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Can Mean Platelet Volume be an Inflammatory Marker in Pediatric Diabetic Ketoacidosis?

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Abstract

This study explores the association between mean platelet volume (MPV) and other hematological parameters in children with diabetic ketoacidosis (DKA), aiming to identify hematological changes and their implications for management and treatment strategies in pediatric type 1 diabetes mellitus (T1DM). In a retrospective, two-center analysis of 323 children, participants were categorized into three groups: DKA, T1DM without ketoacidosis, and healthy controls (95). Hematological parameters and HbA1c levels were collected. Blood pH levels classified DKA severity, and statistical analyses included One-way ANOVA, correlation tests, receiver operating characteristic curve analysis, and logistic regression to assess the predictive value of hematological parameters for DKA. No significant demographic differences were noted among the groups. Patients with DKA exhibited significantly lower MPV and higher neutrophil-to-lymphocyte ratio (NLR) compared with both patients with T1DM without ketoacidosis and healthy controls. Logistic regression showed MPV ≤9.35 and NLR ≥2.73 significantly increased DKA risk. This study demonstrated a significant relationship between DKA and altered hematological parameters (MPV and NLR) in pediatric patients, highlighting their potential as markers for early detection and risk assessment of DKA.

Keywords: Diabetes mellitus, mean platelet volume, diabetic ketoacidosis

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Introduction

Diabetic ketoacidosis (DKA) is a critical acute complication of type 1 diabetes mellitus (T1DM). Ketoacidosis emerges as the primary indicator of T1DM and manifests when insulin demand escalates due to ailments, stressors, or a reduction in insulin administration.[1] Diabetes is an increasing health problem in children; thus, the risk factors, causes, and complications of DKA should be known.[2]

The mean platelet volume (MPV) is a parameter measured during the automatic blood count that increases in cases of increased thrombopoiesis. These young, large platelets that increase in circulation are also known as stress platelets and are more metabolically and functionally active than other platelets.[3] MPV is associated with systemic inflammation and prothrombotic states in various conditions, including cardiovascular and metabolic disorders.[4] In the context of DKA, elevated MPV levels may reflect a hypercoagulable state and a heightened inflammatory response during acute metabolic crises.[5]

Highlights

- Diabetic ketoacidosis (DKA) significantly lowers mean platelet volume (MPV) and elevates neutrophil-to-lymphocyte ratio (NLR) in pediatric patients.
- An MPV value ≤9.35 and an NLR value ≥2.73 can serve as predictive markers for DKA, with NLR offering higher specificity.
- MPV and NLR are accessible, cost-effective parameters useful in diagnosing DKA in children, particularly in settings lacking advanced diagnostics.
- Logistic regression analysis revealed that NLR ≥2.73 increases DKA risk by 28-fold, while MPV ≤9.35 increases it by 3.7-fold.

The neutrophil-to-lymphocyte ratio (NLR) is an indicator of inflammation and immune response. High NLR values may indicate increased inflammation and activation of the immune system.[6-9] Elevated NLR levels have been identified as a marker of systemic inflammation and oxidative stress in metabolic and inflammatory diseases.[10] In DKA, NLR can potentially serve as a prognostic marker correlated with inflammation severity and the risk of complications.[11]

This article explores the association between MPV and NLR in pediatric patients with DKA. The results of this study may reveal the DKA effect on children's hematological parameters of children, helping us better understand this condition's importance in pediatric health and its potential effects on treatment strategies.

Material and Method

Study Design

This retrospective, two-center study included 323 children aged 1-18. This group included 139 individuals diagnosed with DKA, 89 with type 1 diabetes but without ketoacidosis, and 95 healthy, non-diabetic children. Given its retrospective nature, explicit patient consent was deemed unnecessary. Hatay Mustafa Kemal University Ethics Committee gave ethical permission for the research, and the research complied with the principles stated in the Declaration of Helsinki (decision no: 06, date:25/12/2023). The authors did not conduct any experiments involving human participants or animals. The screening period spanned from November 2021 to January 2023, during which time children admitted to the Pediatric Endocrinology services at Hatay Mustafa Kemal University and Mersin City Hospital with DKA were identified through the system. Patients with concurrent health issues, infections, or medication use were excluded from the study.

The MPV, platelet distribution width (PDW) and NLRs of patients with average platelet counts (PLT) from their complete blood counts were recorded. Additionally, the HbA1c values at the time of the blood test were recorded for patients with diabetes. The height and weight of the patients were plotted on percentile curves specific to Turkish children.

Patients with DKA were categorized into three groups based on their pH values: mild, moderate, and severe. Those with a blood gas pH below 7.1 were classified as severe, those with pH values between 7.1 and 7.2 were considered moderate, and those with pH values between 7.2 and 7.3 were classified as mild ketoacidosis. The relationship between the severity of ketoacidosis and MPV values and NLR was assessed by comparing these parameters among the three groups. The study also examined the association between HbA1c levels and MPV and NLR in these patients. Additionally, the hematology profiles of patients with DKA were compared with those of patients with T1DM attending outpatient pediatric endocrinology clinics for routine checkups and healthy children undergoing routine checkups for child health and diseases.

Statistical Analysis

SPSS version 22 for Windows (SPSS Inc., Chicago) was used for all statistical analyses. Statistical data were presented as percentages, whereas continuous data were presented as mean ± standard deviation. A One-way ANOVA and Post-hoc Scheffe alpha tests were employed to assess the mean value differences in a dependent variable across two independent groups. Correlation analysis was performed to determine the magnitude and direction of the association between the two quantitative variables. The Pearson correlation coefficient was applied to data exhibiting a normal distribution, whereas the Spearman rank correlation coefficient was utilized for data not following a normal distribution. To identify the ideal cut-off value along with the sensitivity and specificity of MPV and NLR for predicting DKA, an analysis of the receiver operating characteristic (ROC) curve was conducted. For each testing technique, a p value of 0.05 indicated statistical significance. Logistic regression analysis was performed to examine whether the MPV and NLR thresholds, as determined through ROC curve analysis, indicate a risk of DKA.

Results

The study incorporated a total of 323 participants, distributed among three distinct groups: the DKA group comprised 139 individuals, representing 43% of the total; the T1DM group included 90 participants, accounting for 27.9%; and the healthy control group comprised 94 individuals, making up 29.1% of the study population. The mean age of the participants was 129.39 (range: 2.5-213) ±55.80 months. With p values of 0.143 and 0.998, respectively, statistical analysis revealed no discernible differences in age or sex across the groups.

There were no significant variations in the height, weight, or age of the groups, as indicated by the analysis of the demographic and laboratory data (p values of 0.069, 0.473, and 0.143, respectively. However, the DKA (DKA) group exhibited significantly higher values for PLT, PDW, neutrophil count, and NLR compared with the other groups, all with p values below 0.001. In contrast, the MPV was significantly lower in the DKA group (p<0.001). No significant differences in lymphocyte counts were observed between the groups (p=0.666) (**Table 1**).

In the diabetic patient group, hematological parameters revealed a moderate positive correlation between the severity of DKA and neutrophil counts, as well as a weak positive correlation with the NLR (correlation coefficients r=0.471, p<0.001 and r=0.235, p=0.007, respectively). Additionally, a moderate positive correlation was observed between HbA1c levels and PDW, while a weak positive correlation was noted with neutrophil counts (r=0.402, p<0.001 and r=0.252, p<0.001, respectively). No significant correlations were found between MPV, PLT, and DKA severity or HbA1c levels (**Table 2**).

In patients with diabetes, ROC curve analysis was performed to establish the optimal cut-off values for MPV and NLR for predicting DKA. The results indicated that an MPV value of ≤9.35 predicted DKA with 72% sensitivity and 56% specificity. Additionally, an NLR value of ≥2.73 predicted DKA with 74% sensitivity and 91% specificity (**Table 3**).

Subsequent risk analysis utilizing logistic regression based on these cut-off points indicated that an MPV value ≤9.35 increases the risk of developing DKA by 3.7-fold, whereas an NLR value ≥2.73 elevates the risk of DKA development by 28-fold (**Table 4**).

Discussion

Our research indicates that this is among the first studies to investigate the relationship between MPV, NLR, and DKA. Previous studies have shown a relationship between MPV readings of patients with diabetes and metabolic management. The depletion of circulating platelets may occur in individuals with diabetes due to platelet activation and aggregation triggered by an augmented response to endogenous stimuli. This

Table 1.
Comparison of group-to-group variations in laboratory and demographic data

	Control	Type 1 DM	DKA	P value
Age (months)	125.86±53.38	122.32±54	136.25±54.76	0.143
Height Z score	0.117±1.04	-0.121±1.17	-0.359±1.14	0.069
Weight Z score	0.036±2.53	-0.271±1.341	-0.309±1.37	0.473
HbA1c	-	10.64±2.92[a]	12.44±2.36[b]	**<0.001**
MPV	10.31±1.28[a]	10.05±1.30[a]	9.12±1.27[b]	**<0.001**
PLT	313.712±81.825[a]	328.670±96.215[a]	387.171±114.865[b]	**<0.001**
PDW	15.12±1.49[a]	14.99±1.73[a]	35.32±13.31[b]	**<0.001**
Neutrophil	4.32±1.98[a]	3.90±2.23[a]	12.33±7.39[b]	**<0.001**
Lymphocyte	2.83±1.28	3.05±1.74	2.88±2.05	0.666
NLR	2.01±2.63[a]	1.48±0.90[a]	5.98±6.08[b]	**<0.001**

The difference in mean values between groups a and b was considered statistically significant (p<0.05).
MPV; Mean platelet volume, PLT; Platelet counts, PDW; Platelet distribution width, NLR; Neutrophil-to-lymphocyte ratio, DKA; Diabetic ketoacidosis

Table 2.
DKA severity and the relationship between Hba1c and hematological parameters

		DKA severity	HbA1c
MPV	Pearson correlation	0.039	-0.092
	Sig. (2-tailed)	0.660	0.187
PLT	Pearson correlation	0.108	0.013
	Sig. (2-tailed)	0.231	0.856
PDW	Pearson correlation	-0.004	0.402**
	Sig. (2-tailed)	0.964	0.000
Neutrophil	Pearson correlation	0.471**	0.252**
	Sig. (2-tailed)	0.000	0.000
NLR	Pearson correlation	0.235**	0.100
	Sig. (2-tailed)	0.007	0.150

**; Correlation is significant at the 0.01 level (2-tailed)
MPV; Mean platelet volume, PLT; Platelet counts, PDW; Platelet distribution width, NLR; Neutrophil-to-lymphocyte ratio, DKA; Diabetic ketoacidosis

Table 3.
Identification of optimal cut-off points for predicting diabetic ketoacidosis

	Optimal threshold for diabetic ketoacidosis	AUC	Sensitivity	Specificity	95% CI	P value
MPV	≤9.35	0.704	0.72	0.56	0.634-0.773	<0.001
NLR	≥2.73	0.871	0.74	0.91	0.825-0.918	<0.001

MPV; Mean platelet volume, NLR; Neutrophil-to-lymphocyte ratio, CI; Confidence interval, AUC; Area under the curve

Table 4.
Risk analysis for the development of diabetic ketoacidosis

	OR	95% CI	P value
MPV (≤9.35)	3.7	2.075-6.591	<0.001
NLR (≥2.73)	28	12.325-63.889	<0.001

MPV; Mean platelet volume, NLR; Neutrophil-to-lymphocyte ratio, CI; Confidence interval, OR; Odds ratio

phenomenon may also be associated with variations in platelet production and lifespan observed in patients with diabetes.[12,13] In a study by Pirgon et al.[12] children with type 1 diabetes were compared with healthy controls. The results showed that children with T1DM had significantly higher MPV levels than the controls. In individuals with type 1 diabetes, elevated platelet activity is associated with a higher risk of microvascular and macrovascular complications. Nevertheless, no correlation was observed between MPV and HbA1c levels.

In contrast, a study conducted by Sobü et al.[13] found no difference in MPV values between children with T1DM and robust controls. They also found that MPV levels increased with longer illness duration and higher HbA1c levels in those with poorly managed diabetes, and that these individuals' MPV levels were significantly greater than those of healthy controls. The MPV did not statistically differ significantly in this study between the group of healthy control children and the children with diabetes. In contrast to the diabetic and control groups, MPV was significantly lower in patients with DKA. This finding is consistent with the hypothesis that DKA induces severe inflammation, leading to the consumption and destruction of younger, larger platelets, thereby resulting in lower MPV levels. The inflammatory cascade in DKA is likely mediated by increased oxidative stress, cytokine release, and coagulation pathway activation, all of which contribute to platelet consumption and turnover. From this theory, it can be concluded that DKA induces severe inflammation in the body.[14-16] Furthermore, other studies have suggested that low MPV in acute inflammatory states may indicate a compensatory mechanism in response to heightened platelet consumption or sequestration.[16] This contrasts with chronic inflammatory conditions, in which the MPV is typically elevated, underscoring the dynamic and context-dependent role of the MPV as an inflammatory marker. Comparing these findings with similar acute inflammatory states, such as sepsis and acute pancreatitis, may help delineate the specific pathways influencing MPV in DKA.[17,18] The lack of a significant difference in MPV between children with T1DM without ketoacidosis and healthy controls, in line with studies suggesting an increase in MPV with longer disease duration and elevated HbA1c levels, may be attributed to the young age of the patients and the relatively shorter duration of their condition.[12,13]

In a study evaluating the connection between the NLR and DKA, patients with DKA were compared with those without ketoacidosis, revealing that the NLR was significantly elevated in cases of DKA. Additionally, the severity of ketoacidosis was correlated with an increase in NLR.[19] Another study in adults demonstrated that NLR could be used to predict systemic inflammatory response in the presence of DKA. Similar to our research, children with T1DM without ketoacidosis were compared with healthy controls, and it was found that the NLR was significantly higher in children with T1DM than in the control group, with this ratio further increasing in the presence of ketoacidosis.[11] This study found no significant difference in the NLR between children with T1DM and healthy controls. This result may be associated with the younger patient population and the shorter duration of diabetes. However, in patients with DKA, a significant increase in NLR was observed compared with that in patients with type 1 diabetes without ketoacidosis and healthy controls. Furthermore, an increase in the severity of DKA was associated with an increase in NLR. This result indicates that the presence and severity of DKA are correlated with an increase in inflammation intensity. Based on our findings, when assessing the predictive value of MPV and NLR for DKA, we found that an MPV ≤9.35 predicted DKA with 72% sensitivity and 56% specificity. Likewise, an NLR ≥2.73 demonstrated a sensitivity of 74% and specificity of 91% for predicting DKA. In a study by Scutca et al.[19] an NLR threshold of 1.84 was identified, with a reported sensitivity of 80.2% and specificity of 80% for predicting the onset of DKA. Furthermore, this study's risk analysis showed that a 3.7-fold higher chance of developing DKA was linked to an MPV value of ≤9.35. Moreover, when the NLR is ≥2.73, the risk of DKA increases by 28-fold. Considering the importance of early diagnosis in pediatric patients presenting with high blood sugar levels to emergency departments, especially in healthcare facilities lacking the capability to perform blood gas analysis, MPV and NLR serve as simple, economical, and accessible parameters for predicting DKA.

This retrospective study design limits the ability to capture certain clinical details that could be obtained in a prospective setting. Additionally, the study population was drawn from only two centers, which may limit the generalizability of the findings. The inflammatory markers used, specifically MPV and NLR, are not entirely specific to DKA and may be influenced by other systemic inflammatory conditions. Furthermore, the prognostic value of MPV and NLR for diagnosing DKA should be validated in larger multicenter studies to confirm their broader applicability.

Conclusion

The hematological effects of DKA in pediatric patients provide significant insights into the relationship between systemic inflammation and platelet dynamics in the context of T1DM. Our results highlight a strong association between DKA and specific hematological changes, including reduced MPV and increased NLR, thereby providing a deeper understanding of the complex mechanisms underlying acute diabetic complications.

This study unequivocally demonstrated that the hematological parameters of MPV and NLR can serve as pivotal indicators of DKA, offering a window into the systemic inflammatory state and platelet functionality in pediatric patients. The predictive value of MPV ≤9.35 and NLR ≥2.73 for DKA heralds a significant advancement in our ability to preemptively identify and stratify the risk of DKA in children with T1D. This, in turn, paves the way for timely intervention strategies, potentially mitigating the severity of DKA presentations and improving patient outcomes.

In clinical settings, MPV and NLR are accessible and cost-effective parameters that could be routinely incorporated into initial evaluations for pediatric patients presenting with hyperglycemia or suspected DKA. For example, these markers could help stratify risk in emergency departments, especially in settings where advanced diagnostic tools, such as blood gas analyzers, are not readily available. Furthermore, the dynamic characteristics of MPV and NLR can provide insights into disease progression and the effectiveness of long-term therapeutic interventions.

However, it is important to note the potential limitations of these markers. MPV and NLR are not specific to DKA and may be influenced by other systemic inflammatory or hematological conditions, potentially leading to diagnostic ambiguity. Thus, their use should complement, rather than replace, standard diagnostic approaches. Future multicenter studies with larger sample sizes are necessary to validate these findings and refine their clinical application in diverse healthcare settings.

Ethics

Ethical Approval: Hatay Mustafa Kemal University Ethics Committee gave ethical permission for the research, and the research complied with the principles stated in the Declaration of Helsinki (decision no: 06, date:25/12/2023).

Informed Consent: Given its retrospective nature, explicit patient consent was deemed unnecessary.

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Footnotes

Author Contributions: Trabzon G: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Çiçek D: Design, Data Collection or Processing, Literature Search.; Güngör Ş: Design, Analysis or Interpretation, Literature Search.; Demiray Güllü Ş: Design, Data Collection or Processing, Literature Search.; Yazarlı E: Concept, Design, Data Collection or Processing, Literature Search.; Güllü UU: Concept, Design, Literature Search.; El Ç: Design, Data Collection or Processing, Literature Search.

Conflict of Interest: The authors have no conflicts of interest to declare.

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