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Research article

Evaluation of Diagnostic and Prognostic Accuracy of Serum C-Reactive Protein and Blood Cultures from Acute Infective Endocarditis Patients

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Abstract: Risk identification and early diagnosis in infective endocarditis patients are considered limited approaches due to their poor microbiological outcomes and slow diagnostic accuracy. To reduce these risks, a rapid identification marker is needed. The current study was designed with the objective of assessing C-Reactive Protein (CRP) efficiency as a means of evaluating the diagnosis of infective endocarditis and its prognostic ability, as well in comparison with blood cultures. CRP was performed using a sandwich-based enzyme-linked immunosorbent assay (ELISA), while the blood cultures were performed using a bacterial culture technique. Antibiotic susceptibility testing was performed to ascertain potential antibiotics to treat infective endocarditis. A total of 1789 patients with suspected endocarditis were recruited, of whom 381 were diagnosed as having infective endocarditis. All the serum samples were tested for CRP, and the blood samples were processed for blood cultures. CRP with less than 1.0 mg/dl was considered negative. Out of 1627 patients, a total of 381 had a positive or higher CRP serum level. The blood culture of 139 patients was positive, with *Staphylococcus aureus* being the most predominant (n = 46) pathogen. Hospital death was seen in 23 patients with a significantly high CRP level. During treatment, the responsive interventions showed a 20% decrease in disease severity; however, at the end of the treatment, after eradication of symptoms, CRP level varied in 59 patients. The current study concluded that CRP after the first week of treatment is a significant predictor of clinical outcome and can be used as a good prognostic marker.

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Introduction

Infective endocarditis (IE) is a term used to describe a collection of clinical symptoms all connected to endocardial infection (Cahill et al., 2017). The most serious kind is prosthetic-valve-associated endocarditis, which requires a different diagnostic and treatment strategy than is necessary to successfully treat native valve endocarditis (Wang et al., 2018). IE still has a significant fatality rate despite improvements in treatment with antimicrobial medicines and valve replacement. Despite the fact that the sickness often responds to sufficient antibiotic therapy, recurrent infection and fever might nevertheless arise (Pettersson and Hussain, 2019). As a result, it is challenging to assess whether the infection has responded to therapy. Recurrent infections have been linked to a variety of factors, including the development of biofilms and colonization (Rajani and Klein, 2020). Notwithstanding the fact that the blood antibacterial test is frequently used to

monitor the response, there is no current evidence to suggest that the test has a good predictive value (Iversen et al., 2019).

Current patient populations at risk for endocarditis include the growing number of those with congenital heart disease, those who require frequent medical attention due to various comorbidities, patients who are immunocompromised and receiving hemodialysis, as well as those who misuse IV medications (Hubers et al., 2020). Additional testing, such as magnetic resonance imaging, nuclear imaging, and computed tomography, may be helpful in some patients despite the necessity of trans-esophageal and trans-thoracic for diagnosis. As it is difficult to eradicate germs with medicines alone, and valve impairment usually results in hemodynamic compromise, early surgical intervention in high-risk patients has an impact on mortality (Erba et al., 2019). While treating a patient with endocarditis, good clinicians always expect a less rapidly declining inflammatory marker to assess the prognosis. Blood culture is considered the gold standard for the diagnosis of bacteremia (Źródłowski et al., 2020).

The CRP blood level is widely considered to be the most widely used inflammatory marker, and it plays a crucial role in the diagnosis and prognosis of a wide range of infectious disorders (Wolska and Remaley, 2022). The CRP is a protein made in the liver that has strong ties to infection-fighting capabilities (Lin et al., 2021; Mohanan et al., 2018; Nunes et al., 2018). It is judged that, if CRP levels remain high during the initial stages of treatment and the rate of CRP drop becomes slow, the clinical outcome will be unfavorable. Treatment length and CRP concentration with passing time have a substantial link to infectious diseases (Ris et al., 2019; Şimşek-Yavuz et al., 2021). The CRP has already been investigated as a determinant of diagnostic workup in IE (Rajesh et al., 2022). A poor prognosis has been demonstrated to be predicted by serial measures of a high serum level of CRP that is more than 122 mg/dL and greater than 62 mg/dL one to four weeks after the commencement of treatment, respectively; however, baseline serum CRP levels at the time of diagnosis do not predict the clinical course (Cornelissen et al., 2013). Blood culture evaluation during treatment could be an effective marker for the prognostic efficiency of treatment. However, this can be enacted only in culture bottles with additives that have the ability to neutralize antibiotics if a patient is already on antimicrobial treatment (Tascini et al., 2020). The current study was designed to establish the importance of CRP and blood culture as predictors of IE, and to determine which one has more diagnostic value in the prognosis of IE.

Materials and Methods

Study type and duration

The current cross-sectional study was conducted on patients diagnosed with IE between January 2024 and July 2024 at a tertiary care hospital in Haroonabad, Bahawalnagar, Punjab, Pakistan. Before starting the study, an ethical approval was obtained from the departmental/intuitional review board of the hospital.

Sample collection

Suspected patients were selected on a clinician's initial diagnostics comments, including fever spikes, chest pain, abnormal pulse rate or tachycardia, and history of heart disease or prosthetic devices. A convenient sampling technique was used and 1789 suspected infective endocarditis patients were included from a tertiary care hospital in Haroonabad, Bahawalnagar, Punjab, Pakistan. Blood samples were collected to check serum CRP and bacterial isolates causing IE. To perform the CRP test, the samples were collected in yellow capped gel tube/vacutainer (5 ml) and were allowed to clot first. After the sample clots, the samples were centrifuged at 10,000 rpm to separate the serum for further testing. For blood cultures, the samples were collected in BactAlert media plus aerobic (FA) and anaerobic (FN) bottles (Biomerieux, USA) (Jeverica et al., 2020). Media plus culture bottles have the ability to neutralize antibiotics if patients are on antimicrobial treatment.

Inclusion criteria

Initially, all of the patients suspected for IE were included in the study. Later, only patients who fulfilled Duke's criteria of IE, which includes positive blood cultures for IE, radiological evidence of endocardial involvement, predisposing heart condition, high fever, and vascular and immunological phenomena, were included in the current study for further comparative study (Philip et al., 2020). All of the included patients

were asked for their consent first to participate in the study, and were told about the study protocol. After the patients agreed, a signed consent form was obtained before the collection of samples for blood culture and CRP.

Exclusion criteria

Due to their highly immunocompromised immunity and air contact isolation restrictions, cancer patients and tuberculosis patients were not included in this study. Additionally, children younger than 10 years of age were excluded.

Sample Processing

All serum samples for CRP levels were performed on sandwich-based enzyme-linked immunosorbent assay (ELISA) kit of Thermo Fisher (Human C-Reactive Protein ELISA kit). Blood cultures were inoculated in FA and FN culture bottles and incubated in a Bactalert 3D microbial detection system (Biomerieux, USA) for 7 days until they became positive. After 7 days of incubation, the samples were considered negative.

Bacterial isolates identification

All the positive blood cultures were sub-cultured on blood agar for enrichment of growth, chocolate agar for fastidious organisms such as *Streptococcus pneumoniae*, MacConkey agar for Gram-negative selective and lactose fermenter bacteria, and non-lactose fermenter as differential media.

Bacterial growth isolated from positive blood culture was identified by VITEK 2 COMAPCT, based on a biochemical identification technique that has 100% sensitivity and 96% specificity (Höring et al., 2019). Apart from the identification using VITEK COMPACT, the final identification was counter-checked by bacterial colony morphology, biochemical identification, and Gram staining. The Gram-positive bacteria were grown on blood and chocolate agar, while the Gram-negative bacteria were grown on MacConkey agar. For biochemical identification of Gram-positive bacteria, tests such as catalase, DNAs, and coagulases were performed, while for Gram-negative bacteria, tests such as indole, citrate, oxidase, and analytical profile index (API) were used.

Antibiotic susceptibility testing (AST) of isolated bacterial isolates

After the final identification of bacterial isolates, the isolated colonies of bacteria were used for AST by following the recommended guidelines from clinical laboratory standards institute (CLSI) . The purpose of the AST test was to identify the potential antibiotics to treat IE. The Kirby Bauer disc diffusion test was used to perform the AST of the bacteria, and minimum inhibitory concentrations (MICs) were used wherever specified by the CLSI guidelines for certain antibiotics (for example, vancomycin). The bacterial colonies were diluted, and the turbidity was compared to the 0.5 McFarland standard, in order to examine the susceptibility patterns. Then, using a sterile cotton swab, the mixture was distributed onto a Muller Hinton (MH) agar plate and the antibiotic disks were dispensed on it. The plates were incubated at 37°C for 18 to 24 hours. After incubation, a labelled measuring scale was used to identify the zone of inhibitions (ZOIs). For each antibiotic vs. pathogen, the ZOI was measured, and the findings were interpreted for each pathogen in accordance with CLSI guidelines. Methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA) screening was performed based on the susceptibility pattern of a disc diffusion test using 30 µg of cefoxitin (FOX) at 33–35°C for 16–18 hours.

For possible Gram-positive bacterial isolates, the panel on antibiotics comprised amikacin (30 µg), gentamicin (10 µg), tobramycin (10 µg), chloramphenicol (30 µg), ciprofloxacin (5 µg), levofloxacin (5 µg), cefoxitin (30 µg), erythromycin (15 µg), clindamycin (2 µg), linezolid (30 µg), teicoplanin (30 µg), and Vancomycin. For Gram-negative bacterial isolates, the panel of antibiotics comprised amoxicillin-clavulanate (20 µg), amikacin (30 µg), gentamicin (10 µg), tobramycin (10 µg), levofloxacin (5 µg), ciprofloxacin (5 µg), tetracycline (30 µg), ceftazidime (30 µg), ceftriaxone (30 µg), cefixime (30 µg), and cefepime (30 µg). The ZOIs were determined with millimeters (mm) as the standard unit. The findings were reported as resistant, sensitive, or intermediate based on CLSI reference ranges.

Statistical analysis

Discrete parameters were presented as median or mean ± SD and interquartile range in parenthesis unless stated otherwise. Two groups of non-parametric assessments were also computed. The chi-square test was performed to check the correlation between CRP levels in post-treatment, CRP levels during treatment, and CRP levels at diagnosis or clinician observation. A *p*-value of < 0.05 was considered statistically significant.

Results

From 1789 suspected endocarditis patients, 381 had infective endocarditis, as per the duke criteria; prolonged fever, positive blood culture, and prosthetic valves were common. In total, 381 were blood culture positive among the 1789 suspected patients, and fever (more than 98.6 F) was present in 163 (42%) out of 381 patients during their visit to clinician or admission. The average age of the included patients was 37±19, and 1440/1789 of them were male (almost 80.4%). CRP level below 10 mg/L was considered normal (Yang et al., 2018); this was more than 10 mg/L in 1627 out of 1789 patients, which was about 91%. Other characteristics are mentioned in the **Table 1**.

Table 1. Characteristics and parameter frequency.

Characteristics	**Parameters**	**Out of 1789**
Serum marker	CRP >10 mg/L	1627
Valve	Prosthetic valve	113
Infection acquired	Nosocomial	181
	Community acquired	141
	Other	59
Underlying complications	Heart failure	39
	Bacteremia persistent	73
	CNS involvement	54
	Valve insufficiency	103
	Hospital death	23
	Embolism	17

Infection endocarditis was categorized as nosocomial infection or hospital-acquired infection (47.5%), based on the absence of fever at the time of hospital admission. Community-acquired infection was 37%, based on the very first blood sample being positive before admission among the 381 blood positive patients. Other underlying diseases such as central nervous system (CNS) involvement, valve insufficiency, and embolism were diagnosed as clinical symptoms based on clinician or physician diagnostic comments.

Bacterial Isolation

All the isolated growths were tested on VITEK 2 COMPACT identification cards (Gram-negative Ref # 21341 and Gram-positive Ref # 21342). A selection of cards for specific growth was selected after the Gram staining of all the isolates. Bacterial growth was obtained from positive blood culture, and all the isolated organisms are mentioned in **Figure 1**.

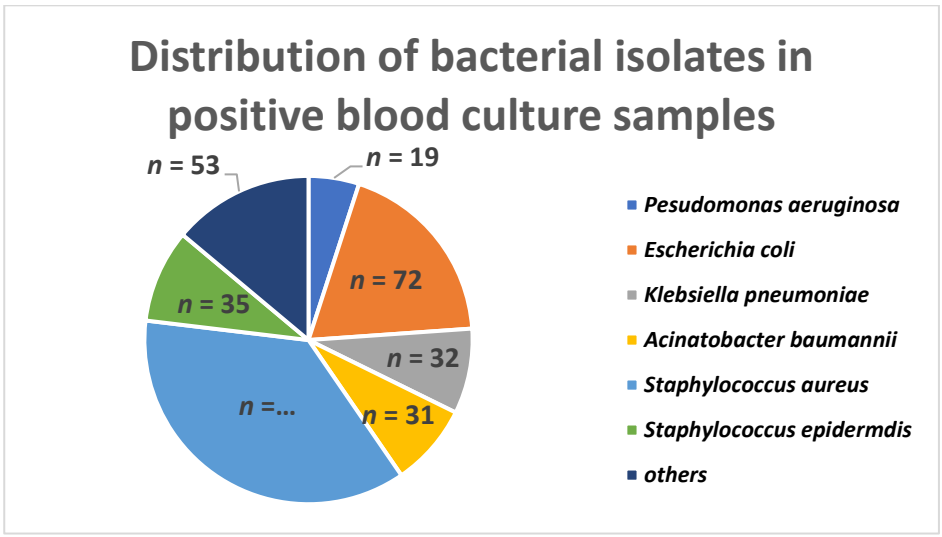

Figure 1. Prevalence of bacterial isolates in positive blood cultures.

Serum CRP over 6.3 mg/dL predicts hospital death by up to 77%, and the ratio of positive CRP and positive blood culture was four CRP positive and three positive blood culture, respectively **(Figure 2)**.

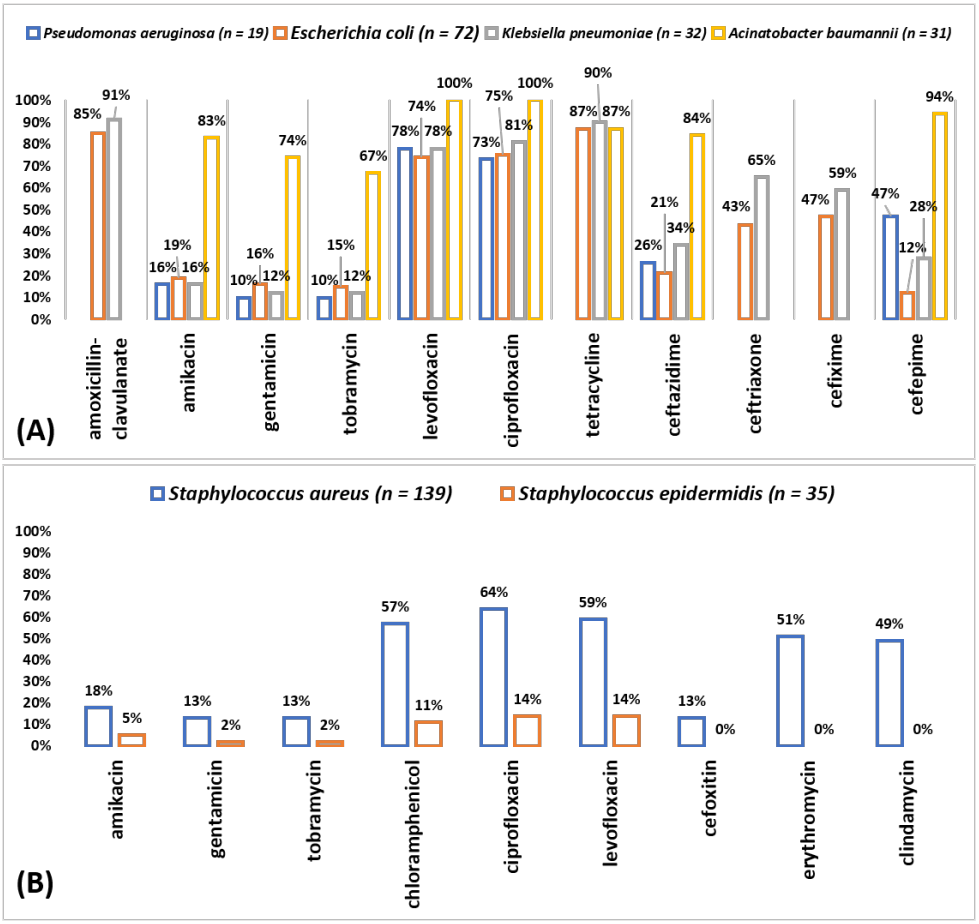

Figure 2. Antibiotic susceptibility patterns (ASP) of isolated bacterial isolates. (A) ASP of Gram-negative bacterial isolates. (B) ASP of Gram-positive bacterial isolates.

We also observed that a decline in CRP of more than 20% in the first week of treatment could eradicate disease complications, resulting in a lowered risk of hospital death. CRP levels of different clinical variables at the time of diagnosis are in **Table 2**. CRP levels of different variables during treatment are shown in **Table 3**.

Table 2. CRP levels at diagnosis or clinician observation.

Clinical variable	N	CRP level (Mean±SD)	*P*-value
Infection acquiring			
Community	141	9.8±7.5 mg/dL	0.040
Nosocomial	181	17.3±09.5 mg/dL	
Valve in infective endocarditis			
Prosthetic	113	12±9.9 mg/dL	0.024
Native (Natural)	268	8.8±5.5 mg/dL	

Table 3. CRP during treatment.

Clinical variable	N	CRP level (Mean±SD)	*P*-value
Hospital Deaths			
Yes	23	13.9±7.3 mg/dL	< 0.001
No	358	4.5±4.8 mg/dL	
Symptoms in infective endocarditis patients			
< 2 weeks	242	8.4±9.1 mg/dL	0.045
> 2 weeks	139	4.6±4.1 mg/dL	

At the end of treatment, 242 out of 381 patients showed normal CRP levels **(Table 4)**. Regarding recurrence, this is associated with increasing CRP values. Reduced values and a rapid fall in CRP serum levels during the first week of IE therapy were related with a lower proportion of problems and mortality. The absence of a normal CRP level at the end of treatment predicted the likelihood of recurrence. The results underline the necessity of dynamic changes in inflammatory parameters rather than considering unique cut-off values. Well-designed prospective studies are needed to elucidate the function of CRP in infective endocarditis.

Table 4. CRP levels after treatment.

Clinical variable	N	CRP level (Mean±SD)	*P*-value
Recurrence			
No	260	1.3±1.0 mg/dL	< 0.001
Yes	121	5.9±4.1 mg/dL	

Initially, 381 patients had positive blood culture but, after the first week of treatment, this decreased to 139 (36%), with a *p*-value less than 0.05; after the second week, positive blood cultures decreased to 73 (19%). These 19% of patients had persistent bacteremia.

Discussion

In this study, we established the role of CRP and blood culture in the diagnosis and prognosis of IE. The CRP serum level regularly changes with treatment responses, as does blood culture positivity. For the confirmation of infective endocarditis, this study followed Duke criteria that states there must be two independent blood cultures, plus proof of endo-cardiac involvements, which are generally identified by echocardiography. Regardless of these factors, IE identification in daily clinical practice requires knowledge and time. As such, a hallmark for IE detection in reported incidents would be highly useful (Hecht and Berger, 1992; Romano et al., 2004). In a previous study conducted by Mueller at al., they established that PCT and CRP were significant biomarkers for the identification of infective endocarditis (Mueller et al., 2004). According to a previous study, the relevance of serial CRP levels as a predictor of clinical success in IE has provided conflicting results. In prospective study, CRP level was evaluated serially in 21 patients with IE who were originally treated utilizing

antimicrobial therapy alone (Ribeyrolles et al., 2019; Zampino et al., 2021). Negative blood cultures for suspected infective endocarditis patients in the current study were 1408 (79%) out of 1789; these values are nearly equal to previously published studies that have found blood culture failure rates as high as 71% (Liesman et al., 2017).

In the current study, we observed that IE patients treated with antibiotics had good responses, which was indicated by a decreasing pattern of CRP as the treatment progressed. In the current study, hospital mortality was evaluated using prognostic efficiency of CRP serum level. As shown in Table 3 there were seven patients who were diagnosed with infective endocarditis with a serum CRP level greater than 7mg/dL, on average; however, patients with low CRP values showed a good response to treatment. Similar results have been identified in previous studies that show the investigation of CRP can be independently evaluated in terms of hospital death, a composite of severe disease complications, some other embolic events, and the requirement for urgent surgery. In a prior prospective investigation, Heiro et al. assessed the predictive role of monitoring CRP levels throughout hospitalization among 134 IE patients, and they found it to be useful (Cornelissen et al., 2013; Heiro et al., 2007; Nunes et al., 2018). High CRP levels were found to be useful in predicting short-term and one-year mortality in another retrospective study of a Finnish population (Heiro et al., 2007).

One of the most difficult critical care decisions that physicians and cardiologists encounter is IE management (Sebastian et al., 2022; Yu et al., 2022). Culture-negative endocarditis, Duke criteria's limited sensitivity, and challenging vegetation characterization are important impediments to early risk classification (Alavi et al., 2009; Polzin et al., 2022). As described in previous study, CRP was discovered as an independent and substantial predictor of complications, in-hospital mortality, and six-month mortality within the first three days of admission. A CRP level greater than 40 mg/l had a sensitivity of 73% and a specificity of 98% for predicting a severe problem. Large-scale prospective studies involving several centers are required to further characterize the prognostic relevance of CRP and to facilitate its incorporation into diagnostic and risk-stratification algorithms for IE (Mohanan et al., 2018). In this study, decreased readings and a significant reduction in CRP serum concentrations in the first week of IE medication were connected to a smaller percentage of complications and death. The lack of normalized CRP levels by the end of therapy suggested the chance of recurrence. In a study conducted by G Cornelissen et al. in 2013 (Cornelissen et al., 2013), a total of 43 (86%) infectious endocarditis patients were identified in terms of CRP (169 had *Staphylococcus aureus* versus all other isolated pathogens 86, $p = 0.11$); however, in the current study, the most raised values of CRP were seen among infection with *Staphylococcus aureus*.

Study Limitations: Although the current study reported many parameters which could help in the diagnosis of IE, but because of the ethical approval restrictions from the study site, the current study does not report the radiological investigations of patients.

Conclusion

CRP can be considered a significant marker for infective endocarditis prognosis. Both during treatment and at its conclusion, a baseline CRP level comparison showed a decreasing trend of CRP with decreasing complications of disease. However, blood culture results also showed a decreasing trend, but persistent bacteremia could be a false positive indicator or lead to uncertain prognostic markers. Additionally, the findings emphasize the importance of dynamic changes in inflammatory markers over single cut-off levels. To better understand the role of CRP and blood culture in infective endocarditis, well-designed prospective studies are required.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Tehsil Headquarter Hospital, Haroonabad, Bahawalnagar, Punjab, Pakistan.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: More data will be provided upon a reasonable request to the corresponding author.

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