

Diagnostic Performance of Procalcitonin/Lactate Ratio (PLR) and Neutrophil-to-Lymphocyte Ratio (NLR) in Predicting Bacterial Infection Across Different Severities of Diabetic Ketoacidosis

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Abstract

Background

Diabetic ketoacidosis is frequently accompanied by systemic inflammatory responses that complicate the early identification of bacterial infection.

Methods

We retrospectively analyzed 158 adult patients admitted with diabetic ketoacidosis and evaluated the diagnostic performance of the PLR (procalcitonin-to-lactate ratio) and the NLR (neutrophil-to-lymphocyte ratio) using ROC analysis.

Results

Patients with infection were significantly older than those without infection (53.97 vs. 44.42 years, $p < 0.001$). Procalcitonin, lactate, PLR, and NLR levels were significantly higher in infected patients ($p < 0.05$ for all). Overall ROC analysis demonstrated significant diagnostic value for both PLR (AUC 0.791, 95% CI 0.722–0.861) and NLR (AUC 0.730, 95% CI 0.651–0.808). When stratified by diabetic ketoacidosis severity, PLR demonstrated higher diagnostic accuracy in patients with severe DKA (AUC 0.875, $p = 0.034$), whereas NLR did not remain statistically significant in this subgroup ($p = 0.572$). In multivariable analyses adjusted for age and renal function, both PLR and NLR remained independently associated with infection, with a stronger association observed for PLR.

Conclusions

The procalcitonin-to-lactate ratio appears to be a reliable biomarker for identifying bacterial infection in diabetic ketoacidosis and may support more rational antibiotic decision-making.

Introduction

Diabetic Ketoacidosis (DKA) is a life-threatening acute complication of uncontrolled diabetes characterized by hyperglycemia, ketosis, and severe metabolic acidosis, requiring emergency medical intervention.[1, 2] Infections are the most common factor triggering DKA, playing a role as a trigger in approximately half of the cases.[1, 3, 4] Early diagnosis of bacterial infections and timely initiation of appropriate antibiotic therapy are of critical importance to reduce morbidity and mortality rates in DKA patients.[5, 6] However, DKA itself mimics infection by causing symptoms of Systemic Inflammatory Response Syndrome (SIRS) (such as leukocytosis, tachycardia, and tachypnea), which makes it difficult to distinguish infection-induced DKA from non-infection-induced DKA.[3, 7, 8] This diagnostic uncertainty leads to unnecessary empirical antibiotic use and, in turn, to an increase in antimicrobial resistance.[6, 9]

Procalcitonin (PCT) is a valuable biomarker for diagnosing bacterial infections and generally does not rise without infection.[6, 10] It can increase during DKA even in the absence of infection due to increased cytokine production (IL-6 and TNF- α) and systemic inflammatory stress.[7, 11, 12] This situation limits the specificity of PCT in diagnosing infection on the basis of DKA.[8, 13] Similarly, lactate levels rise in DKA due to hypoperfusion and disease severity[3, 14], but show only a weak correlation with bacterial infection alone.[5, 15] To overcome these challenges and normalize the metabolic stress caused by DKA, the diagnostic value of new indicators such as the procalcitonin/lactate ratio (PLR) is being investigated. [5] PLR is considered a relative measure of PCT concentration corrected for the hypovolemia and stress caused by DKA.[5] The primary aim of this retrospective study is to evaluate the diagnostic performance of PLR (procalcitonin/lactate ratio) and neutrophil-to-lymphocyte ratio (NLR)—which are inexpensive and accessible inflammatory ratios—in predicting bacterial infection in patients admitted with DKA. Specifically, we aim to determine optimal diagnostic threshold values for reliably diagnosing infection in the complex inflammatory environment of DKA by examining the discriminatory power of these ratios across subgroups stratified by DKA severity. These findings may guide clinical decision-making processes to optimize antibiotic management in DKA.

Patients and Methods

This retrospective study included 158 adult patients diagnosed with diabetic ketoacidosis (DKA) who were admitted to the Emergency Department and/or Endocrinology Department of a tertiary care hospital between 2017 and 2024. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee. Due to the retrospective nature of the study and the use of anonymized medical records, the requirement for informed consent was waived.

DKA was defined by the presence of hyperglycemia, metabolic acidosis, and ketonemia or ketonuria, in accordance with established clinical guidelines.[16] Infection status at admission was determined based on clinical evaluation, microbiological culture results (including blood, urine, sputum, or other relevant cultures when available), and/or radiological findings consistent with an infectious focus. Based on these criteria, patients were classified into an infection group and a non-infection group.

The severity of DKA was classified as mild, moderate, or severe according to arterial blood pH and serum bicarbonate (HCO_3^-) levels at presentation. Mild DKA was defined as a pH of 7.25–7.30 and serum bicarbonate of 15–18 mmol/L; moderate DKA as a pH of 7.00–7.24 and serum bicarbonate of 10–14.9 mmol/L; and severe DKA as a pH < 7.00 and serum bicarbonate < 10 mmol/L, with or without altered mental status. Patients were categorized using the worst laboratory values recorded at admission, prior to initiation of treatment.[1]

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation and/or median (min-max), and categorical data as number and percentage. Normality analyses of continuous variables were performed using the Kolmogorov-Smirnov Test. In cases where continuous data followed a normal distribution, Student's T-Test was used for analyses between independent groups; otherwise, the Mann-Whitney U Test was employed (the Kruskal-Wallis Test was used for analyses involving three groups).[17] The value of PLR and NLR ratios as diagnostic tools in predicting infection was examined using Receiver Operating Characteristics (ROC) analysis. In the presence of significant threshold values, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Statistical significance was accepted at a Type 1 error level of $p < 0.05$. Analyses were performed with IBM SPSS version 26.0.[18] In addition, to evaluate whether baseline differences in age and renal function could confound biomarker–infection associations, multivariable binary logistic regression analyses were performed. Two separate models were constructed due to collinearity and interpretability considerations: Model 1 included PLR, age, and estimated glomerular filtration rate (GFR), and Model 2 included NLR, age, and GFR. Results were reported as odds ratios (OR) with corresponding p-values.

Results

Demographic and Clinical Characteristics

A total of 158 patients with DKA were included. Patients with concomitant infection were significantly older than those without infection (53.97 ± 16.02 vs. 44.42 ± 16.63 years, $p < 0.001$). There was no statistically significant difference between the two groups in sex distribution or DKA severity at presentation ($p > 0.05$ for both)(Table 1).

Laboratory Findings According to Infection Status

Several laboratory parameters were significantly elevated in patients with infection compared with those without. Procalcitonin, creatinine, lactate, leukocyte count, neutrophil count, C-reactive protein (CRP), procalcitonin to lactate ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) were all higher in the infected group ($p < 0.001$ for most parameters; creatinine $p = 0.002$; lactate $p = 0.005$)(Table 2).

Table 2

Comparison of patients' laboratory findings according to the presence of infection. GFR, glomerular filtration rate; CRP, C-reactive protein; PLR, procalcitonin/lactate ratio; NLR, neutrophil-to-lymphocyte ratio

	Non- Infection group [median (min-max)] (n = 85)	Infection group [median (min-max)] (n = 73)	p
Procalcitonin (ng/mL)	0.11 (0.02–4.96)	0.86 (0.05–100)	< 0.001
HgbA1c (%)	10.3 (6.0-17.3)	9.8 (5,9-18.8)	0.373
Creatinine (mg/dL)	0.82 (0.20–2.71)	1.02 (0.45–2.88)	0.002
GFR (mL/min)	90 (22–90)	69 (17–90)	0.001
pH	7.21 (6.90–7.29)	7.20 (6.64–7.32)	0.526
Bicarbonate (mmol/L)	12 (3-23.5)	10.8 (3.4–35)	0.204
Lactate (mmol/L)	2.3 (0.9–18)	3 (1.1–20)	0.005
Leucocytes (/μL)	11640 (3670–26450)	16060 (4620–54000)	< 0.001
Neutrophils (/μL)	9220 (1670–24640)	14120 (3060–39630)	< 0.001
Lymphocyte (/μL)	1400 (370–5960)	1070 (130–3790)	0.014
Glucose (mg/dL)	453 (251–891)	465 (251–972)	0.521
CRP (mg/L)	7 (0.2–308)	94 (0.5–447)	< 0.001
PLR	0.06 (0.01–1.50)	0.25 (0.02–28.20)	< 0.001
NLR	5.75 (1.26–66.59)	12.68 (2.12–39.24)	< 0.001

Median values in the infected versus non-infected groups were as follows: procalcitonin (0.86 vs. 0.11), CRP (94 vs. 7), leukocytes (16.060 vs. 11.640), neutrophils (14.120 vs. 9.220), PLR (0.25 vs. 0.06), and NLR (12.68 vs. 5.75). In contrast, estimated glomerular filtration rate (GFR) and lymphocyte counts were significantly lower in patients with infection ($p = 0.001$ and $p = 0.014$, respectively) (Table 2).

Diagnostic Performance of PLR and NLR for Infection

Receiver operating characteristic (ROC) curve analysis demonstrated that both PLR and NLR were significant predictors of infection in patients with DKA ($p < 0.001$ for both) (Fig. 1). A PLR cut-off value of ≥ 0.13 yielded a sensitivity of 72.6% and specificity of 74.7%, with a positive predictive value (PPV) of 71.6% and a negative predictive value (NPV) of 75.6%. The area under the curve (AUC) for PLR was 0.791 (95% CI 0.722–0.860). For NLR, a cut-off value of ≥ 6.41 yielded a sensitivity of 82.2%, specificity of 56.5%, PPV of 61.9%, and NPV of 78.7%, with an AUC of 0.730 (95% CI 0.652–0.808) (Table 3).

Table 3

Cut-off values and ROC analysis results of PLR and NLR in predicting infection. PLR, procalcitonin/lactate ratio; NLR, neutrophil-to-lymphocyte ratio; AUC, Area under the curve; PPV, Positive predictive value; NPV, Negative predictive value; CI, Confidence interval.

Diagnostic Test	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	95% CI	p
PLR	≥ 0.13	72.6	74.7	71.6	75.6	0.791	0.722–0.861	< 0.001
NLR	≥ 6.41	82.2	56.5	61.9	78.7	0.730	0.651–0.808	< 0.001

Multivariable Analysis Adjusted for Age and Renal Function

To assess whether the associations of PLR and NLR with infection were independent of baseline differences in age and renal function, multivariable logistic regression analyses were conducted. In Model 1 (PLR, age, and GFR), PLR remained independently associated with infection (OR = 5.58, $p = 0.002$), and age also remained significant (OR = 1.028, $p = 0.017$), whereas GFR was not independently associated with infection ($p = 0.137$). In Model 2 (NLR, age, and GFR), NLR remained independently associated with infection (OR = 1.044, $p = 0.033$); both GFR (OR = 0.979, $p = 0.019$) and age (OR = 1.022, $p = 0.047$) were also independently associated with infection. (Table 4)

Table 4

Multivariable logistic regression analyses for predictors of infection

Variable	Model	OR (95% CI)	p value
Age	PLR model	1.03 (1.01–1.05)	0.017
GFR	PLR model	0.99 (0.97–1.00)	0.137
PLR	PLR model	5.58 (1.85–16.87)	0.002
Age	NLR model	1.02 (1.00–1.04)	0.047
GFR	NLR model	0.98 (0.96–1.00)	0.019
NLR	NLR model	1.04 (1.00–1.09)	0.033
Two separate multivariable logistic regression models were constructed to evaluate independent predictors of infection. Model 1 included PLR, age, and GFR; Model 2 included NLR, age, and GFR. Odds ratios (OR) with 95% confidence intervals (CI) are presented.			

Laboratory Changes According to DKA Severity in Infected Patients

Among patients with infection, several inflammatory and metabolic parameters increased progressively with increasing DKA severity. Procalcitonin, leukocyte count, neutrophil count, glucose, PLR, and NLR

values rose significantly from mild to severe DKA ($p = 0.003$, $p = 0.011$, $p = 0.005$, $p = 0.017$, $p = 0.014$, and $p = 0.031$, respectively)(Supplementary Table S1). Median procalcitonin levels increased from 0.32 in mild DKA to 4.21 in severe DKA. Similarly, PLR increased from 0.16 to 0.76, and NLR from 9.00 to 16.77 across severity categories. As expected, arterial pH and serum bicarbonate levels decreased significantly with increasing severity ($p < 0.001$). Although lactate levels demonstrated an upward trend (2.7 to 3.7 mmol/L), this did not reach statistical significance ($p = 0.138$).

ROC Analysis Stratified by DKA Severity

When ROC analyses were stratified according to DKA severity, PLR consistently demonstrated diagnostic value across all severity categories. In patients with mild DKA, PLR showed moderate diagnostic accuracy (AUC 0.768, 95% CI 0.631–0.905, $p = 0.002$), while NLR demonstrated similar discrimination (AUC 0.771, 95% CI 0.635–0.907, $p = 0.001$). In moderate DKA, PLR demonstrated good diagnostic performance (AUC 0.793, 95% CI 0.705–0.881, $p < 0.001$), whereas NLR showed moderate accuracy (AUC 0.720, 95% CI 0.618–0.822, $p < 0.001$). Similarly, NLR (cut-off ≥ 6.61) demonstrated moderate accuracy in this group (AUC 0.720, 95% CI 0.618–0.822, $p < 0.001$). Among patients with severe DKA, PLR showed the highest diagnostic accuracy (AUC 0.875, 95% CI 0.671–1.000, $p = 0.034$), while NLR did not demonstrate significant discrimination (AUC 0.600, 95% CI 0.206–0.994, $p = 0.572$). These findings are summarized in Table 5.

Table 5

Cut-off values and ROC analysis results of PLR and NLR for predicting infection in patients with mild, moderate, and severe diabetic ketoacidosis (DKA) PLR, procalcitonin/lactate ratio; NLR, neutrophil-to-lymphocyte ratio; AUC, Area under the curve; PPV, Positive predictive value; NPV, Negative predictive value; CI, Confidence interval.

Diagnostic test ROC Curve								
	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	95% CI	p
PLR (mild DKA)	≥ 0.10	68.2	72.0	68.2	72.0	0.768	0.631–0.905	0.002
NLR (mild DKA)	≥ 8.20	54.5	92.0	85.7	69.7	0.771	0.637–0.905	0.001
PLR (moderate DKA)	≥ 0.13	78.0	70.4	66.7	80.9	0.793	0.706–0.881	< 0.001
NLR (moderate DKA)	≥ 6.61	87.8	50.0	56.3	84.8	0.720	0.618–0.821	< 0.001
PLR (severe DKA)	≥ 0.19	90.0	75.0	90.0	75.0	0.875	0.670–1.000	0.034
NLR (severe DKA)	-	-	-	-	-	0.600	(0.206–0.994)	0.572

Discussion

This retrospective observational study examined the diagnostic performance of combined inflammatory biomarkers, such as the procalcitonin/lactate Ratio (PLR) and NLR, in the early detection of bacterial infections in DKA patients by stratifying them according to DKA severity. It is known that systemic inflammation and metabolic stress caused by DKA complicate the ability to distinguish infection.[3, 7, 8] Our findings indicate that PLR possesses strong diagnostic potential on this complex background of DKA, overcoming the limitations of using PCT and lactate alone.

The significantly higher mean age in the infected group is consistent with general clinical observations that infections are one of the most common factors triggering DKA, especially in the elderly population. [1, 3] In patients diagnosed with infection, procalcitonin (PCT) values were found to be statistically significantly higher. However, because DKA itself causes a state of severe inflammation through increased cytokine production (such as TNF- α and IL-6), PCT levels can rise even in the absence of infection.[3, 7, 12] In addition to this limitation, our findings show that as DKA severity increases in infected patients, median PCT values also exhibit a significant rise ($p = 0.003$). This confirms that PCT reflects not only the presence of infection but also the severity of metabolic acidosis and systemic stress. Therefore, the literature advocates for caution regarding the standalone use of PCT in DKA patients.[8, 13]

Our study found that lactate levels and creatinine levels were significantly higher in DKA patients with infection, whereas estimated GFR levels were significantly lower. Serum lactate levels in DKA increase due to tissue hypoperfusion, hypovolemia, and disease severity.[5, 8, 14, 15] The lactate elevation observed in the infection group indicates that systemic stress and hypoperfusion are more pronounced in these patients. However, in the examination based on DKA severity, although an increasing trend in lactate levels from mild to severe was observed, this increase was not found to be statistically significant ($p = 0.138$). Additionally, lactate was found not to be effective in distinguishing the difference between sepsis, severe sepsis, and septic shock.[15] This indicates that lactate alone has limited value in distinguishing the presence of bacterial infection.[5]

High creatinine and low GFR findings are consistent with acute kidney injury (AKI) developing as a result of severe dehydration and hypovolemia caused by DKA. Approximately 50% of patients hospitalized due to hyperglycemic crises experience AKI.[1] This situation indicates that kidney function is a critical factor in the interpretation of markers that interact with renal clearance, such as PCT and lactate.[19]

Diabetic ketoacidosis is characterized by profound metabolic derangements accompanied by systemic inflammatory activation, even in the absence of overt infection.[3] Hyperglycemia, insulin deficiency, and ketone body accumulation induce cytokine release, endothelial dysfunction, and stress-related inflammatory responses, which may lead to elevations in infection-related biomarkers independent of bacterial processes.[20] In this context, biomarkers such as procalcitonin and lactate may reflect the severity of metabolic stress and tissue hypoperfusion rather than infection per se, limiting their standalone diagnostic utility in DKA patients.[20, 21]

Ratio-based biomarkers have been proposed as a strategy to mitigate the confounding effects of systemic stress by normalizing inflammation-related parameters to metabolic or perfusion-related markers.[22] The procalcitonin-to-lactate ratio (PLR) provides a relative measure that may better distinguish infection-related procalcitonin elevation from non-infectious increases driven by hypovolemia and metabolic acidosis.[21, 22] Our findings support this concept, demonstrating that PLR maintains superior diagnostic performance, particularly in severe DKA, where conventional markers are most affected by metabolic burden. This suggests that PLR may serve as a more robust indicator of infection in the setting of advanced metabolic stress.

The main hypothesis of our study was to investigate the diagnostic value of the ratio of these markers (PLR) to overcome the limitations of PCT and lactate under the metabolic load of DKA. The potential importance of PLR is that it provides a relative measure of PCT concentration corrected for the hypovolemia and stress conditions caused by DKA.[3, 5] In the general ROC analysis, PLR (AUC 0.791) and NLR (AUC 0.730) were found to be significant in predicting infection.

Stratified analysis showed that as DKA severity increased, there were also significant increases in NLR and PLR. However, this increasing trend affected the diagnostic performance differently:

- **PLR Superiority:** In the severe DKA group, the PLR ratio (cut-off ≥ 0.19) exhibited a strong diagnostic performance with the highest AUC value (0.875). This result demonstrates that PLR successfully normalizes the non-infection-related elevation trend of PCT [7] and the non-infection-related load of lactate [15] and is superior in distinguishing infection even in a severe metabolic acidosis environment. This is compatible with literature reporting high sensitivity and specificity for PLR.[5]
- **NLR Limitation:** In contrast, the severe DKA group's infection prediction NLR ratio was not found to be statistically significant (AUC 0.600, $p = 0.572$). This suggests that DKA-induced neutrophilia and lymphopenia mask the NLR signal, causing this ratio to lose its reliability under severe metabolic stress. [3]

Importantly, the independent association of these biomarkers was further supported by multivariable analyses adjusted for age and renal function. PLR remained a strong independent predictor of infection even after adjustment, suggesting that its diagnostic value is not merely driven by older age or reduced renal function. Although NLR also remained independently associated with infection, the magnitude of association was considerably smaller than that observed for PLR, which may indicate that NLR reflects more general systemic inflammatory activation, whereas PLR may better capture infection-related inflammatory changes in the context of DKA.

Study Limitations

Although the results of this study offer important clinical implications, there are several limitations. First, the retrospective design of the study brings a risk of missing data or variability. Specifically, the lack of sequential (serial) biomarker measurements over time limited the dynamic evaluation of the infection's course and the response to treatment. However, in sepsis and infection management, dynamic monitoring can be more valuable than a single measurement.

Another factor limiting the generalizability of these findings to broader and more heterogeneous populations is that the study was conducted at a single center. Additionally, since the diagnosis of infection relied on bacterial culture results and clinician assessment, there is a risk of diagnostic bias because cultures can be false negatives or may not have been taken at all in some patients. Furthermore, C-reactive protein (CRP), which is one of the commonly used inflammatory markers, could not be included in the analyses due to missing data; this situation narrowed the scope of biomarker comparisons.

Regarding subgroup analyses, the limited number of patients diagnosed with severe diabetic ketoacidosis (DKA) restricted further comparisons to evaluate possible changes in the diagnostic specificity of procalcitonin in this group. Similarly, although sub-analyses were planned according to GFR levels—as procalcitonin is known to be affected by renal functions—the small number of patients in the clinically most problematic $\text{GFR} < 30 \text{ mL/min}$ subgroup limited the reliability of statistical inferences in this group. Therefore, these subgroup analyses were kept at an exploratory level.

Finally, the inability to monitor the kinetic changes of biomarkers such as PCT and PLR within the first 24–48 hours of treatment prevented evaluations regarding the resolution of infection or the early termination of antibiotic therapy.

Conclusion

Our study demonstrates that PLR and NLR are valuable diagnostic tools in DKA patients, but as DKA severity increases, PLR exhibits a more reliable and distinctive performance compared to NLR. The high AUC value of PLR suggests it should be integrated into clinical decision-making as a practical and accessible biomarker capable of correcting for DKA's metabolic stress. These findings provide valuable evidence to improve early infection detection and optimize antibiotic use in the management of DKA.[5, 6] Prospective validation studies are needed to facilitate the wider adoption of these ratios in clinical practice. These findings were consistent in multivariable analyses adjusted for age and renal function, with PLR showing a stronger independent association with infection than NLR.

Abbreviations

DKA, diabetic ketoacidosis; AUC, area under the curve; PLR, procalcitonin/lactate ratio; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; PCT, procalcitonin.

Declarations

Ethics Approval:

This study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee. Due to the retrospective design and use of anonymized data, informed consent was waived.

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The authors declare that no specific funding was received for this study.

Conflict of Interest:

The authors declare that they have no conflicts of interest.

Author Contributions

B.Ö.G and O.G designed the study, performed the data analysis, and wrote the article. O.G and A.T.K. carried out the data collection process and interpreted the analysis. B.Ö.G, G.Y., M.N.K and A.A participated in the article revision. All authors read and approved the final article.

Declaration of Generative AI and AI-Assisted Technologies in the Manuscript Preparation Process

The authors declare that generative artificial intelligence–assisted technologies were used solely for language editing and improvement of grammar and readability during the preparation of this manuscript.

No artificial intelligence tools were used for data analysis, interpretation of results, or generation of scientific content. The authors take full responsibility for the content of the manuscript.

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Table 1

Table 1 is available in the Supplementary Files section.

Figures

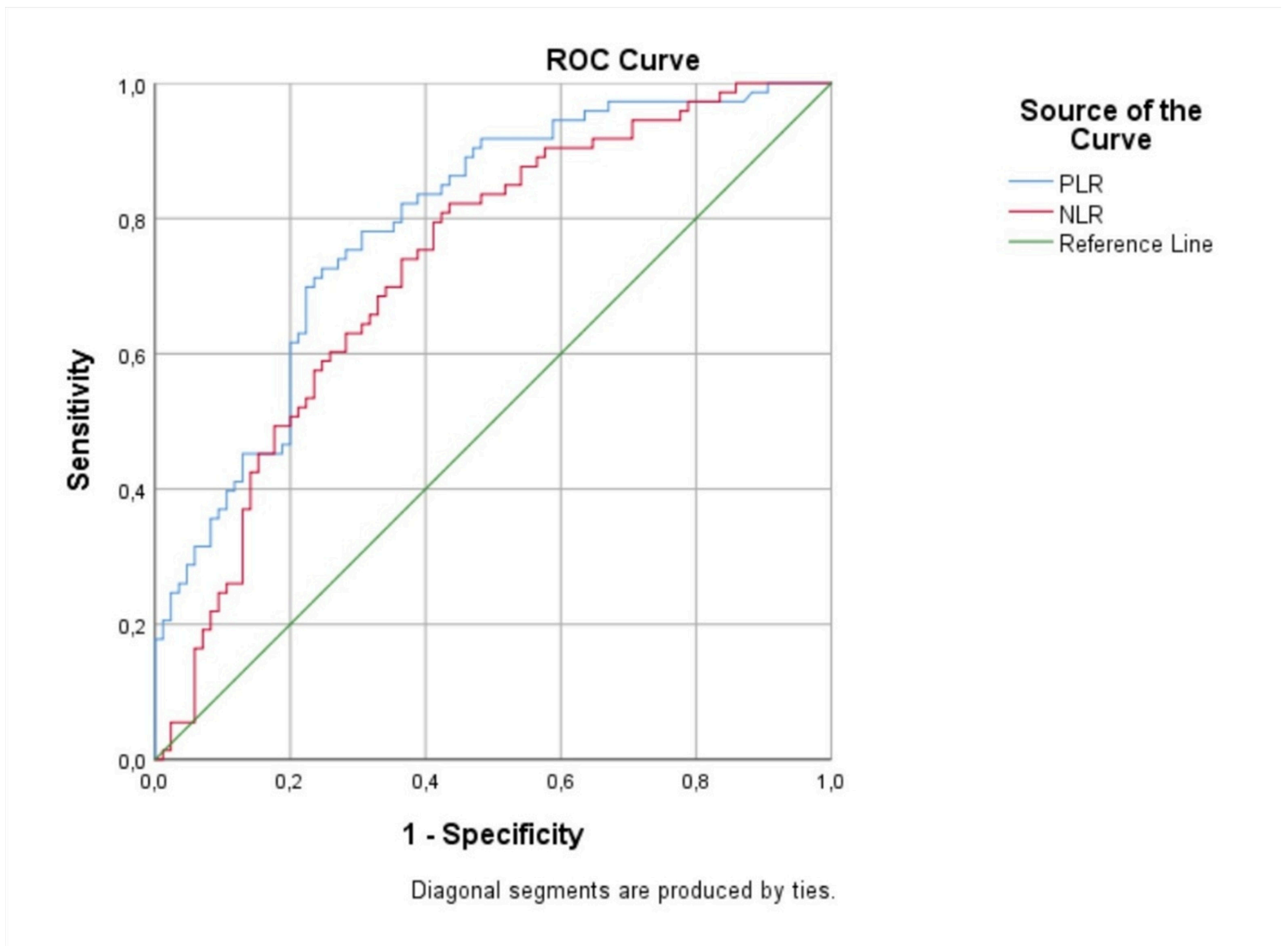


Figure 1

Receiver operating characteristic curves of procalcitonin/lactate ratio and neutrophil-to-lymphocyte ratio in distinguishing infection status in diabetic ketoacidosis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [table1.docx](#)
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