Prognostic accuracy of using lactate in addition to the quick Sequential Organ Failure Assessment score and the National Early Warning Score for emergency department patients with suspected infection

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ABSTRACT

Background The aim of this study was to determine whether: (1) the quick Sequential (Sepsis-related) Organ Failure Assessment (qSOFA) and National Early Warning Score (NEWS) clinical prediction tools alone, (2) modified versions of these prediction tools that integrate lactate into their scores, or (3) use of the two tools in tandem with lactate better predicts in-hospital 28-day mortality among adult EDpatients with suspected infection.

Methods From 1 January through 31 December 2018, this retrospective cohort study enrolled consecutive adult patients with suspected infection evaluated at two EDs in France. Patients were included if blood cultures were obtained and non-prophylactic antibiotics were administered in the ED. qSOFA, NEWS criteria and lactate measurements were recorded when patients were clinically suspected of having an infection. Two composite scores (lactate qSOFA (LqSOFA) and lactate NEWS (LNEWS)) integrating lactate were created. Diagnostic test performances for predicting in-hospital mortality within 28days were assessed for qSOFA≥2, LqSOFA≥2, qSOFA≥2 or lactate≥2 mmol/L, and for NEWS≥7, LNEWS≥7, and NEWS≥7 or lactate≥2 mmol/L.

Results 1003 patients were included, 130 (13%) of whom had died by day 28. Sensitivities for 28-day mortality were 50% (95%CI41% to 59%) for qSOFA≥2,69% (95% CI60% to 77%) for LqSOFA≥2,77% (95% CI69% to 84%) for qSOFA or lactate≥2 mmol/L; and 69% (95% CI60% to 77%) for NEWS≥7, 80% (95% CI72% to 86%) for LNEWS≥7, 87% (95% CI80% to 92%) for NEWS≥7 or lactate≥2 mmol/L.

Conclusion Lactate used in tandem with qSOFA or NEWS yielded higher sensitivities in predicting in-hospital 28-day mortality, as compared with integration of lactate into these prediction tools or usage of the tools independently.

Key messages

What is already known on this topic

⇒ Clinical prediction tools such as the quick Sepsis-related Organ Failure Assessment (qSOFA) and the National Early Warning Score (NEWS) have been used for identifying patients with a suspected infection who are more at risk of having unfavourable outcomes. However, their low respective sensitivities make them poor prediction tools of in-hospital mortality.

⇒ Serum lactate measurements may improve mortality prediction, however, the best way of using lactate in combination with these scores is unknown.

What this study adds

⇒ Our study suggests that using blood lactate in tandem with qSOFA score and NEWS improves their respective sensitivities in predicting in-hospital 28-day mortality among patients with suspected infection at risk of sepsis in the ED.

⇒ The study findings also indicate that lactate with these scoring systems does not optimally predict in-hospital 28-day mortality.

How this study might affect research, practice or policy

⇒ Whether blood lactate can be used as a predictor of poor outcomes in conjunction with qSOFA or NEWS in certain prespecified sub-groups of patients requires further research.

BACKGROUND

Early diagnosis and appropriate treatment of sepsis have been shown to reduce mortality from this condition.[1] However, in many patients, the severity of their illness and consequent risk of mortality are not immediately clear upon their presentation to the ED. Several scores have been developed with the aim of early identification of patients at risk of clinical deterioration.[2]

The quickSequential (Sepsis-related) Organ Failure Assessment (qSOFA) scale is recommended by the authors of the Sepsis-3 International Consensus Definitions for identifying patients with a suspected infection at greater risk of having poor outcomes.[1 3] However, although qSOFA is predictive of mortality in ED patients with suspected infection,[4–7] its sensitivity in several meta-analyses[8–10] ranges from 42% to 54%, insufficient for an early screening tool. Thus, the 2021 Surviving Sepsis Campaign guidelines stated that although qSOFA was designed as a predictor of poor outcome, it should not be used as a screening tool for sepsis or septic shock in these patient populations.[11]

The National Early Warning Score (NEWS) was designed to predict clinical deterioration in a wide range of clinical situations.[12] Although it was not meant to predict mortality, several studies have evaluated its use in this way. Using a cut-off value of≥7, the sensitivity of NEWS for predicting 30-day mortality in ED patients who had initiation of intravenous antibiotics and/or collection of any microbiological culture was only 68% in a recent study.[13] In a recent systematic review comparing NEWS and qSOFA for prognosis in suspected sepsis in ED patients, NEWS had a better sensitivity than qSOFA although qSOFA had better specificity.[14]

Lactatemia≥2 mmol/L is predictive of an adverse outcome in patients with suspected infection in EDs, even in the absence of hypotension.[15 16] Several studies have evaluated the association of lactate with qSOFA in predicting unfavourable outcomes, however their methodologies (either integrating lactate in the qSOFA score or using it independently) and results have been heterogeneous.[3 4 17–19] Despite these uncertainties, qSOFA and lactate are frequently used in tandem with each other. Given that qSOFA, NEWS and lactate each have value in predicting mortality in sepsis, it is reasonable that when used together they might synergistically improve mortality prediction. Whether lactate should be integrated into the qSOFA score and NEWS or used in tandem is not yet known. Furthermore, the utility of lactate in the subgroups of patients deemed at low risk according to qSOFA and NEWS is unknown.

The aim of this study was to determine whether: (1) qSOFA and NEWS clinical prediction tools alone, (2) modified versions of these two prediction tools that integrate lactate into their scores (LqSOFA and LNEWS), or (3) use of the two tools in tandem with lactate better predicts in-hospital 28-day mortality among adult EDpatients with suspected infections. Furthermore, we investigated whether a high lactate level is still significantly associated with mortality when controlled for qSOFA score and NEWS, and the usefulness of lactate in subgroups of patients predicted to be at low risk by qSOFA and NEWS.

METHODS

Study design and setting

We performed this retrospective study at two academic hospitals in Le Mans and Angers, France. Both are tertiary care hospitals, and each hospital's ED provided care to approximately 60 000 patients in 2018.

Selection of participants

The study population consisted of consecutive patients with suspected infection evaluated at either ED from 1 January 2018 through 31 December 2018. Patients were identified through electronic laboratory records as having had blood cultures obtained in the ED, then through electronic patient records to determine if a non-prophylactic antibiotic treatment was administered in the ED. Patients were study eligible if both criteria were met. Diagnostic tests and antibiotic treatments are protocol and guideline based, but the clinical decisions ultimately reside with the treating physician. Patients were excluded from the study if a lactate measurement was not obtained in the ED, the patient was taking a drug known to alter lactate metabolism (eg, metformin or antiretrovirals), or the patient was<18 yearsold or under protective measures (eg, wards of the state or another guardianship). Any patient for whom the primary outcome of in-hospital mortality could not be assessed (eg, transfer to another hospital) also was excluded. As the objective of this study was to evaluate the use of clinical prediction scores in the context of the ED, patients with suspected infection in the ED but for whom this diagnosis was not retained at the end of their hospital stay were excluded from the study.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, reporting or dissemination plans of this study.

Data abstraction

We adhered to the Standards for Reporting of Diagnostic Accuracy studies guidelines.[20] Baseline characteristics, medical history, vital signs, laboratory tests and final diagnosis at hospital discharge were abstracted from the electronic health records of each study participant. All variables were anonymised and collected on standardised electronic case report forms (EpiData software, EpiData, Denmark). The electronic case report form was pilot tested on 40 cases before starting the actual study data collection, which allowed for troubleshooting and abstractor training. For data collected that could vary over time (eg,RR), values proximal to the time when suspected infection was diagnosed were recorded. For simplicity, this time was when the first blood cultures were obtained in the ED.

Clinical prediction tools and lactate measurements

Three sets of clinical prediction tools were calculated: qSOFA and NEWS without lactate, qSOFA andNEWS with lactate integrated into the score (LqSOFA, LNEWS), and qSOFA and NEWS with lactate used in tandem (qSOFA or lactate, NEWS or lactate). qSOFA was calculated from participant data using previously defined methodology,[3] as was NEWS.[12]Cut-off scores for qSOFA (≥2) and NEWS (≥7) used for this study were consistent with previous studies[3 4 13] and guidelines.[1 12] In line with published literature,[3 4] a lactate≥2 mmol/L added 1 point to the LqSOFA. A lactate≥2 mmol/L added 3 points to the LNEWS, which is the maximum number of points allotted per criteria in the NEWS scale. However, the cut-off values for LqSOFA and LNEWS were not altered and thus remained the same as the original qSOFA and NEWS (≥2 and≥7, respectively). For the clinical prediction algorithm that used qSOFA or NEWS in tandem with lactate, prediction was positive if the qSOFA score or NEWS was≥its original cut-off value or if lactatemia was≥2 mmol/L. Missing data were imputed as normal in calculating the clinical prediction tool scores (ie, conferred 0 points in each scale).

Primary and secondary outcomes

The primary outcome was in-hospital 28-day all-cause mortality. The secondary outcome was 3-day all-cause mortality and/or the requirement for intensive care unit (ICU) care in the 3 days following ED admission. When the outcome or the final diagnosis was uncertain, adjudication was made by consensus between at least two co-investigators. We based our sample size calculation for this study on the recommendations for external validation studies of prognostic scales,[21] using a lower limit of 100 events (ie,in-hospital deaths by day 28). With an a priori estimated incidence of 10%in-hospital mortality, 1000 participants were needed. Enrolment ended when this sample size had been exceeded.

Statistical analysis

Continuous variables were summarised as the means and SD and as medians with IQRs based on their distribution. Variables of interest were compared against the measured outcomes with the Mann-Whitney test for independent samples. Categorical

variables were expressed as numbers and percentages and were compared against the measured outcomes with the χ^2 test.

To determine the association between lactate and 28-day mortality for different levels of qSOFA scores and NEWS, an analysis of mortality rates for each score stratified by lactate≥2 mmol/L was conducted, as tested by the Cochran-Mantel-Haenszel statistic.

Test performance characteristics (sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios) with corresponding 95%CIs were calculated for the three sets of clinical prediction tools: qSOFA and NEWS, LqSOFA and LNEWS, qSOFA in tandem with lactate and NEWS in tandem with lactate. The discriminative performance of each tool in predicting mortality versus survival was measured using the area under the receiver operating characteristic (AUROC) curve, with corresponding 95% CIs. qSOFA and NEWS also were compared with LqSOFA and LNEWS and qSOFA in tandem with lactate and NEWS in tandem with lactate according to the methodology published by DeLong*et al*.[22] Bonferroni corrections were used and a two-tailed pvalue of <0.017 was considered significant for these analyses. Subset analyses were conducted in the study populations of patients with scores of qSOFA<2 and NEWS<7 to assess the contribution of a lactate≥2 mmol/L in these lower risk groups. We imputed missing values as normal. The statistical analyses were performed with the MedCalc Statistical Software V.18.5 (MedCalc Software, Ostend, Belgium).

RESULTS

Characteristics of study subjects

During the study period, 120 374 patients presented to the twos-study site EDs, of whom 10 669 had blood cultures obtained. After excluding 7562 patients without a lactate measurement, those who did not receive antibiotics and those transferred, 1003 patients were included in the final study sample (figure 1). After analysis of the discharge diagnoses, 185 patients (18.4%, 95% CI16.0% to 20.8%) had a final diagnosis other than infection. Flow diagrams for each index test are presented in the online supplemental figure S1–S6.

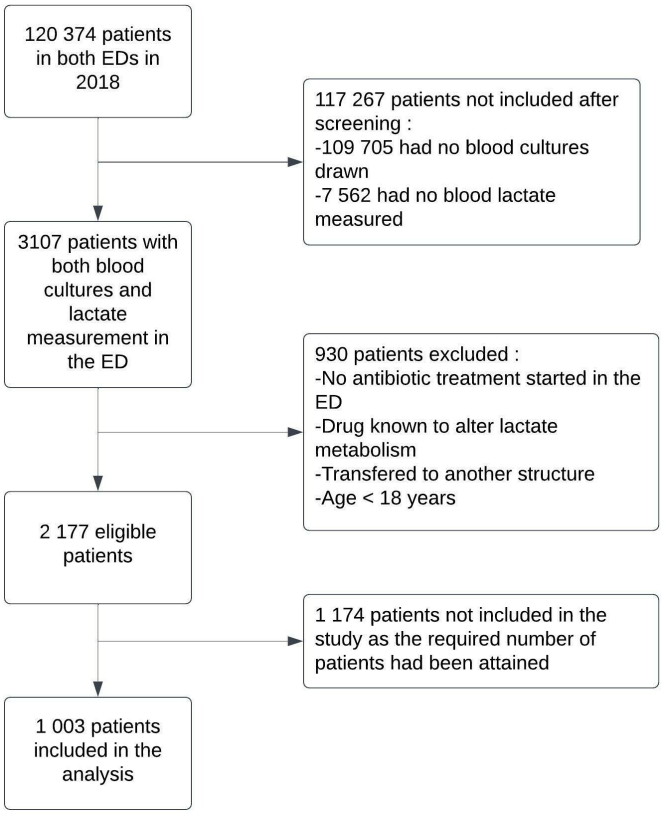

Figure 1 Patient inclusion and exclusion flow diagram.

The majority of participants were older than 75 years and were male (table 1). Seventy-eight patients (7.8%, 95% CI6.1% to 9.4%) died within 72 hours of hospitalisation, and 163 (16.2%, 95% CI14.0% to 18.5%) were hospitalised in ICUs within 72 hours of hospital admission. At 28 days, 130 patients (13.0%, 95% CI10.9% to 15.0%) had died in-hospital.

Prediction of in-hospital mortality and composite outcome of 3-day mortality or ICU admission

Overall population

Univariate analysis showed that non-survivors were significantly older; had a history of cancer or chronic cardiac disease;and had a higher HR andRR, and lower BP, oxygen saturation and temperature. The white cell count, creatinine and lactate were significantly higher among non-survivors (table 1). In-hospital 28-day mortality was highest among patients with a qSOFA≥2 as compared with the other index tests, 28.5% (95% CI22.6% to 34.3%) (online supplemental table S1).

When controlled for severity score, a lactate≥2 mmol/L was independently associated with 28-day mortality for both qSOFA (OR 3.7, 95% CI2.5 to 5.6) and NEWS (OR 4.5, 95% CI3.0 to 6.7). This association was strongest with lower scores: qSOFA score of 0 (OR 7.7, 95% CI2.7 to 22.4), NEWS of 5 or 6 (OR 5.6, 95% CI2.3 to 13.7) (table 2).

As shown in table 3, the highest sensitivities were for qSOFA or NEWS in tandem with lactate. The highest positive predictive valuewas 28% (95% CI24% to 33%), and the highest positive likelihood ratio was 2.68 (95% CI2.15 to 3.34), both for qSOFA. The highest negative predictive valuewas 96% (95% CI94% to 97%), and the lowest negative likelihood ratio was 0.29 (95% CI0.18 to 0.45), both for NEWS in tandem with lactate. These results were similar for the composite outcome of 3-day mortality or ICU admission.

As shown in figure 2, AUROC curves were generally highest for qSOFA and NEWS in tandem with lactate. Pairwise comparisons of qSOFA versus LqSOFA and qSOFA in tandem with lactate showed greater discrimination in predicting mortality. However, discrimination was similar between LqSOFA and qSOFA in tandem with lactate, and was similar in the comparison of NEWS, LNEWS and NEWS in tandem with lactate. These results were consistent in the composite outcome of 3-day mortality or ICU admission for qSOFA, LqSOFA and qSOFA in tandem with lactate. In contrast, LNEWS and NEWS in tandem with lactate had greater discrimination than NEWS alone for this composite outcome.

Low predicted risk populations

Among those with qSOFA<2, 65 patients (8.4%) died within 28 days among whom 35 had an elevated lactate. Among those with a NEWS ≤7, 40 died (7.4%) within 28 days, and 23 had a lactate≥2 mmol/L (online supplemental table S2). Thus, adding an elevated lactate with a low-risk SOFA score increased sensitivity for prediction of 28-day mortality to 54% with a specificity of 80% (table 4),considering lactate plus a NEWS <7 resulted in a sensitivity of 57% and specificity of 80%.

Table 1 Baseline characteristics of study participants

	N missing (%)	All patients	In-hospital 28-day mortality	Alive	Pvalue
N (%)		1003(100)	130(13)	873(87)	
Sex, N (%)					
Male	0	574(57)	68(52)	506(58)	0.22*
Female		429(43)	62(48)	367(42)	
Age, years					
Median (IQR)	0	76 (64–86)	83 (71–90)	75 (62–85)	<0.0001†
N<75 (%)	0	465(46)	41(32)	424(49)	0.0003*
N≥75 (%)		538(54)	89(68)	449(51)	
History of cancer (%)	0	312(31.3)	54(41)	258(30)	0.006*
History of chronic pulmonary disease (%)	0	289(29)	39(30)	250(29)	0.75*
History of chronic cardiac disease (%)	0	204(20)	36(28)	168(19)	0.02*
HR in bpm, median (IQR)	0	98 (84–115)	108 (88–120)	97 (83–113)	0.0008†
SBP in mmHg, median (IQR)	0	125 (106–142)	118 (96–140)	126 (107–143)	0.008†
RR per minute, median (IQR)	136(14)	24 (18–32)	24 (18–30)	30 (23–36)	<0.0001†
Oxygen saturation in %, median (IQR)	0	95 (93–97)	94 (91–97)	96 (94–98)	0.0001†
Supplementary oxygen (%)	0	521(52)	97(75)	424(48)	<0.0001*
GCS<15, n (%)	1(0)	183(18.2)	46(35)	137(16)	<0.0001*
Temperature, median (IQR)	0	38.2 (37.1–38.9)	37.7 (36.6–38.6)	38.2 (37.2–38.9)	0.0001†
qSOFA, median (IQR)	0	1.0 (0–1)	1.5 (1–2)	1.0 (0–1)	<0.0001†
NEWS, median (IQR)	0	6.0 (3.0–8.0)	9.0 (6.0–11.0)	6.0 (3.0–8.0)	<0.0001†
Suspected site of infection, N (%)					
Pulmonary		603(60)	90(60)	513(59)	0.02*
Abdominal		110(11)	19(15)	91(10)	
Urinary		140(14)	11(8)	129(15)	
Skin		50(5)	2(2)	48(5)	
CNS		18(2)	0(0)	18(2)	
Unknown		60(6)	7(5)	53(6)	
Other		22(3)	1(1)	21(2)	
Laboratory measures, median (IQR)					
WBC, 10^9/L	4(0)	12.4 (8.6–17.3)	14.7 (10.6–20.3)	12.0 (8.5–16.8)	0.0002†
Platelet count, g/L	11(1)	223 (164–289)	242 (163–346)	221 (162–280)	0.05†
Creatinine, µmol/L	3(0)	84 (66–127)	107 (76–155)	81 (65–121)	<0.0001†
Bilirubin, µmol/L	10(1)	7.0 (0–15)	7.0 (0–19)	7.0 (0–15)	0.3†
Lactate, mmol/L	0(0)	1.3 (0.9–2.0)	2.3 (1.4–4.2)	1.2 (0.9–1.8)	<0.0001†

*χ^2 pvalue.
†Mann-Whitney test for independent values p value.
bpm, beats per minute; CNS, central nervous system; NEWS, National Early Warning Score; qSOFA, quick Sequential (Sepsis-related) Organ Failure Assessment; SBP, systolic BP; WBC, white blood count.

Table 2 In-hospital 28-day mortality rate stratified by severity score and lactate level

	In-hospital 28-day mortality, N/total per category; % (95% CI)			
	All patients	Lactate<2 mmol/L	Lactate≥2 mmol/L	OR (95% CI)*
Total	130/1003; 13.0 (10.9 to 15.0)	52/722; 7.2 (5.3 to 9.1)	78/281; 27.8 (22.5 to 33.0)	4.9 (3.4to 7.3)
qSOFA				3.7 (2.5 to 5.6)†
0	16/258; 6.2 (3.2 to 9.1)	6/205; 2.9 (0.6 to 5.2)	10/53; 18.9 (8.3 to 29.4)	7.7 (2.7to 22.4)
1	49/517; 9.5 (6.9 to 12.0)	24/398; 6.03 (3.7 to 8.4)	25/119; 21.0 (13.7 to 28.3)	4.1 (2.3to 7.6)
2	54/195; 27.7 (21.4 to 34.0)	20/107; 18.7 (11.3 to 26.1)	34/88; 38.6 (28.5 to 48.8)	2.7 (1.4to 5.2)
3	11/33; 33.3 (17.2 to 49.4)	2/12; 16.7 (0.0 to 37.7)	9/21, 42.8 (21.7 to 64.0)	3.7 (0.6to 21.5)
NEWS				4.5 (3.0 to 6.7)†
0–4	17/327; 5.2 (2.8 to 7.6)	7/253; 2.8 (0.7 to 4.8)	10/74; 13.5 (5.7 to 21.3)	5.5 (2.0to 15.0)
5–6	23/213; 10.8 (6.6 to 15.0)	10/164; 6.1 (2.4 to 9.8)	13/49; 26.5 (14.2 to 38.9)	5.6 (2.3to 13.7)
≥7	90/463; 19.4 (15.8 to 23.0)	35/305; 11.5 (7.9 to 15.0)	55/158; 34.8 (27.4 to 42.2)	4.1 (2.5to 6.7)

*OR for in–hospital 28-day mortality taking into account lactate level.
†Pooled ORs for qSOFA and NEWS for in-hospital mortality taking into account lactate level.
NEWS, National Early Warning Score; qSOFA, quick Sequential (Sepsis-related) Organ Failure Assessment.

Table 3 Test characteristics for each score at the predefined cut-off points

Criteria	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR− (95% CI)
In-hospital 28-day mortality						
qSOFA≥2	50 (41to 59)	81 (79to 84)	28 (24to 33)	92 (90to 93)	2.68 (2.15to 3.34)	0.61 (0.52to 0.73)
LqSOFA≥2	69 (60to 77)	71 (67to 74)	26 (23to 29)	94 (92to 95)	2.35 (2.02to 2.74)	0.44 (0.34to 0.57)
qSOFA≥2 or lactate≥2 mmol/L	77 (69to 84)	66 (62to 69)	25 (23to 27)	95 (93to 96)	2.24 (1.96to 2.55)	0.35 (0.26to 0.48)
NEWS≥7	69 (60to 77)	57 (54to 60)	19 (17to 22)	93 (91to 94)	1.62 (1.41to 1.86)	0.54 (0.41to 0.70)
LNEWS≥7	80 (72to 86)	51 (48to 55)	20 (18to 21)	94 (92to 96)	1.64 (1.47to 1.83)	0.39 (0.28to 0.55)
NEWS≥7 or lactate≥2 mmol/L	87 (80to 92)	46 (42to 50)	19 (18to 21)	96 (94to 97)	1.60 (1.47to 1.76)	0.29 (0.18to 0.45)
Composite endpoint of 3-day mortality or ICU admission						
qSOFA≥2	38 (31to 44)	82 (79to 84)	38 (33to 43)	81 (80to 83)	2.07 (1.66to 2.59)	0.76 (0.68to 0.85)
LqSOFA≥2	57 (51to 64)	72 (69to 75)	38 (34to 42)	85 (83to 87)	2.06 (1.76to 2.42)	0.59 (0.50to 0.69)
qSOFA≥2 or lactate≥2 mmol/L	64 (57to 70)	67 (64to 70)	37 (34to 40)	86 (84to 88)	1.95 (1.70to 2.25)	0.54 (0.45to 0.64)
NEWS≥7	54 (47to 60)	56 (53to 60)	27 (24to 30)	80 (78to 83)	1.23 (1.06to 1.42)	0.82 (0.70to 0.96)
LNEWS≥7	67 (61to 73)	51 (48to 55)	29 (27to 32)	84 (81to 87)	1.39 (1.24to 1.56)	0.63 (0.52to 0.77)
NEWS≥7 or lactate≥2 mmol/L	75 (69to 80)	47 (43to 50)	29 (27to 32)	86 (83to 90)	1.41 (1.27to 1.55)	0.53 (0.42to 0.67)

ICU, intensive care unit; LNEWS, lactate National Early Warning Score; LqSOFA, lactate quick Sequential (Sepsis-related) Organ Failure Assessment; LR−, negative likelihood ratio; LR+, positive likelihood ratio; NEWS, National Early Warning Score; NPV, negative predictive value; PPV, positive predictive value; qSOFA, quick Sequential (Sepsis-related) Organ Failure Assessment.

DISCUSSION

This study assessed whether the predictive capabilities of qSOFA and NEWS can be increased with the use of lactate, either integrated in the score or in tandem, among patients presenting to the ED with suspected infection. Our findings suggest that a measured lactate≥2 mmol/L increases the likelihood of mortality at all levels of both qSOFA and NEWS. Furthermore, the most effective way of using lactate is in tandem with qSOFA or NEWS, as opposed to integrating lactate into these scores. However, the performance characteristics of any of these combinations of tests could preclude useful clinical implementation.

One way in which a clinical prediction tool is helpful is if it identifies patients more likely to have an unfavourable outcome and thus prompts an intervention to prevent such an outcome, especially in time-critical situations such as sepsis. Therefore, minimising the number of missed cases is a priority, and several authors have argued that a clinical prediction tool for sepsis should favour'sensitivity, even at the expense of specificity'.[5 23] Our results concur with the growing literature suggesting that qSOFA≥2 alone (sensitivity 50% in this study) is insufficient to predict unfavourable outcomes in ED patients with suspected sepsis,[8–10] and acts more as a severity assessment score.[11 24] NEWS≥7 alone, with a sensitivity of 69% in our study, suffers from the same predicament. In our study, the sensitivity of both scores was increased when used in tandem with lactate. Still, the improved sensitivity for qSOFA in tandem with lactate to 77% (95% CI69% to 84%) is inadequate. NEWS in tandem with lactate had a sensitivity of 87% for in-hospital 28-day mortality, which although not perfect, outperforms the most commonly used screening tools.[8–10] This result should be validated prospectively with a broader patient population before it is applied in clinical practice.

A clinical prediction tool can also be useful by ruling out an unfavourable outcome, thus preventing unnecessary resource consumption (eg, an ICU bed) or prompting early de-escalation of costly or invasive procedures. In our study, qSOFA or NEWS, with or without lactate, was inadequate for this indication, and we cannot recommend either as 'rule-out' tests based on these results.

The use of lactate with qSOFA≥2 performed significantly better than qSOFA≥2 alone for discriminating between survivors and non-survivors at day 28, whether lactate was integrated into the score or used in tandem. The association of lactate with NEWS≥7, either in the LNEWS or when used in tandem, did not significantly improve the discriminative performance when compared with NEWS≥7 alone. This reflects the fact that the gains in sensitivity when associating lactate to NEWS≥7 were offset by the loss in specificity. In prior studies, NEWS consistently outperforms qSOFA in the ED as a predictor of death or ICU admission among patients with suspected infection.[14] In contrast, in our study, when comparing the two clinical prediction tools using their typical cut-offs, the AUROC curve for the NEWS was lower than that for the qSOFA score. As AUROC curves are not dependent on outcome prevalence, this difference is due to another clinical variability. In particular, our population is relatively elderly and comorbid, factors which could independently influence mortality. This suggests that qSOFA may perform better than NEWS in a more fragile population.

Several other studies have evaluated the contribution of using lactate with qSOFA, with conflicting results. In the original qSOFA study by Seymour *et al*, lactate was not integrated into the qSOFA score because it did not meet the prespecified statistical thresholds for the derivation model.[3] However, these investigators conducted a post hoc analysis that added 1 point to the score for an elevated lactate in a subset of patients. The resulting analysis showed a statistically significant but clinically irrelevant increase in the discriminative performance for in-hospital 28-day mortality of qSOFA. In a prospective multicentre study by Freund *et al* among ED patients with an infection, the addition of lactate to qSOFA did not improve the discriminative performance for in-hospital mortality over qSOFA alone.[4] A retrospective cohort study by Mellhammar *et al* showed similar results.[17] Sinto *et al* performed a similar analysis in a limited-resource ED in Indonesia and found the discriminative performance for predicting in-hospital mortality was significantly higher when lactate was associated with qSOFA as compared with qSOFA alone.[19]

Shetty *et al* compared qSOFA and LqSOFA in a retrospective cohort study of merged datasets of 12 555 patients, with a composite outcome of in-hospital death or ICU stay≥72 hours and found that LqSOFA performed better than qSOFA alone.[25] Baumann *et al* evaluated the screening abilities of qSOFA in combination with lactate for an outcome of ICU stay, vasopressor use or death within 72 hours of presentation to the ED for suspected infection and found that the sensitivity of qSOFA≥2 in tandem with lactate≥2 mmol/L was greater than either qSOFA or lactate alone.[18] These results suggest

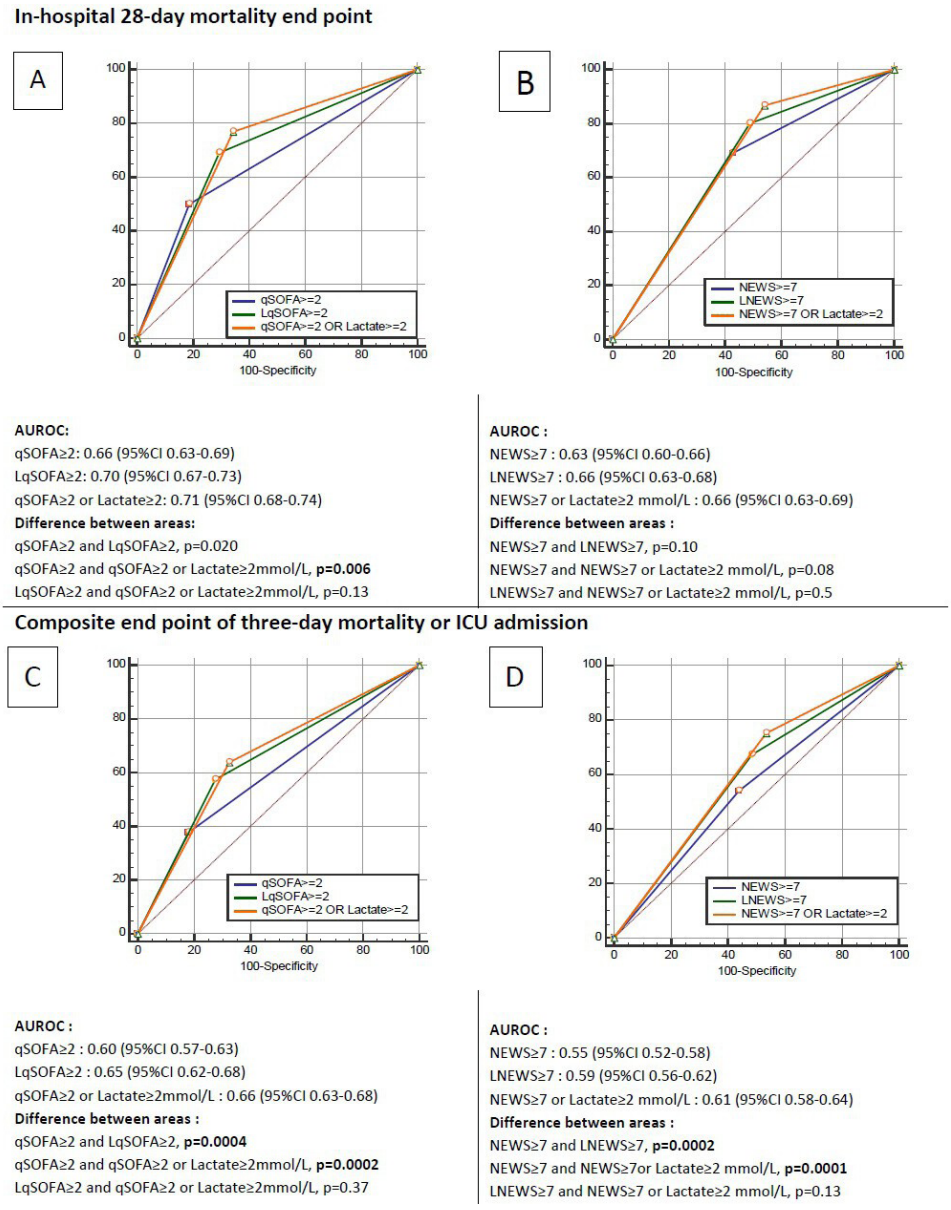

Figure 2 ROC curve analysis for primary and secondary endpoints. (A) Comparison of qSOFA≥2, LqSOFA≥2, and qSOFA≥2 or lactate≥2 mmol/L for in-hospital mortality.(B) Comparison of NEWS≥7, LNEWS≥7, and NEWS≥7 or lactate≥2mmol/L for in-hospital mortality.(C) Comparison of qSOFA≥2, LqSOFA≥2, and qSOFA≥2 or lactate≥2 mmol/L for 3-day mortality or ICU admission.(D) Comparison of NEWS≥7, LNEWS≥7, and NEWS≥7 or lactate≥2mmol/L for 3-day mortality or ICU admission. AUROC, area under the receiver operating characteristic; ICU, intensive care unit; LNEWS, lactate National Early Warning Score; LqSOFA, lactate quick Sequential (Sepsis-related) Organ Failure Assessment; NEWS, National Early Warning Score; qSOFA, quick Sequential (Sepsis-related) Organ Failure Assessment; ROC, receiver operating characteristic.

Table 4 Test characteristics for lactate≥2 mmol/L in the predefined low-risk subgroups of qSOFA≤2 and NEWS≤7

Criteria	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR− (95% CI)	AUROC (95% CI)
In-hospital 28-day mortality endpoint							
qSOFA<2 AND lactate≥2 mmol/L	54 (41to 66)	80 (78to 83)	20 (16to 25)	95 (94to 96)	2.79 (2.13to 3.66)	0.57 (0.44to 0.75)	0.67 (0.64to 0.70)
NEWS<7 ANDlactate≥2 mmol/L	57 (41to 73)	80 (76to 83)	19 (14to 24)	96 (94to 97)	2.88 (2.09to 3.96)	0.53 (0.37to 0.76)	0.69 (0.65to 0.73)
Composite endpoint of 3-day mortality or ICU admission							
qSOFA<2 AND lactate≥2 mmol/L	42 (34to 50)	82 (79to 85)	35 (29to 41)	86 (84to 88)	2.37 (1.83to 3.06)	0.71 (0.61to 0.81)	0.62 (0.59to 0.65)
NEWS<7 ANDlactate≥2 mmol/L	46 (36to 56)	83 (79to 86)	40 (33to 47)	86 (84to 88)	2.71 (2.02to 3.63)	0.65 (0.54to 0.78)	0.65 (0.60to 0.67)

AUROC, area under the receiver operating characteristic; LR+, positive likelihood ratio; LR−, negative likelihood ratio; NEWS, National Early Warning Score; NPV, negative predictive value; PPV, positive predictive value; qSOFA, quick Sequential (Sepsis-related) Organ Failure Assessment.

that using qSOFA and lactate measurements in tandem is the better strategy.

The few studies that have evaluated the contribution of using lactate with NEWS in the ED for patients with suspected infection support our conclusions. Jo *et al* compared NEWS alone with a score created from the sum of NEWS and the measured lactate (in mmol/L) named NEWS-L.[26] In a subset of patients with suspected infection, the AUROC curve of NEWS-L was significantly higher than that of NEWS. Hargreaves *et al* demonstrated that in patients with suspected sepsis and a persistently elevated NEWS ≥5 during prehospital ambulance triage, ED and ward admission, an elevated ED lactate≥2 mmol/L was associated with increased 30-day mortality.[27]

Lactate has also demonstrated its ability to predict mortality independently of hypotension.[15 16] In this study, for the subsets of patients with a predictive score under the predefined thresholds, a serum lactate level≥2 mmol/L identified more than 50% of patients with an unfavourable outcome who would otherwise have been missed. Similarly, in the study by Seymour *etal*, the addition of a lactate level≥2 mmol/L in patients with a qSOFA of 1 identified patients with a risk profile similar to those with a qSOFA of 2.[3] Although far from perfect, these results must be balanced against the rapidity and accessibility of lactate testing in many centres. Associated with careful clinical profiling, that is, identification of patients at risk of deterioration despite normal vital signs and thus normal risk scores, lactate measurements could be used for further risk stratification.

Study limitations

As a retrospective study, there are inherent risks of selection bias, documentation and classification errors. We did not perform 'double' coding by independent investigators. However, we did pilot test the electronic case report form before actual data collection was commenced to limit the risk of collection error. Only patients who had a plasma lactate measurement in the ED were enrolled, which constitutes a selection and diversity bias. Patients with a more severe presentation or in respiratory distress would be more likely to have a lactate measurement taken. We defined suspected infection as patients who had both blood cultures obtained, and non-prophylactic antibiotic treatment administered in the ED. Lower severity patients could thus have been excluded from the study. This definition has been used in other sepsis-related studies.[3 13]

There was a high rate of missing data; the most affected variable being the RR (14%), which is an integral part of the qSOFA score. We imputed missing values as normal, which could constitute information bias and underestimate the qSOFA score and NEWS. This choice was made because of the non-random nature of the missing data: it is more probable that normal data would not be collected than abnormal data. Simply excluding these patients would have thus created a risk of confounding by severity. Furthermore, more complex data substitution methods (such as multiple imputation) are likely less reliable when the missing data are not missing at random.[28]

CONCLUSION

Among patients presenting to the ED with suspected infection, this study suggests that the addition of lactate to either qSOFA or NEWS improves their sensitivity for mortality, and should be used in tandem as opposed to integrating lactate into the scores. Even with this addition, qSOFA and NEWS yielded performance characteristics that were suboptimal for predicting in-hospital mortality within 28 days.

Contributors JJ—collection, analysis and interpretation of data, and manuscript preparation. DD—analysis and interpretation of data, and critical revision of the manuscript. M-SM—collection, analysis and interpretation of data, and manuscript preparation. J-CC—study concept and design, analysis and interpretation of data, drafting the manuscript and manuscript preparation. J-CC is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the ethics committee of both hospitals. According to the French law, the French national data protection commission authorised a waiver of informed consent due to the retrospective nature of the study (CNIL: Commission Nationale de l'Informatique et des Libertés), under the reference number 919452.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets of this study are available upon reasonable request from the corresponding author.

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REFERENCES

1 SingerM, DeutschmanCS, SeymourCW, *et al*. The third International consensusdefinitions for sepsis and septicshock (Sepsis-3). *JAMA*2016; 315: 801–10.
2 RhodesA, EvansLE, AlhazzaniW, *et al*. Surviving sepsiscampaign: internationalguidelines for management of sepsis and septicshock: 2016. *Crit Care Med*2017; 45: 486–552.
3 SeymourCW, LiuVX, IwashynaTJ, *et al*. Assessment of clinicalcriteria for sepsis: for the third International consensusdefinitions for sepsis and septicshock (Sepsis-3). *JAMA*2016; 315: 762–74.
4 FreundY, LemachattiN, KrastinovaE, *et al*. Prognostic accuracy of Sepsis-3 criteria for in-hospitalmortalityamongpatientswithsuspectedinfectionpresenting to the emergencydepartment. *JAMA*2017; 317: 301–8.
5 AskimÅsa, MoserF, GustadLT, *et al*. Poor performance of quick-SOFA (qSOFA) score in predicting severe sepsis and mortality - a prospective study of patients admitted with infection to the emergency department. *ScandJ TraumaResuscEmergMed*2017; 25: 56.
6 SMOBA, SørensenRH, DessauRBC. Prognostic accuracy of qSOFA in predicting 28-day mortality among infected patients in an emergency department: a prospective validation study. *Emerg Med J*2019; 36: 722–8.
7 González Del CastilloJ, Julian-JiménezA, González-MartínezF, *et al*. Prognostic accuracy of SIRS criteria, qSOFA score and GYM score for 30-day-mortality in older non-severely dependent infected patients attended in the emergency department. *Eur J Clin Microbiol Infect Dis*2017; 36: 2361–9.
8 JiangJ, YangJ, MeiJ, *et al*. Head-to-head comparison of qSOFA and SIRS criteria in predicting the mortality of infected patients in the emergency department: a meta-analysis. *Scand J Trauma Resusc Emerg Med*2018; 26: 56.
9 FernandoSM, TranA, TaljaardM, *et al*. Prognostic accuracy of the quicksequentialorganfailureassessment for mortality in patientswithsuspectedinfection: asystematicreview and meta-analysis. *Ann Intern Med*2018; 168: 266–75.
10 LiuY-C, LuoY-Y, ZhangX, *et al*. Quick sequentialorganfailureassessment as a prognostic factor for infected patients outside the intensive care unit: a systematic review and meta-analysis. *Intern Emerg Med*2019; 14: 603–15.

11 EvansL, RhodesA, AlhazzaniW, *et al*. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med*2021; 49: e1063–143.
12 RCP London. National Early Warning Score (NEWS) 2 [Internet], 2017 . Available: https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2 [Accessed 25 Mar 2019].
13 BrinkA, AlsmaJ, VerdonschotRJCG, *et al*. Predicting mortality in patients with suspected sepsis at the emergency department; a retrospective cohort study comparing qSOFA, SIRS and national early warning score. *PLoS One*2019; 14: e0211133.
14 SabirL, RamlakhanS, GoodacreS. Comparison of qSOFA and hospitalearlywarningscores for prognosis in suspected sepsis in emergency department patients: a systematic review. *Emerg Med J*2022; 39: 284-294https://emj.bmj.com/content/early/2021/08/16/emermed-2020-210416
15 ParkYJ, KimDH, KimSC, *et al*. Serum lactate upon emergency department arrival as a predictor of 30-day in-hospital mortality in an unselected population. *PLoS One*2018; 13: e0190519.
16 HowellMD, DonninoM, ClardyP, *et al*. Occult hypoperfusion and mortality in patients with suspected infection. *Intensive Care Med*2007; 33: 1892–9.
17 MellhammarL, LinderA, TverringJ, *et al*. NEWS2 is superior to qSOFA in detectingsepsis with organdysfunction in the emergencydepartment. *J Clin Med*2019; 8 . doi: 10.3390/jcm8081128 . [Epub ahead of print: 29 07 2019].
18 BaumannBM, GreenwoodJC, LewisK, *et al*. Combining qSOFA criteria with initial lactate levels: improved screening of septic patients for critical illness. *Am J Emerg Med*. In Press2020; 38: 883–9.
19 SintoR, SuwartoS, LieKC, *et al*. Prognostic accuracy of the quick Sequential Organ Failure Assessment (qSOFA)-lactate criteria for mortality in adults with suspected bacterial infection in the emergency department of a hospital with limited resources. *Emerg Med J*2020; 37: 363–9.
20 BossuytPM, ReitsmaJB, BrunsDE, *et al*. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ*2015; 351: h5527.
21 CollinsGS, OgundimuEO, AltmanDG. Sample size considerations for the external validation of a multivariable prognostic model: a resampling study. *Stat Med*2016; 35: 214–26.
22 DeLongER, DeLongDM, Clarke-PearsonDL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*1988; 44: 837–45.
23 UsmanOA, UsmanAA, WardMA. Comparison of SIRS, qSOFA, and NEWS for the early identification of sepsis in the emergencydepartment. *Am J Emerg Med*2019; 37: 1490–7.
24 MachadoFR, NsutebuE, AbDulazizS, *et al*. Sepsis 3 from the perspective of clinicians and quality improvement initiatives. *JCrit Care*2017; 40: 315–7.
25 ShettyA, MacDonaldSP, WilliamsJM, *et al*. Lactate ≥2 mmol/L plus qSOFA improves utility over qSOFA alone in emergency department patients presenting with suspected sepsis. *Emerg Med Australas*2017; 29: 626–34.
26 JoS, YoonJ, LeeJB, *et al*. Predictive value of the National earlywarning Score-Lactate for mortality and the need for critical care among General emergency department patients. *J Crit Care*2016; 36: 60–8.
27 HargreavesDS, de CarvalhoJLJ, SmithL, *et al*. Persistently elevated early warning scores and lactate identifies patients at high risk of mortality in suspected sepsis. *Eur J Emerg Med*2020; 27: 125–31.
28 HughesRA, HeronJ, SterneJAC, *et al*. Accounting for missing data in statistical analyses: multiple imputation is not always the answer. *Int J Epidemiol*2019; 48: 1294–304.

Supplementary Appendix

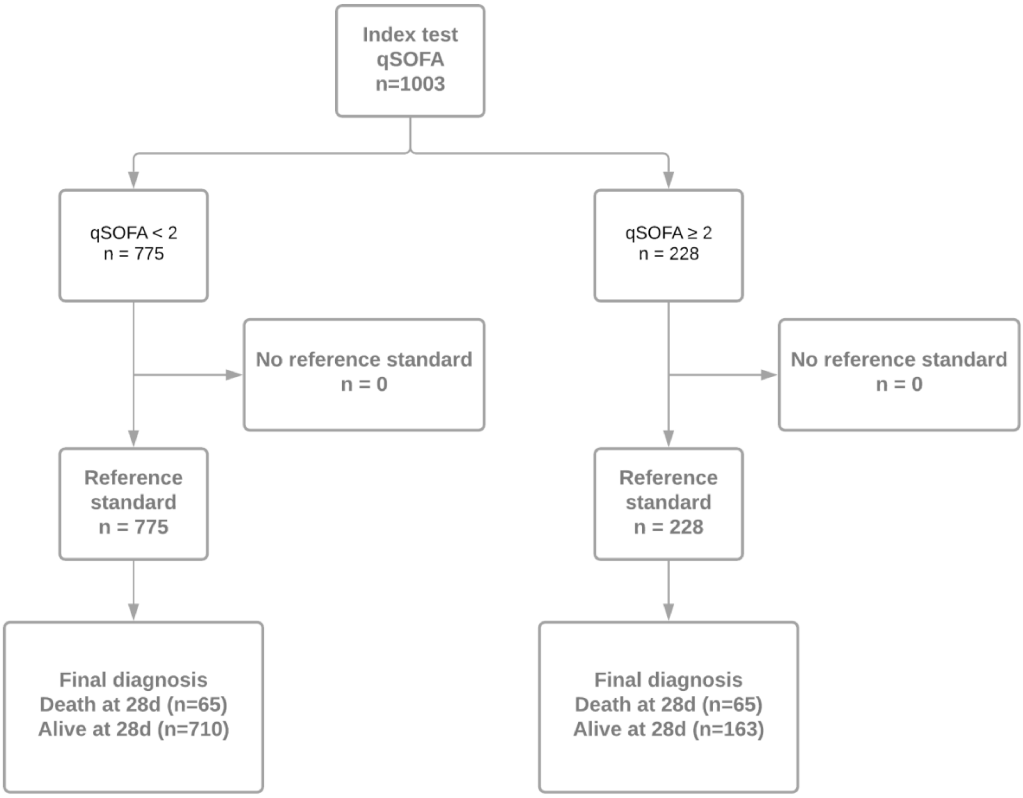

Figure S1: Flow diagram for qSOFA ≥ 2.

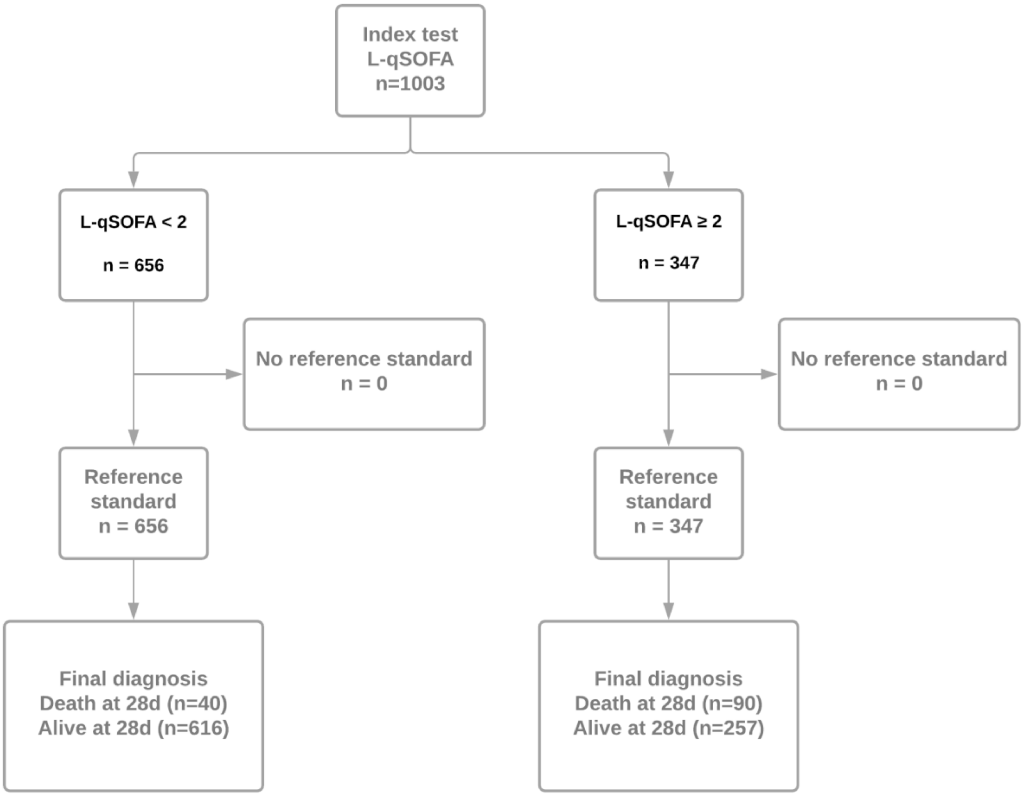

Figure S2: Flow diagram for LqSOFA ≥ 2.

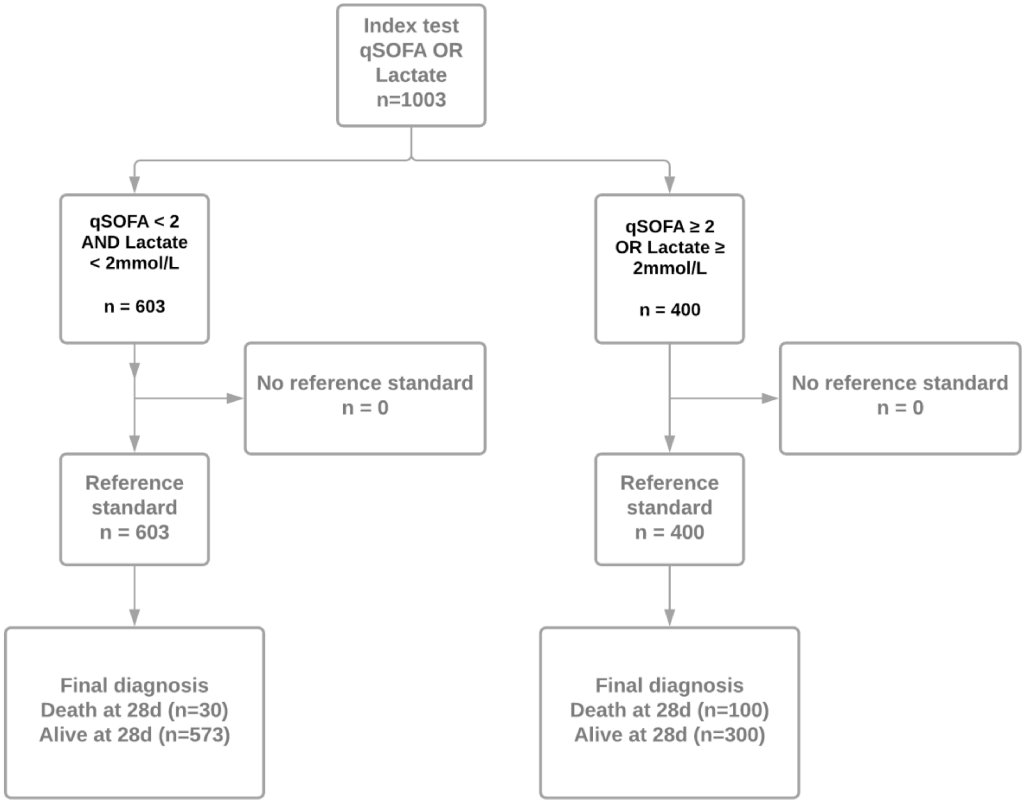

Figure S3: Flow diagram for qSOFA ≥ 2 OR Lactate ≥ 2 mmol/L.

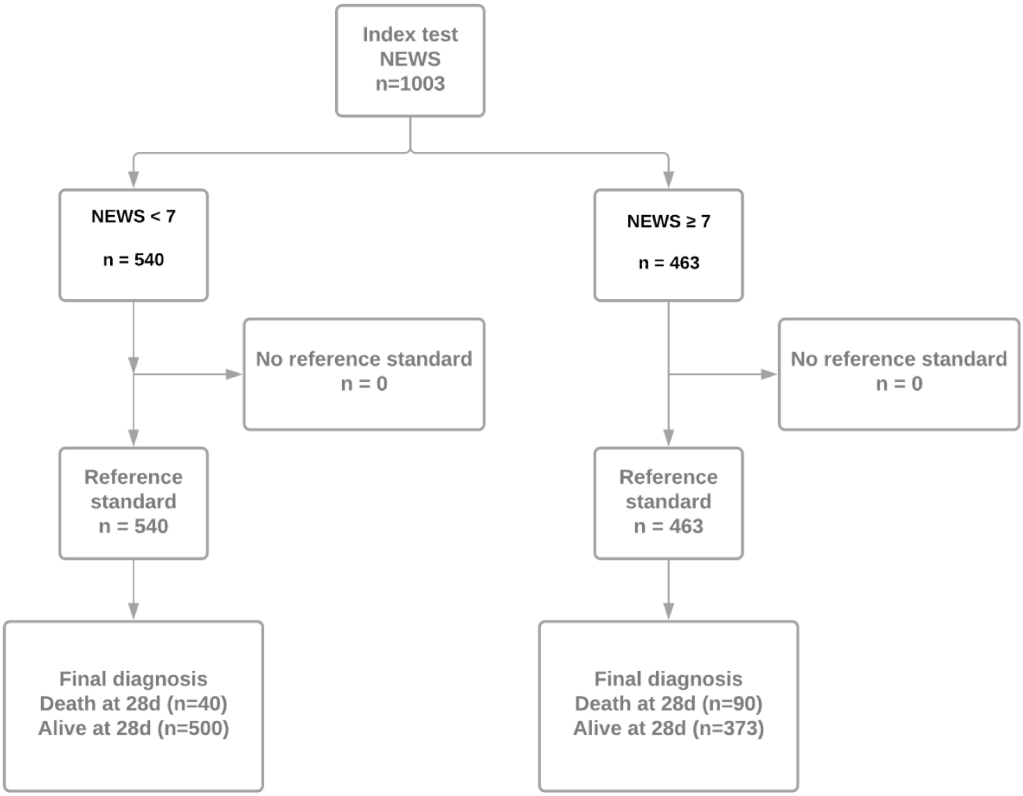

Figure S4: Flow diagram for NEWS ≥ 7.

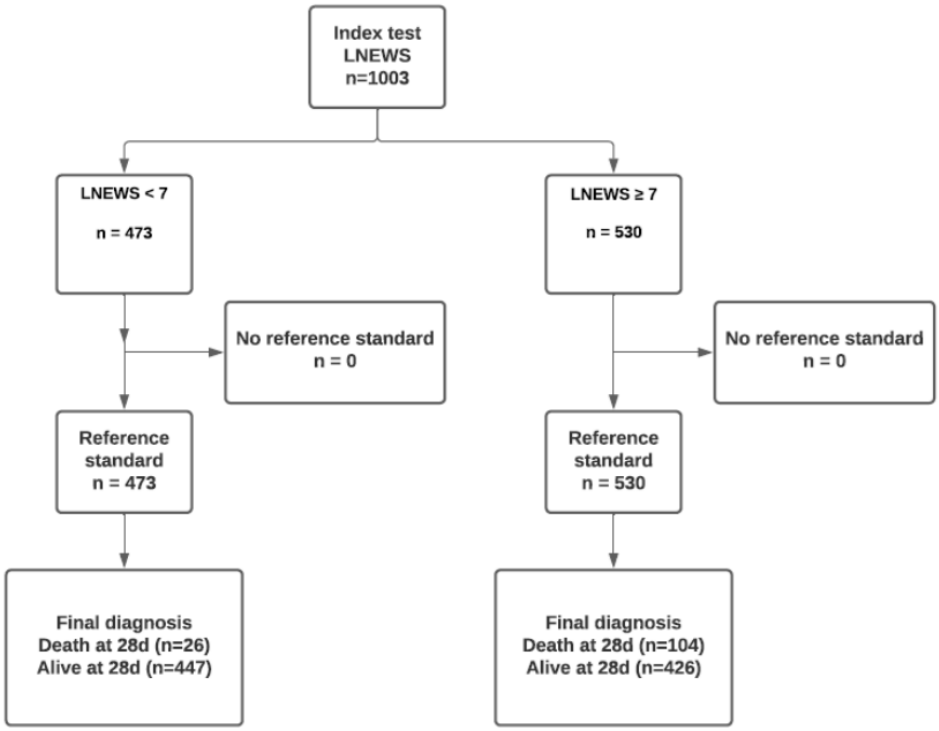

Figure S5: Flow diagram for LNEWS ≥ 7.

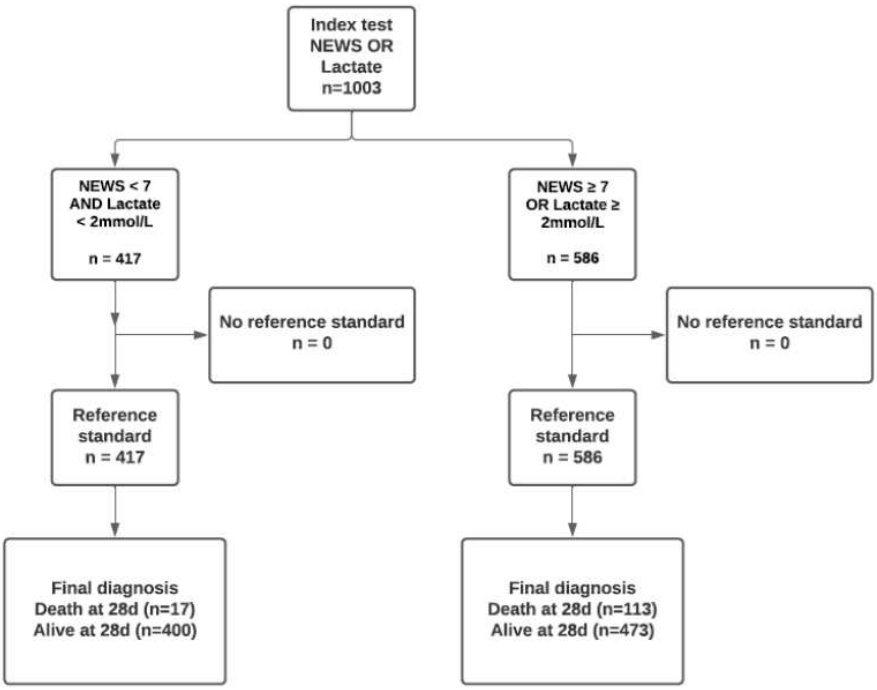

Figure S6: Flow diagram for NEWS ≥ 7 OR Lactate ≥ 2 mmol/L.

Table S1: Primary and secondary outcomes among patients meeting each index test criteria

Index Test		Total, N (%)	In-hospital 28-day mortality, N; % (95% CI)	Composite outcome, N; % (95% CI)
qSOFA≥2	**+**	228 (22.7)	65; 28.5 (22.6-34.3)	87; 38.1 (31.8-44.5)
	-	775 (77.3)	65; 8.4 (6.4-10.3)	143; 18.4 (15.7-21.2)
LqSOFA≥2	**+**	347 (34.6)	90; 25.9 (21.3-30.5)	132; 38.0 (32.9-43.1)
	-	656 (65.4)	40; 6.1 (4.3-7.9)	98; 14.9 (12.2-17.7)
qSOFA≥2 or lactate≥2mmol/L	**+**	400 (39.9)	100; 25.0 (20.7-29.2)	147; 36.7 (32.0-41.5)
	-	603 (60.1)	30; 4.9 (3.2-6.7)	83; 13.8 (11.0-16.5)
NEWS≥7	**+**	463 (46.2)	90; 19.4 (15.8-23.0)	124; 26.8 (22.7-30.8)
	-	540 (53.8)	40; 7.4 (5.2-9.6)	106; 19.6 (16.3-23.0)
LNEWS≥7	**+**	530 (52.8)	104; 19.6 (16.2-23.0)	155; 29.2 (25.4-33.1)
	-	473 (47.1)	26; 5.5 (3.4-7.5)	75; 15.8 (12.6-19.1)
NEWS≥7 or lactate≥2mmol/L	**+**	586 (58.4)	113; 19.3 (16.1-22.5)	173; 29.5 (25.8-33.2)
	-	417 (41.6)	17; 4.1 (2.2-6.0)	57, 13.7 (10.4-17.0)

+: patients meeting the index test criteria; **-:** patients not meeting the index test criteria; **qSOFA:** quick Sequential Organ Failure Assessment; **LqSOFA:** Lactate quick Sequential Organ Failure Assessment**,** **NEWS:** National Early Warning Score; **LNEWS:** Lactate National Early Warning Score

Table S2: Primary and secondary outcomes in prespecified low risk groups according to lactate level

Index test		Total, N (%)	In-hospital 28-day mortality, N; % (95% CI)	Composite outcome, N; % (95% CI)
qSOFA<2		775 (100)	65; 8.4 (6.4-10.3)	143; 18.4 (15.7-21.2)
and Lactate≥2mmol/L	**+**	172 (22.2)	35; 20.3 (14.3-26.4)	60; 34.9 (27.8-42.0)
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+: patients with lactatemia ≥ 2 mmol/L; **-:** patients with lactatemia < 2 mmol/L; **qSOFA:** quick Sequential Organ Failure Assessment; **NEWS:** National Early Warning Score

Supplementary Appendix

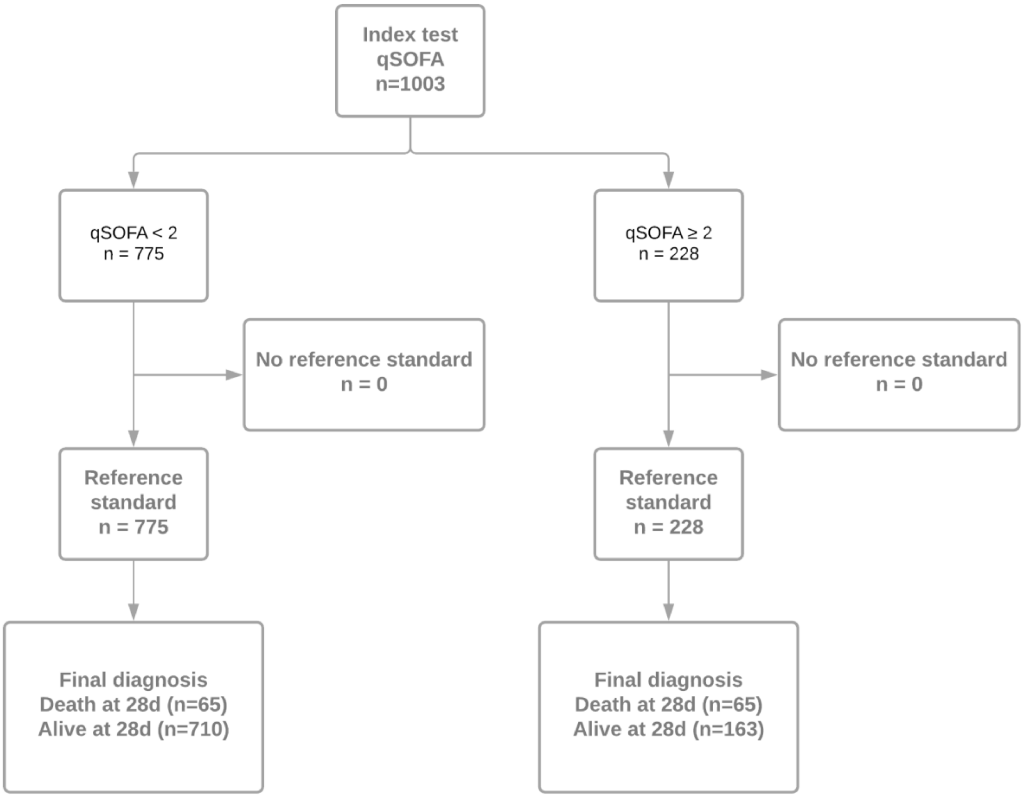


Figure S1: Flow diagram for qSOFA ≥ 2.

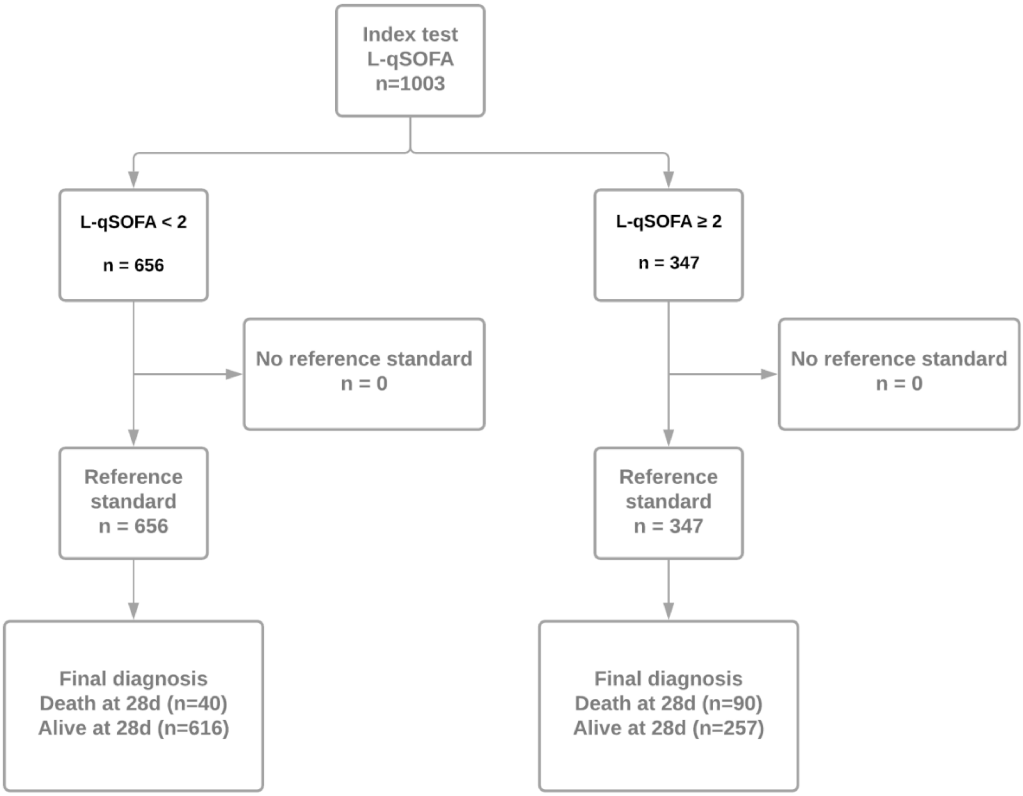


Figure S2: Flow diagram for LqSOFA ≥ 2.

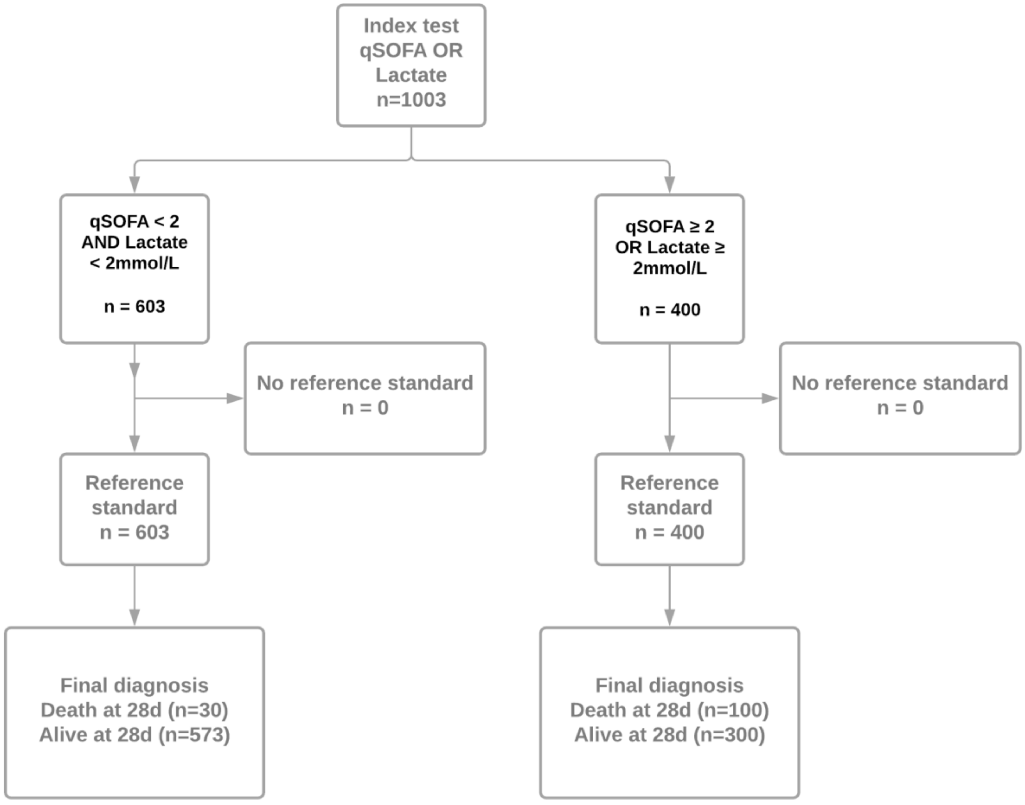


Figure S3: Flow diagram for qSOFA ≥ 2 OR Lactate ≥ 2 mmol/L.

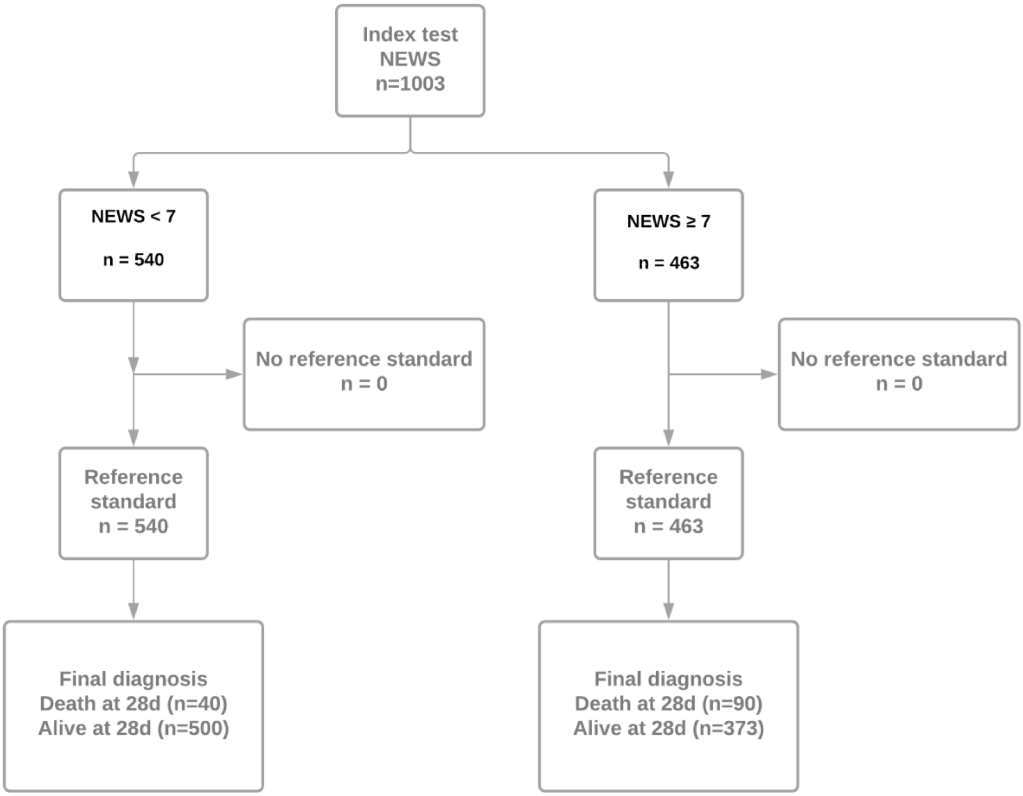


Figure S4: Flow diagram for NEWS ≥ 7.

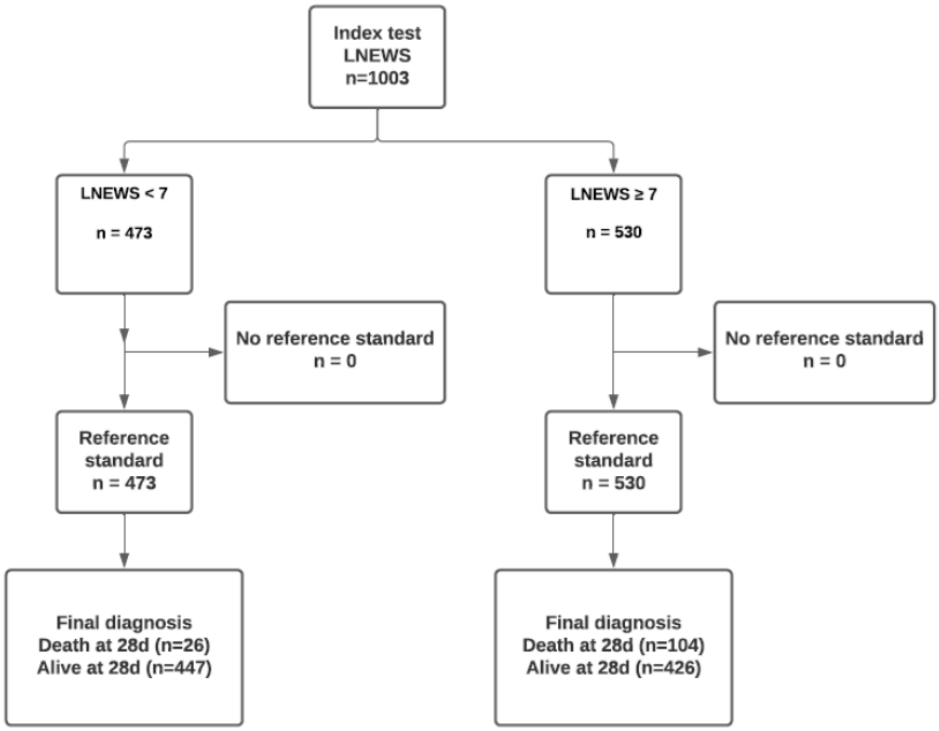
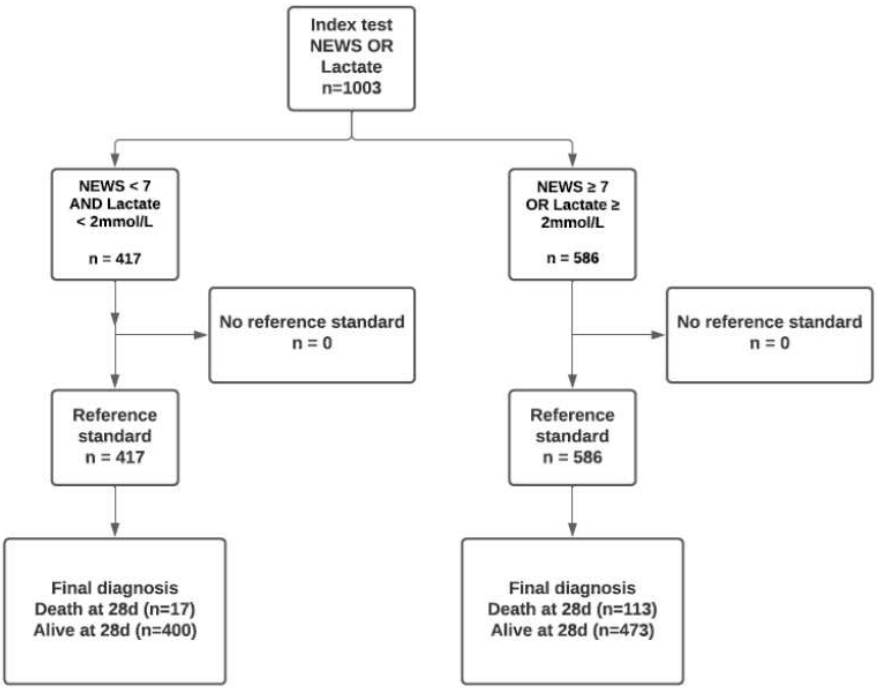


Figure S5: Flow diagram for LNEWS ≥ 7.



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