation. Compatibility follows neither funder type, state ownership, nor a stated mandate. Participation must be tested against a defined instrument within reserved treatment, public purpose, and mission limits.

Suitability analysis is specific to the instrument and date. It documents fund sources and encumbrances, liability horizon, liquidity needs, currency and concentration exposure, expected return, approvals, reporting duties, exit provisions, and non-renewal consequences [143, 144]. Institutional governance codes emphasize fiduciary duty, policy consistency, risk tolerance, liability matching, liquidity, transparency, and accountability, but remain normative guides rather than proof of fit [125, 146].

The design offers a limited participation channel and does not redirect resources automatically. Service capacity defines use of proceeds, obligations outside the arrangement define cash flow needs, and the reserved share remains closed to funder claims [125, 146]. Participation confers predefined investment, information, and report-

ing rights. Non-participation is appropriate when mandates, liabilities, liquidity, currency exposure, concentration limits, fiduciary duties, or political constraints are irreconcilable without weakening the design [143, 144].

Traceability and Programmable Logic: Blockchain, Smart Contracts, and CeFi/DeFi

The corridor places auditable financial execution within a phased CeFi-to-DeFi governance structure. Mandatory rules define enforceable entitlements. A CeFi layer accountable under law first administers identity, custody, know your customer, and anti-money laundering controls, allocation, reporting, and remediation. An affiliated DeFi layer under the same ownership and partnership structure may later record or execute approved operations. The Law Commission [119] treats smart legal contracts as subject to ordinary contract principles. Reserved treatment and community shares are excluded from funder entitlements, collateral, profit entitlements, and decision powers [18, 119].

Programmability remains subordinate to reviewable supervision. Every automated action presupposes a valid claim, validated input, approved rule, exception pathway, responsible operator, and remediable error [19, 116]. Aldasoro et al. [147] show that tokenization does not establish continuity of the underlying entitlement. Approved governance defines rules and exceptions before execution. External sources report relevant conditions, while the ledger performs only permitted actions. A dated control profile records custody, validation, voting power, upgrade and emergency authority, data feed and bridge dependencies, permissions, and beneficial control [18, 20]. Material changes trigger reassessment. Disputes follow a predefined pause, review, remedy, record, and orderly resumption because distributed execution may coexist with concentrated mandate [17, 20].

A DeFi label proves neither decentralization, legality, regulatory acceptance, compliant data processing, nor truth beyond the ledger, while concentrated authority, code defects, external data feed failure, key loss, governance capture, liquidity risk, privacy breach, or mismatch with the underlying entitlement can render execution unreviewable [17, 18]. Individual health data belong outside the ledger, and oversight roles remain identifiable [119, 148]. Responsible organizations retain security, privacy, institutional responsibility, and dispute resolution [20, 148]. No capital layer acquires mandate over treatment judgment, standard setting, service eligibility, or essential service assets.

Evidence of Value: Real-World Evidence and Value-Based Healthcare

Traceability does not establish value. A prespecified system must therefore assess whether and under what conditions the design functions as intended across safety and harm, medical and patient-reported outcomes, experience, continuity, access, coordination, cost, resource use, equity, protection from payment hardship, oversight, analytic integrity, delivered community share, and the external funding layer. These domains answer different questions. Porter [149] links outcomes and costs to value creation, whereas Kutzin [95] links equity and financial protection to distribution and access. Reported outcomes and care experience also require separate interpretation [130, 149].

The plan states which domain answers which question and who may act on the result. The U.S. Food and Drug Administration [150] and Sherman et al. [129] distinguish routinely collected real-world data from real-world evidence produced by design and analysis suited to a specified question. Source systems capture data, monitoring tracks indicators, analyses generate findings, and an external reviewer appraises validity, uncertainty, thresholds, and rival explanations before the responsible authority applies criteria for continuation, adaptation, pause, remediation, or termination [150, 151].

Real-world data are not self-validating, and each question calls for a prespecified design that includes an appropriate comparator, data suited to the question, control of bias and confounding, transparent analysis, and independent review for causal inference [129, 150]. Regulatory experience further depends on alignment among data source, method, governance, and intended decision [150, 151].

Safety, professional independence, mission constraints, privacy, reserved community distribution, and minimum equity thresholds are non-compensatory gates [95, 149]. The governance arrangement preserves authority to pause or terminate even when other indicators are favorable. Organizational convenience cannot replace reports from recipients [129, 130].

Convergence Matrix

The matrix is an error control device (Table 2). Read horizontally, each row binds one literature to one task and allows a transfer to narrow without collapsing unrelated components [40, 98]. Theoretical triangulation names the method, convergence the pattern, and consilience compatibility among bounded explanations [133, 134].

Table 2. Architectural roles, supporting literature, functions, and epistemic boundaries. Each row defines one bounded transfer. The matrix indicates theoretical triangulation and plausibility, not proof. Integrated performance remains pilot-dependent

1. Architectural role (model component)	2. Literature (theoretical base)	3. Representative sources (reference numbers)	4. Proposed function (model use)	5. Epistemic boundary (claim limit)
Adaptation under foundation governance	Dynamic capabilities and hybrid organizing	Battilana and Lee [96], Teece [131], Pache and Santos [135]	Redirects resources while protected purposes remain binding	Cannot establish lawful, equitable, or effective adaptation
Multi-actor interface governance	Ecosystem and platform theory	Adner [98], Ostrom [126], Pache and Santos [135]	Defines decision rights, remedies, replacement, and portability	Fails when reliance precedes rights, remedies, or review
Care pathway across borders	Global value chains and care continuity	Gereffi et al. [124], Crooks et al. [138], Johnston et al. [139]	Links referral, transfer, treatment, discharge, and follow-up	Production network logic does not establish clinical continuity or accountability
Protected financial layering	Blended finance, PPPs, hybrid organizing	Roehrich et al. [100], Pache and Santos [135]	Separates risk, return, authority, and protected allocation from clinical judgment	Cannot prevent extraction, hidden subsidy, or risk transfer
External accreditation assessment	Healthcare accreditation and quality	Lewis and Hinchcliff [103], Greenfield and Braithwaite [127]	Test standards and conformity independently	Accreditation alone proves neither trust, sustained performance, nor improved outcomes
Capital suitability assessment	Sovereign and institutional capital	Bernstein et al. [143], Boubakri et al. [144]	Tests instrument fit with mandates, liabilities, liquidity, and mission	Participation, persistence, and added care capacity remain unproven
Phased CeFi-to-DeFi governance	Blockchain, smart contracts, CeFi and DeFi	Zetzsche et al. [17], Schär [19], Cong and He [116]	Executes approved operations through traceable, reviewable controls	Decentralization, legality, external truth, and accountable control remain unproven
Performance and equity evaluation	Real-world evidence and value-based care	Kutzin [95], Sherman et al. [129], Porter [149] FDA [150]	Separately assesses outcomes, costs, experience, equity, and protection	Causal claims require prespecified design, comparators, bias control, and independent review

CeFi: Centralized finance; DeFi: Decentralized finance; FDA: U.S. Food and Drug Administration; PPPs: Public-private partnerships.

Boundary: Literature-Supported Components, Pilot-Dependent Synthesis

The first boundary applies to the synthesis. A framework drawing on many literatures risks confusing coherence with proof and citation density with independence. The synthesis therefore accepts the limits imposed on each component [133, 134].

Eldridge et al. [39] and Skivington et al. [93] require prespecified comparators, thresholds, stopping conditions, safeguards for uninterrupted service, and separate appraisal before plausibility becomes evidence. If subsidy, guarantee, regulation, market privilege, or another rival mechanism explains the result, the inference must narrow. Progression stops when a mission safeguard is breached. A humane purpose, elegant architecture, or favorable early indicator grants no exemption from refusal, pause, redesign, or termination. The design must relinquish a favored arrangement when prolonged operation weakens the safeguarded mission [40, 93].

These components rest on specialized scholarship, but their integration remains pilot-dependent. Eldridge et al. [39] and Sherman et al. [129] require independent validation gates to examine health outcomes, free cash flow, oversight compliance, recipient experience, equity, and delivered community allocation before assumptions are corrected, narrowed, or rejected [93, 133].

DISCUSSION

Summary of Core Contributions

This study links diagnosis, institutional design, and prospective evaluation within a bounded, testable frame. Financial venous stasis is a theory-building construct, and care-cost insecurity is its candidate mechanism of precautionary retention. Evidence from defined household populations [32, 33, 152] links uncertain medical spending and longevity risk to saving and means-tested social insurance to precautionary wealth. None establishes a universal household mechanism or extends it to companies, financial institutions, pension funds, or sovereign pools. Cross-level inference and the effect of credible care assurance on security-seeking allocation require independent testing.

The architecture combines a non-distributing clinical core, a foundation governing social allocation, phased CeFi-to-DeFi governance, independent accreditation, and a prespecified route from real-world data to evidence. The literature defines functions and limits, not whole-system efficacy. Decentralization depends on control, accountability, custody, and regulation rather than terminology [17, 20]. Accreditation effects are heterogeneous, while evidence drawn from real-world data requires fit-for-purpose design and analysis [103, 129, 153]. Coexisting institutional logics do not harmonize by declaration [97]. "Institutional conscience" is a construct defined by the author and embodied in a protected, transparent, and auditable social allocation function.

Whetten [40] locates originality in relational specification and functional sequencing rather than unprecedented components. The model makes separately examined mechanisms and their interfaces, powers, limits, and failure conditions reviewable. Before capital moves, assumptions governing eligibility, authority, allocation, evidence, continuity, and withdrawal must become visible. Progression depends on prespecified non-compensatory gates because financial performance cannot offset failure in clinical safety, legality, equity, or mission integrity [154, 155]. The program theory specifies what to measure, what cannot be traded away, and when to revise or reject the model.

Addressing Objections and Structural Limitations

The architecture is internally coherent. Its non-distributing clinical core separates clinical judgment from distributable return, while the foundation locates social allocation. Phased CeFi-to-DeFi governance places accountable administration before bounded programmability. Accreditation, real-world data infrastructure, role separation, and stopping rules make quality, authority, allocation, and failure more observable. These features address genuine problems. They remain design features.

That credit is architectural rather than evidentiary. Non-distribution closes one route of extraction but leaves contracting, transfer pricing, procurement, incentives, ownership, and control untested. Traceability records transactions without establishing legality, additionality, value, or resilience. Accreditation defines a standard, but compliance and outcomes require separate evidence. An allocation formula names a destination, not delivery. Skivington et al. [93] provide the complex intervention program theory used here, although its transfer to financing remains an assumption under test.

Tables 3 and 4 organize thirteen objections across six risk families comprising conceptual validity, ethical legitimacy, technological and financial risk, governance vulnerability, scalability and demand uncertainty, and value measurement. Each requires governing oversight, operational ownership, monitoring and challenge, independent assurance, observable failure signals, a non-compensatory gate, and a designated stop authority. The function operating a control cannot serve as its final validator. Management operates controls, specialist functions monitor and challenge them, and internal audit provides independent assurance without assuming management responsibility. Clinical, governing, regulatory, or public authorities designated in advance retain the power to suspend, terminate, or restart. The relevant frameworks [118, 156] support this separation while leaving thresholds application-specific. Thresholds are prespecified or calibrated before progression rather than reconstructed after an adverse event.

TABLE 3. Prespecified tests, failure signals, and noncompensatory gates by risk family

Risk family and numbered objections	Claim to be tested	Observable failure signals	Non-compensatory gate
Conceptual validity (7 metaphorical overreach, 8 net additionality)	The core claim remains informative without imagery, and mobilized capital creates additional capacity after provenance, liabilities, opportunity cost, displacement, and the counterfactual are counted.	Meaning disappears without imagery. Household evidence becomes institutional proof. Benefits are counted twice. Provenance, liabilities, displacement, alternative uses, or the counterfactual are missing. Revaluation is treated as new capacity.	Narrow or withdraw claims that fail metaphor removal. Stop if additionality or the central causal proposition is not demonstrated against a defined counterfactual.
Ethical legitimacy (1 whitewashing and moral licensing, 3 tiered care, 9 clinical core and foundation)	Non-distribution, clinical independence, equitable access, valid consent, protected assets, and mandatory allocation govern consequential decisions.	Related-party extraction, opaque pricing, volume incentives, diverted staff or beds, longer local waits, unjustified exclusion, compromised consent, unverifiable allocation, or past contribution used to excuse breach.	Suspend for preventable harm, impaired consent or independence, unlawful or unjustified exclusion, material loss of local access, blocked assurance, prohibited extraction, or unverifiable allocation. Return, prestige, volume, or social spending cannot compensate.
Technological and financial risk (2 phased CeFi-to-DeFi fragility, 10 dependence on protected capital)	Legally identifiable responsibility precedes bounded programmability. The affiliated layer remains subject to enforceable rights. Protected initial capital is finite, disclosed, and transitional.	Mismatch between the authoritative record and ledger, concentrated keys, custody, data feed, bridge, code, cyber, or KYC/AML failure, automated liquidation reaching essential care assets, liquidity mismatch, declining runway, or protected funding replacing operating revenue.	Suspend the affected layer if enforceability, integrity, asset or data containment, or effective control fails. Clinical decisions, essential assets, and continuity cannot be collateralized or interrupted. Funding that conceals infeasibility ends progression.
Governance vulnerability (5 capture and interference, 12 jurisdictional disruption, 13 procedural complexity)	Decision rights, conflicts, overrides, audit, appeal, removal, maximum decision latency, and continuity remain identifiable, enforceable, contestable, and clinically usable across jurisdictions.	Concealed interests, concentrated appointment power, unexplained override, blocked assurance, incompatible duties, duplicate approval, unresolved responsibility, recurrent deadlock, retaliation, or clinically consequential delay.	No authorization where responsibility outruns accountability, independent clinical authority is absent, or the competent decision-maker is unidentifiable. Capture, illegality, suppressed evidence, or delayed necessary care require suspension.
Scalability and demand uncertainty (4 empirical scalability, 11 projected versus verified demand)	Independently validated demand, deliverable referrals, payer authorization, workforce, logistics, quality, equity, and operating cash flow remain aligned as volume changes.	Low referral-to-treatment completion, unstable use, cancellations, induced volume, workforce loss, cost or time overrun, payer rejection, or declining quality, continuity, patient experience, or local access.	Expansion cannot exceed validated demand, deliverable referrals, and demonstrated capacity. Stop if quality, access, continuity, workforce, equity, or the clinical core deteriorates. A successful pilot permits only the next defined test.

Table 3 (cont). Prespecified tests, failure signals, and noncompensatory gates by risk family

Risk family and numbered objections	Claim to be tested	Observable failure signals	Non-compensatory gate
Value measurement (6 clinical, experiential, social, and financial value)	Definitions, denominators, provenance, comparators, patient-reported measures, equity strata, privacy controls, and analytic rules are prespecified, auditable, and reproducible.	Excessive missingness, unstable definitions or denominators, unverifiable provenance, selective reporting, gaming, model drift, privacy or consent failure, differential attrition, or financial improvement without patient benefit.	Fabrication, suppressed adverse outcomes, irreproducible primary analysis, compromised safety, material privacy failure, or inability to assess clinical, experiential, or equity outcomes prevents any value claim. Financial performance cannot compensate.

AML: Anti-money laundering; CeFi: Centralized finance; DeFi: Decentralized finance; ISO: International Organization for Standardization; KYC: Know your customer. The mapping, indicators, and gates are project-specific. ISO 31000:2018 [118] informs the risk process but does not supply the proposed thresholds. Stopping conditions remain unvalidated and require prospective calibration, independent review, and legal authority specific to each jurisdiction.

Source Note

The mapping, proposed owners, indicators, and gates are project-specific. ISO 31000:2018 [118] informs the risk process. The 2026 Three Lines Model distinguishes management ownership, specialist support and challenge, and independent internal audit assurance. Neither source supplies the proposed thresholds. Stopping conditions remain unvalidated and require prospective calibration, independent review, and jurisdiction-specific legal authority.

A design feature gains evidentiary standing only through a prespecified assumption, a disconfirming observation, and an independent test. Testing begins when the architecture encounters conflict of interest, constrained access, adverse outcome, override, funding shortfall, or tension between financial and clinical priorities. A breach may suspend expansion, admissions, financial issuance, or capital deployment. It cannot interrupt clinically necessary care, records, medicines, follow-up, or safe transfer for patients already under care. Resumption requires evidence that the breached condition was corrected rather than renamed.

The first test concerns the paper's behavioral hinge and its narrow evidence. De Nardi et al. [33] link longevity and medical expenditure risk to precautionary saving among single retirees, not households generally or institutional holders. Both extensions remain falsifiable cross-level hypotheses. The primary test asks whether care assurance changes institutional participation, allocation, holding period, or capital velocity after expected return, guarantees, legal privilege, regulatory treatment, and political direction are made as comparable as the pilot permits.

Capital volume, movement, or declared social purpose do not establish additionality. Assessment therefore covers provenance, opportunity cost, liabilities, displaced public or productive uses, operating costs, resulting clinical capacity, and distributional effects [157].

Coexistence of social and commercial logics leaves unresolved which prevails under pressure [97, 135]. Evidence lies in procurement, related-party transactions, transfer pricing, eligibility, workforce distribution, waiting times, outcomes, and completed social allocation. Social credit does not compensate for a later breach [158].

A benevolent purpose can become its own exemption. When satisfaction with the design replaces evaluation, challenge is recast as obstruction and intention as performance.

The danger is not that one actor intends harm. Each actor can remain locally rational, procedurally compliant, and convinced while the aggregate interval for action closes. Delay, deferral, and unexercised authority therefore become measured outcomes.

Programmability offers greater observability but confers neither legal validity nor solvency. Actual decentralization still depends on control, governance, custody, and infrastructure [19, 116]. The test is whether withdrawal or non-renewal of protected capital reaches clinical eligibility, staffing, supply continuity, or care already underway.

Financial risk here concerns transmission, not scale alone. At the end of June 2025, BIS [48] reported an OTC

Table 4. Role allocation and designated stop authority by risk family

Risk family	Governing oversight	Operational owner	Monitoring and challenge	Independent assurance	Designated stop authority
Conceptual validity	Research steering body	Scientific lead, additionality assessment	Methodological, economic, counterfactual challenge	External scientific and statistical review	One designated research authorizing body
Ethical legitimacy	Foundation board and competent public-interest authority	Clinical core management, access, workforce, procurement, consent, allocation	Clinical governance, ethics, compliance, equity	Internal audit, independent clinical and financial assurance	One designated competent clinical, governing, regulatory, or public authority
Technological and financial risk	Finance and risk governing body	CeFi management, affiliated DeFi operations, technology, custody, compliance, treasury	Cybersecurity, privacy, model risk, data governance, regulation	Internal audit, independent technical, custody, legal, and financial assurance	One designated competent governing or financial regulatory authority
Governance vulnerability	Governing board, competent public authority	Executive, legal, compliance, continuity, integration	Risk, ethics, regulation, clinical governance, and conflict of interest	Internal audit, independent legal, clinical, and process review	One designated competent governing, clinical, regulatory, or public authority
Scalability and demand uncertainty	Pilot governing body	Clinical operations for demand, referrals, payer, workforce, logistics, infrastructure	Quality, workforce planning, finance, epidemiology, capacity assurance	Independent feasibility and health system evaluation	One designated competent pilot governing body, clinical authority, or public authority
Value measurement	Independent quality and research oversight body	Outcomes, data governance, privacy, real-world evidence	Epidemiology, biostatistics, quality, information governance, privacy	Independent clinical, statistical, data quality, and privacy review	One designated competent scientific, clinical, governing, or regulatory authority

CeFi: Centralized finance; DeFi: Decentralized finance; IIA: Institute of Internal Auditors. Source note. The proposed owners and role separation are project-specific. The IIA Three Lines Model [156] informs the distinction among management responsibility for risk, specialist roles that support, monitor, and challenge, and independent internal audit assurance. It does not designate the stop authorities proposed here.

notional amount of USD 845.7 trillion, a gross market value of USD 21.8 trillion, and gross credit exposure after netting of USD 3.0 trillion. These are contractual reference, replacement value, and narrower counterparty exposure measures, not interchangeable estimates of loss. Notional amount marks the surface across which synchronized valuation, collateral, and margin adjustments may propagate. Portfolio overlap, leverage, market impact, deleveraging speed, and illiquid concentration shape threshold effects and spillovers from fire sales [159, 160].

Boards, approvals, audits, and jurisdictional interfaces protect in some settings but may also lengthen handoffs, duplicate authorization, obscure responsibility, and delay care. Each layer has a distinct control function. Once ownership, competent authority, and maximum decision latency are prespecified, delay beyond that interval becomes reportable.

Evidence on cross-border care [138, 139] establishes that the activity exists, not this architecture's volume, payer mix, case complexity, workforce requirement, re-

Table 5. Non-exclusive institutional and financing arrangements compared by return pathway, legal effect, stop authority, and continuity of care

Institutional or financing arrangement	Route by which return may affect clinical decisions	What status alone establishes	Authority to stop finance	Authority to stop clinical operation	Continuity if the arrangement fails
Non-distributing and charitable	No distributable surplus arises, yet related parties may receive value through procurement, leases, management contracts, compensation, or debt.	Bars distribution to owners. It does not prove arm's-length terms, safe incentives, or that revenue concentration will not threaten continuity [161, 162].	Funders and lenders under their own instruments.	Legally competent clinical authority and the charity regulator where empowered.	Depends on reserves and supervised transfer. Status creates no funded closure pathway.
Commercial	Residual claim and appointment rights sit in the ownership chain. Clinical decisions remain subject to professional and regulatory duties.	Identifies the residual claimant and governance chain. It does not show that service mix is independent of profitability or that quality differences are free of method, disease, or data source effects [163–165].	Board, shareholders, and lenders through capital or covenant decisions.	Legally competent clinical authority. Owners may replace management through governance rights.	Governed by insolvency, regulatory intervention, or acquisition unless continuity is separately contracted.
Public-private partnership	Contract allocates decision rights, payments, risk, monitoring, and step-in power. Renegotiation may alter that route.	Allocates risk and reward by contract. It does not prove that risk remains with the party best able to control it, that the public retains information and bargaining capacity, or that renegotiation will not return risk to the public [100].	Public contracting authority and project lenders within contract terms.	Legally competent clinical authority. The contracting authority acts only where step-in rights were reserved.	Depends on agreed step-in, continuity, and handback clauses. Failure is contested where they are absent.
Hybrid and social enterprise	Both logics may reach the same decision unless the design excludes one.	Confirms dual purposes, not which logic governs a contested decision under pressure or when benefit is hard to measure [97, 110, 135].	Investors and funders under their own instruments.	Legally competent authority attached to the chosen legal form.	Not inherent. It depends on separately contracted arrangements.
Impact and blended finance	Usually operates through fund or instrument terms. Concessional capital may also enter operator equity.	Establishes intent and financing terms. It does not establish additionality against a defined counterfactual or societal impact, the least examined element in that literature [166].	Fund governance and the provider of concessional capital. Neither has clinical authority.	No authority arises from the instrument. It remains with the operator's legally competent clinical authority.	Not inherent. It depends on covenants and the operator's continuity plan.

Table 5 (cont). Non-exclusive institutional and financing arrangements compared by return pathway, legal effect, stop authority, and continuity of care

Institutional or financing arrangement	Route by which return may affect clinical decisions	What status alone establishes	Authority to stop finance	Authority to stop clinical operation	Continuity if the arrangement fails
The proposed architecture	The clinical core does not distribute profits. By design, investment rights remain outside decisions on eligibility, professional judgment, and continuity of care, but separation under pressure remains untested.	Specifies intended rights and responsibilities but does not prove separation under financial pressure, related-party dealings, or jurisdictional conflict. No direct evidence of that separation is presented.	The finance and risk governing body and the protected capital provider, each acting under its own terms.	One legally competent stop authority must be designated for each gate before the pilot. Independent assurance assesses whether a gate has been breached but cannot exercise stop authority (Tables 3 and 4).	A funded transfer and wind-down pathway must accompany suspension. Harmful operation must not be prolonged. Performance under stress remains untested.

The return-pathway criterion is analytical rather than a validated ranking or quantitative measure. Stop authority and continuity arrangements vary by jurisdiction and remain proposed rather than established. The comparison concerns what status alone establishes. Any arrangement may add contractual, regulatory, reserve, step-in, transfer, or wind-down protections, but their existence and operation require separate evidence, including for this architecture. No owner, investor, funder, or contracting authority replaces the professional authority of licensed clinicians at the point of care. Evidence that an embedded sustainability orientation can accompany durable performance over the long run concerns firms rather than architectures involving multiple institutions and therefore requires separate demonstration before transfer [167].

ferral completion, or operating durability. Pilot work addresses recruitment, acceptability, delivery, resources, and progression criteria but does not establish effectiveness [39]. Real-world evidence depends on data whose relevance, reliability, provenance, completeness, and fitness for purpose match the question [129, 153]. Missingness, denominators, adverse events, equity strata, privacy, and coding or case-mix changes remain visible before progression. The breached gate governs the decision. Design cannot certify performance.

Comparison with Existing Alternatives

Table 5 neither ranks the arrangements nor treats them as mutually exclusive. It applies the same five tests to institutional and financing arrangements, including this one. It asks how return may affect clinical decisions, what status alone establishes, who may suspend finance, who may suspend clinical operations, and how care continues if the arrangement fails. The architecture is tested by the same standard it applies to its comparators.

Comparison concerns what status alone establishes. Any arrangement may add contractual, regulatory, reserve, step-in, transfer, or wind-down protections, but their existence and operation require separate evidence, including for this architecture. Evidence that an embedded sustainability orientation can accompany durable long-run performance concerns firms, not multi-institution architectures, and requires separate demonstration before transfer [167].

Hansmann [161] shows how the non-distribution constraint addresses unobservable quality and closes one route for surplus extraction. Revenue concentration remains a financial stability concern [162].

A public-private partnership is constituted through contract, and implementation and renegotiation determine whether the intended allocation of risk survives [100]. A hybrid holds multiple logics without settling which governs under pressure [97, 135]. An impact-oriented structure declares intention and financial rights, whereas societal impact remains a separate evidentiary

question [166]. Sovereign investment adds governance, transparency, political involvement, and scale constraints to return objectives [143].

Separating clinical judgment from distributable claims adds coordination demands, jurisdictional dependence, and funded assurance and stopping functions. Multi-actor ecosystems depend on defined roles, shared rules, and specific complementarities rather than hierarchical fiat [99].

The present model borrows selected functions from these traditions. That combination is a design proposition rather than comparative evidence. If a return-bearing interest reaches eligibility, value leaves the protected core, allocation escapes independent scrutiny, or financial stress interrupts care, the architecture will have reorganized these conflicts rather than resolved them.

Boundary Conditions

Pilot eligibility requires four concurrent conditions. Capital must be demonstrably idle or low in velocity. The anchor must hold lawful authority and staffed capacity. Data must support progression decisions. Social allocation rules must be enforceable. No condition compensates for another. Without them, capital is not additional, the anchor is not credible, data are not evidence, and allocation is not delivery.

Idleness is proposed here as holding period, mandate, encumbrance, and no committed alternative use over a defined window, not size. Bates et al. [46] report that the average cash-to-assets ratio more than doubled from 1980 to 2006 among industrial firms in a large advanced economy as cash-flow risk and firm characteristics changed. Additionality is assessed, recorded, disclosed, and later evaluated rather than presumed from mobilization [157].

An anchor is not established by a building, certificate, reputation, or announced capacity. An operable anchor combines licensed authority, staffed capability, referral and payer pathways, supply continuity, and a funded transfer path for care already underway. Accreditation structures external review but does not replace local capability [103]. Feasibility shows whether these functions can be delivered rather than whether they work [39].

Data become evidence only when relevance, reliability, provenance, and analytic fitness have been assessed for the question asked [129, 153]. Denominators, missingness, adverse events, equity strata, privacy controls, and data transformations are prespecified and auditable. Otherwise, incomplete ascertainment and loss to follow-up may produce an unrepresentative record and leave the next decision unsupported.

The proposed allocation rule is eligible only if its base, timing, protected destination, related-party exclusions, independent audit, breach criteria, and suspension authority are fixed before the first disbursement. Allocation is established by delivery rather than announcement.

Policy and Implementation Implications

Legal authority must precede incentive, and financial participation cannot confer clinical authority. World Bank [168] guidance requires public-private frameworks to identify each institution, its legal authority, the clinical core's status, and powers over licensing, assurance, suspension, and continuity before tax relief, guarantees, preferential treatment, or public capital.

Only then are incentives staged, made reversible, and released against published milestones for additionality, clinical readiness, data readiness, allocation governance, and continuity. Each milestone names one authority, a maximum decision latency, restart evidence, and the stop power triggered by breach. Independent assurance reports a breach to that authority but does not exercise stop power. The host authority also publishes how care continues for patients already under care and how workforce depletion or longer waits are detected (Table 3, 4).

Framework Limitations and Transition

The framework remains an ex ante synthesis. It has not established that care-cost insecurity governs institutional allocation, that the architecture operates as specified, or that it would outperform existing arrangements. Evidence that uncertain medical expenditure and longevity risk affect saving among single retirees does not extend to households generally, still less to institutional holders [33].

The components have been specified but not operated together. Program theory, context, implementation, and outcome are distinct objects of evaluation, whereas feasibility work tests whether evaluation is possible rather than whether an intervention works [39, 93]. The correspondences drawn here are constructed relations, not claims of identity, and are valuable only within the limits where they continue to hold [2]. Convergence supports bounded theory construction, not causality or net benefit.

Nor has the framework shown that resources identified as available will be released when a qualifying need is present. A holder may preserve the asset, defer commitment, or await guarantees once the channel has met its admission criteria. A pool may satisfy every condition for availability while remaining withheld through the period in which capacity could have been built and those waiting for it treated.

The primary test must specify comparator, measurement window, rival mechanisms, effect threshold, futility criterion, and decision rule in advance. If a prospectively powered test shows no change in institutional participation, allocation, holding period, or capital velocity after care assurance, the financial venous stasis mechanism proposed here must be rejected as an explanatory basis for progression in that setting. An observed change fully explained by return, guarantees, legal privilege, regulatory treatment, political direction, or another rival mechanism requires the same judgment.

These limitations do not certify the baseline as safe. Proposal and baseline must face the same effects, alternatives, opportunity costs, and failure conditions.

From Structural Risk to Legitimate Action

The examination now changes direction. Having tested its own claims against thirteen objections, the architecture turns toward those able to examine it. Institutional capital, clinical expertise, accreditation capacity, data systems, logistics, and international access may already exist. What is missing is not always capacity. It is the distance between capacity and the authority to act legitimately.

A body able to assemble expertise, finance analysis, or coordinate infrastructure may still lack authority to approve its own proposal, replace clinical judgment, substitute for public decision, or validate its own controls. The expansion of corporate public responsibility does not transfer public authority [169].

Risk described in the abstract permits postponement. Risk that has been named, dated, and assigned does not. What the preceding sections make visible is not misconduct but danger, which is a measurable distance between resources held in protection and needs that remain present, sustained by decisions each of which was defensible alone.

Where need is visible, capacity is known, and comparable actors have begun to respond, continued stillness is no longer invisible. Non-action becomes an observable choice, and its consequences enter the same record as the risks of action. Public positioning by senior leadership is shaped by personal values, stakeholder alignment, organizational identity, brand consistency, implementation, and the capacity to withstand continued scrutiny, but it cannot be reduced to a single statement or a symbolic posture [170–172].

There is a further reason for restraint, and it is not tactical. Mastery inside a domain does not confer the authority, the distance, or the composure required to repair that domain's own architecture, and those most competent to identify a problem are often the least able to authorize its remedy, not because their judgment is poor, but because an instrument cannot validate itself.

Only at this point does the direction change again. The first responsible act is neither approval nor the claim that risk has been resolved. It is to make disciplined examination possible through disclosure of interests, independent multidisciplinary review, consideration by competent public authority, legal and clinical feasibility assessment, and a bounded pilot governed by equity gates, clinical protections, calibrated indicators, stop rules, and publication of results, favorable or otherwise. A governing body may request such examination without approving its own proposal or committing itself to the answer. Requesting an examination and accepting its outcome remain separable acts, and engagement must continue before, during, and after action rather than appear at a single visible moment [172]. Once danger has been made visible, urgency need not prolong alarm. It can shorten the distance between a person in need and a lawful, measurable, and dignity-preserving response. A credible sense of safety does not come from concealing danger, but from constructing a reliable path through it. Physicians are professional problem-solvers. At times, even they may need external support during structural and organizational crises of their own. The US cardiology community experienced institutional division and rivalry. Yet since 1980, the American Heart Association and the American College of Cardiology have jointly translated scientific evidence into clinical practice guidelines [173, 174]. In the broader American medical profession, C. A. Hoffman turned to Abraham Lincoln. "A house divided against itself cannot stand," Lincoln had judged. Hoffman recast that judgment as a question put to his own profession. "This is the House of Medicine. Shall it be a House united, or a House divided?" He framed it explicitly

as the central question, the choice, and the decision before the profession. More than half a century later, JAMA invoked the same house divided frame to call for the reintegration of clinical trials and clinical practice [175, 176]. At those rare and fragile junctures when deferral itself becomes a decision, the impulse is to rush for relief more than prudence permits, yet discipline must remain undivided.

CONCLUSION AND FUTURE DIRECTIONS

Future Directions

The preceding sections identified the framework's principal vulnerabilities. This subsection converts them into a sequenced research agenda. The framework may move from conceptual architecture toward pilot examination only through prespecified tests, independent review, and the possibility of rejection. Eleven directions follow.

Pilot Implementation and Empirical Testing

A bounded pilot should assess capital circulation, clinical outcomes, patient experience, equity, protected social allocation, governance compliance, cash flow, and generated value relative to expected returns through real-world data and the evidence generated from them [150]. At limited scale, feasibility and apparent success remain distinct. Progression depends on prespecified feasibility criteria, evaluation thresholds, and stopping rules rather than post hoc interpretation [39, 93].

Design and Testing of The Governance Model

A model resistant to misuse needs rules for board independence, allocation, conflicts of interest, transparency, appeal, decision latency, assurance, and stop authority. The pilot would test these arrangements under disagreement, delay, and funding pressure. Each function must remain accountable when interests diverge.

Structuring Equity Safeguards

Care across borders creates risks of ethical strain and unequal access. Future work should test rules that preserve local clinical capacity and the workforce, reduce displacement and brain drain effects, return value to domestic public health, and prevent financial participation from influencing eligibility or treatment. Legitimacy depends on whether these safeguards survive operating pressure [138, 139].

Maturation of Value Measurement

Anxiety reduction, dignity, compassion, continuity, and recovery require reviewable indicators that avoid trivialization. Future work should refine patient-reported outcomes and experience measures [130], together with recovery indicators, data on quality of life, and equity measures. The task is to establish a language for evaluation and recalibration while preventing a composite score from concealing harm behind monetary success or obscuring the limits of measurement.

Quantification of Demand and Segment Dynamics

International care demand does not establish segment size. Estimates of volume, geographic distribution, payment capacity, case mix, referral completion, treatment completion, continuity after return, and growth are required before pilot size is fixed or capacity is built around assumed demand [91, 177].

Calibration of Blended-finance Parameters

The required calibration covers the protective layer, the distribution of risk and return, participation rights, loss allocation, and thresholds for institutional capital within the phased CeFi-to-DeFi architecture. Relevant literature informs risk allocation, the governance of social purpose, and organizational sustainability over time, without determining these parameters [100, 110, 167]. The pilot tests whether catalytic capital with a long horizon can recede without weakening clinical continuity, protected social allocation, or operational sustainability. The analysis must preserve the distinction between gross revenue, operating obligations, reinvestment, reserved social allocation, and distributable surplus.

Regulatory and Geopolitical Resilience

If pilot evidence supports clinical feasibility, legal integrity, and operational continuity, the architecture may be implemented as the Reverse Health Silk Road, a complementary international care corridor carrying health cooperation from West to East within broader Silk Road connectivity. Research should test whether participating jurisdictions can align lawful authority, care and accreditation standards, data governance, payment arrangements, and continuity obligations through transparent agreements approved under their own laws. Each state retains sovereignty. Imple-

mentation must preserve patient safety, clinical independence, protected social resources, data protection, accountability, and ongoing treatment. Patient safety comes first. Transparent allocation and uninterrupted treatment remain binding throughout. The aim is a lasting framework in which participants retain their respective roles and sustain corridor reliability and shared purpose over time [126].

Expansion of the Theoretical Foundation and Convergence Matrix

The matrix warrants extension only when each analogy is reexamined at its boundary and added literature performs an independent task, supplies a rival account, or identifies where transfer must stop. A transfer that cannot produce a bounded proposition or survive a counterexample should be narrowed or retired. Expansion is not accumulation.

Comparative Case Studies

Comparison of health initiatives using blended finance, institutional health investments, international care programs, and adjacent service models should identify recurring success conditions, failure mechanisms, and transfer costs before the pilot repeats errors visible elsewhere. Priority failure mechanisms include governance capture, mission drift, workforce displacement, transaction costs, regulatory arbitrage, and subsidy dependence.

Assessment of Patient and Societal Perspectives

The ethical promise depends on how dignity, trust, anxiety, access, and continuity are experienced by patients and interpreted by families, caregivers, workers, and host communities. Qualitative and participatory methods should test whether the model is recognized as shared benefit rather than exclusion. A structure cannot establish that it protects dignity merely because its designers intended it. Those affected must recognize the promise in practice.

Pilot preparation and governance design come first. Equity safeguards and value measurement develop with them. Demand, finance, portability, comparison, and theory can then be refined through evidence generated by the operating core. The sequence prevents learning from being mistaken for success and scale from preceding legitimacy. The largest uncertainties precede the easiest indicators.

The Centralized–Decentralized Dilemma in Artificial Intelligence

The architecture may illuminate an emerging tension between centralized and decentralized artificial intelligence. This is an ethical and institutional warning, not a technical solution. Centralized intelligence may compress decision power into domination, whereas opaque systems may dehumanize by reducing persons to optimization targets [178]. Decentralized intelligence may disperse agency, responsibility, and governance coherence into fragmentation. AI ethics guidelines converge on transparency, accountability, and privacy but diverge in implementation [179]. The framework does not solve the CeAI-DeAI problem. Instead, it can define a similar architecture that such a problem would require, one that includes fundamental accountability without domination and distributed freedom without fragmentation.

Conclusion

This study treats frozen capital and unmet high-value care demand as interconnected dimensions of one proposed circulatory pathology. Capital may withdraw from productive circulation into low-velocity protection amid institutional trust deficits and reputational uncertainty, whereas aging populations and complex care needs require resilient, accredited, and sustainable clinical capacity. Care-cost insecurity is proposed as the behavioral hinge. The framework joins these domains through institutional reperfusion rather than conventional taxation or simple redistribution.

Its contribution is not a single financial asset. It integrates a non-distributing clinical core, a foundation protecting social allocation, an auditable phased CeFi-to-DeFi financial governance architecture, independent accreditation, evidence generated from real-world data, and stratified capital alignment. None validates the others. Together they form a transparent operating cycle linking clinical value, social benefit, and financial sustainability. Originality lies in their sequence, boundaries, and joint examination.

The manuscript does not claim that this arrangement works in practice. Component literatures provide bounded support, whereas the discussion identifies ethical, managerial, financial, technological, and regulatory vulnerabilities. The result is a falsifiable framework, not a validated implementation. The pilot must test the architecture against its clinical, social, governance, and financial claims. Financial performance cannot compensate

FIGURE 8. Medicine's enduring deontological heritage (AI-generated, © 2026 ktekesin). The closing visual gives visible form to the continuity between inherited medical duty and service that preserves dignity without presenting the image as historical or clinical evidence. It is the manuscript's final scholarly coda, not a further proposition. The person remains the measure of every system.

for failure in clinical safety, legality, equity, or mission integrity. An adverse result must be able to reject the mechanism while preserving clinically valuable service.

The argument rejects reducing concentrated institutional capital to a macroeconomic hazard or clinical care to a fiscal cost. The architecture asks whether capital can serve care without governing the clinical core and whether care can receive capital without becoming its instrument. Before capital moves, the architecture submits its claims, powers, and limits to examination. If that relation survives testing, dormant wealth may become capacity for clinical and social repair.

Homeostasis and the Living Conscience of Medicine

The epistemic boundary of the manuscript remains unchanged, and this ex ante conceptual manuscript is open to pilot evaluation, correction, or rejection. Epistemic restraint is one side of the balance. Moral answerability is the other. Method becomes morally incomplete when it detaches from lived vulnerability, the patient's lifeworld, and human dignity. Heubel and Biller-Andorno [180] and Svenaeus [181] locate this boundary in medical ethics and the lived experience of illness. Sackett et al. [182] and Greenhalgh et al. [183] show why evidence-based medicine cannot be reduced to mechanical rule-following. Ruckenstein and Schüll [184], Danaher [185], and Sharon [186] extend the warning to health datafication, algorithmic governance, and digital health capitalism. Financial, digital, and clinical systems must remain answerable to the human being they are designed to serve, and no financial, digital, or algorithmic abstraction may dominate the clinical core (Fig. 8).

Medicine gives this boundary a living form. Formal duty alone does not exhaust it. Gardiner [187] locates moral character within clinical judgment, whereas Chochinov [106] places dignity at the center of care. Cruz [188] and Dutton et al. [189] show how care and compassion become credible through accountable responses to suffering. Mittelstadt [190] and Hagendorff [191] show why ethical principles require operational responsibility and accountable practice. Humanity is the art of reaching those in need before their dignity is ever compromised, and of doing so in a way that never compromises it.

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Letter to the Editor

Beyond nutritional knowledge: Dietary supplement use in preschool children

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To the Editor,

I read with interest the study by Cam et al. [1] on maternal nutritional knowledge and child anthropometric outcomes in preschool children, which found no association between maternal knowledge and children's height-for-age or weight-for-age z-scores. Nutrition is among the strongest modifiable determinants of linear growth in early childhood, and the preschool years are when feeding practices and dietary habits are gained. Maternal nutritional knowledge might therefore be expected to leave a measurable trace on child anthropometry. Their findings suggest that, in this well-nourished sample, knowledge alone did not translate into measurable differences in growth. In their own sample, 56.7% of mothers scored in the good or very good categories for basic nutritional knowledge, while only 44.7% did so for food preference. As the authors note, knowing what a balanced diet is and providing it every day are two different things. What matters is how parents apply this knowledge to their daily food choices, especially when they cannot always follow it. Dietary supplements are one such response. They promise nutrition without requiring a change in diet, and their use is common in this age group. The authors report that even mothers with poor knowledge scores rated their own diet at a median of 6 out of 10. Many mothers may overestimate the quality of their diet, and those who believe they already eat well may be less likely to seek help. Supplements may be used instead of making changes to the diet, rather than to address a known nutritional deficiency. In one Turkish study, 35.6% of children aged 3–6 years receive a dietary supplement; 85.9% of parents cite protection from illness and 26.6% mental performance, whereas only 10.9% report an existing health problem [2]. In NHANES 2007–2010, the prevalence of supplement use among US children was 31%, peaking at 45% among 2–5-year-olds; only 15.5% of products followed a health-care provider's recommendation [3]. Notably, fewer than a quarter of users gave "supplementing the diet" itself as a reason [3]. Their use is driven less by a known deficiency and more by a general desire to protect health. However, this sense of reassurance may not always be harmless. Among 105 dietary supplements promoted by German influencers on a social media platform, although not specific to children's products approximately more than half of vitamin and most mineral supplements exceeded the maximum daily amounts recommended by the German federal risk assessment authority; no influencer provided dosage information or an overdose warning, and only 2% mentioned adverse effects [4]. Such content forms part of the information environment in which parents make decisions about their children's nutrition. The consequence is not only reassurance but also excessive micronutrient exposure. In a national Danish sample, supplement use raised the proportion of 4–6-year-old users exceeding the tolerable upper intake level (UL) to 43.1% for retinol and 73% for zinc [5]. In that sample, 22% of 4–6-year-olds already exceeded the zinc UL through diet alone [5].

The potential role of supplements in this context could be further examined using the study design adopted by Cam et al. [1]. Including two additional items whether the child receives any supplements and the sources from which parents obtain nutritional information could help clarify how parents respond to the gap between nutritional knowledge and dietary practice. Future studies should also include fathers, as nutritional decisions and practices are not solely determined by mothers.

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