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Research Article

ARCHIVES OF
CLINICAL AND
BIOMEDICAL RESEARCH
ISSN: 2572-5017

Endotoxin is a Promising Biomarker for Identifying Culture-Positive Cases of Sepsis

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Abstract

Background: Sepsis is a dysregulated systemic reaction to infection. Although blood culture is considered as the gold standard, it does not qualify as a single method for diagnosing sepsis. Biomarkers like-endotoxin and C-reactive protein (CRP) levels have the potential to diagnose infections quickly.

Objective: This study aimed to evaluate the endotoxin activity and CRP level for the diagnosis of sepsis.

Methods: This cross-sectional study was conducted at the Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Demographic profiles, clinical features, history of antibiotic intake, invasive procedures, and laboratory parameters of the enrolled participants were collected. Sepsis was leveled by quick sequential organ failure assessment (qSOFA) scores. A blood culture was done following standard procedure. Serum CRP level was measured by immuno-nephelometry and kinetic ELISA methods to estimate serum endotoxin level. Data were analyzed and compared by statistical tests.

Result: 50 participants were enrolled. Their mean age was 58.92±18.22 years; the majority belonged to 61-70 years, and males were predominant (58%). Of them, 18 (36%) had detected blood culture positive, where *Acinetobacter* species was predominant (27.77%), followed by *Escherichia coli* (16.67%) and *Ochrobactrum anthropi* (16.67%). Out of 50 study populations, 48 (96%) cases had a serum level of CRP >10 mg/L, while a serum level of endotoxin >0.5 EU/mL was observed in 17 (34.0%) cases. A significant difference was observed in the endotoxin level between culture-positive and culture-negative groups ($p<0.001$). The receiver operating characteristic (ROC) curve analysis revealed that the area under the curve (AUC) was 0.88 for endotoxin, and that was significant ($p<0.05$). CRP had a significant positive correlation with qSOFA ($r= 0.305$; $p= 0.032$).

Conclusion: Endotoxin is a promising biomarker for identifying culture-positive cases of sepsis. C-reactive protein (CRP) level is positively correlated with qSOFA score.

Keywords: Biomarker; C-Reactive Protein (CRP); Endotoxin; Sepsis; Quick Sequential Organ Failure Assessment (qSOFA) Scores

Introduction

Sepsis is a dysregulated host response to systemic infection associated with life-threatening organ dysfunction [1]. It is acknowledged as a global

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Citation: Nazia Mahjabeen, Ahmed Abu Saleh, AKM Akhtaruzzaman, SM Ali Ahmed, Shaila Akhtar, Shaheda Anwar. Endotoxin is a Promising Biomarker for Identifying Culture-Positive Cases of Sepsis. Archives of Clinical and Biomedical Research. 8 (2024): 347-354.

Received: August 12, 2024
Accepted: October 10, 2024
Published: October 22, 2024

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DOI:10.26502/acbr.50170416

health issue of morbidity and mortality and is regarded as the second leading cause of death worldwide [2]. It is one of the most expensive medical conditions to treat, costing an estimated $62 billion annually [3]. In recent decades, sepsis has increased remarkably [4]. Despite advances in medicine, a well-recognized method for diagnosing sepsis is lacking. Septic shock is a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are present, which include persistent hypotension despite adequate volume resuscitation [1]. It has been revealed that among hospitalized patients, 48% of adults and 56% of children are affected with sepsis and septic shock in the USA [3]. Sub-Saharan Africa, Oceania, South Asia, East Asia, and Southeast Asia were considered to have the most significant burdens of sepsis [4]. Among the Southeast Asian countries, India was found to be holding the second-highest mortality rate caused by sepsis, with a 25% reported mortality rate out of 65% of patients with sepsis in the intensive care unit (ICU) [5]. The Centers for Disease Control and Prevention (CDC) recognized sepsis as the third leading cause of mortality in U.S. hospitals, causing harm to approximately 1.7 million patients annually [6]. Sepsis has a highly complex pathogenesis that includes an imbalance in the inflammatory response, immune system dysfunction, mitochondrial damage, coagulopathy, abnormalities in the neuroendocrine-immune network, stresses on the endoplasmic reticulum, autophagy, along with different pathophysiological processes, eventually resulting in organ dysfunction [7]. Initiation of treatments at early stages of sepsis before organ dysfunction can significantly reduce the mortality rate [3]. With such a high global burden of sepsis, there is an urgent need for early and precise identification of sepsis. Therefore, reliable diagnostic techniques are crucial to start appropriate treatment promptly. Sepsis diagnosis is based on clinical signs and symptoms such as fever, tachycardia, and tachypnea, supported by relevant microbiological data, including culture of blood, urine, and cerebrospinal fluid and other investigations (including biomarkers), which may help increase the certainty of diagnosis [8]. Guidelines like- Sequential Organ Failure Assessment (SOFA), quick SOFA (qSOFA), and the Systemic Inflammatory Response Syndrome (SIRS) criteria are used to evaluate patients with sepsis based on typical manifestations of organ dysfunction [9]. The term biomarker or biological marker refers to a character that can be objectively measured and evaluated as an indicator of pathogenic and biological processes or pharmacologic responses to a clinical intervention [10]. Many biomarkers are produced in response to sepsis, and more than 250 distinct biomarkers have already been investigated in clinical contexts with differing degrees of efficacy [11]. Endotoxin is a lipopolysaccharide (LPS) found on the external membrane of all gram-negative bacteria [12]. Endotoxin acts as a pathogen-associated molecular pattern (PAMP) molecule that functions as a ligand for recognizing receptors exposed to the host effector cells of the innate immune system [13]. There is growing evidence that LPS inhibits the transcription of genes related to ribosomal function and translation as well as mitochondrial processes, hence mediating the early direct harm to multiple cell lines of the host and triggering inflammatory cell systems [12]. C-reactive protein (CRP) is a well-established biomarker of infection and inflammation. It is one of a group of acute-phase reactant proteins whose synthesis in the liver is up-regulated by IL-6 [14]. It can attach to the phospholipid components of microorganisms, facilitating their removal by macrophages. Its principal limitation may be its low specificity as an adult sepsis biomarker, yet it is frequently employed for early onset sepsis screening (occurring during the first 24 hours) because its sensitivity is generally considered very high [15]. There are several problems with sepsis diagnosis, as it is a heterogeneous condition [16]. The early manifestations are frequently confusing since 20% to 30% of patients with severe sepsis do not exhibit evidence of organ dysfunction at hospital admission but instead develop septic shock during the first 24 hours following the initial evaluation [17]. It causes delayed diagnosis and treatment, or even overtreatment in some cases; this underscores the necessity for an early diagnostic biomarker. Several potential sepsis biomarkers have been identified and investigated in recent years [18]. This current study aimed to evaluate the level of endotoxin activity and the usefulness of C-reactive protein among patients with sepsis.

Materials and Methods

Study design

This cross-sectional observational study was conducted at the Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from March 2023 to February 2024. This study was approved by the Institutional Review Board (IRB), BSMMU (N- BSMMU/2023/10367) on 05/08/2023.

Study participants

A total of fifty (50) clinically diagnosed patients who were admitted to the Intensive Care Unit (ICU) of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, enrolled by purposive sampling technique following selection criteria.

Selection criteria

Adult patients (Aged≥ 18 years) of both genders with sepsis, as leveled by quick sequential organ failure assessment (qSOFA), patients with a history of chronic organ dysfunction (chronic kidney failure, chronic obstructive pulmonary disease, heart failure), patients having recent surgery, or recent invasive procedures, were enrolled in this

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DOI:10.26502/acbr.50170416

study. Patients having any immunodeficiency disorder or immunodeficiency virus (AIDS) or in immunosuppressive therapy and patients with any hematological diseases (such as a hematological tumor) were excluded from the study.

The sequential organ failure assessment (SOFA) score

The SOFA score is a quantitative scoring index that dynamically describes sepsis-related organ dysfunction, including the respiratory, coagulation, liver, cardiovascular, central nervous, and renal functions. Each organ system received a score ranging from 0 (average) to 4 (most abnormal), with a minimum SOFA score of 0 and a maximum SOFA score of 24 [1].

Quick sequential organ failure assessment (qSOFA) score

Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA, which includes- alteration in mental status, systolic blood pressure ≤100 mm Hg, or respiratory rate ≥22 breaths/minute [1].

Laboratory procedures

Blood sample collection

With all aseptic precautions, the selected venipuncture site was disinfected with povidone-iodine. Blood samples (14 ml venous blood) were collected from each patient using a sterile disposable syringe tagged with a butterfly needle. Fourteen ml (14 ml) of blood was collected and divided into two parts. The first part was for blood culture, which consisted of 10 ml. According to the procedure, this part was inoculated into an automated blood culture bottle (BacT/ ALERT® FA Plus aerobic blood culture bottle, France) [19]. The second part consisted of 4 ml of blood, which was taken in a sterile test tube without anticoagulant for serum preparation and shaken gently for proper mixing. The sample was brought immediately to the Department of Microbiology and Immunology, BSMMU, Dhaka, Bangladesh, in a leak-proof secondary container within a plastic biohazard specimen bag.

Processing of blood for culture

Inoculation of 10 ml of blood into the BacT/ALERT® FA Plus aerobic blood culture bottle was done, and the blood sample was shaken gently to mix with the media. Then, the blood culture bottle was inserted into the BacT/ALERT 3D automated blood culture machine (bioMérieux, France) for incubation at 37°C for five days as recommended [20]. After showing positive indicators on the machine, the bottle was withdrawn and processed accordingly. One ml of broth was withdrawn aseptically from the culture bottles for subculture. Subcultures were made onto 5% sheep blood agar and MacConkey agar plates. The Blood Agar and MacConkey Agar plates were incubated at 37°C for 18 to 24 hours. Identification of species of organism was done by VITEK-2 Compact System (Biomérieux, France).

Endotoxin detection

Serum endotoxin was estimated using a Bacterial Endotoxin Detection Kit (Chromogenic Method). Appropriately preserved serum from sepsis patients was used to determine endotoxin using the Kinetic ELISA method according to the manufacturer's instructions (Genobio Pharmaceuticals Co., Ltd., China, MO2021070301).

Detection of serum C-reactive protein (CRP)

Determination of serum C- reactive protein (CRP) level to screen for inflammatory processes in human serum using automated Siemens Healthineers immuno-nephelometry system.

Data analysis

A descriptive analysis of all relevant variables used frequency, percentage, mean, median, and standard deviation (SD). Collected data were checked and edited, and analysis was performed using the Statistical Package for Social Sciences (SPSS) version- 26. Data was analyzed using the Mann-Whitney test, Kruskal-Wallis H test, Spearman's Correlation test, and Receiver Operator Characteristics (ROC) curve analysis. A p-value <0.05 was considered statistically significant.

Results and Observations

This cross-sectional study was designed to evaluate the endotoxin activity to diagnose sepsis. In this study, blood samples were collected from 50 clinically diagnosed patients with sepsis. Automated blood culture and serum endotoxin and CRP levels were measured in the blood samples.

The mean age of the study patients was 58.92±18.22 years. Of them, 58% were male, whereas 42% of the study population was female. Male to female ratio was 1.4:1. The majority of the participants belonged to 61-70 years (36%) followed by >70 years (26%), then 51-60 years (12%) (Table 1).

Out of 50 study populations, automated blood culture was positive in 18 (36%) patients. Endotoxin showed a positivity of 17 (34%) cases and CRP showed the highest positivity [48 (96%)] among the study population (Table 2).

In this study, 48 (96%) study populations showed serum CRP levels>10mg/L, whereas 17 (34%) cases had serum endotoxin levels>0.5 EU/mL (Table 3).

In this study, culture-positive cases were 18 (36.0%) and culture-negative cases were 32 (64%). Serum CRP and endotoxin levels among culture-positive (n= 18) and culture-

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DOI:10.26502/acbr.50170416

Table 1: Age and gender distribution of the study population (N= 50).

Variables	Number (n)	Percentage (%)
Age (years)		
Age groups		
18-30 years	5	10
31-40 years	5	10
41-50 years	3	6
51-60 years	6	12
61-70 years	18	36
>70 years	13	26
Mean±SD	58.92±18.22 years	
Range (minimum-maximum)	18-75 years	
Gender		
Male	29	58
Female	21	42
Male to female ratio	1.4:1	

Table 2: Laboratory test results of the study population (N= 50).

Laboratory findings	Positive	
	Frequency (n)	Percentage (%)
Automated blood culture	18	36
Endotoxin	17	34
CRP	48	96

Table 3: Serum level of CRP and endotoxin among the study population (N= 50).

Biomarkers	Cut-off value	Frequency (percentage)
CRP mg/L)	>10 mg/L	48 (96.0%)
	≤10 mg/L	2 (4.0%)
Endotoxin (EU/mL)	>0.5 EU/mL	17 (34.0%)
	≤0.5 EU/mL	33 (66.0%)

negative cases (n= 32) have been compared. It was found that, the mean endotoxin level (0.78±0.39 EU/mL) and mean CRP level (132.10±88.62 mg/L) were higher in culture-positive cases than in culture-negative cases. A significant difference was observed in endotoxin levels between culture-positive and culture-negative cases (p<0.001). No significant difference was observed while comparing CRP between culture-positive and negative cases (p= 0.100) (Table 4).

The ROC curve analysis evaluates the predictive performance of endotoxin and CRP in identifying culture-positive cases of sepsis (n=18). Endotoxin exhibits the highest AUC (0.880), indicating excellent discriminative ability, with an optimal cut-off value of 0.541 EU/mL, achieving high sensitivity (83.3%) and specificity (93.3%). The p-values associated with AUCs indicate significant predictive performance for endotoxin (p<0.05), while CRP showed non-significant results (p>0.05) (Figure 1).

Table 5 demonstrates notable changes in CRP levels with endotoxin activity (EA) levels rise. A median CRP level did not exhibit any significant difference across EA levels (p= 0.424).

Figure 2 shows the correlation between CRP (mg/L) and qSOFA score among sepsis patients. Pearson correlation coefficient between CRP level and qSOFA showed a positive correlation and the correlation was significant (r=0.305; p=0.031).

Figure 3 displays the correlation between endotoxin (EU/mL) and qSOFA score in sepsis patients. Pearson correlation coefficient between endotoxin level and qSOFA showed a negative correlation and the correlation was not significant (r=-0.04; p=0.778).

Table 4: Comparison of serum endotoxin and CRP levels between culture-positive and culture-negative cases (N= 50).

Biomarkers	Culture		p-value
	Positive (n= 18)	Negative (n= 32)	
Endotoxin (EU/mL)			
Mean±SD	0.781±0.385	0.127±0.207	<0.001
Median	0.899	0.045	
CRP (mg/L)			
Mean±SD	132.10±88.62	92.85±71.21	0.1
Median	121.29	66.72	
***The p-value obtained by the Mann-Whitney test, p<0.05 was considered a level of significant**			

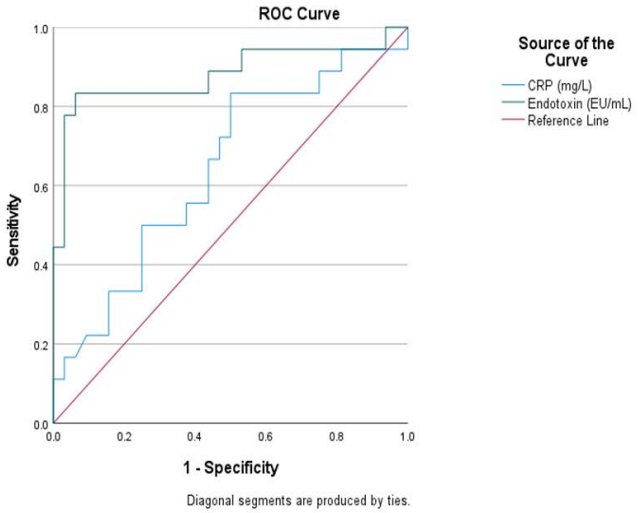

Figure 1: ROC curve analysis performed to predict the best cut-off value endotoxin (EU/mL) and CRP (mg/L) with culture-positive cases (n=18).

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DOI:10.26502/acbr.50170416

Table 5: Comparison of Endotoxin Activity (EA) levels with CRP level (n=50).

Biomarker	Endotoxin Activity (EA) levels					p-value
	<0.2 (n=30)	0.2-0.4 (n=3)	0.4-0.6 (n=3)	0.6-0.9 (n=4)	>0.9 (n=10)	
CRP (mg/L)						
Mean±SD	104.9±87.9	106.1±81.9	129.3±37.3	93.4±81.0	112.1±71.4	0.424
Median	66.7	93.1	107.8	91.9	80.3	
**** The p-value obtained by the Kruskal-Wallis H test, p<0.05 was considered a level of significant***						

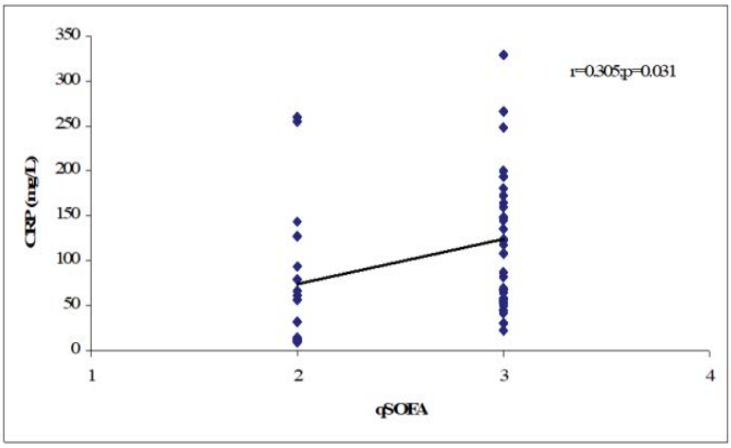

Figure 2: Correlation between qSOFA with CRP in sepsis patients.

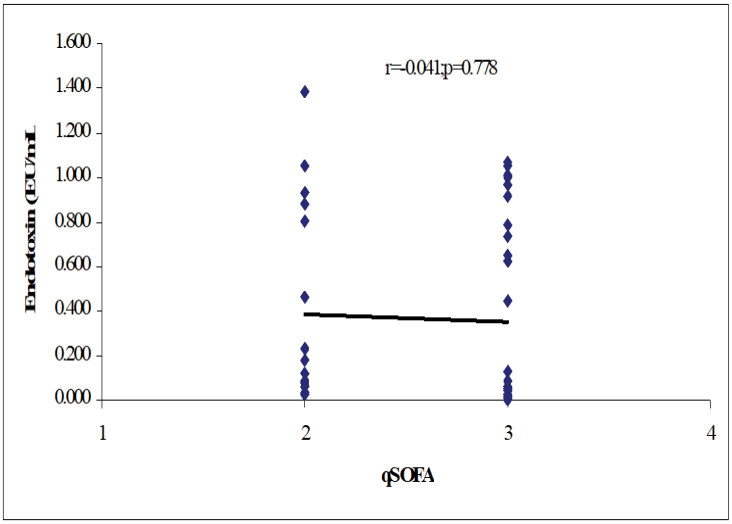

Figure 3: Correlation between qSOFA with endotoxin in sepsis patients.

Discussion

Sepsis is one of the primary healthcare problems affecting millions of people each year. One suggested strategy for preventing unfavorable outcomes is the early detection of at-risk patients and the guidance of early treatment. Less than one-half of the patients with sepsis signs and symptoms have positive blood culture or other microbiological confirmation of an infectious focus [21]. The present study evaluated the endotoxin activity level and usefulness of C-reactive protein as biomarkers in the serum of patients admitted to the Intensive Care Unit (ICU) to diagnose sepsis. In this study, most of the cases were from age group 61-70 years (36%) followed by >70 years (26%). The mean±SD age was 58.92±18.22 years. Older adults are more likely to develop sepsis probably due to impaired age-related immunologic defense and chronic health problems such as diabetes, COPD, kidney disease, or heart failure than any other age group [22]. The study by Kotfis et al. [23] showed that older people are

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more likely to develop sepsis than younger patients [23]. In this study, out of 50 study populations, gender distribution showed males predominantly develop sepsis, composing 29 (58%), while females are 21 (42%). Here, the male-to-female ratio was 1.4:1. Increasing evidence suggests that gender affects the host's response to sepsis. An important reason is that male sex hormones, i.e., androgen, suppress cell-mediated immune response. In contrast, the female sex hormone, i.e., estrogen, induces efficient cell-mediated and humoral immune responses [24].

In this study, the study participants had several comorbidities like- hypertension (40%), diabetes mellitus (39%), ischemic heart disease (16%), chronic kidney disease (14%), and others. According to a CDC report published in 2016, 238 (97%) patients had at least one comorbidity, 87 (35%) had diabetes mellitus, 79 (32%) had cardiovascular disease, and 50 (20%) had chronic obstructive pulmonary disease [25]. In the present study, among 50 study patients, 48 (96%) patients had a history of urinary catheterization with a mean duration of catheterization of 6.56±5.68 days, and 13 (26%) patients had CV line access with a mean duration of 4.15±2.88 days. This is consistent with the study by Abu-Humaidan et al. [26], in which it was shown that invasive procedures were significantly higher in patients with sepsis, where the use of a urinary catheter was almost 84.4%, followed by the central venous line (51.1%) [26]. The current study showed participants' mean leucocyte (WBC) count was 15±3.88/mm^3. Sepsis often coincides with high white blood cell counts [27]. In this study, 8 (16%) patients had died among a total of 50 study participants. This finding was consistent with the outcomes evident in a previous study, where a similar (16%) mortality was observed [28].

In this study, out of 50 study cases, the automated blood culture was positive in 18 cases. Here, culture-negative cases, 32 (64%), were higher than culture-positive cases, 18 (36%), which may be firstly due to patients receiving prescribed empirical antibiotics at local clinics before developing sepsis. Secondly, the proportion of sepsis cases caused by atypical pathogens, including fungal and viral infections, might increase. In addition, non-infectious causes, i.e., tissue injury, inflammatory diseases, metabolic disorders, malignancies, subarachnoid hemorrhage, and adverse effects of drugs, could have caused culture-negative sepsis [29].

In this study, out of 50 study populations, 17 (34.0%) had more than 0.5 EU/mL serum levels of endotoxin. The number of endotoxin positivity cases was lower in comparison to CRP. Multiple factors might be responsible for this. Endotoxins are released when a bacterial cell is lyzed by antibiotics or cytokines secreted by immune cells. Patients admitted to the ICU in critical condition receive antibiotic medication for an extended period. In a related study, endotoxin level in 32 out of 42 patients was found to be below the detection limit, possibly because endotoxin can bind to monocytes, red cells, and platelets [30]. Median endotoxin level was higher in the culture-positive group than the culture-negative group (0.899 versus 0.045), and the difference was statistically significant ($p<0.001$), indicating a potential association between endotoxin presence and positive-culture results. Endotoxin is the sole component of the outer cell wall of gram-negative bacteria, and it is specific for gram-negative sepsis [7]. The above finding aligns with the study by Adamik et al. [31], where it has been identified that infection with gram-negative bacteria is usually associated with a high level of endotoxemia [31]. For comparison between endotoxin activity (EA) level and CRP, 50 participants were divided into 5 groups based on their EA levels: less than 0.2 (<0.2), equal to or higher than 0.2, and lower than 0.4 (0.2-0.4), equal to or higher than 0.4 and lower than 0.6 (0.4-0.6), equal to or higher than 0.6 and lower than 0.9 (0.6-0.9) and equal to or higher than 0.9 (>0.9). Although the EA levels of most patients were in the (0.4-0.6) range, these levels were widely distributed in the range of 0-1. EA levels of most patients were in the <0.2 range, and the level of CRP changed as the EA value increased. The median CRP levels across different EA levels did not show significant variation ($p= 0.424$). This suggests a consistent inflammatory response regardless of endotoxin activity.

In this study, the ROC curve analysis evaluated the predictive performance of endotoxin and CRP in identifying culture-positive cases of sepsis. Endotoxin exhibited the highest AUC (0.880), indicating excellent discriminative ability, with an optimal cut-off value of 0.541 EU/mL, achieving high sensitivity (83.3%) and specificity (93.3%). In accordance, Shimizu et al. [32] showed in a study that endotoxin had 81.1% sensitivity and 76.6% specificity [32]. In this study, CRP showed moderate discriminative ability with an AUC value of 0.641. The p-values associated with AUCs indicated significant predictive performance for endotoxin ($p<0.05$), while CRP showed non-significant results ($p>0.05$). This finding highlights endotoxin may be a promising biomarker for identifying culture-positive cases of sepsis, providing valuable guidance for clinical decision-making in sepsis management. Each tested biomarker exhibited different characteristics, which likely reflect the differences in the mechanism by which the levels of these markers arose. Endotoxins are released into the circulation upon disruption of intact bacteria (death, cell lysis) [33]. CRP is secreted by the liver, which is up-regulated by IL-6 [15]. The timing of each biomarker increase is also different [34].

In the current study, the correlation between endotoxin count and CRP showed a positive correlation, but the correlation was not significant ($r= 0.060$; $p= 0.678$). As the diagnostic standard of sepsis, the qSOFA score is calculated according to the severity of organ failure. It is the predictor with the highest correlation in patients with sepsis. The

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DOI:10.26502/acbr.50170416

correlation analysis indicated that endotoxin level was negatively correlated with the qSOFA score but was not statistically significant. Conversely, qSOFA and CRP showed a significant positive correlation (r=0.305; p=0.032). This finding was supported by a related previous study [35].

The current gold standard for detecting sepsis is blood culture. Still, it is not flawless for several reasons, e.g., it depends on organism growth and requires days to become positive, even with other clinical signs and symptoms suggesting sepsis. In this study, the level of endotoxin activity and the usefulness of C-reactive protein among patients with sepsis were evaluated. In addition, endotoxin activity levels were compared with automated blood cultures. In summary, *Acinetobacter* species were predominant in culture-positive cases. Endotoxin exhibited a valuable marker for identifying culture-positive species. C-reactive protein (CRP) level changed with endotoxin activity (EA). CRP was positively correlated with a qSOFA score.

Conclusion

This study concluded that there is a significant difference in endotoxin activity level between culture-positive and culture-negative cases; endotoxin is a promising biomarker for identifying culture-positive cases of sepsis, providing valuable guidance for clinical decision-making in sepsis management. C-reactive protein (CRP) levels changed as the endotoxin activity (EA) value increased. Spearman correlation coefficients illustrated that serum CRP level displayed a non-significant positive correlation with endotoxin. Conversely, a non-significant negative correlation exists between qSOFA and endotoxin. Serum C-reactive protein levels are positively correlated with qSOFA scores.

Limitations of the Study

The current study has several limitations. It was a single-center study with a relatively small sample size. Endotoxin can only detect gram-negative sepsis, and C-reactive protein has low specificity as a biomarker of sepsis in adults.

Recommendations

Future studies may be recommended to evaluate the level of endotoxin activity and various biomarkers in severe sepsis and septic shock patients for a larger sample group.

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