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Research Article

The relationship between leukocyte-based inflammation indices and essential tremor

Lökosit bazlı enflamasyon indeksleri ile esansiyel tremor arasındaki ilişki

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Abstract

Aim: Previous limited studies have indicated that pro-inflammatory cytokines are elevated in patients with essential tremor (ET). This elevation could lead to a more pronounced inflammatory response in these patients. Thus, this study aimed to investigate the relationship between leukocyte-based inflammatory indices and ET.

Material and Methods: In this retrospective study, 103 patients diagnosed with ET between January 2021 and December 2023 were included, along with 103 healthy individuals who were matched by age and gender, participated in check-up programs, and had no other comorbidities. To evaluate tremor severity, the Fahn-Tolosa-Marin (FTM) tremor rating scale was utilized. The leukocyte-based inflammatory indices were calculated as follows: NLR= neutrophils / lymphocytes, PLR = platelets / lymphocytes, systemic immune-inflammation index (SII) = platelets × neutrophils / lymphocytes, and systemic inflammatory response index (SIRI) = neutrophils × monocytes / lymphocytes.

Results: The ET group exhibited higher levels of leukocytes, their subtypes, CRP and leukocyte-based inflammatory indices compared to the control group. Increased CRP (OR= 3.71, $p < 0.001$) and SIRI (OR= 11.73, $p < 0.001$) levels were independent predictors of ET. In predicting ET. SIRI exhibited superior diagnostic performance compared to other inflammatory parameters. The threshold for SIRI levels was set at 7 and above, with a sensitivity of 85.4% and a specificity of 82.5%. There was a positive correlation between SIRI and FTM scores.

Conclusion: Among the leukocyte-based inflammation indices, SIRI demonstrated superior diagnostic performance in predicting ET and was associated with higher tremor severity. This suggests that inflammation may play a potential role in the pathophysiology of ET.

Keywords: essential tremor, inflammation, tremor severity, systemic immune-inflammation index

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Öz

Amaç: Daha önce yapılan sınırlı çalışmalar, esansiyel tremor (ET) hastalarında proinflamatuar sitokinlerin arttığını göstermiştir. Bu artış, bu hastalarda daha belirgin bir inflamatuar yanıtı tetikleyebilir. Bu nedenle, bu çalışma lökosit bazlı inflamasyon indeksleri ile ET arasındaki ilişkiyi araştırmayı amaçladı.

Gereç ve Yöntemler: Bu retrospektif çalışmaya, Ocak 2021 ile Aralık 2023 arasında ET tanısı alan 103 hasta ile yaş ve cinsiyet açısından eşleştirilen, check-up programlarına katılan ve başka komorbiditesi olmayan 103 sağlıklı birey dahil edilmiştir. Tremor şiddetini değerlendirmek için Fahn-Tolosa-Marin (FTM) tremor derecelendirme skalası kullanılmıştır. Lökosit bazlı inflamasyon indeksleri şu şekilde hesaplanmıştır: NLR = nötrofiller / lenfositler, PLR = trombositler / lenfositler, sistemik immün-enflamasyon indeksi (SII) = trombositler × nötrofiller / lenfositler ve sistemik inflamatuar yanıt indeksi (SIRI) = nötrofiller × monositler / lenfositler.

Bulgular: ET grubunda lökosit, alt tipleri, CRP ve lökosit bazlı inflamasyon indeksleri kontrol grubuna göre daha yüksek seviyelerdeydi. Artmış CRP (OR = 3.71, $p < 0.001$) ve SIRI (OR = 11.73, $p < 0.001$) seviyeleri, ET'nin bağımsız öngörücüleri olarak belirlendi. ET'yi öngörmede, SIRI diğer inflamatuar parametrelere göre üstün bir tanısal performans sergilemiştir. SIRI seviyeleri için eşik değer 7 ve üzeri olarak belirlendi ve bu değer %85.4 duyarlılık ve %82.5 özgüllük gösterdi. SIRI ile FTM skorları arasında pozitif bir korelasyon bulundu.

Sonuçlar: Lökosit bazlı inflamasyon indeksleri arasında, SIRI ET'yi öngörmede üstün bir tanısal performans sergilemiş ve daha yüksek tremor şiddeti ile ilişkilendirilmiştir. Bu da inflamasyonun ET'nin patofizyolojisinde potansiyel bir rol oynayabileceğini düşündürmektedir.

Anahtar Kelimeler: esansiyel tremor, inflamasyon, tremor şiddeti, sistemik immün-enflamasyon indeksi

Introduction

Essential tremor is characterized as a "bilateral upper extremity action tremor" and ranks as one of the most prevalent movement disorders affecting adults. Globally, the basic prevalence rates of essential tremor among adults vary between 0.4% and 6%. It is estimated that about 1% of the general population and 4-5% of individuals over the age of 65 are affected by essential tremor [1]. The underlying pathophysiology of essential tremor remains poorly understood. However, there is increasing evidence suggesting that inflammation and neurodegeneration may play roles in the pathophysiology of essential tremor.

Recently, a growing body of research has shown that the clinical presentation of essential tremor encompasses more than just motor symptoms like tremor and gait ataxia. It also includes a range of non-motor features, such as depression, anxiety, cognitive alterations, and sensory changes [2, 3]. Motor and non-motor symptoms manifest in various combinations in essential tremor, contributing to the clinical heterogeneity of the condition [4]. Some researchers report that the diverse clinical features observed in essential tremor resemble those in Parkinson's disease, suggesting that neurodegeneration plays a role in the pathophysiology of essential tremor [5]. It is widely accepted that neuroinflammation plays a role in the pathophysiology of neurodegeneration. However, the extent of its contribution to the progression of neurodegenerative diseases remains a focal point of intensive research, particularly concerning the most prevalent conditions such as Parkinson's disease and Alzheimer's disease [6-8]. It has been reported that pro-inflammatory cytokines are elevated in patients with essential tremor [9]. However, the relationship between blood inflammatory parameters or indices derived from them and essential tremor remains elusive and under-researched [10].

Due to the increase in pro-inflammatory cytokines in patients with essential tremor, we hypothesized that these patients might exhibit a distinct systemic inflammatory response. This study aims to investigate the connection between blood inflammation parameters and essential tremor.

Material and Methods

Following the principles set forth in the Declaration of Helsinki, this single center retrospective study was conducted at the Istanbul Atlas University Medicine Hospital Neurology Clinical from January 2021 to December 2023. The study received approval from the local ethics committee the Research Ethics Committee (Approval Date: 15.02.2023, Decision No: E-22686390-050.99-24274). The local ethics committee waived the requirement of informed consent due to the retrospective nature of the research.

Study population

A total of 173 patients diagnosed with essential tremor were retrospectively examined. The exclusion criteria included: patients over the age of 65, those with a history of surgical intervention in the last year, those with any history of

systemic inflammatory or autoimmune diseases, those with any comorbid conditions (such as Parkinson's disease, heart diseases, thyroid dysfunction, liver diseases, malignancy, renal failure, chronic neurological diseases), those with a history of sepsis, those with a history of anti-inflammatory or chronic corticosteroid medication use, those taking antibiotics, antivirals, antiplatelet agents, anticoagulants, and immunosuppressive agents, those who are pregnant or have given birth in the last 90 days, those with a history of breastfeeding, and those with incomplete clinical data. After this exclusion process, 103 essential tremor patients were enrolled in this study. Additionally, the study included a control group of 103 healthy individuals who were enrolled in and examined through a check-up program, matched with patients with essential tremor in terms of age and gender, and who had no additional comorbidities.

Study protocol

Demographic and clinical data were collected using the hospital's electronic information system and patient files. Venous blood samples, collected after a 12-hour fasting period during outpatient evaluations, were used to analyze biochemical parameters. These samples were processed in a single laboratory, employing the consistent methodology outlined below.

The diagnosis of essential tremor was established by following the diagnostic criteria specified by the Tremor Task Force of the International Parkinson and Movement Disorder Society in their 2018 Criteria [11]. To evaluate tremor severity, the Fahn-Tolosa-Marin (FTM) tremor rating scale was utilized [12]. Severity was determined via dividing the total score by the maximum score. Scores below 50% indicated low severity (encompassing no functional disability and mild/moderate disability), while scores above 50% indicated high severity (including marked and severe disability).

Biochemical analysis

A Cell-Dyn 3700 SL device (Abbott Diagnostics, Chicago, USA) was used to evaluate patients' venous blood samples. Levels of hemoglobin (photometrically), platelet count (impedance method), and C-reactive protein (CRP) (immunoturbidimetric method) were determined. The inflammatory indices were respectively calculated as follows: NLR = neutrophil count / lymphocyte count, PLR = platelet count / lymphocyte count, SII = platelet count × neutrophil count / lymphocyte count, and SIRI = neutrophil count × monocyte count / lymphocyte count.

Statistical analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean (standard deviation [SD]) values while non-normally distributed variables are given as median (25th-75th quartile) values. For comparisons between groups, Student t-test and Mann-Whitney U test were used in line with the normality of the considered distribution. Categorical variables are given as numbers and percentages, and inter-group comparisons were conducted with Chi-square and Fisher exact tests. Spearman correlation analyses were applied to evaluate the relationships between numerical variables. Spearman correlation coefficient of <0.10 were evaluated as negligible correlation, 0.10–0.39 as weak correlation, 0.40–0.69 as moderate correlation, 0.70–0.89 as strong correlation, and 0.90–1.00 as almost perfect very strong correlation [13]. Multivariable logistic regression analysis with the backward Wald method was subsequently performed to identify any possible independent predictors of essential tremor. The receiver operating characteristic (ROC) curve analysis was applied to assess diagnostic performance. Threshold values were determined by the Youden index method. Comparison of the AUC curves was performed with a nonparametric approach using using the theory on generalized U-statistics to generate an estimated covariance matrix previously reported by DeLong et al [14]. Significance was accepted at $P < 0.05$ (*) for all statistical analyses.

Results

The study included 103 control participants (mean age: 46.7±15.7 years) and 103 individuals with essential tremor (mean age: 44.9±15.2 years). The majority of patients with essential tremor had left-hand dominance (81.6%). The proportion of patients with bilateral tremor affecting primarily the head was 39.8%. None of the patients exhibited tremors in the face, tongue, voice, or torso.

In the essential tremor group compared to the control group, the mean leukocyte counts was higher (6.9 ± 1.7 vs. 6.3 ± 1.3 ×103 µL, $p = 0.016$), median neutrophil counts (3.6 vs. 2.9 ×103 µL, $p < 0.001$), mean monocyte counts (0.6 ± 0.2 vs. 0.4 ± 0.1 ×103 µL, $p < 0.001$), and median CRP level (2.9 vs. 1.8 mg/dL, $p < 0.001$), while the median lymphocyte counts was found to be lower (2.2 ± 0.6 vs. 2.4 ± 0.5 ×103 µL, $p = 0.002$). Also, in the essential tremor group, inflammation indices (NLR, PLR, SII, and SIRI) were found to be higher (Table 1). Parameters associated with essential tremor were included in a multiple regression analysis. According to this analysis, increased levels of CRP and SIRI were identified as independent predictors of essential tremor (Table 2).

In predicting essential tremor, the SIRI demonstrated superior diagnostic performance compared to other inflammation parameters (Figure 1) (Table 3). The threshold for SIRI levels was set at 7 and above, with a sensitivity of 85.4% and a specificity of 82.5%. Increased SIRI scores were found to be associated with higher scores on the FTM scale (Table 4).

Table 1. Demographic and laboratory findings.

Variables	Essential tremor n=103	Control n=103	p
Age, years	44.9 ± 15.2	46.7 ± 15.7	0.406
Gender, n (%)			
Female	60 (58.3)	57 (55.3)	0.673
Male	43 (41.7)	46 (44.7)	
Dominant hand, n (%)			
Left	84(81,6)	-	-
Right	19(18,4)	-	
Bilateral tremor, n (%)	41(39,8)	-	-
Hemoglobin, g/dL	13.5 ± 1.9	13.7 ± 1.1	0.384
RBC, ×106 µL	4.7 ± 0.6	4.7 ± 0.5	0.490
Leukocytes, ×103 µL	6.9 ± 1.7	6.3 ± 1.3	0.016*
Lymphocytes, ×103 µL	2.2 ± 0.6	2.4 ± 0.5	0.002*
Neutrophils, ×103 µL	3.6 (2.9-4.8)	2.9 (2.4-3.8)	<0.001*
Monocytes, ×103 µL	0.6 ± 0.2	0.4 ± 0.1	<0.001*
Platelets, ×103 µL	252.3 ± 62.6	252.9 ± 59.3	0.946
MPV, fL	9.8 ± 1.0	9.7 ± 0.7	0.172
PDW, fL	10.9 ± 1.8	10.6 ± 1.0	0.116
CRP, mg/dL	2.9 (2.5-3.4)	1.8 (0.9-2.3)	<0.001*
NLR	1.8 (1.2-2.3)	1.0 (0.9-1.6)	<0.001*
PLR	119.4 (92.3-154.3)	95 (90.2-122.2)	0.001*
SII	382.2 (294.5-625)	260.8 (233.4-450.4)	<0.001*
SIRI	1.1 (0.8-1.7)	0.5 (0.1-0.7)	<0.001*

Data are mean ± standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Abbreviations: RBC, red blood cells; MPV, mean platelet volume; PDW, platelet distribution width, CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index

Table 2. Independent predictors of essential tremor.

Variables	Univariable Regression			Multivariable Regression		
	OR	95% CI	p	OR	95% CI	p
CRP	2.84	2.05 – 3.94	<0.001*	3.71	2.37 – 5.81	<0.001*
SII	1.04	1.02 – 1.06	<0.001*	-	-	-
SIRI	19.3	7.89 – 47.22	<0.001*	38.52	11.73 – 126.43	<0.001*
				Nagelkerke R^2= 0.54		

The effects of age and gender were adjusted in the regression analysis. *p<0.05 indicates statistical significance. Abbreviations: CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index.

Table 3. Diagnostic performance of inflammatory parameters and indices for predicting essential tremor.

Variables	AUC±SE	95% CI	Sens. (%)	Spec. (%)	Threshold
Leukocytes	0.557 ± 0.04	0.479 - 0.636	39.8	83.5	7.0 ×103 µL
Lymphocytes	0.402 ± 0.04	0.325 - 0.479	6.8	100.0	3.2 ×103 µL
Neutrophils*	0.686 ± 0.04	0.614 - 0.759	76.7	57.3	2.9 ×103 µL
Monocytes*	0.825 ± 0.03	0.768 - 0.882	77.7	84.5	0.5 ×103 µL
Platelets	0.499 ± 0.04	0.420 - 0.579	83.5	32.0	208 ×103 µL
NLR*	0.733 ± 0.03	0.665 - 0.801	90.3	52.4	1.1
PLR*	0.629 ± 0.04	0.553 - 0.705	45.6	82.5	123.8
SII*	0.729 ± 0.03	0.660 - 0.798	90.3	62.1	273.6
SIRI*	0.849 ± 0.03	0.796 - 0.903	85.4	82.5	0.7
CRP*	0.795 ± 0.03	0.734 - 0.857	79.6	77.7	2.4 mg/dL

*p<0.05 indicates statistical significance. Abbreviations: CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; Sens, sensitivity; SII, systemic immune-inflammation index; Spec, specificity; SIRI, systemic inflammatory response index.

Table 4. Demographic characteristics of essential tremor patients according to quartile of systemic inflammatory response index (SIRI).

Variables	SIRI				p
	Q1	Q2	Q3	Q4	
	n=26	n=27	n=25	n=25	
Age, years	43.0 (27.5 - 52.8)	48.0 (27.5 - 57.0)	47.0 (28.0 - 60.0)	51.0 (38.0 - 64.0)	0.227
Gender, n (%)					
Female	13 (50.0)	17 (63.0)	12 (48.0)	18 (72.0)	0.262
Male	13 (50.0)	10 (37.0)	13 (52.0)	7 (28.0)	
Dominant hand, n (%)					
Left	18 (69.2)	24 (88.9)	21 (84.0)	21 (84.0)	0.285
Right	8 (30.8)	3 (11.1)	4 (16.0)	4 (16.0)	
Bilateral tremor, n (%)	10 (38.5)	11 (40.7)	9 (36.0)	11 (44.0)	0.477
FTMS scale	11.0 (11.0 - 12.0)	12.0 (11.0 - 19.0)	14.0 (10.0 - 18.0)	20.0 (18.0 - 22.0)	<0.001*

Data are mean ± standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Abbreviations: FTMS, Fahn-Tolosa-Marin tremor rating scale.

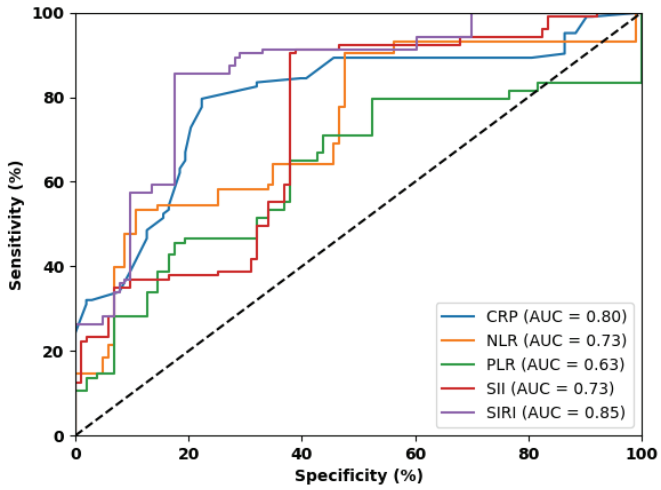

Figure 1. Diagnostic performance of leukocyte-based inflammation indices for predicting essential tremor.

Discussion

To the best of our knowledge, this study is among the few that investigate the connection between essential tremor and leukocyte-driven inflammatory indices. This study also marks the first time that the connection between SII, SIRI, and essential tremor has been evaluated. In patients with essential tremor, leukocyte-based inflammatory indices were elevated, and SIRI was identified as an independent predictor. Furthermore, SIRI surpassed other inflammatory markers in diagnostic performance. An increased SIRI levels correlated with increased FTM scores.

Inflammation, a fundamental biological response to harmful stimuli, has been increasingly recognized in various neurological disorders, suggesting a possible similar impact in essential tremor. Research has demonstrated that individuals with Parkinson's disease exhibit elevated levels of interleukin-8 (IL-8) in their serum. Moreover, there is an observed association between the heightened levels of IL-8 and the severity of clinical symptoms in Parkinson's disease. Specifically, those with the highest serum IL-8 concentrations experience the greatest impairment in daily functioning due to the disease [15]. One significant study explored the relationship between various serum inflammation markers such as interleukin-1β, interleukin-6, interleukin-8, interleukin-10, and tumor necrosis factor-α, and clinical features of essential tremor like tremor severity, cognitive decline, and depression. The aim was to identify any direct correlations between these markers and the clinical manifestations of essential tremor [8]. It has been demonstrated that pro-inflammatory cytokines such as IL-6 are elevated in patients with essential tremor [16]. In an Essential Tremor rat model, it has been shown that Dapagliflozin suppresses the inflammatory cascade and mimics neuronal damage through triggering the LKB1/p-AMPK/GABA B R2 signaling pathway [17]. Additionally, IL-6 has the potential to modulate the AMPK signaling pathway [18]. These findings support the possibility that inflammation and the inflammatory response triggered by immune cells may play a role in the pathogenesis of essential tremor.

Protein heteromers of neutrophil and platelet cells promote monocyte recruitment [19]. Moreover, neutrophils have the potential to modulate macrophages to the anti-inflammatory phenotype, while platelets can affect neutrophil functions [20]. Additionally, neutrophils can release reactive oxygen species (ROS), granular components, and pro-inflammatory mediators [21]. It is suggested that ROS may play a role in the pathogenesis of essential tremor [22]. Additionally, genes

such as APOE, SENP6, and ZNF148 have been found to be differentially expressed in patients with essential tremor [23]. It is also suggested that this genes may regulate ROS and neutrophil functions [24-26]. In patients with essential tremor, leukocytes and their subtypes show significant differences. These findings support the potential role of the immune system in the pathogenesis of essential tremor.

Our study builds upon previous findings that inflammation might influence the neurodegenerative process seen in essential tremor. The recruitment of monocytes facilitated by protein heteromers of neutrophil and platelet cells [27] and the modulatory effects of neutrophils on macrophages to adopt an anti-inflammatory phenotype [28], are examples of potential mechanisms. Furthermore, the role of ROS and cytokines such as IL-6, which were found to be elevated in essential tremor patients, suggests an inflammatory cascade that could exacerbate or contribute to the pathophysiology of essential tremor [12]. A previous study reported that levels of NLR and PLR did not differ between patients with essential tremor and a control group [10]. However, there is a lack of studies that thoroughly evaluate blood inflammation parameters in detail. Inflammatory indices such as CRP, NLR, PLR, SII, and SIRI were consistently higher in ET patients, which corresponds with emerging literature suggesting a pathological link between inflammation and essential tremor [29]. Among these, SIRI emerged as a robust independent predictor of essential tremor, providing a potential new avenue for diagnostic improvement in clinical settings. The utility of SIRI in diagnosing essential tremor was supported by its superior performance in ROC curve analysis, distinguishing it from other inflammatory markers.

The clinical implications of our findings extend beyond mere diagnosis, suggesting that inflammatory markers could also serve as therapeutic targets in essential tremor. Interventions that modulate inflammation, such as the use of anti-inflammatory drugs or lifestyle modifications aimed at reducing systemic inflammation, could potentially alleviate the symptoms or slow the progression of essential tremor. This approach is supported by studies in other neurodegenerative disorders where anti-inflammatory treatments have shown promise in mitigating disease [30]. Therefore, identifying patients with elevated inflammatory markers could not only help in earlier and more accurate diagnosis but also tailor more specific anti-inflammatory therapeutic strategies that may be beneficial in managing essential tremor. Moreover, the interrelation between inflammation and essential tremor provides a compelling argument for the role of the peripheral immune system in central nervous system disorders. The cross-talk between peripheral inflammation and central neurodegeneration might involve complex biochemical pathways that include cytokine signaling and immune cell activation, which can subsequently affect neuronal function and health. Understanding these pathways in greater detail could offer new insights into the etiology of essential tremor and other similar movement disorders, potentially leading to breakthroughs in how these conditions are treated

Our study has several limitations that should be considered. Initially, the low sample size and the single-center retrospective nature were significant limitations. Second, cytokines or chemokines that may play a role in leukocyte trafficking were not analyzed. Evaluation of subtypes of leukocytes by flow cytometry analysis may be more revealing in the development of essential tremor. While our study focused on broad leukocyte-based inflammation indices, flow cytometry analysis of leukocyte subtypes could offer more detailed insights into immune cell involvement in essential tremor. Identifying specific immune cell subtypes may reveal key differences in systemic inflammatory responses during the progression of essential tremor. Evaluations of these factors in future studies might further illuminate the role of systemic inflammatory indices differing throughout the pathogenesis in cases of essential tremor.

Conclusion

The findings gathered from our retrospective study indicates a pronounced inflammatory component in essential tremor patients. This study has highlighted the potential role of systemic inflammation in the pathogenesis of essential tremor, with significant associations between elevated inflammatory markers and the severity of the condition. The novel inflammatory marker SIRI, in particular, presents as a promising diagnostic tool with potential utility in the clinical assessment of essential tremor.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Istanbul Atlas University Medicine Hospital Clinical Research Ethics Committee (Date: 15.02.2023, Decision No: E-22686390-050.99-24274).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author.

Authors' contribution

Concept – D.A.Ü., Design – D.A.Ü., Supervision – D.A.Ü, Data collection and/or processing – D.A.Ü. and B.D., Analysis and/or interpretation – D.A.Ü. and B.D., Writing – D.A.Ü., Critical review- B.D. All authors read and approved the final version of the manuscript.

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