ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Systemic-Immune Inflammation Index (SII) Provides Valuable Insights into the Severity of Acidosis and Asidosis Resolution Time in Children with Diabetic Ketoacidosis

Systemic-Immune İnflammation Index [SII], Diyabetik Ketoasidozlu Çocuklarda Asidoz Şiddetini Belirlemeye Yardımcıdır

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Abstract

Introduction: DKA is a life-threatening disease that occurs early in type 1 diabetes. A lack of diagnostic resources can delay DKA diagnosis in some centers. In chronic disorders, hematologic inflammatory indicators are gaining attention. These markers' impact on DKA diagnosis and severity was the purpose of this cross-sectional investigation.

Materials and Methods: The study included 54 DKA-diagnosed T1DM children and 50 healthy controls from a single center. From the total blood count, SII, SIRI, NLR, and PLR values were computed, and Platecrit, MPV and PDW values were recorded.DKA is categorized into three groups: mild, moderate, or severe DKA using ISPAD criteria. We then analyzed uninfected T1DM patients' independent DKA predictors. Variable diagnostic performance was determined via ROC curve analysis. Multivariate logistic regression analysis examined all significant parameters.

Results: SII, NLR, and Platecrit significantly predict DKA severity (X2[3]SII=2973.23, X2[3]PCT =0,063, X2[3]NLR=93.29; pSII: 0,0001,pPCT: 0,0001,pNLR: 0,01). SII was the best marker for recognizing severe acidosis and T1DM with 94.44% sensitivity, and 81.48% specificity [AUC: 0.925 and 0,875]. This is one of the first SII/SIRI investigations in DKA children.

Conclusion: SII, NLR, and Platecrit may accurately predict DKA severity, with SII being the most effective marker for diagnosing DM and recognizing severe acidosis. In resource-limited settings, SII may be a viable alternative to blood gas tests for severe acidosis assessment.

Keywords
Diabetic ketoacidosis, neutrophil-to-lymphocyte ratio, plateletcrit, platelet-to-lymphocyte ratio, systemic immune-inflammation index, type 1 diabetes mellitus

Anahtar kelimeler
Diyabetik ketoasidoz, nötrofil-lenfosit oranı, plateletcrit, platelet-lenfosit oranı, sistemik immün-enflamasyon indeksi, tip 1 diyabetes mellitus

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Öz

Giriş: DKA, tip 1 diyabette erken dönemde ortaya çıkan, hayatı tehdit eden bir hastalıktır. Bazı merkezlerde tanısal kaynak eksiklikleri, DKA tanısının gecikmesine neden olabilir. Kronik hastalıklarda, hematolojik inflamatuar göstergelere olan ilgi artmaktadır. Bu parametrelerin DKA tanısı ve şiddeti üzerindeki etkisi, bu kesitsel araştırmanın amacını oluşturmuştur.

Gereç ve Yöntem: Çalışma, tek bir merkezden 54 DKA tanısı almış T1DM çocukları ve 50 sağlıklı kontrolü içermektedir. Tam kan sayımından, SII, SIRI, NLR ve PLR değerleri hesaplanmış, Platecrit, MPV ve PDW değerleri kaydedilmiştir. DKA, ISPAD kriterlerine göre hafif, orta veya şiddetli olarak üç gruba ayrılmıştır. Ardından,

enfekte olmayan T1DM hastalarının bağımsız DKA prediktörleri analiz edilmiştir. Değişken tanısal performans, ROC eğrisi analizi ile belirlenmiştir. Çoklu lojistik regresyon analizi, tüm önemli parametreleri incelemiştir.
Bulgular: SII, NLR ve Platecrit, DKA şiddetini anlamlı şekilde öngörmektedir (X2[3]SII=2973.23, X2[3]PCT =0,063, X2[3]NLR=93.29; pSII: 0,0001, pPCT: 0,0001, pNLR: 0,01). SII, şiddetli asidoz ve T1DM tanısını tanımada en iyi belirteçti ve %94,44 hassasiyet ve %81,48 özgüllük ile [AUC: 0,925 ve 0,875] en yüksek performansı gösterdi. Bu, DKA çocuklarında yapılan ilk SII/SIRI araştırmalarından biridir
Sonuç: SII, NLR ve Platecrit, DKA şiddetini doğru şekilde tahmin edebilir, ancak SII, DM tanısı ve şiddetli asidozun tanınması için en etkili belirteçtir. Kaynakların sınırlı olduğu ortamlarda, SII şiddetli asidoz değerlendirmesi için kan gazı testlerine alternatif olarak uygun bir seçenek olabilir.

Introduction

Diabetic ketoacidosis (DKA) is a hyperglycemic emergency defined by hyperglycemia, ketosis, and metabolic acidosis (1,2). In children with type 1 diabetes mellitus (T1DM), this condition presents as the initial manifestation in 30-40% of cases (1,3). The most common complication associated with DKA is cerebral edema, which increases the risk of mortality and morbidity, primarily due to severe acidosis and osmotic diuresis (1,4-5). As the diagnosis of DKA is delayed, the risk of complications rises significantly, with mortality rates escalating to 24% as acidosis worsens. Therefore, early diagnosis of DKA and prompt treatment initiation are crucial for improving prognosis (5,6).

Limited diagnostic resources in some centers can lead to delays in DKA diagnosis. Consequently, there is a pressing need for reliable alternative biomarkers that can be easily assessed in all healthcare settings to recognize acidosis. The complete blood count (CBC) is a low-cost test that provides information on various cells involved in inflammation and can be performed in most centers. Hematological inflammatory parameters, such as the systemic immune response index (SIRI), systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), can be derived from this test. The use of these biomarkers is currently recommended in the context of inflammatory, rheumatological, and cardiac diseases, as well as malignancies and obesity (6-10). Recent studies indicate that some inflammatory markers are elevated in patients with T1DM and are associated with glycemic control (11). Consequently, NLR has been identified as a new biomarker for recognizing DKA (12). However, SII, among other markers, has not been extensively studied with DKA, highlighting a research gap that necessitates further exploration to understand their potential roles in this condition. Currently, further research is needed to evaluate the sensitivity and specificity of these biomarkers. This study aims to evaluate the diagnostic and prognostic value of hematological inflammatory markers in children with DKA, particularly in assessing acidosis severity and potential correlations with hospital stay and recovery time.

Materials and Methods

Patient Recruitment

This study was conducted with 81 T1DM patients and 49 healthy controls followed at the Pediatric Endocrinology Clinic of Zonguldak Bülent Ecevit University between April 2022 and January 2024, following the principles of the Declaration of Helsinki. Ethical approval was received from the ethics committee at our university. (ethics no:2024/07-6). We retrospectively evaluated the patients' medical files.

T1DM patients were categorized into 2 groups, DKA and Non-DKA groups, according to the presentation at the time of diagnosis. Patients with a concurrent infection, concomitant autoimmune or external diseases, diabetes types other than type 1, syndromic appearance, or recurrent DKA episodes were excluded from the study.

T1DM and DKA were diagnosed by the guidelines established by the International Society for Pediatric and Adolescent Diabetes (ISPAD). For DKA diagnosis, the thresholds were defined as a plasma glucose level >200 mg/dL, a urine ketone level >+2, and an arterial pH value <7.3. Patients were classified into three groups based on DKA severity, using the ISPAD criteria: mild DKA ($7.20 \leq pH < 7.30$ or $10 \leq HCO3 < 15$ mmol/L), moderate DKA ($7.10 \leq pH < 7.20$ or $5 \leq HCO3 < 10$ mmol/L), and severe DKA ($pH < 7.10$ or $HCO3 < 5$ mmol/L). We evaluated blood gas analysis results, hyperglycemia levels, CBC parameters such as plateletcrit (PCT), mean platelet volume (MPV), platelet redistribution width (PDW), C-reactive protein (CRP), glycated hemoglobin (HbA1c), and C-peptide levels at the time of diagnosis to assess possible changes due to treatment. From the CBC parameters, PLR (platelet/lymphocyte), NLR (neutrophil/lymphocyte), and SII (platelet x neutrophil/lymphocyte) were calculated. The variability of inflammatory markers was evaluated between healthy controls and non-DKA and DKA

groups. At the same time, the sensitivity of hematological inflammation markers in determining the severity of DKA was evaluated. Receiver Operating Characteristic (ROC) curve analysis was performed to analyze the effectiveness of these markers. We reevaluated our data to determine the best marker and cutoff for detecting severe DKA, categorizing patients into two groups based on an arterial pH value <7.1 or HCO3 <5 mmol/L according to the clinical two-group classification of DKA.

The healthy control group was composed of children who applied to the clinic for growth and development evaluation but were found to be within normal limits according to the Turkish children's percentile curves.

Biochemical Assays

We collected the blood samples immediately before initiating the treatment during the patient's admission. In our hospital laboratories, we processed blood gas analysis and CBC parameters, routine biochemistry, and HbA1c levels. CBC parameters are studied with the Sysmex XN-550 (Sysmex Corporation, Kobe, Japan) automated system. We calculated hematological inflammatory parameters such as SII, NLR, and PLR from CBC data for all groups. For HbA1c measurement, we utilized a high-performance liquid chromatography kit (Lifotronic H9 Hemoglobin Analyzer).

Statistical Analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS), version 19 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk Test was utilized to verify the normality of the data distribution. For normally distributed data, we employed the T-test and One–way ANOVA; for non-normally distributed data, we used the Mann-Whitney U test and the Kruskal-Wallis test.

To compare the hematological inflammatory parameters based on the severity of DKA, we applied the Kruskal-Wallis Test. Multiple comparisons were conducted via post hoc analysis utilizing Dunn's (1964) procedure along with Bonferroni adjustment. To evaluate the discriminative capacities of SII, NLR, and PCT in predicting the severity of ketoacidosis and for optimal marker detection, we performed an ROC curve analysis. We determined the optimal cut-off values by maximizing the Youden index (calculated as sensitivity + specificity - 1, ranging from 0 to 1) and the area under the curve (AUC). Spearman's correlation test examined the relationship between hematologic parameters and the duration of diabetes, whereas Pearson's correlation test was applied for the connection between parameters. P-values < 0.05 were considered statistically significant.

Results

Basal Characteristics of Patients

The study included 54 patients diagnosed with T1DM who presented with DKA, 27 patients with T1DM who were diagnosed with isolated hyperglycemia and/or ketosis but not with DKA, and 50 healthy controls. In the DKA group, the mean age was 8.89 ± 4.12 years, with 53.3% being male. The cases were divided into three groups based on the severity of DKA: mild DKA (n=17), moderate DKA (n=18), and severe DKA (n=19). There were no significant differences between the groups in terms of age and sex distribution (p=0.16; p=0.23). The standard deviation scores (SDS) for height, body weight, and body mass index (BMI) were significantly higher as the severity of acidosis increased (p=0.005, p=0.005, p=0.044, respectively). Blood gas analysis revealed significant differences in pH and HCO3 levels, as expected (p<0.001). There were no significant differences in the blood sugar and HbA1c levels among the groups. C-peptide levels were significantly lower as the severity of acidosis increased (p=0.003).

Association Between Inflammatory Parameters and DKA Severity

As shown in Table 1, we found significant differences in complete blood count parameters among the three groups. We observed that as DKA severity increased, total white blood cells, neutrophils, monocytes, and platelet count also significantly increased (p < 0.001).

Among the hematological inflammatory parameters, SII, NLR, and PCT showed significant differences between the DKA groups (p<0.001), while PLR, PDW, and MPV levels were similar across the groups (Table 2).

As shown in Figure 1, all three parameters were significantly effective in predicting the severity of DKA (p<0.0001). The distributions of SII, PCT, and NLR scores were significantly different between groups ($X^2(3)^{SII}$ = 2973.23, $X^2(3)^{PCT}$ = 0.063, $X^2(3)^{NLR}$ = 93.293; p^{SII}= 0.0001, p^{PCT}= 0.0001, p^{NLR}=0.01).

Multiple comparisons were conducted via post hoc analysis utilizing Dunn's (1964) procedure along with Bonferroni adjustment. This post hoc analysis revealed statistically significant differences in the median scores of all three markers between those with severe DKA and those

Table 1. Laboratory and anthropometric findings in patients stratified by DKA severity				
	MILD DKA n=17	**MODERATE DKA n=18**	**SEVERE DKA n=19**	**p**
Age [years]	11.06 [6-17.66]	9.12 [0.91-16.91]	7.45 [2.58-13]	**0.026**
Height SDS	0.01±1.49	-0.13±0.86	1.01±0.86 [b]	**0.005**
Weight SDS	-1.12±0.77	-0.34±1.45	0.56±1.12 [b]	**0.005**
Body Mass Index SDS	-1.62±1.23	-0.29±1.77	-0.09±1.55	**0.044**
Serum pH	7.24±0.02[b]	7.16±0.02[a]	6.93±0.09[a,b]	**<0.001**
Serum HCO3	13.86±2.09[b]	10.15±1.32[a]	6.23±1.69[a,b]	**<0.001**
HbA1c [%]	12.2±1.49	10.9±2.22	12.26±1.99	0.134
Glucose [mg/dl]	484.9±172.88	437.76±174.05	462.94±86.8	0.176
C-peptide [ng/ml]	0.24±0.13	0.34±0.22	0.16±0.08[b]	**0.003**
WBCs [×10³/mm³]	8.76±3.21	10.18±3.28	25.33±8.8[a,b]	**<0.001**
Neutrophils [×10³/mm³]	5.79±2.61	6.74±2.84	20.46±6.86[a,b]	**<0.001**
Lymphocytes [×10³/mm³]	2.14±0.97	3.00±2.67	3.14±0.9	0.305
Monocytes [×10³/mm³]	0.56±0.27	0.58±0.37	3.37±7.39[a,b]	**<0.001**
Thrombocytes [×10³/mm³]	297.6±53.81	335.23±95.34	449.72±89.67[a,b]	**<0.001**
Acidosis recovery time (hours)	6,6±3,2 (3-14)	13,1 ±7,3 (5-36)	23,6±9,3(9-76)	**0,007**
Hospitalization stay (day)	9,1±2,5	7,5±4,0	10,1±4,3	**0,162**

Kruskal-Wallis Test and One Way ANOVA. Data are presented as mean±standard deviation, median [minimum, maximum], and percentage [%]. Statistically significant differences are indicated in bold and italicized with a p-value <0.05. HCO3: bicarbonate; HbA1c: glycated hemoglobin; WBC: white blood cell count; SDS: standard deviation score

Table 2. Comparison of hematologic inflammatory markers by DKA severity				
	Mild DKA n=17	**Moderate DKA n=18**	**Severe DKA n=19**	**p**
SII	981.98±705.04	1269.95±1005.03	3499.68±1442.64[a,b]	**<0.001**
NLR	3.21±2.15	4.17±3.57	7.9±3.29 [a,b]	**<0.001**
PLR	167.82±82.06	184.38±115.61	186.36±94.3	0.944
PCT [%]	0.25±0.005	0.29±0.08	0.38±0.06 [a,b]	**<0.001**
PDW	17.18±0.72	17.21±0.53	17.01±0.39	0.569
MPV [fL]	8.56±0.83	9.08±1.24	8.55±0.62	0.265

Kruskal-Wallis Test and One-Way ANOVA. Data are presented as mean±standard deviation and percentage [%]. Statistically significant differences are indicated in bold and italicized with a p-value <0.05. SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PCT: plateletcrit; PDW: platelet distribution width; MPV: mean platelet volume. Compared with the mild-DKA group, [a] $p < 0.016$. Compared with the moderate DKA group, [b] $p < 0.016$.

with moderate (p^{SII}= 0.0001, p^{PCT}= 0.003, p^{NLR}= 0.004), and mild DKA (p^{SII}= 0.0001, p^{PCT}= 0.0001, p^{NLR}= 0.02), but not between those with mild DKA and moderate DKA (p^{SII}= 1.00, p^{PCT}=0.28, p^{NLR}=1.00).

To demonstrate the diagnostic efficacy of SII, NLR, and PCT in predicting DKA severity, we performed an ROC curve analysis. When we reclassified the groups into mild-moderate DKA (pH > 7.1 or HCO3>5 mmol/L) and severe DKA (pH ≤ 7.1 or HCO3<5 mmol/L), we found that all three parameters were significantly effective in predicting DKA severity (p<0.0001) (Figure 1). Comparing the discriminative abilities of these three parameters for predicting DKA severity, we determined that SII was the most valuable parameter for discriminating severe acidosis from others. The statistical cut-off value for SII was determined to be 1612.29, with a sensitivity of 94.44% and a specificity of 81.48% (AUC=0.928) (Figure 1).

In the comparison of mild DKA, moderate DKA, and severe DKA groups, the acidosis resolution time was found to be significantly different (6.6±3.2 [3-14] hours, 13.1±7.3 [5-36] hours, and 23.6±9.3 [9-76] hours, respectively; p =

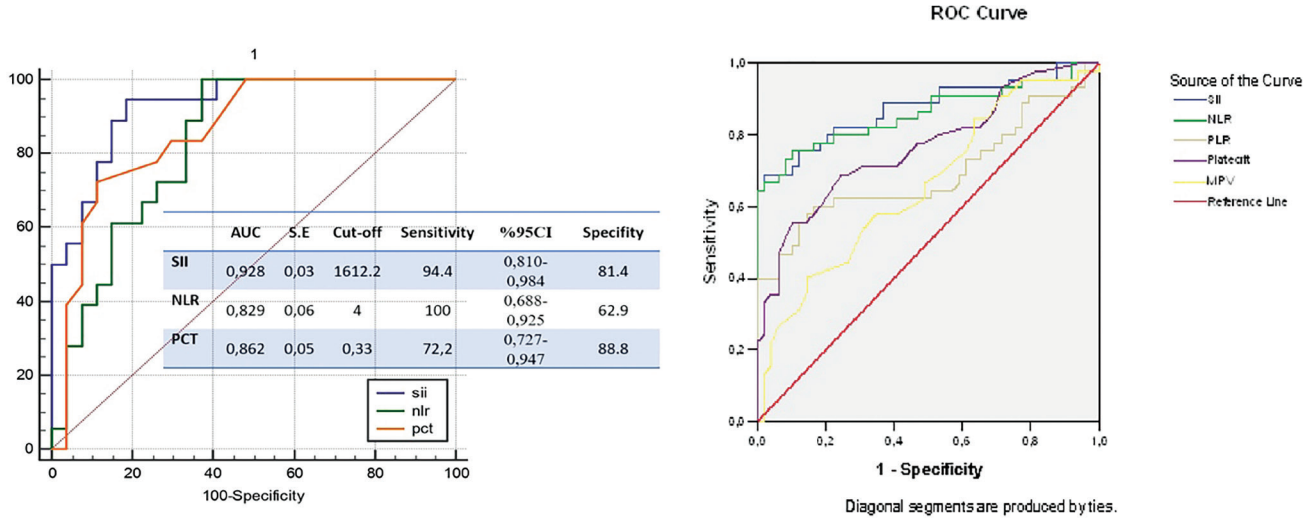

Figure 1. ROC curve analysis of inflammatory parameters in distinguishing DKA from healthy control and in determining DKA severity

ROC: Receiver operating characteristic, SII: systemic immune-inflammation index, NLR: Neutrophil-to-lymphocyte ratio, PCT: plateletcrit, AUC: Area under the curve, S.E: Standard error, CI: confidence interval

P<0,0001 for all three markers

Table 3. Characteristics data and comparison of DKA group, Non-DKA T1DM group, and healthy controls

	DKA Group n=54	Non-DKA T1DM Group (n=27)	Control Group n=49	p
Age [years]	8.89±4.12	10,48±5,0	9.83±3.956	0.294
Height SDS	0.36±1.148[a]	0,49±1,12	-0.117±1.041	**0.037**
Weight SDS	-0.155±1.349	0,43±1,78	0.275±1.211	0.177
BMI SDS	-0.51±1.663[a]	0,07±1,94	0.405±1.095	**0.017**
WBC [×10³/mm³]	13.4 [3.6-45.6][a,b]	8,2 [4,9-16.9][c]	7.4 [3.9-12.6]	**<0.001**
Neutrophil [×10³/mm³]	10 [2-37.1][a,b]	4,9 [1.1-6.7].[c]	3.3 [0-7.5]	**<0.001**
Lymphocyte [×10³/mm³]	2.2 [0.5-9.2][b]	4,3 [2-10.8][a,c]	2.5 [0-5.3]	**<0.001**
Platelet [×10³/mm³]	348 [194-596][a,b]	290 [148-536].[c]	290 [164-549]	**<0.001**
SII	1612.29[221.9-6090][a,b]	442,3 [175-1957,5][c]	407.555 [82-1092.6]	**<0.001**
NLR	4.68 [0.62-14][a,b]	1,43 [0,63-7,0][c]	1.434 [0.5-3.95]	**<0.001**
PLR	154.1 [47.2-442][a,b]	95,1 [54,7-253,6][c]	119.629 [40.75-207]	**0.001**
Plateletcrit [%]	0.3202±0.0861[a,b]	0.247±0.030[c]	0.2433±0.0525	**<0.001**
MPV [fL]	8.7 [6.6-11.1][a]	8.4 [6.5-11][c]	8.2 [6.8-11.3]	**0.046**

Kruskal-Wallis Test and One Way ANOVA Data are presented as mean±standard deviation, median [minimum, maximum]. Statistically significant differences are indicated in bold and italicized with a p-value <0.05. WBC: white blood cell count; PLT: platelet count; SII: systemic immune-inflammation index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PCT: plateletcrit; MPV: mean platelet volume; SDS: standard deviation score. Compared with healthy controls, [a] $p < 0.016$. Compared with Non-DKA T1DM group, [b] $p < 0.016$. Compared with DKA group [c] $p<0.016$

0.007). However, no significant difference was observed in hospitalization time between the groups (9.1±2.5, 7.5±4.0, and 10.1±4.3 days, respectively; p = 0.162). (Table 2)

Upon categorizing the individuals into severe DKA and mild to moderate DKA, the median acidosis resolution time for the severe DKA group was 23.6 hours, substantially exceeding the 10 hours recorded for the mild-moderate DKA group (p=0.003). The median hospitalization duration in the severe DKA group was 10.1 days, whereas the other group had a median of 8 days (p= 0.09).

Table 4. ROC analysis of hematologic inflammatory markers for differentiating DKA patients from healthy controls						
	AUC	S.E	Cut-off	Sensitivity[%]	Specificity[%]	p
SII	0,875	0,038	673,2	75.5	87.7	**<0.0001**
NLR	0,860	0,041	2.12	77,7	83,6	**<0.0001**
PLR	0,693	0,058	134,6	62,2	77,6	**0.001**
Plateletcrit	0,767	0,049	0,27	68,8	75,5	**<0.0001**
MPV	0,656	0,056	8,65	57,7	63,5	**0.009**

ROC, receiver operating characteristic; SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; PCT, plateletcrit. PLR, platelet-to-lymphocyte ratio; MPV, mean platelet volume; AUC, area under the curve; S.E., standard error

Comparison of Inflammatory Markers Between DKA Patients, Non-DKA Patients, and Healthy Controls in T1DM

When comparing T1DM cases from both groups with healthy children, it was observed that all groups showed similar age and gender distributions. When comparing the three groups, significant differences were found in all parameters except for weight SDS, and age. In the comparison between Non-DKA T1DM and the healthy group, no significant changes were found in anthropometric and inflammatory parameters ($p>0.05$), except for lymphocyte levels ($p<0.001$). Post-hoc analysis revealed that this change was mostly observed between the DKA group and the healthy group.

Significant differences of weight values were found between the Non-DKA T1DM and DKA T1DM groups ($p=0.031$), white blood cells, platelets, PCT, neutrophils, lymphocytes, SII, NLR, and PLR (all $p <0.001$). No significant change was observed in MPV ($p= 0.43$).

In the anthropometric assessment between the DKA patients and the healthy control group, we found that height and BMI SDS were significant in distinguishing the DKA group ($p = 0.037$ and $p = 0.002$, respectively). The DKA group had significantly higher levels of white blood cells, neutrophils, lymphocytes, platelets, PCT, SII, NLR, and PLR compared to both the Non-DKA and healthy control groups. The MPV level showed a significant difference only between the DKA and healthy control groups (Table 3). In the ROC analysis, when we compared DKA patients with healthy controls in terms of inflammatory markers, SII was identified as the most valuable parameter for diagnosing DKA (AUC = 0.875, cut-off = 673.2, sensitivity = 75.5%, specificity = 87.7%) (Table 4) (Figure 1).

A significant correlation was found between DKA severity and acidosis resolution time ($p= 0.001$, $r= 0.55$), while no correlation was observed between hospitalization duration and DKA severity ($p= 0.27$). Among the inflammatory markers, a correlation was found between SII and acidosis resolution time ($p= 0.002$, $r=0.340$), but no relationship was observed with hospitalization duration ($p= 0.73$). No correlation was found between NLR and PLR with either acidosis resolution time ($p= 0.07$, $p= 0.67$, respectively) or hospitalization duration ($p= 0.58$, $p= 0.43$, respectively).

Discussion

In the current study, we found that specific inflammatory markers- particularly the SII, NLR, and Plateletcrit significantly correlate with the severity of DKA. SII is emerging as the most reliable indicator. SII's reliability is particularly high in distinguishing severe acidosis from mild and moderate cases. Notably, a cut-off value of 1612.29 for SII was identified, demonstrating significant predictive value for severe DKA, with high specificity and sensitivity.

As the most common hyperglycemic emergency, DKA is characterized not only by insulin deficiency but also by inflammatory processes activated as a stress response by the body. In this context, insulin deficiency triggers the release of counter-regulatory hormones such as glucagon, cortisol, and catecholamines, which in turn stimulate gluconeogenesis and ketogenesis in the liver. These hormonal changes enhance the inflammatory response by increasing the release of cytokines and other inflammatory mediators, thereby amplifying cellular stress and damage critical role in the pathophysiology of DKA. Elevated cytokine levels further worsen insulin resistance and disrupt metabolic balance (13). These interrelated processes contribute not only to the worsening of acidosis but also pave the way for complications. The inflammatory response's effects are more pronounced in DKA, especially in severe cases, leading to significant morbidity (14). Consequently, rapid and accurate recognition of DKA is crucial for initiating an effective treatment process.

Blood gas analysis is a common diagnostic tool for DKA, allowing for rapid assessment of a patient's acid-base status, with pH and bicarbonate parameters used for severity scoring. While blood gas analysis is the gold standard for assessing acid-base balance, challenges -such as delays

in sample collection, transport, analysis, and potential laboratory errors -can limit its effectiveness. This makes the availability of blood gas analysis a significant concern in various healthcare settings (13-15). These limitations have led to the exploration of alternative markers for assessment. The use of inflammatory markers to assess DKA severity has gained traction in recent research (11-12). Studies have shown that hematological inflammatory markers derived from CBC can serve as straightforward, practical, and cost-effective tools for predicting DKA severity. Researchers have particularly focused on markers like NLR, PLR, and SII, which have demonstrated their value across multiple studies in various inflammation-related immunological diseases (6-10,16).

The Systemic Immune-Inflammation Index derived from platelets, neutrophils, and lymphocytes, has emerged as a novel marker for inflammation and immune response, initially introduced by Hu et al. (17) in liver cancer. This index correlates significantly with disease severity and prognosis in both cancer and inflammatory conditions (9-10,16). A meta-analysis assessing the diagnostic role of SII in immunological diseases reviewed 16 studies, revealing elevated SII levels in affected individuals versus controls, achieving an AUC of 85% for diagnostic accuracy, with increased sensitivity during active disease (16). Comparative studies have identified SII as the most valuable parameter among various hematological indices (18,19), aligning with findings that indicate a stronger inflammatory response is linked to more severe clinical presentations. SII has demonstrated significant associations with clinical outcomes across different cancers and other disease states (19-21). Additionally, in patients with atherosclerosis, SII showed prognostic superiority over traditional risk factors, and in COVID-19 cases, it was independently linked to adverse outcomes (15,20). Aon et al. (21) reported that SII progressively increased with DKA severity, with the highest quartile identified as an independent risk factor, and the optimal SII cutoff for predicting DKA severity was determined to be 2524.24, demonstrating 85.3% specificity and 34.4% sensitivity. Their study focused on a group of young adults with an average age of 17. values. In the NHANES study, which evaluated its relationship with the prevalence of diabetes, it was shown that every 1 unit increase in SII in adults over the age of 20 increased the likelihood of diabetes by 4% (22). SII has been associated with other diabetes complications. SIRI and SII are potential biomarkers for early-onset atherosclerotic processes in diabetic children. To the best of our knowledge, this is the first study in children demonstrating the association between SII and DKA severity in T1DM. In our study, we determined an SII cut-off point of 1612.29, which provides 94.44% sensitivity and 81.48% specificity for the detection of severe acidosis. We showed that SII is the most reliable parameter when compared to other parameters.

In our study, we observed that the severity of DKA was strongly associated with the acidosis resolution time (p: 0.001, r: 0.55). This emphasizes that as the severity of DKA increases, the acidosis resolution time prolongs and that a more intensive approach is required in the treatment and follow-up of these patients. However, no significant correlation was found between the severity of DKA and the duration of hospitalization (p: 0.27), indicating that the duration of hospitalization may be affected by different factors. Aon et al. (21) similarly found no correlation between the length of hospitalization and the severity of DKA (21). Interestingly, among the inflammatory markers examined, SII (Systemic Immunity-Inflammation Index) stood out as an important factor. A correlation was found between SII and the acidosis resolution time (p: 0.002, r: 0.340), indicating that SII may be an important marker in assessing the severity and recovery time in DKA patients. However, no significant correlation was found between NLR (Neutrophil/Lymphocyte Ratio) and PLR (Platelet/Lymphocyte Ratio), and neither acidosis resolution time nor hospitalization duration (p= 0.07, p= 0.67 and p= 0.58, p= 0.43, respectively). These results suggest that, unlike SII, NLR and PLR may not be more reliable in predicting DKA clinical outcomes in this context. Our study is the only study examining this relationship and provides important contributions to the literature. Future studies should conduct more detailed investigations to confirm the role of inflammatory markers, especially SII, in the management and prognosis of DKA.

T1DM is one of the most prevalent chronic illnesses in the pediatric population (1-3). While the frequency of DKA in T1DM is 30-40%, in our country, it is seen up to 50% and most cases present with severe acidosis (2-5,15). The frequency of diagnosing DKA in T1DM has been rising significantly in recent years (3,4,22,23). This increase in diagnosis may be attributed to factors such as improved awareness among healthcare professionals, rising incidence rates of T1DM, and potentially delayed diagnosis of diabetes in younger populations (24-26). Our study indicates that most cases presenting with DKA had moderate to severe DKA in the northwest region of Turkey, which aligns with previous regional studies (20). This emphasizes the need for healthcare providers to be vigilant in recognizing the symptoms of both diabetes and DKA. Addressing the underlying causes is crucial for implementing

effective prevention strategies and improving clinical outcomes for patients with T1DM. Additionally, it highlights the importance of easily accessible tools for early diagnosis.

Research investigating the correlation between DKA and age has demonstrated that in univariate analysis, being less than 3 years old or older than 12 increases the probability of DKA at T1DM diagnosis. While some research indicates a slight relationship between age and the severity of DKA (23), similar to other studies, our study also demonstrated that younger children present with more severe acidosis (24). Because they often show less awareness of the symptoms of diabetes. This lack of recognition can delay diagnosis and treatment, leading to more pronounced metabolic disturbances, increasing their risk for complications, and necessitating more intensive management. Furthermore, while lower C-peptide levels are known to increase the risk of DKA in T1DM, we also determined that as C-peptide levels decrease, higher glucose levels are associated with increased DKA severity. C-peptide, as a marker of endogenous insulin secretion, indicates that a low C-peptide level reflects diminished β-cell function. In young children, low C-peptide levels are frequently associated with severe acidosis, aggressive diabetes, and delayed detection of diabetes symptoms. Enrolling in a prospective cohort that educated parents about diabetes symptoms reduced the risk of developing DKA at T1DM diagnosis in young children (24).

In studies investigating the risk factors associated with DKA, both leukocytosis and thrombocytosis be associated with severe metabolic acidosis (5,24). In our study, neutrophil, platelet, and monocyte counts were higher in the severe DKA group, while lymphocyte counts were relatively lower, though not statistically significant. Changes in the white blood cell percentage formula (an increase in neutrophils, monocytes, and total WBCs; a decrease in lymphocytes and eosinophils) matched those reported in the literature (12, 25).

The body's inflammatory response balance is mainly reflected in the neutrophil-to-lymphocyte ratio. NLR is considered a parameter that determines the severity of the inflammatory process; high NLR values indicate a stronger inflammatory response (25). While neutrophils act as active components of the inflammatory response, lymphocytes play a regulatory role and have a reducing effect. Both cell groups are regulated by the autonomic nervous system. Neutrophils are stimulated by sympathetic nerves through adrenergic receptors on their surfaces, while lymphocytes are affected by parasympathetic nerves through cholinergic receptors (26). In DKA patients, stimulation of the sympathetic nervous system results in enhanced neutrophil stimulation and the release of pro-inflammatory chemicals such as TNF-α, CRP, and IL-6 (26-27). Abnormalities in oxygenation caused by DKA cause episodes of hypoxemia, during which inflammatory responses may be triggered. Furthermore, hypoxia inhibits neutrophil apoptosis in DKA patients. WBCs activated by advanced glycation end-products produce pro-inflammatory cytokines (12). Acute hyperglycemia and fluctuations in blood sugar levels in diabetic patients lead to increased reactive oxygen species (ROS), causing damage to peripheral lymphocyte DNA and triggering apoptosis (27). According to studies, leukocytes in DM patients may produce more ROS, which increases oxidative DNA damage occurring in lymphocytes during hyperglycemia episodes (28,29). All these processes prepare the ground for the emergence of a systemic inflammatory response without infection.

The relationship between DKA severity and NLR has been examined in several studies (11-12,25). In a study involving newly diagnosed children with T1DM, the median NLR score increased as DKA severity increased. Correlation between NLR and cerebral edema has also been demonstrated (30). Our study also showed that NLR is a reliable marker for both diagnosing diabetes and determining acidosis severity. Compared to other studies, SII proved to be a better marker for recognizing DKA.

PLR, MPV, PDW, and PCT parameters derived from platelets are also important for inflammation (13,29-31). In individuals with diabetes, platelet hyperreactivity exists. This hyperreactivity causes platelets to become larger or more hyperfunctional due to prothrombinase activity.

In our study, all thrombocyte-derived markers except PCT were not significant in determining the severity of DKA; they were all useful in distinguishing T1DM from healthy cases. Various studies in the literature have reported differing results regarding these markers. While studies have shown that MPV and PCT can serve as poor prognostic indicators in colorectal cancer and pulmonary hypertension, there are relatively few studies specifically focused on PCT (31). Liu et al. (29) found that patients with PLR > 267.37 had a higher likelihood of readmission and death within 90 days in critically ill adult patients with DKA. MPV studies show conflicting results. Previous studies have suggested that MPV values reflect platelet activity in diabetic patients and are related to insulin resistance (32,33). Another study indicates that MPV can be a helpful risk marker for DKA diagnosis, even though it does not predict the severity of DKA (34). However, other studies noted that factors such as the time between blood sample collection and analysis, analysis techniques, and the use of anticoagulants could affect MPV, indicating

that there is no well-standardized test to measure platelet activity effectively (32).

Study Limitations

Although our study achieved important results regarding hematological inflammatory parameters, it also had some limitations. Firstly, our sample size was relatively small, especially in the non-DKA T1DM group, which may have limited the power of the analyses. Secondly, only values at the time of patient admission were considered, and longitudinal measurements could not be performed. Therefore, the dynamic trends of these parameters could not be monitored. Hence, multicenter studies with a larger patient population are needed, and we hope our study serves as a guiding resource for these future endeavors. Future studies should include larger patient cohorts to better differentiate the specific inflammatory response associated with ketoacidosis from the general inflammation in T1DM.

Its strengths are that only newly diagnosed DKA cases were included in the study; cases with known diagnoses were not included because it is one of the risk factors that increase the severity of DKA. Multiple markers were compared simultaneously and reliable results with high sensitivity and specificity were obtained.

Conclusion

In conclusion, our study underscores the significant correlation between SII and the severity of DKA. The findings indicate that elevated SII levels can serve as a reliable biomarker for predicting severe DKA, offering high sensitivity and specificity. This suggests that incorporating SII into routine clinical assessments may facilitate the earlier recognition of severe cases, enabling more proactive management strategies. Furthermore, understanding the inflammatory response in DKA could provide insights into the underlying pathophysiology, potentially guiding future therapeutic approaches. Overall, the utility of SII as a predictive tool highlights the importance of monitoring inflammatory markers in managing pediatric patients with T1DM and DKA. Further research is needed to establish standardized cutoff values and explore the broader implications of SII in various clinical contexts.

Ethics

Ethical Approval: This study was conducted with 81 T1DM patients and 49 healthy controls followed at the Pediatric Endocrinology Clinic of Zonguldak Bülent Ecevit University between April 2022 and January 2024, following the principles of the Declaration of Helsinki. Ethical approval was received from the ethics committee at our university. (ethics no:2024/07-6).

Footnotes

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

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References

1. Calimag APP, Chlebek S, Lerma EV, Chaiban JT. Diabetic ketoacidosis. Dis Mon. 2023;69:101418.
2. Wolfsdorf J, Glaser N, Sperling MA; American diabetes association. Diabetic ketoacidosis in infants, children, and adolescents: a consensus statement from the American Diabetes Association. Diabetes Care. 2006;29:1150-9.
3. Jensen ET, Stafford JM, Saydah S, D'Agostino RB, Dolan LM, Lawrence JM, et al. Increase in prevalence of diabetic ketoacidosis at diagnosis among youth with type 1 diabetes: the SEARCH for diabetes in youth study. Diabetes Care. 2021;44:1573-8.
4. Usher-Smith JA, Thompson M, Ercole A, Walter FM. Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: a systematic review. Diabetologia. 2012;55:2878-94.
5. Yeşilkaya E, Cinaz P, Andıran N, Bideci A, Hatun Ş, Sarı E, et al. First report on the nationwide incidence and prevalence of Type 1 diabetes among children in Turkey. Diabet Med. 2017;34:405-10.
6. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int Arch Med. 2012;5:2.
7. Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD. The platelet-to-lymphocyte ratio as an ınflammatory marker in rheumatic diseases. Ann Lab Med. 2019;39:345-57.
8. Russell CD, Parajuli A, Gale HJ, Bulteel NS, Schuetz P, de Jager CPC, et al. The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: a systematic review and meta-analysis. J Infect. 2019;78:339-48.
9. Zhou B, Zhan C, Wu J, Liu J, Zhou J, Zheng S. Prognostic significance of preoperative neutrophil-to-lymphocyte ratio in surgically resectable pancreatic neuroendocrine tumors. Med Sci Monit. 2017;23:5574-88.
10. Rodríguez-Rodríguez E, López-Sobaler AM, Ortega RM, Delgado-Losada ML, López-Parra AM, Aparicio A. Association between neutrophil-to-lymphocyte ratio with abdominal obesity and healthy eating ındex in a representative older spanish population. Nutrients. 2020;12:855.
11. Baghersalimi A, Koohmanaee S, Darbandi B, Farzamfard V, Hassanzadeh Rad A, Zare R, et al. Platelet indices alterations in children with type 1 diabetes mellitus. J Pediatr Hematol Oncol. 2019;41:e227-32.
12. Scutca AC, Nicoară DM, Mărăzan M, Brad GF, Mărginean O. Neutrophil-to-lymphocyte ratio adds valuable ınformation

regarding the presence of DKA in children with new-onset T1DM. J Clin Med. 2022;12:221.

13. Karavanaki K, Karanika E, Georga S, Bartzeliotou A, Tsouvalas M, Konstantopoulos I, et al. Cytokine response to diabetic ketoacidosis (DKA) in children with type 1 diabetes (T1DM). Endocr J. 2011;58:1045-53.
14. Dhatariya KK, Glaser NS, Codner E, Umpierrez GE. Diabetic ketoacidosis. Nat Rev Dis Primers. 2020;6:40.
15. Poyrazoğlu Ş, Bundak R, Yavaş Abalı Z, Önal H, Sarıkaya S, Akgün A, et al. Incidence of type 1 diabetes in children aged below 18 years during 2013-2015 in Northwest Turkey. J Clin Res Pediatr Endocrinol. 2018;10:336-42.
16. Mangoni AA, Zinellu A. The diagnostic role of the systemic inflammation index in patients with immunological diseases: a systematic review and meta-analysis. Clin Exp Med. 2024;24:27.
17. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20:6212-22.
18. Kawalec A, Stojanowski J, Mazurkiewicz P, Choma A, Gaik M, Pluta M, et al. Systemic ımmune ınflammation ındex as a key predictor of dialysis in pediatric chronic kidney disease with the use of random forest classifier. J Clin Med. 2023;12:6911.
19. Ozde S, Akture G, Ozel MA, Yavuzyilmaz F, Arslanoglu I, Ozde C, et al. Evaluation of the systemic-immune inflammation index (SII) and systemic immune-inflammation response index (SIRI) in children with type 1 diabetes mellitus and its relationship with cumulative glycemic exposure. J Pediatr Endocrinol Metab. 2024;37:635-43.
20. Fois AG, Paliogiannis P, Scano V, Cau S, Babudieri S, Perra R, et al. The systemic ınflammation ındex on admission predicts ın-hospital mortality in COVID-19 patients. Molecules. 2020;25:5725.
21. Aon M, Aoun AH, Alshami A, Alharbi A, Alshammari F, Alnajjar M, et al. Association of the systemic immune-inflammation index (SII) and severity of diabetic ketoacidosis in patients with type 1 diabetes mellitus: a retrospective cohort study. Ann Med Surg (Lond). 2024;86:3865-72.
22. Nie Y, Zhou H, Wang J, Kan H. Association between systemic immune-inflammation index and diabetes: a population-based study from the NHANES. Front Endocrinol (Lausanne). 2023;14:1245199.
23. Lee HJ, Yu HW, Jung HW, Lee YA, Kim JH, Chung HR, et al. Factors associated with the presence and severity of diabetic ketoacidosis at diagnosis of type 1 diabetes in Korean Children and Adolescents. J Korean Med Sci. 2017;32:303-9.
24. Sehgal M, Batra M, Jha P, Sanchez O. Risk factors and laboratory findings associated with diabetic ketoacidosis in hospitalized pediatric patients. Cureus. 2022;14:e25410.
25. İsmail NA, Abeer M, El Baky NED. Neutrophil-lymphocyte ratio, platelet-lymphocyte ratio in well controlled and uncontrolled children and adolescents with type 1 diabetes mellitus. Res J Pharm Biol Chem. 2021;12:13.
26. Abo T, Kawamura T. Immunomodulation by the autonomic nervous system: therapeutic approach for cancer, collagen diseases, and inflammatory bowel diseases. Ther Apher. 2002;6:348-57.
27. Mirzaei S, Hadadi Z, Attar F, Mousavi SE, Zargar SS, Tajik A, et al. ROS-mediated heme degradation and cytotoxicity induced by iron nanoparticles: hemoglobin and lymphocyte cells as targets. J Biomol Struct Dyn. 2018;36:4235-45.
28. Chibber R, Ben-Mahmud BM, Chibber S, Kohner EM. Leukocytes in diabetic retinopathy. Curr Diabetes Rev. 2007;3:3-14.
29. Liu WY, Lin SG, Wang LR, Fang CC, Lin YQ, Braddock M, et al. Platelet-to-lymphocyte ratio: a novel prognostic factor for prediction of 90-day outcomes in critically ıll patients with diabetic ketoacidosis. Medicine (Baltimore). 2016;95:e2596.
30. Scutca AC, Nicoară DM, Mang N, Jugănaru I, Brad GF, Mărginean O. Correlation between neutrophil-to-lymphocyte ratio and cerebral edema in children with severe diabetic ketoacidosis. Biomedicines. 2023;11:2976.
31. Awad A, Elnemr S, Hodeib H, El Amrousy D. Platelet activation markers in children with pulmonary arterial hypertension associated with congenital heart disease. Pediatr Cardiol. 2022;43:1264-70.
32. Kiskac M, Zorlu M, Cakirca M, Karatoprak C, Kesgin S, Büyükaydın B, et al. Evaluation of the relationship between serum apelin levels and vitamin D and mean platelet volume in diabetic patients. Ann Endocrinol (Paris). 2014;75:200-5.
33. Beyan C, Beyan E. Mean platelet volume and vitamin D deficiency may not be related in diabetic patients. Ann Endocrinol (Paris). 2015;76:75-6.
34. Mousa SO, Sayed SZ, Moussa MM, Hassan AH. Assessment of platelets morphological changes and serum butyrylcholinesterase activity in children with diabetic ketoacidosis: a case control study. BMC Endocr Disord. 2017;17:23.