Diagnostic Utility of Procalcitonin and Neutrophil-Lymphocyte Ratio in Bacterial Septicaemia - A Retrospective Case Control Study from a Tertiary Care Institute

Mamatha T. Shenoy[1], Hariharan Alexander[2], Jeyakumar Manavalan[3], K. Suganthy[4], Pradipta Kumar Mohanty[5]

[1, 2, 3, 4, 5] Department of Biochemistry, Velammal Medical College Hospital and Research Institute, Madurai, Tamilnadu, India.

ABSTRACT

BACKGROUND

Sepsis is a frequently encountered critical care problem wherein great emphasis is laid on early and accurate diagnosis of the infective organism. Blood culture though precise, is time consuming. Empiric antibiotic therapy leads to development of antibiotic resistance amongst organisms. Thus, there is a need for a biomarker that is cost effective, simple and rapid to perform. Procalcitonin elevates in response to chemical mediators produced due to bacteraemia within 2 - 4 hours and serves as an early marker. Neutrophil-Lymphocyte Ratio is available universally and is highly cost-effective. We wanted to assess the utility of Procalcitonin (PCT) and Neutrophil-Lymphocyte Ratio (NLR) in detecting the bloodstream infections and determine their usefulness in establishing the nature of infective organisms.

METHODS

A retrospective case control study was undertaken from January 2018 to December 2018 in a tertiary care teaching hospital in Madurai, Tamil Nadu. Patients tested for serum PCT, complete blood count and blood culture simultaneously prior to antibiotic therapy were included in the study (n = 288). The study cohort was classified into two groups. Group I, controls (n = 155) and group II, cases (n = 133). Out of 133 patients, 73 % (98) were infected by Gram-negative bacteria and 27 % (35) by Gram-positive bacteria. Data was analysed using SPSS V.16 software (SPSS Inc., Chicago, IL, USA). Students unpaired t test and Mann-Whitney U test were used for intergroup comparisons of continuous variables. $p < 0.05$ was considered to be statistically significant. Cut off for detecting bacteriemia and gram negative bacteriemia was created using Receiver Operating Characteristic (ROC) curve.

RESULTS

The area under ROC of PCT to detect gram negative bacteraemia was 0.752 (95 % CI = 0.692 – 0.812).

CONCLUSIONS

Escherichia coli was the most frequent cause of sepsis. Higher levels of PCT and NLR were associated with gram negative organisms. PCT levels can help in determining the cause of infection. NLR and PCT are able to establish the presence of bacteraemia in a short span of time, thus alleviating the over dependence on blood culture reporting. Such earlier decision-making tools help in reducing empirical antibiotic usage and thereby lessen the burden of bacterial resistance to antibiotics.

KEYWORDS

Procalcitonin, PCT, Neutrophil Lymphocyte Ratio, NLR, Gram Negative Bacteria, Sepsis, Biomarker

Corresponding Author:
Dr. Hariharan Alexander,
Assistant Professor,
Department of Biochemistry,
Velammal Medical College Hospital and Research Institute, Madurai,
Tamilnadu, India.
E-mail: ahariharan.in@gmail.com

DOI: 10.18410/jebmh/2020/585

How to Cite This Article:
Shenoy MT, Alexander H, Manavalan J, et al. Diagnostic utility of procalcitonin and neutrophil-lymphocyte ratio in bacterial septicaemia: a retrospective case control study from a tertiary care institute. J Evid Based Med Healthc 2020; 7(48), 2856-2861. DOI: 10.18410/jebmh/2020/585

Submission 29-08-2020,
Peer Review 05-09-2020,
Acceptance 10-10-2020,
Publish 30-11-2020.

BACKGROUND

Sepsis is a life-threatening condition requiring immediate diagnosis and treatment particularly in immunocompromised individuals, paediatric and elderly population. So, an early and accurate diagnosis of the infective organism is necessary. Blood-Stream Infections (BSIs) lead to significant mortality and morbidity in the patients admitted to intensive care units.[1] 56 % of sepsis cases succumb to death in our country.[2] Detection of growth of the microorganism in the blood by culture testing has been regarded as most precise method for the diagnosis of sepsis. The results are typically accessible only after 12 - 48 hours which causes a delay in administering the appropriate antimicrobial.[3]

Empirical antibiotic therapy leads to resistance, about 30 % of the samples yield a negative result and possibility of false positive outcome due to local contamination also exists.[4] Polymerase Chain Reaction (PCR) based diagnostic systems yield results in 6 hours. The test is expensive and requires trained personnel to handle the instruments.[4,5] All these limitations warrant the requirement of an easy, fast and reliable test for detection of sepsis.

Procalcitonin, is a prohormone, synthesized in the thyroid gland by the C cells. It serves as a precursor to calcitonin. Its production is directed by the calcitonin 1 gene (CALC-1) on chromosome 11. PCT is produced after proteolytic cleavage of pre PCT, which on maturation produces calcitonin molecule.[6] The production of PCT is triggered by endotoxins released by microorganisms or by mediators of bacterial infection.[7,8]

Neutrophil count increases in response to infection and other stressful events. This physiological response is accompanied by lowering of lymphocyte count.[9] White Blood Cell (WBC) count is readily available in all health centres and its subgroup analysis for finding neutrophil lymphocyte ratio is closely related to physiological response to endotoxin, thus making it another biomarker available to detect sepsis.

PCT and NLR are less time and effort consuming when compared to blood culture investigation to confirm BSI. We undertook this study with objective of assessing the utility of PCT and NLR in detecting the BSIs. We also made direct comparisons between PCT and NLR showing potential in diagnosing gram negative BSI.

METHODS

We have retrospectively analysed the blood culture reports and clinical chemistry results of the inpatients between January 1 and December 31, 2018 with the help of patients' electronic medical records. The data was generated at a tertiary care teaching hospital located in Madurai, Tamil Nadu, India. This study was approved by the Institutional Ethics Committee. We reviewed the laboratory records of all patients who underwent serum PCT investigation during the study period and included only those patients who had fulfilled the criteria of having undergone simultaneous PCT and blood culture testing.

All routine clinical chemistry analysis like renal & liver functions, serum electrolytes, complete blood count were done as part of routine baseline assessment. Blood markers such as PCT and WBC count were collected from the laboratory records of study subjects. NLR was calculated as ratio of the neutrophil count to lymphocyte count. The normal value of NLR is 2 – 4.[9] All clinical chemistry investigations were performed on fully automated analyser (Toshiba TBA 120FR), serum PCT was measured by fluorescent immunoassay using i-chroma analyser. Complete blood count was performed by haematology Beckmann Coulter LH 780 analyser. Blood culture investigations were performed by BD BACTEC™ FX40.

Total PCT estimations (N = 1590) were carried out in our laboratory during the study period, of which, adults who were in agreement with the diagnostic protocol consisting of a blood culture and simultaneous measurement of serum PCT prior to antibiotic administration (N = 288) were considered as study subjects. The study subjects were divided into two groups based on their blood culture reports, i.e., blood culture positive (N = 133) and blood culture negative (N = 155). Patients whose blood culture report suggested growth were considered as 'Cases' and those with nil growth were considered as 'Controls'. Those with blood culture positive (N = 133) results were further subgrouped on the basis of their gram staining with 98 Gram Negative Blood Culture (GNBC) and 35 Gram Positive Blood Culture (GPBC) cases. Comprehensive assessment of case files was carried out to exclude patients with kidney disease / malignancy, immunocompromise status, recent trauma / surgery and antibiotic therapy prior to blood culture.

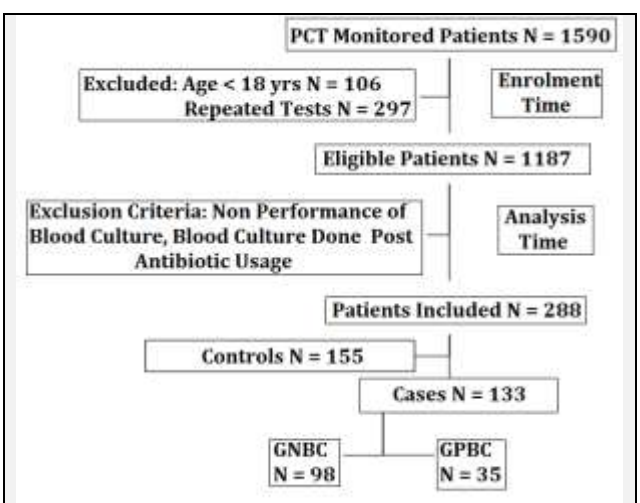

Figure 1. Flow Diagram Demonstrating Criteria for Selection and Grouping of Patient Population

Statistical Analysis

The continuous variables which had non-normal distribution ($p < 0.05$ for Kolmogorov-Smirnov´s test) were expressed as the median (25^{th} percentile, 75^{th} percentile). Data that was continuous and equally distributed was reported as mean values with standard deviation. The categorical variables were summarised as frequencies and percentages. Students unpaired t test and Mann-Whitney U test were used for two-group comparisons of continuous variables in

different groups. Statistical significance was assumed if the null hypothesis could be rejected at $p < 0.05$. Observations with missing values were excluded. Receiver Operating Characteristic (ROC) curve analysis was performed to determine the diagnostic utility of various cut-offs of sepsis biomarkers. Data was analysed using SPSS v.16.0 software (SPSS Inc., Chicago, IL, USA). The measures of diagnostic accuracy including the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio were calculated using MedCalc's diagnostic test evaluation calculator.[10] In order to assess association between PCT and septicaemia, the Odds Ratio (OR) and its 95 % Confidence Interval (95 % CI) were computed.

RESULTS

The study cohort was classified into two groups as defined in the methodology. Group I, controls (n = 155) and group II, cases (n = 133). Out of 133 patients, 73 % (98) were infected by gram-negative bacteria and 27 % (35) by gram-positive bacteria.

Sepsis Biomarkers	Cases (n = 133)	Controls (n = 155)	p Value
Serum Procalcitonin (ng / mL)	37.01 (3.34, 91.69)	1.99 (0.56, 14.43)	< 0.001*
Total White cell count (cells / mm^3)	12650 (9175, 17650)	8700 (6950, 10400)	< 0.001*
Neutrophil Lymphocyte count ratio	13.67 (8.17, 22.46)	6.02 (3.18, 10.20)	< 0.001*

Table 1. Sepsis Biomarkers in Cases and Controls were Presented as Median (25th Percentile, 75th Percentile)

*p < 0.001

Laboratory Parameters		GPBC (n = 35)	GNBC (n = 97)	p Value
Serum Procalcitonin (ng / mL)	Median (25th Percentile, 75th Percentile)	9.48 (0.81, 44.64)	41.25 (8.83-100)	0.002*
Total White Cell Count (cells / mm^3)		14280 (9400, 18250)	12400 (9300, 17000)	0.587
Neutrophil-Lymphocyte Count Ratio		12.08 (7.45, 25.72)	15.16 (8.3, 22.25)	0.521
Total Protein (g / dL)	Mean ± SD	5.7 ± 0.9	5.6 ± 0.9	0.175
Albumin (g / dL)		3.2 ± 0.6	3.1 ± 0.6	0.848
Sodium (mEq / L)		137 ± 10	133 ± 8	0.041#
Potassium (mEq / L)		3.9 ± 0.9	4.2 ± 1.0	0.247
Aspartate Transaminase (IU / L)		53(36, 125)	50 (32, 83)	0.298
Alanine Transaminase (IU / L)	Median (25th Percentile, 75th Percentile)	36 (24, 69)	33 (20, 60)	0.471
Alkaline Phosphatase (IU / L)		123 (72, 150)	112 (78,203)	0.416
Urea (mg / dL)		81 (40, 122)	66 (31, 114)	0.378
Creatinine (mg / dL)		1.85 (0.85, 3.65)	1.75 (0.9, 3.5)	0.973

Table 2. Comparison of Biochemical Parameters in Gram Positive Blood Culture Patients and Gram-Negative Blood Culture Patients

*p < 0.01; # p < 0.05

The Kolmogorov-Smirmov test was used to test statistical distribution of various markers in different groups. The data was distributed non-parametrically which was indicated by $p < 0.001$, and non-parametric tests were conducted in the analysis of the various test parameters in this study.

Sepsis markers in cases and controls was analysed using Mann-Whitney U test. The PCT, WBC count and NLR were significantly higher in cases compared with those in controls. (Table 1) These biomarkers were then compared amongst cases and only PCT found to be significantly different between GNBC & GPBC. (Table 2) Comparison of biochemical parameters in cases is depicted in table 2.

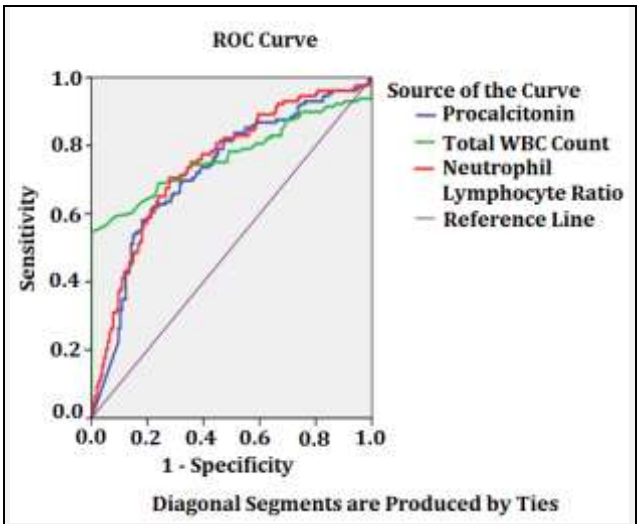

Figure 2A. ROC Curve for PCT Values, WBC Count and NLR for Detecting Subjects with Bacteraemia

ROC: receiver operating characteristic; PCT: procalcitonin, NLR: neutrophil lymphocyte count ratio, WBC: white blood cell

Biomarker (Cut-Off)	Sensitivity (95 % CI)	Specificity (95 % CI)	PPV (95 % CI)	NPV (95 % CI)	Positive Likelihood Ratio	Negative Likelihood Ratio
PCT: (2ng / mL)	85.11 % (76.28 - 91.61)	28.57 % (14.64 - 46.30)	76.19 % (71.85-80.04)	41.67 % (25.94 - 59.30)	1.19 (0.95 - 1.49)	0.52 (0.26 - 1.06)
PCT: (3 ng / mL)	80.85 % (71.44 - 88.24)	34.29 % (19.13 - 52.21)	76.77 % (71.84-81.06)	40.00 % (26.42 - 55.31)	1.23 (0.95 - 1.59)	0.56 (0.30 - 1.04)
PCT: (5 ng / mL)	78.72% (69.07 - 86.49)	45.71 % (28.83 - 63.35)	79.57 % (73.85 - 84.31)	44.44 % (32.00 - 57.63)	1.45 (1.05 - 2.00)	0.47 (0.27 - 0.79)

Table 3. Performance Characteristics of Procalcitonin in Diagnosing Confirmed Gram-Negative Bacterial Sepsis

Bacterial Species	PCT (ng / mL)
Escherichia coli (N = 43)	45.81 (17.09 - 100)
Klebsiella pneumoniae (N=30)	31.57 (2.39 - 75.12)
Staphylococcus aureus (N = 18)	11.57 (2.87 - 40.33)
Enterococcus (N = 13)	4.58 (0.27 - 51.78)
Pseudomonas aeruginosa (N = 10)	31.39 (3.19 - 100)

Table 4. Procalcitonin Levels in Different Cohorts According to Blood Culture Results Presented as Median (25th Percentile, 75th Percentile)

The ROC curve was used for discriminating between cases and controls by using biomarkers like PCT, WBC count and NLR (Figure 2A). The Area Under the ROC curve (AUROC) for PCT was 0.725 (95 % CI 0.664 – 0.785), for NLR the AUROC was 0.747 (95 % CI = 0.689 – 0.804) and for WBC count AUROC of 0.770 (95 % CI 0.710 – 0.830) was obtained. The PCT value showed an optimum cut-off value of 4.53 with sensitivity 73.6 % and specificity 60.6 % and NLR showed an optimum cut-off value of 7.29 with sensitivity 77.5 % and specificity 57.4 % could be considered for diagnosis of sepsis. In the cases, PCT was used to discriminate between gram negative and gram-positive

organisms. (Figure 2B) The AUROC of PCT to detect gram negative bacteraemia 0.752 (95 % CI = 0.692 – 0.812). The sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios of PCT at several cut-offs are shown in Table 3.

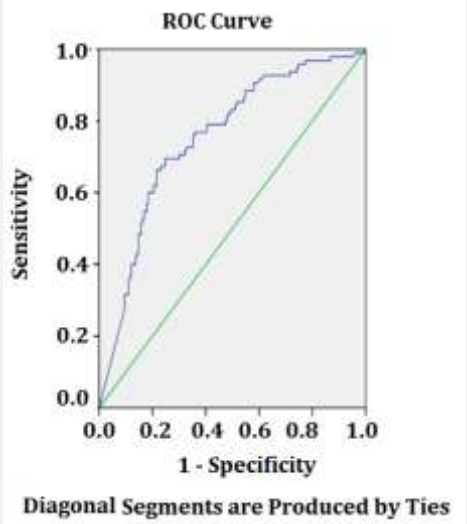

Figure 2B. ROC Curve for PCT Values for Detecting Subjects with Gram Negative Bacteraemia

ROC: receiver operating characteristic; PCT: procalcitonin, NLR: neutrophil lymphocyte count ratio, WBC: white blood cell.
95 % CI- 95 % confidence interval; NPV- negative predictive value; PCT- procalcitonin; PPV- predictive positive value.

	Biomarker (Cut-off)	Odds Ratio	95 % Confidence Interval	p Value
To Detect Septicaemia	PCT: (2 ng / mL)	1.545	0.464-5.150	0.000**
	PCT: (3 ng / mL)	2.074	0.672-6.398	0.000**
	PCT: (5 ng / mL)	7.421	2.125-25.922	0.000**
To Detect Gram Negative Bacteraemia	PCT: (2 ng / mL)	3.838	2.099-7.018	0.074
	PCT: (3 ng / mL)	3.565	1.998-6.347	0.062
	PCT: (5 ng / mL)	3.749	2.115-6.647	0.007**

Table 5. Diagnostic Odds Ratio for Detecting Infection Using Various Cut-Offs of Procalcitonin

PCT, procalcitonin **p < 0.01

Escherichia coli and *Staphylococcus aureus* were the most frequently detected gram negative and gram-positive organism respectively. Table 4 shows the median PCT concentration in the most frequently detected organisms and highlights higher PCT concentrations in gram negative as compared to gram positive microorganisms. Table 5 highlights the odds ratio to detect septicaemia and gram-negative bacteraemia stratified based on the optimal cut-off values of PCT.

DISCUSSION

Empirical antibiotic usage for sepsis and delay in antibiotic sensitivity report, leads to need for identification of easy, fast and reliable biomarker for aiding treatment. In this study, we assessed the relationship between various biomarkers for sepsis and the blood culture results in patients who were suspected to have sepsis. The results show that PCT, total WBC count and NLR levels were significantly elevated in blood culture positive cases. WBC count and NLR were not able to prefigure the type of organism causing sepsis. Serum PCT levels were significantly higher in GNBC than in GPBC. These results were consistent with previous reports.[4,5,8] The authors considered a cut-off value for PCT, 6.26 ng / mL with a sensitivity of 76.6 % and specificity of 61.1 % could be considered for diagnosing GNBC.

Our study upholds the findings noted previously that PCT values are higher in patients who had positive blood culture results as compared to those with no growth in blood culture.[3,6,11,12] PCT is a 116-amino acid peptide, weighing 14.5 kDa. It consists of three sections; the amino terminus (57 amino acids), immature calcitonin (33 amino acids) and Calcitonin Carboxyl-terminus Peptide 1 (CCP-1) also known as katacalcin (21 amino acids). The thyroid C-cells are responsible for expression of CALC-1. During bacterial infection all parenchymal tissues respond to cytokine exposure by producing PCT. These other tissues lack the ability to cleave PCT to calcitonin, thereby contributing to elevation of serum PCT.[6,13] PCT is produced universally when an endotoxin or chemical mediators such as IL (Interleukin)-1β, TNF (Tumor Necrosis Factor) - α and IL-6 are released in blood stream in response to bacterial infections. It strongly correlates with the amount and severity of bacterial infections.[14,15]

Infectious diseases are seen to be associated with elevated serum inflammatory markers such as PCT and CRP. PCT elevates within 2 hours after the onset of infectious disease as opposed to a 6-hour delay exhibited by CRP. Blood PCT has a half-life of 22 hours whereas CRP which has a half-life of only 4 – 6 hours.[14] CRP which has been widely used as an inflammatory marker, tends to increase non-specifically in patients with trauma, burns, myocardial infarction, cancer, inflammatory diseases other than bacterial infection.[16] Earlier and prolonged elevation has boosted dependence on PCT for diagnostic purposes and its specificity for bacterial infections is an added advantage over CRP.

Cells of immune system and other non-immune cells express Toll-Like Receptors (TLR) which are involved in signalling pathways help recognise various bacteria. PCT release is boosted by production of distinct pro-inflammatory cytokines. Endotoxin producing bacteria cause cell death leading to persistently high levels of PCT.[15] The lipopolysaccharide act through TLR-4 in gram-negative bacteria by activating neutrophils, whereas TLR-2 activation by lipoteichoic acid from gram-positive bacteria triggers production of proinflammatory cytokines and acute phase proteins.[7] Increase in plasma levels of interleukin (IL)-1, IL-6, IL-10, IL-8 and tumour necrosis factor alpha is more in cases of gram-negative organisms than gram-positive microorganisms. Such increased inflammatory response by gram-negative microbes may help explain the higher PCT levels in gram-negative bacteraemia causing imbalance between pro- and anti-inflammatory mechanisms, which makes the patient susceptible to multiple organ dysfunction syndrome.[17] Interferon-γ produced in viral infections causes attenuation of PCT production.[6] This feature makes PCT a more specific marker for bacterial infection. It also helps in differentiating bacterial and viral infections thus helping in appropriate management.[7] A meta-analysis by Lai et al

concludes PCT may be helpful in detecting patients infected with GNBC.[5] Our study results have a similar outcome which is also corroborated by other studies conducted by Guo et al[7] and Honnore et al.[18]

During bacterial invasion, body responds by producing cytokines in response to chemokines released from the microorganisms. Large numbers of neutrophils are produced in the bone marrow and are released into systemic circulation. Lymphocytes being apoptotic in nature, lead to reduced proliferation of T lymphocytes, leading to lymphopenia.[19] Neutrophil count increases due to reduced apoptosis and migration of activated lymphocytes to tissues with inflammation causes decrease in their count in peripheral blood.[9] NLR is a simple test that can be obtained from calculations based on differential leucocyte count. It also is a better indicator of systemic inflammation than either neutrophils or lymphocytes alone, as it helps to reduce the influence of physiological factors. In this study we found NLR to be elevated in GNBC in comparison to GPBC but not statistically significant. A study by Liu et al found NLR to be elevated in sepsis.[20] We too have recorded such increase in cases against controls. (Table 1) The elevation in NLR in GNBC, along with the ease of testing, makes it a dependable biomarker in sepsis in our opinion. A study by Zheng et al[21] opined that NLR is not comparable to conventional biomarkers like CRP, PCT for evaluating hospital acquired pneumonia.

Patients with infection due to *Escherichia coli, Klebsiella* spp. and *Pseudomonas* spp presented with higher PCT levels in blood. This finding in our study was in agreement with a study by Guo et al.[7] The body responds to invasion by microorganisms depending on the pathogen associated molecular patterns, which act as ligands for TLRs. Host response to different microorganisms varies due to the underlying differences in bacterial virulence.[22] This leads to varying activation of certain signalling cascades and cell apoptosis pathways. Early initiation of appropriate antimicrobial therapy plays a crucial role in the treatment of sepsis.

Liver being the organ responsible for clearing toxins from bloodstream, plays a crucial role in immune response and mortality of patients. Lipopolysaccharide, from bacteria, induces inflammation and requires liver for its clearance.[23] This interaction with bacterial toxins can cause injury to hepatocytes, and cause liver enzymes to be elevated. Proinflammatory state with increased IL 6, activation of neutrophils and macrophages, decrease in IL 10, an anti-inflammatory cytokine, dysregulation of microcirculation are few proposed theories for acute kidney damage that is associated with sepsis.[24] A study by Doi K states acute kidney injury associated with sepsis can act as an amplifier of injury to other organs and worse prognosis.[24] Our study also shows elevated renal parameters in cases of sepsis.

The elevation of PCT was significantly connected to bacteraemia. PCT values were statistically higher in GNBC infections than in GPBC infections. PCT was more useful tool than NLR for predicting bacteraemia's and for establishing cause of infection. PCT value ≥ 2.0, indicated onset of bacteraemia. Thus, PCT may be considered as a superior diagnostic tool in comparison to NLR for the detecting bacterial infections.

This being a single centre, time bound retrospective study has a few limitations. The results of the study are derived by including patients with single organism bacteraemia, established with the help of blood culture. PCR based rapid molecular diagnostic tests that recognise pathogenic DNA was unavailable. In spite of being an easy and quick test, PCT has a few drawbacks, such as its falsely high values in conditions such as babies who are newly born, children, severe distress due to trauma and inflammation, infections such as malaria, malignancies such as medullary thyroid cancer and paraneoplastic syndromes.[25] Other prominent drawback is the cost factor. NLR could be derived from a basic investigation such as differential leucocyte count and very much affordable. In situations where PCT is beyond the scope of consideration, NLR serves as a novel marker of bacteraemia and / or sepsis.

CONCLUSIONS

Rapid diagnosis and accurate identification of the causative organism goes a long way in reducing mortality significantly. Paucity of specific biomarker hinders diagnosis and prediction of sepsis outcomes. In the recent past, PCT has been hailed as a biomarker to detect presence of bacterial infection and to aid in the management of the patients worldwide. Our study shows that both PCT and NLR to be useful in establishing septicaemia, but PCT has an advantage over NLR, as it can detect GNB infections. PCT can be used to narrow down the species involved in sepsis and thus help in reducing resistance amongst bacteria due to empirical antibiotic therapy. It is projected as an initial diagnostic tool.[14]

PCT alone may not be effective in diagnosing critical cases of BSIs but it has an advantage of cueing towards the possible pathogen. When used with array of other laboratory facilities it aids in effective risk stratification. Higher levels of PCT and NLR are associated with gram negative organisms and it helps immensely in initial management of the infected individual.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

REFERENCES

[1] Shokouhi B, Bookani KR, Ghasemi H, et al. Diagnostic and prognostic performances of serum procalcitonin in patients with bloodstream infections: a parallel, case-control study comprising adults and elderly. Rev Assoc Med Bras 2017;63(6):521-526.

[2] Gupta S, Jaswani P, Sharma RK, et al. Procalcitonin as a diagnostic biomarker of sepsis: a tertiary care centre experience. Journal of Infection and Public Health 2019;12(3):323-329.
[3] Watanabe Y, Oikawa N, Hariu M, et al. Ability of procalcitonin to diagnose bacterial infection and bacteria types compared with blood culture findings. Int J Gen Med 2016;9:325-331.
[4] Bilgili B, Haliloğlu M, Aslan MS, et al. Diagnostic accuracy of procalcitonin for differentiating bacteraemic gram-negative sepsis from gram-positive sepsis. Turk J Anaesthesiol Reanim 2018;46(1):38-43.
[5] Lai L, Lai Y, Wang H, et al. Diagnostic Accuracy of procalcitonin compared to C-reactive protein and interleukin 6 in recognizing gram-negative bloodstream infection: a meta-analytic study. Dis Markers 2020;2020:4873074.
[6] Samsudin I, Vasikaran SD. Clinical utility and measurement of procalcitonin. Clin Biochem Rev 2017;38(2):59-68.
[7] Guo SY, Zhou Y, Hu QF, et al. Procalcitonin is a marker of gram-negative bacteremia in patients with sepsis. Am J Med Sci 2015;349(6):499-504.
[8] Bassetti M, Russo A, Righi E, et al. Role of procalcitonin in bacteremic patients and its potential use in predicting infection etiology. Expert Review of Anti-infective Therapy 2019;17(2):99-105.
[9] Westerdijk K, Simons KS, Zegers M, et al. The value of the neutrophil-lymphocyte count ratio in the diagnosis of sepsis in patients admitted to the Intensive Care Unit: a retrospective cohort study. PLoS One 2019;14(2):e0212861.
[10] Gardner IA, Greiner M. Receiver-operating characteristic curves and likelihood ratios: improvements over traditional methods for the evaluation and application of veterinary clinical pathology tests. Vet Clin Pathol 2006;35(1):8-17.
[11] So-Ngern A, Leelasupasri S, Chulavatnatol S, et al. Prognostic value of serum procalcitonin level for the diagnosis of bacterial infections in critically-ill patients. Infection & Chemotherapy 2019;51(3):263-273.
[12] Yunus I, Fasih A, Wang Y. The use of procalcitonin in the determination of severity of sepsis, patient outcomes and infection characteristics. PLoS One 2018;13(11):e0206527.
[13] Chaudhary S, Bhatta NK, Lamsal M, et al. Serum procalcitonin in bacterial & non-bacterial meningitis in children. BMC Pediatr 2018;18:342.
[14] Reinhart K, Bauer M, Riedemann NC, et al. New approaches to sepsis: molecular diagnostics and biomarkers. Clin Microbiol Rev 2012;25(4):609-634.
[15] Yan ST, Sun LC, Jia HB, et al. Procalcitonin levels in bloodstream infections caused by different sources and species of bacteria. Am J Emerg Med 2017;35(4):579-583.
[16] Wu H, Chen L, Sun Y, et al. The role of serum procalcitonin and C-reactive protein levels in predicting spontaneous bacterial peritonitis in patients with advanced liver cirrhosis. Pak J Med Sci 2016;32(6):1484-1488.
[17] Virzì GM, Clementi A, Brocca A, et al. Endotoxin effects on cardiac and renal functions and cardiorenal syndromes. Blood Purif 2017;44(4):314-326.
[18] Honore PM, De Bels D, Attou R, et al. Influence of pathogen and focus of infection on procalcitonin values in sepsis: are there additional confounding factors? Crit Care 2019;23(1):1-2.
[19] Qu J, Yuan HY, Huang Y, et al. Evaluation of neutrophil-lymphocyte ratio in predicting bloodstream infection. Biomark Med 2019;13(15):1255-1261.
[20] Liu X, Shen Y, Wang H, et al. Prognostic significance of neutrophil-to-lymphocyte ratio in patients with sepsis: a prospective observational study. Mediators of Inflammation 2016;2016:8191254.
[21] Zheng N, Zhu D, Han Y. Procalcitonin and C-reactive protein perform better than the neutrophil/lymphocyte count ratio in evaluating hospital acquired pneumonia. BMC Pulm Med 2020;20:166.
[22] Abe R, Oda S, Sadahiro T, et al. Gram-negative bacteremia induces greater magnitude of inflammatory response than Gram-positive bacteremia. Crit Care 2010;14(2):1-7.
[23] Yan J, Li S, Li S. The role of the liver in sepsis. Int Rev Immunol 2014;33(6):498-510.
[24] Doi K. Role of kidney injury in sepsis. Journal of Intensive Care 2016;4(1):17.
[25] Schuetz P, Aujesky D, Mueller C, et al. Biomarker-guided personalised emergency medicine for all-hope for another hype? Swiss Med Wkly 2015;145:w14079.