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Diagnostic and prognostic values of selected biomarkers as a vital indicator in critically ill patients

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Abstract

Objectives: The accurate diagnosis and prognostic assessment of Critically ill patients with pneumonia remain challenging, necessitating the evaluation of multiple biomarkers to enhance clinical decision-making. This study aimed to investigate the diagnostic and prognostic value of interleukin-6 (IL-6), procalcitonin (PCT), C-reactive protein (CRP), selenium, lactate, soluble urokinase plasminogen activator receptor (suPAR), and peptidyl arginine deiminase 2 (PAD2), and to determine their associations with disease severity and mortality.

Methods: A prospective observational cohort study was conducted on 130 critically ill pneumonia patients and 45 non-critically ill outpatient controls. Biomarker levels were assessed using ELISA, PCR, and standard biochemical assays, and correlated with severity indices and clinical outcomes.

Results: Lactate, PCT, CRP, IL-6, and PAD2 levels were significantly elevated in patients versus controls ($p < 0.001$), with higher levels observed in non-survivors ($p < 0.001$) except for PAD2 levels were not significantly associated with survival status ($p = 0.346$). Although suPAR and selenium differed between patients and controls, they did not distinguish survivors from non-survivors. suPAR correlated positively with PCT, while PAD2 showed significant associations with inflammatory markers and severity scores. No biomarker demonstrated superior prognostic accuracy.

Conclusion: Lactate, PCT, CRP, IL-6, and PAD2 exhibit diagnostic relevance in pneumonia. Several biomarkers, including IL-6 gene expression, IL-6, CRP, PCT, and lactate, demonstrated excellent prognostic discrimination (AUC >0.95). However, comparative ROC analysis revealed no statistically significant superiority of any single biomarker over the others, suggesting that a multimarker approach may provide greater clinical value than reliance on an individual marker.

Keywords: CRP; IL-6; Pneumonia; PCT; suPAR

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Introduction

The Sepsis is associated with a high mortality rate and one of the leading causes of death in intensive care unit (ICU) patients[1]. Blood culture is the gold standard for diagnosing infection, but it is time-consuming and has a high negative rate. So, the need for blood biomarkers became essential, not only fast and accurate, but also reflecting the severity of the condition[2]. Furthermore, biomarkers play an important role in prognosis and evaluation of infections. Respiratory infection is one of the most common complications in ICU patients, mainly caused by pneumonia[3]. Staphylococcus aureus, Streptococcus pneumoniae, Gram-negative bacteria are common organisms, while legionella,

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Clostridium difficile, and fungal infection represent minor but aggressive groups[4]. Management is challenging and should include early antibiotics, tissue perfusion, and controlling the source of infection source [5].

Currently, more than 150 biomarkers have been described [6]. Some of these biomarkers are commonly used, eg procalcitonin (PCT), C-reactive protein (CRP), interleukin (IL-6) and pre-sepsin [7]. Procalcitonin is a common marker and is used as a potential marker of infection; it increases in the first 12 hours after stimulation and is capable of discriminating infection from systemic inflammation of another origin. Furthermore, procalcitonin levels correlate with the severity of the infection (Barichello et al.2022)[7]. C-reactive protein (CRP) is a classic biomarker of inflammation. It is a marker of discrimination between patients with pneumonia and those with tracheal infections[8]. CRP is an aid in separating bacterial infection from viral and elevated values associated with the risk of organ failure and mortality [9]. Interleukin-6 is one of the most biomarkers in sepsis and has proinflammatory and anti-inflammatory activity. In addition, it reflects the response to stress and coagulation. The magnitude of IL-6 elevation is correlated with the extent of tissue injury[10].

Today, more biomarkers are used, for example, urokinase type soluble plasminogen activator receptor (suPAR), peptidyl arginine deiminase 2 (PAD2) and lactate. The level of suPAR reflects the degree of immune activation in the subject. It is an excellent prognostic biomarker in critical patients, but it cannot discriminate infection from other types of pathology [11]. Peptidyl arginine deiminases (PADs) are a group of enzymes that convert arginine into citrulline, including PAD 1-4 and PAD6. PAD2 is the most famous member and is expressed in multiple tissues. It is an important inflammatory mediator in the pathogenesis of sepsis [12].

Lactate is a marker of perfusion and a product of anaerobic metabolism; it is used for diagnosis of hypoperfusion in which in hypoxia, pyruvate cannot go through the Krebs cycle and is reduced to lactate. In lactate elevation, the following conditions must be taken into account: liver failure, seizures, brain tumor, carbon monoxide poisoning, and vit. B1 deficiency. Elevated lactate levels reflect tissue hypoperfusion, impaired oxygen utilization, and metabolic stress in critically ill patients. Numerous studies have demonstrated that hyperlactatemia is associated with increased organ dysfunction, septic shock severity, and mortality. Serial lactate measurements and lactate clearance have also been proposed as indicators of treatment response and adequacy of hemodynamic resuscitation [11].

The present study aimed to evaluate the diagnostic and prognostic performance of IL-6, IL-6 gene expression, PCT, CRP, lactate, selenium, suPAR, and PAD2 in critically ill patients with bacterial pneumonia. We hypothesized that inflammatory and metabolic biomarkers, individually or in combination, would correlate with disease severity and mortality and may improve prognostic assessment in critically ill pneumonia patients.

Materials and methods

Study Design and Participants

This is a prospective observational cohort study conducted in the Anesthesia Intensive Care Unit, the Pulmonary Department, and the Biochemistry Department of the Faculty of Medicine of Assiut University between June 2022 and May 2024. The study included 175 subjects divided into two groups. Group A consisted of 130 patients suffering from pneumonia admitted to the ICU Department for Anesthesia and pulmonary disease and ICU Department. Based on the bacteriological examination of sputum and blood cultures, these patients were classified as having Staphylococcus aureus (n=78), Streptococcus pneumoniae (n = 32), Gram-negative organisms (n=18), Clostridium difficile (n = 1) or fungal pneumonia (n=1). The age range was 55-72 years (mean ± SD: 62 ± 7.5 years), with 93 males and 37 females. Group B included 45 non-critically ill outpatient subjects serving as the control group.

Inclusion and Exclusion Criteria

Patients were included if they had pneumonia due to bacterial infection (pneumonia was diagnosed according to clinical symptoms together with new pulmonary infiltrates on chest radiography or computed tomography. Bacterial etiology was confirmed by positive sputum and/or blood cultures). Exclusion criteria were malignancy, liver disease, immunodeficiency disorder, pulmonary tuberculosis, and viral pneumonia.

Clinical and Laboratory Evaluation

For each patient, a detailed medical history was ob-

tained, together with a thorough clinical examination, plain chest radiograph, CT scan, routine laboratory tests (liver and kidney function, blood glucose, complete blood count, prothrombin time and serum electrolytes), sputum and blood culture, and arterial blood gas analysis. Venous blood samples were collected within 24 hours of ICU admission and before initiation of antibiotic therapy whenever *feasible, with 1.5 ml in an EDTA tube for analysis of interleukin-6 (IL-6) gene expression and 4-5 mL in a plain tube to measure serum levels of procalcitonin, CRP, PAD2, urokinase-type plasminogen activator receptor (suPAR), lactate, IL-6, and selenium.*

Treatment plan

*Patients received individualized treatment acc*ording to their clinical condition at the discretion of the treating physicians. All patients received empirical intravenous antibiotic therapy, which consisted of an anti-MRSA agent (vancomycin or linezolid) combined with antipseudomonal antibiotics, including a β-lactam agent (piperacillin–tazobactam, cefepime, ceftazidime, imipenem, meropenem, or aztreonam) together with a second non-β-lactam antipseudomonal agent (ciprofloxacin, levofloxacin, amikacin, gentamicin, tobramycin, colistin, or polymyxin B), as appropriate according to the patient's clinical condition and microbiological findings. Supportive management included oxygen therapy, intravenous fluids, antipyretics, bronchodilators when indicated, corticosteroids in selected patients, and intensive care support, including mechanical ventilation and vasopressor therapy, when clinically required. Antibiotic regimens were modified or de-escalated based on culture and antimicrobial susceptibility results whenever available.

Biomarker Measurements

Serum suPAR levels were measured using a commercially available human enzyme-linked immunosorbent assay (ELISA) kit (Boster Biological Technology, California, USA). Serum IL-6 was estimated by immunoassay (Cat. No. MBS 5726707). IL-6 gene expression was evaluated by real-time PCR, with RNA extraction using the Qiagen RNeasy total RNA isolation kit, followed by cDNA synthesis and quantitative PCR using SYBR Green. Relative gene expression was calculated using the $2^{-\Delta\Delta Ct}$ method, normalized to the glyceraldehyde 3-phosphate dehydrogenase (GAPD) reference gene. Primer used for the expression IL-6: Forward : 5'-ACAAAGCCAGAGTCCTCAG-3' and

Reverse: 5'-AGAGCATGGAAATTGGGT-3' Primer for GAPD:

Forward: 5'-CACGATGGAGGGGACTCATC- 3' and

Reverse: 5'-TAAAGACCTCTATGCCAACAGT-3'

Serum PAD2 concentration was measured by ELISA (Cayman). Procalcitonin levels were determined using a kit (RIK 6025 N-proCT, Peninsula Laboratories, Inc.). CRP was measured by immunoturbidimetric assay. Serum selenium was analyzed by atomic absorption/flame emission spectroscopy (Shimadzu AA-630-02). Lactate levels were assessed spectrophotometrically [13].

Disease Severity Assessment

The pneumonia severity index (PSI) and the CURB-65 score were calculated to evaluate the severity of the disease.

Pneumonia Severity Index (PSI): According to Fine et al. [14]

PSI assigns points based on patient age, comorbidities (neoplastic, liver, heart, cerebrovascular, renal disease), residence in the nursing home, mental status, vital signs (respiratory rate, blood pressure, temperature, pulse), laboratory tests (arterial blood gas, blood nitrogen urea, sodium, glucose, hematocrit, oxygenation) and presence of pleural effusion. Patients were classified into risk classes I-V, with higher scores indicating greater risk. Classes IV and V were recommended for hospitalization.

CURB-65 score: According to Lim et al. [15]

CURB-65 assigns 1 point each for confusion, elevated blood urea nitrogen, high respiratory rate, low blood pressure, and age 65 years. Scores of 0-I indicated low risk of mortality and potential home treatment. II scores suggested a likely admission or close outpatient follow-up. III-V scores indicated severe pneumonia requiring admission.

These validated scoring systems guided clinical management decisions based on the severity of pneumonia.

Statistical analysis

Data were analyzed with SPSS 25.0, MedCalc 20.1, and Prism 9.0 software. Categorical variables were expressed as numbers (%) and compared using the chi-square test. Normally distributed data were represented as mean ± SD and compared using Student's t test, while nonnormally distributed data were presented as

medians and compared using Mann-Whitney U test. The correlations were analyzed using Spearman's correlation test. To determine cut-off values for different parameters to discriminate non-survival from survival critically ill patients, we employed receiver operating curve (ROC) analysis. We also performed a time-to-event analysis using the Kaplan-Meier curve of biomarkers associated with critically ill patients. To assess risk and risk (HR) as well as calculate a 95% confidence interval (CI), Cox regression was used. Statistical significance with a P value less than 0.05 was considered. No formal correction for multiple comparisons was applied because the biomarker analyses were considered exploratory. Consequently, the findings should be interpreted with caution and confirmed in larger validation studies.

Ethical Considerations

The study was initially approved by the Assiut Faculty of Medicine Institutional Review Board (Ethical approval code:04-2024-300400) at April 2022 and complied with the Declaration of Helsinki. Informed written consent was obtained from each participant after explaining the study objectives. The initial approval from the Ethics Committee was obtained prior to the commencement of the study in April 2022. However, the final official approval was issued in April 2024 in accordance with the institutional regulations, procedures, and administrative requirements.

Results

The present study is a prospective observational cohort study that included 175 subjects, divided into two groups. The first group included 130 patients admitted to the ICU at Assiut Hospital, Faculty of Medicine, and the second group included 45 non-critically ill subjects who served as control-matched patients in both age and sex.

The baseline characteristics revealed several significant differences between the control group (n = 45), the critically ill group (n=130), and the survival subgroups (n = 95) vs. the non-survival subgroup (n = 35) within the critically ill group. While age (median 63-65 years) and prevalence were similar, the non-survival subgroup had higher CURB-65 scores (45.7% score III, 31.4% score IV, 22.9% score V) and a shorter median stay in the ICU (5 days) compared to the survival subgroup (13 days). The critically ill group exhibited elevated inflammatory markers such as PAD2 (median 36.5 ng/mL), procalcitonin (median 85 ng/mL), CRP (median 20 mg/L), IL-6 (median 290 pg / mL) and lactate (median 2.0 mmol / L) versus controls. Crucially, the non-survival subgroup had significantly higher procalcitonin (median 110 ng/mL), CRP (median 35 mg/L), IL-6 (median 430 pg / mL), expression of IL-6 (median 4.1), and lactate (median 4.0 mmol/L) compared to survivors (Table 1).

Correlation analysis revealed strong positive correlations observed among inflammatory markers, particularly between IL-6 and procalcitonin (r = 0.919), procalcitonin and CRP (r = 0.805), and IL-6 and CRP (r = 0.755). PAD2 demonstrated positive correlations with procalcitonin (r = 0.602), CRP (r = 0.443), IL-6 (r = 0.550), selenium (r = 0.590), and suPAR (r = 0.596). Similarly, suPAR was positively correlated with IL-6 (r = 0.564), procalcitonin (r = 0.588), CRP (r = 0.407), selenium (r = 0.568), and PAD2 (r = 0.596), indicating a close association among inflammatory biomarkers. In contrast, IL-6 expression exhibited a distinct correlation pattern. It showed strong positive correlations with lactate (r = 0.838), CURB-65 (r = 0.759), severity index (r = 0.725), and mortality (r = 0.738), whereas it was negatively correlated with PAD2 (r = −0.600), suPAR (r = −0.596), selenium (r = −0.616), procalcitonin (r = −0.249), and IL-6 concentration (r = −0.177). Lactate was positively associated with CURB-65 (r = 0.717), severity index (r = 0.698), and mortality (r = 0.702), while demonstrating inverse correlations with selenium (r = −0.437), PAD2 (r = −0.394), and suPAR (r = −0.365). Clinical severity measures were strongly associated with mortality, with CURB-65 showing the highest correlation (r = 0.848), followed by IL-6 expression (r = 0.738), IL-6 (r = 0.724), CRP (r = 0.717), procalcitonin (r = 0.707), lactate (r = 0.702), and the severity index (r = 0.687). ICU length of stay was inversely correlated with several inflammatory biomarkers, including procalcitonin (r = −0.814), IL-6 (r = −0.786), CRP (r = −0.712), suPAR (r = −0.687), PAD2 (r = −0.632), as well as mortality (r = −0.681), whereas a modest positive correlation was observed with IL-6 expression (r = 0.380). Overall, these findings indicate that elevated inflammatory biomarkers and clinical severity scores are closely associated with adverse clinical outcomes and mortality in critically ill patients, (Figure 1).

The ROC curve analysis evaluated the discriminatory performance of various biomarkers in differentiating non-survival from survival among critically ill pa-

Table 1. Baseline characteristics of the study population.

Variables	Control group (n = 45)	Critically ill group (n = 130)	P-value	Critically ill group		
				Survival (n = 95)	Non-survival (n = 35)	P-value
Age, year	65.00 (59.00-72.00)	63.00 (54.00-70.00)	0.282	63.00 (54.00-70.00)	63.00 (52.00-68.00)	
Sex, n (%)						
Male	23 (51.1%)	75 (57.7%)	0.443	53 (55.8%)	22 (62.9%)	0.469
Female	22 (48.9%)	55 (42.3%)		42 (44.2%)	13 (37.1%)	
Comorbidities, n (%)						
Diabetes	9 (20.0%)	27 (20.8%)	0.912	20 (21.1%)	7 (20.0%)	0.896
Hypertensive	31 (68.9%)	75 (57.7%)	0.185	57 (60.0%)	18 (51.4%)	0.38
Coronary heart disease	4 (8.9%)	22 (16.9%)	0.192	15 (15.8%)	7 (20.0%)	0.57
Cerebral ischemic stroke	5 (11.1%)	16 (12.3%)	0.928	10 (10.5%)	6 (17.1%)	0.308
Chronic renal failure	1 (2.2%)	6 (4.6%)	0.48	4 (4.2%)	2 (5.7%)	0.717
ICU length of stay, day	-	11.00 (7.00-15.00)		13.00 (10.00-16.00)	5.00 (4.00-7.00)	<0.001*
CURB-65, n (%)						
II	0 (0.0%)	83 (63.8%)		83 (87.4%)	0 (0.0%)	
III	0 (0.0%)	28 (21.5%)		12 (12.6%)	16 (45.7%)	<0.001*
IV	0 (0.0%)	11 (8.5%)		0 (0.0%)	11 (31.4%)	
V	0 (0.0%)	8 (6.2%)		0 (0.0%)	8 (22.9%)	
Severity index		115.00 (100.00-130.00		110.00 (90.00 - 120.00)	135.00 (130.00-140.00)	<0.001*
Laboratory results						
suPAR (ng/ml)	3.78 (2.80-3.97)	10.00 (7.00-11.00)	0.113	9.00 (7.00-11.00)	10.00 (6.00-11.00)	0.704
PAD2 (ng/mL)	16.98 (14.60-18.80)	36.50 (30.00-40.00)	<0.001*	37.00 (31.00-40.00)	36.00 (28.00-40.00)	0.346
Procalcitonin (ng/mL)	17.87 (15.20-19.00)	85.00 (70.00-103.00)	<0.001*	77.00 (69.00-90.00)	110.00 (103.00-113.00)	<0.001*
CRP (mg/L)	3.50 (2.90-4.10)	20.00 (16.00-30.00)	<0.001*	18.00 (16.00-20.00)	35.00 (30.00-36.00)	<0.001*
Selenium (µg/dL)	15.00 (13.00-17.00)	9.00 (8.00-11.00)	<0.001*	10.00 (8.00-11.00)	9.00 (9.00-10.00)	0.882
IL-6 (pg/ml)	4.00 (2.00-5.00)	290.00 (200.00-400.00)	<0.001*	210.00 (190.00-310.00)	430.00 (400.00-490.00)	<0.001*
IL-6 expression	0.79 (0.58-1.00)	2.70 (2.00-3.90)	<0.001*	2.10 (1.70-3.00)	4.10 (4.00-4.30)	<0.001*
Lactate (mmol/L)	0.88 (0.60-1.20)	2.00 (1.60-3.10)	<0.001*	1.90 (1.60-2.10)	4.00 (3.80-4.00)	<0.001*

AUC: Area Under a Curve ,

p value for comparing between the two studied groups, *: Statistically significant at $p \leq 0.05$

tients. Procalcitonin (AUC 0.959), CRP (AUC 0.961), IL-6 (AUC 0.971), IL-6 expression (AUC 0.979), and lactate (AUC 0.955) exhibited excellent discriminatory ability, with AUC values greater than 0.9 and statistically significant p-values (<0.001). Optimal cut-off points for these markers provided high sensitivity and specificity, for example, procalcitonin 98.5 ng / mL (100% sensitivity, 89.5% specificity), CRP 25.5 mg / L (100% sensitivity, 85.3% specificity), IL-6 397.5 pg / mL (100% sensitivity, 92.6% specificity), IL-6 expression 3.35 (97.1% sensitivity, 84.2% specificity) and lactate 2.05 mmol / L (98% sensitivity, 70.5% specificity). In contrast, suPAR, PAD2, and selenium exhibited poor discriminatory ability, with AUC values around 0.5 and non-significant p-values (Table 4 and Figure 2).

Patients with procalcitonin levels <98.5 ng/mL demonstrated significantly longer survival than those with levels >98.5 ng/mL. The estimated mean survival time was 18.91 days in the lower procalcitonin group compared with 6.49 days in the higher procalcitonin group,

Table 2. Supportive care measures across study groups and by in-hospital mortality

Supportive measure	Survivors (n = 95)	Non-survivors (n = 35)	p-value
Oxygen therapy, n (%)	83 (87.4)	34 (97.1)	0.099
Mechanical ventilation, n (%)	32 (33.7)	20 (57.1)	0.015*
Vasopressors, n (%)	37 (38.9)	21 (60.0)	0.032*
Corticosteroids, n (%)	0 (0.0)	0 (0.0)	—

Data are n (%). p-values from Pearson χ^2 test (Fisher's exact where applicable). * Significant at $p \leq 0.05$. "—": not computed; corticosteroids were not administered to any participant (constant variable).

Table 3. Biomarker concentrations according to supportive care requirement.

Biomarkers	Oxygen therapy		p	Mechanical ventilation		p	Vasopressors (1=Yes)		p
	No	Yes		No	Yes		No	Yes	
suPAR (ng/mL)	0.90 (0.80–1.10)	10.0 (8.0–11.0)	<0.001*	6.0 (0.9–10.0)	10.0 (9.0–12.0)	<0.001*	6.0 (0.9–10.0)	10.0 (9.0–12.0)	<0.001*
PAD2 (ng/mL)	0.70 (0.60–1.10)	39.0 (32.0–41.0)	<0.001*	29.0 (0.7–36.0)	40.0 (37.0–42.5)	<0.001*	28.0 (0.7–36.0)	40.0 (36.0–42.0)	<0.001*
Procalcitonin (ng/L)	4.40 (3.60–6.00)	90.0 (71.0–105.0)	<0.001*	66.0 (4.5–83.0)	100.0 (78.5–110.0)	<0.001*	63.0 (4.5–83.0)	95.0 (78.0–110.0)	<0.001*
CRP (mg/L)	16.0 (14.0–17.0)	20.0 (17.0–30.0)	<0.001*	16.0 (16.0–20.0)	30.0 (19.0–35.0)	<0.001*	16.0 (16.0–18.0)	28.0 (19.0–32.0)	<0.001*
Selenium (µg/dL)	3.75 (3.00–5.00)	10.0 (9.0–11.0)	<0.001*	8.0 (4.0–9.0)	10.0 (9.0–12.0)	<0.001*	8.0 (3.9–9.0)	10.0 (9.0–12.0)	<0.001*
IL6 (pg/mL)	19.0 (16.0–22.0)	300 (210–410)	<0.001*	197 (20–310)	390 (205–420)	<0.001*	190 (19–300)	350 (200–420)	<0.001*
IL6 expression	13.5 (9.0–20.0)	2.80 (2.00–4.00)	<0.001*	3.90 (2.30–13.0)	3.10 (2.00–4.00)	0.002*	4.00 (2.30–13.0)	3.00 (1.90–4.00)	<0.001*
Lactate (mmol/L)	3.60 (2.10–4.20)	2.00 (1.70–3.70)	<0.001*	2.70 (1.90–4.00)	2.20 (1.65–3.85)	0.054	2.80 (1.90–4.00)	2.05 (1.60–3.80)	0.014*

Data are median (25th–75th percentile). p-values from Mann–Whitney U test. * Significant at $p \leq 0.05$. Corticosteroids omitted (no patient treated). Where a "No" subgroup includes controls, the lower quartile approaches zero, widening the reported interval.

while the median survival time was 16.00 days and 6.00 days, respectively. The log-rank test showed a statistically significant difference between the survival distributions of the two groups ($\chi^2 = 136.933$, $p < 0.001$), (Figure 3).

The Cox regression analyzes were designed to identify biomarkers associated with outcomes in critically ill patients. In the univariate analysis, procalcitonin (HR 1.122), CRP (HR 1.211), IL-6 (HR 1.016), IL-6 expression (HR 8.073), and lactate (HR 5.178) were significantly associated with an increased risk of adverse outcomes (p<0.001). However, in the multivariate analysis, the model was adjusted for age, sex, comorbidities, and clinical severity scores, only procalcitonin (HR 1.071, 95% CI 1.020-1.126, p=0.006) and lactate (HR 2.379, 95% CI 1.228-4.608, p=0.001) remained as significant independent predictors of poor outcomes. suPAR, PAD2, CRP, selenium, and IL-6 were not significant independent predictors in the multivariate model (Table 5)

Discussion

The present study revealed that serum lactate levels were significantly elevated in patients compared to control (P<0.001). Furthermore, lactate levels were significantly increased in the non-survival group compared to the survival group (P<0.001). Our data are consistent with many previous research, for example [16-18]. Bakker et al.[16] mentioned that a lactate value greater than 2 mmol/L is considered a marker of hypoperfusion in septic shock. Furthermore, Hernandez et al. [17]reported a marked increase in lactate in sepsis, and that elevation implies a worse prognosis. The authors added that liver disease, brain trauma, thiamine deficiency, and carbon monoxide poisoning must be excluded be-

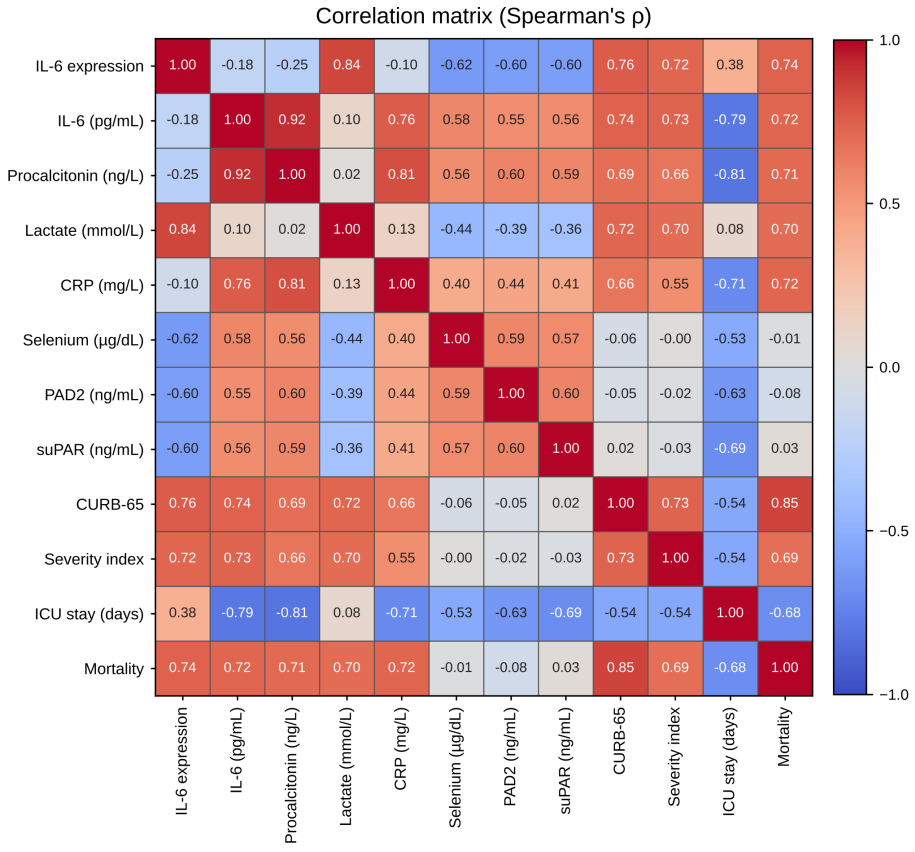


Figure 1. The correlation heat map shows the relationships between different inflammatory and clinical severity scores, ICU length of stay, and mortality. Values are Spearman's rank correlation coefficients (ρ). Warm (red) cells indicate positive correlations and cool (blue) cells indicate negative correlations; color intensity is proportional to the strength of association

fore making a diagnosis. Meanwhile, Singer et al. [18] revealed that lactate acts as a good marker of hypoperfusion, and the authors added that a decrease in lactate after treatment is associated with better results.

Our study revealed a significant decrease in serum selenium levels in patients compared to controls (P<0.001). However, there was no significant decrease in the non-survival group compared to the survival group. Selenium is a trace element involved in many antioxidant processes, present in many tissues in our body. Selenium is also involved in immunopathology and acts as a protective, antioxidant, and anti-inflammatory agent. Its deficiency means deterioration in general nutrition and specifically in the antioxidant glutathione pathway.

We described that the patients had an insignificantly higher serum suPAR level than controls (P<0.113). Furthermore, the non-survival group did not show a significant increase compared to the survival group (P<0.704). Hoenigl et al.[19] and Ni et al. [20] reported that serum suPAR concentrations increase in inflammatory and infectious diseases. Furthermore, the study by Georgescu et al.[21] revealed that suPAR is a good diagnostic marker in septic patients and may exceed CRP and procalcitonin. Saada et al. [22] reported that suPAR is a fair diagnostic marker for septic ICU patients, but does not surpass that of PCT or CRP. On the other hand, Henriquez-Camacho and Losa [23] reported that data on these markers as diagnostic tools for sepsis are controversial. The study by Georgescu et al. [21] reported that at a cut-off point of 10.6 ng / mL, suPAR was superior to PCT and CRP in critically ill septic patients. Furthermore, Saada et al. [22] mentioned that suPAR is positively correlated with PCT and CRP levels. The authors added that it is a fair diagnostic test for sepsis in patients with a cutoff of 3.98 ng/mL but does not surpass that of PCT or CRP. Savva et al. [24] found that the value of the soluble urokinase plasminogen activator receptor (suPAR) >12.9 ng/mL corresponds to high mortality at 28 days in ventilator-associated pneumonia (VAP) in the ICU. However, Huang

Table 4. ROC curves for different parameters to discriminate non-survival from survival critically ill patients.

Test Result Variable(s)	AUC	P value	Asymptotic 95% Confidence Interval		Cutoff point	Sensitivity	Specificity
			Lower Bound	Upper Bound			
suPAR (ng/mL)	0.522	0.707	0.402	0.641	≥ 9.5	57.10%	50.50%
PAD2 (ng/mL)	0.554	0.347	0.431	0.676	≤ 35.5	51.40%	40.00%
Procalcitonin (ng/mL)	0.959	<0.001*	0.928	0.99	≥ 98.5	100.00%	89.50%
CRP (mg/L)	0.961	<0.001*	0.932	0.989	≥25.5	100.00%	85.30%
Selenium (µg/dL)	0.507	0.056	0.399	0.618	≤9.5	49.50%	57.00%
IL-6 (pg/ml)	0.971	<0.001*	0.945	0.996	≥ 397.5	100.00%	92.60%
IL-6 expression	0.979	<0.001*	0.959	0.998	≥ 3.35	97.10%	84.20%
Lactate (mmol/L)	0.955	<0.001*	0.913	0.997	≥ 2.05	98.00%	70.50%

AUC: Area Under a Curve ,
p value for comparing the two studied groups
*: Statistically significant at p ≤ 0.05

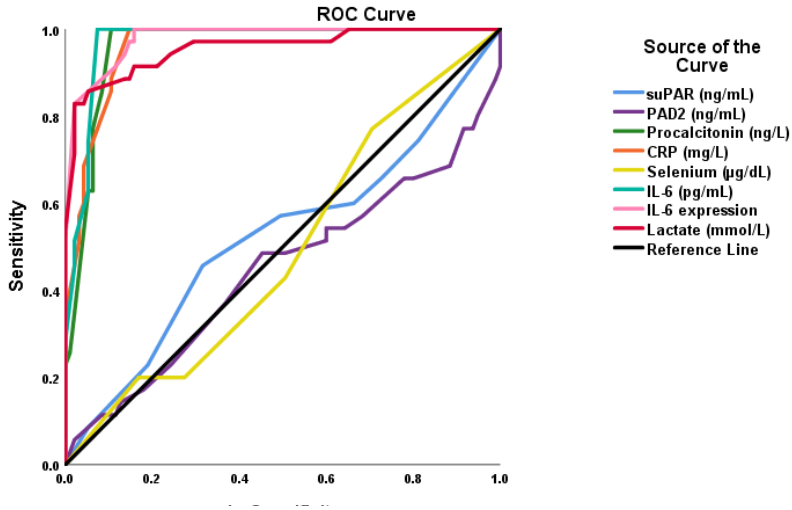


Figure 2. ROC curves for different parameters to discriminate non-survival from survival critically ill patients.

et al.[25] reported that suPAR proved to be an excellent prognostic biomarker in critical patients, but it cannot discriminate between sepsis and other pathologies.

Giamarellos-Bourboulis et al. [26] said that the normal value of suPAR in 50-70 years is 3 ng / mL, and 5.6 ng / ml requires admission to the ICU. The authors added that a level >12 ng/mL is associated with increased mortality. Additionally, Backes et al. [27] reported that levels >6.0 ng/mL identify risk and serious disease.

We also found that the serum PAD2 level is significantly increased in patients compared to controls (P<0.001), while it was insignificantly increased in non-survival patients compared to survival patients (P<0.346). Wu et al.[28] said that PAD2 translocate to the neutrophil and macrophage nucleolus, leading to neutrophil/macrophage death and the release of extracellular traps that activate pyroptosis through the caspase I and II pathways. They added that the previous data suggest that PAD2 could be an important inflammatory mediator in the pathogenesis of sepsis. Wang et al. [12] reported that white blood cell count (WBC), CRP, suPAR, PCT, PAD2, lactate and prothrombin time (PT) were significantly higher in the sepsis group than in the control group. However, lymphocyte count and blood platelets were significantly lower in patients compared to controls. The authors added that the SOFA score, PAD2, WBC, platelets, CRP, PCT, urea and lactate were correlated with sepsis. Wu et al. [29] reported that PAD2 participated in the inflammatory process through citrullinated apoptosis-mediated speck-like proteins, activated the caspase pathway, and promoted the expression of some inflammatory mediators, such as IL-1B, IL-8, and IL-6, which expanded the inflammatory response.

Wu et al. [28] and Liang [30] mentioned that inhibition of PAD2 could reduce inflammatory concentrations and organ damage in mice, confirming that PAD2 may be a potential therapeutic target for clinical

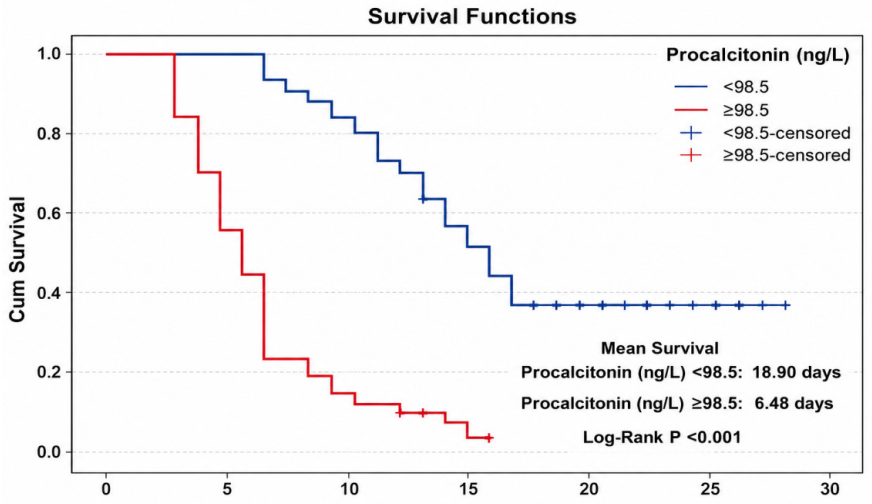


Figure 3. Kaplan–Meier survival curves analysis stratified by procalcitonin level.

Table 5. Univariate and multivariate Cox regression analysis of biomarkers associated in critically ill patients.

Parameters	Univariable HR	95% C.I		P value	Multivariable HR	95% C.I		P value
		lower	upper			lower	upper	
suPAR (ng/mL)	1.006	0.869	1.166	0.93				
PAD2 (ng/mL)	0.973	0.932	1.016	0.215				
Procalcitonin (ng/mL)	1.122	1.081	1.164	<0.001*	1.071	1.02	1.126	0.006*
CRP (mg/L)	1.211	1.148	1.277	<0.001*	1.019	0.915	1.135	0.341
Selenium (µg/dL)	0.981	0.775	1.241	0.879				
IL-6 (pg/mL)	1.016	1.012	1.021	<0.001*	1	0.988	1.013	0.931
IL-6 expression	8.073	4.234	15.392	<0.001*	2.233	0.469	7.644	0.542
Lactate (mmol/L)	5.178	3.274	8.189	<0.001*	2.379	1.228	4.608	0.001*

patients with sepsis. Wang et al. [12] reported that a PAD2 concentration >48.6 ng/mL had a higher mortality rate. The authors added that PAD2 had a diagnostic and prognostic value for sepsis and could be combined with other markers and clinical parameters to establish a more accurate.

Our results revealed that serum procalcitonin levels were significantly higher in patients than in controls (P<0.001) and in the non-survival group than in the survival group (P<0.001). Procalcitonin is the precursor of calcitonin and is produced by almost all organs and macrophages. It starts to increase 3-4 hours after an inflammatory stimulus and peaks at about 24 hours. Furthermore, its levels are influenced by the rate of glomerular filtration and renal replacement therapy[31]. However, Meier et al. [32] reported that the utility of PCT in predicting ICU sepsis is limited. Christ et al. [33] said that there was no definite cut-off value for the diagnosis of sepsis, but the values used range from 0.5-2.0 µg/L. However, Evans et al. [34] reported that PCT may be superior to CRP in patients with sepsis. Using PCT as a marker to distinguish viral from bacterial infections is still controversial[35]. Seligman et al. [36] said that in VAP patients, estimation at the beginning and on day 4 of treatment could predict survival and persistently high levels indicate failure of infection control. Furthermore, Pepper et al. [37] reported that PCT has an impact on mortality and duration of antibiotics in ICU patients. Baumann et al. [38]reported that levels greater than 2 ng/mL of PCT within 4-6 hours indicate bacterial infection, and previously Hoshina et al.[39] noted that PCT values greater than 0.2 ng/mL with a sensitivity of 86% and a specificity of 80% diagnose bacterial infection. Van Nieuwkoop et al. [40] said that it is easy to discriminate infection from systemic inflammation of another origin by PCT estimation. The authors added that PCT also correlates with the severity of the infection and the bacterial load. Further-

more, they added that PCT can differentiate between bacterial and viral infections and is not attenuated by the use of corticosteroids, so it does not depend on leukocytes. Schuetz et al.[41] advised discontinuing antibiotics once PCT normalizes or decreases by 80-90% from its peak.

Leli et al. reported that Gram-negative bacterial (GNB) infections are associated with higher levels of PCT than gram-positive bacteria (GPB), and an increase of 2 ng/mL should raise suspicion of GNB infection [42].

Our finding revealed that C-reactive protein (CRP) levels were significantly increased in patients compared to controls (P<0.001) and in non-survivors compared to survivors (P<0.001). Travlos et al.[8] stated that CRP could serve as a marker to discriminate between patients with pneumonia and those with tracheal infections, as well as to differentiate bacteria from viral infections. The authors added that elevated CRP levels in ICU patients were associated with an increased risk of mortality. Garvik et al. reported that when CRP starts to increase in the three preceding blood samples, bloodstream infection is the definite diagnosis[43].

Parlato et al. [44] reported that no single biomarker or combination performed better than CRP alone or procalcitonin to discriminate sepsis from non-septic inflammatory responses. Regarding the response to therapy, Póvoa et al. [45] found four patterns: a fast response when the CRP decreased to 0.4 on day 4, a slow decline with CRP >0.4 and <0.8 on day 4, no response, and a biphasic pattern (drop in CRP followed by an increase). However, Molano-Franco et al. [5]mentioned that there was no relationship between CRP levels and the risk of mortality. Bhuiyan et al. [46]showed that CRP was more than six times higher in bacterial infections than in viral infections. Furthermore, Nieuwkoop et al. [40] stated that combining clinical data (heart rate, respiratory rate, oxygen saturation, and auscultation findings) slightly improved the predictive value, with a sensitivity of 64% and a specificity of 88%.

Our results revealed a significant increase in both IL-6 levels and gene expression in patients compared to the control group (P<0.001 and P<0.001, respectively). Furthermore, a significant elevation was reported in the non-survival group compared to the survival group (P<0.001 and P<0.001, respectively). Interleukin-6 (IL-6) is one of the most important biomarkers in sepsis, showing pro- and anti-inflammatory actions. Furthermore, it is involved in modulating immunity, stress response, and coagulation [47] IL-6 levels increase after surgery, trauma, and critical illness, with the elevation correlating with the severity of the disease. Values can range from 40 pg/mL in systemic inflammatory response syndrome to 100 pg/mL in sepsis and up to 500 pg/mL in septic shock [48] .Barchillo et al. [7] stated that IL-6, in addition to CRP, PCT, and pre-sepsin, individually or in combination, could serve as markers for both diagnosis and prognosis. However, Molano-Franco et al.[5] reported that out of 94 studies focusing on baseline IL-6 levels and mortality rate, the results were variable, with some showing no role for IL-6 in predicting mortality prognosis. The authors added that a single baseline estimate of biomarkers (IL-6, CRP, PCT, or sCD14) is not useful to prognosticating ICU patients. Furthermore, they advised that combining good clinical data with multiple biomarkers could aid both in diagnosis and prognosis. Liu et al. [49] reported that IL-6 was higher in respiratory infections than in controls; however, they found no difference between patients with chronic obstructive pulmonary disease (COPD) and patients with community-acquired pneumonia (CAP). On the other hand, Jung et al. [50] reported an increase in IL-6 levels in CAP compared to COPD patients.

The present study found that while suPAR levels tended to be higher in patients, they did not differ significantly between survivors and non-survivors. Saada et al. [22] reported a positive correlation between suPAR and PCT levels but did not find a correlation between suPAR and CRP. Wang et al. [12] showed that PAD2 concentration was positively correlated with PCT, white blood cell count, CRP, total bilirubin, and SOFA score (P<0.05 for all). Meanwhile, Molano-Franco et al. [5] did not report any correlation between PCT, CRP, and mortality rate.

The remarkably high AUC values observed in the present study may reflect the marked clinical distinction between severe and non-severe pneumonia in our cohort, strict patient selection criteria, and biomarker measurement at the time of admission before substantial therapeutic intervention. In addition, the relatively modest sample size may have contributed to optimistic estimates of diagnostic performance. Therefore, although these findings are encouraging, external validation in larger multicenter cohorts is necessary before routine clinical implementation

When selecting biomarkers, it is important to consider which marker(s) will be most useful for diagno-

sis, management, and prediction of prognosis, and how long they will provide clinical benefit. As evidenced in previous studies, including ours, a combination of multiple biomarkers is likely to be more beneficial, provided it is accompanied by comprehensive clinical data and an assessment of both infection and immune status. No biomarker alone appears sufficient for accurate diagnosis, monitoring of treatment response, and prognostication in different patient populations and clinical scenarios. An integrative approach that uses multiple complementary biomarkers along with careful clinical evaluation can offer the most robust strategy for optimizing patient care in critical illness.

Strengths of the study include the simultaneous assessment of multiple diagnostic and prognostic biomarkers, allowing a comprehensive evaluation of disease status. The inclusion of PAD2 as a novel biomarker adds potential clinical relevance and expands current knowledge in this field. Furthermore, the integration of both IL-6 protein and gene expression analyses provides a multidimensional approach to biomarker evaluation. Finally, the assessment of mortality outcomes enhances the prognostic significance and clinical applicability of the study findings.

This study has several limitations. First, it was conducted at a single center with a relatively small sample size. Second, the control group may not fully represent healthy individuals, potentially affecting diagnostic comparisons. Third, serial measurements of biomarkers were not performed. Fourth, microbial subgroups were small, precluding pathogen-specific analyses, as microbial etiology may significantly influence biomarker expression and interpretation. Additionally, the absence of correction for multiple comparisons increases the possibility of type I error and represents a limitation of the present study. Finally, external validation in independent cohorts is needed before clinical implementation.

CONCLUSIONS:

This study confirms the diagnostic relevance of lactate, PCT, CRP, IL-6(protein/Gene), and PAD2 in critically ill pneumonia patients. Significant elevations of lactate, PCT, CRP, and IL-6(protein/Gene) in non-survivors highlighted their prognostic value, although no biomarker demonstrated statistically significant superiority over the others when ROC curves were compared regarding to mortality prediction. Positive correlations between certain biomarkers (e.g. suPAR with PCT, PAD2 with PCT/CRP) suggest that combining complementary markers may enhance their clinical utility. An approach that integrates multiple biomarkers and comprehensive clinical evaluation appears to be more prudent to optimize diagnostic accuracy, monitor treatment response, and improve prognostic predictions in this population of patients. Future multicenter studies are warranted to validate biomarker panels and determine their utility in individualized risk stratification and clinical decision-making.

AUTHOR CONTRIBUTIONS:

Conceptualization: NFA, THS. Methodology: NFA, HAH, MKF, EMF, THS. Software: NFA, AKS, GAO, HN, HAH, MKF,MHH, EMF Validation: NFA, HAH, MKF,MHH, EMF. Formal analysis: NFA, HAH, MKF, MHH, EMF. Investigation: NFA, HAH, MKF, EMF. THS Resources: NFA, HAH, MKF, MHH, EMF, THS Data curation: NFA, HAH, MKF, EMF, MHH, THS Writing – Original Draft: NFA, GAO, AKS, HAH, MKF, EMF, THS, HN, MHH, MDS Writing – Review & Editing: NFA, GAO, AKS, HAH, MKF, EMF, THS, MHH, HN, MDS. Visualization: NFA, THS, Supervision NFA, THS Project administration: NFA, THS.

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CONFLICT OF INTEREST:

The authors declare that they have no conflicts of interest.

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