CORRELATION OF SERUM PROCALCITONIN, LACTATE LEVELS WITH MICROBIAL PATTERN IN PATIENTS WITH SEPSIS

Mamidi V Sandeep Kumar¹, P.K. Ananthakumar², C. Nirmala Devi¹, C. Ramakrishnan¹, D. Rajasekaran¹, V. R. Mohan Rao¹*

1. Department of General Medicine, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Tamil Nadu, India.

*Corresponding author

Dr. V. R. Mohan Rao
Professor & Head
Department of General Medicine
Chettinad Hospital and Research Institute,
Chettinad Academy of Research and Education,
Kelambakkam-603103, Tamil Nadu, India.
Phone no: 9841210011
E-mail ID: vrmohan_rao@yahoo.co.in

ABSTRACT

Sepsis is defined as life-threatening organ dysfunction due to dysregulated host response to infection. To ensure a better outcome early identification of sepsis and a goal directed therapy is must. The objective of the study is to identify the correlation between levels of Serum Procalcitonin and Blood lactate with culture positive sepsis. This is a Retrospective and Prospective study that included 78 patients admitted in Chettinad Hospital And Research Institute with Sepsis. Procalcitonin with a cut off value of 2.4 ng/ml shows a significant correlation with culture positive bacterial infection, AUROC (0.759, p value of 0.002) sensitivity, specificity of 69.8%, 73.3% respectively. Blood samples were drawn at time of admission before initiation of treatment and were processed within 30 minutes of collection using an autoanalyser. Serum Procalcitonin, Lactate was done to all subjects included in the study. Analysis of Serum Procalcitonin was done using immunochromatographic test. The findings suggested that higher procalciton in levels are found to be significantly correlated with bacterial infection, especially Gram negative bacterial infection, when compared with Lactate. Procalcitonin levels can be used as predictor of bacterial infection; especially Gram negative bacterial infection even before obtaining culture results, so early effective empirical antibiotics can be started.

KEY WORDS: Sepsis, procalcitonin, lactate
INTRODUCTION

Sepsis is the most important cause of acute hospital mortality and usually results in multi-organ dysfunction secondary to culture - positive or negative infection. Sepsis is a complex condition characterized by the synchronized commencement of inflammation and coagulation in reaction to microbial insult \(^{(1)}\). Though culture, as well as identification and drug susceptibility testing, needs at least 12–48 h thus early diagnosis is very important. In the past two decades, Procalcitonin has been used for early diagnosis. Numerous studies in the past have examined the role in the risk stratification or the discriminative capacity of lactate in the treatment of the bacterial sepsis in emergency patients \(^{(2)}\). Numerous studies have established procalcitonin and lactate as diagnostic and prognostic markers of sepsis \(^{(3)}\). Predicting the microbial organism even before obtaining culture, depending on biomarker of sepsis may help in starting early appropriate empirical antibiotics.

This study alerts on the differences in the performances of Procalcitonin, Lactate and their combinations for predicting positive blood bacterial culture in adult patients and also the capability of these tests to predict positive culture for any Gram-positive bacteria (GPB), and Gram-negative bacteria (GNB). Provide references in the introduction

MATERIALS AND METHODS

The study has adopted Retrospective (Data has been taken from the Patients medical record) and Prospective study (allocated the patients through the census method and included the patients admitted with sepsis). All the patients admitted to intensive care unit (ICU) of Chettinad Hospital and Research Institute, Kelambakkam, Chennai, TN, India. Sampling size: CENSUS method - All patients admitted with sepsis in Chettinad Hospital during study period.

STATISTICAL METHODS

- Culture results are considered as outcome variables.
- Procalcitonin, lactate were primary explanatory variable Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables.
Non normally distributed quantitative variables were summarized by median and interquartile range (IQR). Data was also represented using appropriate diagrams like bar diagram, pie diagram and box plots.

For non normally distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared between study groups using Kruskal Wallis test. Categorical outcomes were compared between study groups using Chi square test.

P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

DISCUSSION

Sepsis is one of the major causes of death in hospitalized patients. Improving survival among critically ill patients with sepsis depends on many interventions, among which the prompt usage of the suitable antibiotics is noticeably a key factor. Of late been revealed that the so called "door-to-needle" time is a critical factor in the survival of patients with sepsis. In spite of improvements in antimicrobial therapy, it is still associated with high mortality. Postponement in initial adequate antibiotic treatment is an independent predictor of high mortality. Empirical antimicrobial therapy must be initiated upon suspicion of sepsis prior to availability of culture results. Though, in 1/3 rd of sepsis patients, the causative pathogens cannot be acknowledged. If the infectious pathogen might be rapidly recognized by laboratory tests within an hour, it will permit a more timely and accurate clinical decision and more appropriate empirical antibiotic therapy.

Gold standard for diagnosis of bacterial infection is bacterial culture. It is time consuming to get culture results. Surrogate markers are hence required to make the appropriate choice more rapidly. As a result, a predictive tool to diagnose bacterial infections is crucial for early diagnosis of bacterial infection. Numerous inflammatory markers have been studied for the diagnosis of infection. Among them, Procalcitonin is often used and is a good marker of infection. Procalcitonin (PCT) is a pro-hormone of calcitonin produced from cells of the thyroid gland, and has been used as a candidate marker for diagnosis of active bacterial infections. Procalcitonin is extensively used to distinguish bacterial infections from non-bacterial infections or other inflammatory conditions. Numerous studies in the past have examined the role in the risk stratification or the discriminative ability of lactate in the management of the bacterial sepsis. Though, few studies have focused on the discriminative power of elevated lactate levels in blood to predict bacterial infection in the literature.
The results of the tests for procalcitonin, and lactate can be obtained within 1 h, which may significantly shorten the time of decision-making for prescribing appropriate antibiotics if bacterial infection is highly suggested by the results of the above tests. Other new approaches such as universal polymerase chain reaction (PCR) make it possible to identify bacteria quickly and reliably, but these are not routinely available in most centers.

The purpose of present study is to identify differences in the performances of procalcitonin, lactate for predicting bacterial infection in adult patients and analyzed the discriminative ability of these tests to predict type of organism (Gram-positive bacteria /Gram-negative bacteria).

If one patient present with two same type of bacterial infection (either Gram positive/Gram negative) they are included only once in same group according to species isolated. In this present study fungal organisms, patients with both gram positive and gram negative organism combined infection was not obtained in any culture, so culture positive results obtained are categorized in to Gram positive bacterial infection and Gram negative bacterial infection.

**DEMOGRAPHICS**

Present study indicated that there was no significant correlation between Age and bacterial infection, even with type of bacterial infection (Gram positive /Gram negative) with a p value of 0.062 and 0.398 respectively.

In a study by Tuna Demirdal, Pinar Sen et al. (5) results showed that there is no significant correlation between Age and culture positive bacterial infection with mean value of 59.8±17.6 in culture positive bacterial infection group, 61.0±16 in culture negative group, p value of 0.837.

In present study Age in years and Type of bacterial infection also showed no significant correlation with mean value of 59.28 ± 16.17, 55.56 ± 15.09 in Gram positive bacterial infection, Gram negative bacterial infection patients respectively, with a P-value of 0.398. This result is consistent with H.H. Liu, M.W. Zhang et al. (6) they established that there is no statistically significant difference in Age between types of organism with mean value of Age in years was 59±2.78 in Gram positive group, 59.41±1.92 in Gram negative group, p value of 0.95. Present study indicated that there was no significant correlation between Gender and incidence bacterial infection, even with type of bacterial infection (Gram positive/ Gram negative) with a p value of 0.673 and 0.903 respectively.

In a study by Chia-Peng Chang, Cheng-Ting Hsia et.al (7) they showed that there is no significant correlation between Gender and culture positive bacterial infection with p value of 0.958.
In a study by Pierre Emmanuel Charles, Sylvain Ladoire et al. (8) they established that there is no significant statistical difference between Gender and bacterial infection with p value of 0.115.

**SEPTIC SHOCK, MECHANICAL VENTILATION AND MORTALITY**

In a study by Tuna Demirdal, Pinar Sen et al. (5) results showed that there is no significant correlation between septic shock and culture positive bacterial infection with 29 patients in culture positive bacterial infection group, 41 patients in culture negative group, were in septic shock with a p value of 0.926. These results are consistent with present study in which 12 patients in culture negative group, 38 patients in culture positive bacterial infection group were in septic shock with a p value of 0.153.

In present study there was no significant correlation between incidence of septic shock and type of organism (Gram positive/Gram negative) obtained in culture, 10 patients in Gram positive bacterial infection group, 28 patients in Gram negative bacterial infection are having septic shock with a p value of 0.625. This was consistent with results of Pierre Emmanuel Charles, Sylvain Ladoire et al. 6 8 on 97 patients, they established that there is no significant correlation between septic shock and type of organism obtained in culture results (Gram positive / Gram negative) with p value of 0.789.

In a study by Tuna Demirdal, Pinar Sen et al. (5) results showed that there is no statistical significant difference between requirement of mechanical ventilation and bacterial infection in which 48 patients are in Culture positive bacterial infection, 76 patients are in culture negative group with p value of 0.247.

In present study there was no statistically significant correlation between mortality and culture positive bacterial infection with 11 out of 63 patients in culture positive group and 3 out of 15 patients in culture negative group, p value of 1.00. These results are consistent with Tuna Demirdal, Pinar Sen et al. (5) results showed that there is no statistical significant difference between overall mortality and culture positive bacterial infection with p value of 0.418.

There is also no significant correlation between mortality and type of organism (Gram positive/ Gram negative) obtained in culture results in present study with 5 out of 18 patients in Gram positive group and 6 out of 45 patients in Gram negative group, p value of 0.172. This result was consistent with study by Pierre Emmanuel Charles, Sylvain Ladoire et al. (8) on 97 patients, they established that there is no significant correlation between mortality and type of organism causing infection (Gram positive /Gram negative); overall mortality in the ICU was 40.4% in the GN bacteremia group and 20.9% in the GP group P-value of 0.070.
qSOFA

In a study by Tuna Demirdal, Pinar Sen et al. \(^{(5)}\) results showed that there is no statistical significant difference between mean value of qSOFA score and culture positive bacterial infection with SOFA score (mean± SD) 9.4±4.1 in Culture positive bacterial infection group and 9.1±4.3 in Culture negative group, \(P\)-value of 0.804 . In present study results regarding qSOFA score and culture positive bacterial infection showed (mean± SD) 2.317 ± 0.469 in culture positive bacterial infection group and 2.4±0.50 in culture negative group, \(p\) value of 0.538. These results are consistent with above study results.

In present study there is also no statistical significant correlation between qSOFA score and type of organism (Gram positive/Gram negative) yielded in culture with (mean± SD) 2.388 ±0.50 in Gram positive bacterial infection and 2.31 ± 0.4 6 in Gram negative bacterial infection, \(p\) value of 0.59. This result is consistent with results in a study by Pierre Emmanuel Charles, Sylvain Ladoire et.al \(^{(8)}\) regarding qSOFA score there is no significant correlation with type of organism yielded in culture ( Gram positive/Gram negative) \(p\) value is 0.466.

RISK FACTORS

Present study indicated that the risk factors like diabetes mellitus had no significant correlation to the culture positive bacterial infection and also type of organism (Gram positive/Gram negative) \([\text{TABLE 27,28}]\) obtained in culture . In which 40 patients out of 63 patients are in culture positive bacterial infection group and 9 patients out of 15 patients are in culture negative group, indicates Diabetic patients are more in number in culture positive group, with \(p\) value of 0.801.

This result is consistent with study by Demirdal, Pinar Sen et al. \(^{(5)}\) on 226 patients in which 19 patients out of 64 patients are in culture positive group and 24 out of 92 patients are in culture negative group, with \(p\) value of 0.621 showing that there is no significant correlation between Diabetes and culture positive bacterial infection.

In a study by Enas M. Ghonima, Ghada R. El Hindawy et.al. \(^{(9)}\) they established that there is no significant correlation between Diabetes and Gram positive bacterial infection / Gram positive infection with \(\chi^2 =1.08\) , \(p\) value of 0.90 and \(\chi^2 =4.97\) , \(p\) value of 0.93 respectively.

In present study there is no significant correlation between types of organism (Gram positive/Gram negative) obtained in culture and Diabetes, in which 12 patients out of 18 are in Gram positive bacterial infection group, 28 patients out of 45 are in Gram negative group with \(p\) value of 0.74.

PROCALCITONIN
Present study indicated that higher level Procalcitonin during admission correlated with the culture positive bacterial infection with median value of 5.25 ng/ml in Culture positive group bacterial infection group, 1.1 2 ng/ml in culture negative group, p value of 0.002. In present study Procalcitonin levels correlated with the Culture positive bacterial infection with area under the ROC curve of 0.759, 95% C.I. of 0.637 t0 0.880 , p value of 0.002 with cutoff value of 2.40 ng/ml , sensitivity, specificity were 69.8 % and 73.3% respectively.

In a study by Dae Yong Kim, MD Yoon-Seon Lee et.al. The area under the curve of Procalcitonin was 74.8% for predicting culture positive bacterial infection, pvalue< 0.05, with a PCT cut-off value of 0.5 ng/ml, sensitivity and specificity were 60.5% and 82.3%, showing that Procalcitonin is good predictor of culture positive bacterial infection.

In a study by Chiung-Tsung Lin, Jang-Jih Lu, et.al the AUROC of procalcitonin for predicting bacterial infection was 0.72 (95% CI [0.69–0.75]) with a derived optimal cutoff at 3.9 ng/ml , P value <0.001.

In a study by Shun Yuan Guo, MD, Yin Zhou, MD et. al. a cutoff value of 3.39 ng/ml for PCT showed a sensitivity of 80%, a specificity of 71%, a positive predictive value of 35%, a negative predictive value of 91% and an area under the curve of 0.73 for gramnegative bacterial infection.

In a study by H. H. Liu, M. W. Zhang et. al. they established that Serum Procalcitonin levels are higher in Gram negative bacterial infection than Gram positive bacterial infection in 72 h. The area under the receiver-operating characteristic (ROC) curve of Procalcitonin was 0.73 for Gram negative bacterial infection (95 % confidence interval 0.65–0.81) and a positive predictive value of 72.5 % and a negative predictive value of 67.9 % were achieved with a PCT cutoff value of 2.1 ng/ml.

In particular, Gram-positive bacteria activate the TLR2 pathway whereas Gram-negative bacteria the TLR4 pathway , by activating TLR4 pathway resulting in different production of inflammatory cytokines, such as interleukin-1, interleukin-6 (IL6), and tumor necrosis factor, that ultimately stimulate ubiquitous transcription of
calcitonin-mRNA and release of PCT from multiple tissues throughout the body. Intestinal bacterial translocation and accompanying endotoxemia are further reasons for magnitude of elevation in PCT in GN bacteremia.

LACTATE

Present study indicated that levels of Lactate during admission has no significant correlation with the culture positive bacterial infection in which median value of Lactate is 2 mmol/l in patients with Culture positive bacterial infection and 1.8 mmol/l in Culture negative group, p value of 0.884. Area under the receiver operating characteristic curve of Lactate was 0.512 (95% Confidence interval 0.343 -0.681), p value of 0.884 and sensitivity of 50.8%, specificity of 53.55 with cutoff value of 1.95 mmol/l.

These results are consistent with study by Seo DY et. al, they denoted that, the C-statistic of the lactate level was 0.67 (95% CI, 0.60-0.73) at a cutoff value of 1.4 mmol/l, the lactate level predicted culture positive bacterial infection with a sensitivity (53.7%), specificity (72.3%), positive predictive value (55.5%), negative predictive value (70.8%), positive likelihood ratio (1.93), and negative likelihood ratio (0.64). They finally accomplished that the initial serum lactate level showed poor discriminative performance for predicting bacterial infection in female patients with Acute Pyelonephritis.

In the current study there is no significant correlation between Lactate levels and Gram positive bacterial infection with AUROC was 0.605 (95% C.I. 0.446-0.764), with a cut off value of 1.2, sensitivity of 50%, specificity of 81%. Lactate had higher AUROC when compared to Procalcitonin for Gram positive bacterial infection.

In a study by Chiung- Tsung Lin, Jang-Jih Lu, et .al. AUROC of Lactate with culture positive for Gram positive bacterial infection was 0.66, 95% C.I.(0.63-0.701), p value of 0.001, that of procalcitonin was 0.61, 95%(C.I 0.57-0.64), p value of 0.003. They finally established that elevatedprocalcitonin; Lactate can predict Gram positive bacterial infection with a much lower diagnostic odds ratio than that for Gram negative bacterial infection. Interestingly, they found elevated lactate is better than elevated procalcitonin in terms of producing a higher diagnostic odds ratio with a two - to threefold increase in the prediction of Gram positive bacterial infection.

CONCLUSION

This research, conducted to study the correlation of levels of serum Procalcitonin and Blood Lactate with culture positive bacterial infection, type of organism (Gram positive/Gram negative) obtained in culture, concluded that
Procalcitonin showed statistically significant correlation with culture positive bacterial infection, Gram negative bacterial infection when compared to lactate.

Lactate showed no significant correlation in either with Culture positive bacterial infection or type of organism (Gram positive /Gram negative) obtained in culture.

Procalcitonin is better predictor of bacterial infection, especially Gram negative bacterial infection when compared to lactate. Measurement of serum PCT may be adopted as a component of a diagnostic strategy to guide appropriate empirical antimicrobial therapy regimens in sepsis patients, further studies needed to confirm results.

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