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Improved Prognostic Accuracy of NEWS2 Score with Triage Data in Adults with Bacterial Sepsis: A Retrospective Cohort Study

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Abstract

Background: It is estimated that most patients with severe sepsis are admitted through the emergency department. Early identification and subsequent early appropriate therapy remain cornerstones of sepsis management. Early recognition of sepsis in the emergency department (ED) is crucial. The National Early Warning Score 2 (NEWS2) has shown limitations in prognostic accuracy. We aimed to develop and evaluate a prognostic model combining NEWS2 with triage data to predict 28- and 90-day mortality in adult patients with bacterial sepsis. **Methods**: We conducted a retrospective cohort study of 557 patients admitted to the ED with suspected bacterial infection between March 2017 and September 2019. Candidate predictors included triage variables (vital signs, comorbidities, blood gas data) and clinical scores (NEWS2, SOFA, qSOFA, APACHE2, and SIRS). Outcomes were 28- and 90-day mortality. Logit analysis was used to develop prognostic models, with assessment of discrimination and calibration. **Results**: Overall mortality was 24.6% at 28 days and 36.4% at 90 days. Models combining NEWS2, age, and lactates outperformed NEWS2 alone (28-day: 73.8% vs. 69%; 90-day: 71.6% vs. 67%). Including terminal status further improved accuracy. Finally, this paper proposes new criteria for the early identification of patients with sepsis in triage, with positive outcomes. **Conclusions**: Combining NEWS2 with age and lactates enhances prognostic accuracy at triage. This model may inform improved sepsis management.

Keywords: sepsis; NEWS2; lactate; emergency department; prognostic model; TRIPOD

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1. Introduction

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection.

The traditional definition of sepsis, since 1992, refers to it as the presence or suspected infection associated with a systemic inflammatory response syndrome (SIRS) [1]. This

changed in 2016 [2] when it was replaced by the new criteria of SEPSIS-3, so that sepsis is currently defined as infection with organ dysfunction, assessed by the Sequential Organ Failure Assessment (SOFA score) [3], while the previous expression "severe sepsis" is no longer adopted to increase predictive accuracy.

Sepsis is a major global health problem and accurate early risk stratification is crucial in the emergency department (ED). From a recent epidemiological study, there were an estimated 11 million total sepsis-related deaths worldwide in 2017, representing 16.5% of all deaths in that year [4].

If not diagnosed and treated promptly, mortality can range from 40 to 70% [5].

It is estimated that most patients with severe sepsis are admitted through the emergency department (ED) [6,7].

Wang et al. [8] reported that approximately 21% of adult ED visits presented with a serious infection.

Sepsis can have either a bacterial, viral, or fungal origin. Since the onset of the COVID-19 epidemic, emergency departments have been at the forefront of managing an increasing number of patients with varying degrees of severity of the same clinical syndrome [9–11].

However, early identification and consequent early appropriated therapy remain cornerstones of sepsis treatment. According to the Guidelines of the Surviving Sepsis Campaign (SSC), when sepsis is definite or probable, the antimicrobials must be administered ideally within 1 h of recognition [12]. For this, the bundle's effectiveness in terms of diagnosis and treatment must be maximized.

Despite the existence of several scores (SIRS, SOFA [3], qSOFA [11], and NEWS2), no gold standard exists for use at triage. Numerous studies have shown that NEWS2 has better diagnostic accuracy than QSOFA in terms of detecting severe sepsis progression but prognostic accuracy often remains less than 70% [13–19]. There is no definitive "gold standard" clinical score for diagnosing sepsis.

Due to the poor sensitivity of QSOFA [13–16], the panel of the latest guidelines issued a strong recommendation against its use as a single screening tool [12]. Biomarkers can be important [20–27] but the results of these tests can only be obtained a few hours after the patient enters the emergency room.

The only tests that can be used in triage are the blood gas data and among these the lactates. The association between lactate levels and mortality in septic patients has been proven [28–32], and resuscitative strategies aimed at their normalization are associated with improved 28-day survival [33–37].

This study aimed to evaluate whether combining NEWS2 with other variables measured during triage improves prediction of 28- and 90-day mortality.

2. Materials and Methods

2.1. Study Design

This is a retrospective cohort study conducted at the Policlinic Consortium Hospital of Bari. Patients who visited the Emergency Unit with suspected bacterial infection between March 2017 and September 2019 were included. To avoid bias due to the overlapping of the COVID-19 epidemic, we decided to use pre-2020 data, reserving the right to compare our results with a COVID population at a later date.

Our trial included all patients aged 16 and over. The medical staff assessed patients for suspected infections based on their clinical history, symptoms, and any indications of fever or relevant signs. Vital signs and arterial blood gas analysis (EGA) were studied during triage to classify patients using the Sepsis-3 criteria. For the EGA the GEM 5000 (Instrumentation Laboratory by Werfen) was used. The diagnosis of infection was later confirmed with

the results of culture tests, sepsis markers, and instrumental examinations. Cases without essential registry data and without explanation were excluded the fact (52 patients). The final cohort consisted of 557 patients.

The study received approval from the ethical committee (nr. 6698: 11/2/2021) of the Policlinic of Bari, in compliance with the Helsinki Declaration. Each patient or their legal representative provided consent for the data to be processed.

To ensure clarity and objectivity, the study followed the Third International Consensus definitions for Sepsis and Septic Shock (Sepsis-3) and the Guidelines of the Surviving Sepsis Campaign. Specifically, the clinical situation of sepsis was first considered for all patients with infection and a SOFA score of 2 or more points. Patients with infection and a SOFA score <2 were considered to be simply infected; they are useful to validate the results obtained in a less severely infected patient population. Septic shock is defined as a patient with sepsis who, after receiving 20–30 mL/kg of volume resuscitation, requires vasoactive drug support to maintain a mean arterial pressure (MAP) of over 65 mmHg and presents a lactate level over 2 mmol/L.

2.2. Data Collection

This study evaluated the data recorded in triage: demographics (age, sex, and nursing home residence), comorbidities, vital signs (respiratory rate, oxygen saturation, systolic and diastolic blood pressure, heart rate, temperature, and GCS), arterial blood gas results (with a focus on lactates), clinical scores (SIRS, qSOFA, SOFA, NEWS2, and APACHE2), and terminal patient status. The LifePAK® 15 monitor–defibrillator was used to determine pulse oxygen saturation, blood pressure, and pulse, while the ThermoScan® PRO 6000 thermometer was used to measure temperature.

Anamnestic data taken into consideration included the presence of cirrhosis, neoplasms, Alzheimer's disease, hemopathy, nephropathy, dialysis, heart disease, lung disease, diabetes, cortisone therapy in the last three months, and terminal stage.

The scores considered were SIRS, QSOFA, SOFA, NEWS2, and APACHE2. The SIRS criteria include a temperature above 38 °C; a heart rate above 90; a respiratory rate above 20 or a PaCO2 below 32 mmHg; and a WBC count above 12,000/mm^3, below 4000/mm^3, or with more than 10% bands [1]. The QSOFA scoring system assesses three criteria: a respiratory rate of 22 or higher, a systolic blood pressure of 100 or lower, and an altered mental status with a Glasgow Coma Scale score of less than 13 [2]. The SOFA score is based on six different scores, one each for the respiratory (P/F), cardiovascular (Pressure Arterial Media with or without vasopressors), hepatic (bilirubin mg/dL), coagulation (platelet 10^3/mm^3), renal (creatinine mg/dL or urine flow), and neurological systems (Glagow Coma Scale). NEWS2 includes respiratory rate, oxygen saturation with or without hypercapnia, oxygen support, systolic blood pressure, heart rate, temperature, and level of consciousness. The level of consciousness is considered abnormal if the Glasgow Coma Scale (GCS) score is lower than 15 points [38–44]. The APACHE2 score evaluates the severity of illness and predicts patient outcomes by considering the patient's medical history, age, vital signs (temperature, mean arterial pressure, heart rate/pulse, and respiratory rate), laboratory values (sodium, potassium, creatinine, hematocrit, and white blood cell count), and Glasgow Coma Scale score, as well as the fraction of inspired oxygen.

Primary outcomes evaluated all-cause mortality at 28 and 90 days after ED admission.

2.3. Statistical Analysis

Quantitative variables were described as mean and s.d., but also as median and Tukey's hinges (25th and 75th percentiles); due to the large sample size, the scores can also be considered as quantitative variables, with some caution. For average comparison

purposes, both samples were well-sized (>100 cases in both groups of survivors and non-survivors), so the powerful Z-test was used.

All variables considered ($p < 0.05$; $p < 0.01$; $p < 0.005$; and $p < 0.001$) were selected for subsequent analysis, excluding those presenting more than 10% of missing data.

For visual assessment of the distribution of patient survival at 28 and 90 days, histograms were provided.

Kendall's tau-b rank correlation test was used to explore univariate relationships between variables and survival at the defined thresholds.

Contingency tables were used to describe binary variables, and differences between survivors and non-survivors were tested using the Z-test (Tables S1 and S2, Supplementary Materials). Again, Kendall's tau-b rank correlation test was used to explore univariate relationships between these variables and survival at the defined thresholds.

In this study we instead identified two follow-up thresholds (28 and 90 days) to investigate survival in sepsis patients; therefore, the Cox model [45,46] was not useful in this case, and we opted for logistic regression (with dichotomous response, dead or alive, at each threshold) as a multivariate statistical method to identify variables that significantly increase the probability of the occurrence of the target variable [47,48]. This model allows for the analysis of categorical prognostic factors, including nominal or ordinal classes, as well as quantitative variables.

In this study, reducing asymmetry is also important for the use of retrospective data as exploratory data, similar to prospective studies.

The dataset showed a severe imbalance, with 63.6% of patients still alive at 90 days and more than 75% at 28 days. To address this issue, we applied a post-stratification technique to the sample based on the event of interest [49–51].

Two different subsamples were extracted from the dataset. The first subsample, comprising all deaths within the cut-off date and a randomly selected group of survivors (almost 33%), resulted in a balanced sample of 137 deceased and 138 survivors for the 28-day survival study.

The second subsample consists of all deceased at day 90 and a randomly selected group of 56,5% of survivors from the dataset. Therefore, the study subsample for the 90-day survival study includes 203 deceased and 200 survivors.

Several logit regression models were applied to the two re-proportioned subsamples, using the stepwise elimination method to remove less significant variables, with a significance level of $\alpha = 0.05$. The goodness of fit of those models was assessed using both Nagelkerke R2 and Cox-Snell R2, as well as the models' predictive power, which was provided by the confusion matrices (the standard output of the procedure). The model's parameters were then used to test their ability to predict outcomes for the entire set of data in the observational registry, guided by the subsamples.

In this experimental study, we aimed to improve the predictive power of our models. Therefore, we investigated some alternatives, such as including 'terminal patient' (patients near the end of life with no possibility of cure) status as a prognostic factor to predict survival at 28 and 90 days, which yielded positive outcomes.

As the measures were binary and the samples were correlated (deaths and survivals in the same subjects applying different criteria), powerful tests such as the *t*-test, useful for quantitative data, or Wilcoxon's test (for ordinal data) were not applicable. Therefore, we employed the sign test, which is specific to this case.

These analyses were performed using the IBM SPSS Statistics 25 program.

3. Results

Among 557 patients—median age 75 years with ±s.d. 18.4 (IQR: 16–98 years), 43.4% female—sepsis was diagnosed in 373 (61.7%), septic shock in 55 (9.1%), and infection without organ dysfunction in 129 (21.4%) patients. Mortality was 24.6% (137 patients) at 28 days, 36.4% (203 patients) at 90 days (see Table 1). The rate of institutionalized patients was 3.8% (21 cases).

Table 1. Characteristics of patients with bacterial infection at triage admission, by clinical diagnosis.

Parameters (Min-Max or %)	Total	Infection	Sepsis	Septic Shock
Number	557	129	373	55
Age, Median (Min–Max)	75 (16–98)	64 (16–91)	78 (18–98)	80 (44–91)
Sex, Female (%)	242 (43.4%)	57 (44.2%)	156 (41.8%)	29 (52.7%)
Nursing Home (%)	21 (3.8%)	1 (0.8%)	15 (4.0%)	5 (9.1%)
Vital Signs				
O_2 Therapy (%)	113 (20.3%)	7 (5.4%)	85 (22.8%)	21 (38.2%)
O_2 Saturation (Min–Max)	96.1 (70–100)	97.3 (82–100)	95.8 (70–100)	94.7 (70–100)
Temperature °C	37.1 (31–41)	37.3 (35–40)	37.1 (31–41)	36.6 (32–39.5)
SBP (Mmhg)	117.4 (50–240)	125.4 (70–210)	118.5 (60–240)	90.6 (50–150)
DBP Mmhg	68.1 (30–110)	71.7 (35–100)	68.7 (30–110)	54.6 (30–80)
MHB Mmhg	84.5 (37–137)	89.7 (55–137)	85.4 (40–137)	66.6 (37–97)
HR (Hearts Rate)	95.1 (40–160)	96.2 (40–150)	94.5 (40–160)	97.7 (40–150)
RR(Breathe/Min)	25.4 (6–48)	22.9 (16–40)	26.1 (16–48)	27.3 (6–45)
GCS (Points)	14.1 (3–15)	14.9 (13–15)	14.1 (3–15)	12.4 (3–15)
Symptoms				
Fever (%)	249 (44.7%)	79 (61.2%)	156 (41.8%)	14 (25.5%)
Respiratory Symptoms (%)	95 (17.1%)	16 (12.4%)	72 (19.3%)	7 (12.7%)
Gastrointestinal Symptoms (%)	24 (4.3%)	6 (4.7%)	16 (4.3%)	2 (3.6%)
Cardiovascular Symptoms (%)	45 (8.1%)	3 (2.3%)	33 (8.8%)	9 (16.4%)
Urinary Symptoms (%)	22 (3.9%)	7 (5.4%)	13 (3.5%)	2 (3.6%)
Neurological Symptoms (%)	85 (15.3%)	14 (10.9%)	56 (15.0%)	15 (27.3%)
Other (%)	40 (7.2%)	11 (8.5%)	26 (7.0%)	5 (9.1%)
Comorbidities				
Cirrhosis (%)	47 (8.4%)	6 (4.7%)	34 (9.1%)	7 (12.7%)
Cancer (%)	89 (16.0%)	15 (11.6%)	64 (17.2%)	10 (18.2%)
Neuro Alzheimer's (%)	86 (14.4%)	8 (6.2%)	60 (16.1%)	18 (32.7%)
Hemopathy (%)	47 (7.8%)	5 (3.9%)	30 (8.0%)	7 (12.7%)
Chronic Renal Failure (%)	109 (19.5%)	14 (10.9%)	80 (21.4%)	15 (27.3%)
Hemodialysis (%)	23 (4.1%)	7 (5.4%)	14 (3.8%)	2 (3.6%)
Heart Disease (%)	238 (42.7%)	31 (24%)	176 (47.2%)	31 (56.4%)
Lung Diseases (%)	121 (21.7%)	15 (11.6%)	89 (23.9%)	17 (30.9%)
Diabetes Mellitus (%)	113 (20.3%)	17 (13.2%)	75 (20.1%)	21 (38.2%)

Table 1. *Cont.*

Parameters (Min-Max or %)	Total	Infection	Sepsis	Septic Shock
Oliguria (%)	124 (22.3%)	129 (9.3%)	373 (20.6%)	55 (63.6%)
Terminal Patient (%)	67 (12.9%)	5 (3.9%)	48 (12.9%)	14 (25.5%)
Blood Gas Data				
Ph	7.42 (6.88–7.79)	7.45 (7.08–7.79)	7.42 (6.88–7.69)	7.41 (6.99–7.59)
PO2 at T0	81.4 (30–375)	90.7 (55–203)	77.1 (30–340)	88.1 (37–375)
P/F	314.7 (62–850)	407.5 (229–812)	301.2 (66–850)	296.1 (62–517)
Lactates 0h	2.5 (0.3–20)	1.3 (0.3–4.6)	2.1 (0.5–18.9)	5.5 (2–20)
Clinical Score				
SIRS	2.02 (0–11)	1.79 (0–11)	2.05 (0–9)	2.33 (0–4)
QSOFA, Points	1.12 (0–3)	0.60 (0–2)	1.15 (0–3)	2.07 (1–3)
SOFA, Points	3.39 (0–14)	0.59 (0–4)	3.77 (0–14)	7.33 (2–12)
APACHE2, Points	12.62 (0–41)	7.17 (0–20)	13.44 (0–41)	19.85 (2–39)
NEWS-2	5.13 (0–19)	3.14 (0–11)	5.26 (0–19)	8.95 (3–16)
Survival				
28-Day Mortality (%)	137 (24.6%)	11 (8.5%)	92 (24.7%)	34 (61.8%)
90-Day Mortality (%)	203 (36.4%)	22 (17.1%)	137 (36.7%)	44 (80.4%)

To explore the relationships between survival and prognostic factors, the parameters considered in our dataset were compared between the surviving and non-surviving cases at the 28-day threshold (Table 2). The Z-test showed many statistically significant differences between the two groups studied, for almost all variables except heart rate, PO2 at time 0, and P/F ratio. Most of the tau-b coefficients were also statistically significant, also confirming the Z-test results at the individual level, rather than at the aggregate level.

Table 2. Baseline characteristics (mean ± s.d.) of patients by survival status at the 28-day threshold. Z-test for the differences, and Kendall's Tau-b related to survival.

Prognostic Factors, Tests and Scores	Deceased	Survivors	Z Sig.	*Tau-b*	*Tau Sig.*
Age	77.58 ± 13.90	66.44 ± 18.82	****	*−0.240*	****
O_2 Saturation	95.18 ± 5.22	96.42 ± 3.89	*	*0.080*	*
Temperature	36.72 ± 1.43	37.23 ± 1.29	****	*0.141*	****
Systolic Blood Pressure	107.66± 26.68	120.59 ± 24.13	****	*0.193*	****
Diastolic Blood Pressure	62.78 ± 13.51	69.80 ± 13.58	****	*0.209*	****
Mean Blood Pressure	77.74 ± 16.81	86.73 ± 15.82	****	*0.202*	****
Respiratory Rate	27.67 ± 6.14	24.70 ± 5.57	****	*−0.214*	****
Glasgow Coma Scale	13.26 ± 2.88	14.40 ± 1.86	****	*0.253*	****
SIRS	2.29 ± 1.04	1.93 ± 1.23	***	*−0.150*	****
qSOFA	1.65 ± 0.85	0.94 ± 0.75	****	*−0.328*	****
SOFA	5.18 ± 3.38	2.81 ± 2.46	****	*−0.275*	****
APACHE 2	17.40 ± 6.67	11.05 ± 6.28	****	*−0.328*	****
NEWS-2	7.30 ± 3.56	4.42 ± 3.04	****	*−0.300*	****

Table 2. *Cont.*

Prognostic Factors, Tests and Scores	Deceased	Survivors	Z Sig.	*Tau-b*	*Tau Sig.*
P/F ratio	294.67 ± 134.82	323.24 ± 120.82	*	*0.101*	**
Lactates (T0)	3.55 ± 3.38	2.03 ± 2.43	****	*−0.259*	****

Symbols used for statistical significance: $p < 0.05$: *; $p < 0.01$: **; $p < 0.005$: ***; $p < 0.001$: ****.

However, because of the unknown relationships between the individual variables themselves, some of these significant results may be spurious and could only be investigated by multivariate analyses.

Approximately the same observations and conclusions are made at the 90th day threshold (Table 3), but in this case only the differences in the variables PO2 at time 0 and P/F ratio between survivors and non-survivors are not significant. Some sporadic minor variations are also observed for the significance of Kendall's tau-b.

Table 3. Baseline characteristics (mean ± s.d.) of patients by survival status at the 90-day threshold. Z-test for the differences, and Kendall's Tau-b related to survival.

Prognostic Factors, Tests and Scores	Deceased	Survivors	Z Sig.	*Tau-b*	*Tau Sig.*
Age	76.98 ± 13.6	64.71 ± 19.3	****	*−0.280*	****
O_2 Saturation	95.56 ± 4.9	96.42 ± 3.9	*	*0.042*	-
Temperature	36.88 ± 1.4	37.24 ± 1.3	***	*0.100*	***
Systolic Blood Pressure	108.11 ± 25.1	122.75 ± 24	****	*0.244*	****
Diastolic Blood Pressure	62.92 ± 14	71.03 ± 12.9	****	*0.267*	****
Mean Blood Pressure	77.98 ± 16.6	88.27 ± 15	****	*0.259*	****
Heart Rate	97.96 ± 21.3	93.53 ± 18.9	*	*−0.091*	**
Respiratory Rate	27.24 ± 6.2	24.4 ± 5.3	****	*−0.217*	****
Glasgow Coma Scale	13.46 ± 2.7	14.5 ± 1.8	****	*0.267*	****
SIRS	2.32 (±1.2)	1.84 (±1.2)	****	*−0.195*	****
qSOFA	1.54 ± 0.9	0.87 ± 0.7	****	*−0.351*	****
SOFA	4.72 ± 3.3	2.62 ± 2.4	****	*−0.285*	****
APACHE 2	16.46 ± 6.7	10.41 ± 6	****	*−0.356*	****
NEWS-2	6.9 ± 3.5	4.12 ± 2.9	****	*−0.330*	****
Lactates (T0)	3.25 ± 3.3	1.9 ± 2.2	****	*−0.250*	****

Symbols used for statistical significance: $p < 0.05$: *; $p < 0.01$: **; $p < 0.005$: ***; and $p < 0.001$: ****.

Finally, all the individually significant prognostic factors highlighted in Tables 2–5 were subjected to the logit procedure described in Section 2.3. Age, sex, some anamnestic information, lactates at time 0 (with three levels: "2 mmol/L", "2–2.5 mmol/L", and "2.5 mmol/L"), and the "NEWS2" score were selected as potentially important variables for survival in the set of information available at triage (see histograms relating to their frequency in the Supplementary Materials).

In a further model, "terminal patient" status was also included, despite the seriousness of this anamnesis; in fact, such a status is undoubtedly a prominent "a priori" risk factor, but it does not cause distortions in the model because, fortunately, more than 40% of these patients survive to the end of the 28th day and more than 30% survive to the end of the 90th day. Thus, in relation to the post-stratified sample at the 28-day threshold, logit analysis with stepwise elimination produced the following two models:

Table 4. (**a**). Logit analysis for patient survival at 28-day threshold, using stepwise elimination. (**b**). Logit analysis for patient survival at 28-day threshold, using stepwise elimination (including 'terminal status').

(a)				
Prognostic Factors	**B**	**s.e.**	***p***	**Log-Odds**
Age	−0.050	0.011	<0.001	0.951
Lactate 2–2.5 mmo/L	−0.876	0.619	0.157	0.416
≥2.5 mmo/L	−1.418	0.387	<0.001	0.242
NEWS2	−0.224	0.051	<0.001	0.799
Constant	4.555	0.845		
(Nagelkerke R^2 = 0.41; Cox-Snell R^2 = 0.30).				
Confusion Matrix	**Predicted 28-Day Status**			***Correct %***
Observed 28-day Status	Deceased	Survivors	Total	
Deceased	105	32	137	*76.6*
Survivors	30	106	136	*77.9*
Total	135	138	273	
Overall Correct %				*77.3*
(**b**)				
Prognostic Factors	**B**	**s.e.**	***p***	**Log-Odds**
Age	−0.055	0.011	<0.001	0.946
Terminal patient	−1.205	0.407	0.003	0.300
Lactate 2–2.5 mmo/L	−0.815	0.639	0.202	0.442
≥2.5 mmo/L	−1.426	0.393	<0.001	0.240
NEWS2	−0.206	0.051	<0.001	0.814
Constant	4.461	0.881		
(Nagelkerke R^2 = 0.43; Cox-Snell R^2 = 0.32).				
Confusion Matrix	**Predicted 28 Day Status**			***Correct %***
Observed 28-day Status	Deceased	Survivors	Total	
Deceased	106	31	137	*77.4*
Survivors	27	109	136	*80.1*
Total	133	140	273	
Overall Correct %				*78.8*

The model for the 28-day threshold Table 4a correctly predicts 77.3% of outcomes in the balanced subsample, and if we extend its rules to the whole dataset, we find good predictive capacity for 28-day survival (73.8% overall, 72.9% for survivors, and 76.6% for deaths). By adding the status of 'terminal patient' to the prognostic factors Table 4b the model's predictive ability improves slightly: it correctly identifies almost 79% of cases in the balanced subsample and 74.5% in all patients, accurately identifying 73.6% of survival events and 77.4% of deaths. For the first model without the terminal status (Table 4a), for every additional year of age, the odds of surviving decrease by about 4.9%. Lactate ≥ 2.5 mmol/L strongly reduces the odds of survival (about a 76% reduction) and each additional point in NEWS2 decreases the odds of survival by about 20%.

For the second model, including the terminal status (Table 4b), patients in a terminal condition have survival odds reduced by about 70% compared to non-terminal patients. Each additional year reduces survival odds by about 5.4%, Lactate ≥ 2.5 mmol/L strongly reduces the odds of survival (about a 76% reduction), and each additional point in NEWS2 decreases survival odds by about 18.6%.

Table 5. (**a**). Logit analysis for patient survival at 90-day threshold, using stepwise elimination. (**b**). Logit analysis for patient survival at 90-day threshold, using stepwise elimination (including 'terminal status').

(a)				
Prognostic Factors	**B**	**s.e.**	***p***	**Log-Odds**
Age	−0.042	0.008	<0.001	0.959
Lactate 2–2.5 mmo/L	*−0.774*	*0.553*	*0.162*	*0.461*
≥2.5 mmo/L	−0.864	0.293	0.003	0.421
NEWS2	−0.197	0.039	<0.001	0.821
Constant	3.747	0.642		
(Nagelkerke R^2 = 0.32; Cox-Snell R^2 = 0.24).				
Confusion Matrix	**Predicted 90-Day Status**			***Correct %***
Observed 90-day Status	Deceased	Survivors	Total	
Deceased	146	57	202	71.9
Survivors	60	140	200	70.0
Total	206	197	404	
Overall Correct %				71.0
(**b**)				
Prognostic Factors	**B**	**s.e.**	***p***	**Log-Odds**
Age	−0.044	0.008	<0.001	0.957
Terminal patient	−1.382	0.380	<0.001	0.251
Lactate 2–2.5 mmo/L	−0.697	0.565	0.217	0.498
≥2.5 mmo/L	−0.825	0.297	0.005	0.438
NEWS2	−0.180	0.039	<0.001	0.836
Constant	3.352	0.676		
(Nagelkerke R^2 = 0.36; Cox-Snell R^2 = 0.27).				
Confusion Matrix	**Predicted 90 Day Status**			***Correct %***
Observed 90-day Status	Deceased	Survivors	Total	
Deceased	153	50	202	75.4
Survivors	50	150	200	75.0
Total	203	200	404	
Overall Correct %				75.2

The model for the 90-day threshold (Table 5a) correctly predicts 71% of the balanced sample, and by applying its parameters to the entire dataset, we find that it correctly classifies 71.6% of the outcomes (71.5% of survivals and 71.9% of deaths). By adding the "terminal patient" status, the identified model correctly classifies 75.2% of the balanced sample, and the same percentage by applying its parameters to the original sample (75.1% of survivors and 75.4% of deaths). For the model without the terminal status (Table 5a), for every additional year of age, the odds of surviving decrease by about 4.1%. Lactate ≥ 2.5 mmol/L strongly reduces the odds of survival (about a 58% reduction) and each additional point in NEWS2 decreases the odds of survival by about 17.9%.

For the model that includes the terminal status (Table 5b), patients with a terminal condition have survival odds reduced by about 74.9% compared to non-terminal patients. Each additional year reduces survival odds by about 4.3%, lactate ≥ 2.5 mmol/L strongly reduces the odds of survival (about a 56.2% reduction), and each additional point in NEWS2 decreases survival odds by about 16.4%.

When comparing the previous results with the usual triage procedures, the NEWS2 score alone correctly classifies approximately 72% of the balanced sample and 69% of the total

outcomes at the 28-day threshold. However, its forecast accuracy was worse at 90 days, with an accuracy of only 67.5% in both the balanced and total samples. On the other hand, the Apache2 score has a similar predictive capacity to our models, but it uses parameters that are not immediately available in triage.

Our proposal was to enhance the standard criterion by combining the NEWS2 score with the criteria presented above. It is important to note that these are not clinical scores (which need to be validated in the field), but rather simple approximations. They are as follows: 'NEWS2/A', which triggers an immediate alert if a patient meets the NEWS2 criteria or if they have a lactate level above the norm or an older age; and 'NEWS2/B', which also considers the recognition of 'terminal patient' status. Age was analyzed using the ROC curve for death and survival, which identified a cut-off at 79.5 years.

However, in order to evaluate the practical results of our technique, the following paragraphs show the results of the decisions that triage staff would have made on the basis of NEWS2 alone, compared with those they would have made using our new criteria.

Table 6 shows that, using the NEWS2 criterion alone, only 27.1% of patients would have been placed under close clinical monitoring at the 28-day threshold. The mortality rates were 47% in this risk group and 16.3% in the 'No alert' group (24.6% overall). The joint probabilities enable us to calculate an odds ratio close to 0.22; in other words, the 'no-risk' group has about a 20% probability of dying compared to the 'Alert' group. Thus, a strong interdependence exists between the two probability distributions.

Table 6. Alerts at the 28-day threshold using the criteria NEWS2, NEWS2/A, and NEWS2/B.

	Outcomes			**Joint Probability Distrib.**			***Groups***
Criteria	Deceased	Survivor	Total	Deceased	Survivor	Total	*mortality rate*
NEWS2							
No alert	66	340	406	11.8	61.0	72.9	*16.3*
Alert	71	80	151	12.7	14.4	27.1	*47.0*
Total	137	420	557	24.6	75.4	100.0	*24.6*
				Odds Ratio:		*0.219*	
NEWS2/A							
No alert	12	262	274	2.2	47.0	49.2	*4.4*
Alert	125	158	283	22.4	28.4	50.8	*44.2*
Total	137	420	557	24.6	75.4	100.0	*24.6*
				Odds Ratio		*0.058*	
Results assuming constant care outcomes							
No alert	12	262	274	2.2	47.0	49.2	*4.4*
Alert	96	187	283	17.2	33.6	50.8	*33.9*
Total	108	449	557	19.4	80.6	100.0	*19.4*
Results assuming half survival rate							
No alert	12	262	274	2.2	47.0	49.2	4.4
Alert	111	172	283	19.9	30.9	50.8	39.2
Total	123	434	557	22.1	77.9	100.0	22.1
NEWS2/B							
No alert	10	255	265	1.8	45.8	47.6	*3.8*
Alert	127	165	292	22.8	29.6	52.4	*43.5*
Total	137	420	557	24.6	75.4	100.0	*24.6*
				Odds Ratio		*0.051*	

Table 6. *Cont.*

	Outcomes			Joint Probability Distrib.			*Groups*
Results assuming constant care outcomes							
No alert	10	255	265	1.8	45.8	47.6	*3.8*
Alert	97	195	292	17.4	35.0	52.4	*33.2*
Total	107	450	557	19.2	80.8	100.0	*19.2*
Results assuming half survival rate							
No alert	10	255	265	1.8	45.8	47.6	*3.8*
Alert	112	180	292	20.1	32.3	52.4	*38.4*
Total	122	435	557	21.9	78.1	100.0	*21.9*

Instead, by applying the NEWS2/A criterion, the 'Alert' group increases to 60% of the total, while its raw mortality rate decreases to 44.2%. The mortality rate of the 'No alert' group decreases to 4.4%. The odds ratio is drastically reduced (OR = 0.058), indicating a stronger dependence of the risk of death on group membership.

Note that the use of the term 'raw' in this context refers to mortality under the assumption that all patients who actually died in the 'no alert' group would have had the same outcome even if they had been under careful management. However, if medical surveillance provided to the new 'at risk' patients yielded the same outcome as the group using the NEWS2 criterion alone (i.e., 53% of new patients survive, referred to as 'constant care outcomes'), the mortality rate in the 'Alert' group would decrease to 33.9%, resulting in an overall mortality rate of 19.4%.

Indeed, if the new patients in the 'Alert' group have a lower survival rate, due to some accident (26.5% instead of 53%), the mortality rate of this group would drop to 39.2% when using the NEWS/A criterion, and the overall mortality rate would be 22.1%.

The sign test for correlated samples and binary distribution provided a p-value < 0.001, assuming both constant and worst-case survival rates. Therefore, within the limits of the performed simulation, the NEWS2/A and NEWS2/B criteria are statistically confirmed to be better than NEWS2 alone.

Of course, the NEWS2/A or NEWS2/B criteria also have positive indirect impacts on survival at the 90-day threshold. However, reporting these results here may be unnecessary and confusing.

4. Discussion

Models integrating NEWS2 with age and lactates improved prognostic accuracy compared to NEWS2 alone. These predictors are readily available at triage, making the model feasible in emergency settings.

The time of triage access is the zero time from which we start counting to maximize the bundles for the diagnosis and treatment of these patients and for this reason it is essential to recognize them early on.

The main actor in triage is the nurse who has only clinical parameters or at most blood gas data available. For this reason, scores such as SIRS, Apache2, or SOFA cannot be proposed in triage because they require the results of laboratory tests.

The NEWS2 is a quick score based on a system of clinical parameters useful for detecting and monitoring the worsening patient [14].

NEWS2 has been shown in multiple studies to have better diagnostic accuracy than qSOFA in detecting severe evolution of sepsis [14–17].

NEWS2 does not distinguish the etiological agent but still remains a reliable tool in identifying the negative evolution of the syndrome even when linked to COVID [18,19].

In our population its predictive power in septic patients of bacterial etiology was 67–69%. There are currently no studies investigating the utility of prehospital NEWS2 and lactates and age in an infectious population.

Lactates play a key role in patients' cellular metabolism and mitochondrial energy production and are not only a direct measure of tissue perfusion. Sepsis-associated hyperlactatemia (SAHL) arises from the fact that the uptake of lactates into the mitochondrion increases during shock as it represents the main energy substrate which is oxidized to pyruvate [38]. The increased production of lactates derives not only from anaerobic glycolysis but above all from aerobic glycolysis and this above all in the tissues where the energy need is higher, such as in the brain, muscles, or heart [39–43].

Dadeh et al. [52] analyzed the predictive ability of NEWS and NEWS–lactate 2-day mortality among infected patients and obtained AUCs of 0.79 and 0.81, respectively. These data suggest that these early warning scores may be useful in short-term prognostic assessment, making them very useful for the management of patients in prehospital care.

The association between lactate levels and mortality in septic patients is a fact and the resuscitative strategies that aim at their normalization are associated with better survival at 28 days. A study following the 2016 definitions reports that initial lactate levels $\geq$2.5 mmol/L have moderate prognostic value (AUC 0.70 [95% CI, 0.62–0.79]) in predicting mortality at 28 days in both patients with sepsis and septic shock [29]. Other studies have confirmed this finding [30–32].

However, it is the lactate value at 6h and, above all, its clearance at 6h, which actually has a greater predictive significance regarding early mortality. Nguyen defines lactate clearance at 6 h as the percentage decrease in lactate levels from the time of ED entry to 6 h later [33]. According to this study, a lactate clearance < 10% is the optimal cut-off value with a sensitivity of 44.7% and a specificity of 84.4% for predicting in-hospital mortality. Nguyen concluded that 'lactate clearance in the early hospital course may indicate a resolution of global tissue hypoxia and that this is associated with decreased mortality rates.' Jones and colleagues then extended this concept as an indicator of restoration of tissue oxygenation [34].

A recent study also concluded that 6 h lactate levels and 6 h clearance correlate with 28-day mortality rates in patients with septic shock [35]. A previous study reported that the optimal cut-off values for predicting short-term survival are <3.7mmol/L for the second lactate measurement and $\geq$32% for lactate clearance [36]. According to another study, lactate $\geq$ 3.5 mmol/L at 6 h and its clearance at 6 h < 24.4% are useful for predicting 30-day mortality [37].

Our study was necessarily limited to evaluating the initial value of lactates and, according to our cases, an initial value $\geq$ 2 is associated with a 28-day mortality of 49.2% and a 90-day mortality of 62.9% (89/154 pts) among patients with bacterial sepsis. This is why we categorized lactate level and did not consider it as a metric variable.

Improving NEWS2 performance with the initial lactate value is not a new achievement. Other works have found it, especially in the pre-hospital phase, and coined the term NEWS2-L [53]. In 2019, to evaluate the ability of this score to predict the early mortality of septic patients in the prehospital phase, 707 patients were studied and AUCs at 2, 7, and 30 days of 0.91, 0.86, and 0.82 were reported, respectively.

In 2020 Martin-Rodriguez et al. demonstrated that an initial lactate value > 4 significantly increases the 48h mortality prediction of NEWS2 with a score > 3 (from 1.5 to 20% OR 15.75 $p < 0.001$) [54]. In another study performed in an emergency department on 201 patients, Clar et al. [55] demonstrated that amplifying the NEWS2 score with blood glucose, CO_2, and lactate values increased its prognostic accuracy from an AUC of 0.699 $\pm$ 0.05 to 0.727 $\pm$ 0.054. Küçükceran et al. [56] analyzed a population of 244 patients arriving in the

ER with suspected COVID infection and reported that the lactate-amplified NEWS2 score increases its ability to predict in-hospital mortality from an AUC of 0.735 (0.634–0.836) to 0.757 (0.647–0.867).

Our study in the emergency department is the first to evaluate the predictive power of NEWS2 integrated with age and lactates, achieving an accuracy of 73.8% and 71.6% in predicting outcomes at 28 and 90 days in patients with bacterial sepsis, respectively, compared with an accuracy of 69 and 67% using the NEWS2 score alone.

Limitations of the Study

This study was carried out on a large population, there are a number of potential limitations. First, it is a single-center study. Second, a significant percentage of the participants were elderly patients, which leads to a greater number of comorbidities and therefore a greater number of factors influencing the survival of our patients. Third, analysis excluded patients with missing data, reducing the sample size and potentially introducing bias if data were not missing completely at random.

Fourth, the method of analyzing a homogeneous subpopulation and then extending the results to the entire study population must be validated in a larger, more homogeneous population in prospective studies [57].

5. Conclusions

Our study demonstrates that the combination of the NEWS2 score, initial lactate values, and patient age significantly improves the early prediction of short- and long-term mortality in patients with bacterial sepsis presenting to the emergency department. Given the urgency of initiating sepsis bundles at the time of triage, identifying high-risk patients promptly is essential. Since triage nurses typically have access only to clinical parameters and point-of-care data, tools like NEWS2 that are rapid and based solely on vital signs are particularly valuable.

While lactates are commonly associated with tissue hypoperfusion, emerging evidence suggests a broader role in cellular metabolism and organ-specific responses. Our findings confirm that an initial lactate $\geq$ 2 mmol/L is strongly associated with increased mortality at both 28 and 90 days. Importantly, we observed that augmenting NEWS2 with lactate and age (forming a NEWS2-LA model) increased predictive accuracy from 69–67% to 73.8–71.6%.

This model aligns with previous research supporting lactate-enhanced early warning scores and adds novel evidence by evaluating its utility specifically in patients with bacterial sepsis at triage. Given its simplicity and improved prognostic performance, the NEWS2-LA score may be a valuable tool for guiding early clinical decisions in emergency settings, especially where laboratory data are limited.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijtm5040044/s1, Table S1: Percent distributions of prognostic factors in patients by survival status at the 28-day threshold. Z-test for the differences, and Kendall's Tau-b related to survival; Table S2: Percent distributions of prognostic factors in patients by survival status at the 90-day threshold. Z-test for the differences, and Kendall's Tau-b related to survival; Figure S1: Histograms of Age, Lat (T0), and NEWS2 by Survival (Legend: no/yes).

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