

Systemic Infection Predictive Value of Procalcitonin to Lactic Acid Ratio in Diabetes Ketoacidosis Patients

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Introduction: Early detection of bacterial infections associated with adequate antibiotic treatment is key to improving diabetic ketoacidosis (DKA) outcomes. Our study aimed to investigate the different sepsis markers (including procalcitonin to lactic acid ratio, PLR) to diagnose bacterial infection in patients with DKA within one hour after admission.

Methods: A total of 165 patients diagnosed with DKA were enrolled between July 2014 and July 2018 and divided into an infection group (N=62) and a non-infection group (N=103) based on the positive aetiological tests such as blood culture, sputum culture, urine culture, or definite focus of pulmonary, soft tissue, kidney, etc.

Results: Our findings suggest the following: 1) leucocytes (threshold above 10×10^9 /L) and PLR (threshold above 0.438) within one hour after admission can help to identify patients with infection in the context of DKA. 2) A subgroup analysis demonstrated that PLR also has a high diagnostic efficacy for infection in patients with DKA, regardless of the type of diabetes.

Conclusion: This study concludes that leucocyte count (threshold $> 10 \times 10^9$ /L) and PLR (threshold above 0.438) show a diagnostic value to help distinguish DKA patients with infection. By combining these two markers, the reduction of antibiotic misuse may be possible.

Keywords: diabetic ketoacidosis, infections, procalcitonin to lactic acid ratio, diagnostic value

Introduction

Diabetic ketoacidosis (DKA) accounts for 4–9% of all hospital discharge summaries in patients with diabetes.¹ Despite a 50% drop in mortality since 1980 due to standardised protocols, recent studies still report a mortality rate of approximately 2%–5%.² Infections and discontinuation of insulin therapy are the most frequent triggering factors. Bacterial infections, most commonly urinary tract infections, followed by pneumonia, account for approximately 50% of ketoacidosis cases.³ In DKA, bacterial infections are reported to increase both the mortality rate and duration of hospital stay.⁴ Early detection of bacterial infections combined with adequate antibiotic treatment is the key to improving patient outcomes.

Typically, the diagnosis of infection depends primarily on clinical symptoms and culture of secretions. The early sites of infection are usually concealed, and microbiological culture reports take 24–48 hours.⁵ In addition, patients with DKA can have fever, elevated procalcitonin (PCT) and C-reactive protein (CRP) levels, leukocyte count, and percentage of neutrophils (N%), regardless of infection, making predictions of early infection biased.⁶ Many patients with clinical suspicion of infection are overtreated with antibiotics, leading to bacteriological resistance. Therefore, there is a clinical need to find a rapid and effective index for the early diagnosis of infections to guide physicians in the appropriate use of antibiotics.

Serum PCT is a precursor of calcitonin without hormonal activity and has been recommended for the diagnosis and treatment of bacterial infections. Nevertheless, some data suggest that stress conditions such as trauma, surgery, shock, and severe hyperglycaemia can elevate levels of PCT, CRP, and white blood cells even in the absence of infection;

therefore, caution is advised when using these indicators to diagnose infection.⁷ DKA is a critical acute complication that causes severe dehydration, resulting in elevated serum lactic acid (Lac) levels; increased Lac levels often indicate hypovolaemia and disorders of microcirculation.⁸ The potential significance of the PCT to Lac ratio (PLR) may be the relative PCT concentration corrected for hypovolaemia and the stress induced by DKA itself. We conducted a retrospective study in which we attempted to investigate the different sepsis markers (including PLR) to diagnose bacterial infection in patients with DKA within one hour of admission.

Materials and Methods

Participants

A total of 165 patients diagnosed with DKA were enrolled in this study from the Department of Endocrinology of the First Affiliated Hospital (Anhui Provincial Hospital) of the University of Science and Technology of China (USTC) between July 2014 and July 2018. The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of the Research Ethics Committee, The First Affiliated Hospital of USTC. It was agreed that the requirement for informed consent be waived because this study was designed to collect available data from participants' medical records retrospectively. DKA was defined as a glucose concentration >11.1 mmol/L, a pH <7.35 , or $\text{HCO}_3^- <15$ mmol/L, and the presence of ketones (either in the blood or urine).⁹ The diagnosis of infection was based on positive aetiological tests such as blood culture, sputum culture, urine culture, or definite focus of pulmonary, soft tissue, kidney, etc., by computed tomography or ultrasound. Patients were divided into an infection group ($N = 62$) and a non-infection group ($N=103$). The exclusion criteria were as follows: 1) complication with rheumatism, haematological system diseases, and mental illness; 2) stress stimulation such as operation and trauma in the past 3 months; 3) severe damage to the liver (defined as total bilirubin >2 times the upper limit of normal and aspartate transaminase/alanine transaminase (AST/ALT) >3 times the upper limit of normal) and kidney function (defined as estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73 m²); 4) use of antibiotics in the past two weeks; 5) one or more criteria known to increase PCT without any indication of bacterial infection, such as small cell lung cancer, cardiac arrest, heat stroke, medullary thyroid carcinoma, or severe trauma; and 6) inability to communicate using standard methods.

Methods

Data regarding the duration and type of diabetes, along with age, sex, and BMI (body mass index), were obtained from the participants' medical records. All patients were tested for emergency laboratory data, which included routine blood work (leucocytes, N%, CRP), bacteriology (blood, urine, sputum, wound exudate, liver function (ALT, AST, total bilirubin), renal function (serum creatinine, blood urea nitrogen), inflammatory index (PCT), and a coagulation marker (D-dimer) within 1 hour of admission, and blood gas analysis was performed using a pH blood gas analyser (ABL 50; Radiometer, Copenhagen, Denmark). These results provide both a definite DKA diagnosis and data on lactic acid levels. The PLR was defined as serum PCT divided by lactic acid. The eGFR was calculated as follows: $194 \times \text{Cr}^{-1.094} \times \text{Age}^{-0.287}$ ($\times 0.739$ for female patients). Two experienced clinicians reviewed and summarised the data.

Statistical Analysis

We compared the differences in general data, clinical symptoms, and laboratory measures among patients with DKA. Continuous measurements were presented as means (SD) if they were normally distributed or medians [interquartile range (IQR)] if not normally distributed, and categorical variables were described as frequency rates and percentages (%). IBM SPSS Statistics ver. 26.0 (IBM Co., Armonk, NY, USA) was used. Independent tests including the *t*-test, chi-square test, or Mann–Whitney *U*-test, were used to compare the two patient groups. Logistic regression analysis was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for the predictive value of DKA infection, and this was determined after adjusting for potential confounding variables. In order to evaluate the efficacy of each index on infection in this category of patients, a receiver operating curve (ROC) was drawn and the area under the curve (AUC) was calculated. Statistical significance was set at $p < 0.05$.

Results

Demographic and Metabolism Characterisation of Study Participants

Data from 165 patients diagnosed with DKA (52.12% male and 28.48% T1DM) were evaluated. The mean age of the population was 45.37 ± 17.48 years. Participant age ranged from 18 to 87 years, and the duration of diabetes in the patients ranged from 0–40 years. The duration of diabetes, levels of leukocytes, N%, CRP, PCT, Lac, PLR, serum creatinine were significantly higher in the infection group than the non-infection group, and lower eGFR was observed in the infection group than in the non-infection group (both $p < 0.05$). There were no significant differences in sex, age, BMI, blood pressure, proportion of fever, type of diabetes, ALT, AST, TBil, D-D, PH value, or HCO_3^- between the two groups (all $p > 0.05$) (Table 1).

Adjusted Odds Ratios for Infection in Patients with Diabetic Ketoacidosis

The multivariate logistic regression model was adjusted for all variables showing significant associations in the univariate analysis. The estimated OR for patients in the infection group with leukocytes $\geq 10 \times 10^9/\text{L}$ compared to those with normal leukocytes ($< 10 \times 10^9/\text{L}$) was 4.145 (95% CI: 1.153–14.90, $P=0.029$). The odds of infection with DKA increased by 7.732 with each IQR unit increase of PLR (Table 2).

Diagnostic Value of PLR and Leucocytes in DKA Infection

To estimate the predictive value of PLR and leukocytes on DKA infection, the ROC curve of PLR and leukocytes on admission was obtained. For PLR and leukocytes, the AUC was 0.907 (95% CI: 0.8472–0.9659) and 0.809 (95% CI:

Table 1 Demographic and Metabolism Characterisation of Study Participants

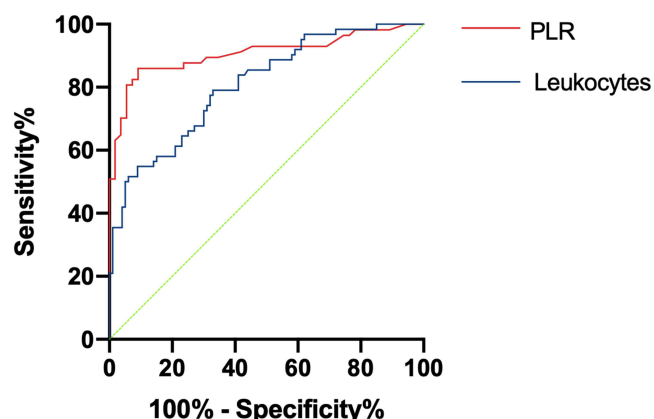
	Infection (n=62)	Non-Infection (n=103)	T/F/ χ^2 value	P-value
General data				
Gender (Male/Female)	33/29	53/50	0.049	0.826
Age (year)	44.69 ± 17.91	46.86 ± 17.37	0.768	0.443
BMI (kg/m^2)	22.55 ± 3.69	22.03 ± 4.19	-0.546	0.587
Duration of diabetes (year)	5(0–10)	2(0–10)	-4.46	<0.001
Type of diabetes (T1DM/T2DM)	19/43	28/75	0.228	0.633
Blood pressure	126.46 ± 12.53	124.92 ± 13.26	-0.737	0.462
Fever $\geq 38.1^\circ\text{C}$ (Number)	21	22	2.920	0.087
Laboratory indicators				
Leucocytes ($\times 10^9/\text{L}$)	14.45 ± 3.83	$7.65(5.62-10.69)$	-6.590	<0.001
Increased (Number)	43	33		
Neutrophils (%)	$83.65(76.58-86.40)$	$74.35(63.73-82.45)$	-5.464	<0.001
Increased (Number)	57	59		
CRP (mg/L)	$47.38(14.00-133.73)$	$17.05(5-42.85)$	-3.954	<0.001
Increased (Number)	47	73		
PCT (ng/mL)	$1.56(0.91-3.99)$	$0.43(0.23-0.78)$	-6.409	<0.001
Increased (Number)	58	94		
Lac (mmol/L)	2.63 ± 1.38	2.20 ± 1.29	-2.020	0.045
PLR	$1.09(0.58-2.24)$	$0.22(0.17-0.32)$	-7.447	<0.001
Cr ($\mu\text{mol}/\text{L}$)	$94(69.00-128.00)$	$70.30(50.95-89.80)$	-3.135	0.002
eGFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$)	92.42 ± 18.56	117.23 ± 21.45	7.560	<0.001
ALT (U/L)	17(9–23)	18(12–26)	0.257	0.781
AST (U/L)	17(8–22)	16(10–21)	-0.146	0.824
TBil ($\mu\text{mol}/\text{L}$)	10.56 ± 3.02	11.25 ± 3.43	1.308	0.193
D-dimer ($\mu\text{g}/\text{L}$)	$0.61(0.27-1.16)$	$0.55(0.19-1.08)$	-0.503	0.624
PH	7.23 ± 0.05	7.24 ± 0.04	1.414	0.159
HCO_3^- (mmo/L)	12.36 ± 3.25	13.42 ± 3.67	1.874	0.063

Note: Data are mean \pm SD, or median (interquartile range).

Table 2 Mutually Adjusted Odds Ratios for Infection in DKA Patients

Factor	Multivariate Model*		
	OR	95% CI	P-value
Leucocytes ($\geq 10 \times 10^9/L$ vs. $< 10 \times 10^9/L$)	4.145	1.153–14.900	0.029
PLR (IQR)	7.732	3.403–17.569	<0.001

Notes: *Variables with $p < 0.05$ in univariate analysis (duration of diabetes, leucocytes, N%, CRP, PCT, Lac, eGFR, and PCT/Lac ratio) were included in the multivariable analysis.

**Figure 1** Receiver operating characteristics curve of PCT/Lac ratio and WBC.

0.7409–0.8760), respectively. A PLR with an optimal cut-off of 0.438 led to a sensitivity and specificity of 0.86 and 0.907, respectively (Figure 1).

Performance of PLR and Leukocytes for the Diagnosis of Infection

The combined diagnostic value of PLR level and leukocytes was further verified. There were 94.12% infection episodes with a PLR and leukocyte count of more than 0.438 and $10 \times 10^9/L$. The presence of one of these two markers was associated with 51.02% of infection episodes, and 4.88% of infection episodes were associated with a PLR and leukocyte count of less than 0.438 and $10 \times 10^9/L$, respectively (Figure 2).

Diagnostic Value of PLR for DKA Infection in Different Types of Diabetes

A subgroup analysis was performed to estimate the predictive value of PLR for DKA infection in different types of diabetes. For T2DM patients, the AUC was 0.9250 (95% CI: 0.8584–0.9916) and for T1DM patients, the AUC was 0.8662 (95% CI: 0.7449–0.9872), indicating that PLR had a good predictive value (Figure 3).

Discussion

The aim of our study was to assess the diagnostic performance of different markers to predict early stages of infection for patients with DKA. Identifying leucocytes (threshold $> 10 \times 10^9/L$) and PLR (threshold > 0.438) within one hour of admission can help detect patients with infection in the context of DKA. A subgroup analysis demonstrated that PLR also has a high diagnostic efficacy for infection in patients with DKA, regardless of the type of diabetes.

DKA is a common complication of diabetes and is associated with significant patient morbidity and mortality.¹⁰ Despite remarkable progress in hypoglycaemic drugs, monitoring methods, and awareness of this disease, all-cause mortality rates due to DKA, as well as the number of patients who require hospitalisation, have continued to increase in the past 10 years.¹¹ Infection is the most common cause of DKA, and it is directly related to the risk of death. An investigation by 15 hospitals in China revealed that the common causes of DKA were infection (40.1%), discontinuation

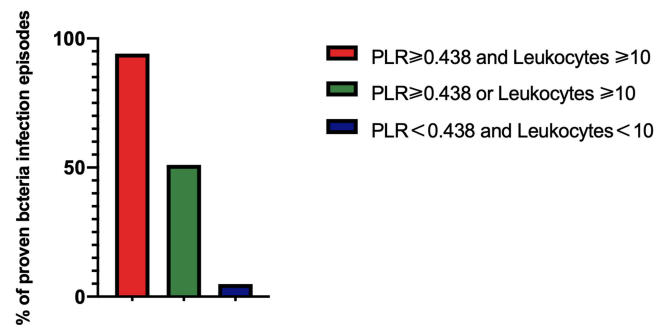


Figure 2 PLR and WBC as markers for the diagnosis of DKA infection.

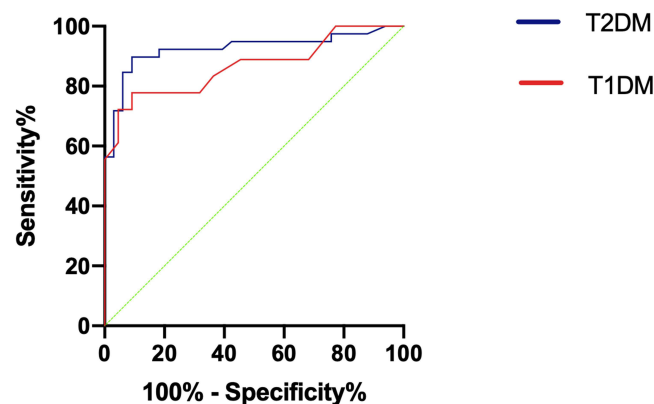


Figure 3 Receiver operating characteristics curve of T1DM and T2DM.

of hypoglycaemic agents (16.8%), and unknown causes (36.9%).¹² Therefore, the early detection of bacterial infections combined with adequate antibiotic treatment is the key to improving patient outcomes. However, DKA can mimic infections; therefore, differentiating between septic and non-septic inflammatory response and/or symptoms may be difficult. Hyperglycemia can stimulate the production and release of cytokines. Plasma CRP, IL-6, IL-1 β and TNF- α were elevated without infection in patients with diabetes.¹³ Previous Studies have shown that CRP is increased in young patients with severe DKA, even in the absence of an infection.¹⁴ What is more, unlike patients without DKA, a high frequency of the DKA patients had significant elevations at the time of admission in virtually all cytokines in the study of William H. Hoffman.¹⁵ The results of this study found that the levels of N%, leukocytes, and CRP in peripheral blood in DKA with infection were higher than Non-infection patients, which is consistent with those studies above.

PCT is one of the major relevant markers for the diagnosis of bacterial infections because it is related to bacterial load and infection severity.¹⁶ However, current studies suggest that PCT may be a secondary inflammatory mediator, which amplifies and aggravates the inflammatory response, but it is not the initiating factor.¹⁷ In non-infected patients, PCT levels may be increased due to various stress conditions, such as trauma, stroke, and severe hyperglycaemia.¹⁸ Anno et al showed that PCT levels were significantly elevated in patients with DKA even in the absence of infection.¹⁹ It has been speculated that metabolic cytokine storms and some signal transductions are associated with such elevations; however, the exact mechanism remains unknown. Combined with the above results, this suggests that the assessment of infection in patients with DKA by PCT alone is of limited value. Our logistic analysis also indicated that PCT was not an independent diagnostic factor of DKA infection. Lac is often used as an indicator of tissue hypoperfusion and hypoxia, which may indicate the severity of the disease, but which it has little to do with the presence or absence of bacterial infection.²⁰ DKA is a critical acute complication that causes severe body fluid loss, resulting in reduced tissue perfusion, thus leading to the formation of Lac.²¹ In the DKA state, the concentration of Lac can be used for assessing body fluid volume and stress intensity. The study by Wei Xu demonstrated that more total leukocytes were

significantly correlated with DKA, and leukocyte counts can add valuable information to indicate the presence of hyperglycaemic crisis and acute infection.²² Combinations of different indicators could be helpful to clinicians in making clinical diagnosis or prediction. The potential significance of the PLR may be the relative PCT concentration corrected for hypovolaemia and the stress induced by DKA itself. This study shows that leukocytes (threshold $>10 \times 10^9$ /L) and PLR (threshold >0.438) may help identify early stages of infection in patients with DKA, and combining these two markers may help with specificity. Although DKA usually occurs in patients with T1DM, patients with T2DM are also susceptible to DKA under stressful conditions such as trauma, surgery, or infections.²³ DKA may be the first manifestation of unrecognised T1DM or T2DM. Magliano confirm that patients with diabetes have an increased mortality from a range of infections, compared with the general population, and that the increased risk appears to be greater for type 1 than type 2 diabetes.²⁴ Considering that patients with type 1 diabetes are often induced by autoimmune response, we conducted a subgroup analysis on whether such abnormalities would affect PLR values under infection conditions. The analysis demonstrated that PLR also has a high diagnostic efficacy for infection in patients with DKA, regardless of the type of diabetes, proving the applicability of this novel factor.

This study has several limitations. First, the proven bacterial infection was defined by a positive bacterial culture, which may have induced bias. Second, considering that this study was a retrospective study with a Chinese population, the sample size was relatively small; thus, the results may not be widely applicable. Finally, unmeasured confounding factors might not have been fully addressed.

Conclusions

In conclusion, our study indicates that leukocyte count (threshold $>10 \times 10^9$ /L) and PLR (threshold >0.438) have diagnostic value in identifying DKA patients with infection. Combining these two markers may help reduce the misuse of antibiotics.

Declarations

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of the Research Ethics Committee, The First Affiliated Hospital of USTC. It was agreed that the requirement for informed consent be waived because this study was designed to collect available data from participants' medical records retrospectively.

Data Sharing Statement

The datasets analyzed during the current study are available from the corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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