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Combination of National Early Warning Score 2 and procalcitonin: accuracy for early sepsis recognition in patients admitted from the emergency department for infection

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Key words: sepsis diagnosis, emergency department, procalcitonin, National Early Warning Score 2 (NEWS2).

Abstract

Prompt recognition of sepsis in the Emergency Department (ED) is challenging. In this study, we performed a prospective study to explore, for the first time, the diagnostic accuracy for sepsis of the combination of National Early Warning Score 2 (NEWS2) and Procalcitonin (PCT) in ED population admitted for infection. The endpoint was Sepsis-3-defined sepsis. NEWS2 was calculated at triage using dedicated software, while PCT was measured within 6 hours of triage registration. The diagnostic accuracy of NEWS2+PCT was compared with that of NEWS2, PCT and qSOFA using Receiver Operating Characteristics analysis. 1041 patients were enrolled. Sensitivity and specificity for sepsis diagnosis were as follows: 54%/78.8% for NEWS2 $\geq$ 5; 73.4%/58.3% for PCT $\geq$ 0.5 ng/ml; 70.9%/67.8% for NEWS2+PCT $\geq$ 5 and 25%/97.3% for qSOFA. The area under the curve of NEWS2+PCT (0.77, 95% CI 0.74-0.80) was significantly higher than that of NEWS2 (0.72, 95% CI 0.69-0.75; $p=0.04$), PCT

(0.71,95% CI 0.68-0.75;p=0.01) and qSOFA (0.70,95% CI 0.67-0.73;p<0.001). Adding PCT to NEWS2 improved diagnostic accuracy for sepsis. In crowded ED, the balance between sensitivity and specificity ensured by NEWS2+PCT $\geq$ 5 can help to promptly identify patients with sepsis without overwhelming staff.

Introduction

Sepsis is a life-threatening condition that requires prompt recognition and immediate management.^{1,2} It is defined as organ dysfunction resulting from a dysregulated host response to infection, identified by a rise of at least 2 points in the Sequential Organ Failure Assessment (SOFA) score.³ Worldwide, sepsis is estimated to affect over 30 million individuals annually, with mortality rates ranging from 15 to 56%.⁴ Patients with sepsis present to the Emergency Department (ED) with heterogeneous signs and symptoms, making diagnosis challenging.⁵ Over the years, numerous clinical scores and laboratory tests have been investigated for early recognition and risk stratification of sepsis in the ED,⁶⁻⁸ as well as various combinations of them.⁹⁻¹¹ Currently, NEWS2 (National Early Warning Score 2), the updated version of NEWS, is considered a valid tool for predicting poor prognosis in the ED (primarily death or the need of intensive care).^{12,13} However, its role in early sepsis detection, remains relatively under-explored compared to the majority of studies that focus on NEWS.^{6,7,14}

To date, no "gold standard" screening tool has been identified, probably due to the complex pathophysiological changes occurring in patients with sepsis. In 2016, the authors who introduced the new sepsis definition (Sepsis-3), proposed using quick SOFA (qSOFA) at triage.³ Subsequent studies, revealing its limited sensitivity, led the 2021 Surviving Sepsis Campaign (SSC) to strongly discourage the use of qSOFA as the sole screening tool for sepsis or septic shock.¹⁵⁻¹⁷ Fernando *et al.*, in a meta-analysis assessing the prediction of mortality in adult patients with suspected infection, reported a low pooled sensitivity of 51.2% (95% CI, 43.6% to 58.7%) for qSOFA in non-ICU settings, including emergency departments and hospital wards.¹⁶ More recently, a meta-analysis by Qiu *et al.*, including 57 studies on sepsis prediction, reported that qSOFA showed low pooled sensitivity (42%; 95% CI, 41% to 43%) and high specificity (98%; 95% CI, 98% to 98%), whereas NEWS exhibited high pooled

sensitivity (71%; 95% CI, 69% to 73%) and specificity (85%; 95% CI, 85% to 85%).¹⁷ We emphasize again that the meta-analysis focuses on NEWS rather than NEWS2.

Procalcitonin (PCT), whose serum concentration increases dramatically during systemic bacterial infections, is considered a useful marker of sepsis,¹⁸ although its diagnostic performance may be limited in certain populations, such as cancer patients.¹⁹ The assessment of blood tests at the time of ED presentation may add diagnostic information, potentially enhancing the value of early warning scores.²⁰

This study was the first to prospectively investigate the accuracy of the association between NEWS2 and PCT (NEWS2+PCT) in predicting sepsis among patients admitted for infection from the ED, and to compare it with NEWS2, PCT, and qSOFA.

Materials and Methods

Study design and population

Prospective single-center diagnostic accuracy study including all consecutive adult patients referred to the ED of a tertiary care university hospital, with about 120,000 accesses/year (IRCCS AOU di Bologna, Italy), between February 1st, 2023, and July 31st, 2023. Patients were enrolled if they were subsequently hospitalized for infection. The endpoint was the diagnosis of sepsis according to Sepsis-3 definition. The diagnosis of probable infection was made by the ED physician on duty considering a combination of symptoms suggestive of infection on arrival (fever, confusion, asthenia, dyspnea, reduced urinary output, etc.), positive imaging studies (ultrasound, x-ray, CT scan) and laboratory findings, such as white blood cells, PCT, C-reactive protein, and lactates. Blood and urine samples for microbiological investigations were collected when deemed appropriate by the physician. Exclusion criteria were pregnancy, acute viral infection and the inability to collect blood samples for PCT within 6 hours of triage. In addition, patients initially enrolled were excluded if the ward discharge summary did not confirm the infection. All patients received an antigen swab at triage for the detection of SARS-CoV-2, influenza, and respiratory syncytial virus. Blood samples for PCT detection were collected at first medical contact in the ED, within 6 hours of triage registration. PCT was quantified in plasma using electrochemiluminescence immunoassays (Roche Diagnostics GmbH, Mannheim, Germany) and expressed in ng/mL. NEWS2, based on body temperature, systolic blood pressure, heart

rate, level of consciousness, respiratory rate, oxygen saturation according to two different scales for type I and type II respiratory failure, and need for supplemental oxygen,²¹ was calculated at triage by a nurse using specific software; the same was done for qSOFA.³ The Charlson Comorbidity Index was determined for classifying comorbidities.²² The presence of a tumor was also recorded. The diagnosis of sepsis was independently made by two doctors from our research group according to the Sepsis-3 definition.^{3,23} Specifically, sepsis was defined if the delta SOFA score was ≥ 2 (indicating a SOFA score ≥ 2 or 2 points higher than the patient's score before the infection) in patients with infection. Baseline SOFA values were extracted from the Electronic Health Record (a national online registry containing citizens' medical information, shared with healthcare professionals) for the 6 months preceding ED admission. In approximately 7% of cases, not all data required to fully calculate the baseline SOFA score were available. However, these patients generally had no major comorbidities or only mild chronic conditions and were clinically stable before ED presentation, with no evidence of pre-existing organ dysfunction. Therefore, in accordance with the approach commonly adopted in Sepsis-3 studies when baseline organ dysfunction is not documented, a baseline SOFA score of 0 was assumed for these patients. Written informed consent was provided by patients or legal representative within 72 hours of hospital admission, before study enrollment. Patients who died within 72 hours of hospital admission were also included. The study was approved by the local ethics committee (637/20222/0ss/AOUBo).

Statistical analysis

Quantitative variables were presented as median and min-max values, while categorical variables were expressed as percentages. Comparisons of quantitative variables were conducted using either the Student t-test or Mann-Whitney U-test depending on data distribution, which was determined through the Kolmogorov-Smirnov test. Diagnostic accuracy of NEWS2, PCT, NEWS2+PCT, and qSOFA was evaluated using Receiver Operating Characteristic (ROC) analysis, with the Areas Under the Receiver Operating Characteristic curve (AUROC) calculated accordingly.

Multivariate analysis was performed using a logistic regression model that included PCT and NEWS2 values. From this model, the odds ratios, the regression coefficients and the intercept were obtained, and 95% confidence intervals (95% CI) are reported

where applicable. To evaluate the practical application of these predictors, the combination of NEWS2 and PCT (expressed in ng/mL) was formulated as a simplified cumulative sum (NEWS2 + PCT). Comparison of the AUROCs was performed using the Hanley and McNeil method, while any potential loss of discriminative performance between the models was evaluated using the McNemar test. Sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) were also calculated. To rigorously evaluate the mathematical validity of combining NEWS2 and PCT into this simplified cumulative score, we explicitly assessed the impact of score composition on patient outcomes. First, because NEWS2 (0–20 points) and PCT operate on fundamentally different scales, PCT values were log-transformed (logPCT) for the analyses described below to account for the highly skewed distribution of the biomarker; the calibrated linear predictor reported in the Results was instead derived using PCT on its original (ng/mL) scale. Second, to test the validity of an equal-weight linear sum, we compared a restricted model (where the coefficients of NEWS2 and logPCT were constrained to be equal) against an unrestricted model with free coefficients using a likelihood-ratio test. Standardized effect sizes were calculated for both predictors to determine their relative prognostic weight. Third, to quantify whether different clinical profiles yielding the same total score corresponded to varying risks, we stratified the cohort by fixed sum totals and narrow score intervals (e.g., total scores of 4–6 and ~10). Within these strata, the association between score composition (*i.e.*, PCT-predominant *vs.* NEWS2-predominant profiles) and the primary outcome (sepsis) was analyzed using Fisher’s exact test.

For NEWS2, PCT and qSOFA we considered the cut-off already established in the literature.^{3,21,24,25} NEWS2 ≥ 5 indicates the need for an urgent response and the possibility of sepsis.²¹ PCT ≥ 0.5 suggests a bacterial infection and potential sepsis, while PCT ≥ 2 is significantly associated with the development of septic shock and in-hospital mortality.²⁴⁻²⁵ qSOFA ≥ 2 is used to identify patients at risk of sepsis.³ The NEWS2+PCT operating threshold was selected as the point on the ROC curve closest to the upper-left corner (best sensitivity–specificity balance). Performance was compared with NEWS2, PCT and qSOFA.

The Log-rank test was employed to analyze survival between patients with and without sepsis. Statistical significance was defined as $p < 0.05$. All analyses were conducted using SPSS software, version 28 (IBM Corp, Armonk, NY, USA) and Jamovi 2.6.7.

Results

Patients' characteristics

A total of 1137 patients were potentially eligible. However, written informed consent was not collected in 84 of them due to study participation rejection or patient's clinical conditions that prevented a valid informed consent. Moreover, the discharge summary did not confirm the infection in other 12 patients. A total of 1041 patients were thus enrolled (559 males and 482 females). Sepsis was diagnosed in 520 patients (50.4%). 170 patients (16.3%) died during hospitalization, with 80 deaths occurring within the first 72 hours (7.7% of the total cohort). A subset of 125 patients (12%) required admission to intensive (34 patients) or sub-intensive (91 patients) care units. The median length of hospital stay was 10 days (1-181). The primary source of infection was identified as follows: respiratory tract (34%), urinary tract (27.9%), abdomen (11.1%), soft tissues (8.1%), joint/bone (2.1%), central venous catheter (1.4%), other (4.9%); in 110 cases (10.6%) the source of infection remained unknown. 289 patients (27.8%) had active tumor.

Blood cultures, performed in 51.6% of non-septic patients and in 63.3% of septic patients, were positive in 21.3% and 35.9% of cases, respectively.

The minimum value of NEWS2 was 1, the maximum 17. Median NEWS2 was higher in septic (5, 0-17) compared to non-septic patients (2, 0-12) and in non survivors (7, 0-17) compared to survivors (3, 0-14) ($p<0.001$). Median PCT levels differed between septic and non-septic patients, with a value of 1.6 (0-470) ng/ml and 0.3 (0-734) ng/mL respectively ($p<0.001$). Similarly, median PCT was significantly higher between non survivors (1.4, 0-734 ng/ml) compared to survivors (0.6, 0-470 ng/ml; $p<0.001$). As already known, the presence of sepsis affected mortality (log rank <0.001). Baseline characteristics, clinical scores distribution, and mortality outcomes of the study population are reported in Tables 1 and 2.

Diagnostic role of NEWS2, PCT, NEWS2+PCT and qSOFA

The AUROC of NEWS2 was 0.72 (95% CI 0.69-0.75) and that of PCT 0.71 (95% CI 0.68-0.75). The AUROC of NEWS2+PCT was 0.77 (95% CI 0.74-0.80), significantly higher than the one of NEWS2 ($p=0.04$) and PCT ($p=0.01$; Figure 1). As expected,

qSOFA performed less effectively with an AUROC of 0.70 (95% CI 0.67-0.73; $p < 0.001$ vs AUROC of NEWS2+PCT; $p = \text{ns}$ vs AUROC of both NEWS2 alone and PCT alone; Figure 1).

Multivariate analysis for sepsis diagnosis revealed an OR of 1.01 for PCT and 1.30 for NEWS2. A calibrated linear predictor (log-odds) was derived from the model β -coefficients and intercept: (NEWS2 * 0.2616783 + PCT * 0.0095007) - 1.07613. This model achieved an AUROC of 0.75 (95% CI 0.72-0.78), which was slightly lower than that obtained with the simpler NEWS2+PCT sum approach ($p = 0.04$), confirming comparable discrimination of the more feasible unweighted combination. At the selected operating point, classification by the sum and by the calibrated formula did not differ significantly (McNemar $p = 0.24$). A model with free coefficients fitted significantly better than the equal-weight sum (likelihood-ratio test $\chi^2 = 138$, $p < 0.001$), and the standardized effect of NEWS2 ($\beta = 0.91$) exceeded that of log-PCT ($\beta = 0.67$). Nevertheless, at a fixed total the association between score composition and sepsis was modest and not statistically significant (within a sum of 4–6, $p = 0.14$; at a sum of approximately 10, sepsis occurred in 0.69 of PCT-predominant versus 0.77 of NEWS2-predominant profiles), indicating that the total drove most of the discriminative signal.

An additional subgroup analysis demonstrated comparable diagnostic performance of the NEWS2+PCT combination between patients assigned high-priority triage categories (red and orange codes according to the local color-coded triage system) and those assigned lower-priority categories (*i.e.*, all codes other than red and orange), with AUROC values of 0.74 (95% CI 0.69-0.78) and 0.75 (95% CI 0.71-0.79), respectively ($p = \text{n.s.}$).

NEWS2 ≥ 5 exhibited a sensitivity of 54.0% and a specificity of 78.8% for predicting sepsis. PCT showed a sensitivity of 73.4% and a specificity of 58.3% at the cutoff ≥ 0.5 ng/mL, and 44.1% and 80.2% at the cutoff ≥ 2 ng/mL, respectively. The sensitivity and specificity were 70.9% and 67.8% for NEWS2+PCT ≥ 5 , and 41.9% and 87.8% for NEWS2+PCT ≥ 10 , respectively. Finally, qSOFA ≥ 2 showed a sensitivity of 25.0% and a specificity of 97.3% in predicting sepsis (Table 3).

A NEWS2+PCT cutoff of ≥ 5 was selected as the best balance between sensitivity and specificity, corresponding to the point on the ROC curve closest to the upper-left corner, with balanced sensitivity (0.71) and specificity (0.68), a negative predictive value

of 70% and a positive likelihood ratio of 2.2. Compared with the cutoff maximizing the Youden index (approximately 4), a value of 5 favors specificity, reducing over-triage at the cost of a modest reduction in sensitivity. Moreover, being an integer value, it is more readily applied in clinical practice. At this cutoff, approximately 29% of patients with sepsis fell below this value; a cutoff of 5 should therefore be regarded as a risk-stratification tool rather than a rule-out tool.

Discussion

In busy ED, identifying septic patients can be challenging. Using the SOFA score, which is part of the most recent definition of sepsis (Sepsis-3), can be complicated because it requires multiple data points that are often missing in the ED, and the baseline SOFA score is frequently unknown. Even though NEWS2, promoted by the Royal College of Physicians (RCP) and easy to calculate, is considered a valuable tool for risk stratification in this setting, it has still not been extensively studied for early sepsis recognition. Moreover, RCP suggests considering sepsis when its score is ≥ 5 , but it did not design this tool specifically for sepsis.²¹ The addition of PCT, recognized as a reasonably sensitive marker of sepsis,¹⁸ may complement NEWS2's lack of specific infection indicators. To the best of our knowledge, this is the first prospective study assessing the diagnostic value of NEWS2+PCT for sepsis, in patients with infection admitted from the ED.

We observed a significant improvement in the accuracy of sepsis diagnosis when PCT was added to NEWS2. NEWS2 ≥ 5 exhibited low sensitivity (54%) and good specificity (78.8%) in predicting sepsis. In the literature, a few studies, mainly retrospective, investigated NEWS (not NEWS2) for sepsis diagnosis, instead of focusing on prognosis.^{6,7,26} Oduncu reported a sensitivity of 58% for NEWS ≥ 5 , consistent with our results.²⁶ Similarly, Ortega observed a relatively low sensitivity of 61.5%,⁶ whereas Usman showed a higher sensitivity of 74.3%.⁷ It is important to note that these studies evaluated NEWS, not NEWS2. Several authors have suggested that NEWS2 may be less sensitive than NEWS in predicting adverse outcomes, potentially due to lower scores obtained through a different scale for oxygen saturation in patients with hypercapnic respiratory failure.²⁷⁻²⁸ We enrolled a significant proportion of patients (17.8%) with Chronic Obstructive Pulmonary Disease (COPD) and respiratory tract infection

was the primary acute illness (34%). Hodgson *et al.* demonstrated that among 123 patients who died during hospitalization for acute exacerbation of COPD, the median admission NEWS was 7 compared to 4 using NEWS2. With a threshold of ≥ 7 , the sensitivity for in-hospital mortality of NEWS2 versus NEWS dropped by almost 50%.²⁸

Interestingly, we found only one study exploring the diagnostic role of NEWS2 in the ED. The study evaluated a composite endpoint including also mortality and admission to the intensive care unit, and showed that NEWS2 was superior to qSOFA.¹⁴

With a sensitivity of 70.9% and a specificity of 67.8%, NEWS2+PCT ≥ 5 made it possible to enhance the low sensitivity of NEWS2 alone, while maintaining a reasonable specificity. Notably, lower NEWS2 values showed even higher sensitivity than NEWS2+PCT ≥ 5 , but at the expense of specificity. For instance, NEWS2 ≥ 3 showed a sensitivity of 75.0% with a specificity of only 55.6%. In an overcrowded ED, the balance between sensitivity and specificity ensured by NEWS2+PCT ≥ 5 can help to promptly identify patients with sepsis while limiting false-positive alerts. The simple calculation of the sum requires only a few seconds for clinicians, making it a practical and efficient tool.

Regarding qSOFA, which the SSC does not recommend as a standalone screening tool, our study confirms a low sensitivity of 25%. Therefore, although qSOFA shows the highest positive predictive value (as reported in Table 3), its use alone may result in a high proportion of sepsis cases being missed.

In recent years, point-of-care PCT tests, providing rapid results within minutes, have been validated.²⁹ The integration of this test at triage, together with NEWS2, in patients with suspected infection, can enable the early recognition of possible sepsis within minutes of their arrival in the ED. The authors of the 2021 Surviving Sepsis Campaign revised the previous recommendation to administer antibiotics within the first hour in patients with suspected sepsis, with the aim to prevent their excessive use and the associated risk of adverse drug reactions and antimicrobial resistance.¹⁵ Currently, the authors recommend initiating antibiotics within the first hour for cases with a certain or probable diagnosis of sepsis. For cases with only a possible diagnosis, an antibiotic should be started within three hours, after further investigations to rule out causes other than sepsis. NEWS2+PCT ≥ 10 showed a specificity of 87.8% and a sensitivity of 41.9% for diagnosing sepsis. This cut-off, due to its excellent specificity,

could help clinicians identify patients in whom sepsis is considered “certain/probable”, allowing for prompt antibiotic administration within the first hour.

NEWS2+PCT $\geq$ 5 can assist in selecting patients for whom to proceed with further investigations, potentially leading to antibiotic initiation within three hours.

Our study has notable strengths. We were the first to investigate the diagnostic value of combining PCT with NEWS2, offering novel insights into early sepsis recognition in the ED. Moreover, this study is prospective, with NEWS2 calculated directly at triage, minimizing selection bias and concerns about missing data.

Limitations

The monocentric nature of our study, although mitigated by the enrollment of a relatively large population, is a limitation. The proportion of septic patients (50%) is higher than commonly reported. This finding is largely explained by the study design, which specifically included hospitalized patients with suspected infection rather than an unselected ED population. Moreover, the hospital manages a relatively large number of severely ill patients, being a referral center for cancer, hematologic, cardiovascular, and kidney disease, as well as for patients awaiting or living with organ transplants and for elderly population, which is more vulnerable and prone to sepsis. Although the high prevalence may have influenced predictive values, particularly the positive predictive value, the primary measures of diagnostic performance evaluated in this study—sensitivity, specificity, and AUROC—are substantially less affected by disease prevalence. Nevertheless, caution is warranted when extrapolating these findings to lower-acuity or community emergency departments, and larger prospective multicenter studies are needed to externally validate these findings.

Additionally, NEWS2 was assessed at emergency department triage, whereas PCT measurements could be obtained up to 6 hours after presentation. Although this temporal discrepancy may theoretically introduce bias in a dynamic condition such as sepsis, the timing reflected routine clinical practice in our emergency department. Importantly, in patients assigned high-priority triage categories, who were at greater risk of rapid clinical deterioration, clinical evaluation and blood sampling were typically performed within 20–30 minutes of triage, resulting in near-simultaneous NEWS2 assessment and PCT measurement. By contrast, the longer intervals mainly concerned

patients assigned lower-priority triage categories who generally exhibited less physiological instability. Furthermore, an additional subgroup analysis demonstrated comparable diagnostic performance of the NEWS2+PCT combination in high-priority and lower-priority patients, suggesting that the temporal difference between NEWS2 assessment and PCT measurement had a limited impact on the overall performance of the model.

Another potential limitation relates to the classification of the source of infection. In 110 cases (10.6%), it remained unknown. However, we do not believe this affected the study's results, as the presence of infection was indicated by the occurrence of acute-onset symptoms—such as fever, asthenia, mental confusion, tachycardia, or dyspnea—along with elevated inflammatory markers and resolution of the clinical condition following antibiotic therapy. In addition, the diagnosis was corroborated by positive blood or urine cultures, when available.

Finally, the NEWS2+PCT score was intentionally constructed as a simple additive model, directly combining NEWS2 and PCT values (expressed in ng/mL) to maximize bedside applicability and facilitate implementation in routine clinical practice. Consequently, identical combined scores may arise from different combinations of physiological derangement and biomarker elevation. These patterns could potentially represent distinct clinical phenotypes, stages of infection, or risks of deterioration that are not fully captured by the simplified score. Indeed, being an unweighted sum of variables measured on different scales, a given score may reflect different combinations of NEWS2 and PCT, which do not carry equal prognostic weight, and is numerically dominated by PCT at higher values. The composite is therefore intended as a triage adjunct, interpreted alongside the individual component values and clinical judgement rather than as a standalone individual risk estimate. Although the diagnostic performance of the simple NEWS2+PCT sum was comparable to that obtained using a multivariable logistic regression model, future studies should explore alternative weighting strategies, nonlinear approaches, and phenotype-based analyses to determine whether additional prognostic information can be extracted from different NEWS2 and PCT profiles.

Conclusions

In patients admitted from the ED for infection, NEWS2+PCT $\geq$ 5 enhances the sensitivity of NEWS2 $\geq$ 5 for recognizing sepsis without substantially compromising specificity, thus facilitating early management of critically ill patients. Additionally, NEWS2+PCT $\geq$ 10 could help identify patients requiring antibiotic therapy within the first hour. Further research is warranted to explore the impact of combining NEWS2 and PCT in the ED population with infection/sepsis.

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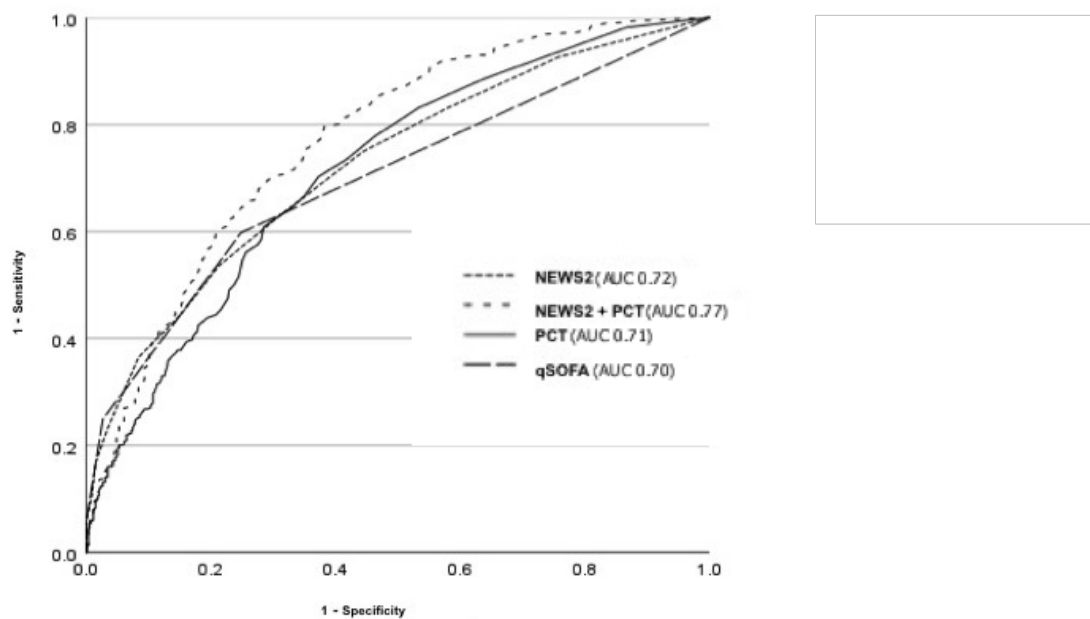


Figure 1. Receiver operator characteristics (ROC) curve for NEWS2, PCT, NEWS2+PCT and qSOFA for sepsis diagnosis. AUC, area under the curve. NEWS2, national early warning score 2. PCT, procalcitonin. qSOFA, quick sequential organ failure assessment.

Table 1 Baseline characteristics of the study population.

* Data expressed as median (min-max)

	All patients (1041)	Non-septic (521)	Septic (520)
Sex (N Male/Female)	559/482	283/238	277/243

Age *	77 (18-103)	71 (18-100)	82 (20-103)
Mean arterial pressure (mmHg) *	87 (30-148)	90 (54-133)	83 (30-148)
Glasgow coma scale N (%)	15: 828 (79.5) 13-14:136 (13.1) 9-12: 40 (3.8) £8: 37 (3.6)	15: 491 (94.2) 13-14:30 (5.8) 0-12: 0 (0.0)	15: 337 (64.8) 13-14:106 (20.0) 9-12: 40 (7.7) £8: 37 (7.1)
Heart rate (beat/minute) *	95 (45-227)	93 (45-178)	98 (46-227)
Respiratory rate (breath/minute) *	17 (10-45)	16 (11-45)	18 (10-40)
White blood cells (10 ⁹ /L) *	12.3 (0-226)	11.8 (0-71)	13.1 (0-226)
Platelets count (10 ⁹ /L) *	222 (4-724)	231 (4-724)	209 (4-667)
Creatinine (mg/dl) *	1.2 (0.1-12)	0.9 (0.1-10)	1.5 (0.1-12)
Total bilirubin (mg/dL) *	0.8 (0.1-21)	0.1 (0.1-20)	0.9 (0.1-21)
Lactates (mmol/L) *	1.4 (0-605)	1.0 (0-6)	1.7 (0-605)
Procalcitonin (ng/mL) *	0.7 (0-734)	0.3 (0-734)	1.6 (0-470)
C-reactive protein (mg/dL)*	11.7 (0-57)	10.5 (0-57)	13.3 (0-55)

Table 2 Distribution of clinical scores and mortality outcomes in the study population. NEWS2, national early warning score2. qSOFA, quick sequential organ failure assessment.

All patients (1041)	Non-septic (521)	Septic (520)
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Mortality, N (%)	170 (16.3)	38 (7.3)	132 (25.4)
Mortality within 72 hours, N (%)	80 (7.7)	10 (1.9)	70 (13.5)
NEWS2, N (%)	0-4: 647 (62.2)	0-4: 410 (78.8)	0-4: 239 (46.0)
	5-6: 154 (14.8)	5-6: 64 (12.2)	5-6: 88 (16.9)
	³ 7: 240 (23.1)	³ 7: 47 (9.0)	³ 7: 193 (37.1)
qSOFA, N (%)	0: 599 (57.5)	0: 391 (75.1)	0: 208 (40.0)
	1: 298 (28.6)	1: 116 (22.3)	1: 182 (35.0)
	2-3: 144 (13.8)	2-3: 14 (2.7)	2-3: 130 (25.0)

Table 3. Accuracy of NEWS2, PCT, NEWS2+PCT and qSOFA for sepsis diagnosis. NEWS2, national early warning score 2. PCT, procalcitonin. qSOFA, quick sequential organ failure assessment. PPV, positive predictive value. NPV, negative predictive value.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	P
NEWS2 ³ 3	75.0	55.6	63.3	68.5	P<0.001
NEWS2 ³ 4	62.8	69.2	67.5	64.6	P<0.001
NEWS2 ³ 5	54.0	78.8	72.0	62.5	P<0.001
NEWS2 ³ 6	44.7	84.7	74.8	60.0	P<0.001
NEWS2 ³ 7	37.1	91.0	81.5	58.6	P<0.001
PCT ³ 0.5 ng/ml	73.4	58.3	64.1	68.3	P<0.001
PCT ³ 1 ng/ml	60.9	71.4	68.4	64.3	P<0.001

PCT ³² ng/ml	44.1	80.2	69.4	58.6	P<0.001
NEWS2+PCT ³³	88.2	47.4	63.0	79.8	P<0.001
NEWS2+PCT ³⁵	70.9	67.8	69.1	69.6	P<0.001
NEWS2+PCT ³⁷	59.7	79.2	74.5	65.8	P<0.001
NEWS2+PCT ³¹⁰	41.9	87.8	77.8	59.8	P<0.001
qSOFA ³²	25.0	97.3	90.3	56.0	P<0.001

Contributions: Antonella Viola and Veronica Salvatore worked to the study conception and design and obtained the approval of all the co-authors. Material preparation and data collection were performed by all the co-authors. Data analysis was performed by Antonella Viola and Veronica Salvatore. The manuscript was written by Antonella Viola and all co-authors commented on previous versions of it. All co-authors have had the opportunity to review the final manuscript and have provided their permission to publish the manuscript.

Conflict of interest: all the authors declare that they have no competing interests

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Ethical statements: the study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee “Area Vasta Emilia Centro - AVEC” (637/20222/0ss/AOUBo). Written informed consent was provided by patients or legal representative within 72 hours of hospital admission, before study enrolment.

Availability of data and materials: the datasets used and/or analyzed during the current study are available upon reasonable request from the corresponding author.

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