

# Prevalence of celiac disease in pediatric patients with type 1 diabetes

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## ABSTRACT

**Objective:** The aim of this study is to determine the frequency of celiac disease (CD) in children with T1DM at the time of diabetes diagnosis and during follow-up, and to evaluate the effect of CD on growth and metabolic control in diabetic patients.

**Material and Methods:** In this study, celiac autoantibody screening was performed at the time of diabetes diagnosis and during follow-up in 243 regularly followed-up patients who were diagnosed with T1DM between January 2007 and December 2018 at a university hospital and had a diabetes duration of at least 1 year. In serology-positive patients, the diagnosis of CD was confirmed by small bowel biopsy. The effects of CD and dietary compliance on growth and metabolic control were evaluated.

**Results:** The mean age of the 243 patients (124 boys, 119 girls) at the time of the study was 12.3±4.9 years, the mean duration of diabetes was 4.4±2.6 years, and the mean age at T1DM diagnosis was 7.6±4.6 years. The average glycated hemoglobin level (HbA1c) of the patients when they were diagnosed with T1DM was 11.9±2.57%. The prevalence of CD in the patients was 7% (n=17), with 88% of the patients being diagnosed with diabetes at the time of diagnosis, and 12% diagnosed with CD during follow-up.

**Conclusion:** In our study, the prevalence of celiac disease in patients with type 1 diabetes was found to be 7%, similar to previous studies. It was determined that the majority of diabetic patients with CD were diagnosed at the time of diabetes diagnosis, and a small number of patients were diagnosed in the first 4 years of follow-up. We found that CD negatively affects the metabolic control of diabetes, either directly or due to non-compliance with the gluten-free diet, but does not affect growth in children with diabetes.

**Keywords:** Celiac disease; child; gluten-free diet; metabolic control; type 1 diabetes.

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# Tip 1 diyabetes mellitus tanılı çocuklarda çölyak hastalığı sıklığının araştırılması

## ÖZET

**Amaç:** Bu çalışma, tip 1 diyabetes mellitus (T1DM) tanılı çocuk hastalarda tanı anında ve izlemde çölyak hastalığı (ÇH) gelişme sıklığının saptanması ve ÇH'nin T1DM'li olgularda büyüme ve metabolik kontrol üzerine etkisinin değerlendirilmesi amacıyla yapılmıştır.

**Gereç ve Yöntemler:** Bu çalışmada, bir üniversite hastanesinde Ocak 2007-Aralık 2018 yılları arasında T1DM tanısı alan ve diyabet süresi en az 1 yıl olan, düzenli takip edilen 243 olguda diyabet tanı anında ve takipte çölyak otoantikör taraması yapılmış ve pozitif olgularda ince barsak biopsisi ile ÇH tanısı doğrulanmıştır. ÇH'nin ve diyetle uyumun büyüme ve metabolik kontrol üzerine etkisi değerlendirilmiştir.

**Bulgular:** Çalışmaya alınan 243 olgunun (124 erkek, 119 kız) çalışma anındaki ortalama yaşı 12,3±4,9 yıl, diyabet süresi ortalama 4,4±2,6 yıl ve T1DM tanı yaşı ortalama 7,6±4,6 yıldır. Olguların T1DM tanısı aldıklarında ortalama glikolize hemoglobin düzeyi (HbA1c) %11,9±2,57 idi. Çalışmaya alınan 243 T1DM'li olgunun %7'sinde (n=17) ÇH saptandı. ÇH tanısı alan olguların %88'i diyabet tanı anında, %12'si ise izlem sırasında tanı almıştı.

**Tartışma:** Çalışmamızda tip 1 diyabetli olgularda çölyak hastalığı sıklığı %7 oranında bulunmuş ve bu oran literatür verileriyle benzerlik göstermiştir. ÇH tanısı alan diyabetik olguların büyük çoğunluğunun diyabet tanı anında, az sayıda olgunun ise izlemin ilk 4 yılında tanı aldığı saptanmıştır. ÇH'nin doğrudan veya glutensiz diyetle uyumsuzluğa bağlı olarak yalnızca diyabetin metabolik kontrolünü olumsuz etkilediği, ancak büyüme üzerine olumsuz bir etkisi olmadığı belirlenmiştir.

**Anahtar Kelimeler:** Çocuk; çölyak hastalığı; glutensiz diyet; metabolik kontrol; tip 1 diyabetes mellitus.

## INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is an autoimmune disease characterized by the absence or insufficiency of insulin, which develops by the destruction of pancreatic beta cells due to viral, chemical, or toxic effects in individuals carrying certain human leukocyte antigen (HLA) types, and is the most common chronic endocrine disease in childhood (1). There is a high probability of other autoimmune diseases occurring at the time of diagnosis of T1DM or during follow-up. The most common are autoimmune thyroiditis and celiac disease (CD). The incidence of CD in patients with T1DM is between 2.5–13% (2–6).

The co-occurrence of T1DM and CD may result in inadequate blood sugar regulation, poor metabolic control, frequent hypoglycemia attacks, short stature, delayed puberty, vitamin and mineral insufficiency, and a decrease in bone mineral density (7, 8).

Because of the high prevalence of CD among children with T1DM, the potential clinical consequences, and the fact that it is usually asymptomatic, screening for CD is recommended for all patients with T1DM after diagnosis. It is also recommended that screening be performed at intervals of 2–5 years, or earlier if the patient is symptomatic or has a first-degree relative with CD (9–11).

In this study, we aimed to determine the frequency of CD in Turkish pediatric patients with T1DM at the time of diagnosis and during follow-up, and to evaluate.

## MATERIAL AND METHODS

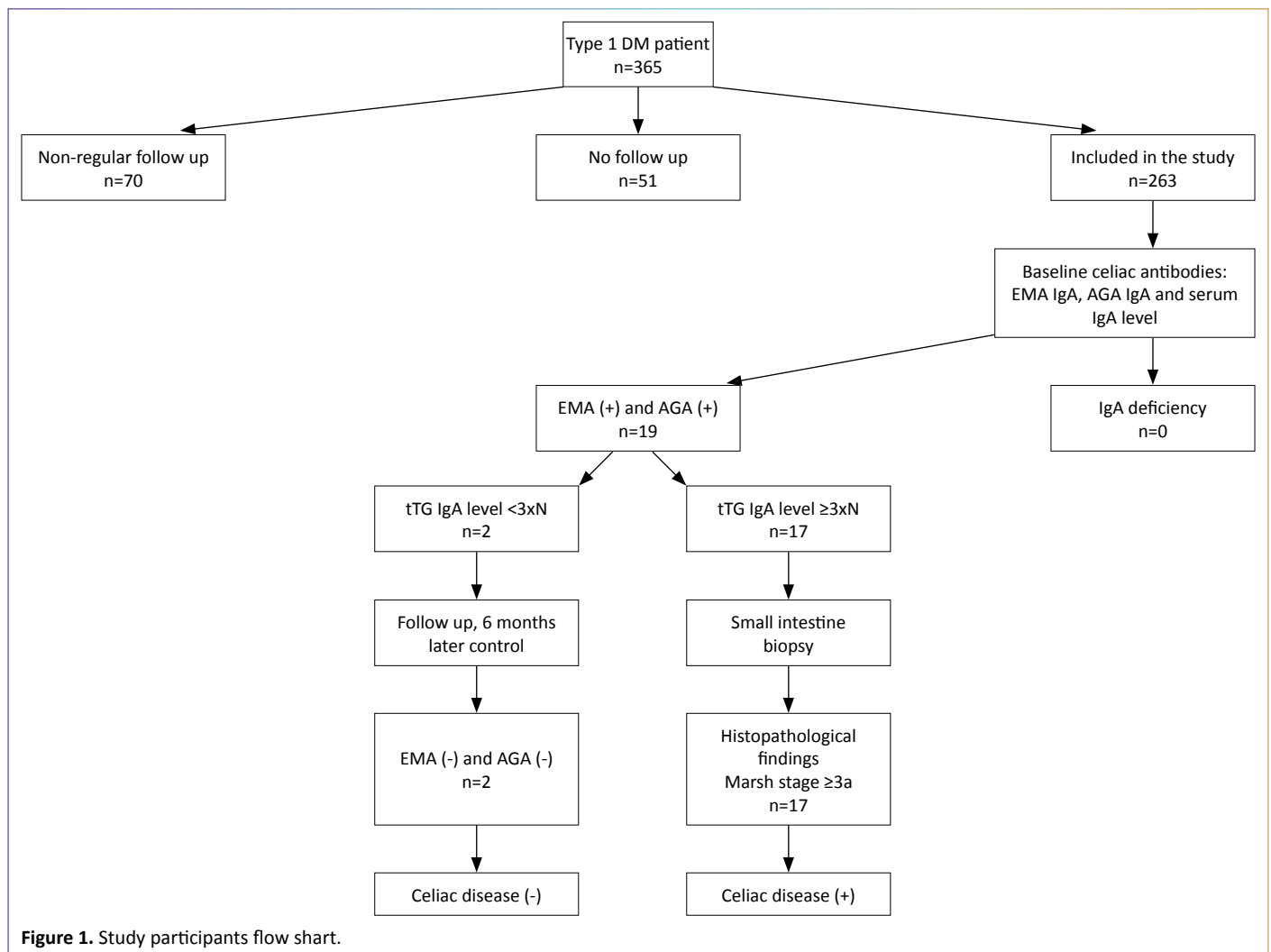
### Study Design, Type, and Sample

The study is a retrospective cohort study, based on medical files and electronic medical records review. All T1DM patients

attending the pediatric endocrinology clinic at a university hospital between 2007 and 2018 were included. Pediatric patients who had T1DM for at least one year and had regular follow-up were included in the study. Age and sex of the patients, duration of diabetes, history of autoimmune disease in the patient and family, anthropometry, puberty, anti-endomysium antibody (EMA) and anti-gliadin antibody (AGA) positivity, tissue transglutaminase antibody (tTG) level, results of duodenal biopsies, hemoglobin A1c (HbA1c) levels at the time of T1DM diagnosis and last visit, level of hemoglobin, ferritin, and serum immunoglobulin A (IgA), the frequency of hypoglycemia at the last visit, and the daily average insulin dose used were recorded. In order to evaluate the effect of celiac disease on growth and metabolic control in T1DM, an equal number of patients with T1DM without celiac disease, of the same gender and age, were randomly selected as T1DM patients with celiac disease. Anthropometric and metabolic findings were compared between groups. In addition, in order to evaluate the effect of diet compliance on growth and metabolic control in T1DM patients with CD, the patients were divided into 2 subgroups: diet incompatible and diet compliant, according to serological test positivity at the time of the study. Anthropometric and metabolic findings were compared between groups.

### Measurements

The average insulin dose was calculated by dividing the total daily insulin requirement by the current weight (unit/kg). CD serology testing included total IgA, EMA, and AGA. tTG IgA antibody testing was conducted in cases where either both celiac autoantibodies or only EMA were positive. tTG IgA levels were measured using the ELISA method, with a normal range of



0–20 RU/ml. Small bowel biopsy was performed by a pediatric gastroenterologist in patients whose tTG IgA levels were found to be  $\geq 3$  times the upper normal limit. CD was diagnosed if the patient had a Marsh score of  $\geq 3a$  in the duodenal biopsy (Fig. 1). Gluten was eliminated from the diet of patients diagnosed with CD. The diet compliance of patients with CD and T1DM was assessed by serological tests conducted at 6-month intervals. Additionally, serological tests were performed annually in patients where CD was excluded.

### Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Product and Service Solutions, IBM) version 22.0 (License No: 12388245294). Categorical variables were presented as numbers (n) and percentage (%). The variables were investigated using the Kolmogorov-Smirnov test to determine whether they were normally distributed. Descriptive analyses were presented using medians for the non-normally distributed variables. The Mann-Whitney U test was conducted to compare variables. A p-value of  $<0.05$  was considered to indicate a statistically significant result.

### Ethics

Ethics committee approval was obtained from the Ethics Committee of the relevant hospital on February 25, 2019, with decision number 04/18. The study was carried out in accordance with the latest version of the Declaration of Helsinki.

### RESULTS

A total of 243 children (124 boys, 51%) were included in the study. The mean age of patients was  $12.3 \pm 4.9$  years and the mean duration of T1DM at the time of the study was  $4.4 \pm 2.6$  years. The mean age at T1DM diagnosis was  $7.6 \pm 4.6$  years. The prevalence of patients with autoimmune thyroid disease was 31 (12.7%), CD was 17 (7%) and vitiligo was 2 (0.8%) (Table 1). Of a total of 17 patients (10 male, 58%), 15 (88%) were diagnosed with CD at the time of T1DM diagnosis, 1 (6%) was in the 2<sup>nd</sup> year of follow-up, and 1 (6%) was in the 3<sup>rd</sup> year of follow-up. 16 (94%) patients were asymptomatic when CD was diagnosed, 1 (6%) patient had diarrhea, weight loss, and recurrent hypoglycemia attacks for the last 3 months. The mean age of patients at the diagnosis of CD was  $7.8 \pm 4.9$  years.

Table 1. Characteristics of T1 DM study population

Characteristics	T1 DM patients (n=243)
Present age (mean years±SD)	12.3±4.9
Age at diabetes diagnosis (mean years±SD)	7.6±4.6
0–4.9 years (n, %)	55 (23)
5–9.9 years	89 (36)
≥10 years	99 (41)
Diabetes duration (mean years±SD)	4.4±2.6
1–1.9 years (n, %)	18 (8)
2–4.9 years	64 (26)
≥5 years	161(66)
Gender	
Female (n, %)	119 (49)
Male (n, %)	124 (51)
HbA1c level at diagnosis (%)	11.9±2.57
Autoimmune disease	
Autoimmune thyroid disease (n, %)	31 (12.7)
Celiac disease	17 (7)
Vitiligo	2 (0.8)
Family history for autoimmun disease	
Autoimmune thyroid disease (n, %)	24 (10)
T1 DM	14 (6)
Celiac disease	1 (0.4)
Rheumatoid arthritis	1 (0.4)

HbA1c: Hemoglobin A1c; SD: Standard deviation; T1 DM: Type 1 diabetes mellitus.

In order to evaluate the effect of CD on growth and metabolic control in T1DM, an equal number of patients with T1DM without celiac disease (CD-), of the same gender and age, were randomly selected as T1DM patients with celiac disease (CD+) (Table 2). The groups were similar for weight, height, and BMI z-scores, hemoglobin, ferritin, and serum IgA levels, and daily average insulin dose. There were no patients with low serum IgA. The 1-year average HbA1c and frequency of hypoglycemia were significantly higher in the CD+ group (respectively  $p=0.020$ ,  $p=0.030$ ).

EMA and AGA were positive in 8 (47%) patients with CD at the time of the study, and they were incompatible with the gluten-free diet. Patients with CD were divided into two subgroups: diet incompatible and diet compliant, according to serological test positivity at the time of the study (Table 3). The number of male patients was significantly higher in the diet-incompatible group ( $p=0.050$ ). The groups were similar for weight, height, and BMI z-scores, HbA1c levels, and frequency of hypoglycemia.

## DISCUSSION

In our study, CD was diagnosed in 7% of the patients with T1DM. This frequency is similar to the rates reported in previous studies (3, 5–7, 12–14). CD is diagnosed in patients at the time of T1DM diagnosis and usually within the first 5 years of follow-up (7, 14, 15). In our study, 15 (88%) of the patients were diagnosed with CD at the time of T1DM diagnosis, and 2 (12%) were diagnosed during follow-up. One of these 2 patients was diagnosed in the 2<sup>nd</sup> year of follow-up and the other in the 3<sup>rd</sup> year. These findings are similar to those of Slae et al. (16) and Pham-Short et al. (15), showing that the risk of developing CD in patients with T1DM is especially high at the time of diabetes diagnosis and in the recent years of follow-up. The International Society for Pediatric and Adolescent Diabetes (ISPAD) guideline recommends routine screening for CD in patients with T1DM at the time of diabetes diagnosis and especially in the first 5 years of follow-up (10). There is no definitive opinion for screening after the first five years (17). Many organizations, including the National Institute for Health and Care Excellence (NICE), agree that there is no evidence to determine the appropriate screening interval or duration (18, 19). According to these findings, it would be appropriate to perform CD screening in patients with T1DM, especially at the time of diabetes diagnosis and in the first 5 years of follow-up. Classical findings specific to CD are rare in patients with T1DM, and most patients are asymptomatic. CD is suspected in the presence of irregular blood sugar levels, recurrent hypoglycemic attacks, and growth retardation in children and adolescents with T1DM (14). In the study by Singh et al. (14), although none of the 17 patients with CD and T1DM had signs and symptoms specific to classical celiac disease, 88% (15 cases) were found to have recurrent hypoglycemic attacks. In Forde et al.'s (7) study, no signs or symptoms of CD were detected in 88.3% of the cases. In Aktay et al.'s (20) study, while 7 out of 10 patients with CD and T1DM were asymptomatic, 2 patients had growth retardation, and 1 patient had abdominal pain and diarrhea. However, it was stated that 2 children with growth retardation also had Down syndrome, and this condition might also be caused by Down syndrome. In our study, 16 (94%) of the patients with T1DM and CD were asymptomatic, while 1 (6%) patient had chronic diarrhea, weight loss, and recurrent hypoglycemia attacks for the last 3 months. No growth retardation, puberty delay, or iron deficiency anemia was detected in any of the patients diagnosed with CD at the time of T1DM diagnosis and during follow-up.

In previous studies conducted to evaluate the effect of CD on growth and metabolic control in T1DM patients, as in our study, no significant difference was found in mean age, VA SDS, height SDS, BMI SDS, and mean insulin dose used between T1DM groups with and without CD (6, 21, 22). In our study, the last 1-year average HbA1c level and hypoglycemia frequency were found to be significantly higher in the CD+ group. Similarly, previous studies have shown that patients with T1DM and CD have more hypoglycemia attacks and worse metabolic control (6, 14).

**Table 2. Comparison of anthropometric and metabolic characteristics of CD+ and CD- groups (expressed as mean±SD)**

	CD+ n=17	CD- n=17	p
Age (decimal year)	12.2±5.02	12.3±4.9	
Diabetes duration (year)	4.8±2.9	4.1±2.3	0.290
Gender			
Male (n, %)	10 (58)	10 (58)	
Female (n, %)	7 (42)	7 (42)	
Weight SDS	0.03±1.58	-0.34±1.07	0.410
Height SDS	-0.29±1.02	-0.02±0.86	0.400
BMI SDS	0.12±1.42	-0.42±1.09	0.250
Puberty stage (n, %)			
Prepubertal	6 (35)	6 (35)	
Pubertal	11 (65)	11 (65)	
Last HbA1c level (%)	9.14±2.59	7.9±1.08	0.070
1-year average HbA1c level (%)	9.26±2.24	7.84±0.87	<b>0.020</b>
Hemoglobin (g/dl)	12.46±2.11	13.42±1.33	0.250
Ferritin (ng/ml)	25.62±22.11	28.08 ±20.57	0.800
Serum IgA (mg/dl)	218±55.77	245.24±49.16	0.100
Daily average insulin dose (U/kg)	0.83±0.29	0.80±0.25	0.710
Frequency of hypoglycemia (per month)	8±7	2±2	<b>0.030</b>

BMI: Body mass index; CD+: Celiac disease positive; CD-: Celiac disease negative; HbA1c: Hemoglobin A1c; IgA: Immunoglobulin A; SDS: Standard deviation score.

**Table 3. Comparison of diet incompatible and diet compliant groups**

	Diet incompatible n=8	Diet compliant n=9	p
Age (mean±SD)	13.1±4.8	11.4±4.3	0.510
Age at diabetes diagnosis (mean±SD)	8.7±5.8	6.5±4.4	0.410
Diabetes duration, year (mean±SD)	4.6±3.3	5±2.7	0.810
Gender (n, %)			0.050
Female	1 (13)	6 (67)	
Male	7 (87)	3 (33)	
Puberty (n, %)			0.800
Prepubertal	3 (38)	3 (33)	
Pubertal	5 (62)	6 (67)	
Weight SDS	-0.19±1.88	0.21±1.30	0.590
Height SDS	-0.61±1.10	-0.02±0.88	0.240
BMI SDS	0.10±1.55	0.14±1.40	0.960
Last HbA1c level (%)	10.2±3.2	8.2±1.5	0.140
1-year average HbA1c level (%)	10.2±2.7	8.43±1.4	0.120
Frequency of hypoglycemia (per month)	7±4	6±4	0.950

BMI: Body mass index; HbA1c: Hemoglobin A1c; SD: Standard deviation; SDS: Standard deviation score.

In our study, to evaluate the effect of compliance with a gluten-free diet on growth and metabolic control in T1DM patients with CD, when the groups were divided into two as diet compliant and diet incompatible according to serology positivity and compared, no significant difference was detected between both groups in terms of both anthropometric and metabolic findings. While there are studies reporting that adherence to a gluten-free diet has a positive effect on growth and metabolic control of diabetes in T1DM patients with CD (14, 23, 24), there are also studies reporting that a gluten-free diet has no effect on growth or metabolic control in T1DM patients with CD (25–27). However, in the diet-incompatible group, the average HbA1c level at the last follow-up and the average last 1-year HbA1c level were found to be higher than the diet-compliant group, although not statistically significant. The average HbA1c levels in the diet-incompatible group were in poor metabolic control, and the average HbA1c levels in the diet-compliant group were in moderate metabolic control. In our study, we found that the gluten-free diet had a negative effect on the metabolic control of diabetes and had no significant effect on growth.

### Limitations and Strengths

The limitation of this study is that, since tTG IgA testing could not be performed in our center, screening was performed using serum IgA, EMA, and AGA simultaneously. Moreover, since the study was conducted in a single center, this CD prevalence may not reflect the situation in children with T1DM across the entire country, considering the geographical characteristics. The strength of our study lies in its significant contribution to the literature in this field.

### CONCLUSIONS

The frequency of celiac disease in patients with T1DM in our study was found to be similar to previous studies, with a frequency of 7%. It was observed that CD was diagnosed at the time of diabetes diagnosis in the majority of patients with T1DM, and in a small number of patients during the first 4 years of follow-up. This study determined that CD negatively affects the metabolic control of diabetes, either directly or due to non-compliance with the gluten-free diet, but does not negatively impact growth. Given these results, larger series and long-term studies are necessary.

**Ethics Committee Approval:** The Trakya University Clinical Research Ethics Committee granted approval for this study (date: 25.02.2019, number: 04/18).

**Authorship Contributions:** Concept – FY, FTK; Design – FY, FTK; Supervision – FY, FTK; Fundings – FY, FTK; Data collection and/or processing – FY; Analysis and/or interpretation – FY, FTK; Literature review – FY, FTK; Writing – FY, FTK; Critical review – FTK.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Use of AI for Writing Assistance:** Not declared.

**Informed Consent:** Written informed consent was obtained from the families of the patients who participated in this study.

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**Yazarlık Katkıları:** Fikir – FY, FTK; Tasarım – FY, FTK; Denetleme – FY, FTK; Kaynaklar – FY, FTK; Veri Toplanması ve/veya İşlemesi – FY; Analiz ve/veya Yorum – FY, FTK; Literatür Taraması – FY, FTK; Yazıyı Yazan – FY, FTK; Eleştirel İnceleme – FTK.

**Çıkar Çatışması:** Yazarlar çıkar çatışması bildirmemişlerdir.

**Yazma Yardımı için Yapay Zeka Kullanımı:** Beyan edilmedi.

**Hasta Onamı:** Yazılı hasta onamı bu çalışmaya katılan hastaların ailelerinden alınmıştır.

**Mali Destek:** Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

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