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Combination of the National Early Warning Score (NEWS) and inflammatory biomarkers for early risk stratification in emergency department patients: results of a prospective, multi-national, observational study

Short title: Inflammatory blood markers improve the predictive value of NEWS

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ABSTRACT

Objectives: The National Early Warning Score (NEWS) helps to estimate mortality risk in emergency department (ED) patients. This study aimed to investigate whether the prognostic value of the NEWS at ED admission could be further improved by adding inflammatory blood markers (i.e. white blood cell count (WBC), procalcitonin (PCT), and MR-ProAdrenomedullin (MR-proADM).

Design: Secondary analysis of a multinational, prospective, observational study. (TRIAGE study, March 2013 to October 2014)

Setting: Three tertiary care centers in France, Switzerland, and the USA.

Participants: A total of 1303 adult medical patients with complete NEWS data seeking ED care were included in the final analysis. NEWS was calculated retrospectively based on admission data.

Main outcome measures: The primary outcome was all-cause 30-day mortality. Secondary outcome was ICU admission. We used multivariate regression analyses to investigate associations of NEWS and blood markers with outcomes and area under the receiver operating curve (AUC) as a measure of discrimination.

Results: Of the 1303 included patients, 54 (4.1%) died within 30 days. The NEWS alone showed fair prognostic accuracy for all-cause 30-day mortality (AUC 0.73), with a multivariate adjusted odds ratio (OR) of 1.26 (95% CI 1.13–1.40, p<0.001). The AUCs for the prediction of mortality using the inflammatory markers WBC, PCT, and MR-proADM were 0.64, 0.71, and 0.78, respectively. Combining NEWS with all three blood markers or only with MR-proADM clearly improved discrimination with an AUC 0.82 Combining the three inflammatory markers with NEWS improved risk stratification with regard to ICU admission compared to NEWS alone from AUC 0.70 vs. 0.65.

Conclusion: NEWS is helpful in risk stratification of ED patients and can be further improved by the addition inflammatory blood markers. Future studies should investigate whether risk stratification by NEWS in addition to biomarkers improve site-of-care decision in this patient population.

Trial registration number: ClinicalTrials.gov; Identifier: NCT01768494

ARCTICLE SUMMARY

Strength and limitations of this study

- This is the first multinational study investigating the association of the National Early Warning Score (NEWS) and adverse outcomes at emergency department (ED) admission.
- This is the first study evaluating additional impact of inflammatory biomarkers on NEWS.
- Due to its design as a secondary analysis of an observational study, results are at best hypothesis generating.
- There is the possibility of a selection bias due to exclusion of patients with missing vital status data.

INTRODUCTION

With increasingly overwhelmed emergency departments (ED), it is vital that well-validated risk stratification systems are implemented to rapidly identify and efficiently respond to patients at risk since delays in treatment may result in poor outcomes [1, 2]. At the same time, risk stratification systems should ensure reliable identification of patients who may not need urgent care. Risk scores such as the pneumonia severity index (PSI) for patients presenting with pneumonia [3] or the Global Registry of Acute Coronary Events (GRACE) risk score for patients with myocardial infarction are applicable mainly to specific patient populations [4].

Emerging data suggest that in unselected medical patients presenting to the ED, early warning scores (i.e., track-and-trigger systems) are gaining importance for risk stratification and that their usage for this purpose may exceed that of classical triage tools such as the Manchester Triage System (MTS) [5, 6]. Of the numerous early warning scores (EWS) that have been investigated for this purpose, the National Early Warning Score (NEWS) may be the best evaluated and most widely used [6]. It was originally developed in the United Kingdom by the Royal College of Physicians to standardize and improve detection of patients at risk for deterioration, with the routine recording of a minimum of physiological parameters [7, 8]. Multiple studies have revealed its superiority over other risk stratification tools with regard to prediction of mortality [6, 9]. Since its introduction in 2012, NEWS has been validated and widely implemented in different patient populations [5, 10-12] worldwide [5, 11, 13-16]. It has also been used recently for early risk stratification in unselected ED patients and has shown promise in the prediction of mortality [6]. Moreover, the Royal College of

Physicians now recommends its use in EDs in its updated NEWS 2 report issued in 2017 [7]. However, risk stratification at this early stage in patient care immediately following presentation to the ED is challenging due to lack of clinical information. Moreover, NEWS and other triage scores are based on vital signs and represent a patient's clinical state at a single timepoint when vital signs are frequently still unremarkable, as a consequence of which they may miss patients at risk.

The use of blood markers assessed at the time of ED presentation may add prognostic information [17] and even improve the prognostic value of early warning scores. Although investigations trying to improve the discriminative value of NEWS by combining different markers such as serum lactate [12, 16] or D-dimer [18] with NEWS have been undertaken, their results are contradictory. This may be due to inadequate selection of blood markers. The inflammatory blood marker procalcitonin (PCT) is a marker for bacterial infections. It has been employed for stewardship of antibiotic therapy [19] and has been shown to improve risk assessment in different patient populations such as those with sepsis [20] or malignant disease [21], and in patients at cardiovascular risk [22]. Adrenomedullin (ADM) is a potent vasodilator peptide hormone widely expressed by many tissues that acts both as an autocrine and paracrine mediator [23, 24]. It is released in higher quantities in infectious and inflammatory states [25, 26]. Midregional pro-Adrenomedullin (MR-proADM) is generated during the processing of the prohormone of adrenomedullin, is stable in human plasma, and may directly reflect the release of ADM [27]. Several studies have revealed MR-proADM to be highly predictive of adverse outcomes in specific patient populations such as those with chronic heart failure [28], sepsis [24], lower respiratory tract infections [29, 30], myocardial infarction

[31], and urinary tract infections [32]. Moreover, MR-proADM has been shown to predict adverse outcomes in patients presenting to the ED with nonspecific complaints [33].

The first aim of this study was to investigate the prognostic accuracy of NEWS in an unselected multinational cohort of medical patients presenting to the ED. In a second step we aimed to investigate whether adding the inflammatory blood markers white blood cell count (WBC), PCT, and MR-proADM would improve the predictive value of NEWS at the time of ED presentation.

METHODS

Study design

This is a secondary analysis of data from a prospective, multinational, observational cohort study that enrolled patients from March 2013 to October 2014 at three tertiary care hospitals in Aarau (Switzerland), Paris (France), and Clearwater (FL, USA) with the aim of determining whether the addition of biomarkers from distinct biological pathways would improve early risk stratification and initial triage of patients upon ED admission. Since it was an observational quality control study, the Institutional Review Boards (IRB) of the three hospitals approved the study and waived the need for individual informed consent (main Swiss IRB: Ethikkommission Kanton Aargau [EK 2012/059]; French IRB: CCTIRS—Le Comité consultatif sur le traitement de l'information en matière de recherche [C.C.T.I.R.S.; CPP ID RCB: 2013-A00129-36]; US IRB MPM-SAH Institutional Review Board, Clearwater Florida [IRB number 2013_005]). The study was registered at "ClinicalTrials.gov" (NCT01768494). The study protocol and details regarding the study design have been published previously [34, 35].

Patient and Public Involvement

Patients were not involved in the development of the research question or the design of the study.

Patient samples

All adult medical patients seeking ED care at one of the participating hospitals were consecutively enrolled. They were included in this analysis if an initial blood draw had been performed as part of the routine assessment in the ED. Surgical and pediatric

patients were excluded. There were no further exclusion criteria so as to reflect patient diversity and challenges of “real-life”.

Data collection and score assignment

At time of admission to the ED, all patients were assessed by a triage nurse and assigned an initial triage priority based on the routine hospital algorithm. All participants provided a thorough medical history and underwent a physical examination, including measurement of vital signs and laboratory assessment with collection of leftover blood samples for later analysis. Additionally, we recorded the main presenting clinical symptoms and complaints, sociodemographic characteristics, and comorbidities. All information was initially entered in a case report form and subsequently stored in a centralized, password-secured databank (SecuTrial®; interActive Systems GmbH, Berlin, Germany).

Throughout the hospital stay the patients were managed by physicians, nurses, and social workers independent of the research team. All patients were contacted by telephone interview 30 days after admission using a predefined questionnaire to assess vital and functional status, unplanned hospital readmission, and other clinical outcomes.

The NEWS was calculated retrospectively based on available admission data pertaining to the following six parameters: respiratory rate, oxygen saturation, temperature, blood pressure, pulse rate, and level of consciousness. Corresponding to the NEWS 2 score chart of the Royal College of Physicians of the UK [7], continuous variables were awarded a range of zero to three points, while the level of consciousness was binary

coded with zero points if absent and three points if altered. Since data on whether supplemental oxygen was given were not available, the additional 2 points that would have been assigned if supplemental oxygen was given were not included in the calculation. Using the resulting aggregate score, patients were classified into three NEWS categories representing low (0-4 points), moderate (5-6 points), or high (≥7 points) risk. Additionally, patients in the low risk group scoring three points for a single physiological parameter were reclassified in the moderate risk group, as recommended by the Royal College of Physicians [7].

Study endpoints, overall hypothesis, and research aim

The primary endpoint of this analysis was all-cause mortality within 30 days of ED admission. The secondary endpoint was admission to the intensive care unit (ICU) during hospital stay. The decision regarding ICU admission was left to the discretion of the treating physicians. To assess the endpoints, patients were followed throughout their hospital stay and phone interviews were conducted 30 days after admission. If the patient could not be reached, the patient's family or general practitioner was contacted. The aim of this secondary analysis was to investigate the association of a single calculation of NEWS at time of admission with the respective outcomes. In a second step, we aimed to assess whether the predictive value of NEWS could be improved by combining these prognostic biomarkers with the NEWS.

Blood draws and biomarkers

We decided to investigate associations of three inflammatory biomarkers namely white blood cell count (WBC), midregional pro-Adrenomedullin (MR-proADM), and

procalcitonin (PCT). The WBC count was part of the routine laboratory measurement at ED admission. Based on the normal range of WBC (4.0 to 10.0 G/L), we defined the following cut-offs: <4.0 G/L representing levels lower than normal, 4.0 to 10.0 G/L representing the normal range, 10.01 to 15.0 G/L representing low-to-moderate inflammatory response, and >15.0 G/L representing marked inflammation. Both PCT and MR-proADM were batch-measured later from leftover blood samples. The samples were routinely collected at admission, immediately centrifuged, aliquoted and frozen at −20°C. The results of these analyses were not available at time of hospitalization. Thus, physicians and patients were blinded to their results. The PCT levels were measured with a highly sensitive time-resolved amplified cryptate emission (TRACE) technology assay (PCT Kryptor®, B.R.A.H.M.S. AG, Hennigsdorf, Germany) with a lower detection limit of 0.02 ug/L and assay sensitivity of 0.06 µg/L [36]. The MR-proADM levels were measured in plasma with a sandwich immunoassay as described elsewhere [27]. The assay has an analytical detection limit of 0.08 nmol/L. We defined cut-offs of PCT and MR-proADM corresponding to quartiles.

Statistical Analyses

For statistical analyses, we used STATA 12.1 (Stata Corp, College Station, Texas, USA). Two-tailed tests were used and p-values of <0.05 were considered significant. We used descriptive statistics such as mean with standard deviation (SD), median with interquartile range (IQR), and frequencies to describe the population, as appropriate. We performed logistic regression analyses to investigate associations of NEWS and biomarkers with primary and secondary outcomes, respectively. We developed different models with stepwise adjustment for potential important confounders (i.e., age, gender,

main diagnoses leading to ED admission, and comorbidities). Results of the regression analyses are presented as odds ratios (OR) with 95% confidence intervals (95% CI). The raw distribution of the biomarker data was skewed. After log transformation with a base of ten, the distribution of the biomarker data approximated a normal distribution. Therefore, ORs correspond to a tenfold increase in log-transformed values. Regression analyses were repeated in predefined subgroups stratified by diagnoses leading to ED admission. Discriminative performance was determined by means of area under the receiver operating characteristics (AUC), where AUC 0.6 to 0.7 is considered poor, 0.7 to 0.8 fair, 0.8 to 0.9 good, and >0.9 excellent. For further illustration, we generated Kaplan-Meier survival plots by NEWS category and for each of the three biomarkers stratified by quartiles.

RESULTS

Patient Population

Of a total of 7,132 patients presenting to the EDs of the participating hospitals, 1,303 patients had complete information for calculation of NEWS and were included in the final analysis. A comparison of the total cohort and the cohort selected for this analysis can be found in the online supplementary materials (Table A1). The median age of included patients was 66 years and 50.5% were male. The most frequent main complaints were respiratory symptoms (27.3%), thoracic pain (18.4%), and non-thoracic pain (9.5%). The most prevalent diagnoses at ED admission were cardiovascular disease (37.3%), infections (14.6%), neurological disease (13.5%), and gastrointestinal disease (12.3%). Patients had a high burden of comorbidities including hypertension (43.6%), diabetes (20.6%), coronary heart disease (12.6%) and congestive heart failure (11.8%). Additional baseline characteristics of the general population and stratified by NEWS categories are listed in Table 1.

Table 1: Baseline characteristics in the total cohort and stratified by admission NEWS category.

		NEWS category			
	Total cohort	**Low**	**Moderate**	**High**	**p-Value**
Number of Patients, n (%)	1,303	966 (74.1%)	262 (20.1%)	75 (5.8%)	
Sociodemographics					
Age, median (IQR)	66 (52, 80)	63 (50, 79)	72 (58, 84)	69 (58, 81)	<0.001
Male gender, n (%)	658 (50.5%)	498 (51.6%)	122 (46.6%)	38 (50.7%)	0.36
Vital signs, median (IQR)					
Blood pressure diastolic (mmHg)	78 (67, 89)	79 (69, 89)	76 (65, 90)	72 (60, 88)	0.015
Blood pressure sytolic (mmHg)	139 (121, 159)	140 (124, 159)	137 (117, 160)	126 (91, 151)	<0.001
Confusion, n (%)	44 (3.4%)	0 (0.0%)	32 (12.2%)	12 (16.0%)	<0.001
Pulse (bpm)	83 (71, 98)	81 (70, 94)	88 (71, 107)	110 (95, 123)	<0.001
Respiratory rate (per minute)	18 (18, 20)	18 (17, 20)	20 (18, 28)	26 (22, 30)	<0.001
SpO2 (%)	97 (95, 99)	98 (96, 99)	96 (93, 98)	91 (88, 95)	<0.001
Temperature (°C)	36.6 (36.2, 36.9)	36.6 (36.2, 36.9)	36.6 (36.2, 37.0)	36.7 (36.0, 37.7)	0.003
Initial blood biomarkers, median (IQR)					
Creatinine (µmol/L)	79.6 (70.7, 106.1)	79.6 (70.7, 97.2)	79.6 (68.0, 107.0)	88.4 (68.0, 140.0)	0.068
Glucose (mmol/L)	6.3 (5.3, 8.1)	6.2 (5.2, 7.7)	6.5 (5.3, 8.3)	8.2 (5.8, 12.7)	<0.001
White blood cells (G/L)	8.2 (6.3, 10.8)	7.9 (6.1, 10.4)	9.0 (6.8, 13.0)	10.9 (7.5, 15.6)	<0.001
PCT (µg/L)	0.08 (0.06, 0.14)	0.08 (0.06, 0.13)	0.09 (0.06, 0.17)	0.12 (0.07, 0.31)	<0.001
MR-proADM (nmol/L)	0.9 (0.6, 1.5)	0.8 (0.6, 1.3)	1.2 (0.7, 1.8)	1.6 (1.1, 2.8)	<0.001
Main symptom at ED admission, n (%)					<0.001
Diarrhea, vomitus, dysuria	106 (8.1%)	90 (9.3%)	12 (4.6%)	4 (5.3%)	
Fever	23 (1.8%)	14 (1.4%)	8 (3.1%)	1 (1.3%)	
Gastrointestinal bleeding	31 (2.4%)	27 (2.8%)	4 (1.5%)	0 (0.0%)	
Neurological symptoms	90 (6.9%)	71 (7.3%)	17 (6.5%)	2 (2.7%)	
Nonthoracic pain	124 (9.5%)	112 (11.6%)	11 (4.2%)	1 (1.3%)	
Respiratory symptoms	356 (27.3%)	211 (21.8%)	103 (39.3%)	42 (56.0%)	
Thoracic pain	240 (18.4%)	212 (21.9%)	25 (9.5%)	3 (4.0%)	
Miscellaneous	333 (25.6%)	229 (23.7%)	82 (31.3%)	22 (29.3%)	
Main diagnosis, n (%)					<0.001
Cancer	52 (4.0%)	44 (4.6%)	6 (2.3%)	2 (2.7%)	
Cardiovascular	486 (37.3%)	386 (40.0%)	83 (31.7%)	17 (22.7%)	
Gastrointestinal	160 (12.3%)	137 (14.2%)	17 (6.5%)	6 (8.0%)	
Infection	190 (14.6%)	102 (10.6%)	57 (21.8%)	31 (41.3%)	
Metabolic	49 (3.8%)	33 (3.4%)	15 (5.7%)	1 (1.3%)	
Neurological	176 (13.5%)	140 (14.5%)	33 (12.6%)	3 (4.0%)	
Pulmonary	110 (8.4%)	60 (6.2%)	37 (14.1%)	13 (17.3%)	
Miscellaneous	80 (6.1%)	64 (6.6%)	14 (5.3%)	2 (2.7%)	
Comorbidities, n (%)					
Cancer	123 (9.4%)	73 (7.6%)	37 (14.1%)	13 (17.3%)	<0.001
Chronic renal disease	96 (7.4%)	55 (5.7%)	26 (9.9%)	15 (20.0%)	<0.001
Congestive heart failure	154 (11.8%)	88 (9.1%)	46 (17.6%)	20 (26.7%)	<0.001
COPD	94 (7.2%)	46 (4.8%)	36 (13.7%)	12 (16.0%)	<0.001
Coronary heart disease	164 (12.6%)	110 (11.4%)	43 (16.4%)	11 (14.7%)	0.080
Diabetes	269 (20.6%)	187 (19.4%)	64 (24.4%)	18 (24.0%)	0.15
History of stroke	22 (1.7%)	12 (1.2%)	7 (2.7%)	3 (4.0%)	0.078
Hypertension	568 (43.6%)	432 (44.7%)	108 (41.2%)	28 (37.3%)	0.32

COPD, chronic obstructive pulmonary disease; ED, emergency department; IQR, interquartile range; NEWS, national early warning score; PCT, procalcitonin; MR-proADM, midregional pro-Adrenomedullin; SpO_2, peripheral oxygen saturation (%)

NEWS and mortality

The 30-day mortality rate following admission to the ED was 4.1%. In unadjusted logistic regression analyses, we found a significant association between 30-day mortality and NEWS overall (OR 1.35, 95% CI 1.23 to 1.48, p<0.001) and stratified into risk groups with corresponding ORs of 2.45 (95% CI 1.29 to 4.66, p=0.006) for the moderate risk NEWS category, and 7.89 (95% CI 3.85 to 16.18, p<0.001) for the high risk NEWS category, respectively, compared to the low risk NEWS category. These associations remained robust after stepwise adjustment for confounders (see Table 2 for univariate and fully adjusted ORs. Data on all of the remaining models are presented in the supplementary materials table A2). Receiver operating statistics showed fair discriminative performance with regard to 30-day all-cause mortality, with an AUC of 0.73 (95% CI 0.66 to 0.80).

Table 2: Regression analyses for associations of NEWS and blood markers with primary and secondary outcomes

	30 day mortality			ICU admission		
		Regression analyses, OR (95% CI), p-Value			Regression analyses, OR (95% CI), p-Value	
	Events, n (%)	Unadjusted	Fully Adjusted	Events, n (%)	Unadjusted	Fully Adjusted
Total cohort	54/1,303 (4.1)			171/1,303 (13.1)		
NEWS						
Low	25/966 (2.6)	Ref.	Ref.	89/966 (9.2)	Ref.	Ref.
Moderate	16/262 (6.1)	2.45 (1.29 to 4.66), p=0.006	1.71 (0.87 to 3.37), p=0.123	57/262 (21.8)	2.74 (1.90 to 3.95), p<0.001	2.71 (1.85 to 3.98), p<0.001
High	13/75 (17.3)	7.89 (3.85 to 16.18), p<0.001	4.89 (2.22 to 10.75), p<0.001	25/75 (33.3)	4.93 (2.91 to 8.35), p<0.001	4.33 (2.48 to 7.57), p<0.001
Continuous		1.35 (1.23 to 1.48), p<0.001	1.26 (1.13 to 1.40), p<0.001		1.25 (1.17 to 1.33), p<0.001	1.24 (1.15 to 1.32), p<0.001
WBC (G/L)						
4.0-10.0	27/829 (3.3)	Ref.	Ref.	84/829 (10.1)	Ref.	Ref.
10.01-15.0	10/299 (3.3)	1.03 (0.49 to 2.15), p=0.942	1.07 (0.50 to 2.31), p=0.855	41/299 (13.7)	1.41 (0.95 to 2.10), p=0.092	1.52 (1.01 to 2.29), p=0.045
>15.0	15/111 (13.5)	4.64 (2.39 to 9.03), p<0.001	3.73 (1.80 to 7.75), p<0.001	27/111 (24.3)	2.85 (1.75 to 4.65), p<0.001	2.78 (1.67 to 4.62), p<0.001
<4.0	2/46 (4.4)	1.35 (0.31 to 5.86), p=0.689	1.05 (0.22 to 4.99), p=0.951	15/46 (32.6)	4.29 (2.23 to 8.27), p<0.001	4.42 (2.21 to 8.84), p<0.001
Continuous		1.02 (1.00 to 1.03), p=0.051	1.02 (1.00 to 1.03), p=0.036		1.01 (0.99 to 1.02), p=0.355	1.01 (0.99 to 1.02), p=0.267
PCT						
1st Quartile	5/321 (1.6)	Ref.	Ref.	27/321 (8.4)	Ref.	Ref.
2nd Quartile	7/321 (2.2)	1.41 (0.44 to 4.49), p=0.562	1.24 (0.38 to 4.09), p=0.722	34/321 (10.6)	1.29 (0.76 to 2.19), p=0.347	1.23 (0.72 to 2.11), p=0.449
3rd Quartile	10/321 (3.1)	2.03 (0.69 to 6.01), p=0.200	1.79 (0.59 to 5.45), p=0.306	36/321 (11.2)	1.38 (0.81 to 2.32), p=0.234	1.35 (0.79 to 2.29), p=0.276
4th Quartile	32/322 (9.9)	6.97 (2.68 to 18.14), p<0.001	5.17 (1.88 to 14.18), p=0.001	73/322 (22.7)	3.19 (1.99 to 5.12), p<0.001	2.78 (1.68 to 4.59), p<0.001
Continuous		2.66 (1.81 to 3.92), p<0.001	2.45 (1.54 to 3.89), p<0.001		2.33 (1.76 to 3.08), p<0.001	2.18 (1.61 to 2.96), p<0.001
MR-proADM						
1st Quartile	1/324 (0.3)	Ref.	Ref.	20/324 (6.2)	Ref.	Ref.
2nd Quartile	6/325 (1.9)	6.08 (0.73 to 50.75), p=0.096	4.93 (0.57 to 42.58), p=0.147	36/325 (11.1)	1.89 (1.07 to 3.35), p=0.028	2.26 (1.24 to 4.13), p=0.008
3rd Quartile	12/323 (3.7)	12.46 (1.61 to 96.42), p=0.016	7.93 (0.96 to 65.37), p=0.054	34/323 (10.5)	1.79 (1.01 to 3.18), p=0.048	2.25 (1.19 to 4.27), p=0.013
4th Quartile	35/326 (10.7)	38.85 (5.29 to 285.36), p<0.001	17.18 (2.15 to 137.36), p=0.007	81/326 (24.9)	5.03 (3.00 to 8.43), p<0.001	6.27 (3.36 to 11.68), p<0.001
Continuous		17.58 (8.05 to 38.38), p<0.001	10.33 (3.77 to 28.34), p<0.001		7.65 (4.59 to 12.75), p<0.001	9.20 (4.83 to 17.51), p<0.001

Fully adjusted model adjusted for age, sex, main diagnosis, and comorbidities

For regression analysis with continues values, PCT and Pro-ADM were log transformed with a base of ten before entering into statistical models. Therefore, the ORs correspond to a tenfold increase in CRP values.

CI, confidence interval; ICU, intensive care unit; NEWS, national early warning score; PCT, procalcitonin; MR-proADM, midregional pro-Adrenomedullin; Ref, reference; WBC, white blood cell count

Incremental impact of inflammatory blood markers on prediction of mortality

The inflammatory blood markers WBC, PCT, and MR-proADM showed low to fair prognostic accuracy for prediction of 30-day mortality with AUCs of 0.64 (95% CI 0.56 to 0.72), 0.71 (95% CI 0.64 to 0.79), and 0.78 (95% CI 0.73 to 0.84), respectively. Corresponding regression analyses for continuous values and stratified by cut-offs are shown in Table 2. Adding all three markers to NEWS significantly improved the predictive value to an AUC of 0.82 (95% CI 0.77 to 0.88). Interestingly, adding only MR-proADM to a model with NEWS showed a similar AUC of 0.82 (95% CI 0.77 to 0.87) for prediction of mortality (Table 3, Figure 1). We further calculated Kaplan-Meier survival estimates (Figure 2).

Table 3: Discriminative performance of NEWS and biomarkers for the prediction of primary and secondary outcomes

	AUC (95% CI)	
	30-day mortality	ICU admission
NEWS	0.73 (0.66 to 0.80)	0.65 (0.61 to 0.70)
WBC	0.64 (0.56 to 0.72)	0.54 (0.49 to 0.59)
PCT	0.71 (0.64 to 0.79)	0.62 (0.57 to 0.67)
MR-proADM	0.78 (0.73 to 0.84)	0.67 (0.62 to 0.72)
all combined	0.82 (0.77 to 0.88)	0.70 (0.65 to 0.75)
NEWS & WBC	0.74 (0.67 to 0.81)	0.65 (0.60 to 0.70)
NEWS & PCT	0.78 (0.72 to 0.84)	0.68 (0.64 to 0.73)
NEWS & MR-proADM	0.82 (0.77 to 0.87)	0.70 (0.65 to 0.74)

CI, confidence interval; ICU, intensive care unit; NEWS, national early warning score; PCT, procalcitonin; MR-proADM, midregional Pro-Adrenomedullin; WBC, white blood cell count

NEWS and ICU admission

During their hospital stay, 13.1% of patients were admitted to the ICU. Similar to findings with the primary endpoint, unadjusted regression analyses showed significant associations of NEWS with ICU admission (OR 1.25, 95% CI 1.17 to 1.33, p<0.001). Stratification of NEWS by risk categories showed respective ORs of 2.74 (95% CI 1.90 to 3.95, p<0.001) for the moderate risk category and 4.93 (95% CI 2.91 to 8.35, p<0.001) for the high risk category, compared with the low risk category. As before, the results stayed robust after adjusting for important confounders (see Table 2 for univariate and fully adjusted ORs. All of the remaining models are presented in the supplementary materials Table A3).

When receiver operating statistics were determined, NEWS showed low discriminative performance with regard to ICU admission (AUC 0.65, 95% CI 0.61 to 0.70).

Incremental impact of inflammatory blood markers on prediction of ICU admission

The predictive value of the blood markers WBC (AUC 0.54, 95% CI 0.49 to 0.59), PCT (AUC 0.62, 95% CI 0.57 to 0.67), and MR-proADM (AUC 0.67, 95% CI 0.62 to 0.72) for ICU admission was low, with only MR-proADM showing slightly better prognostic accuracy than NEWS. For univariate and multivariate regression analyses for associations of blood markers with ICU admission, see Table 2. A combined model of NEWS with all three blood markers again improved discriminative performance (AUC 0.70, 95% CI 0.65 to 0.75). Similar to the association with mortality, a model including only NEWS and MR-proADM showed equal results for prediction of ICU admission (AUC 0.70, 95% CI 0.65 to 0.74) (Table 3, Figure 1).

Subgroup analyses

Analyses of subgroups showed similar association of NEWS with 30-day mortality among different diagnoses leading to ED admission (supplementary materials Figure A1).

DISCUSSION

This multinational study of heterogenous medical ED patients found a fair performance of the National Early Warning Score (NEWS) for prediction of 30-day mortality when calculated at a single timepoint at ED admission. Results remained robust after adjustment for potential confounders and among different subgroups. Additionally, we found that the predictive value of NEWS was improved by adding inflammatory blood markers, in particular MR-proADM. We also found the discriminative value of NEWS for prediction of our secondary outcome, ICU admission, was less strong but was also improved by adding PCT and MR-proADM to the model.

The 30-day mortality in our study (4.1%) was in line with the 4.0% to 5.7% reported in other investigations that included similar patient populations and examined similar outcome measures [18 37]. Prevalence of ICU admission during hospital stay in our study (13.1%) was within ICU admission rates in several other studies that reported a range between 1% and 17.4% [5 10 13 16 37 38]. This wide range may be a reflection of different healthcare systems studied and particularly of different follow-up periods, as the different investigations examined short-term outcomes within 24 or 48 hours of admission, respectively. In this respect, our results are most notably consistent with the findings of several Scandinavian studies [5 13 15].

Regarding predictive performance, other studies investigating discriminative power of NEWS documented at the time of ED arrival, found similar AUCs for prediction of in-hospital mortality or 30-day mortality, with reported AUCs of 0.65 to 0.77 in patients with

suspected infection/sepsis [39-41] and AUCs of 0.77 to 0.84 in general ED patients, respectively [16 37].

Predictive performance for ICU admission in our study (AUC 0.65, 95% CI 0.61 to 0.70) was slightly lower than the AUCs in other publications that report AUCs of 0.67 to 0.857 for prediction of ICU admission in different patient populations [9 16 40 42].
Our finding of MR-proADM as a solitary predictor of 30-day mortality (AUC 0.78, 95% CI 0.73 to 0.84) is in line with the result of another Swiss study reporting an AUC of 0.732 for the same purpose in a cohort of patients with nonspecific complaints presenting to the ED [33].

To the best of our knowledge, this is the first study investigating NEWS in a multinational cohort of medical ED patients. Moreover, this is the first study investigating the potential additional impact of promising inflammatory markers, namely PCT and MR-proADM, on NEWS for the prediction of adverse outcome.

One could argue that adding blood markers to a clinical score might complicate its calculation, but in EDs initial blood draws are part of routine care, which is why the additional determination of inflammatory marker levels do not change existing processes. In contrast, results are available rapidly and indeed point-of-care tests that provide results within minutes are being developed [43]. Measurements of additional blood markers thus might partially overcome user-dependency of early warning scores and might therefore improve early risk stratification. Our study reveals that MR-proADM could be a particularly suitable and promising blood marker for early risk stratification

when combined with a clinical score such as NEWS. As a result, identification of patients needing urgent care could be improved.

This study has some limitations. First, since it is a secondary analysis of a prospective study, associations between NEWS and biomarkers and outcomes are likely confounded. We addressed this limitation at least partially by adjusting for important confounders. Moreover, with later batch measurement of blood markers, we did address selection bias. However, with residual confounding being likely, our results are at best hypothesis generating. Second, NEWS was calculated retrospectively, and vital signs were not measured more frequently than standard clinical practice. However, we addressed possible bias regarding a treatment paradox since observed mortality may be lower in studies where NEWS is acted upon. Third, due to missing vital sign data—particularly respiratory rate—a large number of patients were not eligible for final analysis. This is in line with other studies reporting that early warning scores were often incomplete [44] and that among others respiratory rate was documented in only 30% to 60% of cases [44 45]. However, our sample is still relatively large and represents a multinational cohort of unselected medical ED patients. Moreover, given that health system organization strongly influences populations at EDs, the multinational nature of our study provides external validity. However, there is the possibility of a selection bias as the cohort included in this analysis differed to the initial total cohort in age, some of the main symptoms and main diagnoses at ED admission, and comorbidities. This was addressed in the regression models by adjusting for the aforementioned confounders. The results remained robust. Fourth, information on the use of oxygen support was not available retrospectively and therefore did not contribute to NEWS calculation, which

reduced the maximum score from 20 to 18. This might have led to misclassification of patients and might have diminished the discriminatory power of NEWS. However, the Royal College of Physicians recommends addition of a weighting score of 2 not by default for all patients with supplemental oxygen but only for patients requiring supplemental oxygen to maintain their optimal oxygen saturation [7]. As the optimal oxygen saturation may be different in varying patient groups, most notably in patients with hypercapnic respiratory failure, the actual requirement of supplemental oxygen is hard to determine and requires evaluation of a qualified and experienced physician. As a result, certain patients might mistakenly score 2 additional points for supplemental oxygen, which can again result in misclassification of the NEWS risk category. However, as mentioned before, the discriminative power of NEWS in our study is comparable to other similar investigations. Fifth, we only had a few events, which could limit reliability and is reflected in the rather broad 95% confidence intervals. This was addressed at least in part by hard endpoints and a structured follow-up with phone interviews 30 days after admission or through contacting the patient's family or general practitioner. Sixth, the decision regarding ICU admission was left to the discretion of treating physicians. This reflects procedures followed in the included centers and may be different from those in other hospitals. Last, NEWS was not designed to be a single time point tool but rather a "track-and-trigger" system in individual patients. Accuracy of NEWS may thus be different if multiple measurements at different time points are considered.

CONCLUSION

Combining NEWS calculated upon admission to the ED with markers of inflammation such as MR-proADM and PCT improves the predictive value of NEWS in unselected

medical patients. The combination of NEWS and MR-proADM might prove to be a particularly promising tool for early risk stratification. Whether these theoretical benefits of improved risk stratification at ED admission can be translated into improved outcomes has to be examined in future interventional studies.

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Author contributions

All authors made substantive intellectual contributions to this study regarding conception and design, have taken an active part in acquisition, analysis, and interpretation of data, and approved the final version of the manuscript. AE, SH, and PS conducted the statistical analyses and initially drafted the manuscript. AE and SH contributed equally to this work.

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Competing interests

AK, BM, PH, and PS have received research grants and support from B·R·A·H·M·S AG (now ThermoFisher Scientific Biomarkers) and bioMérieux for attending meetings and fulfilling speaking engagements. BM has served as a consultant to both companies. All other authors have no conflicts of interest relevant to this paper. The funding organization had no role in the design or conduct of the study, analysis and interpretation of the data, writing of the manuscript, or the decision to submit the manuscript for publication.

Data sharing statement: Part of the dataset will be available from the Dryad repository.

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FIGURES

Figure 1: Discriminative performance of NEWS, blood markers, and combination of NEWS and blood markers for the prediction of all-cause 30-day mortality (A) and ICU admission (B)

Legend: NEWS, national early warning score; PCT, procalcitonin; MR-proADM, midregional Pro-Adrenomedullin; WBC, white blood cell count

Figure 2: Kaplan-Meier survival estimates stratified by admission NEWS category (A), white blood cell count (WBC) (B), procalcitonin (PCT) (C), and MR-pro-adrenomedullin (MR-proADM) (D)

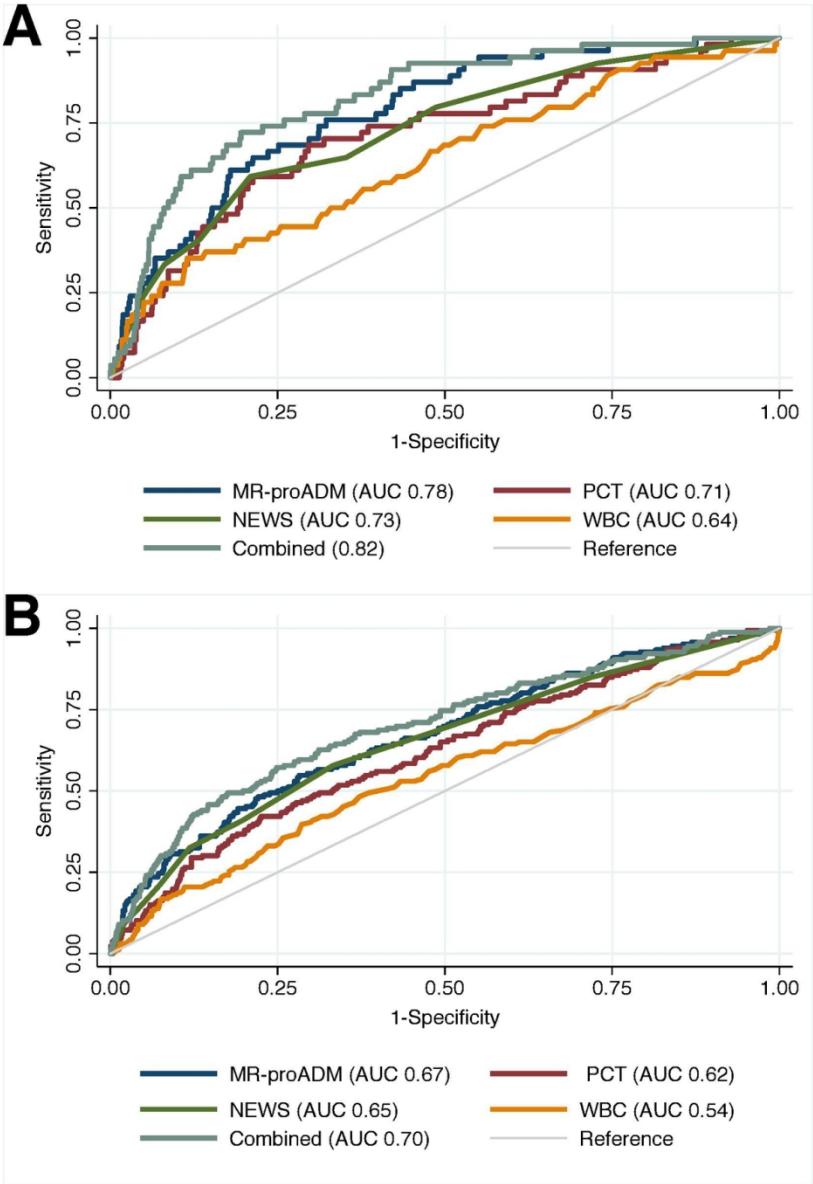


Figure 1: Discriminative performance of NEWS, blood markers, and combination of NEWS and blood markers for the prediction of all-cause 30-day mortality (A) and ICU admission (B)

Legend: NEWS, national early warning score; PCT, procalcitonin; MR-proADM, midregional Pro-Adrenomedullin; WBC, white blood cell count

103x150mm (300 x 300 DPI)

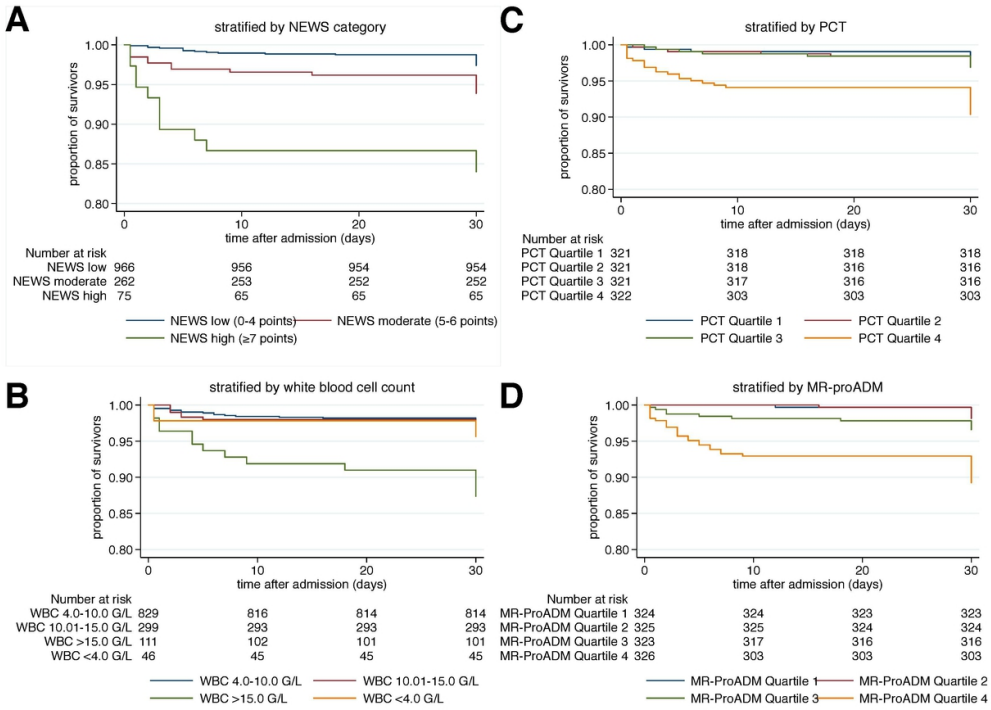


Figure 2: Kaplan-Meier survival estimates stratified by admission NEWS category (A), white blood cell count (WBC) (B), procalcitonin (PCT) (C), and MR-pro-adrenomedullin (MR-proADM) (D)

103x75mm (300 x 300 DPI)

Table A1: Comparison of the total cohort and cohort selected for analysis

Number of Patients, n (%)	Total Cohort 7132	Selected Cohort 1303
Sociodemographics		
Age, median (IQR)	62 (46, 76)	66 (52, 80)
Male gender, n (%)	3767 (53.3%)	658 (50.5%)
Vital signs, median (IQR)		
Blood pressure diastolic (mmHg)	80 (70, 90)	78 (67, 89)
Blood pressure systolic (mmHg)	137 (121, 154)	139 (121, 159)
Confusion, n (%)	522 (7.3%)	44 (3.4%)
Pulse (bpm)	83 (71, 97)	83 (71, 98)
Respiratory rate (per minute)	18 (18, 20)	18 (18, 20)
SpO2 (%)	96.8 (94, 98)	97 (95, 99)
Temperature (°C)	36.8 (36.4, 37.2)	36.6 (36.2, 36.9)
Intial blood biomarkers, median (IQR)		
Creatinine (µmol/L)	81.0 (67.0, 103.0)	79.6 (70.7, 106.1)
Glucose (mmol/L)	6.1 (5.3, 7.5)	6.3 (5.3, 8.1)
White blood cells (G/L)	8.385 (6.58, 10.98)	8.2 (6.3, 10.8)
PCT (µg/L)	0.08 (0.06, 0.13)	0.08 (0.06, 0.14)
ProADM (nmol/L)	0.8 (0.6, 1.2)	0.9 (0.6, 1.5)
Main symptom at ED admission, n (%)		
Diarrhea, vomitus, dysuria	495 (6.9%)	106 (8.1%)
Fever	343 (4.8%)	23 (1.8%)
Gastrointestinal bleeding	199 (2.8%)	31 (2.4%)
Neurological symptoms	1379 (19.3%)	90 (6.9%)
Nonthoracic pain	1217 (17.1%)	124 (9.5%)
Respiratory symptoms	948 (13.3%)	356 (27.3%)
Thoracic pain	1038 (14.6%)	240 (18.4%)
Worsening of general condition	837 (11.7%)	333 (25.6%)
Main diagnosis, n (%)		
Cancer	344 (4.8%)	52 (4.0%)
Cardiovascular	1660 (23.3%)	486 (37.3%)
Gastrointestinal	983 (13.8%)	160 (12.3%)
Infection	1039 (14.6%)	190 (14.6%)
Metabolic	192 (2.7%)	49 (3.8%)
Neurological	1566 (22.0%)	176 (13.5%)
Pulmonary	297 (4.2%)	110 (8.4%)
Miscellaneous	1051 (14.7%)	80 (6.1%)
Comorbidities, n (%)		
Cancer	968 (13.6%)	123 (9.4%)
Chronic renal disease	872 (12.2%)	96 (7.4%)
Congestive heart failure	487 (6.8%)	154 (11.8%)
COPD	359 (5.0%)	94 (7.2%)
Coronary heart disease	838 (11.7%)	164 (12.6%)
Diabetes	1088 (15.3%)	269 (20.6%)
History of stroke	566 (7.9%)	22 (1.7%)
Hypertension	2795 (39.2%)	568 (43.6%)
Events, n (%)		
Death 30 days	331 (4.6%)	54 (4.1%)
Intensive Care	453 (6.4%)	171 (13.1%)

Table A2: Regression analyses for associations of NEWS and blood markers with primary outcome

		30 day mortality			
		Regression analyses, OR (95% CI), p-value			
	Events, n (%)	Unadjusted	Model 1	Model 2	Model 3
NEWS					
Low	25/966 (2.6)	Ref.	Ref.	Ref.	Ref.
Moderate	16/262 (6.1)	2.45 (1.29 to 4.66), p=0.006	2.04 (1.06 to 3.92), p=0.032	2.01 (1.05 to 3.87), p=0.036	1.71 (0.87 to 3.37), p=0.123
High	13/75 (17.3)	7.89 (3.85 to 16.18), p<0.001	7.01 (3.36 to 14.63), p<0.001	6.79 (3.23 to 14.3), p<0.001	4.89 (2.22 to 10.75), p<0.001
Continuous		1.35 (1.23 to 1.48), p<0.001	1.32 (1.2 to 1.46), p<0.001	1.32 (1.19 to 1.45), p<0.001	1.26 (1.13 to 1.40), p<0.001
WBC					
4.0-10.0	27/829 (3.3)	Ref.	Ref.	Ref.	Ref.
10.01-15.0	10/299 (3.3)	1.03 (0.49 to 2.15), p=0.942	1.05 (0.5 to 2.21), p=0.893	1.05 (0.5 to 2.21), p=0.9	1.07 (0.50 to 2.31), p=0.855
>15.0	15/111 (13.5)	4.64 (2.39 to 9.03), p<0.001	4.41 (2.22 to 8.76), p=0	4.37 (2.2 to 8.69), p=0	3.73 (1.80 to 7.75), p<0.001
<4.0	2/46 (4.4)	1.35 (0.31 to 5.86), p=0.689	1.52 (0.34 to 6.74), p=0.583	1.52 (0.34 to 6.76), p=0.58	1.05 (0.22 to 4.99), p=0.951
Continuous		1.02 (1.00 to 1.03), p=0.051	1.02 (1 to 1.03), p=0.033	1.02 (1 to 1.03), p=0.028	1.02 (1.00 to 1.03), p=0.036
PCT					
1st Quartile	5/321 (1.6)	Ref.	Ref.	Ref.	Ref.
2nd Quartile	7/321 (2.2)	1.41 (0.44 to 4.49), p=0.562	1.32 (0.41 to 4.22), p=0.642	1.33 (0.41 to 4.26), p=0.632	1.24 (0.38 to 4.09), p=0.722
3rd Quartile	10/321 (3.1)	2.03 (0.69 to 6.01), p=0.2	1.77 (0.59 to 5.26), p=0.307	1.84 (0.62 to 5.48), p=0.276	1.79 (0.59 to 5.45), p=0.306
4th Quartile	32/322 (9.9)	6.97 (2.68 to 18.14), p<0.001	6.01 (2.29 to 15.79), p<0.001	6.12 (2.33 to 16.09), p<0.001	5.17 (1.88 to 14.18), p=0.001
Continuous		2.66 (1.81 to 3.92), p<0.001	2.77 (1.85 to 4.17), p<0.001	2.71 (1.79 to 4.08), p<0.001	2.45 (1.54 to 3.89), p<0.001
MR-proADM					
1st Quartile	1/324 (0.3)	Ref.	Ref.	Ref.	Ref.
2nd Quartile	6/325 (1.9)	6.08 (0.73 to 50.75), p=0.096	4.42 (0.52 to 37.78), p=0.175	4.44 (0.52 to 37.93), p=0.174	4.93 (0.57 to 42.58), p=0.147
3rd Quartile	12/323 (3.7)	12.46 (1.61 to 96.42), p=0.016	7.66 (0.94 to 62.38), p=0.057	7.77 (0.96 to 63.12), p=0.055	7.93 (0.96 to 65.37), p=0.054
4th Quartile	35/326 (10.7)	38.85 (5.29 to 285.36), p<0.001	22.46 (2.87 to 175.82), p=0.003	22.22 (2.84 to 173.70), p=0.003	17.18 (2.15 to 137.36), p=0.007
Continuous		17.58 (8.05 to 38.38), p<0.001	13.89 (5.94 to 32.49), p<0.001	13.40 (5.70 to 31.54), p<0.001	10.33 (3.77 to 28.34), p<0.001

Adjustments: Model 1: age and sex; Model 2: age, sex, and main diagnosis; Model 3: fully adjusted for age, sex, main diagnosis, and comorbidities

For regression analysis with continues values, PCT and Pro-ADM were log transformed with a base of ten before entering into statistical models. Therefore, the ORs correspond to a tenfold increase in CRP values.

CI, confidence interval; ICU, intensive care unit; NEWS, national early warning score; PCT, procalcitonin; MR-proADM, midregional pro-Adrenomedullin; Ref, reference; WBC, white blood cell count

Table A3: Regression analyses for associations of NEWS and blood markers with secondary outcome

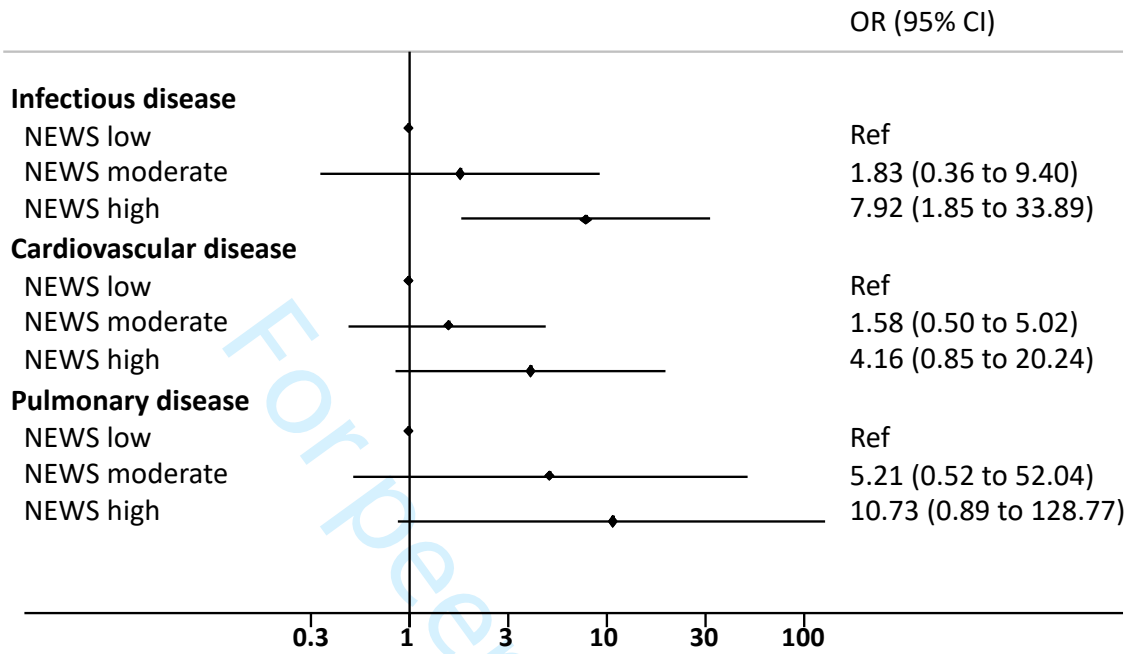
		ICU admission			
		Regression analyses, OR (95% CI), p-value			
	events, n (%)	unadjusted	model 1	model 2	model 3
NEWS					
Low	89/966 (9.2)	Ref.	Ref.	Ref.	Ref.
Moderate	57/262 (21.8)	2.74 (1.90 to 3.95), p<0.001	2.75 (1.90 to 3.99), p<0.001	2.75 (1.90 to 3.99), p<0.001	2.71 (1.85 to 3.98), p<0.001
High	25/75 (33.3)	4.93 (2.91 to 8.35), p<0.001	4.90 (2.88 to 8.35), p<0.001	4.88 (2.86 to 8.33), p<0.001	4.33 (2.48 to 7.57), p<0.001
Continuous		1.25 (1.17 to 1.33), p<0.001	1.25 (1.17 to 1.33), p<0.001	1.25 (1.17 to 1.33), p<0.001	1.24 (1.15 to 1.32), p<0.001
WBC					
4.0-10.0	84/829 (10.1)	Ref.	Ref.	Ref.	Ref.
10.01-15.0	41/299 (13.7)	1.41 (0.95 to 2.10), p=0.092	1.43 (0.96 to 2.13), p=0.081	1.43 (0.96 to 2.13), p=0.081	1.52 (1.01 to 2.29), p=0.045
>15.0	27/111 (24.3)	2.85 (1.75 to 4.65), p<0.001	2.75 (1.68 to 4.49), p<0.001	2.74 (1.68 to 4.49), p<0.001	2.78 (1.67 to 4.62), p<0.001
<4.0	15/46 (32.6)	4.29 (2.23 to 8.27), p<0.001	4.19 (2.16 to 8.12), p<0.001	4.18 (2.15 to 8.10), p<0.001	4.42 (2.21 to 8.84), p<0.001
Continuous		1.01 (0.99 to 1.02), p=0.355	1.01 (0.99 to 1.02), p=0.317	1.01 (0.99 to 1.02), p=0.313	1.01 (0.99 to 1.02), p=0.267
PCT					
1st Quartile	27/321 (8.4)	Ref.	Ref.	Ref.	Ref.
2nd Quartile	34/321 (10.6)	1.29 (0.76 to 2.19), p=0.347	1.27 (0.74 to 2.15), p=0.386	1.27 (0.75 to 2.16), p=0.381	1.23 (0.72 to 2.11), p=0.449
3rd Quartile	36/321 (11.2)	1.38 (0.81 to 2.32), p=0.234	1.33 (0.78 to 2.25), p=0.294	1.34 (0.79 to 2.27), p=0.276	1.35 (0.79 to 2.29), p=0.276
4th Quartile	73/322 (22.7)	3.19 (1.99 to 5.12), p<0.001	2.99 (1.86 to 4.81), p<0.001	3.00 (1.86 to 4.84), p<0.001	2.78 (1.68 to 4.59), p<0.001
Continuous		2.33 (1.76 to 3.08), p<0.001	2.31 (1.74 to 3.07), p<0.001	2.31 (1.74 to 3.06), p<0.001	2.18 (1.61 to 2.96), p<0.001
MR-proADM					
1st Quartile	20/324 (6.2)	Ref.	Ref.	Ref.	Ref.
2nd Quartile	36/325 (11.1)	1.89 (1.07 to 3.35), p=0.028	2.26 (1.24 to 4.09), p=0.007	2.26 (1.25 to 4.09), p=0.007	2.26 (1.24 to 4.13), p=0.008
3rd Quartile	34/323 (10.5)	1.79 (1.01 to 3.18), p=0.048	2.24 (1.20 to 4.20), p=0.011	2.25 (1.20 to 4.20), p=0.011	2.25 (1.19 to 4.27), p=0.013
4th Quartile	81/326 (24.9)	5.03 (3.00 to 8.43), p<0.001	6.36 (3.53 to 11.48), p<0.001	6.35 (3.52 to 11.44), p<0.001	6.27 (3.36 to 11.68), p<0.001
Continuous		7.65 (4.59 to 12.75), p<0.001	8.64 (5.00 to 14.95), p<0.001	8.62 (4.98 to 14.95), p<0.001	9.20 (4.83 to 17.51), p<0.001

Adjustments: Model 1: age and sex; Model 2: age, sex, and main diagnosis; Model 3: fully adjusted for age, sex, main diagnosis, and comorbidities

For regression analysis with continues values, PCT and Pro-ADM were log transformed with a base of ten before entering into statistical models. Therefore, the ORs correspond to a tenfold increase in CRP values.

CI, confidence interval; ICU, intensive care unit; NEWS, national early warning score; PCT, procalcitonin; MR-proADM, midregional pro-Adrenomedullin; Ref, reference; WBC, white blood cell count

Figure A1: Subgroup analyses. Association of NEWS category with all-cause 30-day mortality among different diagnoses leading to ED admission



CI, Confidence interval; ED, emergency department; NEWS, national early warning score; OR, Odds ratio

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9, 11*
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	8, 13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	12
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	13
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	15, 18
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-16
		(*b*) Report category boundaries when continuous variables were categorized	11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	19
Discussion			
Key results	18	Summarise key results with reference to study objectives	20-21
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	23
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Combination of the National Early Warning Score (NEWS) and inflammatory biomarkers for early risk stratification in emergency department patients: results of a multi-national, observational study

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Combination of the National Early Warning Score (NEWS) and inflammatory biomarkers for early risk stratification in emergency department patients: results of a multi-national, observational study

Short title: Inflammatory blood markers improve the predictive value of NEWS

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Supplementary material: Number of Tables: 3, Number of Figures: 1

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ABSTRACT

Objectives: The National Early Warning Score (NEWS) helps to estimate mortality risk in emergency department (ED) patients. This study aimed to investigate whether the prognostic value of the NEWS at ED admission could be further improved by adding inflammatory blood markers (i.e. white blood cell count (WBC), procalcitonin (PCT), and MR-ProAdrenomedullin (MR-proADM).

Design: Secondary analysis of a multinational, observational study. (TRIAGE study, March 2013 to October 2014)

Setting: Three tertiary care centers in France, Switzerland, and the USA.

Participants: A total of 1303 adult medical patients with complete NEWS data seeking ED care were included in the final analysis. NEWS was calculated retrospectively based on admission data.

Main outcome measures: The primary outcome was all-cause 30-day mortality. Secondary outcome was ICU admission. We used multivariate regression analyses to investigate associations of NEWS and blood markers with outcomes and area under the receiver operating curve (AUC) as a measure of discrimination.

Results: Of the 1303 included patients, 54 (4.1%) died within 30 days. The NEWS alone showed fair prognostic accuracy for all-cause 30-day mortality (AUC 0.73), with a multivariate adjusted odds ratio (OR) of 1.26 (95% CI 1.13–1.40, p<0.001). The AUCs for the prediction of mortality using the inflammatory markers WBC, PCT, and MR-proADM were 0.64, 0.71, and 0.78, respectively. Combining NEWS with all three blood markers or only with MR-proADM clearly improved discrimination with an AUC 0.82 (p= 0.002). Combining the three inflammatory markers with NEWS improved prediction of ICU admission (AUC 0.70 vs. 0.65 when using NEWS alone, p=0.006).

Conclusion: NEWS is helpful in risk stratification of ED patients and can be further improved by the addition inflammatory blood markers. Future studies should investigate whether risk stratification by NEWS in addition to biomarkers improve site-of-care decision in this patient population.

Trial registration number: ClinicalTrials.gov; Identifier: NCT01768494

ARCTICLE SUMMARY

Strength and limitations of this study

- This is the first multinational study investigating the association of the National Early Warning Score (NEWS) and adverse outcomes at emergency department (ED) admission.
- This is the first study evaluating additional impact of inflammatory biomarkers on NEWS.
- Due to its design as a secondary analysis of an observational study, results are at best hypothesis generating.
- There is the possibility of a selection bias due to exclusion of patients with missing vital status data.

INTRODUCTION

With increasingly overwhelmed emergency departments (ED), it is vital that well-validated risk stratification systems are implemented to rapidly identify and efficiently respond to patients at risk since delays in treatment may result in poor outcomes [1 2]. At the same time, risk stratification systems should ensure reliable identification of patients who may not need urgent care. Risk scores such as the pneumonia severity index (PSI) for patients presenting with pneumonia [3] or the Global Registry of Acute Coronary Events (GRACE) risk score for patients with myocardial infarction are applicable mainly to specific patient populations [4].

Emerging data suggest that in unselected medical patients presenting to the ED, early warning scores (i.e., track-and-trigger systems) are gaining importance for risk stratification and that their usage for this purpose may exceed that of classical triage tools such as the Manchester Triage System (MTS) [5 6]. Of the numerous early warning scores (EWS) that have been investigated for this purpose, the National Early Warning Score (NEWS) may be the best evaluated and most widely used [6]. It was originally developed in the United Kingdom by the Royal College of Physicians to standardize and improve detection of patients at risk for deterioration, with the routine recording of a minimum of physiological parameters [7 8]. Multiple studies have revealed its superiority over other risk stratification tools with regard to prediction of mortality [6 9]. Since its introduction in 2012, NEWS has been validated and widely implemented in different patient populations [5 10-12] worldwide [5 11 13-16]. It has also been used recently for early risk stratification in unselected ED patients and has shown promise in the prediction of mortality [6]. The Royal College of Physicians now recommends its use in EDs in its

updated NEWS 2 report issued in 2017 [7]. However, risk stratification at this early stage in patient care immediately following presentation to the ED is challenging due to lack of clinical information. Moreover, NEWS and other triage scores are based on vital signs and represent a patient's clinical state at a single timepoint when vital signs are frequently still unremarkable, as a consequence of which they may miss patients at risk.

The use of blood markers assessed at the time of ED presentation may add prognostic information [17] and even improve the prognostic value of early warning scores. Although investigations trying to improve the discriminative value of NEWS by combining different markers such as serum lactate [16 18] or D-dimer [19] with NEWS have been undertaken, their results are contradictory. This may be due to inadequate selection of blood markers. The inflammatory blood marker procalcitonin (PCT) is a marker for bacterial infections. It has been employed for stewardship of antibiotic therapy [20] and has been shown to improve risk assessment in different patient populations such as those with sepsis [21] or malignant disease [22], and in patients at cardiovascular risk [23]. Adrenomedullin (ADM) is a potent vasodilator peptide hormone widely expressed by many tissues that acts both as an autocrine and paracrine mediator [24 25]. It is released in higher quantities in infectious and inflammatory states [26 27]. Midregional pro-Adrenomedullin (MR-proADM) is generated during the processing of the prohormone of adrenomedullin, is stable in human plasma, and may directly reflect the release of ADM [28]. Several studies have revealed MR-proADM to be highly predictive of adverse outcomes in specific patient populations such as those with chronic heart failure [29], sepsis [25], lower respiratory tract infections [30 31], myocardial infarction [32], and urinary tract

infections [33]. Moreover, MR-proADM has been shown to predict adverse outcomes in patients presenting to the ED with nonspecific complaints [34].

The first aim of this study was to investigate the prognostic accuracy of NEWS in an unselected multinational cohort of medical patients presenting to the ED. In a second step we aimed to investigate whether adding the inflammatory blood markers white blood cell count (WBC), PCT, and MR-proADM would improve the predictive value of NEWS at the time of ED presentation.

METHODS

Study design

This is a retrospective analysis of data from a multinational, observational cohort study that enrolled patients from March 2013 to October 2014 at three tertiary care hospitals in Aarau (Switzerland), Paris (France), and Clearwater (FL, USA) with the aim of determining whether the addition of biomarkers from distinct biological pathways would improve early risk stratification and initial triage of patients upon ED admission. Since it was an observational quality control study, the Institutional Review Boards (IRB) of the three hospitals approved the study and waived the need for individual informed consent (main Swiss IRB: Ethikkommission Kanton Aargau [EK 2012/059]; French IRB: CCTIRS—Le Comité consultatif sur le traitement de l'information en matière de recherche [C.C.T.I.R.S.; CPP ID RCB: 2013-A00129-36]; US IRB MPM-SAH Institutional Review Board, Clearwater Florida [IRB number 2013_005]). The study was registered at "ClinicalTrials.gov" (NCT01768494). The study protocol and details regarding the study design have been published previously [35 36].

Patient and Public Involvement

Patients were not involved in the development of the research question or the design of the study.

Patient samples

All adult medical patients seeking ED care at one of the participating hospitals were consecutively enrolled. They were included in this analysis if an initial blood draw had been performed as part of the routine assessment in the ED. Surgical and pediatric

patients were excluded. There were no further exclusion criteria so as to reflect patient diversity and challenges of “real-life”.

Data collection and score assignment

At time of admission to the ED, all patients were assessed by a triage nurse and assigned an initial triage priority based on the routine hospital algorithm. All participants provided a thorough medical history and underwent a physical examination, including measurement of vital signs and laboratory assessment with collection of leftover blood samples for later analysis. Additionally, we recorded the main presenting clinical symptoms and complaints, sociodemographic characteristics, and comorbidities. All information was initially entered in a case report form and subsequently stored in a centralized, password-secured databank (SecuTrial®; interActive Systems GmbH, Berlin, Germany).

Throughout the hospital stay the patients were managed by physicians, nurses, and social workers independent of the research team. All patients were contacted by telephone interview 30 days after admission using a predefined questionnaire to assess vital and functional status, unplanned hospital readmission, and other clinical outcomes.

The NEWS was calculated retrospectively based on available admission data pertaining to the following six parameters: respiratory rate, oxygen saturation, temperature, blood pressure, pulse rate, and level of consciousness. Corresponding to the NEWS 2 score chart of the Royal College of Physicians of the UK [7], continuous variables were awarded a range of zero to three points, while the level of consciousness was binary coded with

zero points if absent and three points if altered. Since data on whether supplemental oxygen was given were not available, the additional 2 points that would have been assigned if supplemental oxygen was given were not included in the calculation. Using the resulting aggregate score, patients were classified into three NEWS categories representing low (0-4 points), moderate (5-6 points), or high (≥7 points) risk. Additionally, patients in the low risk group scoring three points for a single physiological parameter were reclassified in the moderate risk group, as recommended by the Royal College of Physicians [7]. As data on supplemental oxygen was not available, results in this paper correspond to a NEWS – potentially minus 2 points.

Study endpoints, overall hypothesis, and research aim

The primary endpoint of this analysis was all-cause mortality within 30 days of ED admission. The secondary endpoint was admission to the intensive care unit (ICU) during hospital stay. The decision regarding ICU admission was left to the discretion of the treating physicians. To assess the endpoints, patients were followed throughout their hospital stay and phone interviews were conducted 30 days after admission. If the patient could not be reached, the patient's family or general practitioner was contacted. The aim of this secondary analysis was to investigate the association of a single calculation of NEWS at time of admission with the respective outcomes. In a second step, we aimed to assess whether the predictive value of NEWS could be improved by combining these prognostic biomarkers with the NEWS.

Blood draws and biomarkers

We decided to investigate associations of three inflammatory biomarkers namely white blood cell count (WBC), midregional pro-Adrenomedullin (MR-proADM), and procalcitonin (PCT). The WBC count was part of the routine laboratory measurement at ED admission. Based on the normal range of WBC (4.0 to 10.0 G/L), we defined the following cut-offs: <4.0 G/L representing levels lower than normal, 4.0 to 10.0 G/L representing the normal range, 10.01 to 15.0 G/L representing low-to-moderate inflammatory response, and >15.0 G/L representing marked inflammation. Both PCT and MR-proADM were batch-measured later from leftover blood samples. The samples were routinely collected at admission, immediately centrifuged, aliquoted and frozen at −20°C. The results of these analyses were not available at time of hospitalization. Thus, physicians and patients were blinded to their results. The PCT levels were measured with a highly sensitive time-resolved amplified cryptate emission (TRACE) technology assay (PCT Kryptor®, B.R.A.H.M.S. AG, Hennigsdorf, Germany) with a lower detection limit of 0.02 ug/L and assay sensitivity of 0.06 µg/L [37]. The MR-proADM levels were measured in plasma with a sandwich immunoassay as described elsewhere [28]. The assay has an analytical detection limit of 0.08 nmol/L. We defined cut-offs of PCT and MR-proADM corresponding to quartiles.

Statistical Analyses

For statistical analyses, we used STATA 12.1 (Stata Corp, College Station, Texas, USA). Two-tailed tests were used and p-values of <0.05 were considered significant. We used descriptive statistics such as median with quartiles, and frequencies to describe the population, as appropriate. To assess group differences we used Kruskal-Wallis test for continuous, skew variables, and Pearson's chi-squared test for categorial and binary

variables. We performed logistic regression analyses to investigate associations of NEWS and biomarkers with primary and secondary outcomes, respectively. We developed different models with stepwise adjustment for potential important confounders (i.e., age, gender, main diagnoses leading to ED admission, and comorbidities). Age was used as a linear covariate. According to the main admission diagnosis the following diagnostic groups were generated: Infectious disease, cardiovascular disease, metabolic disorder, malignant disease, neurological disease, gastrointestinal disease, pulmonary disease, and other disease. Comorbidities were assigned using patients' medical history and ICD-10 diagnostic codes and include chronic obstructive lung disease, heart failure, coronary heart disease, diabetes, hypertension, stroke, malignant disease and renal failure. In statistical models comorbidities were coded as binary variables. Results of the regression analyses are presented as odds ratios (OR) with 95% confidence intervals (95% CI). The raw distribution of the biomarker data was skewed. After log transformation with a base of ten, the distribution of the biomarker data approximated a normal distribution. Therefore, ORs correspond to a tenfold increase in log-transformed values. Regression analyses were repeated in predefined subgroups stratified by diagnoses leading to ED admission. Discriminative performance was determined by means of area under the receiver operating characteristics (AUC), where AUC 0.6 to 0.7 is considered poor, 0.7 to 0.8 fair, 0.8 to 0.9 good, and >0.9 excellent. The AUCs were systematically calculated for univariate models including NEWS and/or inflammatory markers and not for models adjusted for the afore-mentioned confounders. We used Pearson's chi-squared test to compare areas under the receiver operating curve. For further illustration, we generated Kaplan-Meier survival plots by NEWS category and for each of the three biomarkers stratified by quartiles.

RESULTS

Patient Population

Of a total of 7,132 patients presenting to the EDs of the participating hospitals (1,000 Clearwater, 1,553 Paris, 4,579 Aarau), 1,303 (940 Clearwater, 355 Paris, 8 Aarau) patients had complete information for calculation of NEWS (excluding data on supplemental oxygen) and were included in the final analysis. A comparison of the total cohort and the cohort selected for this analysis can be found in the online supplementary materials (Table A1). The median age of included patients was 66 years and 50.5% were male. The most frequent main complaints were respiratory symptoms (27.3%), thoracic pain (18.4%), and non-thoracic pain (9.5%). The most prevalent diagnoses at ED admission were cardiovascular disease (37.3%), infections (14.6%), neurological disease (13.5%), and gastrointestinal disease (12.3%). Patients had a high burden of comorbidities including hypertension (43.6%), diabetes (20.6%), coronary heart disease (12.6%) and congestive heart failure (11.8%). Additional baseline characteristics of the general population and stratified by NEWS categories are listed in Table 1.

Table 1: Baseline characteristics in the total cohort and stratified by admission NEWS category.

		NEWS category			
	Total cohort	**Low**	**Moderate**	**High**	**p-Value**
Number of Patients, n (%)	1,303	966 (74.1%)	262 (20.1%)	75 (5.8%)	
Sociodemographics					
Age, median (quartiles)	66 (52, 80)	63 (50, 79)	72 (58, 84)	69 (58, 81)	<0.001
Male gender, n (%)	658 (50.5%)	498 (51.6%)	122 (46.6%)	38 (50.7%)	0.36
Vital signs, median (quartiles)					
Blood pressure diastolic (mmHg)	78 (67, 89)	79 (69, 89)	76 (65, 90)	72 (60, 88)	0.015
Blood pressure sytolic (mmHg)	139 (121, 159)	140 (124, 159)	137 (117, 160)	126 (91, 151)	<0.001
Confusion, n (%)	44 (3.4%)	0 (0.0%)	32 (12.2%)	12 (16.0%)	<0.001
Pulse (bpm)	83 (71, 98)	81 (70, 94)	88 (71, 107)	110 (95, 123)	<0.001
Respiratory rate (per minute)	18 (18, 20)	18 (17, 20)	20 (18, 28)	26 (22, 30)	<0.001
SpO2 (%)	97 (95, 99)	98 (96, 99)	96 (93, 98)	91 (88, 95)	<0.001
Temperature (°C)	36.6 (36.2, 36.9)	36.6 (36.2, 36.9)	36.6 (36.2, 37.0)	36.7 (36.0, 37.7)	0.003
Initial blood biomarkers, median (quartiles)					
Creatinine (µmol/L)	79.6 (70.7, 106.1)	79.6 (70.7, 97.2)	79.6 (68.0, 107.0)	88.4 (68.0, 140.0)	0.068
Glucose (mmol/L)	6.3 (5.3, 8.1)	6.2 (5.2, 7.7)	6.5 (5.3, 8.3)	8.2 (5.8, 12.7)	<0.001
White blood cells (G/L)	8.2 (6.3, 10.8)	7.9 (6.1, 10.4)	9.0 (6.8, 13.0)	10.9 (7.5, 15.6)	<0.001
PCT (µg/L)	0.08 (0.06, 0.14)	0.08 (0.06, 0.13)	0.09 (0.06, 0.17)	0.12 (0.07, 0.31)	<0.001
MR-proADM (nmol/L)	0.9 (0.6, 1.5)	0.8 (0.6, 1.3)	1.2 (0.7, 1.8)	1.6 (1.1, 2.8)	<0.001
Main symptom at ED admission, n (%)					<0.001
Diarrhea, vomitus, dysuria	106 (8.1%)	90 (9.3%)	12 (4.6%)	4 (5.3%)	
Fever	23 (1.8%)	14 (1.4%)	8 (3.1%)	1 (1.3%)	
Gastrointestinal bleeding	31 (2.4%)	27 (2.8%)	4 (1.5%)	0 (0.0%)	
Neurological symptoms	90 (6.9%)	71 (7.3%)	17 (6.5%)	2 (2.7%)	
Nonthoracic pain	124 (9.5%)	112 (11.6%)	11 (4.2%)	1 (1.3%)	
Respiratory symptoms	356 (27.3%)	211 (21.8%)	103 (39.3%)	42 (56.0%)	
Thoracic pain	240 (18.4%)	212 (21.9%)	25 (9.5%)	3 (4.0%)	
Miscellaneous	333 (25.6%)	229 (23.7%)	82 (31.3%)	22 (29.3%)	
Main diagnosis, n (%)					<0.001
Cancer	52 (4.0%)	44 (4.6%)	6 (2.3%)	2 (2.7%)	
Cardiovascular	486 (37.3%)	386 (40.0%)	83 (31.7%)	17 (22.7%)	
Gastrointestinal	160 (12.3%)	137 (14.2%)	17 (6.5%)	6 (8.0%)	
Infection	190 (14.6%)	102 (10.6%)	57 (21.8%)	31 (41.3%)	
Metabolic	49 (3.8%)	33 (3.4%)	15 (5.7%)	1 (1.3%)	
Neurological	176 (13.5%)	140 (14.5%)	33 (12.6%)	3 (4.0%)	
Pulmonary	110 (8.4%)	60 (6.2%)	37 (14.1%)	13 (17.3%)	
Miscellaneous	80 (6.1%)	64 (6.6%)	14 (5.3%)	2 (2.7%)	
Comorbidities, n (%)					
Cancer	123 (9.4%)	73 (7.6%)	37 (14.1%)	13 (17.3%)	<0.001
Chronic renal disease	96 (7.4%)	55 (5.7%)	26 (9.9%)	15 (20.0%)	<0.001
Congestive heart failure	154 (11.8%)	88 (9.1%)	46 (17.6%)	20 (26.7%)	<0.001
COPD	94 (7.2%)	46 (4.8%)	36 (13.7%)	12 (16.0%)	<0.001
Coronary heart disease	164 (12.6%)	110 (11.4%)	43 (16.4%)	11 (14.7%)	0.080
Diabetes	269 (20.6%)	187 (19.4%)	64 (24.4%)	18 (24.0%)	0.15
History of stroke	22 (1.7%)	12 (1.2%)	7 (2.7%)	3 (4.0%)	0.078
Hypertension	568 (43.6%)	432 (44.7%)	108 (41.2%)	28 (37.3%)	0.32

COPD, chronic obstructive pulmonary disease; ED, emergency department; NEWS, national early warning score; PCT, procalcitonin; MR-proADM, midregional pro-Adrenomedullin; SpO_2, peripheral oxygen saturation (%).
NEWS was calculated without oxygen supplementation data and thus represents "NEWS - potentially minus 2"
To assess group differences we used Kruskal-Wallis test for continuous, skew variables, and Pearson's chi-squared test for categorial and binary variables.

NEWS and mortality

The 30-day mortality rate following admission to the ED was 4.1%. In unadjusted logistic regression analyses, we found a significant association between 30-day mortality and NEWS overall (OR 1.35, 95% CI 1.23 to 1.48, p<0.001) and stratified into risk groups with corresponding ORs of 2.45 (95% CI 1.29 to 4.66, p=0.006) for the moderate risk NEWS category, and 7.89 (95% CI 3.85 to 16.18, p<0.001) for the high risk NEWS category, respectively, compared to the low risk NEWS category. These associations remained robust after stepwise adjustment for confounders (see Table 2 for univariate and fully adjusted ORs. Data on all of the remaining models are presented in the supplementary materials table A2). Receiver operating statistics showed fair discriminative performance with regard to 30-day all-cause mortality, with an AUC of 0.73 (95% CI 0.66 to 0.80).

Table 2: Regression analyses for associations of NEWS and blood markers with primary and secondary outcomes

	30 day mortality			ICU admission		
		Regression analyses, OR (95% CI), p-Value			Regression analyses, OR (95% CI), p-Value	
	Events, n (%)	Unadjusted	Fully Adjusted	Events, n (%)	Unadjusted	Fully Adjusted
Total cohort	54/1,303 (4.1)			171/1,303 (13.1)		
NEWS						
Low	25/966 (2.6)	Ref.	Ref.	89/966 (9.2)	Ref.	Ref.
Moderate	16/262 (6.1)	2.45 (1.29 to 4.66), p=0.006	1.71 (0.87 to 3.37), p=0.123	57/262 (21.8)	2.74 (1.90 to 3.95), p<0.001	2.71 (1.85 to 3.98), p<0.001
High	13/75 (17.3)	7.89 (3.85 to 16.18), p<0.001	4.89 (2.22 to 10.75), p<0.001	25/75 (33.3)	4.93 (2.91 to 8.35), p<0.001	4.33 (2.48 to 7.57), p<0.001
Continuous		1.35 (1.23 to 1.48), p<0.001	1.26 (1.13 to 1.40), p<0.001		1.25 (1.17 to 1.33), p<0.001	1.24 (1.15 to 1.32), p<0.001
WBC (G/L)						
4.0-10.0	27/829 (3.3)	Ref.	Ref.	84/829 (10.1)	Ref.	Ref.
10.01-15.0	10/299 (3.3)	1.03 (0.49 to 2.15), p=0.942	1.07 (0.50 to 2.31), p=0.855	41/299 (13.7)	1.41 (0.95 to 2.10), p=0.092	1.52 (1.01 to 2.29), p=0.045
>15.0	15/111 (13.5)	4.64 (2.39 to 9.03), p<0.001	3.73 (1.80 to 7.75), p<0.001	27/111 (24.3)	2.85 (1.75 to 4.65), p<0.001	2.78 (1.67 to 4.62), p<0.001
<4.0	2/46 (4.4)	1.35 (0.31 to 5.86), p=0.689	1.05 (0.22 to 4.99), p=0.951	15/46 (32.6)	4.29 (2.23 to 8.27), p<0.001	4.42 (2.21 to 8.84), p<0.001
Continuous		1.02 (1.00 to 1.03), p=0.051	1.02 (1.00 to 1.03), p=0.036		1.01 (0.99 to 1.02), p=0.355	1.01 (0.99 to 1.02), p=0.267
PCT						
1st Quartile	5/321 (1.6)	Ref.	Ref.	27/321 (8.4)	Ref.	Ref.
2nd Quartile	7/321 (2.2)	1.41 (0.44 to 4.49), p=0.562	1.24 (0.38 to 4.09), p=0.722	34/321 (10.6)	1.29 (0.76 to 2.19), p=0.347	1.23 (0.72 to 2.11), p=0.449
3rd Quartile	10/321 (3.1)	2.03 (0.69 to 6.01), p=0.200	1.79 (0.59 to 5.45), p=0.306	36/321 (11.2)	1.38 (0.81 to 2.32), p=0.234	1.35 (0.79 to 2.29), p=0.276
4th Quartile	32/322 (9.9)	6.97 (2.68 to 18.14), p<0.001	5.17 (1.88 to 14.18), p=0.001	73/322 (22.7)	3.19 (1.99 to 5.12), p<0.001	2.78 (1.68 to 4.59), p<0.001
Continuous		2.66 (1.81 to 3.92), p<0.001	2.45 (1.54 to 3.89), p<0.001		2.33 (1.76 to 3.08), p<0.001	2.18 (1.61 to 2.96), p<0.001
MR-proADM						
1st Quartile	1/324 (0.3)	Ref.	Ref.	20/324 (6.2)	Ref.	Ref.
2nd Quartile	6/325 (1.9)	6.08 (0.73 to 50.75), p=0.096	4.93 (0.57 to 42.58), p=0.147	36/325 (11.1)	1.89 (1.07 to 3.35), p=0.028	2.26 (1.24 to 4.13), p=0.008
3rd Quartile	12/323 (3.7)	12.46 (1.61 to 96.42), p=0.016	7.93 (0.96 to 65.37), p=0.054	34/323 (10.5)	1.79 (1.01 to 3.18), p=0.048	2.25 (1.19 to 4.27), p=0.013
4th Quartile	35/326 (10.7)	38.85 (5.29 to 285.36), p<0.001	17.18 (2.15 to 137.36), p=0.007	81/326 (24.9)	5.03 (3.00 to 8.43), p<0.001	6.27 (3.36 to 11.68), p<0.001
Continuous		17.58 (8.05 to 38.38), p<0.001	10.33 (3.77 to 28.34), p<0.001		7.65 (4.59 to 12.75), p<0.001	9.20 (4.83 to 17.51), p<0.001

Fully adjusted model adjusted for age, sex, main diagnosis, and comorbidities

For regression analysis with continues values, PCT and Pro-ADM were log transformed with a base of ten before entering into statistical models. Therefore, the ORs correspond to a tenfold increase in PCT and MR-proADM values.

CI, confidence interval; ICU, intensive care unit; NEWS, national early warning score; PCT, procalcitonin; MR-proADM, midregional pro-Adrenomedullin; Ref, reference; WBC, white blood cell count

NEWS was calculated without oxygen supplementation data and thus represents “NEWS - potentially minus 2”

Incremental impact of inflammatory blood markers on prediction of mortality

The inflammatory blood markers WBC, PCT, and MR-proADM showed low to fair prognostic accuracy for prediction of 30-day mortality with AUCs of 0.64 (95% CI 0.56 to 0.72), 0.71 (95% CI 0.64 to 0.79), and 0.78 (95% CI 0.73 to 0.84), respectively. Corresponding regression analyses for continuous values and stratified by cut-offs are shown in Table 2. Adding all three markers to NEWS significantly improved the predictive value to an AUC of 0.82 (95% CI 0.77 to 0.88, p=0.002). Interestingly, adding only MR-proADM to a model with NEWS showed a similar AUC of 0.82 (95% CI 0.77 to 0.87, p=0.002) for prediction of mortality (Table 3, Figure 1). We further calculated Kaplan-Meier survival estimates (Figure 2).

Table 3: Discriminative performance of NEWS and biomarkers for the prediction of primary and secondary outcomes

	AUROC (95% CI)			
	30-day mortality	P-value	ICU admission	p-value
NEWS	0.73 (0.66 to 0.80)		0.65 (0.61 to 0.70)	
WBC	0.64 (0.56 to 0.72)		0.54 (0.49 to 0.59)	
PCT	0.71 (0.64 to 0.79)		0.62 (0.57 to 0.67)	
ProADM	0.78 (0.73 to 0.84)		0.67 (0.62 to 0.72)	
all combined	0.82 (0.77 to 0.88)	0.002	0.70 (0.65 to 0.75)	0.006
NEWS & WBC	0.74 (0.67 to 0.81)	0.196	0.65 (0.60 to 0.70)	0.792
NEWS & PCT	0.78 (0.72 to 0.84)	0.004	0.68 (0.64 to 0.73)	0.017
NEWS & proADM	0.82 (0.77 to 0.87)	0.002	0.70 (0.65 to 0.74)	0.009

CI, confidence interval; ICU, intensive care unit; NEWS, national early warning score; PCT, procalcitonin; MR-proADM, midregional Pro-Adrenomedullin; WBC, white blood cell count.
NEWS was calculated without oxygen supplementation data and thus represents “NEWS - potentially minus 2”
P-values correspond to the AUCs of the respective models compared to the AUC of NEWS alone and were assessed using Pearson’s chi-squared test.

NEWS and ICU admission

During their hospital stay, 13.1% of patients were admitted to the ICU. Similar to findings with the primary endpoint, unadjusted regression analyses showed significant associations of NEWS with ICU admission (OR 1.25, 95% CI 1.17 to 1.33, p<0.001). Stratification of NEWS by risk categories showed respective ORs of 2.74 (95% CI 1.90 to 3.95, p<0.001) for the moderate risk category and 4.93 (95% CI 2.91 to 8.35, p<0.001) for the high risk category, compared with the low risk category. As before, the results stayed robust after adjusting for important confounders (see Table 2 for univariate and fully adjusted ORs. All of the remaining models are presented in the supplementary materials Table A3).

When receiver operating statistics were determined, NEWS showed low discriminative performance with regard to ICU admission (AUC 0.65, 95% CI 0.61 to 0.70).

Incremental impact of inflammatory blood markers on prediction of ICU admission

The predictive value of the blood markers WBC (AUC 0.54, 95% CI 0.49 to 0.59), PCT (AUC 0.62, 95% CI 0.57 to 0.67), and MR-proADM (AUC 0.67, 95% CI 0.62 to 0.72) for ICU admission was low, with only MR-proADM showing slightly better prognostic accuracy than NEWS. For univariate and multivariate regression analyses for associations of blood markers with ICU admission, see Table 2. A combined model of NEWS with all three blood markers again improved discriminative performance (AUC 0.70, 95% CI 0.65 to 0.75, p=0.006). Similar to the association with mortality, a model including only NEWS and MR-proADM showed equal results for prediction of ICU admission (AUC 0.70, 95% CI 0.65 to 0.74, p=0.009) (Table 3, Figure 1).

Subgroup analyses

Analyses of subgroups showed similar association of NEWS with 30-day mortality among different diagnoses leading to ED admission (supplementary materials Figure A1).

DISCUSSION

This multinational study of heterogenous medical ED patients found a fair performance of the National Early Warning Score (NEWS) for prediction of 30-day mortality when calculated at a single timepoint at ED admission. Results remained robust after adjustment for potential confounders and among different subgroups. Additionally, we found that the predictive value of NEWS was improved by adding inflammatory blood markers, in particular MR-proADM. We also found the discriminative value of NEWS for prediction of our secondary outcome, ICU admission, was less strong but was also improved by adding PCT and MR-proADM to the model.

The 30-day mortality in our study (4.1%) was in line with the 4.0% to 5.7% reported in other investigations that included similar patient populations and examined similar outcome measures [19 38]. Prevalence of ICU admission during hospital stay in our study (13.1%) was within ICU admission rates in several other studies that reported a range between 1% and 17.4% [5 10 13 16 38 39]. This wide range may be a reflection of different healthcare systems studied and particularly of different follow-up periods, as the different investigations examined short-term outcomes within 24 or 48 hours of admission, respectively. In this respect, our results are most notably consistent with the findings of several Scandinavian studies [5 13 15].

Regarding predictive performance, other studies investigating discriminative power of NEWS documented at the time of ED arrival, found similar AUCs for prediction of in-hospital mortality or 30-day mortality, with reported AUCs of 0.65 to 0.77 in patients with

suspected infection/sepsis [40-42] and AUCs of 0.77 to 0.84 in general ED patients, respectively [16 38].

Predictive performance for ICU admission in our study (AUC 0.65, 95% CI 0.61 to 0.70) was slightly lower than the AUCs in other publications that report AUCs of 0.67 to 0.857 for prediction of ICU admission in different patient populations [9 16 41 43].
Our finding of MR-proADM as a solitary predictor of 30-day mortality (AUC 0.78, 95% CI 0.73 to 0.84) is in line with the result of another Swiss study reporting an AUC of 0.732 for the same purpose in a cohort of patients with nonspecific complaints presenting to the ED [34].

To the best of our knowledge, this is the first study investigating NEWS in a multinational cohort of medical ED patients. Moreover, this is the first study investigating the potential additional impact of promising inflammatory markers, namely PCT and MR-proADM, on NEWS for the prediction of adverse outcome.

One could argue that adding blood markers to a clinical score might complicate its calculation, but in EDs initial blood draws are part of routine care, which is why the additional determination of inflammatory marker levels do not change existing processes. In contrast, WBC results are available rapidly, and indeed PCT- point-of-care tests that provide results within minutes are being developed [44]. Measurements of additional blood markers thus might partially overcome user-dependency of early warning scores and might therefore improve early risk stratification. Our study reveals that MR-proADM could be a particularly suitable and promising blood marker for early

risk stratification when combined with a clinical score such as NEWS. As a result, identification of patients needing urgent care could be improved. However, right now there is no point of care test available that would allow rapid measurement of MR-proADM. Clinicians would likely evaluate results from biomarker assays in the light of the patient's condition at the time the test results become available, not at time the blood sample was drawn. As ED patients are in a dynamic situation, NEWS and the patient's condition might have changed already when results become available.

This study has some limitations. First, since it is a study where NEWS was calculated retrospectively, associations between NEWS and biomarkers and outcomes are likely confounded. We addressed this limitation at least partially by adjusting for important confounders. However, with residual confounding being likely, our results are at best hypothesis generating. Second, NEWS was calculated retrospectively, and vital signs were not measured more frequently than standard clinical practice. However, we addressed possible bias regarding a treatment paradox since observed mortality may be lower in studies where NEWS is acted upon. Third, due to missing vital sign data—particularly respiratory rate—a large number of patients were not eligible for final analysis. This is in line with other studies reporting that early warning scores were often incomplete [45] and that among others respiratory rate was documented in only 30% to 60% of cases [45 46]. However, our sample is still relatively large and represents a multinational cohort of unselected medical ED patients. Moreover, given that health system organization strongly influences populations at EDs, the multinational nature of our study provides external validity. However, there is the possibility of a selection bias as the cohort included in this analysis differed to the initial total cohort in age, some of

the main symptoms and main diagnoses at ED admission, and comorbidities. This was addressed in the regression models by adjusting for the aforementioned confounders. The results remained robust. Fourth, information on the use of oxygen support was not available retrospectively and therefore did not contribute to NEWS calculation, which reduced the maximum score from 20 to 18. This might have led to misclassification of patients and might have diminished the discriminatory power of NEWS. It is likely that the fraction of patients that were under-rated by 2 points due to missing information on oxygen supplements would increase from the low via the moderate to the high-risk NEWS group. This could represent at systematical bias where sicker patients (probably with worse outcomes) would potentially be misclassified with fewer points in the NEWS score, possibly resulting in statistical inflation of the effect of the lower NEWS values. However, the Royal College of Physicians recommends addition of a weighting score of 2 not by default for all patients with supplemental oxygen but only for patients requiring supplemental oxygen to maintain their optimal oxygen saturation [7]. As the optimal oxygen saturation may be different in varying patient groups, most notably in patients with hypercapnic respiratory failure, the actual requirement of supplemental oxygen is hard to determine and requires evaluation of a qualified and experienced physician. As a result, certain patients might mistakenly score 2 additional points for supplemental oxygen, which can again result in misclassification of the NEWS risk category. However, as mentioned before, the discriminative power of NEWS in our study is comparable to other similar investigations. Fifth, we only had a few events, which could limit reliability and is reflected in the rather broad 95% confidence intervals. This was addressed at least in part by hard endpoints and a structured follow-up with phone interviews 30 days after admission or through contacting the patient's family or general practitioner. Sixth,

the decision regarding ICU admission was left to the discretion of treating physicians. This reflects procedures followed in the included centers and may be different from those in other hospitals. Last, NEWS was not designed to be a single time point tool but rather a “track-and-trigger” system in individual patients. Accuracy of NEWS may thus be different if multiple measurements at different time points are considered.

CONCLUSION

Combining NEWS calculated upon admission to the ED with markers of inflammation such as MR-proADM and PCT improves the predictive value of NEWS in unselected medical patients. The combination of NEWS and MR-proADM might prove to be a particularly promising tool for early risk stratification. Whether these theoretical benefits of improved risk stratification at ED admission can be translated into improved outcomes has to be examined in future interventional studies.

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Author contributions

Prof. Philipp Schuetz had complete access to all study data and takes full responsibility for the integrity of the data and the accuracy of the analyses. BM and PS were involved in the conceptualization and design of the study. PH, DA, AA, AH, and PS were responsible for the acquisition, analysis, or interpretation of the data. AE, SIH, and PS performed the statistical analyses and drafted the manuscript. AK and SH reviewed the draft and revised the manuscript for important intellectual content. All authors approved the final version of the manuscript and the decision to submit the manuscript for publication. AE and SIH contributed equally to this work.

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Competing interests

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Data sharing statement: Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi:10.5061/dryad.d22q6vh

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FIGURES

Figure 1: Discriminative performance of NEWS, blood markers, and combination of NEWS and blood markers for the prediction of all-cause 30-day mortality (A) and ICU admission (B)

Legend: NEWS, national early warning score; PCT, procalcitonin; MR-proADM, midregional Pro-Adrenomedullin; WBC, white blood cell count
NEWS was calculated without oxygen supplementation data and thus represents "NEWS - potentially minus 2"

Figure 2: Kaplan-Meier survival estimates stratified by admission NEWS category (A), white blood cell count (WBC) (B), procalcitonin (PCT) (C), and MR-pro-adrenomedullin (MR-proADM) (D)

Legend: NEWS was calculated without oxygen supplementation data and thus represents "NEWS - potentially minus 2"

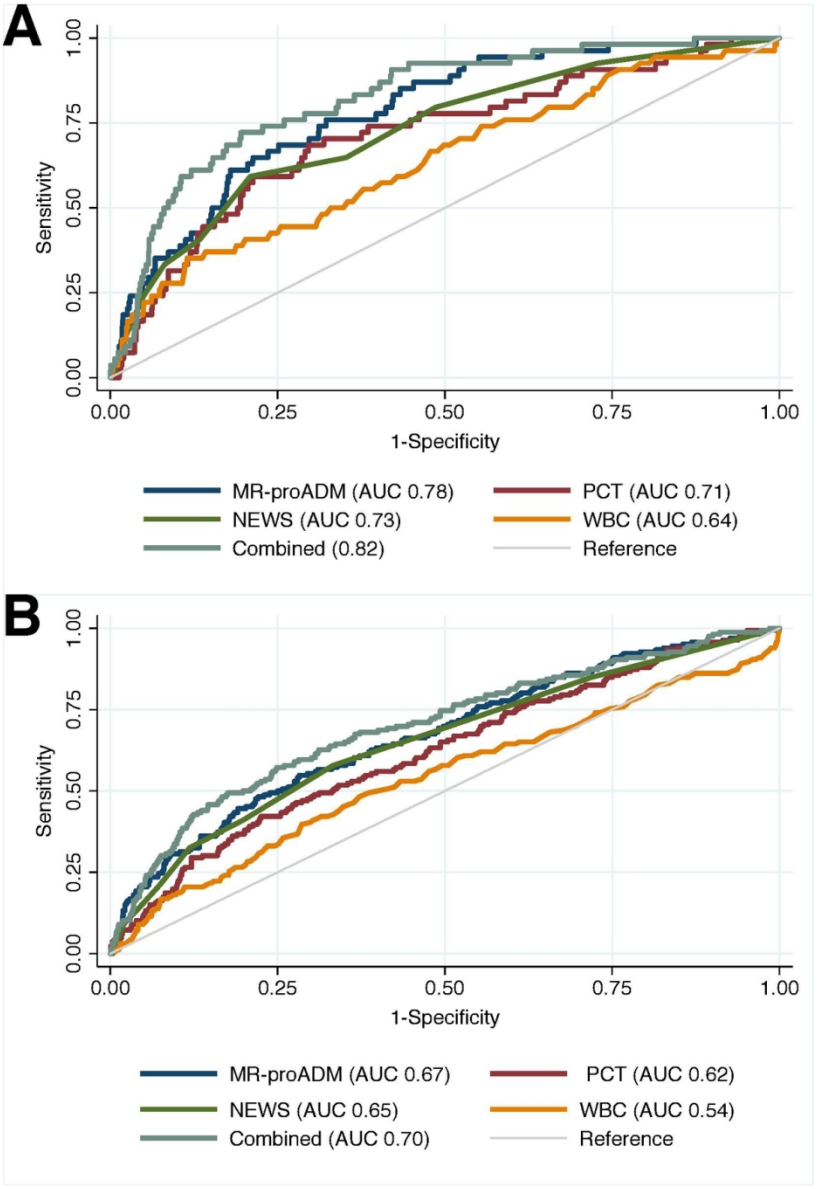


Figure 1: Discriminative performance of NEWS, blood markers, and combination of NEWS and blood markers for the prediction of all-cause 30-day mortality (A) and ICU admission (B)Legend: NEWS, national early warning score; PCT, procalcitonin; MR-proADM, midregional Pro-Adrenomedullin; WBC, white blood cell count. NEWS was calculated without oxygen supplementation data and thus represents "NEWS - potentially minus 2"

103x150mm (300 x 300 DPI)

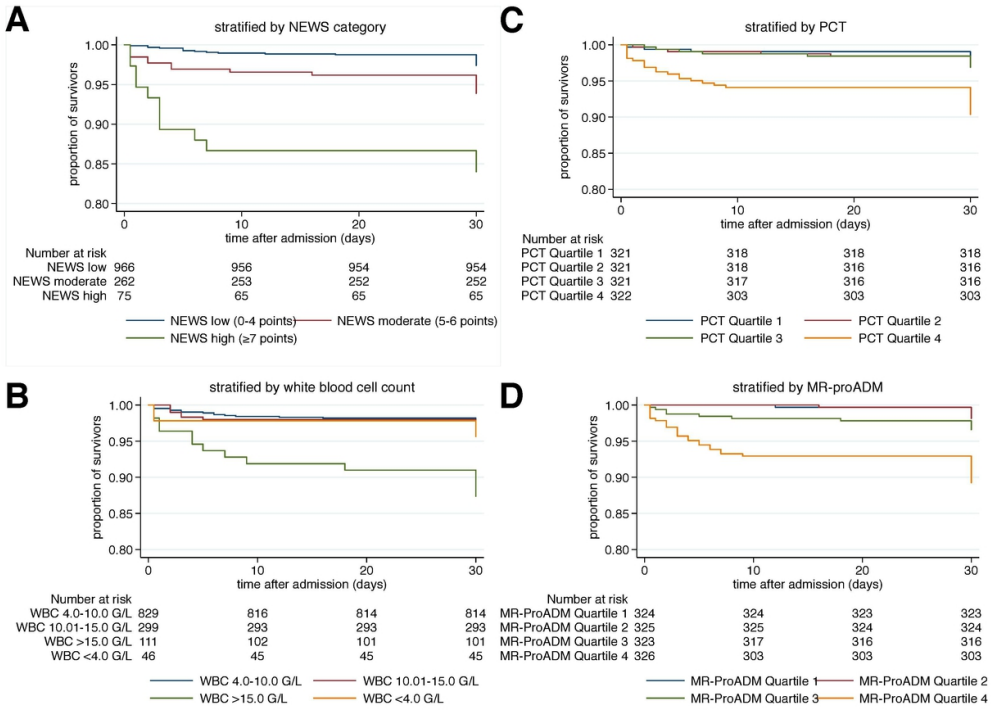


Figure 2: Kaplan-Meier survival estimates stratified by admission NEWS category (A), white blood cell count (WBC) (B), procalcitonin (PCT) (C), and MR-pro-adrenomedullin (MR-proADM) (D). Legend: NEWS was calculated without oxygen supplementation data and thus represents "NEWS - potentially minus 2"

103x75mm (300 x 300 DPI)

Table A1: Comparison of the total cohort and cohort selected for analysis

Number of Patients, n (%)	Total Cohort 7132	Selected Cohort 1303
Sociodemographics		
Age, median (quartiles)	62 (46, 76)	66 (52, 80)
Male gender, n (%)	3767 (53.3%)	658 (50.5%)
Vital signs, median (quartiles)		
Blood pressure diastolic (mmHg)	80 (70, 90)	78 (67, 89)
Blood pressure systolic (mmHg)	137 (121, 154)	139 (121, 159)
Confusion, n (%)	522 (7.3%)	44 (3.4%)
Pulse (bpm)	83 (71, 97)	83 (71, 98)
Respiratory rate (per minute)	18 (18, 20)	18 (18, 20)
SpO2 (%)	96.8 (94, 98)	97 (95, 99)
Temperature (°C)	36.8 (36.4, 37.2)	36.6 (36.2, 36.9)
Intial blood biomarkers, median (quartiles)		
Creatinine (µmol/L)	81.0 (67.0, 103.0)	79.6 (70.7, 106.1)
Glucose (mmol/L)	6.1 (5.3, 7.5)	6.3 (5.3, 8.1)
White blood cells (G/L)	8.385 (6.58, 10.98)	8.2 (6.3, 10.8)
PCT (µg/L)	0.08 (0.06, 0.13)	0.08 (0.06, 0.14)
ProADM (nmol/L)	0.8 (0.6, 1.2)	0.9 (0.6, 1.5)
Main symptom at ED admission, n (%)		
Diarrhea, vomitus, dysuria	495 (6.9%)	106 (8.1%)
Fever	343 (4.8%)	23 (1.8%)
Gastrointestinal bleeding	199 (2.8%)	31 (2.4%)
Neurological symptoms	1379 (19.3%)	90 (6.9%)
Nonthoracic pain	1217 (17.1%)	124 (9.5%)
Respiratory symptoms	948 (13.3%)	356 (27.3%)
Thoracic pain	1038 (14.6%)	240 (18.4%)
Worsening of general condition	837 (11.7%)	333 (25.6%)
Main diagnosis, n (%)		
Cancer	344 (4.8%)	52 (4.0%)
Cardiovascular	1660 (23.3%)	486 (37.3%)
Gastrointestinal	983 (13.8%)	160 (12.3%)
Infection	1039 (14.6%)	190 (14.6%)
Metabolic	192 (2.7%)	49 (3.8%)
Neurological	1566 (22.0%)	176 (13.5%)
Pulmonary	297 (4.2%)	110 (8.4%)
Miscellaneous	1051 (14.7%)	80 (6.1%)
Comorbidities, n (%)		
Cancer	968 (13.6%)	123 (9.4%)
Chronic renal disease	872 (12.2%)	96 (7.4%)
Congestive heart failure	487 (6.8%)	154 (11.8%)
COPD	359 (5.0%)	94 (7.2%)
Coronary heart disease	838 (11.7%)	164 (12.6%)
Diabetes	1088 (15.3%)	269 (20.6%)
History of stroke	566 (7.9%)	22 (1.7%)
Hypertension	2795 (39.2%)	568 (43.6%)
Events, n (%)		
Death 30 days	331 (4.6%)	54 (4.1%)
Intensive Care	453 (6.4%)	171 (13.1%)

COPD, chronic obstructive pulmonary disease; ED, emergency department; NEWS, national early warning score; PCT, procalcitonin; MR-proADM, midregional pro-Adrenomedullin; SpO_2, peripheral oxygen saturation (%).
NEWS was calculated without oxygen supplementation data and thus represents “NEWS - potentially minus 2”

Table A2: Regression analyses for associations of NEWS and blood markers with primary outcome

		30 day mortality			
		Regression analyses, OR (95% CI), p-value			
	Events, n (%)	Unadjusted	Model 1	Model 2	Model 3
NEWS					
Low	25/966 (2.6)	Ref.	Ref.	Ref.	Ref.
Moderate	16/262 (6.1)	2.45 (1.29 to 4.66), p=0.006	2.04 (1.06 to 3.92), p=0.032	2.01 (1.05 to 3.87), p=0.036	1.71 (0.87 to 3.37), p=0.123
High	13/75 (17.3)	7.89 (3.85 to 16.18), p<0.001	7.01 (3.36 to 14.63), p<0.001	6.79 (3.23 to 14.3), p<0.001	4.89 (2.22 to 10.75), p<0.001
Continuous		1.35 (1.23 to 1.48), p<0.001	1.32 (1.2 to 1.46), p<0.001	1.32 (1.19 to 1.45), p<0.001	1.26 (1.13 to 1.40), p<0.001
WBC					
4.0-10.0	27/829 (3.3)	Ref.	Ref.	Ref.	Ref.
10.01-15.0	10/299 (3.3)	1.03 (0.49 to 2.15), p=0.942	1.05 (0.5 to 2.21), p=0.893	1.05 (0.5 to 2.21), p=0.9	1.07 (0.50 to 2.31), p=0.855
>15.0	15/111 (13.5)	4.64 (2.39 to 9.03), p<0.001	4.41 (2.22 to 8.76), p=0	4.37 (2.2 to 8.69), p=0	3.73 (1.80 to 7.75), p<0.001
<4.0	2/46 (4.4)	1.35 (0.31 to 5.86), p=0.689	1.52 (0.34 to 6.74), p=0.583	1.52 (0.34 to 6.76), p=0.58	1.05 (0.22 to 4.99), p=0.951
Continuous		1.02 (1.00 to 1.03), p=0.051	1.02 (1 to 1.03), p=0.033	1.02 (1 to 1.03), p=0.028	1.02 (1.00 to 1.03), p=0.036
PCT					
1st Quartile	5/321 (1.6)	Ref.	Ref.	Ref.	Ref.
2nd Quartile	7/321 (2.2)	1.41 (0.44 to 4.49), p=0.562	1.32 (0.41 to 4.22), p=0.642	1.33 (0.41 to 4.26), p=0.632	1.24 (0.38 to 4.09), p=0.722
3rd Quartile	10/321 (3.1)	2.03 (0.69 to 6.01), p=0.2	1.77 (0.59 to 5.26), p=0.307	1.84 (0.62 to 5.48), p=0.276	1.79 (0.59 to 5.45), p=0.306
4th Quartile	32/322 (9.9)	6.97 (2.68 to 18.14), p<0.001	6.01 (2.29 to 15.79), p<0.001	6.12 (2.33 to 16.09), p<0.001	5.17 (1.88 to 14.18), p=0.001
Continuous		2.66 (1.81 to 3.92), p<0.001	2.77 (1.85 to 4.17), p<0.001	2.71 (1.79 to 4.08), p<0.001	2.45 (1.54 to 3.89), p<0.001
MR-proADM					
1st Quartile	1/324 (0.3)	Ref.	Ref.	Ref.	Ref.
2nd Quartile	6/325 (1.9)	6.08 (0.73 to 50.75), p=0.096	4.42 (0.52 to 37.78), p=0.175	4.44 (0.52 to 37.93), p=0.174	4.93 (0.57 to 42.58), p=0.147
3rd Quartile	12/323 (3.7)	12.46 (1.61 to 96.42), p=0.016	7.66 (0.94 to 62.38), p=0.057	7.77 (0.96 to 63.12), p=0.055	7.93 (0.96 to 65.37), p=0.054
4th Quartile	35/326 (10.7)	38.85 (5.29 to 285.36), p<0.001	22.46 (2.87 to 175.82), p=0.003	22.22 (2.84 to 173.70), p=0.003	17.18 (2.15 to 137.36), p=0.007
Continuous		17.58 (8.05 to 38.38), p<0.001	13.89 (5.94 to 32.49), p<0.001	13.40 (5.70 to 31.54), p<0.001	10.33 (3.77 to 28.34), p<0.001

Adjustments: Model 1: age and sex; Model 2: age, sex, and main diagnosis; Model 3: fully adjusted for age, sex, main diagnosis, and comorbidities

For regression analysis with continues values, PCT and Pro-ADM were log transformed with a base of ten before entering into statistical models. Therefore, the ORs correspond to a tenfold increase in PCT and MR-proADM values.

CI, confidence interval; ICU, intensive care unit; NEWS, national early warning score; PCT, procalcitonin; MR-proADM, midregional pro-Adrenomedullin; Ref, reference; WBC, white blood cell count

NEWS was calculated without oxygen supplementation data and thus represents “NEWS - potentially minus 2”

Table A3: Regression analyses for associations of NEWS and blood markers with secondary outcome

	ICU admission				
		Regression analyses, OR (95% CI), p-value			
	events, n (%)	unadjusted	model 1	model 2	model 3
NEWS					
Low	89/966 (9.2)	Ref.	Ref.	Ref.	Ref.
Moderate	57/262 (21.8)	2.74 (1.90 to 3.95), p<0.001	2.75 (1.90 to 3.99), p<0.001	2.75 (1.90 to 3.99), p<0.001	2.71 (1.85 to 3.98), p<0.001
High	25/75 (33.3)	4.93 (2.91 to 8.35), p<0.001	4.90 (2.88 to 8.35), p<0.001	4.88 (2.86 to 8.33), p<0.001	4.33 (2.48 to 7.57), p<0.001
Continuous		1.25 (1.17 to 1.33), p<0.001	1.25 (1.17 to 1.33), p<0.001	1.25 (1.17 to 1.33), p<0.001	1.24 (1.15 to 1.32), p<0.001
WBC					
4.0-10.0	84/829 (10.1)	Ref.	Ref.	Ref.	Ref.
10.01-15.0	41/299 (13.7)	1.41 (0.95 to 2.10), p=0.092	1.43 (0.96 to 2.13), p=0.081	1.43 (0.96 to 2.13), p=0.081	1.52 (1.01 to 2.29), p=0.045
>15.0	27/111 (24.3)	2.85 (1.75 to 4.65), p<0.001	2.75 (1.68 to 4.49), p<0.001	2.74 (1.68 to 4.49), p<0.001	2.78 (1.67 to 4.62), p<0.001
<4.0	15/46 (32.6)	4.29 (2.23 to 8.27), p<0.001	4.19 (2.16 to 8.12), p<0.001	4.18 (2.15 to 8.10), p<0.001	4.42 (2.21 to 8.84), p<0.001
Continuous		1.01 (0.99 to 1.02), p=0.355	1.01 (0.99 to 1.02), p=0.317	1.01 (0.99 to 1.02), p=0.313	1.01 (0.99 to 1.02), p=0.267
PCT					
1st Quartile	27/321 (8.4)	Ref.	Ref.	Ref.	Ref.
2nd Quartile	34/321 (10.6)	1.29 (0.76 to 2.19), p=0.347	1.27 (0.74 to 2.15), p=0.386	1.27 (0.75 to 2.16), p=0.381	1.23 (0.72 to 2.11), p=0.449
3rd Quartile	36/321 (11.2)	1.38 (0.81 to 2.32), p=0.234	1.33 (0.78 to 2.25), p=0.294	1.34 (0.79 to 2.27), p=0.276	1.35 (0.79 to 2.29), p=0.276
4th Quartile	73/322 (22.7)	3.19 (1.99 to 5.12), p<0.001	2.99 (1.86 to 4.81), p<0.001	3.00 (1.86 to 4.84), p<0.001	2.78 (1.68 to 4.59), p<0.001
Continuous		2.33 (1.76 to 3.08), p<0.001	2.31 (1.74 to 3.07), p<0.001	2.31 (1.74 to 3.06), p<0.001	2.18 (1.61 to 2.96), p<0.001
MR-proADM					
1st Quartile	20/324 (6.2)	Ref.	Ref.	Ref.	Ref.
2nd Quartile	36/325 (11.1)	1.89 (1.07 to 3.35), p=0.028	2.26 (1.24 to 4.09), p=0.007	2.26 (1.25 to 4.09), p=0.007	2.26 (1.24 to 4.13), p=0.008
3rd Quartile	34/323 (10.5)	1.79 (1.01 to 3.18), p=0.048	2.24 (1.20 to 4.20), p=0.011	2.25 (1.20 to 4.20), p=0.011	2.25 (1.19 to 4.27), p=0.013
4th Quartile	81/326 (24.9)	5.03 (3.00 to 8.43), p<0.001	6.36 (3.53 to 11.48), p<0.001	6.35 (3.52 to 11.44), p<0.001	6.27 (3.36 to 11.68), p<0.001
Continuous		7.65 (4.59 to 12.75), p<0.001	8.64 (5.00 to 14.95), p<0.001	8.62 (4.98 to 14.95), p<0.001	9.20 (4.83 to 17.51), p<0.001

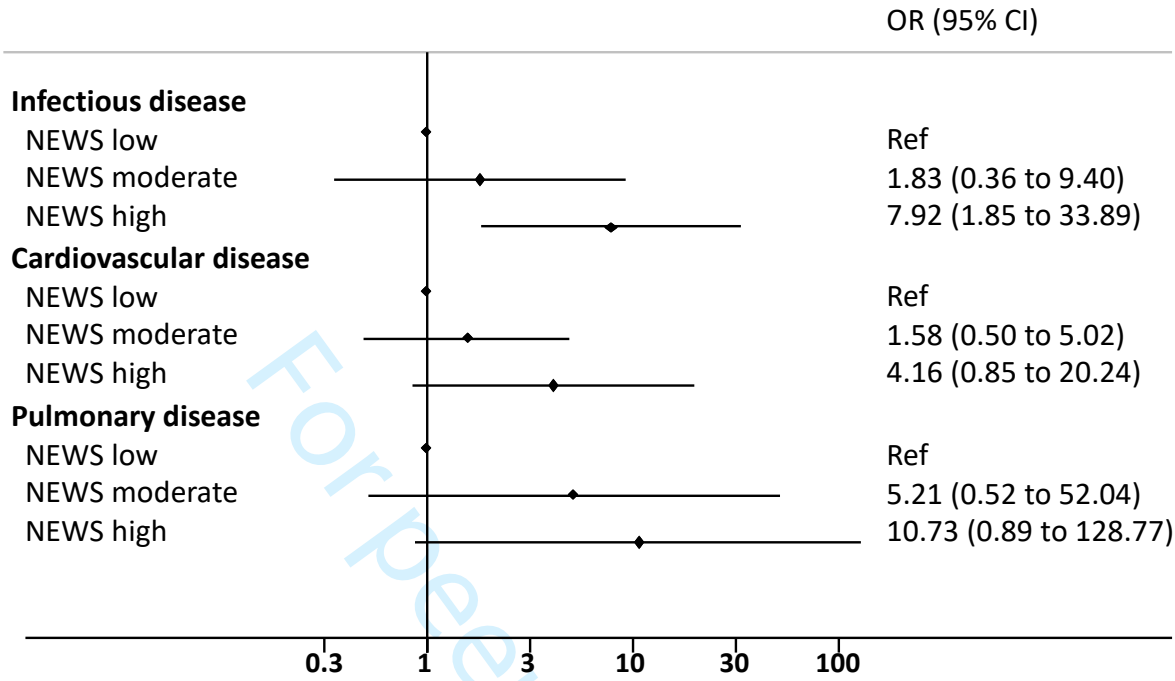
Adjustments: Model 1: age and sex; Model 2: age, sex, and main diagnosis; Model 3: fully adjusted for age, sex, main diagnosis, and comorbidities

For regression analysis with continues values, PCT and Pro-ADM were log transformed with a base of ten before entering into statistical models. Therefore, the ORs correspond to a tenfold increase in PCT and MR-proADM values.

CI, confidence interval; ICU, intensive care unit; NEWS, national early warning score; PCT, procalcitonin; MR-proADM, midregional pro-Adrenomedullin; Ref, reference; WBC, white blood cell count

NEWS was calculated without oxygen supplementation data and thus represents “NEWS - potentially minus 2”

Figure A1: Subgroup analyses. Association of NEWS category with all-cause 30-day mortality among different diagnoses leading to ED admission



CI, Confidence interval; ED, emergency department; NEWS, national early warning score; OR, Odds ratio

NEWS was calculated without oxygen supplementation data and thus represents "NEWS - potentially minus 2"

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9, 11*
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	8, 13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	12
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	13
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	15, 18
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-16
		(*b*) Report category boundaries when continuous variables were categorized	11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	19
Discussion			
Key results	18	Summarise key results with reference to study objectives	20-21
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	23
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.