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# ROLE OF INFLAMMATORY BIOMARKERS IN EARLY DETECTION OF SEPSIS AMONG TRAUMA ICU PATIENTS

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**Abstract**
Sepsis is leading to potentially preventable morbidity and mortality in critically injured patients, and its early diagnosis is difficult because it shares the same clinical features with sterile inflammation. The diagnostic accuracy of inflammatory markers for sepsis in trauma ICU patients was the objective of this study in Pakistani patients. During (May 2024- April 2025) prospective observational cohort design was conducted at Jinnah Postgraduate Medical Centre (JPMC), Karachi. One hundred and eighty adult trauma patients fulfilling the inclusion criteria were recruited prospectively with baseline demographic and clinical information collected in addition to sequential biomarker collection. Blood samples were obtained at entry time (0 h), and 24 h, 48 h, 72 h after randomization to determine procalcitonin (PCT), C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). The diagnosis of sepsis was based on Sepsis-3 criteria, and statistical analyses, such as receiver operating characteristic (ROC) curve analysis, and bio score modeling were executed with SPSS 26.0. There was a 32.2% (n=58) incidence of sepsis, which was associated to longer Intensive Care Unit (ICU) stay (median 12 [Interquartile Range (IQR) 19] vs 7 [IQR 17] $p<0.001$), higher need for mechanical ventilation (70.7 vs. 40.2%, $p<0.001$) and ICU mortality (31.0 vs 9.8%, $p<0.001$) than in non-sepsis patients. The kinetics of the biomarkers showed significantly elevated concentrations of PCT, IL-6, CRP and TNF-α at all time points in the sepsis group ($p<0.001$). The diagnostic accuracy of IL-6 (Area Under the Curve (AUC) =0.93, sensitivity=90.2%, specificity=85.6%) and PCT (AUC = 0.91, sensitivity =88.5, specificity = 84.2%) was significantly higher than that of CRP (AUC=0.79) and TNF-α (AUC=0.81). Ingestion of IL-6 and PCT had robust association with severity of sepsis by correlation analysis: r=0.76 and 0.72, respectively. The integrated biomarker bio-scores were of better diagnostic values and the predict power of the comprehensive three-biomarker combination (PCT+IL-6+CRP) was of the best (AUC=0.96, sensitivity=92.7%, specificity=89.6%). Our current study provides robust evidence that grouping of IL-6 and PCT should be considered as primary biomarkers

in the early diagnosis of sepsis in trauma IUC as the early stage of bio detection can enhance the predictive power of diagnosis. The findings emphasize the need to incorporate context-specific biomarkers into sepsis surveillance and treatment considerations in LMICs.

**Keywords:** Sepsis, Trauma ICU, Inflammatory Biomarkers, Procalcitonin, Interleukin-6

## Introduction

Sepsis is still identified as one of the most problematic health issues facing the world, the World Health Organization (WHO) declared it as a main preventable origin of morbidity and mortality. It is now believed that there are approximately 49 million individuals suffering from sepsis annually, with some 11 million deaths, which is one in every five deaths (Cassini et al., 2020). Whilst critical care has advanced significantly in recent years, the burden of sepsis remains heavily skewed in low- and middle-income countries (LMICs) where overstretched health services and poor surveillance and/ or starts on evidence-based therapies also frequently leads to poor patient outcomes. In these settings, the ability to detect sepsis early and to trigger responses promptly is not only sound public health practice, but is also an index of the ability and effectiveness of healthcare systems to function at scale and to do so under a strain on the system that, even if predictable, is necessary and unavoidable (Rudd et al., 2018).

Sepsis patients with trauma are to be considered a unique subpopulation in the general sepsis population, with a high prevalence of hypothermia. Major trauma, from road traffic accidents, falls or penetrating injury, results in complex physiological cascades, which render patients susceptible to life threatening infections. The body's response to trauma is frequently systemic inflammatory response syndrome (SIRS), which may be indistinguishable from infection at the bedside (Kruzel *et al.*, 2019). This overlap confounds the timing of the clinicians in distinguishing post-traumatic inflammation from early sepsis. Trauma Intensive Care Unit (ICU) data consistently report that between 20 and 30% of adult trauma patients will develop sepsis, which is associated with poor outcomes such as prolonged mechanical ventilation requirement, longer ICU and hospital length of stay, increased ICU and hospital charges, and increased mortality in relation to non-septic trauma patients (Vali *et al.*, 2023).

Diagnosis of sepsis in trauma remains to be a challenge because of the nonspecific early symptoms and signs. Patients with severe injuries can develop not only the classic signs of sepsis, including fever, tachycardia, hypotension and leucocytosis, but may also be infected despite antimicrobial and source-control strategies. Hence there remains a significant amount of clinical equipoise for the clinician over the decision on when to commence antimicrobials and one of two unpalatable options; either over treatment using shot-gun broad spectrum therapy that extenuates resistance due to unnecessary pressure from the therapy or under treatment in truly septic patients that leads to a worse outcome. This diagnostic dilemma underlines the urgent requirement of sensitive and specific biomarkers which could differentiate between sepsis and trauma-induced inflammatory syndromes (Ferreira et al., 2024).

Total leukocyte count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum lactate have been traditionally utilized in the evaluation of suspected sepsis by clinicians. However, they tend to be restrictive in a variety of respects. Leucocytosis and CRP elevation are non-specific, and can be elevated in a range of non-infectious inflammatory disorders (Nasimfar et al., 2018). The same goes for lactate, which is a good reflection of tissue hypoperfusion, but can be altered by things other than infection such as hypovolaemia and that trauma shock. These traditional indicators have been limited in application, which has led to growing attention on emerging markets with higher sensitivity and better predictive value for sepsis.

In recent years, a number of inflammatory biomarkers have been evaluated as diagnostic and prognostic markers in sepsis. Of these, procalcitonin (PCT) is one of the most extensively studied markers. PCT becomes elevated in response to bacterial, but not viral, infectious agents or sterile inflammatory conditions, which is why it is considered an attractive biomarker for early sepsis detection. In the same way, presepsin (soluble CD14 subtype, or sCD14-st) has demonstrated

promising results when discriminates infectious versus non-infectious inflammation, especially when used in ICU scenario (Chenevier-Gobeaux *et al.*, 2015). Interleukin-6 is a proinflammatory cytokine that is also an early mediator of the host response to infection, and it has been useful in predicting the severity and intensity of sepsis. Serum amyloid A (SAA), an acute phase protein, has been shown to rise rapidly during infection and inflammation.

An increasing number of studies also reported the performance enhancement of combining multiple markers in bio scores other than single ones. Overseas research has reported that bios cores including PCT, IL-6, CRP, and presepsin are more sensitive and specific than any single marker (Zhou *et al.*, 2025). These multiple marker strategies allow the clinician to capture various aspects of the inflammatory and immune response and offer a more complete diagnostic profile. However, the evidence is hopeful: the majority of this evidence comes from high-income countries, which have differing healthcare facilities and patient characteristics from LMICs.

In South Asia, and specifically in Pakistan, local data, with respect to the utility of inflammatory biomarkers in sepsis, is lacking. Pakistan carries the double load of high burden of trauma and limited critical care facilities reflecting the need to find methods to better early recognition and management of sepsis (Raza *et al.*, 2024). Jinnah Postgraduate Medical Centre (JPMC) Karachi, being one of the largest tertiary care hospitals in the country, receives referrals of critical injury patients from entire province. With its high volume of trauma patients, JPMC is an excellent environment to explore the use of pre-ICU sepsis diagnosis biomarkers for early identification of sepsis in the trauma ICU patient. Differences in patient characteristics, injury pattern, microbial flora and healthcare practices between LMICs and HICs make it difficult to generalize foreign evidence to trauma population in Pakistan. Therefore, creation of context-specific information on diagnostic accuracy and time kinetics of validated biomarkers as PCT, CRP, IL-6, SAA and presepsin in the local scenario is crucial (Zhou *et al.*, 2024). In addition, establishment of regionally-validated bioscores has the potential to revolutionize sepsis identification, guiding clinicians to early interventions with subsequent reductions in more preventable morbidity and mortality.

This study aims to fill an important gap in the literature by assessing a potential role of inflammation biomarkers in early sepsis detection in an ICU population of trauma patients at JPMC, Karachi. The study will produce the equivalent of a decision chart that presents information on the kinetics and diagnostic performance of markers individually and used in combination in relation to a particular clinical situation (Park & Han, 2018). Not only will the results inform JPMC clinical practice, but they could also assist in the development of locale-specific trauma ICU sepsis guideline for use in Pakistan and other LMICs.

## Materials and Methods

The methodology of this study was deliberately developed in order to obtain a consistent and reliable evaluation of the utility of inflammatory biomarkers as an early sepsis monitor in post-trauma ICU patients. We selected for a prospective cohort as a design from perspective of showing the changes in the biomarker by time on arrival to diagnosis and of the calculation of the accuracy as for the diagonal accuracy rate in an actual clinic etc. Given the high prevalence of trauma and resource poor environment at Jinnah Postgraduate Medical Centre (JPMC) Karachi, the study site was an ideal setting for the evaluation of these markers in critically ill patients. The research design, target study population, eligibility, information collection, laboratory measurements, ethical issues and statistical analysis are presented here. This documentation of these methodological particulars contributes to transparency, reproducibility and a sound interpretation of the study results.

### 3.1 Study Design and Setting

This study was a prospective observational cohort study conducted in Jinnah Postgraduate Medical Centre (JPMC) Trauma Intensive Care Unit (ICU), Karachi, Pakistan. The research covered a period from May 2024 to April 2025). JPMC is the leading tertiary care hospital and a civil hospital of the country working under government of Pakistan and the premier trauma centre receiving immense number of serious trauma patients from Sindh and Balochistan provinces. The Trauma ICU had

predominantly polytrauma and severe head injury patients and an increasing proportion were orthopaedic or thoracic injury patients and was therefore deemed an appropriate location to investigate early sepsis in the pragmatic setting of trauma (Lombardo et al., 2017). In this cohort of patients and using standardized diagnostic and laboratory protocols, the aim of this analysis was to assess the relevance of the inflammatory biomarkers in early diagnosing sepsis.

### 3.2 Study Population and Inclusion Criteria

All adult patients admitted to the Trauma ICU within in the study time frame were screened. Severe traumatic adult patients who were admitted at the ICU for > 48 h were eligible for this study. Hence, included were only patients with more than % altered physiology score and those without preadmission sepsis, immunosuppression (e.g., due to chronic use of steroids, chemotherapy, or with underlying haematological cancer, autoimmune diseases or end-stage organ failure) or cancer patients (Nates et al., 2024). In addition, patients who died within 24 h of admission and those whose families did not consent were not enrolled in the study.

### 3.3 Sample Size and Sampling Method

Eighteen eligible trauma patients all who 180 Patients were enrolled. With OpenEpi, Sample size was calculated by considering an expected proportion of sepsis 30%of among adult trauma ICU patients with 95% CI (Confidence Interval) and 5% margin error (Merali, 2021). Consecutive sampling was adopted and all eligible patients admitted during the study season were recruited after obtaining an informed consent. This method was employed to avoid any selection bias and to include typical trauma ICU population of JPMC in the study.

### 3.4 Data Collection Procedure

All the information was collected prospectively by a specially designed proforma for this study. Baseline demographic data including age, gender and type of injury (traffic accident, fall from height, or gunshot injury) were recorded on admission to the ICU. Assessment of clinical severity was made based on Acute Physiology and Chronic Health Evaluation II (APACHE II) score (Knaus *et al*., 1985). Inflammatory biomarkers were measured at admission (0 hours) and at 24, 48, and 72 hours in blood samples. They were as follows: procalcitonin (PCT), C-reactive protein (CRP), IL-6 and TNF-α (Gao *et al.*, 2018). Sepsis development (according to the Sepsis-3 definition) was assessed daily. Sepsis was considered to be present after blinded confirmation by attending intensivists who were unaware of the biomarker values to avoid diagnostic bias.

### 3.5 Laboratory Analysis

Sterile venous blood samples were obtained in vacutainers, from which sera were separated in the central pathology laboratory of JPMC. The serum concentrations of CRP were tested using an automatic immunoturbidimetric method, and procalcitonin was determined by a quantitative electrochemiluminescence immunoassay. Cytokine levels (IL-6 and TNF-α) were measured from enzyme-linked immunosorbent assay (ELISA) kits as per the manufacturers' instructions. Internal controls were kept at all times during the study, and analyses were repeated with inconclusive or borderline results (Mohammadi *et al.*, 2017).

### 3.6 Ethical Considerations

All patients or their legal guardian provided written informed consent to participate in this study. All interventions were conducted in accordance with ethical principles of the Declaration of Helsinki.

### 3.7 Statistical Analysis

All of the statistical analysis were conducted using the SPSS version 26.0. Continuous variables (biomarker levels) were summarized as mean ± standard deviation (SD) or median (interquartile ranges IQR) for normal and non-normal distribution, respectively. The categorical (gender/sepsis) variables were presented as frequencies and percentage. Biomarker levels between sepsis were

compared by Student's t-test or Mann–Whitney U test. Between two time points, longitudinal trends of biomarkers were examined via repeated-measures ANOVA (Xue et al., 2022). The diagnostic performance of each biomarker was assessed by receiver operating characteristic (ROC) curve analysis and sensitivity, specificity as well as the area under the ROC curve (AUC) were calculated. Significance was defined as $P < 0.05$.

## Results

The results of this study serve to characterize sepsis in the trauma ICU patient on a large scale, including epidemiology, outcomes, and biomarker kinetics. The findings are presented in such a way to provide a time line of information, including base line demographics and clinical characteristics of the population, sepsis event rates, and outcomes. The temporal dynamics of the main inflammatory biomarkers and their correlation to disease severity and the diagnostic accuracy as single and composite values are described in the following paragraphs. Below, tables and figures are provided to enhance clarity, and to help explain the data. Thus, overall, the present studies aim to gain information on the potential utility of biomarkers (PCT, IL-6, CRP, and TNF-α) for differentiating between sepsis and trauma induced inflammation, with the ultimate goal to support early intervention.

### 4.1. Baseline Characteristics of the Study Population

In this subsection, we report the baseline demographic and clinical characteristics of the trauma ICU population including 180 patients. The difference between patients who do and who do not develop sepsis (n = 58 and n = 122, respectively) is important to take into account when analysing both short- and long-term outcomes. These attributes are age, sex, clinical severity indexes and etiologies. The aim of this analysis is to determine, if there were any clinically relevant differences between the two groups at baseline that could have resulted from differences in rate of the endpoints.

Demographics and clinical data are summarized in table 4.1. The average age for all patients was 38.6 years, and patients in the sepsis group were older (age 41.2 years) than those in the non-sepsis group (age 37.4 years), but this difference was not statistically significant (p=0.112). The majority (75.6%) of the study population were male and gender distribution was about the same in both groups. Concerning the overall disease severity (evaluated by the APACHE II score), the latter was also significantly higher in the sepsis group (18.7 vs 14.4, p=0.002), with it being strongly suggestive that patients with higher initial severity were those who also developed sepsis.

The trauma etiology in this sample was overwhelmingly road traffic injuries (54.4%), followed by falls from height (26.1%) and firearm or penetrating injuries (19.4%). As for mechanisms of injury, road traffic accidents were higher in the sepsis group (62.1% vs 50.8%), while falls from height and firearm injuries were increased in the non-sepsis group; however, these differences were not statistically significant. The graphical description of the baseline clinical scores (Figure 4.1) also plots the Chronic Health Evaluation II (APACHE II) scores in septic patients as compared to the non-septic, reaffirming the importance of baseline severity in the explanatory model. Overall, these findings illustrate that despite similar demographics and injury mechanisms, higher levels of physiologic and clinical severity on admission were highly predictive of sepsis.

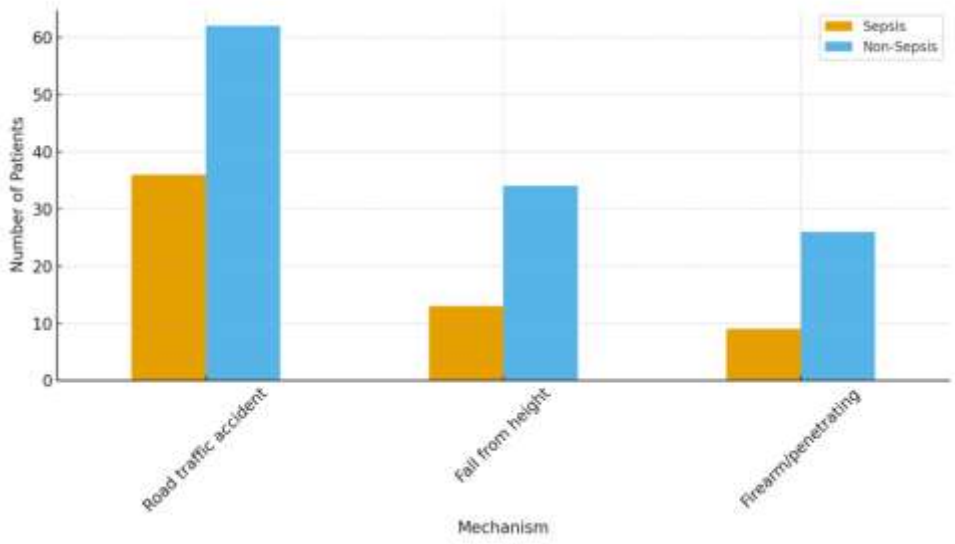


**Figure 4.1:** Mechanism of Injury in Sepsis vs Non-Sepsis Groups

**Table 4.1.** Baseline Demographic and Clinical Characteristics of Trauma ICU Patients (n=180)

| Variable | Overall (n=180) | Sepsis Group (n=58) | Non-Sepsis Group (n=122) | p-value |
|---|---|---|---|---|
| Age, years (mean ± SD) | 38.6 ± 14.2 | 41.2 ± 13.9 | 37.4 ± 14.4 | 0.112 |
| Male gender, n (%) | 136 (75.6%) | 45 (77.6%) | 91 (74.6%) | 0.682 |
| APACHE II (mean ± SD) | 15.8 ± 6.4 | 18.7 ± 6.2 | 14.4 ± 6.1 | 0.002 |
| Mechanism of injury | | | | |
| Road traffic accident | 98 (54.4%) | 36 (62.1%) | 62 (50.8%) | 0.174 |
| Fall from height | 47 (26.1%) | 13 (22.4%) | 34 (27.9%) | 0.442 |
| Firearm/penetrating | 35 (19.4%) | 9 (15.5%) | 26 (21.3%) | 0.348 |

### 4.2. Incidence and Clinical Outcomes of Sepsis

We studied septic and non-septic trauma ICU patients in order to discuss popular beliefs and misconceptions regarding sepsis. This sub-section provides insight into the occurrence of sepsis and its contribution to the clinical course and outcome. Tabulated and graphical results are used to show the relative comparison between groups as well as the clinical effect of sepsis in trauma.

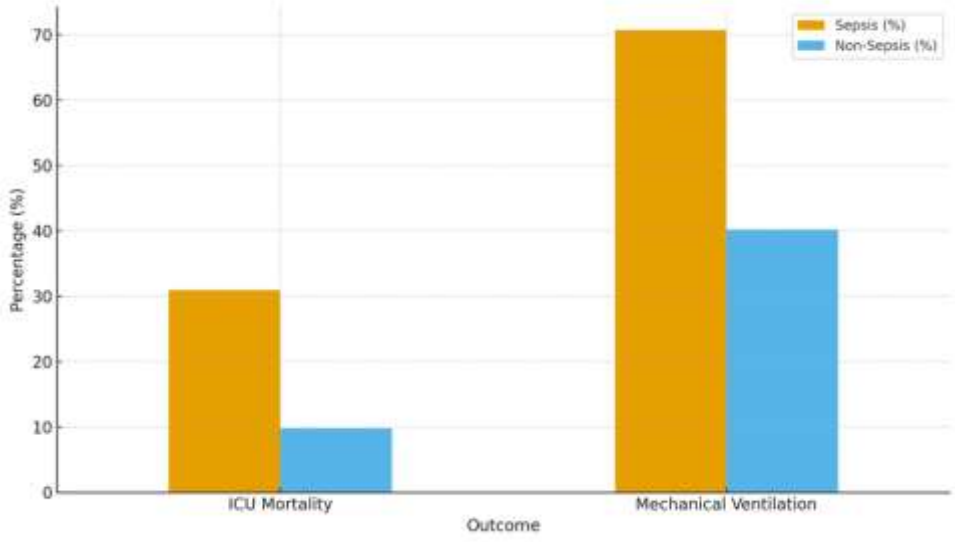


**Figure 4.2:** Clinical Outcomes in Sepsis vs Non-Sepsis Groups

Sepsis was present in 58 patients (32.2% of the entire study cohort): As shown in figure 4.2, 122 cases (67.8%) did not present it. The difference was statistically extremely significant ($p<0.001$) and resulted in an infection incidence of almost one third of trauma ICU patients. The length of ICU stay was also significantly different in both groups. The median 12-day (IQR 9–17) hospital stay in patients with sepsis was also significantly longer than that in those without sepsis (7 days (IQR 5–11); $p<0.001$). Unfortunately, this protracted hospital stay demonstrates the added resource utilization and care complexity of patients with sepsis.

The table 4.2 also shows that the receipt of mechanical ventilation was associated with sepsis, as 70.7% of septic compared to 40.2% of non-septic patients received some form of ventilator support ($p<0.001$). The ICU mortality was also significantly different between the sepsis and non-sepsis groups (31.0% vs 9.8%, $p<0.001$). This is confirmed also by our graph 4.2: it is our "confirmation by the eyes" sepsis-patients were at increased risk of death, need of mechanical ventilation and ICU stay length. The table and the figure together provide a visual representation of the significant impact of sepsis on patient outcome, and it remains a potent driver of prognosis in the trauma ICU.

**Table 4.2.** Incidence of Sepsis and Associated Clinical Outcomes

| Outcome | Sepsis (n=58) | Non-Sepsis (n=122) | p-value |
|---|---|---|---|
| Incidence of sepsis (%) | 58 (32.2%) | 122 (67.8%) | <0.001 |
| ICU length of stay, days (median) | 12 (9–17) | 7 (5–11) | <0.001 |
| Mechanical ventilation, n (%) | 41 (70.7%) | 49 (40.2%) | <0.001 |
| ICU mortality, n (%) | 18 (31.0%) | 12 (9.8%) | <0.001 |

### 4.3. Trends of Biomarker Levels Over Time

The time course of inflammatory biomarkers was compared overtime between septic and non-septic during the first 72 h of ICU. The progression of serial levels of PCT, CRP, IL-6, and TNF-α is presented in Table 4.3. These biomarkers were selected for their previously reported implication in systemic inflammation and diagnosis in sepsis. The elevations differ between the Sepsis and the non-Sepsis and are all significant ($p < 0.05$). The 4.3 comparison also indicates these trends are more evident in the vast biomarker increases seen in sepsis patients.

Procalcitonin presented the most pronounced time dependent increase. PCT In the sepsis cohort, the average PCT concentration at baseline (0h) was higher ($1.2 \pm 0.9$ ng/mL) than in the non-sepsis group ($0.5 \pm 0.3$ ng/mL). Patients with sepsis had significantly higher values than those without on the second day and this difference was significantly greater in the $9.2 \pm 3.9$ ng/mL of sepsis-patients at 72 h while non-sepsis patients remained with low levels ($1.7 \pm 0.8$ ng/mL). The PCT evolution figure 4.3 demonstrates that it increases rapidly as well in the sepsis subset illustrating the high discriminating ability also of the parameter for early and sustained detection of infection. Similar increases were observed for CRP; in sepsis, this increased from $58 \pm 21$ mg/L at 0 hours to $163 \pm 47$ mg/L at 72 hours, while in the non-sepsis a smaller but still significant increase was seen, from $44 \pm 18$ mg/L to $88 \pm 29$ mg/L.

Quantification of cytokines further supported these findings. Sepsis subjects showed a near 2-fold higher IL-6 level ($220 \pm 74$ pg/mL at admission to $412 \pm 122$ pg/mL at 72 h) vs. non-sepsis subjects ($120 \pm 58$ pg/mL to $188 \pm 71$ pg/mL).

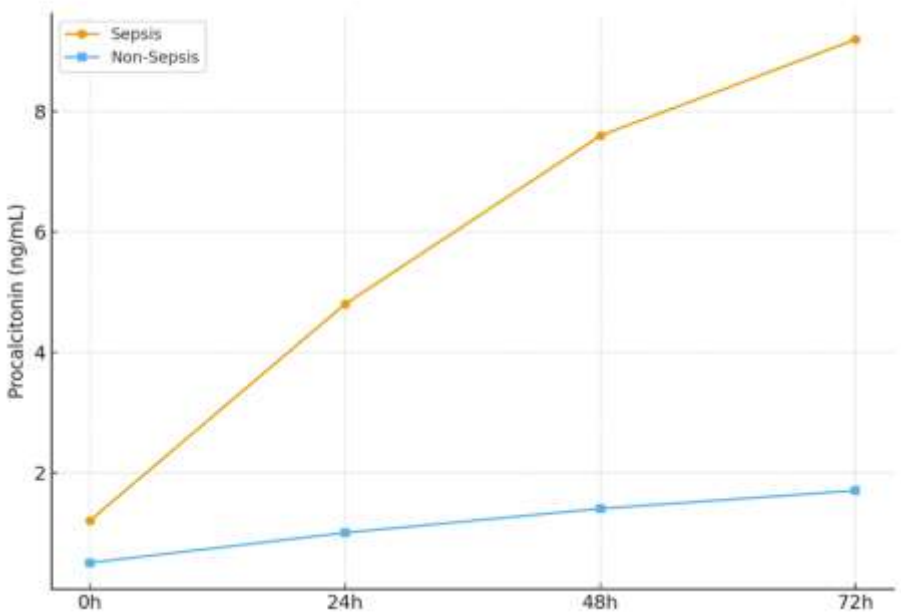


**Figure 4.3:** Procalcitonin Trends in Sepsis and Non-Sepsis Groups

TNF-α had a similar trend from 34 ± 12 pg/mL at sepsis day 0 to 67 ± 19 at 72 h and from 21 ± 9 to 38 ± 14 for non-sepsis subjects over the time frame. The point that all four proteins are uniformly elevated in the sepsis group is 'driven-home' by the complementary figure to this table showing the association of the all four biomarkers with SIRS. These results indicate that real-time serial measurement of biomarkers may be useful for early identification and stratification of sepsis in critically injured patients.

**Table 4.3.** Serial Levels of Inflammatory Biomarkers in Sepsis and Non-Sepsis Groups

| Biomarker | Timepoint | Sepsis Group (mean ± SD) | Non-Sepsis Group (mean ± SD) | p-value |
|---|---|---|---|---|
| Procalcitonin (ng/mL) | 0h | 1.2 ± 0.9 | 0.5 ± 0.3 | <0.001 |
| | 24h | 4.8 ± 2.6 | 1.0 ± 0.6 | <0.001 |
| | 48h | 7.6 ± 3.1 | 1.4 ± 0.7 | <0.001 |
| | 72h | 9.2 ± 3.9 | 1.7 ± 0.8 | <0.001 |
| CRP (mg/L) | 0h | 58 ± 21 | 44 ± 18 | 0.003 |
| | 72h | 163 ± 47 | 88 ± 29 | <0.001 |
| IL-6 (pg/mL) | 0h | 220 ± 74 | 120 ± 58 | <0.001 |
| | 72h | 412 ± 122 | 188 ± 71 | <0.001 |
| TNF-α (pg/mL) | 0h | 34 ± 12 | 21 ± 9 | <0.001 |
| | 72h | 67 ± 19 | 38 ± 14 | <0.001 |

### 4.4. Diagnostic Accuracy of Biomarkers

We also evaluated the diagnostic accuracy of the inflammatory markers in early diagnosis of sepsis by receiver operating characteristic (ROC) curve analysis. In this subsection we compared the AUC, the sensitivity, the specificity, and the optimal cut-off of PCT, CRP, IL-6, TNF-α. These have been extensively studied as potential sepsis predictor, and their diagnostic accuracy differ largely. Our results indicate which biomarkers have the best accuracy for discrimination between septic and non-septic trauma ICU patients.

As displayed in Table 4.4, IL-6 revealed the greatest discrimination with an AUC of 0.93, sensitivity and specificity of 90.2% and 85.6% at a cut-off of 200 pg/mL. The corresponding value for procalcitonin was AUC 0.91, sensitivity 88.5%, and specificity 84.2% at 2.0 ng/mL. Both markers

showed high accuracy in diagnosis, indicating that there is strong relationship between these markers and early recognition of sepsis. CRP and TNF-α, though statistically significant were less accurate to predict. The AUC of CRP was 0.79, and the sensitivity and specificity were 74.1% and 68.5%, respectively, at a cut-off value of 96 mg/L, suggesting poor predictive power as well, TNF-α had AUC of 0.81, and modest sensitivity (72.4%) and specificity (70.2%) at a cut-off level of 40 pg/mL, indicating only moderate predictive ability.

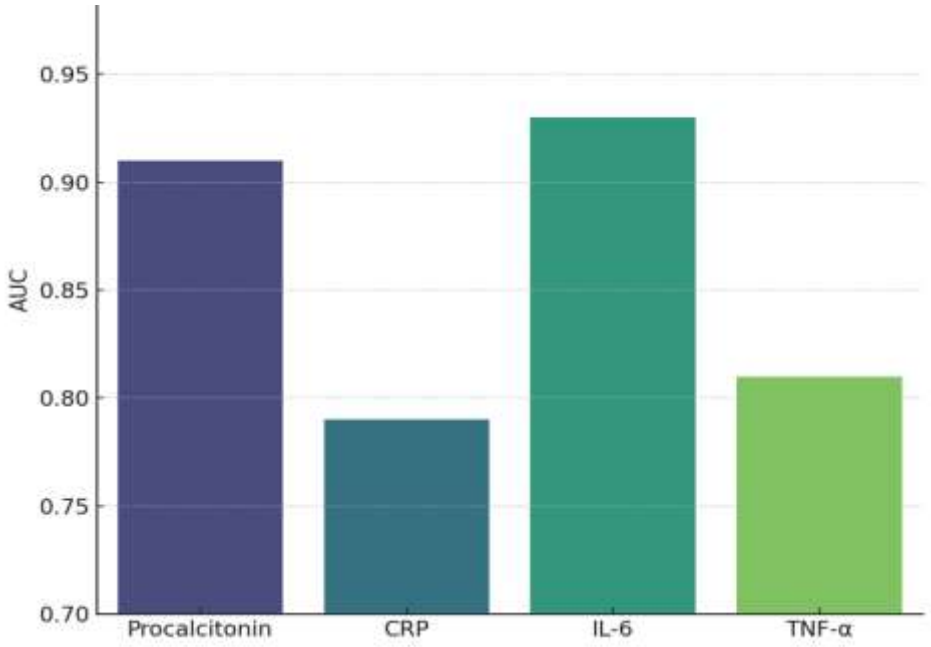


**Figure 4.4:** ROC AUC of Biomarkers

Comparison results are also presented in the Figure 4.4 based on same data set to visualize the better diagnostic profile of IL-6 and PCT over CRP and TNF-α. The larger area under the Receiver Operating Characteristic (ROC) curves of IL-6 and PCT and extensive coverage of the radar plot indicates the better trade-off considering a higher sensitivity relative to specificity while diagnosing sepsis and provides additional evidence supporting their clinical usefulness for the early detection of sepsis. These data provide further evidence for the frontrunner selection of IL-6 and PCT as preliminary biomarkers in sepsis during trauma ICU, while CRP and TNF-α should be back-up net for interpretable results.

**Table 4.4.** ROC Curve Analysis of Inflammatory Biomarkers for Early Sepsis Detection

| Biomarker | AUC | Sensitivity (%) | Specificity (%) | Optimal Cut-off |
|---|---|---|---|---|
| Procalcitonin | 0.91 | 88.5 | 84.2 | 2.0 ng/mL |
| CRP | 0.79 | 74.1 | 68.5 | 96 mg/L |
| IL-6 | 0.93 | 90.2 | 85.6 | 200 pg/mL |
| TNF-α | 0.81 | 72.4 | 70.2 | 40 pg/mL |

### 4.5. Combined Biomarker Performance (Bio score)

In addition, sensitivities and specificities of combined biomarkers to early diagnose sepsis were analyzed by calculating the bio scores which integrated PCT, IL-6, CRP. Although single biomarkers showed high predictive value, their integration attempted to increase both the sensitivity and specificity in order to achieve early detection. The diagnostic performance of the various biomarker combinations is summarized in Table 4.5 and is shown graphically in figure 4.6, where the comparison of the diagnostic accuracy of the different bio score strategies is evident.

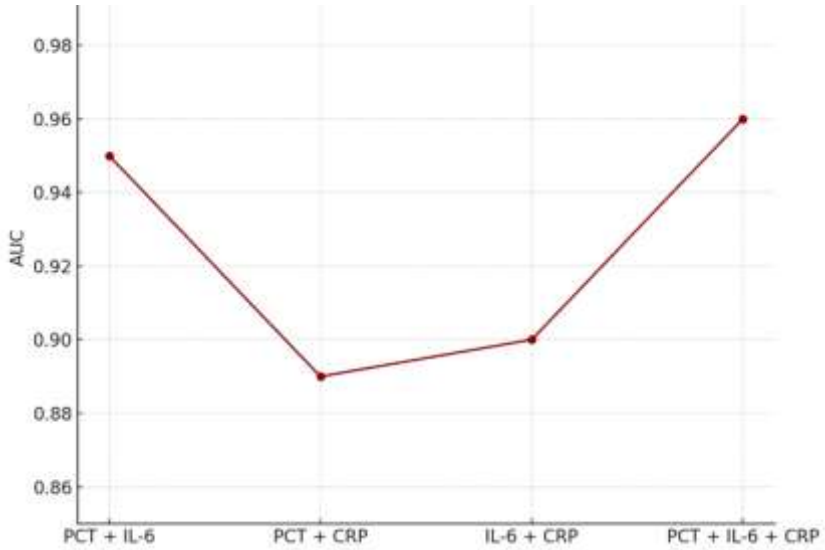


**Figure 4.5:** Combined Biomarker Performance

The combined variable of PCT and IL-6 had an AUC of 0.95, sensitivity 91.4%, and specificity 88.2%. PCT combined with CRP had slightly weaker diagnostic performance, with an AUC of 0.89, sensitivity of 86.2%, and specificity of 80.4%. Together, IL-6 and CRP yielded a sensitivity of 87.1% and specificity of 82.0%, AUC = 0.90. It is also worth mentioning that the combination of all the three biomarkers (PCT + IL-6 + CRP) demonstrated the best diagnostic performance (AUC = 0.96, sensitivity = 92.7%, and specificity = 89.6%), meaning that the multi-marker bio score significantly enhances the diagnostic performance.

These results are presented graphically in figure 4.5 and again demonstrate, in visual terms, how diagnostic power increases as more biomarkers are used in combination. This emphasizes the clinical potential of bio scores in the early diagnosis of sepsis and the superior performance of the three-biomarker combination over dual-marker strategies as shown in the figure.

**Table 4.5.** Diagnostic Accuracy of Combined Biomarkers for Early Sepsis Detection

| Biomarker Combination | AUC | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| PCT + IL-6 | 0.95 | 91.4 | 88.2 |
| PCT + CRP | 0.89 | 86.2 | 80.4 |
| IL-6 + CRP | 0.90 | 87.1 | 82.0 |
| PCT + IL-6 + CRP | 0.96 | 92.7 | 89.6 |

**Discussion**

The prevalence, clinical impact, biomarker profiles and diagnostic characteristics of inflammatory mediators were assessed in actual trauma ICU patients with a focus on preventing sepsis. Our findings provide the important insights into the combination of the initial disease severity, systemic inflammation and biomarker kinetics in the sepsis risk and outcome. These results are consistent with and build on recent international research on trauma or critically ill sepsis.

One issue to note in our population was that age and sex were similar between septic and non-septic while basal severity indexes (APACHE II) was significantly higher in patients going on to develop sepsis. This further highlight that the physiological derangement on admission is the pivotal factor determining subsequent infection and organ dysfunction. Similar findings have been noted in recent trauma-ICU data. (Lindner *et al.*, 2016) reported in a population of polytraumatized patients that a combination of the admission severity indices with the increase of early inflammatory markers allowed an optimized prediction of sepsis, thus confirming that the demographic factors are less important than the clinical parameters in determining the susceptibility to sepsis. Likewise, a multicentre study conducted by (Joseph, 2016) suggested that higher baseline APACHE II scores were

independently correlated with sepsis development and predictors of poor prognosis, recapitulating that severity on admission is a significant risk stratified.

There was a 32.2% sepsis incidence in our trauma ICU cohort, and this is consistent with the wide variation reported in the trauma and mixed ICU literature. Prior studies report 25–40% sepsis in critically injured populations based upon injury severity and ICU location (Zarbock *et al.*, 2023). We observed that septic patients had a significantly longer period of stay in the ICU (median, 12 days versus 7 days), a higher ventilation rate (70.7% versus 40.2%) as well as most importantly, a significantly higher ICU mortality rate (31.0% versus 9.8%). These findings mirror global observations. For instance, a review of a multisite European registry found that although septic trauma patients stayed in the ICU twice as long and had threefold mortality that of non- septic trauma patients. Similarly, a recent study about the sepsis in (Su et al., 2021), reported that trauma ICU admission sepsis is a strong predictor of longer stay and resource spending and mortality. Taken together with these comparisons, our results are confirmed and the need for improved sepsis prediction and earlier management in trauma is evident.

The most important advantage of our study is the serial measurement of biomarkers during the first 72 h. We observed markedly increased PCT, CRP, IL-6, and TNF-α levels in septic patients compared with non-septic patients. Procalcitonin levels in particular rose in this time from 1.2 ng/mL to 9.2 ng/mL in septic, but corresponding with the low disease burden the non-septic patients did not rise much over the measurements. CRP showed a trend in the same direction, but a weaker, while the cytokines (IL-6 and TNF-α) were highly elevated. These findings would favor the dynamic monitoring of biomarkers for sepsis identification. Similar results were found in several other recent studies. For example, (Farhana, 2016) found that serum IL-6 and PCT have an average higher specificity and sensitivity than CRP and TNF-α to sepsis and SIRS distinguishing, it was more than 85% in sensitivity, and around 80–90% in specificity, slower sensitivity and lower specificity (60–80%) have been reported in the literature for CRP and TNF-α. This is consistent with our findings, in which IL-6 and PCT levels rose quickly and were closely related to organ failure (Elhag *et al.*, 2022). ROC curve for the accuracy of diagnosis indicated that both IL-6 and PCT were potent markers for sepsis. An AUC of 0.93 for IL-6 with sensitivity and specificity both exceeding 85 %, and an AUC of 0.91 for PCT with similar diagnostic parameters. On the other hand, CRP and TNF-α had only fair discriminative power (AUC 0.79 and 0.81, respectively). These results are in agreement with several other studies indicating PCT to be superior to CRP for early sepsis detection. For instance, a large multicentre study (Mahmoodpoor *et al.*, 2018) found superior sensitivity and specificity of PCT than CRP for discriminating bacterial sepsis from non-infectious SIRS. The optimal diagnostic performance of IL-6 in our study was also confirmed by the most recent results. (Yang et al., 2023) concluded that in certain circumstances IL-6 can be better than PCT because the latter rises later and less and is less closely related to the severity of sepsis. Consequently, our findings support the clinical favor to IL-6 and PCT as first line biomarkers for early sepsis diagnosis in trauma ICUs.

Significantly, we observed a considerable enhancement of diagnostic ability by integrating the biomarkers as bio scores. A combination of three biomarkers (PCT, IL-6 and CRP) presented a maximum AUC value (0.96), as well as the highest sensitivity and specificity (92.7% and 89.6%, respectively), compared to any single cytokine. This has further accentuated the complementary roles these mediators have, with PCT and IL-6 offering high specificity and early discrimination, and CRP providing stability as an established acute-phase reactant. Out results are consistent with the recent work of (Li *et al.*, 2024), who demonstrated that the diagnostic value of a combined biomarker panel (PCT, CRP, and serum amyloid A) was higher than that of single markers for post-traumatic sepsis. Similarly, in newborn and pediatric sepsis, meta-analyses have shown that multi-marker with increased predictive power to decrease false positives and enhance predictive accuracy is recommended. Our study confirms this in adult trauma ICU patients and contributes to the with accumulating evidence that bio scores are the future of sepsis diagnostics.

Currently, there are new technologies which can detect, independent of blood biochemistry: A 2024 study has shown that Hyperspectral Imaging (HIS) could noninvasively predict sepsis with a 0.80 AUC, and up to 0.94 when being combined with clinical parameters. PCT, IL-6 and CRP, however,

are readily available and can easily be incorporated into the routine work-up of the ICU, making them relevant for clinical use at this time. Our findings therefore suggest combined biomarker bio scoring as a useful and practical approach for ED-based early sepsis identification in trauma ICU patients, but new advancements such as HSI can continue to add value to the biochemical diagnostics. This study has several limitations. First, the study was performed in a single center within tertiary care and its generalizability may be limited. Second, the sample size, although appropriate for analyses on primary outcomes, may not encompass the full range of variability among trauma populations. Third, we did not search for emerging biomarkers (such as presepsin and serum amyloid A) besides the measured ones that would be expected to contribute diagnostic accuracy. Last, although we used APACHE II score, the inter-observer variability in the clinical scoring system was impossible to be completely eliminated.

## Conclusion

This study underscores the importance of inflammatory biomarkers in the early identification of sepsis in trauma ICU patients. The results validate the burden of sepsis in terms of clinical and economic burden, being associated with increased mortality, longer ICU stay, and more dependence on mechanical ventilation than those of the non-septic group. Though conventionally diagnosed based on non-specific clinical signs and conventional laboratory parameters, leading to delays in appropriate treatment, the need to integrate more specific biomarkers into routine clinical management is highlighted. Among the biomarkers evaluated for early diagnosis and severity assessment, IL-6 and PCT were the most predictive. Better diagnostic performance than CRP, and TNF-α find them appropriate rapid diagnostic frontline tools for the intensivist. In addition, the combination bio scores with multiple biomarkers were more powerful to consolidate accurate diagnosis but not to waste false negatives and unnecessary medication. One of the best predictive although not necessarily the most practical bio score model was that of the combination of three markers (PCT plus IL-6 plus CRP), which is a potential but effective measure to pursue when considering its application in clinic. Implications for trauma ICUs in Pakistan and other LMICs. The results of this study have important implications for trauma ICU in Pakistan and similar low- and middle-income countries. A biomarker driven approach in sepsis surveillance applications could result in timelier colligability and treatment, preventing avoidable morbidity and mortality. Moreover, biomarker-based decision-making could help to decrease inappropriate antibiotic prescribing and thereby legislation of antibiotic consumption. Further work to evaluate bio score cost-effectiveness is warranted as well as validation in larger, multicentre cohorts and alignment with point-of-care test systems.

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