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THE STUDY OF PROCALCITONIN AS EARLY BIOMARKER OF SEPSIS IN DIABETIC KETOACIDOSIS AT A TERTIARY CENTRE IN JAIPUR"

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ABSTRACT

Introduction-Diabetic ketoacidosis (DKA) is one of the most serious complications of diabetes mellitus (DM). Precise early prediction of infection and its severity in diabetic patients serves an important role in improving infection control and prognosis. Procalcitonin (PCT), a marker of the inflammatory response during infections, can be elevated by diabetic ketoacidosis (DKA). Early detection and treatment of infections are key elements to improved patient outcomes, and as such, empiric antibiotics are frequently prescribed to patients who present with DKA.

Aims and objectives- Study of procalcitonin as a early marker of sepsis in patients of DKA admitted in SMS Hospital.

Methodology-Hospital based cross sectional study in department of Medicine SMS MEDICAL COLLEGE Jaipur on 60 cases of DKA-20 cases positive bacterial culture (Proven Bacterial Infection group -PBI) and 40 cases of negative blood culture (without Proven Bacterial Infection group – without PBI).

Results- The two groups (PBI and without PBI) were comparable on parameter of TLC, fever intensity (measured by temperature) at time of admission, however TLC and Temperature at 2nd day were significantly higher in PBI group as compared to without PBI group at 2nd day of admission. However the two groups have significant differences on quantitative measurement of serum PCT at time of admission as well at at 2nd day of admission.(PBI group have significantly higher PCT than without PBI group.

Conclusion- PCT can serve as early marker of sepsis in DKA and by use of PCT as a sepsis marker, reduction of antibiotic misuse may be possible. Prospective studies will be needed to confirm the diagnostic thresholds of PCT marker.

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Keywords- Procalcitonin (PCT), diabetic ketoacidosis (DKA).

THE STUDY OF PROCALCITONIN AS EARLY BIOMARKER OF SEPSIS IN DIABETIC KETOACIDOSIS AT A TERTIARY CENTRE IN JAIPUR

Diabetic ketoacidosis (DKA) is a life-threatening condition accounting for 5–9% of all hospital admissions among diabetic patients.[1] The common precipitating factors of DKA include new-onset diabetes, discontinuation or non-compliance with medications, and a high level of medical, surgical, and emotional stress which includes (but not limited to) trauma, heart attacks, strokes, pancreatitis, and infections. The mainstay management of DKA includes aggressive fluid resuscitation, replacing insulin stores, and correction of electrolyte abnormalities and identifying and treating the precipitating cause of DKA .[2] Early detection and treatment of infections are vital elements for good outcomes. Therefore empirical antibiotics are routinely prescribed to patients presented with DKA. Patient presentation characteristics are quite similar in DKA as well as infections, thus resulting in over-usage of antibiotics culminating in higher treatment costs ,irrational medication side effects, and the risk of development of antibiotic resistant bacterial stains.

Nowadays with the advent and usage of clinical biomarkers like C-reactive protein (CRP) and procalcitonin (PCT)] have greatly helped physicians in differentiating patient presentations related to infections as compared to other conditions.[3] This has helped in appropriate antibiotic usage and decreasing hospital costs.[4]

PCT is a 116-amino acid protein precursor to calcitonin secreted by neuroendocrine cells, including thyroid C cells. PCT is one of the major biomarkers for the diagnosis of bacterial infections. In healthy patients, it is produced in very insignificant amounts; but in the bacterial infection and severe systemic inflammation , measurable quantities of PCT can be produced. The proper measurement of PCT can be used for rational use of antibiotic and avoid injudicious use of antibiotic usage.[1,5,6]

There is dearth of literature for evaluation of PCT levels in patients presenting with DKA as a biomarker of sepsis . For filling this lacunae, we conducted this study to assess PCT as an effective biomarker in identifying infection in patients with DKA.

Aim-

Study of procalcitonin as a marker of sepsis in patients of DKA admitted in SMS Hospital.

Methodology

The study was conducted in the department of medicine S.M.S. Hospital, Jaipur on 60 cases of DKA, out of which, 20 cases had positive bacterial culture (Proven Bacterial Infection group -PBI) and 40 cases

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had negative blood culture (without Proven Bacterial Infection group – without PBI) from January 2023 to March 2023 at SMS Hospital Jaipur.

Definition of "Proven bacterial infection"-

Patients with any bacteriological documentation on any bacterial sample (urine culture, sputum analysis, blood culture or other specific sample cultures) were classified as having a "proven bacterial infection" (PBI).

Inclusion Criteria: -

1. A patient of DM with acidosis in ABG (PH≤7.25) with blood glucose level >300 mg/dl and urinary ketones positive by urine strip test between age group 18-65 years.

2. Ready to participate and giving consent for this study.

Exclusion Criteria: -

1. Patients with previous history of chronic kidney disease.

2. Patients with criteria known to increase PCT without any indication of bacterial infection (medullary thyroid carcinoma, small cell lung cancer, cardiac arrest, pancreatitis, malaria and severe trauma.

3. Patient not willing to participate.

Results

Table-1 Comparison of markers of inflammation [Total leucocyte count(TLC) , Temperature, PCT] in PBI and without PBI Group

Parameters	PBI			Without PBI			P value (Mann Whitney U test)
	Q1	Median	Q3	Q1	Median	Q3	
TLC AT ADMISSION	15.8	16.9	19.2	15.6	16.9	18.2	.729
TEMP AT ADMISSION	35.7	36.6	37.4	35.7	36.5	37.1	.752
PCT AT ADMISSION	2.95	4.31	5.43	.41	.48	.54	<.001
TLC at 2 DAYS	9.34	10.85	14.10	7.40	8.30	8.90	<.001
TEMP at 2 DAYS	38.1	38.6	39.4	37.1	37.7	38.0	<.001
PCT at 2 DAYS	5.12	6.32	7.21	.21	.31	.41	<.001

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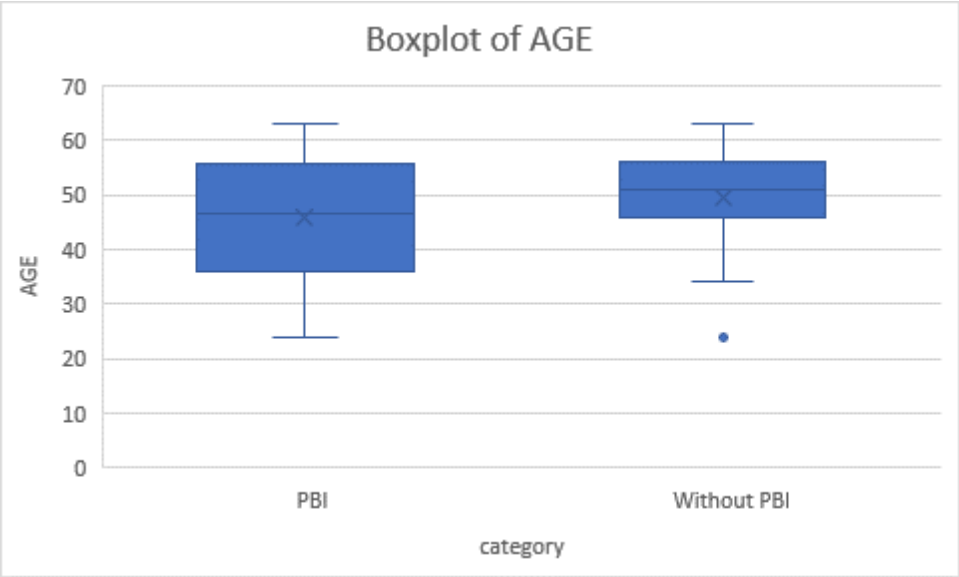

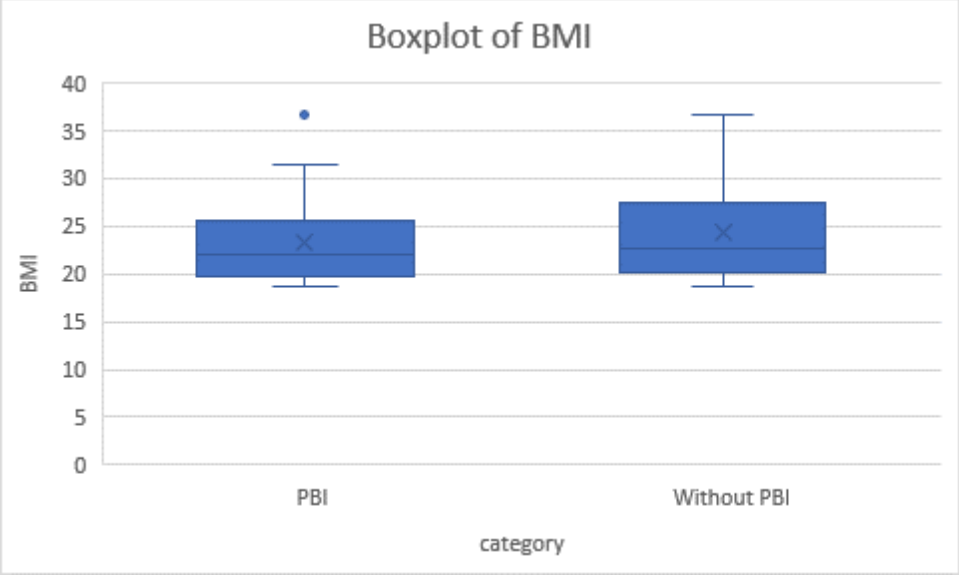

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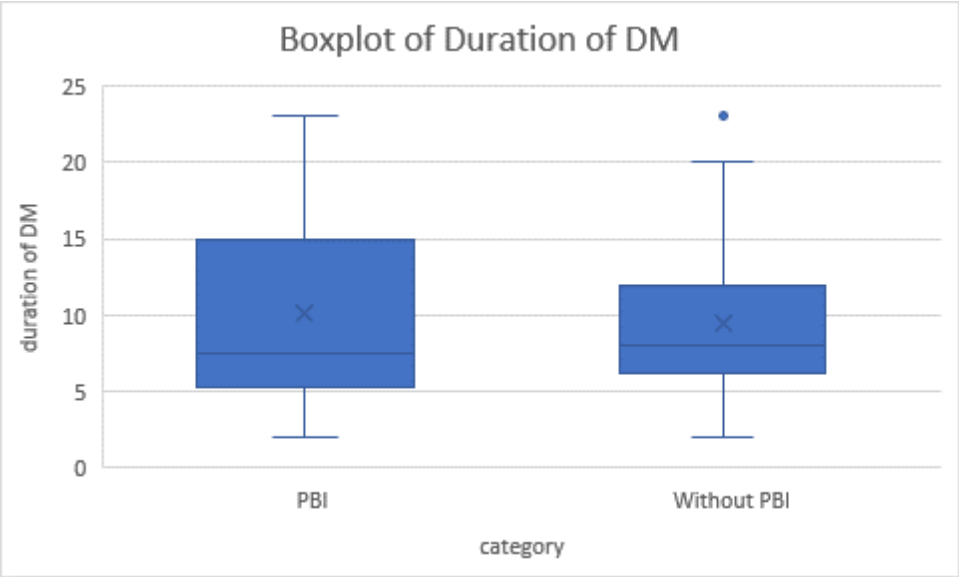

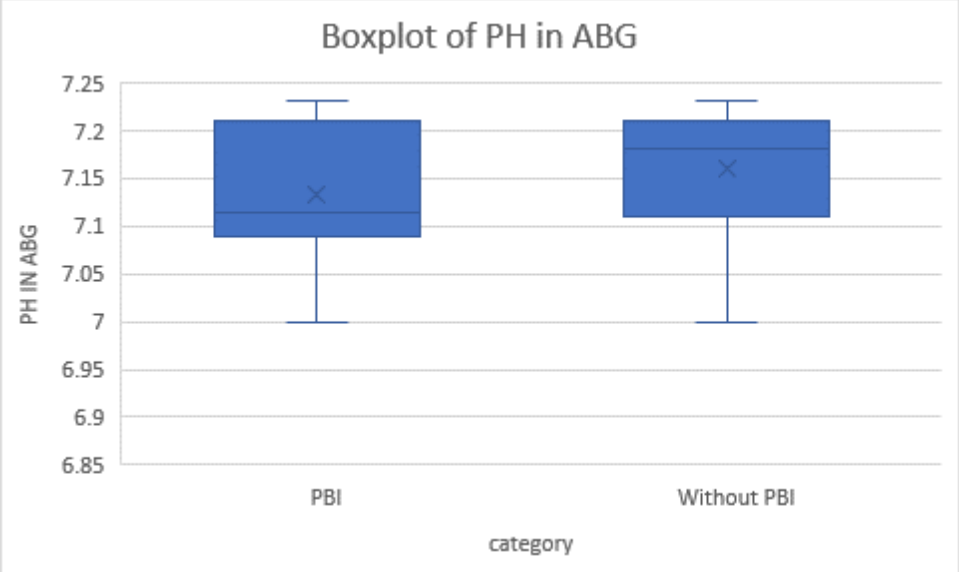

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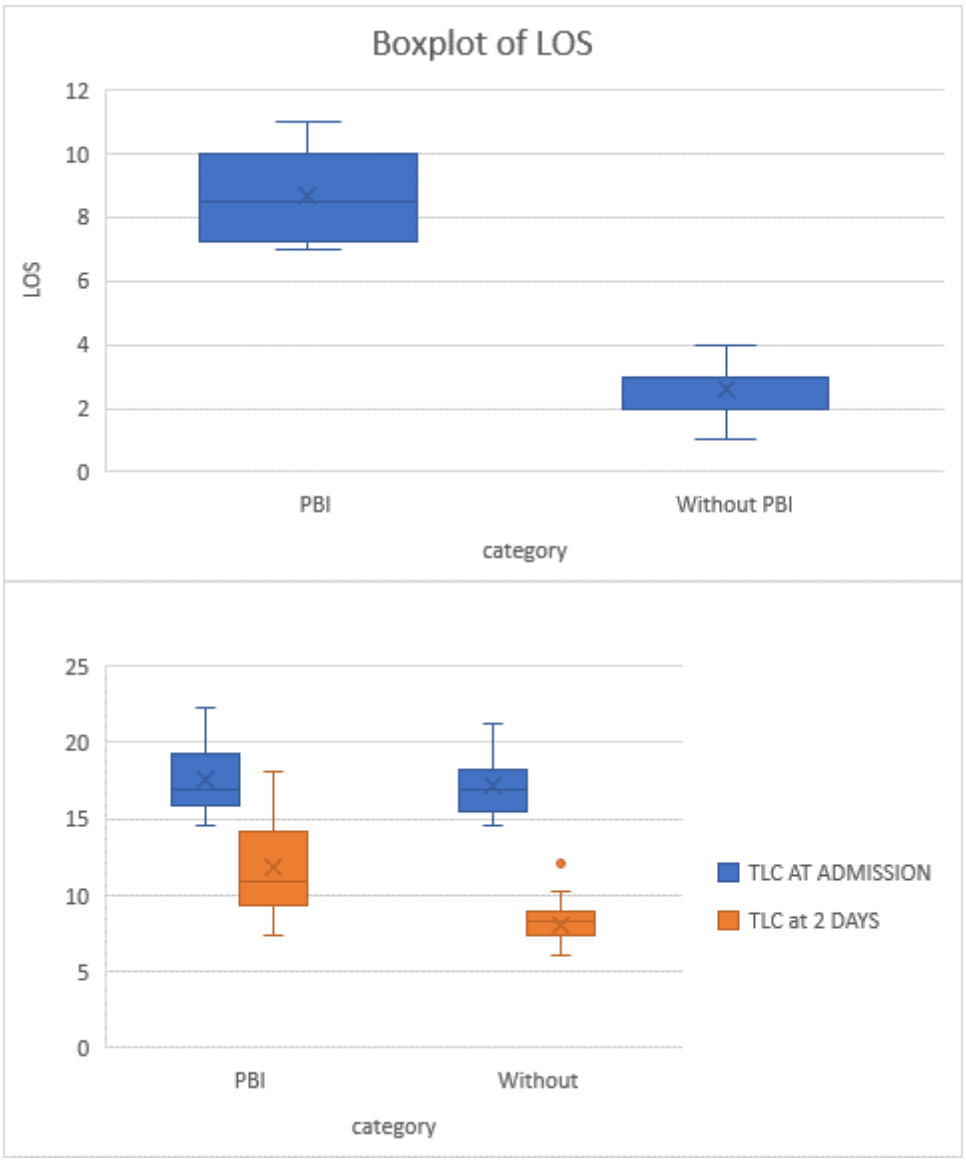

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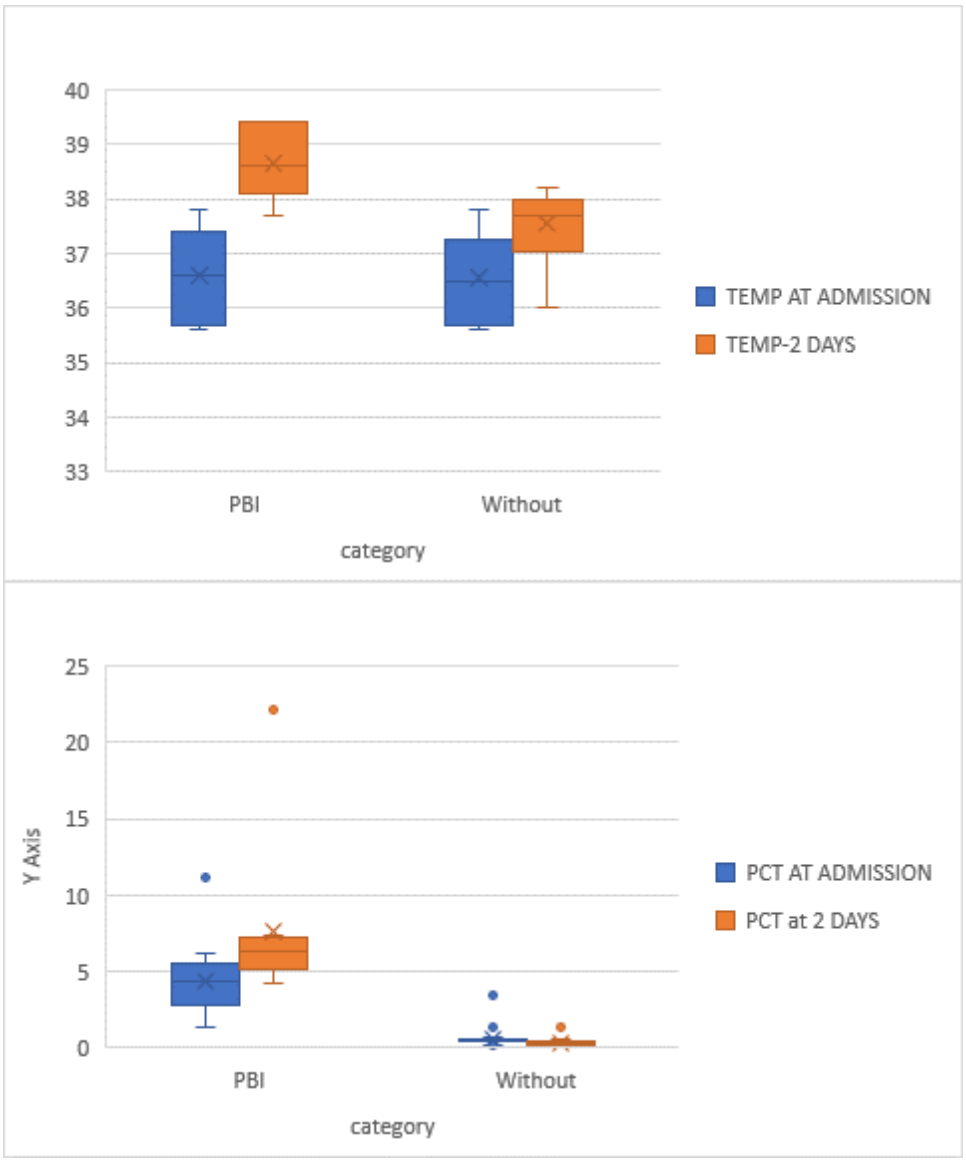

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ROC Analysis for PBI

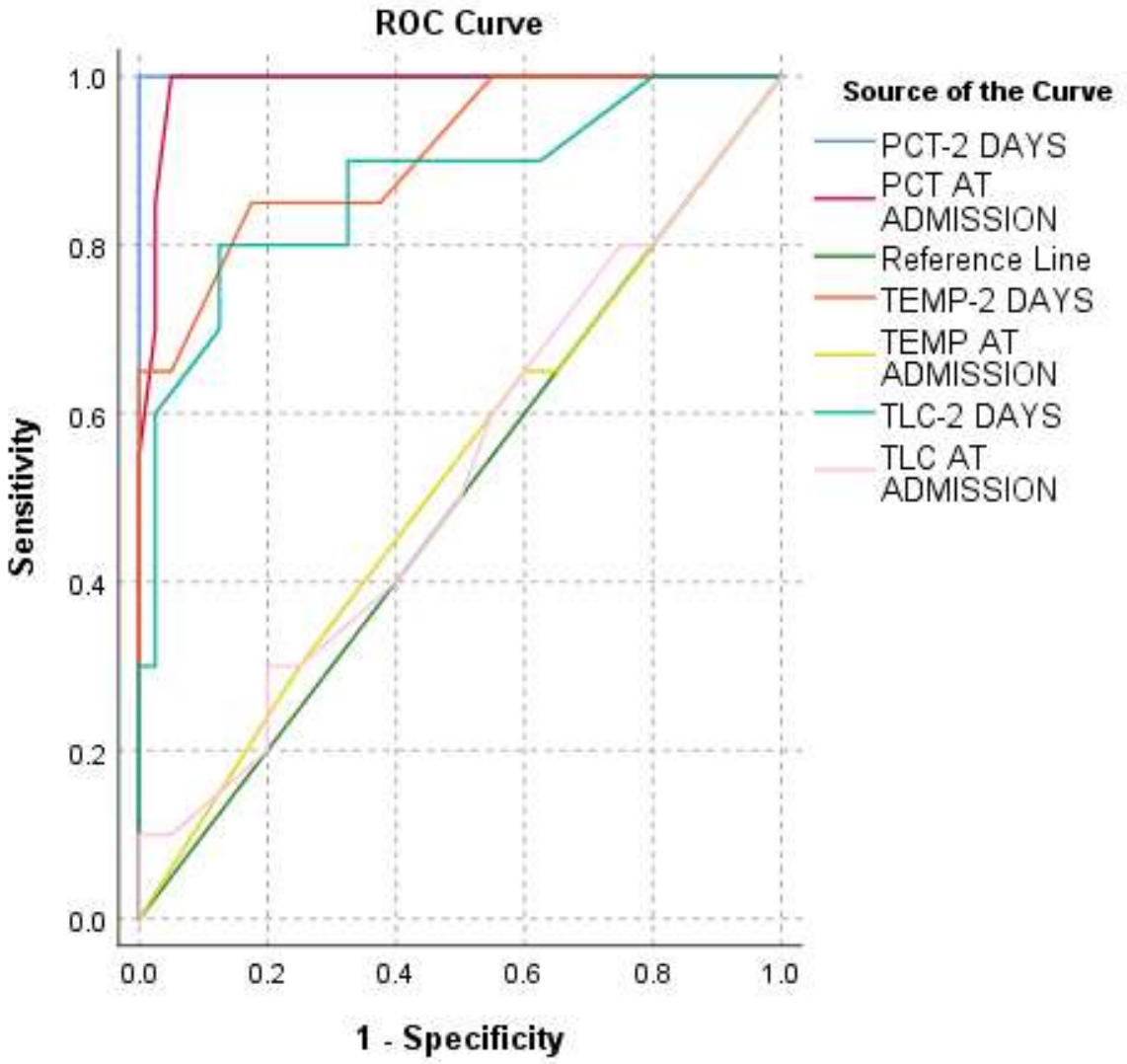

Table-2 Sensitivity and Specificity of various markers to predict sepsis in DKA patients

Parameters	Area	Asymptotic P value	Sensitivity	Specificity
TLC at ADMISSION	.528	.733	80%	25%
TLC at 2 DAYS	.869	.000	80%	87.5%

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TEMP at ADMISSION	.525	.756	65%	40%
TEMP at 2 DAYS	.908	.000	85%	82.5%
PCT at ADMISSION	.989	.000	100%	95%
PCT at2 DAYS	1.000	.000	100%	100%

Markers of Sepsis

The two groups were comparable on parameter of TLC at time of admission, however the TLC at 2nd day were significantly different between the two groups. The median TLC was significantly higher in PBI group than without PBI group at 2nd day of admission. The two groups were comparable on parameter of fever intensity (measured by temperature) at time of admission, however the Temperature at 2nd day were significantly different between the two groups. The median Temperature was significantly higher in PBI group than without PBI group at 2nd day of admission..However the two groups have significant differences on quantitative measurement of serum PCT at time of admission, similarly the quantitative measurement of serum PCT at 2nd day were significantly different between the two groups. The median PCT was significantly higher in PBI group than without PBI group at 2nd day of admission.

The present study evaluated diagnostic performance of different sepsis markers to predict proven bacterial infection for patients with DKA, admitted in ICU. The high PCT (threshold above 0.989) at ICU admission may help to identify patients with proven bacterial infection in the context of DKA. In our study fever not found to be early marker of sepsis in DKA .

Discussion

The high PCT (threshold above 1.44 ng/mL at Day-0) at time of ICU admission may help to identify patients with proven bacterial infection in the setting of DKA. Presence of fever on Day-0 and Day-2 also served as a marker to identify patients with proven bacterial infection in the setting of DKA in previous studies .[7,8] However there occurs huge variation in temperature recording in DKA patients which may be explained on the basis of thermoregulatory function impairment in diabetic patients.[9]

Gale et al.(1978)[10] in their study reported 20 patients with hypothermia during DKA with a high mortality rate (60%). Guerin J-M et al (1987)[11] also reported association of hypothermia with infection .

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In present study we did not found any difference for fever marker between both groups at time of admission.

The other important sepsis markers were also found to be inefficient in present study to differentiating between PBI episodes and those without PBI. We found a high WBC level on Day-0 (with neutrophilic predominance) in episodes of PBI and without PBI. Guerin J-M et al. (1987)[11] and Tullis JL et al. (1948)[12] also reported leukocytosis without PBI in their case reports . This finding makes us to to reconsider the usefulness of WBC to predict bacterial infection at admission. Nowadays the Neutrophil-lymphocyte count ratio(NLCR) was projected to be a more useful diagnostic tool than other blood tests to identify patients with bacterial infection .[13] However, in our study we did not highlight any difference for this marker between both groups at admission

PCT is produced as part of the systemic response to bacterial infections.[14] The present study emphasized the relevance of PCT to predict infection, with a good predictive value above the level of 0.989 ng/mL at Day-0. In present study, PCT was accurate at the admission to distinguish PBI episodes from those without PBI with a sensitivity of 100% and a specificity of 90% at cut-off of 0.989 ng/ml . Wacker et al. [15] in their meta-analysis focusing on the accuracy and clinical value of PCT for diagnosis of sepsis in critically ill patients reported a sensitivity and specificity of 77% and 79%, respectively. Sager et al. [16] stated that for critically ill patients, bacterial infection was considered to be “likely” when PCT level was 0.5–1.0 ng/mL and to be “very likely” when PCT is above 1.0 ng/mL. Florian Blanchard et al. [7] in their study found that PCT was accurate at the admission to distinguish PBI episodes from those without PBI with a sensitivity of 90% and a specificity of 76% at cutoff of 1.44 ng/ml.

The traditional clinical (hypothermia) and biological (WBC, NLCR) signs of bacterial infection proved to be ineffective In early management of DKA , probably due to correlation between hyperglycemia crisis and inflammatory response. In non-diabetic patients, induced hyperglycemia results in amplification of interleukin-6 (IL-6) and other pro-inflammatory markers.[17] an induced hyperglycemia in diabetic patients results in marked secretion of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-6 as compared to healthy controls [18] and increased TNF-α induces the release of large amount of PCT in both animals [19] and humans.[20] Therefore the increase of both PCT and WBC in episodes without PBI on Day-0 is seen. However using both PCT and presence of fever may help physicians to be more specific as only PBI episodes presented with both signs. After administration of insulin and correction of

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increased glycaemia, the near normalization of PCT and WBC in episodes without PBI on day-2 can be explained on the basis of the correction of the inflammatory state, allowing to distinguish between episodes with and without PBI. In the PBI group, episodes of fever occur along with high levels of PCT, WBC, neutrophil count and NLCR still persist on Day-2. In the group without PBI there is a decrease, if not a normalization, of above markers after the correction of glycaemia.

Conclusion-At admission present study showed that WBC, neutrophils count and hypothermia should not be taken into account in the diagnosis process of infection in diabetes ketoacidosis patients admitted in intensive care unit. and PCT may help distinguish patients with and without PBI and by use of PCT as a marker reduction of antibiotic misuse may be possible. Prospective studies will be needed to confirm the diagnostic thresholds of these markers. Thus, a prospective clinical randomized control trial incorporating a decision rule based on procalcitonin to guide the prescription of antibiotics during DKA could be conducted to confirm the clinical findings.

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Declaration of conflicting interest: All authors report no potential conflicts.

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