Persistently elevated early warning scores and lactate identifies patients at high risk of mortality in suspected sepsis

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Objective In the UK, the National early warning score (NEWS) is recommended as part of screening for suspicion of sepsis. Is a change in NEWS a better predictor of mortality than an isolated score when screening for suspicion of sepsis?

Methods A prospectively gathered cohort of 1233 adults brought in by ambulance to two UK nonspecialist hospitals, with suspicion of sepsis at emergency department (ED) triage (2015–2017) was analysed. Associations with 30-day mortality and ICU admission rate were compared between groups with an isolated NEWS ≥ 5 points prehospital and those with persistently elevated NEWS prehospital, in ED and at ward admission. The effect of adding the ED (venous or arterial) lactate was also assessed.

Results Mortality increased if the NEWS persisted ≥ 5 at ED arrival 22.1% vs. 10.2% [odds ratio (OR) 2.5 (1.6–4.0); $P < 0.001$]. Adding an ED lactate ≥ 2 mmol/L was associated with an increase in mortality greater than for NEWS alone [32.2% vs. 13.3%, OR 3.1 (2.2–4.1); $P < 0.001$], and increased ICU admission [13.9% vs. 3.7%,

OR 3.1 (2.2–4.3); $P < 0.001$]. If NEWS remained ≥ 5 at ward admission (predominantly within 4 h of ED arrival), mortality was 32.1% vs. 14.3%, [OR 2.8 (2.1–3.9); $P < 0.001$] and still higher if accompanied by an elevated ED lactate [42.1% vs. 16.4%, OR 3.7 (2.6–5.3); $P < 0.001$].

Conclusion Persistently elevated NEWS, from prehospital through the ED to the time of ward admission, combined with an elevated ED lactate identifies patients with suspicion of sepsis at highest risk of in-hospital mortality. *European Journal of Emergency Medicine* XXX: 000–000 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

European Journal of Emergency Medicine 2019, XXX:000–000

Keywords: ambulance, early warning score, lactate, lactic acid, hospital mortality, National early warning score, screening, sepsis, suspicion of sepsis

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Received 27 April 2019 Accepted 17 July 2019

Introduction

Mortality rates for sepsis remain high, and reported incidence is increasing [1,2]. The concept of ‘suspicion of sepsis’ [3] is central to the recently published UK National Institute for Health and Care Excellence (NICE) guidelines [4]. Identifying which patients with ‘suspicion of sepsis’ are at high risk of deterioration remains a challenge [5,6]. NHS England and The Association of Ambulance Chief Executives recommend the National early warning score (NEWS) as a prehospital screen for this purpose but without significant empirical evidence to support this [7]. Although the Sepsis-3 task force suggested qSOFA as an in-hospital screening tool [8], there is limited evidence evaluating its use in the prehospital environment [9]. eFigures 1 and 2, Supplemental digital content 1, <http://links.lww.com/EJEM/A256> detail NEWS and a comparison with qSOFA parameters for reference. NICE advocates use of NEWS in the emergency department (ED)

and in hospital [4]. However, the significance of early warning scores (EWS) is likely to differ depending on the environment they are measured in [10]. Previous studies have demonstrated, as with any clinical measurement, the trend at reassessment is probably more useful [2].

For patients with ED identified ‘suspicion of sepsis’ transported by emergency medical services (EMS), this study aimed to assess whether change in NEWS (measured prehospital and ED) better predicted mortality and ICU admission than individual scores taken in isolation. We also assessed whether the addition of a third time point (NEWS on ward admission) improved mortality prediction, and whether the addition of a lactate measured at ED arrival (ED lactate) increased mortality prediction alone or in combination with NEWS.

Methods

Study design and setting

A dual-centre cohort study combined prospective data collection with a retrospective notes review over 2 years (2015–2017) in two UK nonspecialist hospitals. The

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hospitals are part of the same Hospital Trust with 870 beds, 22 ICU beds and a combined annual ED attendance of over 135 000. UK EMS approaches to sepsis alerting vary regionally with the South-East Coast Ambulance Service (SECAMB), which covers the study population, using a 'suspicion of sepsis' alert, combining expert opinion and national guidelines. In addition, on arrival at the study ED, all patients undergo a 'suspicion of sepsis' screen by the triage ED nurse consisting of 3 stages: (1) suspicion of infection based on presenting history; (2) ambulance and triage assessment; (3) either ≥ 2 systemic inflammatory response syndrome (SIRS) criteria as previously suggested [11], or since 1st March 2016, following updated Sepsis-3 definitions [1], a NEWS ≥ 5 points [12]. eFigures 1 and 2, Supplemental digital content 1, <http://links.lww.com/EJEM/A256> detail the current NEWS scoring and a comparison with qSOFA parameters for reference. The study centre uses a trigger threshold for urgent review set at NEWS ≥ 5 points.

Population and data

Adult patients (≥ 18 years) were included only if brought in by ambulance and identified as 'suspicion of sepsis' at ED triage. Cases were prospectively entered into a database by the departmental administration team having presented ED triage positive for 'suspicion of sepsis' as described above. Those patients subsequently finally coded as not septic or infected were included in the data as the objective was to stratify mortality within the ED and at ward admission, before final clinical diagnosis had been confirmed (eFigures 3 and 4, Supplemental digital content 1, <http://links.lww.com/EJEM/A256>).

Routinely measured observational parameters, which comprise the NEWS, were recorded in the Ambulance and ED notes prospectively. Venous (or arterial) lactate values are routinely measured in the ED and recorded in the notes. Five researchers (D.H., L.H., L.C., L.S. and G.P.) with no involvement in direct care of the cases reviewed records using ambulance and ED notes and the hospitals' electronic observations system (Patientrack, NSW, Australia), to extract the following: diagnosis, ED lactate, and observations prehospital, ED and at admission to the ward (throughout the study period for $>90\%$ of patients this was within 4 h of ED attendance). The study data comprised anonymised data recorded in the medical record as part of routine patient care and HRA ethical approval and patient consent for the study were not deemed necessary (IRAS ID: 214461).

Outcomes and analysis

Primary outcome was death within 30 days of admission, as recorded in the hospital database. Thirty-day mortality is routinely recorded by the hospital for all admissions. Those patients discharged before day 30 are checked by administrative staff against death registers and GP records before being recorded as alive. Secondary

outcome was need for ICU admission. Cases with persistently elevated NEWS ≥ 5 from either prehospital to ED or persisting at all three points were compared with those cases whose NEWS resolved to <5 points on ED arrival. The effect of adding ED lactate on outcomes was also assessed. Continuous data were summarised as median with interquartile range [IQR] and the Mann–Whitney U test used to compare variables. Pearson's Chi-squared was used to test for differences between categorical variables [odds ratio (OR) and associated 95% confidence interval]. Logistic regression was used to assess whether change in NEWS and ED lactate were independent mortality predictors when analysed alongside other clinical information. SPSS version 25 (IBM Corporation, Somers, New York, USA) was used for data analysis.

STROBE reporting guidance was followed in this observational study (eFigure 5, Supplemental digital content 1, <http://links.lww.com/EJEM/A256>) [13]

Results

A total of 1592 cases were identified and after removal of duplicates ($n = 58$), all cases not brought in by ambulance (i.e. walk-ins) ($n = 133$), and incomplete ambulance observation data ($n = 168$), a final cohort of 1233 cases were analysed. eFigure 3, Supplemental digital content 1, <http://links.lww.com/EJEM/A256> describes cohort selection.

The cohort ($n = 1233$) demographics, past medical history, presentation and outcomes are summarised in Table 1. Thirty-day mortality for the cohort was 19% ($n = 229$). An ED lactate was measured in 93% (1074/1233) of the cohort and a value ≥ 2 mmol/L was associated with higher mortality [27.8% vs. 13.3%, OR 2.6 (1.9–3.5); $P < 0.001$], increased ICU admission [11.4% vs. 3.8%, OR 3.2 (2.0–5.2); $P < 0.001$] and bacteraemia [22.5% vs. 13.4%, OR 1.9 (1.4–2.6); $P < 0.001$].

Primary outcome of 30-day mortality was higher in those cases with a NEWS ≥ 5 points prehospital [19.6% vs. 11.9%, OR 1.8 (1.1–3.0); $P < 0.05$]. Persistence of NEWS ≥ 5 at successive time points was associated with increased mortality (Fig. 1). For cases with NEWS ≥ 5 prehospital and in the ED ($n = 1074$) mortality was 22.1% vs. 10.2% [OR 2.5 (1.6–4.0); $P < 0.001$]. If the NEWS remained ≥ 5 at ward admission for the group with a prehospital NEWS ≥ 5 ($n = 1015$), mortality rose further [32.1% vs. 14.3%, OR 2.8 (2.1–3.9); $P < 0.001$].

Persistence of NEWS ≥ 5 from prehospital to the ED had a sensitivity of 81.7% (76.0–86.5%) for mortality and specificity of 34.2% (31.2–37.2%). If NEWS ≥ 5 persisted at admission to the ward, the specificity for mortality increased to 73.5% (70.5–76.5%) while sensitivity reduced to 51.1% (44.4–57.7%). Diagnostic value of NEWS ≥ 5 measured at different time points for 30-day mortality are summarised in Table 2.

Table 1 Patient demographics, past medical history, presentation and outcomes for whole cohort

Demographics	Total cohort n = 1233	
Male ^a	669	(54%)
Age (years) ^b	79	[68–86]
Past medical history ^a		
Congestive cardiac failure	193	(17%)
Diabetes mellitus	307	(26%)
Vascular disease	308	(26%)
Liver disease	37	(34%)
Organ failure		
Lactate (mmol/L) ^c	2.2	(±1.7)
AKI ^d	63	(7%)
NEWS ^b		
Prehospital	8	[6–10]
ED	6	[4–8]
Ward admission	3	[2–6]
Outcomes		
Mortality at 30 days	229	(19%)
Intensive care admission	80	(6%)
Bacteraemia	207	(17%)
Length of stay (days) ^b	6	[3–12]
Coding		
Sepsis	189	(23%)
Infection	895	(80%)
Suspected source in ED ^e		
Respiratory	541	(44%)
Urinary	188	(15%)
Skin/soft tissue	48	(4%)
Suspected source not documented in ED record	408	(33%)
Abdominal/pelvic	37	(3%)
Central nervous system	3	(<1%)
Musculoskeletal	2	(<1%)
Head and neck/dental	4	(<1%)
Neutropenia	1 ^f	(<1%)

^aCount (%).^bMedian [interquartile range, IQR].^cMean ± SD.^dAKI, acute kidney injury (KDIGO increase in creatinine >1.5 baseline).^eED, emergency department.^fNeutropenic sepsis usually directly admitted to haematology/oncology ward.

An ED lactate ≥ 2 mmol/L, in addition to the persistence of NEWS ≥ 5 prehospital and in the ED, was associated with an increase in mortality, increasing further if NEWS remained ≥ 5 at ward admission (Table 3). The addition of an elevated ED lactate to NEWS measured prehospital and in the ED reduced the sensitivity for 30-day mortality to 55.1% (47.8–62.1%) but increased specificity to 71.6% (68.4–74.7%). When ED lactate was added to NEWS ≥ 5 at all three time points, sensitivity for mortality was 34.9% (28.2–41.9%) and specificity was 87.4% (84.8–89.7%). The effect of adding an ED Lactate on diagnostic value of NEWS ≥ 5 for 30-day mortality is summarised in Table 4.

Secondary outcome of ICU admission was 6% ($n = 80$) for the cohort. In the group with a NEWS ≥ 5 prehospital and in the ED, ICU admission also increased [8.3% vs. 1.8%, OR 5.0 (1.8–13.8); $P < 0.001$], rising further with the addition of an ED lactate ≥ 2 mmol/L [13.9% vs. 4.8%, OR 3.2 (1.9–5.4); $P < 0.001$].

Logistic regression was performed using backward stepwise selection starting with 11 variables including age, change in NEWS, ED lactate, past medical history and acute kidney injury (AKI). Only NEWS ≥ 5 persisting at

all three time points, ED lactate, age, congestive cardiac failure and AKI were found to be independent predictors of 30-day mortality

Discussion

In the setting of ‘suspicion of sepsis, this dual-centre study is the first, to the authors knowledge, to assess NEWS in the prehospital environment and to look at change over successive time points through the admission (ED and ward). Our findings suggest that in this context, persistently deranged physiology reflected by a NEWS ≥ 5 points from prehospital to the ED to the ward is associated with an increased risk of mortality and critical care admission. The risk of these adverse outcomes increased further when combined with an elevated ED lactate. These findings are consistent with others smaller studies looking at ICU admissions with sepsis [14] and other studies have emphasised the importance of changes in score when using NEWS [2].

The focus of recent improvement efforts for sepsis care has been to attempt to prevent advanced sepsis developing [3]. This necessarily must be balanced against the need for antimicrobial stewardship [15]. However, differentiating those at highest risk remains problematic [6]. Initial studies evaluating the qSOFA tool proposed by Sepsis-3 raised concerns regarding adequate sensitivity in setting where treatment is regarded as time critical [16–18]. This continues to be debated, with a more recent study reporting greater prognostic accuracy for in-hospital mortality than did either SIRS or severe sepsis criteria [19]. More recently, Lemachatti *et al.* have evaluated the significance of the change in qSOFA scoring with time as a stratification tool for mortality [20] concluding that early variation of qSOFA in the first 3 h of ED care was significantly and independently associated with in-hospital mortality. As with qSOFA, there are few studies prospectively evaluating NEWS in the prehospital setting. Most recently, a large multicentre prospective study reported the association of initial prehospital qSOFA > 2 with in hospital mortality and ICU stay > 72 h [9].

A recent very large observational study found that NEWS outperformed qSOFA for prediction of in-hospital mortality, regardless of the presence of infection [21]. NEWS rather than qSOFA [22] remains the recommended tool in the UK for screening in ‘suspicion of sepsis’. NEWS has been suggested as a tool providing a ‘common language’ [23] along the chain of care from prehospital to ward, but it is likely to be more challenging to discern the significantly unwell ‘suspicion of sepsis’ group with use of an isolated NEWS. Our study is the first to look at the prognostic potential in the setting of ‘suspicion of sepsis’ of the change in an EWS across the range of timepoints from prehospital through the ED to the ward.

Our findings suggest incorporation of the change in NEWS with ED lactate could be helpful in risk-stratifying in the

Fig. 1

^a 1st comparison Pre-hospital (n=1233)

^b 2nd comparison (in ED) included cohort who had initial pre-hospital NEWS ≥ 5 (n=1074)

^c 3rd comparison (Ward) included cohort who had initial pre-hospital NEWS ≥ 5 and were admitted to the ward, excluding ICU admissions (n=1015)

Thirty-day mortality associated with persistent elevation of NEWS ≥ 5 points.

busy ED to appropriately focus resources. In ‘suspicion of sepsis’, our study showed that elevation of NEWS ≥ 5 prehospital and in the ED was a sensitive screen pre-hospital (92%) and in the ED (82%) for 30-day mortality. With an elevated ED lactate, specificity increased to 72%. If this group continued to have an elevated NEWS at ward admission, NEWS and ED lactate combined had high specificity (87%) for a group with a high mortality (42%), similar to the mortality of the group identified with a worsening qSOFA at 3 h by Lemachatti *et al.* [20]. This has implications for the ED in highlighting a group with infection, who should arguably be considered

for a critical care review in the ED, and immediately on the ward if this has yet to take place. Conversely, for the group where the appropriate ceiling of care is deemed to be the ward, identification of a high-risk group at hospital admission could allow setting of clear parameters of escalation and focus of resources in the busy admissions ward environment.

Our study suggests that change in NEWS and ED lactate could be useful in identifying those patients more likely to require a critical care admission. Of note, ICU admissions for the whole cohort was relatively low (6%), which

Table 2 Diagnostic value of National early warning score ≥ 5 measured at different time points for 30-day mortality in patients with ‘suspicion of sepsis’

Statistic	NEWS ≥ 5 prehospital (n = 1074/1233)			NEWS ≥ 5 prehospital + ED (n = 848/1074)		NEWS ≥ 5 prehospital + ED + ward admission (n = 364/1074)	
	Value	95% CI		Value	95% CI	Value	95% CI
Sensitivity	91.7%	87.3–94.9%		81.7%	76.0–86.5%	51.1%	44.4–57.7%
Specificity	13.9%	11.9–16.2%		34.2%	31.2–37.2%	73.5%	70.5–76.3%
Positive likelihood ratio	1.1	1.0–1.1		1.2	1.2–1.3	1.9	1.6–2.3
Negative likelihood ratio	0.6	0.4–0.9		0.5	0.4–0.7	0.7	0.6–0.8
Positive predictive value	19.6%	18.8–20.3%		22.1%	20.8–23.4%	32.1%	28.6–35.9%
Negative predictive value	88.1 %	82.4–92.1%		89.1 %	86.0–91.6%	86.0%	84.2–87.5%

CI, confidence interval; ED, emergency department; NEWS, National early warning score.

Table 3 For all cases with National early warning score ≥ 5 prehospital, influence of lactate and interaction with subsequent National early warning score ≥ 5 on 30-day mortality in patients with suspicion of sepsis

Comparisons	Mortality		Odds ratio (95% CI)	P
NEWS ≥ 5 prehospital and lactate ^a ≥ 2 (n = 1005)	Yes ^b 29.3% (n = 115/393)	No ^b 13.6% (n = 83/612)	2.6 (1.9–3.6)	<0.001
NEWS ≥ 5 prehospital + in ED + lactate ≥ 2 (n = 1005)	Yes ^b 32.2% (n = 109/338)	No ^b 13.3% (n = 89/667)	3.1 (2.2–4.3)	<0.001
NEWS ≥ 5 prehospital + ED + ward admission ^c + lactate ≥ 2 (n = 951)	Yes ^b 42.1% (n = 69/164)	No ^b 16.4% (n = 129/787)	3.7 (2.6–5.3)	<0.001

CI, confidence interval; ED, emergency department; NEWS, National early warning score.

^aLactate (mmol/L) measured in ED (arterial or venous).^bYes/no denotes presence or absence of NEWS/lactate score in grey bar rather than mortality here.^cPatients admitted to ward, excluding ICU admissions, and patients with no recorded ward NEWS on admission.

may be multifactorial. First, the UK has a significantly lower number of ICU beds than many European countries [24] which may lead to restricted access. Second, the cohort had a high median age (79) typical of the South coast of the UK. It is likely that the critically ill in the ED who were for aggressive care would have been escalated to ICU at this time point. Previous studies have suggested that a high proportion of sepsis deaths are not directly attributable to the acute infection, instead representing an end of life process in a frail cohort [25–27]. Nevertheless, identifying a cohort at very high risk of death could allow discussions to be initiated around whether palliative approaches would be more valid than aggressive invasive management, where appropriate.

Recent attempts have been made to develop a prognostic model for septic patients on admission to hospital [28]. Our study suggests two simple variables, potentially automatable at ED and ward level, which could create an alert upon admission for a high-risk cohort with ‘suspicion on sepsis’. There are two potential advantages of early identification: first, early critical care intervention and restoration of perfusion pressure is an explicit goal of the latest Surviving Sepsis Campaign bundles [29] and delayed ICU admission has been associated with worse outcomes [30,31]. Second, interventions that combine electronic decision support tools with existing care bundles may enhance antimicrobial stewardship in the management of suspected sepsis [32], including timely de-escalation. The shift towards a resolving NEWS ≤ 5 combined with an ED lactate < 2 mmol/L identifies a

group at lower risk of mortality, who could be considered for early clinical review that could include consideration of de-escalation or in some cases cessation of antibiotics where appropriate, as well as supporting decisions over location of care, including early discharge, for example.

Of note, although in this cohort coded diagnosis of infection in patients with ‘suspicion of sepsis’ was 80%, the final coded diagnosis of sepsis was only 23%. This mismatch between physician diagnosis and coding has been well documented [33]. Furthermore, approximately 20% of suspected infections were therefore not finally diagnosed as having infective pathology.

Limitations

First, our conclusions are limited by the observational nature of the study, including partly retrospective retrieval of information. Second, we did not compare the care patients received. Our outcomes may therefore have been affected by differing volumes of fluid resuscitation or time to antibiotic administration prehospital and in the ED. Limitations of the data recorded in the trust electronic records may affect the conclusions about NEWS: we did not, for example, assess prevalence of COPD or cognitive disorders in the groups, and differences in these may have confounded results; we were also not able to analyse changes in lactate with repeat measurements to assess lactate shift [34] recommended in the latest Surviving Sepsis Campaign bundles. As the study period spanned a change in sepsis definitions, ‘suspicion of sepsis’ screening criteria changed midway

Table 4 For all patients with prehospital National early warning score ≥ 5 , diagnostic value of National early warning score ≥ 5 with added emergency department lactate measurement, for 30-day mortality in patients with ‘suspicion of sepsis’

Statistic	NEWS ≥ 5 prehospital + lactate ^a ≥ 2 (n = 393/1005 lactate ≥ 2)		NEWS ≥ 5 prehospital + ED + lactate ≥ 2 (n = 338/1005)		NEWS ≥ 5 prehospital + ED + ward admission + lactate ≥ 2 (n = 164/951)	
	Value	95% CI	Value	95% CI	Value	95% CI
Sensitivity	58.1%	50.9–65.0%	55.1%	47.8–62.1%	34.9%	28.2–41.9%
Specificity	65.6%	62.2–68.8%	71.6%	68.4–74.7%	87.4%	84.8–89.7%
Positive likelihood ratio	1.7	1.5–2.0	1.9	1.6–2.3	2.8	2.1–3.6
Negative likelihood ratio	0.6	0.5–0.8	0.6	0.5–0.7	0.8	0.7–0.8
Positive predictive value	29.3%	25.2–32.5%	32.3%	28.7–36.0%	42.1%	35.7–48.7%
Negative predictive value	86.4%	84.3–88.3%	86.7%	84.7–88.4%	83.6%	82.1–85.0%

CI, confidence interval; ED, emergency department; NEWS, National early warning score.

^aLactate (mmol/L) measured in ED (arterial or venous).

during the study period from likely infection plus SIRS ≥ 2 to likely infection plus NEWS ≥ 5 , which may have altered the cohort. However, given that blood results are not available at nurse triage, the observations required for positive SIRS criteria during screening closely approximate with observations required for a NEWS ≥ 5 (eFigure 6, Supplemental digital content 1, <http://links.lww.com/EJEM/A256>). Although using NEWS ≥ 5 might also be a limitation as it does not directly correspond to a screening tool in suspicion of sepsis such as qSOFA, it is a pragmatic choice given the trust already operates a policy of review at this threshold, and observations are also closely approximated with those required for positive qSOFA (eFigure 2, Supplemental digital content 1, <http://links.lww.com/EJEM/A256>). Other limitations include missing data, and that entry of observations from prehospital and ED notes may have been subject to measurement bias. Although persistently elevated NEWS combined with an elevated ED lactate at ward admission was associated with a high risk of mortality, it is not clear how many of these cases had reversible pathology. Although ED administrative staffs were blinded to the study, selection bias due to reliance on staff setting aside screened patient notes for entry into the database may have occurred. We excluded patients with missing prehospital observations from the main analysis, although incidences of mortality, primary coded diagnosis of sepsis and infection were similar to the main cohort. Finally, the study was performed in an area with an elderly demographic that may limit generalisability.

Conclusion

Persistently elevated NEWS, from prehospital through the ED to the time of ward admission, combined with an elevated ED lactate identifies patients with suspicion of sepsis at highest risk of mortality, and could be used to allow focused management in the acute hospital setting.

Acknowledgements

D.H. and L.H. conceived the study. D.H., L.H. and R.V. designed the analysis. D.H. wrote the first draft of the article. R.V. and L.H. assisted with writeup. D.H., G.P., L.S. and J.C. extracted data from notes. All authors have read and approved the article.

The authors are indebted to Mark Dennis for electronic database extraction, and Dr. Colin Dewar for oversight and support with access to the ED data.

Ethics: The study data comprised anonymised data recorded in the medical record as part of routine patient care and HRA approval for the study was sought (IRAS ID: 214461) but deemed not necessary. In line with standard practice, patient consent for this observational retrospective anonymised analysis was also deemed unnecessary.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data Sharing: Data can be obtained from the corresponding author in accordance with NHS information governance regulations.

Conflicts of Interest

There are no conflicts of interest.

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