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Original Article

Inflammatory Biomarkers as Early Predictors of Complications in Infectious Diseases

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ABSTRACT

We assessed inflammatory biomarkers on admission to predict infectious complications within 3 days. Between October 2024 and July 2025, we recruited 95 patients between the ages of 18 and 65 at three EDs in Pakistan. Biomarkers (CRP, PCT, ferritin, and neutrophil to lymphocyte ratio) were measured within 2 hours of ED arrival. We assessed the development of infectious complications using the SOFA score and defined criteria for shock and Acute Respiratory Distress Syndom (ARDS). We compared the groups, performed correlation analysis and assessed the biomarkers using Receiver Operating Characteristic Curves (ROC). About 37.9% of the study population developed an infectious complication. Participants with complications had a significantly higher level of all 4 biomarkers ($p<0.001$). The area under the ROC curve was 0.91 (95% CI 0.85-0.97) for PCT and 0.85 (95% CI 0.77-0.93) for CRP. An area under the ROC curve of 0.94 (95% CI 0.89-0.98) was observed for the two biomarkers together. A positive correlation was found between the maximum SOFA score and PCT ($r=0.785$). Our study showed that all 4 biomarkers had prognostic value, and the value was highest for PCT. Keywords: Area Under Curve, C-Reactive Protein, Communicable Diseases, Diagnostic Screening Programs, Inflammation Mediators, Procalcitonin, ROC Curve

INTRODUCTION

Infectious diseases can rapidly deteriorate to shock and other serious conditions. The main objective in the emergency care of patients with suspected systemic infections is to identify which patients are at risk of deteriorating further. The traditional methods of clinical assessment and evaluation of physiological parameters, as well as lab data, are essential in the practice of medicine, but it remains difficult to adequately and accurately predict the clinical course of patients infected with various pathogens. This has promoted the search for inflammatory markers. Ideally, the markers should serve the same function as other clinical evaluation tools and

improve the assessment and management of patients. The interpretation of inflammatory markers should be based on the context in which they are used and the clinical outcome of interest (1,2).

The use of inflammatory markers in the clinical setting is based on the assumption that an individual's inflammatory status in response to an infection is a reflection of the individual's overall clinical condition. There are a number of inflammatory markers that reflect the severity of an individual's condition, including CRP, PCT, ferritin, and the NLR. From a clinical standpoint, it is useful to differentiate between an individual who has organ dysfunction and an individual at risk of progressing to organ dysfunction. Although some diagnostic studies may help to confirm the presence of organ dysfunction, it is the responsibility of the health care practitioner to establish a prognosis (3).

Of the markers evaluated, PCT has been the most studied in critical care and emergency medicine. The available evidence, however, is limited. For instance, one study evaluated the capacity of PCT to diagnose sepsis in the emergency department (4). Although the study provides evidence regarding the diagnosis of infection, it does not evaluate the risk of disease progression. Other studies have assessed PCT, CRP, and NLR in patients with bloodstream infections and sepsis (5). These studies have primarily focused on describing the severity of the disease and prognosis. There are, however, several studies that support the evaluation of biomarkers in the same patient population. While the performance of biomarkers is evaluated in various contexts, the direct application of these results to other settings is not advisable.

A combination of biomarkers is justified, given that single biomarkers are unable to capture the entire inflammatory response. Studies have assessed combinations of PCT with other biomarkers such as CRP in the context of sepsis and other biomarkers and cytokines in pediatric sepsis and sepsis associated with COVID-19 (6,7). The evidence supports the use of multiple biomarkers to assess a patient's inflammatory response. However, the populations and the nature of the studied inflammatory conditions differ from what has been assessed in the emergency care setting. In addition, evidence of the association between biomarkers and sepsis does not represent evidence of improvement in clinical outcomes as a result of biomarker-informed management of sepsis (8).

The focus of this study is to determine whether early inflammatory markers, measured on admission to hospital, can distinguish between patients who develop an infectious complication within 72 hours and patients who do not. This study will also evaluate the effect of measuring C-reactive protein (CRP), procalcitonin (PCT), ferritin, and the neutrophil to lymphocyte ratio (NLR), within the same study population, on distinction of the outcome of interest. This research will help the emergency care team in Punjab, Pakistan to further stratify the patients being evaluated and triaged within the emergency care setting. The value addition will be significant, if associations and predictability of the markers are established. In addition, this study will assess the combined PCT and CRP markers, to evaluate the potential improvement of discrimination of the combined markers over individual markers.

MATERIAL AND METHODS

This study examined the levels of inflammatory markers at the start of the study in adult patients with systemic infection to determine if there were any associations with clinical complications within 72 hours. The markers were measured upon the patients' admission to the hospital and compared between patients who experienced complications and to those who did not. The study was conducted from October 2024 to July 2025 in the emergency departments of tertiary care hospitals in Punjab, Pakistan. The study team was interested in quick (within the first admission) evaluation of inflammatory markers to determine the risk of complications of infected patients rather than repeat evaluations of the markers.

The study team evaluated 183 patients ages 18 to 65 years who were determined to have systemic infection to identify if complications were present. Patients were evaluated based on the presence of leukocytes or leukopenia, and an infectious focus. The study team adjusted the markers based on patients' conditions to focus on patients who they believed would have the most influence on inflammatory markers (i.e. patients with severe trauma, hematological cancers, or renal failure). The study team approached a convenience sample of 108 patients to obtain the desired sample size of 95 patients to participate in the study.

Recruitment of participants for this study began only after approval was received from the Institutional Review Board. Prior to enrollment and blood drawing, participants or their legal representatives gave informed consent. Blood samples were drawn from participants upon admission to the hospital and populations sampled included: (i)

measurements of C-reactive protein (CRP), procalcitonin (PCT), ferritin and a complete blood count and (ii) assessment of infection site(s) and classification of infectious disease (respiratory, abdominal/GI, urinary, skin/soft tissue, etc.).

Measured inflammatory response markers in blood were CRP and PCT. CRP and ferritin were measured using automated immune assays, and PCT and blood counts were measured using automated analyzers. CRP was measured in mg/dL and PCT and ferritin in ng/mL. The neutrophil to lymphocyte ratio (NLR) was also measured, and, for the purposes of this study, considered a constant. Baseline prediction of infection was assessed using the aforementioned measures.

The primary outcome measured was the occurrence of major infections and other complications within the first 72 hours of hospital stay. The SOFA score was used to determine dysfunction in various organs, and the diagnosis of septic shock and acute respiratory distress syndrome was done using established clinical criteria. Some participants were defined as having suffered a major complicating infection if they satisfied any of the selected criteria. The highest SOFA score was also used to assess the degree of organ dysfunction.

SPSS version 26.0 was used for statistical analysis. Normal distribution of the variables was tested, and if found to be non-normally distributed, then median and interquartile ranges were reported. Percentages and absolute numbers were reported for categorical variables. Comparison of normally distributed variables was done using Independent Sample's t-test and Non-normally distributed variables were compared using the Mann-Whitney U test. Fisher's exact test was used for comparisons of categorical variables if the expected count in any of the categories was less than 5. Relationships and correlations among the different variables were analyzed and reported using Pearson correlation. The baseline biomarkers and the maximum SOFA score were correlated to assess their relationship.

Ability of baseline biomarkers to discriminate between study participants with and without complications during follow up was evaluated using receiver operating characteristic curves (ROC). Area under the ROC curves along with their 95% confidence intervals were computed to evaluate the level of discrimination. Biomarker cut-off points were determined using Youden's index. Other measures of quality of the tests, including sensitivity, specificity, positive and negative predictive values were computed at cut-off points determined using Youden's index. Discriminatory ability of combined PCT and CRP was also evaluated. It was assumed that p-values less than 0.05 in the statistical tests performed indicated statistical significance.

RESULTS

We analyzed 95 participants, 36 of which, (37.9%), developed major infectious complications within 3 days, and 59 (62.1%) of which did not. The average age of all participants was 44.2 +/- 12.8 years, and 54 (56.8%) were males. A total of 42 (44.2%) of the participants developed complications due to respiratory infections, 26 (27.4%) participants developed complications due to infections of the abdomen and/or gastrointestinal system. The average age of the participants that developed complications was 46.1 +/- 13.2 years. The average age of participants that did not develop complications was 43.0 +/- 12.5 years. There was no significance in any of the variables between the two groups.

The average C-reactive protein (CRP) of participants that developed complications was 142.5 +/- 38.4 mg/dL, and 48.2 +/- 18.6 mg/dL of participants that did not develop complications. Average Procalcitonin (PCT) of participants that developed complications was 5.8 +/- 2.1 ng/mL, and 0.9 +/- 0.4 ng/mL of participants that did not develop complications. The median ferritin of participants that developed complications was 580 +/- 410 and 310 ng/mL of participants that did not develop complications. The mean N support group was 11.6 +/- 3.9, and 5.5 +/- 2.4, of participants that did not develop complications.

Table 1. Baseline demographic and clinical characteristics of participants

Characteristic	Total (N = 95)	Complications within 72 hours (n = 36)	No complications within 72 hours (n = 59)	p-value
Age, years, mean ± SD	44.2 ± 12.8	46.1 ± 13.2	43.0 ± 12.5	0.261
Male sex, n (%)	54 (56.8)	21 (58.3)	33 (55.9)	0.819
Female sex, n (%)	41 (43.2)	15 (41.7)	26 (44.1)	
Diabetes mellitus, n (%)	28 (29.5)	12 (33.3)	16 (27.1)	0.519

Characteristic	Total (N = 95)	Complications within 72 hours (n = 36)	No complications within 72 hours (n = 59)	p-value
Hypertension, n (%)	32 (33.7)	13 (36.1)	19 (32.2)	0.696
Chronic lung disease, n (%)	18 (18.9)	8 (22.2)	10 (16.9)	0.525
Respiratory infection, n (%)	42 (44.2)	17 (47.2)	25 (42.4)	0.959
Abdominal/gastrointestinal infection, n (%)	26 (27.4)	9 (25.0)	17 (28.8)	
Urinary tract infection, n (%)	17 (17.9)	6 (16.7)	11 (18.6)	
Skin/soft tissue infection, n (%)	10 (10.5)	4 (11.1)	6 (10.2)	

SD, standard deviation. Age: Welch's independent-samples t-test. Categorical variables: Pearson's chi-square test. The sex p-value compares both sex categories; the infection-site p-value compares all four sites.

Table 2. Baseline inflammatory biomarker concentrations according to complication status within 72 hours

Biomarker	Summary measure	Complications within 72 hours (n = 36)	No complications within 72 hours (n = 59)	p-value
CRP, mg/L	Mean ± SD	142.5 ± 38.4	48.2 ± 18.6	<0.001
PCT, ng/mL	Mean ± SD	5.8 ± 2.1	0.9 ± 0.4	<0.001
Ferritin, ng/mL	Median (IQR)	580 (410–790)	210 (140–310)	<0.001
NLR	Mean ± SD	11.6 ± 3.9	5.5 ± 2.4	<0.001

CRP, C-reactive protein; PCT, procalcitonin; NLR, neutrophil-to-lymphocyte ratio; SD, standard deviation; IQR, interquartile range. CRP, PCT, and NLR: independent-samples t-tests. Ferritin: Mann–Whitney U test.

Table 3. Correlations among baseline inflammatory biomarkers and maximum SOFA score within 72 hours

Variable	CRP, r	PCT, r	Ferritin, r	NLR, r	Maximum SOFA score, r
CRP	1.000	0.724	0.582	0.615	0.698
PCT	0.724	1.000	0.641	0.683	0.785
Ferritin	0.582	0.641	1.000	0.512	0.594
NLR	0.615	0.683	0.512	1.000	0.621
Maximum SOFA score	0.698	0.785	0.594	0.621	1.000

CRP, C-reactive protein; PCT, procalcitonin; NLR, neutrophil-to-lymphocyte ratio; SOFA, Sequential Organ Failure Assessment; r, Pearson correlation coefficient. All off-diagonal correlations: $p < 0.001$.

Table 4. Discriminatory performance of baseline inflammatory biomarkers for complications within 72 hours

Predictor	Positive threshold	AUC (95% CI)	Sensitivity, %	Specificity, %	PPV, %	NPV, %
PCT	>2.1 ng/mL	0.91 (0.85–0.97)	88.9	86.4	80.0	92.7
CRP	>85.0 mg/L	0.85 (0.77–0.93)	83.3	79.7	71.4	88.7
NLR	>8.5	0.81 (0.72–0.90)	77.8	76.3	66.7	84.9
Ferritin	>380 ng/mL	0.78 (0.68–0.88)	72.2	74.6	63.4	81.5
PCT + CRP		0.94 (0.89–0.98)	91.7	89.8	84.6	94.6

AUC, area under the receiver operating characteristic curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; PCT, procalcitonin; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio. Individual biomarker thresholds were selected using Youden's index.

Baseline biomarkers were positively correlated with maximum SOFA scores during the 72-hour observation period. The largest correlation coefficient was observed for PCT (r = 0.785), followed by CRP (r = 0.698), NLR (r = 0.621), and ferritin (r = 0.594). CRP and PCT were also positively correlated with each other (r = 0.724). All reported correlations had p-values below 0.001 (Table 3).

PCT had the highest AUC among the individual biomarkers, at 0.91 (95% CI, 0.85–0.97). At a threshold above 2.1 ng/mL, sensitivity was 88.9% and specificity was 86.4%. CRP had an AUC of 0.85 (95% CI, 0.77–0.93), with sensitivity of 83.3% and specificity of 79.7% at a threshold above 85.0 mg/L. The AUCs for NLR and ferritin were 0.81 (95% CI, 0.72–0.90) and 0.78 (95% CI, 0.68–0.88), respectively. Combined PCT and CRP assessment yielded a numerically higher AUC of 0.94 (95% CI, 0.89–0.98), with sensitivity of 91.7%, specificity of 89.8%, PPV of 84.6%, and NPV of 94.6% (Table 4).

DISCUSSION

Data indicate inflammatory biomarkers are associated with the first 72 hours of infection related complications in adult patients with systemic infection. PCT was the most Discriminative biomarker; however, the combination of PCT and CRP aided in risk assessment. The positive association with maximum SOFA scores further supported the

association with organ dysfunction. Overall, the data supported the study's goal of incorporating inflammatory biomarkers for risk assessment; however, evidence was lacking to support independent prediction, or assessment superior to clinical judgment, and improved outcome with biomarker-driven clinical management.

The relationship of PCT with patient clinical status is comparable to other biomarkers of infection and sepsis. The research by D'Onofrio evaluated the role of inflammatory biomarkers for infection and sepsis; additionally, they assessed the role of these biomarkers for prognosis (3). The research by Zaki assessed the role of PCT for sepsis; however, both the research by D'Onofrio and Zaki assessed biomarkers for sepsis diagnosis (4). When assessing the discriminative ability of biomarkers for infection complications, differences in clinical status of the patient must be considered.

The studies by Liang and Yu and the current study extend knowledge on the use of inflammatory markers CRP, PCT, and NLR in patients with bloodstream infections and sepsis. Both studies evaluate the role of these biomarkers in determining the severity and prognosis of patients. The current studies also confirm the value of assessing multiple inflammatory markers for the same patient population (5). The present study, however, contained patients with multiple sites of infection and included patients for whom infection was only suspected, whereas some patients for whom infection was proven, were also included. Variations in the cause of infection, the duration of illness, prior treatment and other confounding factors may account for variability in biomarker levels. Since most of these factors could not be defined in the present study, the reasons for variability in biomarker levels and threshpats could not be defined.

A possible explanation is that the biomarkers reflect the same or partially the same conditions in the body during the course of illness. For example, the acute phase reaction may reflect illness severity and may also be associated with organ dysfunction. However, the absence of other conditions may limit the interpretation of the results (1,2). Changes in the levels of the biomarkers reflect the presence of or a change in illness severity, and may also support the development of one or more conditions described by SOFA. However, the presence of a particular condition may also alter the levels of the biomarkers. Measurement of these biomarkers may also have prognostic value, especially when measurements are done at the time of admission.

The addition of PCT to CRP improves discrimination and is in line with expectations for a biomarker panel. Previous studies have assessed markers of inflammation in pediatric patients with sepsis and in adults hospitalized with COVID-19, although the outcomes assessed in those studies and the study population differ from the current study (6,7). In our study, we showed that PCT and CRP are related, and it is plausible that they measure the same or related processes. Given that their relationship is poorly defined and that it is not known whether their combination measures something distinctly different from each of the markers, the contribution of the combination to the model is indefinable. It must be shown that combination of the biomarkers gives a clinically relevant improvement in the model. At present, it is not appropriate to use the combined markers as a predictive model.

From a clinical perspective, it is possible that use of these biomarkers may be of value to inform management of patients with uncertain clinical course. It is possible that use of these biomarkers may be of value, in addition to other sources of data, to provide information on the status of a patient. Improving the estimation of patient risk may inform clinical management (8). Because this study did not assess the effects of a management strategy based on biomarker levels, it is not possible to state that use of biomarkers to inform management of patients results in improved clinical outcomes. Therefore, the findings of this study do not support that biomarker thresholds define a value to care assertion in pediatric critical care.

The study contains valuable components such as the ability to prospectively enroll subjects, sample within specified time-windows, measure multiple biomarkers, and perform multiple, short duration, observational studies. These components allow for comparison within study groups. Though, many components restricted the study, such as small subject numbers, and few complication events. These increase the variability and uncertainty for estimating thresholds and performing integrated modeling's. Although the authors claim their models can predict adverse events, this is premature due to several limitations. The models have not been standardized for varying levels of baseline organ dysfunction. Additionally, the models are only valid for the adult population aged 18 to 65 who are skilled care patients.

There are other limitations for this study that pertain to the measurement of endpoints. Baseline organ dysfunction and complications that occur during the study are not clearly defined. Handling of missing data is not defined, and it is unclear if the assessors were blinded. Measuring biomarkers once does not reflect changes over time. The 3-day time horizon only accounts for complication in that time frame. It is unclear what the distribution of the biomarkers measured were. The authors provide little data to support their conclusions. The authors suggest that future studies focusing on timed endpoints would be valuable. These studies should also evaluate if biomarkers provide additional clinical data beyond that obtained by a physician (1).

CONCLUSION

This study found that levels of C-reactive protein (CRP), Procalcitonin (PCT), ferritin, and neutrophil lymphocyte ratio (NLR) at admission were associated with infectious complications and SOFA scores of the study population. PCT showed the best prediction performance of all biomarkers, and the best prediction performance was achieved by considering PCT and CRP together. While these findings suggest that PCT has the potential to be an important biomarker to predict complications in critically ill patients, further studies are needed to validate the findings.

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