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HAEMATOLOGICAL PARAMETERS AND ITS CORRELATION WITH SEVERITY OF DIABETIC KETOACIDOSIS

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Abstract
Background: Diabetic ketoacidosis (DKA) is the most common acute hyperglycemic emergency in children with type 1 diabetes mellitus and is associated with significant morbidity and mortality. DKA induces a systemic inflammatory response, often altering hematological parameters and mimicking infection.
Objectives: To evaluate the correlation between hematological parameters and DKA severity in pediatric patients, and assess the association between neutrophil-to-lymphocyte ratio (NLR) and cerebral edema.
Methods: This retrospective single-center study included children aged 1–18 years admitted with DKA between January 2024 and March 2025. Hematological parameters including TLC, ANC, NLR, PLR, PMR, eosinophil count, monocyte count, and HbA1c were analyzed according to ISPAD 2022 criteria.
Results: Fifty-four children were included. TLC showed a significant positive correlation with DKA severity (p=0.036).
Conclusion: TLC may serve as a simple accessible marker correlating with DKA severity in pediatric patients.
Keywords: Diabetic ketoacidosis; Pediatrics; Hematological parameters; Total leukocyte count; Neutrophil-to-lymphocyte ratio; Cerebral edema

Introduction:
DKA is the most frequent acute hyperglycaemic emergency in children and adolescents with diabetes mellitus, under the guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD) [1]. It is characterized by the biochemical trio of high anion-gap metabolic acidemia (venous pH < 7.3 and/or bicarbonate < 18 mmol/L), hyperglycemia (serum glucose > 11 mmol/L or >200 mg/dL), and ketonemia (β-hydroxybutyrate concentrations > 3.0 mmol/L) and/or moderate or substantial ketonuria. In children with type 1 diabetes mellitus (T1DM), diabetic ketoacidosis (DKA) is a potentially fatal acute consequence.
It is brought on by an absolute or relative insulin deficiency along with an excess of counterregulatory hormones (such as glucagon, catecholamines, cortisol, and growth hormone). DKA affects about 25–40% of children with newly diagnosed type 1 diabetes and is usually caused by physiologically demanding settings. Several investigations have shown that DKA is associated with an inflammatory response and changes in haematological parameters. DKA alone can resemble an illness. thus it could be challenging to distinguish between septic and nonseptic inflammatory responses . As a result, many patients receive excessive antibiotic treatment, which raises the risk of bacterial resistance, side effects, and insufficient treatment.
According to a number of studies, DKA is linked to changes in haematopathological markers and an inflammatory response . DKA by itself can resemble an infection, as well as the potential difficulty of distinguishing between septic and nonseptic inflammatory responses (5). Therefore, a large number of patients receive excessive antibiotic treatment, which results in adverse effects, bacterial resistance, and insufficient treatment expenses. In children, cerebral edema is a rare but deadly consequence of diabetic ketoacidosis. There is no precise definition of the risk factors for this condition.
Although DKA frequently involves a leukocyte response, little is known about its features, especially with reference to differential leukocyte count. DKA may lead to systemic inflammation, raise the risk of cerebral edema, and interfere with the blood-brain barrier. One important measure of inflammation in both acute and chronic diabetes is the neutrophil-to-lymphocyte ratio (NLR). Several hematological measurements, such as the neutrophil-to-lymphocyte ratio [NLR], absolute neutrophil count [ANC], platelet-to-lymphocyte ratio [PLR], and platelet-to-monocyte ratio [PMR], have been shown to be important in predicting outcomes during and after infection. Certain non infectious inflammatory disorders have also been linked to activity in these hematological indicators. This study's goal is to investigate the hematological parameters.

AIM AND OBJECTIVE: A. To correlate differential leucocyte counts with Severity of Diabetic ketoacidosis

B. Association of Neutrophil Lymphocyte ratio with occurrence of cerebral edema in Diabetic ketoacidosis.

MATERIALS AND METHODOLOGY : STUDY DESIGN

➢ This study is a hospital based retrospective single centered study performed on paediatric diabetic patients in Ramaiah Hospitals, Bangalore, India. We reviewed 55 patients with Type1 DM who presented with DKA to the emergency in Ramaiah Hospital between January 2024 to March 2025. Data were collected based on age, height, weight, family history of diabetes, presence of preceding infections, health insurance status, and parents' education level at diagnosis. The date of diagnosis was defined as the first day of insulin administration. Laboratory results at diagnosis, such as serum glucose, CBC, glycated hemoglobin (HbA1c), venous pH and bicarbonate levels, were also investigated.

Inclusion criteria included children aged 1 to 18 years with diagnosis of Diabetic Ketoacidosis according to ISPAD Clinical Practice Consensus Guidelines 2022 admitted to Paediatric intensive care unit.

Exclusion criteria included children with known hematological/ neurological abnormality, preexisting chronic illness, current use of any long term medication, acute infections.

The primary objective is to correlate differential leucocyte counts such as TLC, ANC, neutrophil lymphocyte ratio(NLR), platelet monocyte ratio(PMR), platelet lymphocyte ratio(PLR), monocyte count as well as eosinophil count with Severity of Diabetic ketoacidosis. The secondary objective is to study the association of Neutrophil Lymphocyte ratio with occurrence of cerebral edema in Diabetic ketoacidosis.

SAMPLE SIZE AND STATISTICAL ANALYSIS:

Data was entered into Microsoft excel data sheet and was analysed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test or Fischer's exact test** (for 2x2 tables only) was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. **ANOVA** was used as test of significance to identify the mean difference between more than two quantitative variables. Receiver operating characteristic curves (ROCs) was constructed for Various parameters and severe DKA. Receiver operating characteristic (ROC) and optimal cut-off points was chosen for the calculation of sensitivity, specificity, positive and negative predictive values. A test that predicts an outcome no better than chance has an area under the ROC curve of 0.5. An area under the ROC curve above 0.8 indicated fairly good prediction.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs

P value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

RESULTS:

The final study sample included 54 children with DKA. There was no significant difference in the data between age, sex distribution. Among the 54 subjects, DKA severity was graded based on ISPAD guidelines revealing 24.1% with mild DKA, 24.1% moderate and 50% with severe DKA. Significant difference was seen in total leucocyte count. The mean TLC in mild DKA was 11524, 12012 in moderate DKA group and 19098 in severe DKA (p= 0.036) The primary outcome of the study NLR, PMR, PLR did not differ significantly between the groups. There was no significant difference in the incidence of cerebral edema. The hemoglobin level, PMR,PLR, eosinophil count, monocyte count and HbA1C values did not significantly differ across the groups either. However, there were notable variations in NLR, ANC and monocyte count amongst the groups.

Positive correlation was seen with **Total Leukocyte Count (TLC)**, the mean TLC progressively increases with the severity of DKA (from mild to severe), showing a significant positive correlation (*P value = 0.036*). This suggests that higher leukocyte counts could be linked to increased severity, possibly due to stress or inflammation in severe cases. **Absolute Neutrophil Count (ANC)** ,Though not statistically significant (*P value = 0.091*), ANC exhibits a trend where levels are higher in severe DKA cases compared to mild and moderate ones. This could imply a positive correlation with severity. A strong possible positive correlation were observed in severe DKA group between females, patients with cerebral edema and duration of ICU stay. A significant negative correlation were observed between PMR, PLR and monocyte count.

Table 1 shows the corelation of different haematological parameters according to the severity of DKA.

	SEVERITY OF DKA						P value
	Mild		Moderate		Severe		
	Mean	SD	Mean	SD	Mean	SD	
HB	12.86	1.50	13.08	1.14	13.05	2.40	0.948
TLC	11524	4946	12012	6702	19098	12973	**0.036**
ANC	7256	5223	7972	5336	12103	9021	0.091
NLR	3.47	3.85	3.04	1.92	5.08	3.72	0.152
PMR	.553	.287	.637	.360	.478	.342	0.368
PLR	.217	.191	.158	.071	.381	.615	0.285

Monocyte	6.47	2.48	6.98	2.20	7.80	3.16	0.330
Eosinophil	1.80	1.98	.92	1.37	1.64	3.95	0.722
HBA1C	13.2	3.1	12.7	2.1	13.3	2.8	0.805

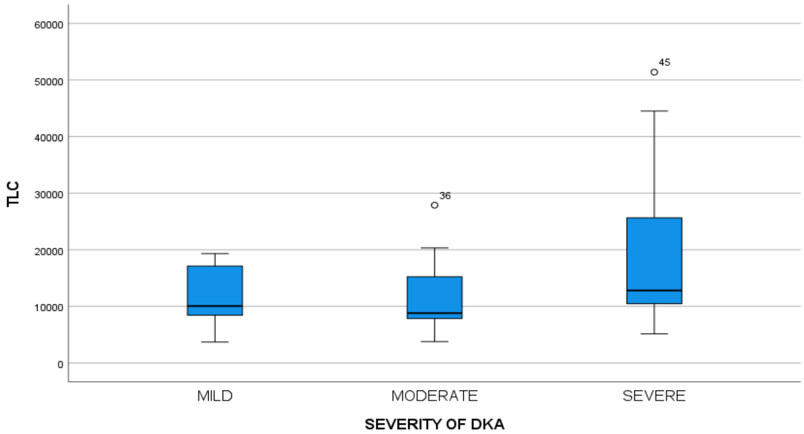

Figure 1 A. Box plot- TLC with severity of DKA,

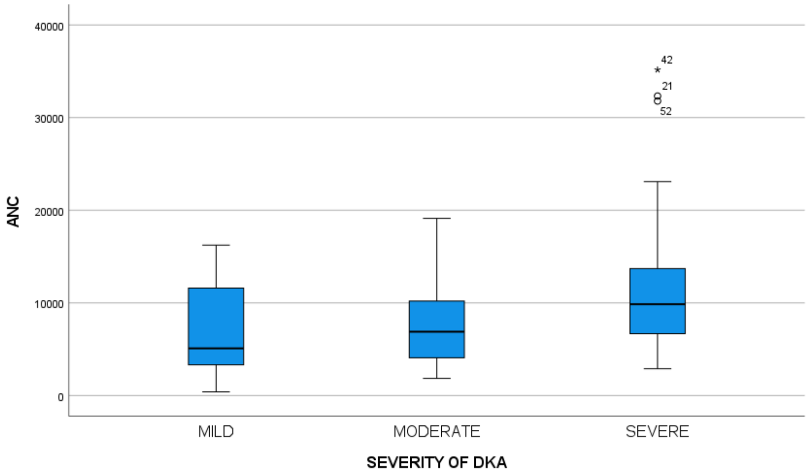

Figure 2 B. - Absolute Neutrophil count with severity of DKA

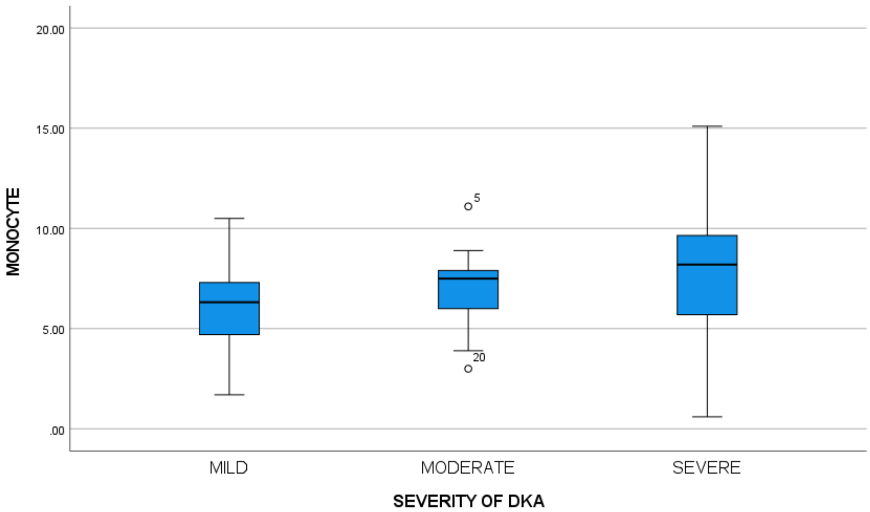

Figure 3 C. - Monocyte count with severity of DKA,

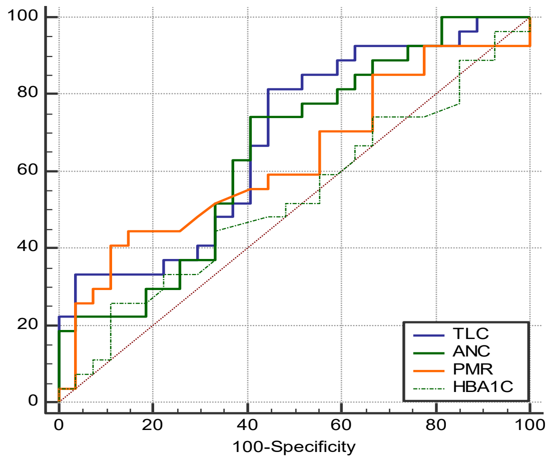

Fig D. ROC curve of TLC, ANC< PMR< HbA1C in predicting severrity of DKA

TLC had the strongest ability to differentiate between mild and severe DKA (AUC 0.683), meaning higher TLC levels were more closely associated with more severe presentation.
ANC also performed reasonably well (AUC 0.653), indicating that neutrophil count also rises with increasing severity, though less accurately than TLC.
PMR and HbA1c had low AUC values (<0.63), showing poor discriminatory power — they did not reliably separate severe from non-severe cases.
Of all markers evaluated, TLC and ANC were the only ones with acceptable predictive usefulness, while PMR and HbA1c were not good predictors of DKA severity.

DISCUSSION

This study explored the The relationship between haematological markers and the severity of diabetic ketoacidosis (DKA) in paediatric patients. Total Leukocyte Count (TLC) and DKA severity was found to be significantly positively correlated, with increasingly higher TLC values seen in severe cases (p = 0.036). This pattern implies that when DKA worsens, there will be a greater inflammatory response and physiological stress.
In a study conducted by Alexandra Cristina et al, included 155 children with Type 1 DM on whom CBC with other routine investigations was done before initiating treatment. Children were classified based on clinical status and laboratory parameters into mild, moderate and severe DKA. This suggests that leukocytosis is closely associated with metabolic stress and inflammatory activation in DKA. This finding is consistent with previous studies. Karavanaki et al. demonstrated that leukocytosis in DKA is often related to stress-induced demargination of leukocytes rather than infection. Similarly, Alexandra Cristina et al. reported that total leukocyte count increases proportionately with the severity of DKA, reflecting systemic inflammatory response. The study revealed total WBC, neutrophils and monocytes, NLR increased with severity of DKA while eosinophils and lymphocytes decreased. The elevation in TLC may be attributed to increased counter-regulatory hormones (catecholamines, cortisol),Dehydration and hemoconcentration, Activation of pro-inflammatory cytokines. Therefore, TLC may be a helpful, accessible marker for determining the severity of DKA, but it should be interpreted carefully when distinguishing infection.
While Absolute Neutrophil Count (ANC) exhibited an increasing trend in severe DKA cases, it did not reach statistical significance (p = 0.091). Higher ANC levels in severe DKA, however, point to an inflammatory response mediated by neutrophils. This finding is consistent with research by Umpierrez et al., who found that stress reaction rather than infection was the cause of neutrophilia in DKA. The increase in neutrophils could be due to bone marrow activation brought on by stress and a rise in neutrophil demargination. This trend, however, indicates a possible association between neutrophilic response and worsening metabolic instability. Notable variations were also observed in Neutrophil-Lymphocyte Ratio (NLR), ANC, and monocyte count, though these differences did not reach statistical significance across severity groups. Interestingly, primary markers such as NLR, Platelet-to-Lymphocyte Ratio (PLR), and PMR did not significantly differ among groups, suggesting that these ratios may have limited utility in distinguishing DKA severity. NLR is considered a marker of systemic inflammation. Studies by Shiny et al. and Alexandra Cristina et al. have reported increased NLR in severe DKA, suggesting its potential role as an inflammatory marker. PLR, PMR, and DKA severity did not significantly correlate, according to the study. On the other hand, some research has connected inflammatory conditions with platelet indices. Nonetheless, comparable results have been documented in pediatric groups in which:Acute metabolic stress may not be accurately reflected in platelet ratios.
In chronic inflammatory illnesses, their role might be more pertinent.
Therefore, it seems that PLR and PMR are not very useful for assessing the severity of acute DKA. Additionally, no significant difference was found in the incidence of cerebral edema, although a strong possible positive correlation was

observed in severe DKA cases between female patients, cerebral edema occurrence, and ICU stay duration. While TLC emerges as a reliable indicator, the roles of ANC, platelet ratios, and monocyte count require further exploration. Future studies should investigate whether these markers can be integrated into DKA severity scoring systems, improving early detection and management strategies.

Conclusion

The current study found that TLC is substantially linked with DKA severity, indicating an underlying inflammatory and stress response. Other hematological indicators showed trends but did not reach statistical significance, indicating that their effect may be supplemental. These findings highlight the need to include metabolic stress when evaluating hematological abnormalities in DKA, rather than solely focusing on infection.

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