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# Diagnostic accuracy of PCT, IL-6, and MR-ProADM for early identification of sepsis in the emergency department

## Precisión diagnóstica de la PCT, la IL-6 y la MR-ProADM para la identificación temprana de la sepsis en el servicio de urgencias

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## Abstract

**Objective:** To evaluate the diagnostic accuracy of the biomarkers procalcitonin (PCT), interleukin-6 (IL-6), and mid-regional pro-adrenomedullin (MR-ProADM), individually and in combination, for early detection of sepsis and septic shock during emergency department (ED) triage.

**Materials and methods:** A retrospective observational study was conducted in adults presenting to the ED with triage levels 2 and 3 between December 2021 and July 2023. Blood samples were collected at admission, prior to any therapeutic intervention. Plasma concentrations of PCT, IL-6, and MR-ProADM were measured using CMIA or ELISA. Diagnostic accuracy was assessed using ROC curves and AUC analysis.

**Results:** A total of 248 patients were included (214 with sepsis and 34 non-septic controls). Simultaneous elevation of PCT, IL-6, and MR-ProADM was observed in 70% of septic patients compared with 3% of controls. Each biomarker showed high diagnostic accuracy for sepsis (AUROC >0.90). The combined assessment increased specificity and was strongly associated with sepsis and septic shock, with progressively higher odds as the number of elevated biomarkers increased. Higher biomarker burden was also associated with indicators of greater clinical severity, including higher SOFA scores and ICU admission.

**Conclusions:** Combined measurement of PCT, IL-6, and MR-ProADM at ED triage, before therapeutic intervention, improves early identification of patients with sepsis and provides relevant information on initial disease severity. This multiplex platform approach may support clinical prioritization and protocol activation in the ED.

**Keywords:** Sepsis. Emergency department. Biomarkers. PCT. IL-6. MR-ProADM.

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## Resumen

**Objetivo:** Evaluar la precisión diagnóstica de los biomarcadores procalcitonina (PCT), interleucina 6 (IL-6) y proadrenomedulina de región media (MR-ProADM), de forma individual y combinada, para la detección temprana de sepsis y shock séptico durante el triaje en el servicio de urgencias (SU).

**Materiales y métodos:** Se realizó un estudio observacional retrospectivo en adultos que acudieron al SU con niveles de triaje 2 y 3 entre diciembre de 2021 y julio de 2023. Las muestras de sangre se recogieron al ingreso, antes de cualquier intervención terapéutica. Las concentraciones plasmáticas de PCT, IL-6 y MR-ProADM se determinaron mediante CMIA o ELISA. La precisión diagnóstica se evaluó mediante curvas ROC y análisis del AUC.

**Resultados:** Se incluyeron un total de 248 pacientes: 214 con sepsis y 34 controles no sépticos. La elevación simultánea de PCT, IL-6 y MR-ProADM se observó en el 70% de los pacientes sépticos, frente al 3% de los controles. Cada biomarcador mostró una alta precisión diagnóstica para la sepsis (AUROC >0,90). La evaluación combinada aumentó la especificidad y se asoció estrechamente con la sepsis y el shock séptico, con odds progresivamente mayores a medida que aumentaba el número de biomarcadores elevados. Una mayor carga de biomarcadores también se asoció con indicadores de mayor gravedad clínica, incluidos valores más altos en la escala SOFA e ingreso en la UCI.

**Conclusiones:** La medición combinada de PCT, IL-6 y MR-ProADM durante el triaje en el SU, antes de la intervención terapéutica, mejora la identificación temprana de pacientes con sepsis y aporta información relevante sobre la gravedad inicial de la enfermedad. Este enfoque de plataforma multiplex puede apoyar la priorización clínica y la activación de protocolos en el SU.


**Palabras clave:** Sepsis. Servicio de urgencias. Biomarcadores. PCT. IL-6. MR-ProADM.

## Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Each hour of delay in diagnosis and treatment increases mortality [2]. Early recognition remains challenging due to its heterogeneous presentation, influenced by factors such as pathogen type, source of infection, immune status, age, sex, comorbidities, and individual inflammatory response [3]. In addition, the rapid transition from hyperinflammation to immunosuppression further complicates early identification [4].

More than two thirds of cases are initially managed in the emergency department (ED) [5,6], where triage relies on clinical criteria and tools such as the *quick Sequential Organ Failure Assessment (qSOFA)* score [7]. However, these tools have limited sensitivity and specificity. Although the SOFA score provides a more comprehensive assessment, it is impractical during triage due to its complexity and the requirement for laboratory testing [8].

Most studies evaluating sepsis biomarkers have been performed after initial clinical assessment or therapeutic intervention, often in ICU or inpatient settings [9–14]. Among these biomarkers, procalcitonin (PCT), interleukin-6 (IL-6), and Mid-regional pro-adrenomedullin (MR-ProADM) stand out, as they reflect different pathophysiological mechanisms involved in the septic response. However, their levels may be influenced by early interventions such as antibiotics, fluid resuscitation, or hemodynamic support, limiting their isolated diagnostic value. Evidence regarding biomarker performance at the earliest point of care, during ED triage, before treatment initiation, remains limited. This gap underscores the need for strategies that incorporate biological information into early triage decision-making.

To date, this is the first study to jointly evaluate the diagnostic accuracy of PCT, IL-6, and MR-ProADM at ED triage, before any therapeutic intervention. The objective was to assess their individual and combined diagnostic accuracy for detecting sepsis and septic shock.

## Material and methods

### Study design and patient selection

This retrospective observational study was conducted in the ED of Hospital Universitario Son Llàtzer (Spain) between December 2021 and July 2023. Adult patients (≥18 years) presenting to the ED with predefined clinical criteria suggestive of sepsis and a triage priority level of 2 (life-threatening) or 3 (non-life-threatening), according to the Spanish Triage System [15,16], were included. The protocol activation system is described in **Supplementary Section 1**.

Control patients were identified consecutively during the same study period and with the same triage levels (2–3), applying the same eligibility framework. Controls were intentionally selected to reflect the heterogeneity of real-world ED presentations and included both non-septic infectious conditions and non-infectious diseases with early symptoms that frequently overlap with sepsis.

### Definitions

Clinical suspicion of sepsis was defined by the presence of at least one of the following: fever ≥38 °C

or hypothermia <36 °C, tachycardia, tachypnea, hypotension or low mean arterial pressure (MAP), decreased oxygen saturation, altered mental status, and/or a presumptive infectious focus documented at first assessment. Consecutive patients meeting these criteria during the study period were included; neither the presence of ≥ 2 SIRS criteria nor antibiotic therapy in the ED was required for inclusion.

The final diagnostic classification of sepsis and septic shock was established strictly according to the Third International Consensus Definitions (Sepsis-3) [1]. As this adjudication is longitudinal and protocol-driven (see **Supplementary Section 1**), no single fixed time interval exists between the index test (obtained at ED triage) and the final diagnostic determination. Although antibiotics and fluid resuscitation could be administered after index sampling as part of routine care, these interventions occurred after biomarker collection and before definitive adjudication.

Non-septic status was defined after complete clinical evaluation based on the same criteria. Initial screening was performed by ED clinical staff and subsequently verified by trained study personnel. Final adjudication, as sepsis or non-sepsis, was performed after comprehensive chart review with access to routine clinical data generated as part of standard care.

## Sample size

No formal sample size calculation was performed prior to the study. Because this investigation was based on a retrospective cohort of consecutive ED presentations during the predefined study period, the final sample size was determined by the number of eligible patients rather than by an a priori statistical power estimation.

## Blinding

Because this was a retrospective diagnostic accuracy study, blinding was inherently incomplete. Diagnostic adjudication was performed with access to routine clinical information generated during standard care; therefore, PCT results could have been available to treating clinicians and adjudicators when ordered as part of the clinical workflow. In contrast, IL-6 and MR-ProADM were measured retrospectively in stored samples and were not available to clinicians or adjudicators at any stage of patient care or diagnostic classification. All laboratory analyses for these biomarkers were performed by research personnel blinded to clinical data, outcomes, and final sepsis status. Accordingly, while analytical blinding was ensured for IL-6 and MR-proADM, the availability of PCT as part of routine care introduces a potential incorporation bias that should be considered when interpreting diagnostic performance.

## Ethical considerations

The study protocol was approved by the Ethics Committee of the Balearic Islands (ref IB 4463/21 PI) in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants by the attending physician or trained staff prior to any study procedures. All experiments were conducted in compliance with relevant guidelines and regulations. This diagnostic accuracy study was not preregistered in a public registry. The full study protocol is available from the corresponding author upon reasonable request.

The study was conducted following the Standards for Reporting Diagnostic Accuracy Studies (STARD) guidelines [17]. See **Supplementary Table S1** for STARD checklist details.

## Data collection

Clinical and laboratory data were collected at ED admission, including age, sex, triage levels (2 and 3), and vital signs (heart rate, respiratory rate, oxygen saturation [$SpO_2$], body temperature, and systolic and diastolic blood pressure). The time from symptom onset to ED contact, white blood cell (WBC) count, C-reactive protein (CRP), and baseline SOFA parameters (platelet count, bilirubin, creatinine, $PaO_2/FiO_2$, Glasgow Coma Scale, and MAP) were also recorded. In cases with missing data, the available value within the first 24 hours was used. Clinical outcomes (ICU admission, hospital length of stay, and mortality) were documented. Plasma concentrations of PCT, IL-6, and MR-ProADM were measured before any therapeutic intervention.

## Biomarker measurement and availability

Blood samples were obtained at ED triage, before the initiation of antibiotics, fluid resuscitation, or other therapeutic interventions. Samples were collected in EDTA vacuum tubes. In patients with suspected sepsis, PCT was measured in the Son Llàtzer Hospital clinical laboratory using a chemiluminescent microparticle immunoassay (CMIA) on an Alinity® analyzer (Abbott), as part of the routine diagnostic practice. PCT measurements in controls, as well as IL-6 and MR-ProADM measurements in all patients, were performed by the study team on platelet-free plasma obtained by double centrifugation. Samples were stored at −80 °C in the IdISBa Biobank until analysis, following standardized pre-analytical protocols to minimize biomarker degradation.

Plasma levels of PCT, IL-6, and MR-ProADM were quantified in duplicate using sandwich ELISA kits: Human PCT (Invitrogen™, detection range 0.01–20 ng/mL), Human IL-6 (Invitrogen™, 7.8–2500 pg/mL), and Human MR-ProADM (Krishgen BioSystems, 15.6–1000 pmol/L), according to the manufacturers' instructions.

Regarding clinical availability, IL-6 and MR-ProADM were measured retrospectively in stored samples and were not available to clinicians or adjudicators at any stage of patient care or diagnostic classification, whereas PCT results could have been available when ordered as part of routine clinical practice.

### Data analysis

Statistical analyses were performed using GraphPad Prism® 10 and R software (v4.4.1). Continuous variables were expressed as means ± standard deviation (SD) or medians with interquartile ranges (IQR) as appropriate. Categorical variables were presented as frequencies and percentages. Group comparisons were conducted using unpaired t-tests (two groups), one-way ANOVA (three groups), or the corresponding non-parametric equivalents.

Diagnostic performance was evaluated using Receiver Operating Characteristic (ROC) curve analysis, and optimal cut-off values were determined using the Youden index. All positivity thresholds for PCT, IL-6, and MR-ProADM were derived exploratorily within the present cohort; no cut-offs were prespecified prior to data collection.

To assess the cumulative effect of biomarker combinations, a categorical variable (n_ROC) was created to represent the number of biomarkers exceeding their respective ROC-derived cut-off values (with corresponding 95% confidence intervals). This variable was included in logistic regression models to evaluate the association with sepsis and septic shock. Results were presented as odds ratios (OR) with corresponding 95% confidence intervals. No pre-specified heterogeneity or subgroup analyses were defined in an earlier protocol; stratified analyses were performed as exploratory post hoc evaluations to provide contextual information only.

Comparisons across multiple biomarker burden strata were exploratory. No formal post hoc multiplicity correction was applied, and p values should be interpreted descriptively. Between-center variability could not be assessed because this was a single-center study, and limited granularity in time-from-symptom-onset data precluded stratification by disease evolution. A p-value ≤0.05 was considered statistically significant.

Internal validation by 300-iteration bootstrap resampling yielded an optimism-corrected AUC *(95% CI)* of 0.947 (apparent AUC 0.952; mean bootstrap AUC 0.957; optimism 0.0048).

## Results

### Patient characteristics

A total of 248 patients were included, comprising 214 septic patients (33.2% women; mean age 70.8 ± 13.8 years) and 34 non-septic controls (55.9% women; mean age 67.5 ± 20.1 years). A STARD flow diagram of participants is shown in **Figure 1**.

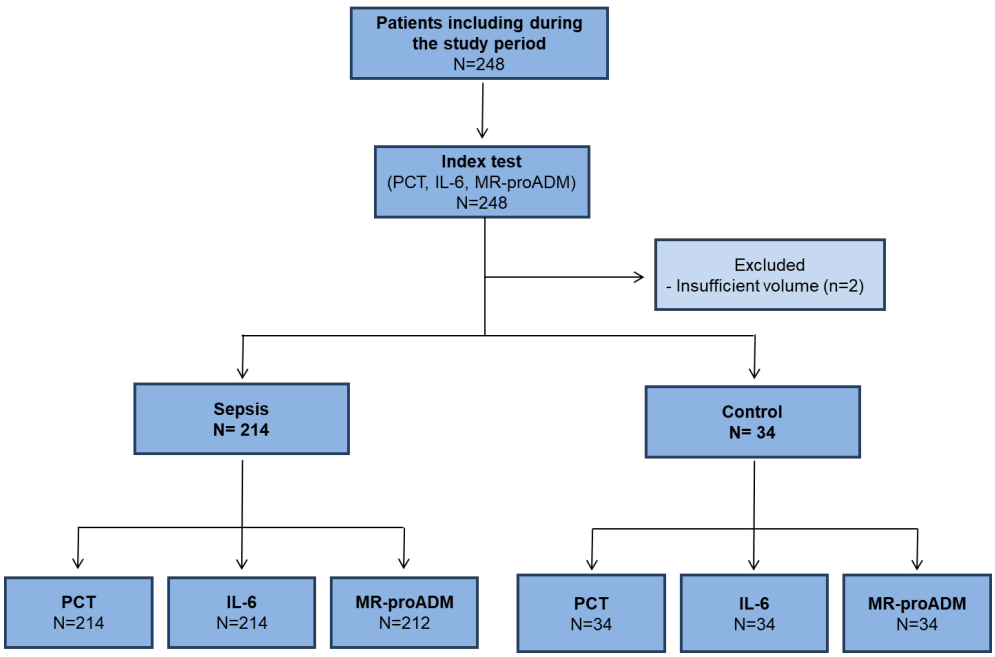


**Figure 1. STARD flow diagram of participants**

**Table 1. Patient characteristics, clinical and laboratory variables, and plasma biomarker levels in septic patients and controls included in the study**

| | Sepsis (n=214) | Control (n=34) | p-value |
|---|---|---|---|
| **Age, median [IQR]** | 72 [62-82] | 70 [54.7-85] | 0.8310 |
| **Sex, n (%)** | | | |
| Male | 143 (66.8) | 19 (55.9) | 0.2457 |
| Female | 71 (33.2) | 15 (44.1) | |
| **Triage at ED, n (%)** | | | |
| 2 | 158 (73.8) | 27 (79.4) | 0.6715 |
| 3 | 56 (26.2) | 7 (20.6) | |
| **Triage assessment, median [IQR]** | | | |
| Heart rate (beats/min) | 102 [87.7-120] | 90 [74.2-113.5] | **0.0086** |
| Breathing rate (breaths/min) | 20 [16-26] | 16 [16-20] | **0.0034** |
| $SpO_2$ (%) | 96 [94-98] | 98 [96.5-99] | **0.0023** |
| Body temperature (ºC) | 36.7 [36.2-37.7] | 36.2 [35.9-36.4] | **<0.0001** |
| Systolic blood pressure (mmHg) | 109.5 [95-128] | 133.5 [113-142] | **0.0003** |
| Diastolic blood pressure (mmHg) | 63.5 [52-74] | 72.5 [57-85.2] | **0.0250** |
| **Time of onset of symptoms before ED contact, n (%)** | | | |
| >24h | 53 (24.7) | 7 (20.5) | 0.8037 |
| <24h | 71 (33.2) | 12 (35.3) | |
| Not Reported | 90 (37.3) | 15 (44.1) | |
| **Variables for Basal SOFA scoring, median [IQR]** | | | |
| Platelets ($x10^9$/L) | 208 [144-311] | 253 [197-311.5] | 0.05 |
| Bilirubin (mg/dL) | 0.8 [0.5-1.6] | 0.4 [0.3-0.8] | **0.0004** |
| Creatinine (mg/dL) | 1.2 [0.8-1.9] | 1 [0.8-1.5] | 0.0564 |
| $PaO_2/FiO_2$ (mmHg) | 219.6 [138.2-291.1] | 212.9 [104.8-285.6] | 0.3907 |
| Glasgow Coma Scale | 14.9 [15-15] | 15 [15-15] | 0.2500 |
| MAP (mmHg) | 79 [68-90] | 92.5 [76-104.5] | **0.0008** |
| **Other laboratory variables, median [IQR]** | | | |
| WBC ($x10^9$/L) | 13.9 [7.6-19.3] | 9.4 [8.1-14.1] | **0.0086** |
| C-reactive protein (mg/dL) | 26.6 [13.7-90.4] | 0.9 [0.4-3.1] | **<0.0001** |
| **ICU admission, n (%)** | 38 (17.7) | 4 (11.7) | 0.4693 |
| **Days of hospitalization*, median [IQR]** | 8 [5-13] | 6 [3-7] | **0.0007** |
| **Mortality, n (%)** | 21 (9.8) | 1 (2.9) | 0.3276 |
| **Inflammatory biomarkers, median [IQR]** | | | |
| PCT (ng/mL) | 15.7 [1.1-15.1] | 0.2 [0.01-0.3] | **<0.0001** |
| IL-6 (pg/mL) | 8414 [56.5-1176] | 38 [7-12.9] | **<0.0001** |
| MR-ProADM (pmol/L) | 1544 [350.2-1547] | 212.5 [132.9-214.6] | **<0.0001** |

ED: emergency department; ICU: intensive care unit; IL-6: Interleukin-6; IQR: interquartile range; MAP: mean arterial pressure; MR-ProADM: Mid-regional pro-adrenomedullin; PCT: procalcitonin; SOFA: Sequential Organ Failure Assessment; WBC: white blood cells.

*Days from the emergency department admission to discharge among survivors. **Bold** values indicate statistically significant differences ($p \leq 0.05$).

Patient characteristics, including demographics, comorbidities, and baseline laboratory values, are summarized in **Table 1**. Septic patients showed significant alterations in vital signs compared with controls, including a higher heart rate (102 vs. 90 bpm; p=0.0086), respiratory rate (20 vs. 16 breaths/min; p=0.0034), and body temperature (36.7 vs. 36.2 °C; p<0.0001), along with lower $SpO_2$ (96 vs. 98%; p=0.0023) and systolic blood pressure (109.5 vs. 133.5 mmHg; p=0.0003). Triage-level distribution was similar between groups, suggesting that triage level alone may not adequately discriminate between

septic and non-septic patients. Clinical and biomarker characteristics stratified by triage priority levels 2 and 3 are presented in **Supplementary Table S2**.

Laboratory parameters used for SOFA calculation also showed significant differences: bilirubin (0.8 vs. 0.4 mg/dL; p=0.0004) and MAP (79 vs. 92.5 mmHg; p=0.0008) were lower in septic patients. WBC count (13.9 vs. 9.4 × $10^9$/L; p=0.0086) and CRP levels (26.6 vs. 0.9 mg/dL; p<0.0001) were higher in septic patients, indicating an active inflammatory response.

All patients had complete measurements for PCT and IL-6. MR-ProADM measurements were unavailable in two septic patients, who were excluded from analyses requiring MR-ProADM. Plasma concentrations of PCT, IL-6, and MR-ProADM were significantly higher in septic patients than in controls (**Table 1**).

Among septic patients, baseline severity varied: the median SOFA score at presentation was the median SOFA score at presentation was 4 [IQR: 3–6], with 3.7% presenting with SOFA <2, 41.1% with SOFA 2–4, and 38.8% with SOFA >4. No SOFA score was reported in 16.4%. Septic shock occurred in 18 (8.4%) patients, 38 (17.7%) required ICU admission, and 21 (9.8%) patients died during hospitalization. Septic patients had a significantly longer hospital stay compared with controls (8 days [5–13] vs. 6 days [3–7]; p = 0.0007). Mortality was 9.8% in septic patients and 2.9% in controls.

The 34 non-septic control patients presented with a heterogeneous range of conditions. Nine (26.5%) had non-septic infections treated with antibiotics (e.g., mild urinary or respiratory infections). The remaining 25 (73.5%) had non-infectious conditions that could mimic sepsis, including cardiovascular events (32.3%, n=11), upper gastrointestinal bleeding (8.8%, n=3), diabetic ketoacidosis (8.8%, n=3), pulmonary embolism (5.9%, n=2), trauma (5.9%, n=2), acute pancreatitis (2.9%, n=1), anaphylaxis (2.9%, n=1), and other miscellaneous conditions (5.9%, n=2). Mortality was 2.9% in controls.

## Diagnostic performance of PCT, IL-6, and MR-ProADM

**Figure 2** shows the plasma levels of PCT (**Figure 2A**, green dots), IL-6 (**Figure 2B**, red dots), and MR-ProADM (**Figure 2C**, blue dots) across three groups: septic patients without shock (light circles), septic patients with shock (dark circles), and controls (open circles). In all cases, biomarker levels were significantly higher in sepsis and showed even greater elevations in septic shock.

Median plasma concentrations [IQR] for each biomarker are presented in **Figures 2 A–C**. The apparent near-perfect separation observed between cases and controls should be interpreted with caution, as case–control imbalance and limited control heterogeneity

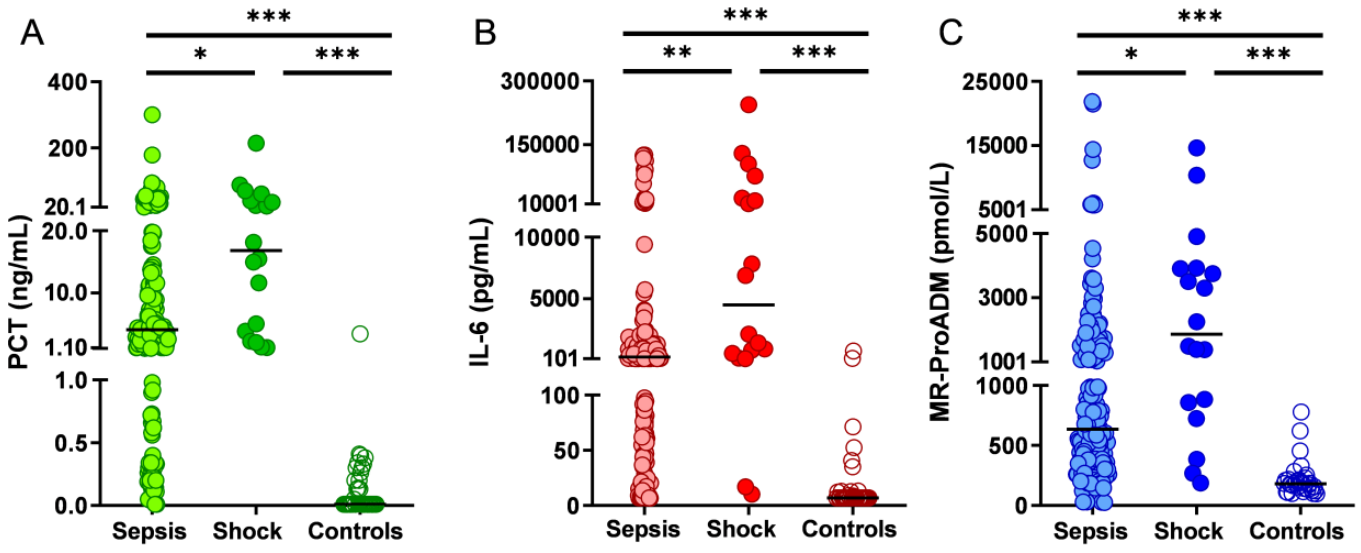


**Figure 2. Plasma levels of inflammatory biomarkers in septic patients and controls at ED triage**

IL-6: interleukin-6; MR-ProADM: Mid-regional pro-adrenomedullin; PCT: procalcitonin.

**A)** Plasma PCT levels (green); **B)** IL-6 (red); **C)** MR-ProADM (blue) in control patients (open circles) and septic patients with or without shock (dark and light filled circles, respectively). Horizontal black lines in panels A, B, and C indicate the median. Kruskal–Wallis test p-values: *p < 0.005, **p < 0.01, ***p < 0.0001.

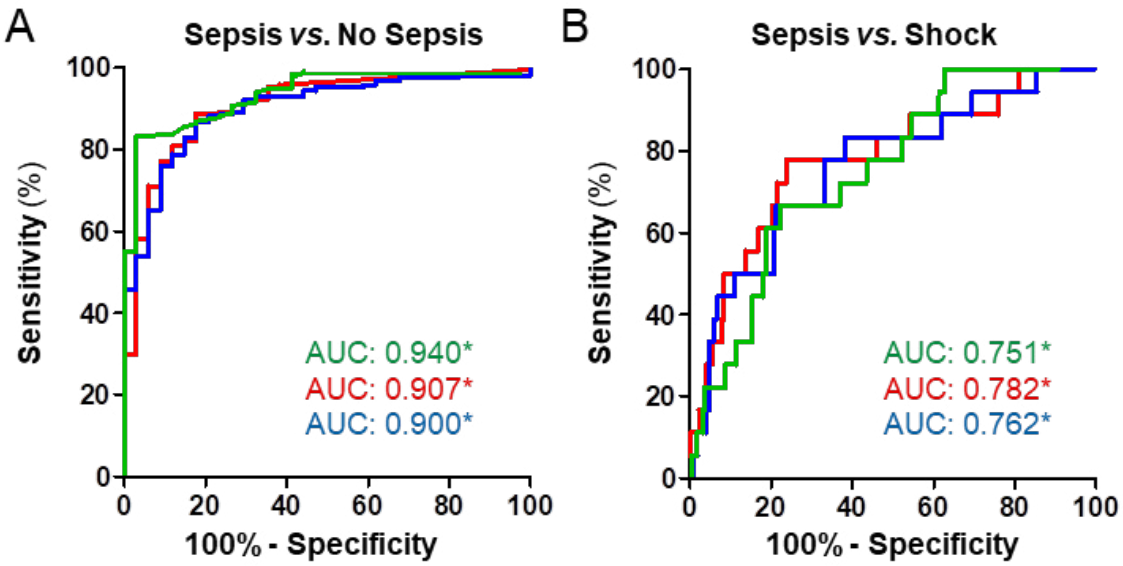


**Figure 3. AUROC curves (95% CI) for plasma levels of PCT (green), IL-6 (red), and MR-ProADM (blue) at ED triage**

AUC: Area Under the Curve; IL-6: Interleukin-6; MR-ProADM: Mid-regional pro-adrenomedullin; PCT: Procalcitonin.

**A)** Sepsis vs. non-sepsis; **B)** Septic shock vs. Sepsis without shock. Statistically significant differences ($p \leq 0.05$) are reported in **Supplementary Table S3**.

may accentuate between-group contrasts. For PCT (**Figure 2A**), controls showed low levels (0.21 ng/mL [0.01–0.27]), whereas concentrations were higher in septic patients without shock (13.9 ng/mL [1.0–13.1]) and markedly higher in septic shock (35.0 ng/mL [3.4–44.9]). A similar pattern was observed for IL-6 (**Figure 2B**), with values of 38.0 pg/mL [7.0–12.9] in controls, increasing in sepsis (5988 pg/mL [53.8–845.1]) and reaching extreme levels in shock (34837 pg/mL [441–37,117]). For MR-ProADM (**Figure 2C**), controls showed concentrations of 212.5 pmol/L [132.9–214.6], while septic patients without shock had 1,388 pmol/L [318–1,350], and those with shock had 3,230 pmol/L [824.5–3,908].

To assess diagnostic performance, AUROC analysis was performed (**Figure 3**). **Figure 3A** shows significant discrimination ($p<0.0001$) between septic patients and controls, with AUC values of 0.94 for PCT (green line), 0.907 for IL-6 (red line), and 0.900 for MR-ProADM (blue line). **Figure 3B** illustrates the ability to differentiate septic patients with and without shock. Performance was moderate, with AUC values of 0.751 for PCT (green line, $p=0.0004$), 0.782 for IL-6 (red line, $p<0.0001$), and 0.762 for MR-ProADM (blue line, $p=0.0002$). Cut-off values used to define biomarker positivity were derived exploratorily by AUROC analysis (with corresponding 95% confidence intervals) and determined using the Youden index within the present cohort, as detailed in **Supplementary Table S3**. Notably, the exploratory threshold obtained for PCT coincided with the widely adopted literature cut-off (0.5 ng/mL), whereas IL-6 and MR-ProADM thresholds were cohort-specific and should be interpreted accordingly.

Beyond discriminative performance, clinically interpretable diagnostic metrics based on ROC-derived cut-offs were summarized (**Supplementary Table S4**). For individual biomarkers, PCT demonstrated high rule-in capacity (LR+ 9.4; LR− 0.2), followed by IL-6 (LR+ 5.1; LR− 0.1) and MR-ProADM (LR+ 4.9; LR− 0.2). Combining biomarkers further improved rule-in performance: PCT+IL-6 and PCT+MR-ProADM yielded LR+ values of 25.8 and 25.2, respectively (both LR− 0.3), and the three-biomarker panel achieved an LR+ of 23.7 with an LR− of 0.3 (**Supplementary Table S5**). In contrast, diagnostic separation between septic shock and sepsis without shock at triage was limited, with LR+ typically in the 0.2–0.4 range and LR− in the 1.8–2.9 range across markers and combinations, consistent with the moderate AUROC observed for this comparison.

Because post-test probabilities are central to triage decisions, predictive values were estimated under realistic emergency-department sepsis prevalences (10%, 20%, and 30%). Under these scenarios,

**Table 2. Logistic regression of PCT, IL-6, and MR-ProADM combinations for sepsis and shock prediction**

| Predictors | Sepsis *vs.* No Sepsis | | | Sepsis *vs.* Shock | | |
|---|---|---|---|---|---|---|
| | OR | CI | *P* value | OR | CI | *P* value |
| **(Intercept)** | 0.12 | 0.03 – 0.34 | **0.001** | 0.02 | 0.00 – 0.06 | **<0.001** |
| **Elevated biomarkers*** | | | | | | |
| 1 biomarker | 23.61 | 5.83 – 128.71 | **<0.001** | 3.75 | 0.60 – 29.24 | 0.156 |
| 2 biomarkers | 183.33 | 35.55 – 1608.73 | **<0.001** | 7.00 | 1.30 – 5.28 | **0.029** |
| 3 biomarkers | 1233.33 | 181.99 – 26334.56 | **<0.001** | 27.8 | 6.50 – 193.10 | **<0.001** |
| **Observations** | 246 (212 sepsis and 34 no sepsis) | | | 212 (194 sepsis and 18 shock) | | |
| **$R^2$Tjur** | 0.658 | | | 0.139 | | |

OR: *odds ratio*; CI: Confidence Interval; IL-6: interleukin-6; MR-ProADM: Mid-regional pro-adrenomedullin; PCT: procalcitonin.
*Elevated biomarkers in Part II and III according to cut-off values detailed in **Supplementary Table S3**. **Bold** values indicate statistically significant differences (p ≤ 0.05).

PCT alone provided PPV values of 50–79% and NPV values of 98–92%. The three-biomarker combination increased the PPV to 73–92% while maintaining the NPV between 96–89%, supporting a complementary rule-in/rule-out profile at the bedside (**Supplementary Tables S6**).

Model calibration was assessed using univariate calibration plots for PCT, IL-6, and MR-ProADM and a multivariable model combining the three biomarkers, constructed by decile-based grouping of predicted probabilities. All models showed acceptable agreement between predicted and observed risks, with mild overestimation at lower predicted probabilities and slight underestimation in the highest deciles, findings consistent with the case–control imbalance of the cohort (**Supplementary Figure S1**).

**Table 2** presents the multivariate logistic regression analysis for the combined use of biomarkers (based on cut-off values from **Supplementary Table S3**). For sepsis, the presence of one elevated biomarker was associated with an OR of 23.61 (5.83–128.71; p<0.001), two biomarkers with an OR of 183.33 (35.55–1608.73; p<0.001), and three biomarkers with an OR of 1233.33 (181.99–26334.56; p<0.001). For shock, predictive performance was lower: two elevated biomarkers showed an OR of 7.00 (1.30–5.28; p=0.029), and three biomarkers showed an OR of 27.8 (6.50–193.10; p<0.001). One elevated biomarker alone was not significantly associated with shock. The very high ORs observed when all three biomarkers were elevated likely reflect cumulative risk and spectrum effects in a selected population, rather than clinically applicable probability estimates. Accordingly, these values should be interpreted as indicators of strong association rather than as measures of effect size.

## Assessment of multiple biomarkers in the ED to estimate severity

To estimate sepsis severity, patients were stratified according to the number of elevated biomarkers using AUROC-derived cut-off points (**Table 3**). Among septic patients, 70% (n=148) had three elevated biomarkers, 21% (n=44) had two elevated biomarkers, and 8% (n=17) had only one. In the control group, only one patient (3%) showed elevation of all three biomarkers and was later diagnosed with acute pancreatitis.

Septic patients with ≥2 elevated biomarkers were significantly older (72 vs. 75 vs. 67 years; p=0.021), with no significant differences in sex. Biomarker concentrations increased progressively with the number of elevated biomarkers (p<0.0001). Vital signs at triage showed no significant differences between groups, suggesting that conventional triage parameters do not adequately reflect inflammatory severity in early sepsis.

Regarding SOFA-related parameters, both bilirubin and creatinine levels were significantly higher in patients with two and three elevated biomarkers (p=0.0104 and p=0.0495, respectively). The proportion of patients with SOFA > 4 increased with the number of elevated biomarkers, reaching 52% in the group with three elevated biomarkers (p=0.0009), which also showed the highest ICU admission rate (18.9%, p=0.024).

Hospital length of stay was longer in patients with three elevated biomarkers (13.3 vs. 7.9 vs. 6.8 days), although this difference was not statistically significant. Shock and mortality were more frequent among patients with two and three elevated biomarkers, but the differences did not reach statistical significance.

**Table 3. Clinical and laboratory characteristics of septic patients stratified according to the number of elevated biomarkers, based on AUROC-derived cut-off points**

| | 1 biomarker* (n=17) | 2 biomarkers* (n=44) | 3 biomarkers* (n=148) | p-value |
|---|---|---|---|---|
| **Age, median [IQR]** | 67.0 [49.0-72.0] | 75.0 [64.0-86.2] | 72.0 [62.0-80.0] | **0.021** |
| **Sex, n (%)** | | | | |
| Male | 8 (47.1) | 34 (77.3) | 99 (66.9) | 0.075 |
| Female | 9 (52.9) | 10 (22.7) | 49 (33.1) | |
| **Inflammatory biomarkers, median [IQR]** | | | | |
| PCT (ng/mL) | 0.22 [0.12-1.63] | 0.45 [0.22-3.33] | 8.91 [2.32-25.4] | **<0.0001** |
| IL-6 (pg/mL) | 8.58 [7.0-53.7] | 117 [19.8-219] | 401 [109-2169] | **<0.0001** |
| MR-ProADM (pmol/L) | 212 [172-250] | 409 [206-754] | 922 [516-2033] | **<0.0001** |
| **Triage assessment, median [IQR]** | | | | |
| Heart rate (beats/min) | 108 [95-117] | 98 [78.5-112] | 105 [88-120] | 0.137 |
| Breathing rate (breaths/min) | 21 [18-29.5] | 22 [18-27] | 20 [16-25] | 0.231 |
| $SpO_2$ (%) | 96.5 [95-98] | 96 [94-98] | 96 [93.5-98] | 0.635 |
| Body temperature (ºC) | 37.1 [36.4-38.2] | 36.8 [36.4-37.9] | 36.7 [36.1-37.6] | 0.390 |
| Systolic blood pressure (mmHg) | 114 [105-129] | 106 [95.8-124] | 109 [93.8-128] | 0.590 |
| Diastolic blood pressure (mmHg) | 63 [55-73] | 62.5 [51.5-73.2] | 64 [52-74] | 0.850 |
| **Basal SOFA, median [IQR]** | | | | |
| Platelets ($x10^9$/L) | 283.9 [133.5-405.5] | 272.5 [168.8-314.8] | 227.0 [134-297] | 0.0795 |
| Bilirubin (mg/dL) | 1.35 [0.32-1.5] | 1.11 [0.51-1.3] | 1.74 [0.59-1.8] | **0.0104** |
| Creatinine (mg/dL) | 1.51 [0.77-1.42] | 1.78 [0.90-2.13] | 1.81 [0.96-1.87] | **0.0495** |
| $PaO_2/FiO_2$ (mmHg) | 236.5 [108.5-340.5] | 215.7 [108.1-302.9] | 223.8 [154.8-284.3] | 0.9045 |
| Glasgow Coma Scale | 14.9 [15-15] | 15 [15-15] | 14.9 [15-15] | 0.3773 |
| MAP (mmHg) | 85.4 [71.5-94.5] | 80.3 [68.2-89.7] | 80.4 [68.0-90.0] | 0.6955 |
| **Frequency of patients with SOFA, n (%)** | | | | |
| <2 | 4 (23.5) | 5 (11.4) | 3 (2.0) | **0.0009** |
| ≥2 and ≤4 | 10 (58.8) | 22 (50.0) | 58 (39.2) | |
| >4 | 3 (17.6) | 15 (34.1) | 66 (44.6) | |
| NR | 0 (0.0) | 2 (4.5) | 21 (14.2) | |
| **Other laboratory variables, median [IQR]** | | | | |
| WBC ($x10^9$/L) | 13.8 [7.4-17.5] | 19.4 [9.6-22.9] | 14.2 [6.6-18.7] | 0.0718 |
| C-reactive protein (mg/dL) | 87.2 [13.4-130.2] | 47.3 [10.8-37.1] | 84.7 [15.3-122.7] | **0.0495** |
| **ICU admission, n (%)** | | | | |
| No | 17 (100) | 41 (93.2) | 120 (81.1) | **0.024** |
| Yes | 0 (0.0) | 3 (6.8) | 28 (18.9) | |
| **Days of hospitalization**, median [IQR]** | 6.8 [4-8] | 7.9 [4-7.7] | 13.3 [4-15] | 0.1629 |
| **Septic shock, n (%)** | | | | |
| No | 17 (100) | 42 (95.5) | 132 (89.2) | 0.289 |
| Yes | 0 (0.0) | 2 (4.5) | 16 (10.8) | |
| **Mortality, n (%)** | | | | |
| No | 17 (100) | 36 (81.8) | 136 (91.9) | 0.059 |
| Yes | 0 (0.0) | 8 (18.2) | 12 (8.11) | |

ICU: Intensive Care Unit; IQR: Interquartile Range; NR: Not Reported; SOFA: Sequential Organ Failure Assessment.

*Elevated biomarkers refer to procalcitonin (PCT), interleukin-6 (IL-6), and Mid-regional pro-adrenomedullin (MR-ProADM), defined according to the cut-off values derived from the AUROC analysis (**Supplementary Table S3**).

**Days from Emergency Department admission to hospital discharge in surviving cases. **Bold** values indicate statistically significant differences ($p \leq 0.05$).

## Discussion

This study demonstrates that measuring PCT, IL-6, and MR-ProADM at triage, before any intervention, significantly improves the early identification of sepsis in the ED. Each biomarker showed excellent diagnostic performance (AUROC > 0.9), and simultaneous elevation of all three increased specificity and the association with sepsis, a pattern observed in 70% of septic cases. Only one control patient exhibited this combination and was later diagnosed with acute pancreatitis. To date, this is the first study to evaluate this biomarker panel in the ED setting, where clinical criteria are often insufficient and laboratory results are not yet available.

Our findings support the growing consensus that multibiomarker strategies outperform individual markers. Each biomarker reflects different pathophysiological mechanisms: PCT is a well-established marker of early bacterial infection [18,19]; IL-6 is a key cytokine in the acute inflammatory response, associated with greater severity and mortality [20], and its persistent elevation contributes to inflammatory and hemodynamic alterations [21,22], despite its moderate sensitivity and specificity [23]. MR-ProADM, primarily a prognostic marker, is linked to endothelial dysfunction and progression to shock [24–27]. However, its isolated use is limited by overlap with non-infectious conditions such as trauma or pancreatitis [24–26, 28–32]. Combining these markers improves specificity and diagnostic confidence, particularly in the ED.

Recent evidence supports the combined use of biomarkers to enhance early sepsis detection and risk stratification. For example, Spoto et al.[33] demonstrated that combining PCT and MR-ProADM improves diagnostic accuracy even when clinical criteria are negative, while Cai et al.[34] showed that combining PCT and IL-6 enhances sensitivity for identifying bacterial sepsis. However, most studies have been conducted in inpatient or ICU settings, resulting in limited data on biomarker behavior in the earliest phases of care. As noted by Turgman et al.[35], although numerous biomarkers have been proposed, few are used routinely, and none fulfill the criteria of an ideal marker for diagnosis, prognosis, and treatment in the heterogeneous ED population. Collectively, these studies [36–39] support the use of multibiomarker panels, aligning with the present findings and highlighting their potential role in future ED sepsis management.

Our results suggest that integrating biomarkers into triage may improve decision-making by prioritizing patients with multiple elevated biomarkers, addressing the limitations of conventional triage which can underestimate sepsis severity. Although septic patients showed altered vital signs compared with controls, triage levels alone (levels 2 and 3) did not adequately reflect severity. When patients were grouped according to the number of elevated biomarkers, differences in vital signs disappeared, indicating that early inflammatory activity may not be captured by physiological parameters alone. Patients classified as triage levels 2 and 3 often exhibited elevated biomarkers and substantial organ dysfunction, reinforcing previous evidence that symptom-based triage alone is insufficient [40,41]. These findings support a differentiated triage strategy, assigning higher priority to patients with simultaneous elevation of all three biomarkers.

The intended clinical use of this biomarker panel is complementary to standard triage rather than a replacement for clinical judgement. In routine ED workflows, simultaneous measurement of PCT, IL-6, and MR-ProADM at triage could serve as an early screening tool for patients presenting with non-specific symptoms suggestive of infection. Patients with three elevated biomarkers represent a high-risk profile, for whom earlier evaluation, expedited antimicrobial therapy, or rapid activation of sepsis pathways may be warranted. Conversely, patients with no elevated biomarkers may constitute a lower-risk group, supporting more conservative diagnostic work-up or observation. Thus, the panel may assist clinicians in risk stratification, prioritization, and decisions regarding admission versus safe discharge, particularly when vital signs are ambiguous or inconsistent with underlying severity.

Practical integration of this panel into ED workflows would require either rapid-turnaround assays within the emergency laboratory (24/7 availability, target turnaround time of <60 minutes) or selected point-of-care testing for predefined high-suspicion scenarios. While PCT is already widely available in routine clinical practice, IL-6 and MR-ProADM are not routinely accessible and would require rapid platforms or multiplex solutions. Beyond analytical performance, successful implementation depends on operational factors including sample-to-answer time, staffing, maintenance and quality control, training, and IT connectivity, as well as sufficient patient volume to ensure sustainable throughput. Economic deployment should be guided by formal budget-impact and cost-effectiveness evaluations, considering both direct costs (assays, instrumentation, consumables, and service contracts) and potential savings from earlier risk identification (e.g., reduced time-to-antibiotics, prevention of deterioration and ICU admissions, and optimized admissions decisions).

In addition, the applicability of IL-6 and MR-ProADM in routine clinical triage remains constrained. In

this study, both biomarkers were measured using ELISA-based methods on stored samples, with analytical turnaround times incompatible with real-time decision-making. Therefore, although the diagnostic performance of the panel is promising, its clinical utility in routine practice will depend on the availability of rapid or point-of-care platforms capable of delivering results within clinically relevant timeframes (<60 minutes). Prospective validation in settings with such technologies is required before integration into standard emergency workflows can be considered.

This analysis is based on a cohort of patients attending the ED concurrently, comparing septic cases with non-septic controls assigned to the same triage level. Although reasons for consultation were heterogeneous, 26.5% of controls had infectious conditions, reinforcing the clinical relevance of the comparison. Controls were selected from among patients with similar clinical presentations but without a final diagnosis of sepsis, allowing assessment of biomarker specificity in a realistic ED context where early symptoms are often non-specific. The inclusion of both non-septic infections (26.5%) and non-infectious conditions (73.5%) reflects the heterogeneity of real-world emergency care and supports the external validity of our findings. Patients with three elevated biomarkers were older, which may reflect age-related impairment in the regulation of inflammatory responses. Importantly, this biomarker-based approach is not intended to replace established sepsis definitions or clinical judgment, but to complement triage by providing objective biological information at a time when clinical signs may be subtle or misleading.

Although this study was not designed to evaluate prognosis, patients with a higher number of elevated biomarkers exhibited higher SOFA scores, increased of ICU admission rates, and longer hospital stays. This finding suggests that the cumulative elevation of biomarkers may reflect not only the presence of sepsis but also early disease severity. This observation should be interpreted cautiously and requires confirmation in prospective studies, but it supports the potential value of biomarker assessment at the earliest point of care, when clinical criteria alone may be insufficient.

Several commercial platforms currently enable measurement of individual biomarkers such as PCT and IL-6. For example, RAMP® Procalcitonin (Response Biomedical) provides results in 15 minutes from whole blood [42], and systems such as Finecare™ PCT and Fluorecare® PCT MF-27 enable rapid quantification with detection limits of 0.1 ng/mL [43,44]. For IL-6, available options include Milenia® IL-6 (range: 100–10,000 pg/mL) and Fluorecare® IL-6 MF-73 [45,46]. The AQT90 FLEX system (Radiometer) can measure PCT in less than 21 minutes at the point of care without sample preparation [47]. However, no existing platform allows real-time multiplex detection of PCT, IL-6, and MR-ProADM. The development of portable or rapid laboratory systems capable of simultaneously quantifying these three biomarkers would substantially facilitate their integration into ED workflows and enhance early risk stratification and clinical decision-making.

## Limitations

This study has several limitations that should be considered when interpreting the results. The limited number of non-septic controls (n=34) and the approximately 6:1 case–control imbalance may reduce the precision of specificity estimates and potentially inflate discrimination metrics in heterogeneous ED populations. Controls were enrolled consecutively and intentionally included both infectious non-septic and non-infectious conditions to approximate routine clinical ED triage. However, spectrum effects likely contributed to the observed separation between groups. Clinical adjudication was performed with access to routine care data (PCT could have been available when ordered), whereas IL-6 and MR-ProADM results were not available to clinicians, which may influence the magnitude and generalizability of the reported diagnostic accuracy.

The number of patients with septic shock was limited (n=18), restricting the robustness of subgroup analyses. Nevertheless, most patients with shock exhibited simultaneous elevation of all three biomarkers, and all in-hospital deaths occurred in patients with at least two elevated biomarkers, with an association close to statistical significance (p=0.059). These findings suggest that cumulative biomarker elevation may reflect early disease severity; however, this observation is exploratory.

Although commercially available ELISA kits were used for IL-6 and MR-ProADM, the manufacturers had no involvement in any stage of the study. All measurements were independently performed by the research team using standardized protocols and internal quality controls, minimizing the risk of measurement or interpretation bias.

This investigation was conducted at a single tertiary-care hospital, which limits generalizability to ED settings with different patient profiles and resource availability. Accordingly, multicenter prospective studies across diverse environments, including community hospitals, are warranted to confirm performance and operational feasibility.

The pronounced separation observed for IL-6 and MR-ProADM likely reflects spectrum effects. Many septic patients presented with a substantial inflammatory burden, contrasted with a relatively small and less variable control group. In routine ED practice, a broader "grey zone" is expected, including non-septic infections, inflammatory non-infectious conditions, and frail older adults with multimorbidity, which may narrow biomarker gaps and reduce discriminatory performance. Accordingly, interpretation of AUROC values was deliberately tempered, and the need for prospective validation in larger, more heterogeneous ED populations was emphasized to assess performance across the full clinical spectrum encountered at triage.

This study did not evaluate clinical process indicators such as time to antibiotic or fluid administration, nor did it assess changes in clinical decision-making attributable to biomarker availability. In addition, no head-to-head comparisons were performed with established triage or bedside scores (e.g., qSOFA, NEWS2, SIRS), nor were formal reclassification metrics such as the net reclassification improvement (NRI) calculated. Reconstruction of qSOFA or SIRS at the exact time of triage was not feasible, as several clinical parameters were inconsistently available or documented with sufficient temporal precision. Consequently, the incremental diagnostic value of the biomarker panel over existing bedside tools cannot be determined.

This diagnostic accuracy study was not designed to determine whether the use of these biomarkers in routine clinical practice would improve clinical outcomes. Early biomarker-based identification may or may not shorten time-to-antibiotics, influence treatment decisions, increase sepsis pathway activation, or improve outcomes such as ICU admission, hospital length of stay, or mortality. All biomarker cut-offs (PCT, IL-6, and MR-ProADM) were derived post hoc within the study cohort and should be regarded as exploratory. Although the PCT threshold coincided with the commonly used 0.5 ng/mL cut-off, prospective validation in independent, heterogeneous ED cohorts is required before threshold-based implementation. Because no a priori sample-size calculation was undertaken, the study was not powered to detect small differences between individual biomarkers or to support formal comparative AUROC analyses, which typically require considerably larger cohorts. As a result, comparisons across biomarkers should be interpreted as exploratory. Future prospective studies specifically designed and powered for comparative accuracy will be required to confirm these observations.

In addition, the available cohort was not powered or structured to support multivariable adjustment. Variables such as age, renal function, infection focus, and comorbidity may act as confounders for biomarker concentrations, particularly MR-ProADM, and their independent contribution cannot be quantified within this retrospective design. Future prospective studies with predefined covariate collection and an adequate sample size will be required to incorporate multivariable adjustment and determine the independent diagnostic value of each biomarker.

As an observational, retrospective study, causal inferences cannot be drawn. The impact of biomarker measurement on clinical decision-making, time to antibiotic administration, fluid resuscitation, or activation of sepsis protocols, as well as effects on patient-centered outcomes or resource utilization, was not assessed. Subgroup analyses were exploratory and not prespecified, and the limited number of events further constrains definitive interpretation. In addition, this single-center design precluded assessment of inter-institutional variability, and incomplete data on symptom onset limited stratified analyses by disease evolution. Accordingly, heterogeneity in diagnostic performance across subgroups should be interpreted with caution and validated prospectively.

Finally, decisions regarding implementation in routine clinical practice should be guided by local budget-impact and cost-effectiveness analyses. These analyses should account for platform availability, assay and infrastructure costs, workflow integration, and potential downstream savings from earlier risk identification and prioritization. These operational and economic aspects, together with clinical effectiveness, warrant evaluation in prospective, multicenter, pragmatic studies before widespread adoption can be considered.

## Strengths and future steps

Despite these limitations, this study has several important strengths. Measurements of PCT, IL-6, and MR-ProADM were obtained at the earliest point of care, directly at ED triage and before any therapeutic intervention, capturing the patient's initial inflammatory state and avoiding the confounding effects introduced by antibiotics, fluids, or hemodynamic support. This timing represents a major differential advantage compared with many previous studies in which biomarker sampling occurred after initial clinical management.

Second, the combination of biomarkers reflects complementary pathophysiological pathways: i) PCT, a marker of systemic bacterial infection; ii) IL-6, an indicator of the intensity of the inflammatory response

and cytokine activation; and iii) MR-ProADM, a marker associated with endothelial dysfunction and early risk of shock. This mechanistic complementarity supports the biological plausibility of their joint use at triage.

Third, the study introduces the concept of *biomarker burden*, defined as the number of elevated biomarkers (1, 2, or 3), as a simple and clinically interpretable index that correlates with early disease severity. This stratification is easily communicable to clinicians and has potential for integration into future triage algorithms or decision-support tools. In addition, each biomarker demonstrated excellent diagnostic performance (AUROC > 0.9), and their combined use further increased specificity for sepsis and septic shock. The observed associations with SOFA parameters, ICU admission, and hospital length of stay reinforce their potential clinical relevance.

Future studies should prospectively evaluate this biomarker panel in real-time settings with predefined turnaround times (<60 minutes), include direct comparisons with established clinical scores (qSOFA, NEWS2, SIRS, and MTS), and quantify incremental diagnostic value through methods such as decision-curve analysis. Pragmatic endpoints should include time-to-antibiotics, protocol activation rates, ICU admission, and short-term mortality, to determine whether early biomarker information improves triage prioritization and patient-centered outcomes beyond usual care.

## Conclusions

Measurements of PCT, IL-6, and MR-ProADM at triage reflect the initial inflammatory state and, when combined, show promising diagnostic performance for the early identification of sepsis and the preliminary assessment of disease severity. These findings suggest a potential complementary role to traditional clinical criteria, although prospective validation in larger, more balanced cohorts is required to determine their true clinical impact.

The development of rapid or multiplex point-of-care platforms capable of measuring these biomarkers could facilitate their evaluation in real-time clinical settings. However, implementation within ED workflows should first be evaluated in prospective studies before integration into routine triage or protocol activation is considered.

Confirmation of clinical utility will require prospective interventional studies applying this biomarker panel in real time to guide decision-making and determine whether its use improves patient-centered outcomes, including time-to-antibiotics, progression to shock, ICU admission, hospital length of stay, or mortality.

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### Author contributions

Conceptualization: A.C., M.B., and R.R.; investigation: S.T., A.C., M.B., and R.R.; methodology: S.T., A.C., A.G., A.S., M.A., A.d.C., J.M., J.M.R., L.M., K.M.L., M.M.A., M.A., M.B., and R.R.; statistical analysis: A.C., and S.T.; data curation: S.T., A.C., A.G., A.S., M.A., A.d.C., J.M., J.M.R., L.M., K.M.L., M.M.A., and M.A.; writing – original draft: S.T. and A.C.; review and editing: A.G., A.S., M.A., A.d.C., J.M., J.M.R., L.M., K.M.L., M.M.A., M.A., M.B., and R.R.; supervision: A.C., M.B., and R.R.; funding acquisition: M.B. and R.R. All authors read and approved the final manuscript.

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### Conflict of interest

The authors declare that they have no conflicts of interest related to this article.

### AI statement

The authors declare that no Generative AI was used in the creation of this manuscript.

### Supplementary material

The supplementary material is available on the website of the Revista Española de Quimioterapia.

## References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801–10. Available from: https://doi.org/10.1001/jama.2016.0287
2. Guarino M, Perna B, Cesaro AE, Maritati M, Spampinato MD, Contini C, et al. 2023 Update on Sepsis and Septic Shock in Adult Patients: Management in the Emergency

Department. J Clin Med. 2023;12:3188. Available from: https://doi.org/10.3390/jcm12093188

3. Iskander KN, Osuchowski MF, Stearns-Kurosawa DJ, Kurosawa S, Stepien D, Valentine C, et al. Sepsis: Multiple Abnormalities, Heterogeneous Responses, and Evolving Understanding. Physiol Rev. 2013;93:1247–88. Available from: https://doi.org/10.1152/physrev.00037.2012
4. Nedeva C. Inflammation and Cell Death of the Innate and Adaptive Immune System during Sepsis. Biomolecules. 2021;11:1011. Available from: https://doi.org/10.3390/biom11071011
5. Wang HE, Weaver MD, Shapiro NI, Yealy DM. Opportunities for Emergency Medical Services care of sepsis. Resuscitation. 2010;81:193–7. Available from: https://doi.org/10.1016/j.resuscitation.2009.11.008
6. Groenewoudt M, Roest AA, Leijten FMM, Stassen PM. Septic patients arriving with emergency medical services: a seriously ill population. Eur J Emerg Med. 2014;21:330–5. Available from: https://doi.org/10.1097/MEJ.0000000000000091
7. Tian H, Zhou J, Weng L, Hu X, Peng J, Wang C, et al. Accuracy of qSOFA for the diagnosis of sepsis-3: a secondary analysis of a population-based cohort study. J Thorac Dis. 2019;11:2034–42. Available from: https://doi.org/10.21037/jtd.2019.04.90
8. A Cabrita J, Pinheiro I, Menezes Falcão L. Rethinking the concept of sepsis and septic shock. Eur J Intern Med. 2018;54:1–5. Available from: https://doi.org/10.1016/j.ejim.2018.06.002
9. Rello J, Valenzuela-Sánchez F, Ruiz-Rodriguez M, Moyano S. Sepsis: A Review of Advances in Management. Adv Ther. 2017;34:2393–411. Available from: https://doi.org/10.1007/s12325-017-0622-8
10. Lvovschi V, Arnaud L, Parizot C, Freund Y, Juillien G, Ghillani-Dalbin P, et al. Cytokine profiles in sepsis have limited relevance for stratifying patients in the emergency department: a prospective observational study. PLoS One. 2011;6:e28870. Available from: https://doi.org/10.1371/journal.pone.0028870
11. Mera S, Tatulescu D, Cismaru C, Bondor C, Slavcovici A, Zanc V, et al. Multiplex cytokine profiling in patients with sepsis. APMIS. 2011;119:155–63. Available from: https://doi.org/10.1111/j.1600-0463.2010.02705.x
12. Xu X-J, Tang Y-M, Song H, Yang S-L, Xu W-Q, Shi S-W, et al. A multiplex cytokine score for the prediction of disease severity in pediatric hematology/oncology patients with septic shock. Cytokine. 2013;64:590–6. Available from: https://doi.org/10.1016/j.cyto.2013.08.012
13. Gouel-Chéron A, Allaouchiche B, Guignant C, Davin F, Floccard B, Monneret G, et al. Early interleukin-6 and slope of monocyte human leukocyte antigen-DR: a powerful association to predict the development of sepsis after major trauma. PLoS One. 2012;7:e33095. Available from: https://doi.org/10.1371/journal.pone.0033095
14. Vänskä M, Koivula I, Jantunen E, Hämäläinen S, Purhonen A-K, Pulkki K, et al. IL-10 combined with procalcitonin improves early prediction of complications of febrile neutropenia in hematological patients. Cytokine. 2012;60:787–92. Available from: https://doi.org/10.1016/j.cyto.2012.07.023
15. Kuriyama A, Urushidani S, Nakayama T. Five-level emergency triage systems: variation in assessment of validity. Emerg Med J. 2017;34:703–10. Available from: https://doi.org/10.1136/emermed-2016-206295
16. Rancaño-García I, Cobo-Barquín JC, Cachero-Fernández R, Noya-Mejuto JA, Delgado-González JM, Hernández-Mejía R. [Triage in primary care emergency services]. Semergen. 2013;39:70–6. Available from: https://doi.org/10.1016/j.semerg.2012.06.003
17. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open. 2016;6:e012799. Available from: https://doi.org/10.1136/bmjopen-2016-012799
18. Reddy V, Wante M, Nirhale DS, Puvvada P, Gaudani RH. The Prospective Analysis of Biomarkers in Sepsis: Correlation With Clinical Outcomes. Cureus. 2024;16:e70965. Available from: https://doi.org/10.7759/cureus.70965
19. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet. 1993;341:515–8. Available from: https://doi.org/10.1016/0140-6736(93)90277-n
20. Doganyigit Z, Eroglu E, Akyuz E. Inflammatory mediators of cytokines and chemokines in sepsis: From bench to bedside. Hum Exp Toxicol. 2022;41:9603271221078871. Available from: https://doi.org/10.1177/09603271221078871
21. Gan K, Chen Y, Tao L, Li J. Diagnostic value of circulating IL-6 in adult sepsis: a meta-analysis. Minerva Anestesiol. 2024;90:1041–50. Available from: https://doi.org/10.23736/S0375-9393.24.18100-X.
22. Yu B, Chen M, Zhang Y, Cao Y, Yang J, Wei B, et al. Diagnostic and Prognostic Value of Interleukin-6 in Emergency Department Sepsis Patients. Infect Drug Resist. 2022;15:5557–66. Available from: https://doi.org/10.2147/IDR.S384351.
23. Molano Franco D, Arevalo-Rodriguez I, Roqué I Figuls M, Montero Oleas NG, Nuvials X, Zamora J. Plasma interleukin-6 concentration for the diagnosis of sepsis in critically ill adults. Cochrane Database Syst Rev. 2019;4:CD011811. Available from: https://doi.org/10.1002/14651858.CD011811.pub2
24. Myhre PL, Liu Y, Kulac IJ, Claggett BL, Prescott MF, Felker GM, et al. Changes in mid-regional pro-adrenomedullin during treatment with sacubitril/valsartan. Eur J Heart Fail. 2023;25:1396–405. Available from: https://doi.org/10.1002/ejhf.2957
25. Benedetti I, Spinelli D, Callegari T, Bonometti R, Molinaro E, Novara E, et al. High levels of mid-regional proadrenomedullin in ARDS COVID-19 patients: the experience of a single, Italian Center. Eur Rev Med Pharmacol Sci. 2021;25:1743–51. Available from: https://doi.org/10.26355/eurrev_202102_24885
26. Gillmann H-J, Meinders A, Larmann J, Sahlmann B, Schrimpf C, Aper T, et al. Adrenomedullin Is Associated With Surgical Trauma and Impaired Renal Function in Vascular Surgery Patients. J Intensive Care Med. 2019;34:67–76. Available from: https://doi.org/10.1177/0885066616689554
27. Kitamura K, Kangawa K, Kawamoto M, Ichiki Y, Nakamura S, Matsuo H, et al. Adrenomedullin: a novel hypotensive peptide isolated from human pheochromocytoma. Biochem Biophys Res Commun. 1993;192:553–60. Available from: https://doi.org/10.1006/bbrc.1993.1451

28. Larsen FF, Petersen JA. Novel biomarkers for sepsis: A narrative review. Eur J Intern Med. 2017;45:46–50. Available from: https://doi.org/10.1016/j.ejim.2017.09.030
29. Xu C-F, Huo M-C, Huang J-H, Liu C-F, Xu W. Early changes in white blood cell, C-reactive protein and procalcitonin levels in children with severe multiple trauma. World J Emerg Med. 2022;13:448–52. Available from: https://doi.org/10.5847/wjem.j.1920-8642.2022.093
30. Xinyu X, Jiang Z, Qing A, Lihua L, Xiehong L, Lin Z. Clinical significance of PCT, CRP, IL-6, NLR, and TyG Index in early diagnosis and severity assessment of acute pancreatitis: A retrospective analysis. Sci Rep. 2025;15:2924. Available from: https://doi.org/10.1038/s41598-025-86664-x
31. Smith SE, Muir J, Kalabalik-Hoganson J. Procalcitonin in special patient populations: Guidance for antimicrobial therapy. Am J Health Syst Pharm. 2020;77:745–58. Available from: https://doi.org/10.1093/ajhp/zxaa089
32. Zaki HA, Bensliman S, Bashir K, Iftikhar H, Fayed MH, Salem W, et al. Accuracy of procalcitonin for diagnosing sepsis in adult patients admitted to the emergency department: a systematic review and meta-analysis. Syst Rev. 2024;13:37. Available from: https://doi.org/10.1186/s13643-023-02432-w
33. Spoto S, Nobile E, Carnà EPR, Fogolari M, Caputo D, De Florio L, et al. Best diagnostic accuracy of sepsis combining SIRS criteria or qSOFA score with Procalcitonin and Mid-Regional pro-Adrenomedullin outside ICU. Sci Rep. 2020;10:16605. Available from: https://doi.org/10.1038/s41598-020-73676-y
34. Cai S-Q, Xia T, Xu X-P. Usefulness of neutrophil-to-lymphocyte count ratio, procalcitonin, and interleukin-6 for severity assessment of bacterial sepsis. J Laboratory Med. 2024;48(4):187–93. Available from: https://doi.org/10.1515/labmed-2024-0007
35. Turgman O, Schinkel M, Wiersinga WJ. Host Response Biomarkers for Sepsis in the Emergency Room. Crit Care. 2023;27(1):97. Available from: https://doi.org/10.1186/s13054-023-04367-z
36. Bourika V, Rekoumi E-A, Giamarellos-Bourboulis EJ. Biomarkers to guide sepsis management. Ann Intensive Care. 2025;15(1):103. Available from: https://doi.org/10.1186/s13613-025-01524-1
37. Reijnders E, Turgman O, Joosten SCM, Schinkel M, Slim MA, Douma RA, et al. Towards novel BIOmarkers to diagnose SEPsis (BIOSEP) in the emergency room: a protocol for a multicentre, prospective cohort study. BMJ Open. 2025;15(7):e103138.Available from: https://doi.org/10.1136/bmjopen-2025-103138
38. He R-R, Yue G-L, Dong M-L, Wang J-Q, Cheng C. Sepsis Biomarkers: Advancements and Clinical Applications—A Narrative Review. Int J Mol Sci. 2024;25:9010. Available from: https://doi.org/10.3390/ijms25169010
39. Zhou X, Liu C, Xu Z, Song J, Jin H, Wu H, et al. Combining host immune response biomarkers and clinical scores for early prediction of sepsis in infection patients. Ann Med. 2024;56:2396569. Available from: https://doi.org/10.1080/07853890.2024.2396569
40. Rangan ES, Pathinarupothi RK, Anand KJS, Snyder MP. Performance effectiveness of vital parameter combinations for early warning of sepsis—an exhaustive study using machine learning. Jamia Open. 2022;5:ooac080. Available from: https://doi.org/10.1093/jamiaopen/ooac080
41. Dewitte K, Scheurwegs E, Van Ierssel S, Jansens H, Dams K, Roelant E. Audit of a computerized version of the Manchester triage system and a SIRS-based system for the detection of sepsis at triage in the emergency department. Int J Emerg Med. 2022;15(1):67. Available from: https://doi.org/10.1186/s12245-022-00472-y
42. Response Biomedical. RAMP Procalcitonina | Sepsis | Response Biomedical. [s. l.]: Response Biomedical. Available from: https://kabla.mx/response/sepsis/
43. Mazlan MZ, Wan Azman WN, Yaacob NM, Koon TS, Yahya NK. Analytical Evaluation of Point-of-Care Finecare™ Procalcitonin Rapid Quantitative Test in Sepsis Population as Compared with Elecsys® BRAHMS Procalcitonin Immunoassay. Diagnostics (Basel) 2024;14:1080. Available from: https://doi.org/10.3390/diagnostics14111080.
44. Microprofit. fluorecare Procalcitonin (PCT) Diagnostic Kit MF-27. Available from: https://www.microprofit-bio.com/fluorecare-Procalcitonin-PCT-Diagnostic-Kit-MF27-139.html
45. Milenia Biotec GmbH. Milenia QuickLine IL-6. Giessen: Milenia Biotec GmbH. Available from: https://www.milenia-biotec.com/en/product/il6/
46. Microprofit. fluorecare Interleukin-6 (IL-6) Diagnostic Kit (Immunochromatographic Assay) MF-73. Available from: https://www.microprofit-bio.com/fluorecare-Interleukin6-IL6-Diagnostic-Kit-Immunochromatographic-Assay-MF73-142.html
47. Radiometer. AQT90 FLEX analyzer. Available from: https://www.radiometer.com/en/products/immunoassay-testing/aqt90-flex-immunoassay-analyzer