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Results from a 6 year follow-up

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The National Early Warning Score (NEWS) reliably improves adverse clinical outcome prediction in community-acquired pneumonia

Results from a 6 year follow-up

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Key words: National Early Warning Score (NEWS), community-acquired pneumonia (CAP), Pneumonia Severity Index (PSI), CURB-65, ICU-admission

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ABSTRACT

Objective: To compare the accuracy of NEWS to predict mortality and adverse clinical outcomes for patients with community acquired pneumonia with standard risk tools (PSI and CURB-65).

Design: Secondary analysis of a prospective cohort study with a median follow-up of 6.1 years.

Settings: Data from the ProHOSP Trial, a multicentre, noninferiority, randomized controlled trial in emergency departments of 6 tertiary care hospitals in Switzerland.

Participants: A total of 925 patients with diagnosis of community acquired pneumonia were included. For all of them the NEWS, PSI and CURB-65 scores were calculated.

Main outcome measure: Our primary outcome was all-cause mortality within 6 years of follow-up. Secondary outcomes were adverse clinical outcome defined as intensive care unit (ICU) admission, complications (empyema) and unplanned hospital readmission all within 30 days.

Results: Six-year overall mortality was 45.1% (n=417) with a step-wise increase with higher NEWS categories. For 30-days and 6-year mortality prediction, NEWS showed only moderate discrimination (AUC 0.65 and 0.60) inferior compared to PSI and CURB-65. For prediction of ICU admission, NEWS showed high discrimination (AUC 0.73) and improved the prognostic accuracy of PSI (AUC from 0.66 to 0.74, p=0.001) and CURB-65 (AUC from 0.64 to 0.73, p=0.015). NEWS was also superior to PSI and CURB-65 for prediction of complications, but did not well predict rehospitalisation.

Conclusion: NEWS provides additional prognostic information in regard to risk of ICU admission and complications thereby improves traditional clinical risk scores in the management of CAP patients in the emergency department setting.

Trial registration: ISRCTN 95122877

STRENGHTS AND LIMITATIONS OF THIS STUDY

Strenghts

- In the pre-hospital and emergency department, NEWS is an adequate tool for risk stratification.
- NEWS improves prediction for risk of ICU admission and clinical complications.
- NEWS enhances traditional clinical risk scores in the management of CAP patients in the emergency department setting.

Limitations

- Although NEWS is associated with mortality, this score has a lower prognostic performance compared to standard of care scores and did not improve their performance.
- This study was limited to Swiss, predominantly Caucasian patients, impairing reproducibility to other countries or regions.

INTRODUCTION

Today, it is recommended that clinical decisions regarding patient management in the emergency department (ED) setting are supported by objective risk scores [1]. In patients with community-acquired pneumonia (CAP) risk scores may support practitioners to decide whether a patient is at higher risk for mortality and, thus, may need inpatient treatment [2-5]. Several scores have been developed and validated for accuracy of predicting 30-day mortality in patients with CAP [6-10]. To date, the Pneumonia severity index (PSI) and CURB-65 are recommended by most international guidelines for this purpose [11 12]. The CURB-65 is a five point score that is predominantly used in Europe. The PSI is mostly used in the US and has been validated in several studies [7 13-18]. As a limitation, both scores have the main focus on 30-day mortality prediction, but other outcomes such as disease severity (e.g. requiring ICU admission) are not well predicted [19]. This raises the question whether these scores can be improved by combination with other instruments focusing on the initial severity of disease, such as generalized early warning scores (EWS).

Among different EWS, the National Early Warning Score (NEWS), that was derived in the UK by the National Early Warning Score Development and Implementation Group (NEWSDIG) on behalf of the Royal College of Physicians has been well established [20]. Its purpose was to introduce a standardised trigger-system to identify acutely ill patients upon hospital admission. NEWS consists of six physiological measurements classifying the patients into three risk-groups. Several studies found NEWS to be superior compared to other risk stratification tools [21-24] and a valid tool in different settings (ED, prehospital setting) [25-27]. Yet, there is currently no study investigating NEWS to predict severity and adverse clinical outcome in patients with CAP.

The aim of our study was to compare the accuracy of NEWS to predict mortality and adverse clinical outcomes with standard CAP risk tools (PSI and CURB-65) in a well characterised cohort of CAP patients. We hypothesized that NEWS may improve these scores in regard to severity assessment and prediction of adverse clinical outcome.

METHODS

Study design

This secondary analysis of a prospective randomized non-inferiority trial included 925 CAP patients with a 6 years follow-up. The initial trial enrolled patients from October 2006 to March 2008 at six Swiss secondary or tertiary care, academic or non-academic hospitals [28]. The primary aim of the study was to examine whether a PCT-guided algorithm could reduce antibiotic use without compromising the safety of those patients [29]. Patients were not involved in the design of the study not in the selection of outcome measures.

All local ethical committees approved the study protocol. All patients gave written informed consent. The study was also registered in the "Current Controlled Trial Database" (ISRCTN 95122877) at http://www.controlled-trials.com and a study protocol was published previously [29].

Study procedures

Consecutive adults (age ≥ 18 years) were included with a diagnosis of CAP presenting from the community or a nursing home to one of the participating hospitals. All patients fulfilled the following criteria: at least one symptom of cough,

sputum production, dyspnoea, tachypnoea or pleuritic pain in addition to one finding during auscultation (rales or crepitation) or one infectious sign (core body temperature > 38.0°C, shivering or white blood cell count > 10 or < 4 cells x 10^9/L). The diagnosis of CAP was confirmed in all patients by a new or increasing lung infiltrate on chest X-ray.

The exclusion criteria were defined as follows: language restriction or dementia precluding informed consent, intravenous drug abuse, sever immunosuppression other than corticosteroids, chronic antibiotic therapy, medical comorbidities with imminent risk of death, hospital acquired pneumonia (defined as newly appearing pulmonary infiltrate ≥ 48h postindex admission or during hospitalization within 2 weeks pre-ProHOSP enrolment).

Assessment of vital status and score assignment

Patients were clinically and biochemically evaluated upon admission and throughout the hospital stay. Data on demographics, comorbidities, medication, laboratory variables and imaging as well as vital signs were collected.

Vital status was ascertained by trained medical students by means of phone interviews at days 30, 180 and 540 as well as 6 years after discharge. Patients or their household members were contacted first, if not attainable, the primary care physicians were called. In cases of missing vital status, patients were categorized as survivors and the latest hospital discharge date derived from medical records was used to calculate survival time.

For all patients, PSI, CURB-65 scores and NEWS were calculated upon admission [7 8 20]. The PSI includes 20 variables and categorizes the patients with CAP into five risk

classes whereas the CURB-65 score uses a five point system (Confusion, Urea, Respiratory rate, Blood Pressure, Age > 65 years) classifying the patients into three risk classes. NEWS comprises the following six physiological parameters: respiratory rate, oxygen saturation, temperature, systolic blood pressure, pulse rate and level of consciousness. Every continuous variable scores a maximum of 3 points, whereas the need for supplemental oxygen and the level of consciousness are binary coded with zero points if absent/normal and 2 or 3 points if present/altered respectively. The resulting aggregate divides the patients into three groups with low (0-4 points), medium (5-6 points) or high (≥ 7 points) risk. As an exception, a single physiological parameter scoring 3 points classifies a patient at medium risk instead of low risk, denominated as RED score.

Statistical analyses

For the statistical analysis we used STATA 12.1 (Stata Corp, College Station, TX, USA). Statistical significance was defined as a p-value < 0.05; two-tailed tests were used.

The categorical variables are presented as percentages (numbers) and the continuous variables as medians (interquartile range [IQRs]) with confidence intervals (CIs), wherever applicable. Frequency comparison was estimated by chi-square (Wald) test and two-group comparisons by Mann-Whitney U-test.

The primary endpoint of this study was mortality within 6 years. Mortality was reported at short term (day 30), and long term (day 180 and six years). Secondary outcomes were adverse clinical outcomes including ICU-admission, CAP-associated

complications (empyema) and re-hospitalisation, all occurring within 30 days after randomisation.

We used univariate and multivariate regression analyses to assess the association between the prognostic scores and the different outcomes. We report odds ratios (ORs) with 95% CIs and significance levels for the chi-square (Wald) test. We calculated different multivariate regression models including age and gender (model 1) and age, gender and main comorbidities (chronic obstructive pulmonary disease [COPD], congestive heart failure, neoplastic disease, diabetes mellitus, coronary artery disease, cerebrovascular disease, peripheral artery occlusive disease [PAOD], chronic renal failure) (model 2). Discrimination was assessed by means of the area under the receiver operating characteristics (ROC) curve (AUC) with the 95% CI. For further illustration, we generated Kaplan-Meier plots for mortality and adverse outcomes by NEWS category. For this time-to-event analysis, censoring occurred at the time of death or at the last contact for patients lost to follow-up. Finally, we also investigated whether NEWS improves PSI and CURB-65 by comparing the AUC of a model limited to the CAP scores to a combined model including the CAP scores and NEWS.

RESULTS

Patient population

Overall, we included 925 CAP patients and the median follow- up was 6.1 year. Baseline characteristics overall and according to NEWS category are presented in **Table 1.** There were 349, 236 and 340 patients in each NEWS category, respectively. The study population showed a considerably burden of comorbidities (e.g. COPD, chronic renal failure, coronary artery disease), with higher frequency in higher NEWS categories.

Table 1 Baseline characteristics and outcomes of the study population

Characteristics	Entire cohort (n=925)	NEWS categories			
		1 (n=349)	2 (n=236)	3 (n=340)	p value
Demographic characteristics					
Age	73 (59-82)	67 (50-82)	74 (62-83)	75 (63-82)	<0.001
Male	544 (58.8%)	195 (55.9%)	131 (55.5%)	218 (64.1%)	0.044
Comorbidities					
Congestive heart failure	159 (17.2%)	38 (10.9%)	44 (18.6%)	77 (22.6%)	<0.001
Chronic renal failure	206 (22.3%)	56 (16.0%)	59 (25.0%)	91 (26.8%)	0.002
Diabetes mellitus	162 (17.5%)	51 (14.6%)	45 (19.1%)	66 (19.4%)	0.19
COPD	282 (30.5%)	75 (21.5%)	73 (30.9%)	134 (39.4%)	<0.001
Neoplastic disease	118 (12.8%)	42 (12.0%)	31 (13.1%)	45 (13.2%)	0.88
Cerebrovascular disease	82 (8.9%)	18 (5.2%)	23 (9.7%)	41 (12.1%)	0.005
Coronary artery disease	183 (19.8%)	46 (13.2%)	53 (22.5%)	84 (24.7%)	<0.001
PAOD	47 (5.1%)	13 (3.7%)	16 (6.8%)	18 (5.3%)	0.25
Clinical history and risk factors					
Chills	301 (32.5%)	108 (35.3%)	80 (39.6%)	113 (37.8%)	0.71
Fever	618 (67.2%)	240 (68.8%)	152 (65.2%)	226 (67.1%)	0.67
Average Smoking (pack-years)	40 (20-50)	30 (12-50)	35 (15-50)	40 (30-60)	0.001
Clinical findings					
Confusion	74 (8.8%)	0 (0.0%)	22 (10.3%)	52 (17.0%)	<0.001
Body temperature, °C	38.1 (37.2-38.9)	37.8 (37.1-38.6)	37.8 (37.1-38.7)	38.5 (37.6-39.1)	<0.001
Systolic blood pressure, mmHg	132 (119-148)	134 (120-150)	133 (120-148)	130 (110-148)	0.001
Peripheral oxgen saturation	95 (92-97)	96.0 (94.0-97.0)	96.0 (92.5-97.0)	94.0 (92.0-96.0)	0.041
Respiratory rate	20 (16-25)	17 (15-20)	20 (16-24)	25 (22-31)	<0.001
Oxygen therapy, non invasive	460 (49.7%)	81 (23.2%)	113 (47.9%)	266 (78.2%)	<0.001
Scores					
PSI class I	104 (11.2%)	73 (20.9%)	17 (7.2%)	14 (4.1%)	<0.001
PSI class II	139 (15.0%)	74 (21.2%)	31 (13.1%)	34 (10.0%)	
PSI class III	180 (19.5%)	76 (21.8%)	53 (22.5%)	51 (15.0%)	
PSI class IV	351 (37.9%)	97 (27.8%)	96 (40.7%)	158 (46.5%)	
PSI class V	151 (16.3%)	29 (8.3%)	39 (16.5%)	83 (24.4%)	
CURB-65 class 0	206 (22.3%)	124 (35.5%)	45 (19.1%)	37 (10.9%)	<0.001
CURB-65 class 1	253 (27.4%)	109 (31.2%)	71 (30.1%)	73 (21.5%)	
CURB-65 class 2	306 (33.1%)	102 (29.2%)	82 (34.7%)	122 (35.9%)	
CURB-65 class 3	134 (14.5%)	14 (4.0%)	35 (14.8%)	85 (25.0%)	
CURB-65 class 4	25 (2.7%)	0 (0.0%)	3 (1.3%)	22 (6.5%)	
CURB-65 class 5	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	
Outcomes					
30-day mortality	50 (5.4%)	7 (2.0%)	16 (6.8%)	27 (7.9%)	0.001
180-day mortality	106 (11.5%)	22 (6.3%)	30 (12.7%)	54 (15.9%)	<0.001
6-year mortality	417 (45.1%)	118 (33.8%)	115 (48.7%)	184 (54.1%)	<0.001
ICU admission	83 (9.0%)	7 (2.0%)	21 (8.9%)	55 (16.2%)	<0.001
Disease-specific complications (empyem)	31 (3.4%)	5 (1.4%)	9 (3.8%)	17 (5.0%)	0.031
Relapse / Rehospitalisation	39 (4.2%)	10 (2.9%)	13 (5.5%)	16 (4.7%)	0.25
Lenght of stay, days	8 (5-12)	6.0 (3.0-10.0)	8.0 (6.0-12.0)	10.0 (6.0-14.5)	<0.001

Data are presented as percentage (n) or median (interquartile range). COPD: chronic obstructive pulmonary disease; PAOD : peripheral artery occlusive disease ; NEWS: National Early Warning Score ; PSI: Pneumonia Severity Index, CURB-65: confusion, urea > 7mmol/L^{-1}, respiratory frequency ≥ 30 breaths/min^{-1}, low blood pressure (systolic value < 90 mmHg or diastolic value ≤ 60 mmHg) and age ≥ 65 yrs ; ICU : intensive care unit

NEWS and mortality outcomes

The overall 30-day mortality was 5.4% and increased to 45.1% after 6 years. 30-day mortality was significantly higher in NEWS category 3 compared to category 1 and 2 as presented in Kaplan-Meier survival curves (**Figure 1)**.

Table 2 shows the unadjusted and adjusted regression analyses assessing the association of NEWS with all-cause mortality at 30 day, 180 days and 6 years. For 30-day mortality, an increase in NEWS category was associated with a 16% increase in odds for reaching the event (OR 1.16, 95% 1.07 to 1.27), p=0.001). These results were similar for longer term mortality and also after rigorous adjustment in the different models. Yet, mortality discrimination analysis show only moderate results for NEWS with AUCs of 0.65, 0.62 and 0.60 after 30-days, 180-days and 6 years. In contrast, PSI and CURB-65 showed better mortality discrimination with AUC between 0.76 and 0.80 for PSI and 0.69 and 0.73 for CURB-65. Adding NEWS to the PSI or CURB-65 score did not improve the predictive value of these established scores in regard to mortality.

Table 2 ***NEWS as a mortality predictor compared to the PSI and CURB-65 scores***

	Mortality 30 days	Mortality 180 days	Mortality 6 years
Unadjusted OR	1.16 (1.07 to 1.27), p=0.001	1.13 (1.06 to 1.20), p<0.001	1.13 (95%CI 1.08 to 1.17), p<0.001
Adjusted OR (model 1)*	1.15 (1.05 to 1.25), p=0.003	1.11 (1.04 to 1.18), p=0.002	1.10 (95%CI 1.05 to 1.16), p<0.001
Adjusted OR (model 2)**	1.10 (1.01 to 1.21), p=0.035	1.07 (1.00 to 1.15), p=0.038	1.08 (95%CI 1.02 to 1.13), p=0.007
Discrimination			
AUC NEWS	0.65 (0.58 to 0.72)	0.62 (0.57 to 0.67)	0.60 (95%CI 0.57 to 0.64)
AUC PSI	0.80 (0.76 to 0.84)	0.76 (0.72 to 0.80)	0.79 (95%CI 0.76 to 0.81)
p value (NEWS vs PSI)	*<0.001*	*<0.001*	*<0.001*
AUC NEWS and PSI	0.82 (0.77 to 0.86)	0.77 (0.73 to 0.81)	0.79 (95%CI 0.76 to 0.82)
p value (NEWS & PSI vs PSI)	*0.084*	*0.074*	*0.911*
AUC CURB-65	0.72 (0.65 to 0.78)	0.69 (0.64 to 0.74)	0.73 (95%CI 0.69 to 0.76)
p value (NEWS vs CURB-65)	*0.076*	*0.015*	*<0.001*
AUC NEWS and CURB-65	0.73 (0.67 to 0.79)	0.70 (0.66 to 0.75)	0.73 (95%CI 0.70 to 0.76)
p value (NEWS & CURB-65 vs CURB-65)	*0.178*	*0.091*	*0.29*

Data from univariate and multivariate analysis are given as odds ratio (95%CI), p value. Data from the ROC analysis are given as AUC (95%CI) or p value. OR: odds ratio; AUC: area under the curve; NEWS: National Early Warning Score; PSI: Pneumonia Severity Index; CURB-65: confusion, urea > 7mmol/L^{-1}, respiratory frequency ≥ 30 breaths/min^{-1}, low blood pressure (systolic value < 90 mmHg or diastolic value ≤ 60 mmHg) and age ≥ 65 yrs ;

**** adjusted for age, gender***

***** adjusted for age, gender, comorbidities (COPD, congestive heart failure, neoplastic disease, diabetes mellitus, coronary artery disease, cerebrovascular disease, PAOD, chronic renal failure)***

NEWS and adverse clinical outcomes

The risk for ICU admission and complications significantly increased with increasing NEWS categories. **Figure 2** shows a significant separation in time to ICU admission with increasing NEWS categories.

Table 3 shows the unadjusted and adjusted regression analysis investigating the association of NEWS with adverse clinical outcomes, namely ICU-admission, complications and re-hospitalisation. The results were statistically significant for NEWS as a predictor for ICU-admission and complications within 30 days after admission. This was also true after adjustment for age, gender and comorbidities. Concerning re-hospitalization, no significant association was found.

In regard to discrimination, NEWS showed the highest AUC for all three outcomes compared to PSI and CURB-65. For ICU admission prediction, NEWS significantly improved PSI (from AUC 0.66 to 0.74, p=*0.001*) and CURB-65 (from AUC 0.64 to 0.73, p=*0.002*). For complications, NEWS also tended to improve PSI (from AUC 0.50 to 0.64, p=0.086) and significantly improved CURB-65 (from AUC 0.50 to 0.65, p=*0.025*). For re-hospitalization, no significant improvement was found.

Table 3 ***NEWS as adverse outcome predictor compared to the PSI and CURB-65 scores***

	ICU-Admission within 30 days	**Complications (Empyem)** within 30 days	**Re-Hospitalisation** within 30 days
Unadjusted OR	1.29 (1.20 to 1.39), p<0.001	1.16 (1.04 to 1.29), p=0.007	1.08 (0.98 to 1.18), p=0.143
Adjusted OR (model 1)*	1.30 (1.20 to 1.40), p<0.001	1.18 (1.06 to 1.32), p=0.003	1.08 (0.98 to 1.20), p=0.106
Adjusted OR (model 2)**	1.27 (1.18 to 1.37), p<0.001	1.17 (1.05 to 1.30), p=0.005	1.07 (0.97 to 1.18), p=0.184
Discrimination			
AUC NEWS	0.73 (0.67 to 0.78)	0.64 (0.54 to 0.73)	0.58 (0.49 to 0.66)
AUC PSI	0.66 (0.60 to 0.72)	0.50 (0.40 to 0.60)	0.53 (0.43 to 0.63)
p value (NEWS vs PSI)	*0.072*	*0.042*	*0.358*
AUC NEWS and PSI	0.74 (0.69 to 0.79)	0.64 (0.54 to 0.73)	0.58 (0.49 to 0.66)
p value (NEWS & PSI vs PSI)	*0.001*	*0.086*	*0.414*
AUC CURB-65	0.64 (0.58 to 0.70)	0.50 (0.40 to 0.59)	0.50 (0.41 to 0.59)
p value (NEWS vs CURB-65)	*0.015*	*0.011*	*0.118*
AUC NEWS and CURB-65	0.73 (0.68 to 0.79)	0.65 (0.55 to 0.74)	0.58 (0.49 to 0.67)
p value (NEWS & CURB-65 vs CURB-65)	*0.002*	*0.025*	*0.246*

Data from univariate and multivariate analysis are given as odds ratio (95%CI), p value. Data from the ROC analysis are given as AUC (95%CI) or p value. OR: odds ratio; AUC: area under the curve; NEWS: National Early Warning Score; PSI: Pneumonia Severity Index; CURB-65: confusion, urea > 7mmol/L^{-1}, respiratory frequency ≥ 30 breaths/min^{-1}, low blood pressure (systolic value < 90 mmHg or diastolic value ≤ 60 mmHg) and age ≥ 65 yrs ; ICU : intensive care unit

**** adjusted for age, gender***

***** adjusted for age, gender, comorbidities (COPD, congestive heart failure, neoplastic disease, diabetes mellitus, coronary artery disease, cerebrovascular disease, PAOD, chronic renal failure)***

DISCUSSION

This first study evaluating NEWS in a large population with CAP from a multicentre study with 6 year follow-up has three key findings. First, NEWS is a strong predictor for adverse clinical outcomes particularly ICU admission and to a lesser degree for complication (empyema) in patients presenting with CAP to the emergency department. Second, NEWS improves the predictive accuracy of the two well-established risk scores PSI and CURB-65 scores` for ICU admission. Third, although NEWS is also associated with mortality, this score has a lower prognostic performance compared to standard of care scores and did not improve their performance.

NEWS has been originally established and validated as a track-and-trigger system for acute illness and a first study showed its superiority comparing it to other EWS currently in use [20 21]. Most subsequent research validated the power and superior performance of this new warning score compared to other algorithms [22-24 26] or analysed the validity of its constitution (e.g. trigger-threshold) and factors affecting the response to it [30-32]. To date, efficiency of NEWS in specific patient subpopulations was less investigated. For example, Keep et. al. analysed NEWS as early indicator of patients with severe sepsis or septic shock [27]. In general, data mostly originated from single-centre studies and were collected over a short period, leaving open the question about external and long-term validity of the NEWS, respectively.

Reflecting the data of our clinical findings [see **Table 1**], mortality and adverse clinical outcomes occurred more frequently in higher NEWS categories, confirming the basic utility of NEWS as a severity indicator. However, a majority of the clinical trials were performed in a heterogeneous patient population with diverse principal morbidities [21 24-27 30-32]. Our study focused on patients with CAP, a disease with a relatively high

short-term mortality [2 33]. Therefore, early recognition of severity is crucial for the further patient management and the use of predictive tools is currently recommended by American and European guidelines [11 12]. Our analyses reveal a strong predictive value for 30-day ICU-admission and complications (empyema), even superior to the PSI and CURB-65 scores, using the NEWS. Despite the rather aged patient population with a high burden of comorbidities, results remained significant after adjustment for these factors. This main finding underlines its purpose as an EWS and reveals NEWS as an equivalent predicting tool regarding short-term adverse clinical outcomes compared to the PSI and CURB-65 scores in CAP patients. Interestingly, the PSI contains very similar physiological parameters as used for NEWS calculation. Still, NEWS was superior for adverse outcome prediction but inferior in regard to mortality prediction. This may be explained by the fact that PSI is age-dominated and while age is a good predictor for mortality, aged people at the end of life may be less often admitted to the ICU. NEWS sets the main focus on the acute condition (e.g. need for supplemental oxygen or altered level of consciousness) allowing better evaluation for the eventual of need for ICU-admission.

Further, we showed that adding NEWS to established CAP-specific scores improves the prognostic accuracy regarding 30-day ICU-admission. The application of the PSI in patients with CAP is widespread in the US, whereas the CURB-65 is mostly used in Europe. Despite a potentially increased complexity adding the NEWS, most EDs already use an EWS, usually surveyed by the nursing staff. As an additional benefit, using NEWS would significantly help to better identify patients at risk, leading to a more appropriate management.

Most of the previous studies analysed and proved association between NEWS and short-term mortality at maximal 30 days [21 22 24]. In our regression models for mortality

outcomes, we could show an association of NEWS with 30-day, 180-day and 6-year mortality. However, PSI and CURB-65 were superior as mortality predictors. Probably this is due to the simple six point system of basic physiological parameter reflecting the very acute condition of a patient and thus the trigger and track nature of the NEWS. Whereas the PSI and CURB-65 scores include more variables taking into consideration the all-over morbidity of the patient (e.g. age, comorbidities, laboratory parameters), giving them an advantage about mortality prediction beyond the emergency setting.

The strength of our study is the considerable patient number originating from a multicentre setting with well-defined CAP criteria and a consistent distribution to the three NEWS categories. Further, the long follow-up of 6 years with repeated telephone interviews allowed an insight into short and long-term outcomes, while most previous studies focused on short-term data.

There were several limitations. Despite the multicentre character, the study was conducted exclusively in Switzerland with predominantly Caucasian patients. Reproducibility to other countries or regions may not be given. Furthermore, this was a secondary analysis which may induce confounding. In addition, 25.7% of the patient population was already pre-treated with antibiotics upon admission to the ED. NEWS has been recommended to be used not only in the initial setting but also as a trigger score for patient deterioration during hospital stay. As we disposed only about the initial dataset of parameters upon admission, this aspect could not be considered. Nevertheless, our results support the use of NEWS in this population as an additional screening tool for patients at risk for adverse clinical outcome.

CONCLUSION

We found NEWS to provide additional prognostic information in regard to risk of ICU admission and complications thereby improves traditional clinical risk scores in the management of CAP patients in the emergency department setting.

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DATA SHARING STATEMENT

No additional data available.

AUTHOR CONTRIBUTIONS

All authors made substantive intellectual contributions to this study. DS, AK, PS and BM had the idea for and conducted statistical analyses and drafted the first manuscript. MCC, RT, WZ, CHo, and CHe were in charge of the acquisition of patient data during the ProHOSP study, and provided individual patient data from their hospitals. For this manuscript they have made substantial contributions to conception and design, and have taken an active part in acquisition, analysis and interpretation of data. All authors contributed to the interpretation of data and to the revising of the manuscript critically for important intellectual content. All authors approved the final version of the manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

COMPETING INTEREST

AK, MCC, BM, and PS received support from B·R·A·H·M·S/Thermo Scientific Biomarkers to attend meetings and fulfill speaking engagements. PS and BM received unrestricted research grants from, and BM has served as a consultant to these firms. All other authors have no relationships to industry relevant to this paper.

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LIST OF ETHICAL BODIES

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CONFLICT OF INTEREST STATEMENT

All authors confirm that they do not have a conflict of interest associated with this manuscript.

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LIST OF ABBREVIATIONS

NEWS – National Early Warning Score

CAP – community-acquired pneumonia

PSI – Pneumonia Severity Index

CURB-65 – new-onset confusion, urea >7 mmol L-1, respiratory rate ≥30 breaths per min, systolic or diastolic blood pressure <90mmHg or ≤60mmHg, respectively, age ≥65 years (pneumonia risk scoring system)

ICU – Intensive Care Unit

AUC – area under the receiver operating characteristic curve

ED – emergency department

EWS – Early Warning Score

PCT – Procalcitonin

IQR – interquartile range

CI – confidence interval

OR – Odds Ratio

ROC – Receiver Operating Characteristics

COPD – chronic obstructive pulmonary disease

PAOD – peripheral artery occlusive disease

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LEGENDS

Figure 1 *Kaplan-Meier plots showing the association between mortality outcomes and NEWS categories*

Figure 2 *Kaplan-Meier plots showing the association between adverse outcomes and NEWS categories*

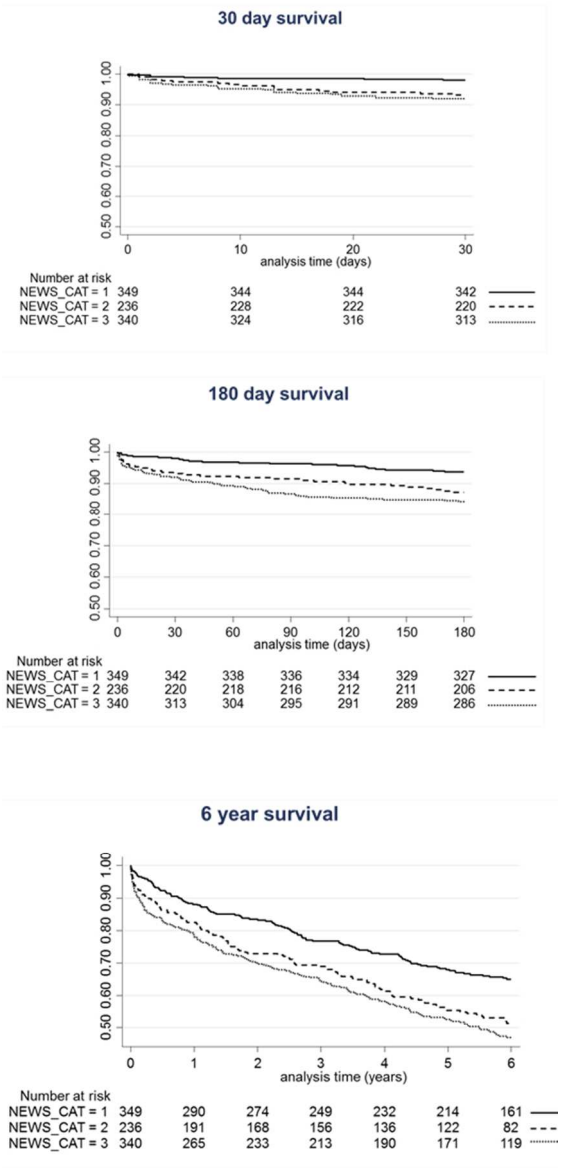

Figure 1 Kaplan-Meier plots showing the association between mortality outcomes and NEWS categories

138x300mm (96 x 96 DPI)

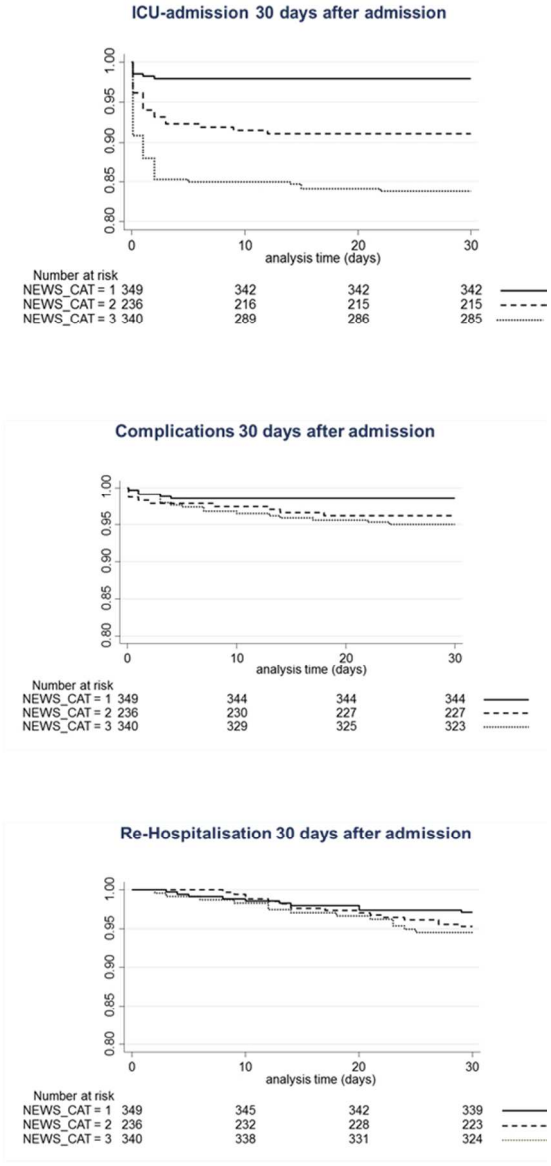

Figure 2 Kaplan-Meier plots showing the association between adverse outcomes and NEWS categories

138x300mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1/2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ~~*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls~~ ~~*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants~~	5/6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed ~~*Case-control study*—For matched studies, give matching criteria and the number of controls per case~~	n.a.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6/7/8
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	n.a.
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5/6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	n.a.
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed ~~*Case-control study*—If applicable, explain how matching of cases and controls was addressed~~ ~~*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy~~	6
		(*e*) Describe any sensitivity analyses	n.a.

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	5
		(b) Give reasons for non-participation at each stage	5
		(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	5
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11
		~~*Case-control study*—Report numbers in each exposure category, or summary measures of exposure~~	
		~~*Cross-sectional study*—Report numbers of outcome events or summary measures~~	
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	11-14
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*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	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15/16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
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	21

*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

The National Early Warning Score (NEWS) for outcome prediction in emergency department patients with community-acquired pneumonia: Results from a 6 year prospective cohort study

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Primary Subject Heading:	Emergency medicine
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Keywords:	National Early warning score, Community-acquired pneumonia, Pneumonia severity index, CURB-65, ICU-admission

The National Early Warning Score (NEWS) for outcome prediction in emergency department patients with community-acquired pneumonia: *Results from a 6 year prospective cohort study*

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Key words: National Early Warning Score (NEWS), community-acquired pneumonia (CAP), Pneumonia Severity Index (PSI), CURB-65, ICU-admission

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ABSTRACT

Objective: To investigate the accuracy of NEWS to predict mortality and adverse clinical outcomes for patients with community acquired pneumonia compared to standard risk scores such as the pneumonia severity index (PSI) and CURB-65.

Design: Secondary analysis of a prospective cohort study with patients included in a previous randomized trial with a median follow-up of 6.1 years.

Settings: Patients with community acquired pneumonia included upon admission to emergency departments of six tertiary care hospitals in Switzerland.

Participants: A total of 925 patients with confirmed diagnosis of community acquired pneumonia were included. NEWS as well as PSI and CURB-65 scores were calculated upon admission to the emergency department.

Main outcome measure: Our primary outcome was all-cause mortality within 6 years of follow-up. Secondary outcomes were adverse clinical outcome defined as intensive care unit (ICU) admission, complications (empyema) and unplanned hospital readmission all within 30 days after admission. We used regression models to study associations of baseline risk scores and outcomes with the area under the receiver operating curve (AUC) as a measure of discrimination.

Results: Six-year overall mortality was 45.1% (n=417) with a step-wise increase with higher NEWS categories. For 30-days and 6-year mortality prediction, NEWS showed only low discrimination (AUC 0.65 and 0.60) inferior compared to PSI and CURB-65. For prediction of intensive care unit admission, NEWS showed high discrimination (AUC 0.73) and improved the prognostic accuracy of a regression model including PSI (AUC from 0.66 to 0.74, p=0.001) and CURB-65 (AUC from 0.64

to 0.73, p=0.015). NEWS was also superior to PSI and CURB-65 for prediction of complications, but did not well predict rehospitalisation.

Conclusion: NEWS provides additional prognostic information in regard to risk of intensive care unit admission and complications and thereby improves traditional clinical risk scores in the management of community-acquired pneumonia patients in the emergency department setting.

Trial registration: ISRCTN 95122877

STRENGHTS AND LIMITATIONS OF THIS STUDY

Strengths

- This is the first large-scale study with a long-term follow up investigating the association of NEWS and adverse outcome in community-acquired pneumonia patients
- In the emergency department setting, NEWS was an adequate tool for risk stratification in regard to ICU admission and clinical complications

Limitations

- The study was observational and it remains unclear whether use of NEWS would improve patient management
- This study was limited to Swiss, predominantly Caucasian patients, limiting the generalizability of results

INTRODUCTION

Today, it is recommended that clinical decisions regarding patient management in the emergency department (ED) setting are supported by objective risk scores [1-3]. In patients with community-acquired pneumonia (CAP) risk scores may support practitioners to decide whether a patient is at higher risk for mortality and, thus, may need inpatient treatment [4-7]. Several scores have been developed and validated for predicting 30-day mortality in patients with CAP [8-12]. To date, the Pneumonia severity index (PSI) and CURB-65 are recommended by most international guidelines for this purpose [2 13]. The CURB-65 is a five point score that is predominantly used in Europe. The PSI is mostly used in the US and has been validated in several studies [9 14-19]. As a limitation, both scores have the main focus on 30-day mortality prediction, but other outcomes such as disease severity (e.g. requiring intensive care unit (ICU) admission) are not well predicted [20]. This raises the question whether these scores can be improved by combination with other instruments focusing on the initial severity of disease, such as generalized early warning scores (EWS).

Among different EWS, the National Early Warning Score (NEWS), that was derived in the UK by the National Early Warning Score Development and Implementation Group (NEWSDIG) on behalf of the Royal College of Physicians has been well established [21]. Its purpose was to introduce a standardised trigger-system to identify acutely ill patients upon hospital admission. NEWS consists of six physiological measurements classifying the patients into three risk-groups (low, moderate, high). Several studies found NEWS to be superior compared to other risk stratification tools [22-25] and a valid tool in different settings (ED, prehospital setting) [26-28]. Yet, there is currently no study investigating NEWS to predict severity and adverse clinical outcome in patients with CAP upon admission to the ED.

Our hypothesis was that NEWS would show an association with short and long-term adverse outcome in patients with CAP and possibly improve risk prediction compared to established risk assessment tools such as PSI and CURB-65. The aim of our study was thus to compare the accuracy of NEWS with PSI and CURB-65 to predict mortality and adverse clinical outcomes in a well characterised cohort of CAP patients.

METHODS

Study design

This is a prospective cohort study using data of 925 patients included in a previous prospective randomized non-inferiority trial with a 6 years follow-up. The initial trial enrolled patients from October 2006 to March 2008 at six Swiss secondary or tertiary care, academic or non-academic hospitals [29]. The primary aim of the initial trial was to examine whether a procalcitonin (PCT)-guided algorithm could reduce antibiotic use without compromising the safety of those patients [30]. All local ethical committees approved the initial trial protocol, and also gave permission to do a 6-year follow-up study. All patients gave written informed consent to the initial study and the follow-up analysis including the current analysis. The study was also registered in the “Current Controlled Trial Database” (ISRCTN 95122877) at http://www.controlled-trials.com and a study protocol was published previously [30].

Study procedures

Consecutive adults (age ≥ 18 years) were included with a diagnosis of CAP presenting from the community or a nursing home to the emergency department of

one of the participating hospitals. All patients fulfilling the following CAP criteria based on the American Thoracic Society guidelines [2] were eligible: at least one symptom of cough, sputum production, dyspnoea, tachypnoea or pleuritic pain in addition to one finding during auscultation (rales or crepitation) or one infectious sign (core body temperature > 38.0°C, shivering or white blood cell count > 10 or < 4 cells x 10^9/L). The diagnosis of CAP was confirmed in all patients by a new or increasing lung infiltrate on chest X-ray. Inpatients and outpatients were eligible for the study. As previously reported, we included 1381 out of from 1825 screened patients in the study of which 925 had CAP and were used for the current analysis [29].

The exclusion criteria were defined as follows: language restriction or dementia precluding informed consent, intravenous drug abuse, severe immunosuppression other than corticosteroids, chronic antibiotic therapy, medical comorbidities with imminent risk of death, hospital acquired pneumonia (defined as newly appearing pulmonary infiltrate ≥ 48h postindex admission or during hospitalization within 2 weeks before enrolment).

Assessment of vital status and score assignment

Patients were clinically and biochemically evaluated upon admission and throughout the hospital stay. Data on demographics, comorbidities, medication, laboratory variables and imaging as well as vital signs were collected.

Vital status was ascertained by trained medical students by means of phone interviews at days 30, 180 and 540 as well as 6 years after discharge. Patients or their household members were contacted first, if not attainable, the primary care physicians were called. In cases of missing vital status, patients were categorized as

survivors and the latest hospital discharge date derived from medical records was used to calculate survival time. The decision for ICU transfer was up to the discretion of the treating physicians who were not aware of the NEWS score.

For all patients, PSI and CURB-65 scores were calculated upon admission to the emergency department as part of the routine [9 10 21]. The PSI includes 20 variables and categorizes the patients with CAP into five risk classes whereas the CURB-65 score uses a five point system (Confusion, Urea, Respiratory rate, Blood Pressure, Age > 65 years) classifying the patients into three risk classes. NEWS was calculated retrospectively on admission data based on the following six physiological parameters: respiratory rate, oxygen saturation, temperature, systolic blood pressure, pulse rate and level of consciousness. Every continuous variable scores a maximum of 3 points, whereas the need for supplemental oxygen and the level of consciousness are binary coded with zero points if absent/normal and 2 or 3 points if present/altered respectively. The resulting aggregate divides the patients into three groups with low (0-4 points), medium (5-6 points) or high (≥ 7 points) risk. As an exception, a single physiological parameter scoring 3 points classifies a patient at medium risk instead of low risk, denominated as RED score.

Statistical analyses

For the statistical analysis we used STATA 12.1 (Stata Corp, College Station, TX, USA). Statistical significance was defined as a p-value < 0.05; two-tailed tests were used.

The categorical variables are presented as percentages (numbers) and the continuous variables as medians (interquartile range [IQRs]) with 95% confidence

intervals (CIs), wherever applicable. Frequency comparison was estimated by chi-square (Wald) test and two-group comparisons by Mann-Whitney U-test.

The primary endpoint of this study was mortality within 6 years. Mortality was reported at short term (day 30), and long term (day 180 and six years). Secondary outcomes were adverse clinical outcomes including ICU-admission, CAP-associated complications (empyema) and re-hospitalisation, all occurring within 30 days after randomisation admission.

We used univariate and multivariate regression analyses to assess the association between the prognostic scores and the different outcomes. We report hazard ratio (HR) for all time to event analyses, and odds ratios (ORs) for all logistic regression analyses. We calculated different multivariate regression models including age and gender (model 1) and age, gender and main comorbidities (chronic obstructive pulmonary disease [COPD], congestive heart failure, neoplastic disease, diabetes mellitus, coronary artery disease, cerebrovascular disease, peripheral artery occlusive disease [PAOD], chronic renal failure) (model 2). Discrimination was assessed by means of the area under the receiver operating characteristics (ROC) curve (AUC) with the 95% CI. For further illustration, we generated Kaplan-Meier plots for mortality and adverse outcomes by NEWS category. For this time-to-event analysis, censoring occurred at the time of death or at the last contact for patients lost to follow-up. Finally, we also investigated whether NEWS improves PSI and CURB-65 by comparing the AUC of a statistical model limited to the single CAP scores alone with a joint statistical regression model combining the CAP score and NEWS each.

RESULTS

Patient population

Overall, we included 925 CAP patients and the median follow- up was 6.1 year. Baseline characteristics overall and according to NEWS categories (low (0-4 points), medium (5-6 points) or high (≥ 7 points)) risk are presented in **Table 1.** The study population showed a considerably burden of comorbidities (e.g. COPD, chronic renal failure, coronary artery disease), with higher frequency in higher NEWS categories. Most patients were treated as inpatients with 8.8% of patients being treated on an outpatient basis.

Table 1 Baseline characteristics and outcomes of the study population

Characteristics	Entire cohort (n=925)	NEWS categories			
		low(n=349)	moderate (n=236)	high (n=340)	p value
Demographic characteristics					
Age	73 (59-82)	67 (50-82)	74 (62-83)	75 (63-82)	<0.001
Male	544 (58.8%)	195 (55.9%)	131 (55.5%)	218 (64.1%)	0.044
Comorbidities					
Congestive heart failure	159 (17.2%)	38 (10.9%)	44 (18.6%)	77 (22.6%)	<0.001
Chronic renal failure	206 (22.3%)	56 (16.0%)	59 (25.0%)	91 (26.8%)	0.002
Diabetes mellitus	162 (17.5%)	51 (14.6%)	45 (19.1%)	66 (19.4%)	0.19
COPD	282 (30.5%)	75 (21.5%)	73 (30.9%)	134 (39.4%)	<0.001
Neoplastic disease	118 (12.8%)	42 (12.0%)	31 (13.1%)	45 (13.2%)	0.88
Cerebrovascular disease	82 (8.9%)	18 (5.2%)	23 (9.7%)	41 (12.1%)	0.005
Coronary artery disease	183 (19.8%)	46 (13.2%)	53 (22.5%)	84 (24.7%)	<0.001
PAOD	47 (5.1%)	13 (3.7%)	16 (6.8%)	18 (5.3%)	0.25
Clinical history and risk factors					
Chills	301 (32.5%)	108 (35.3%)	80 (39.6%)	113 (37.8%)	0.71
Fever	618 (67.2%)	240 (68.8%)	152 (65.2%)	226 (67.1%)	0.67
Average Smoking (pack-years)	40 (20-50)	30 (12-50)	35 (15-50)	40 (30-60)	0.001
Clinical findings					
Confusion	74 (8.8%)	0 (0.0%)	22 (10.3%)	52 (17.0%)	<0.001
Body temperature, °C	38.1 (37.2-38.9)	37.8 (37.1-38.6)	37.8 (37.1-38.7)	38.5 (37.6-39.1)	<0.001
Systolic blood pressure, mmHg	132 (119-148)	134 (120-150)	133 (120-148)	130 (110-148)	0.001
Peripheral oxgen saturation	95 (92-97)	96.0 (94.0-97.0)	96.0 (92.5-97.0)	94.0 (92.0-96.0)	0.041
Respiratory rate	20 (16-25)	17 (15-20)	20 (16-24)	25 (22-31)	<0.001
Oxygen therapy, non invasive	460 (49.7%)	81 (23.2%)	113 (47.9%)	266 (78.2%)	<0.001
Scores					
PSI class I	104 (11.2%)	73 (20.9%)	17 (7.2%)	14 (4.1%)	<0.001
PSI class II	139 (15.0%)	74 (21.2%)	31 (13.1%)	34 (10.0%)	
PSI class III	180 (19.5%)	76 (21.8%)	53 (22.5%)	51 (15.0%)	
PSI class IV	351 (37.9%)	97 (27.8%)	96 (40.7%)	158 (46.5%)	
PSI class V	151 (16.3%)	29 (8.3%)	39 (16.5%)	83 (24.4%)	
CURB-65 class 0	206 (22.3%)	124 (35.5%)	45 (19.1%)	37 (10.9%)	<0.001
CURB-65 class 1	253 (27.4%)	109 (31.2%)	71 (30.1%)	73 (21.5%)	
CURB-65 class 2	306 (33.1%)	102 (29.2%)	82 (34.7%)	122 (35.9%)	
CURB-65 class 3	134 (14.5%)	14 (4.0%)	35 (14.8%)	85 (25.0%)	
CURB-65 class 4	25 (2.7%)	0 (0.0%)	3 (1.3%)	22 (6.5%)	
CURB-65 class 5	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	
Outcomes					
30-day mortality	50 (5.4%)	7 (2.0%)	16 (6.8%)	27 (7.9%)	0.001
180-day mortality	106 (11.5%)	22 (6.3%)	30 (12.7%)	54 (15.9%)	<0.001
6-year mortality	417 (45.1%)	118 (33.8%)	115 (48.7%)	184 (54.1%)	<0.001
ICU admission	83 (9.0%)	7 (2.0%)	21 (8.9%)	55 (16.2%)	<0.001
Disease-specific complications (empyem)	31 (3.4%)	5 (1.4%)	9 (3.8%)	17 (5.0%)	0.031
Relapse / Rehospitalisation	39 (4.2%)	10 (2.9%)	13 (5.5%)	16 (4.7%)	0.25
Lenght of stay, days	8 (5-12)	6.0 (3.0-10.0)	8.0 (6.0-12.0)	10.0 (6.0-14.5)	<0.001

Data are presented as percentage (n) or median (interquartile range). COPD: chronic obstructive pulmonary disease; PAOD : peripheral artery occlusive disease ; NEWS: National Early Warning Score ; PSI: Pneumonia Severity Index, CURB-65: confusion, urea > 7mmol/L^{-1}, respiratory frequency ≥ 30 breaths/min^{-1}, low blood pressure (systolic value < 90 mmHg or diastolic value ≤ 60 mmHg) and age ≥ 65 yrs ; ICU : intensive care unit. NEWS categories refers to low (0-4 points), medium (5-6 points) or high (≥ 7 points).

NEWS and mortality outcomes

The overall 30-day mortality was 5.4% and increased to 45.1% after 6 years. 30-day mortality was significantly higher in NEWS category 3 compared to category 1 and 2 as presented in Kaplan-Meier survival curves (**Figure 1)**.

Table 2 shows the unadjusted and adjusted regression analyses assessing the association of NEWS with all-cause mortality at 30 day, 180 days and 6 years. For 30-day mortality, an increase in NEWS category was associated with a 16% increase in odds for reaching the event (OR 1.16, 95% 1.07 to 1.27), p=0.001). These results were similar for longer term mortality and also after rigorous adjustment in the different models. Yet, mortality discrimination analysis show only low results for NEWS with AUCs of 0.65, 0.62 and 0.60 after 30-days, 180-days and 6 years. In contrast, PSI and CURB-65 showed better mortality discrimination with AUC between 0.76 and 0.80 for PSI and 0.69 and 0.73 for CURB-65. Adding NEWS to the PSI or CURB-65 score did not improve the predictive value of these established scores in regard to mortality compared to the scores alone.

Table 2 ***NEWS as a mortality predictor compared to the PSI and CURB-65 scores***

	Mortality 30 days	Mortality 180 days	Mortality 6 years
Unadjusted OR	1.16 (1.07 to 1.27), p=0.001	1.13 (1.06 to 1.20), p<0.001	1.13 (95%CI 1.08 to 1.17), p<0.001
Adjusted OR (model 1)*	1.15 (1.05 to 1.25), p=0.003	1.11 (1.04 to 1.18), p=0.002	1.10 (95%CI 1.05 to 1.16), p<0.001
Adjusted OR (model 2)**	1.10 (1.01 to 1.21), p=0.035	1.07 (1.00 to 1.15), p=0.038	1.08 (95%CI 1.02 to 1.13), p=0.007
Discrimination			
AUC NEWS	0.65 (0.58 to 0.72)	0.62 (0.57 to 0.67)	0.60 (95%CI 0.57 to 0.64)
AUC PSI	0.80 (0.76 to 0.84)	0.76 (0.72 to 0.80)	0.79 (95%CI 0.76 to 0.81)
p value (NEWS vs PSI)	*<0.001*	*<0.001*	*<0.001*
AUC NEWS and PSI	0.82 (0.77 to 0.86)	0.77 (0.73 to 0.81)	0.79 (95%CI 0.76 to 0.82)
p value (NEWS & PSI vs PSI)	*0.084*	*0.074*	*0.911*
AUC CURB-65	0.72 (0.65 to 0.78)	0.69 (0.64 to 0.74)	0.73 (95%CI 0.69 to 0.76)
p value (NEWS vs CURB-65)	*0.076*	*0.015*	*<0.001*
AUC NEWS and CURB-65	0.73 (0.67 to 0.79)	0.70 (0.66 to 0.75)	0.73 (95%CI 0.70 to 0.76)
p value (NEWS & CURB-65 vs CURB-65)	*0.178*	*0.091*	*0.29*

Data from univariate and multivariate analysis are given as odds ratio (95%CI) per point increase, p value. Data from the ROC analysis are given as AUC (95%CI) or p value. OR: odds ratio; AUC: area under the curve; NEWS: National Early Warning Score; PSI: Pneumonia Severity Index; CURB-65: confusion, urea > 7mmol/L^{-1}, respiratory frequency ≥ 30 breaths/min^{-1}, low blood pressure (systolic value < 90 mmHg or diastolic value ≤ 60 mmHg) and age ≥ 65 yrs ;

**** adjusted for age, gender***

***** adjusted for age, gender, comorbidities (COPD, congestive heart failure, neoplastic disease, diabetes mellitus, coronary artery disease, cerebrovascular disease, PAOD, chronic renal failure)***

NEWS and adverse clinical outcomes

The risk for ICU admission and complications significantly increased with increasing NEWS categories. **Figure 2** shows a significant separation in time to ICU admission with increasing NEWS categories.

Table 3 shows the unadjusted and adjusted regression analysis investigating the association of NEWS with adverse clinical outcomes, namely ICU-admission, complications and re-hospitalisation. The results were statistically significant for NEWS as a predictor for ICU-admission and complications within 30 days after admission. This was also true after adjustment for age, gender and comorbidities. Concerning re-hospitalization, no significant association was found.

In regard to discrimination, NEWS showed the highest AUC for all three outcomes compared to PSI and CURB-65. For ICU admission, NEWS significantly improved PSI (from AUC 0.66 to 0.74, p=*0.001*) and CURB-65 (from AUC 0.64 to 0.73, p=*0.002*). For complications, NEWS also tended to improve PSI (from AUC 0.50 to 0.64, p=0.086) and significantly improved CURB-65 (from AUC 0.50 to 0.65, p=*0.025*). For re-hospitalization, no significant improvement was found.

Patients that were misclassified by the PSI score as low risk (PSI class 1 or 2) but correctly identified by NEWS had a younger age (median age 49 years vs 74 years), less comorbidities (heart and renal failure, coronary heart disease) and more frequent deterioration (chills, oxygenation) of vital signs compared to patients that were correctly identified by both scores.

Table 3 ***NEWS as adverse outcome predictor compared to the PSI and CURB-65 scores***

	ICU-Admission within 30 days	**Complications (Empyem)** within 30 days	**Re-Hospitalisation** within 30 days
Unadjusted OR	1.29 (1.20 to 1.39), p<0.001	1.16 (1.04 to 1.29), p=0.007	1.08 (0.98 to 1.18), p=0.143
Adjusted OR (model 1)*	1.30 (1.20 to 1.40), p<0.001	1.18 (1.06 to 1.32), p=0.003	1.08 (0.98 to 1.20), p=0.106
Adjusted OR (model 2)**	1.27 (1.18 to 1.37), p<0.001	1.17 (1.05 to 1.30), p=0.005	1.07 (0.97 to 1.18), p=0.184
Discrimination			
AUC NEWS	0.73 (0.67 to 0.78)	0.64 (0.54 to 0.73)	0.58 (0.49 to 0.66)
AUC PSI	0.66 (0.60 to 0.72)	0.50 (0.40 to 0.60)	0.53 (0.43 to 0.63)
p value (NEWS vs PSI)	*0.072*	*0.042*	*0.358*
AUC NEWS and PSI	0.74 (0.69 to 0.79)	0.64 (0.54 to 0.73)	0.58 (0.49 to 0.66)
p value (NEWS & PSI vs PSI)	*0.001*	*0.086*	*0.414*
AUC CURB-65	0.64 (0.58 to 0.70)	0.50 (0.40 to 0.59)	0.50 (0.41 to 0.59)
p value (NEWS vs CURB-65)	*0.015*	*0.011*	*0.118*
AUC NEWS and CURB-65	0.73 (0.68 to 0.79)	0.65 (0.55 to 0.74)	0.58 (0.49 to 0.67)
p value (NEWS & CURB-65 vs CURB-65)	*0.002*	*0.025*	*0.246*

Data from univariate and multivariate analysis are given as odds ratio (95%CI) per point increase. Data from the ROC analysis are given as AUC (95%CI) or p value. OR: odds ratio; AUC: area under the curve; NEWS: National Early Warning Score; PSI: Pneumonia Severity Index; CURB-65: confusion, urea > 7mmol/L^{-1}, respiratory frequency ≥ 30 breaths/min^{-1}, low blood pressure (systolic value < 90 mmHg or diastolic value ≤ 60 mmHg) and age ≥ 65 yrs ; ICU : intensive care unit

**** adjusted for age, gender***

***** adjusted for age, gender, comorbidities (COPD, congestive heart failure, neoplastic disease, diabetes mellitus, coronary artery disease, cerebrovascular disease, PAOD, chronic renal failure)***

DISCUSSION

This first study evaluating NEWS in a large population with CAP from a multicentre study with 6 year follow-up has three key findings. First, NEWS is a strong predictor for adverse clinical outcomes particularly ICU admission and to a lesser degree for complication (empyema) in patients presenting with CAP to the ED. Second, NEWS improves the predictive accuracy of the two well-established risk scores PSI and CURB-65 scores` for ICU admission. Third, although NEWS is associated with mortality, this score has a lower prognostic performance compared to standard of care scores and did not improve their performance.

NEWS has been originally established and validated as a track-and-trigger system for acute illness and a first study showed its superiority comparing it to other EWS currently in use [21 22]. Most subsequent research validated the power and superior performance of this new warning score compared to other algorithms [23-25 27] or analysed the validity of its constitution (e.g. trigger-threshold) and factors affecting the response to it [31-33]. To date, efficiency of NEWS in specific patient subpopulations is less investigated. For example, Keep et. al. analysed NEWS as early indicator of patients with severe sepsis or septic shock [28]. In general, data mostly originated from single-centre studies and were collected over a short period, leaving open the question about external and long-term validity of the NEWS, respectively.

Reflecting the data of our clinical findings [see **Table 1**], mortality and adverse clinical outcomes occurred more frequently in higher NEWS categories, confirming the basic utility of NEWS as a severity indicator. However, a majority of the clinical trials were performed in a heterogeneous patient population with diverse principal morbidities [22 25-28 31-33]. Our study focused on patients with CAP, a disease with a relatively high short-term mortality [4 34]. Therefore, early recognition of severity is crucial for the

further patient management and the use of predictive tools is currently recommended by American and European guidelines [2 13]. Our analyses reveal a strong predictive value for 30-day ICU-admission and complications (empyema) using NEWS. Despite the rather aged patient population with a high burden of comorbidities, results remained significant after adjustment for these factors. This main finding supports the routine use of NEWS in CAP patients. Interestingly, the PSI contains very similar physiological parameters as used for NEWS calculation. Still, NEWS was superior for adverse outcome prediction but inferior in regard to mortality prediction. This may be explained by the fact that PSI is age-dominated and while age is a good predictor for mortality, aged people at the end of life may be less often admitted to the ICU. NEWS sets the main focus on the acute condition (e.g. need for supplemental oxygen or altered level of consciousness) allowing better evaluation for the eventual of need for ICU-admission. Interestingly, in line with this, we found that younger patients with lower burden of comorbidities and more severe deterioration of vital signs were at higher risk for being misclassified as “low risk” with PSI but correctly identified with NEWS. This patient population may thus show the most benefit of combination of both scores.

Further, we showed that adding NEWS to established CAP-specific scores in a joint regression models improves the prognostic accuracy regarding 30-day ICU-admission. The application of the PSI in patients with CAP is widespread in the US, whereas the CURB-65 is mostly used in Europe. Our data support the calculation of both scores upon admission to the ED in the CAP patient population. Although, this may increase resource use, EWS as well as CAP scores are routinely calculated in many hospitals. Indeed, further studies should be done to compare patient management based on these combined scores to routine care to ultimately understand the benefit for patients.

Most of the previous studies analysed and proved association between NEWS and short-term mortality at maximal 30 days [22 23 25]. In our regression models for mortality outcomes, we could show an association of NEWS with 30-day, 180-day and 6-year mortality. However, PSI and CURB-65 were superior as mortality predictors. Probably this is due to the simple six point system of basic physiological parameter reflecting the very acute condition of a patient and thus the trigger and track nature of the NEWS. Whereas the PSI and CURB-65 scores include more variables taking into consideration the all-over morbidity of the patient (e.g. age, comorbidities, laboratory parameters), giving them an advantage about mortality prediction beyond the emergency setting.

The strength of our study is the considerable patient number originating from a multicentre setting with well-defined CAP criteria and a consistent distribution to the three NEWS categories. Further, the long follow-up of 6 years with repeated telephone interviews allows the investigation of short and long-term outcomes, while most previous studies focused on short-term data. There are, however, several limitations to this report. Despite the multicentre character, the study was conducted exclusively in Switzerland with predominantly Caucasian patients limiting generalizability. Furthermore, this was a secondary analysis of a previous trial which had some exclusion criteria inducing potential confounding. NEWS has been recommended to be used not only in the initial setting but also as a trigger score for patient deterioration during hospital stay[21]. Because parameters for calculation of NEWS were only collected upon admission to the ED, no follow-up analyses were done.

CONCLUSION

We found NEWS to provide additional prognostic information in regard to risk of ICU admission and complications thereby improving traditional clinical CAP risk scores in the management of patients in the ED setting.

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DATA SHARING STATEMENT

No additional data available.

AUTHOR CONTRIBUTIONS

All authors made substantive intellectual contributions to this study. DS, AK, PS and BM had the idea for and conducted statistical analyses and drafted the first manuscript. MCC, RT, WZ, CHo, and CHe were in charge of the acquisition of patient data during the trial, and provided individual patient data from their hospitals. For this manuscript they have made substantial contributions to conception and design, and have taken an active part in acquisition, analysis and interpretation of data. All authors contributed to the interpretation of data and to the revising of the manuscript critically for important intellectual content. All authors approved the final version of the manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

COMPETING INTEREST

AK, MCC, BM, and PS received support from B·R·A·H·M·S/Thermo Scientific Biomarkers and BioMerieux to attend meetings and fulfill speaking engagements. PS and BM received unrestricted research grants from, and BM has served as a consultant to these firms. All other authors have no relationships to industry relevant to this paper.

LIST OF ETHICAL BODIES

EKBB, Ethikkommission beider Basel

Kantonale Ethikkommission Aargau/Solothurn

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Ethikkommission des Kantons Thurgau

CONFLICT OF INTEREST STATEMENT

All authors confirm that they do not have a conflict of interest associated with this manuscript.

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LIST OF ABBREVIATIONS

NEWS – National Early Warning Score

CAP – community-acquired pneumonia

PSI – Pneumonia Severity Index

CURB-65 – new-onset confusion, urea >7 mmol L-1, respiratory rate ≥30 breaths per min, systolic or diastolic blood pressure <90mmHg or ≤60mmHg, respectively, age ≥65 years (pneumonia risk scoring system)

ICU – Intensive Care Unit

AUC – area under the receiver operating characteristic curve

ED – emergency department

EWS – Early Warning Score

PCT – Procalcitonin

IQR – interquartile range

CI – confidence interval

OR – Odds Ratio

ROC – Receiver Operating Characteristics

COPD – chronic obstructive pulmonary disease

PAOD – peripheral artery occlusive disease

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LEGENDS

Figure 1 *Kaplan-Meier plots showing the association between mortality outcomes and NEWS categories*

Figure 2 *Kaplan-Meier plots showing the association between adverse outcomes and NEWS categories*

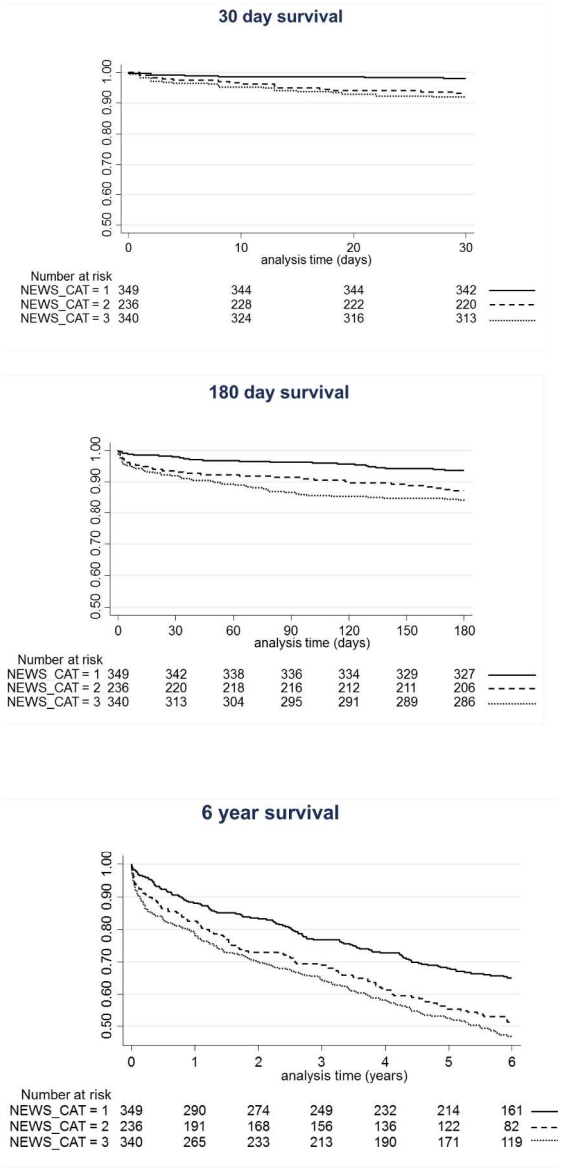
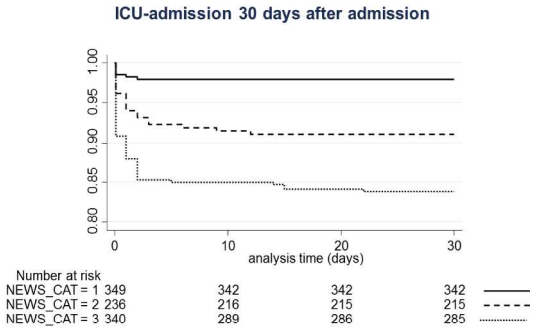
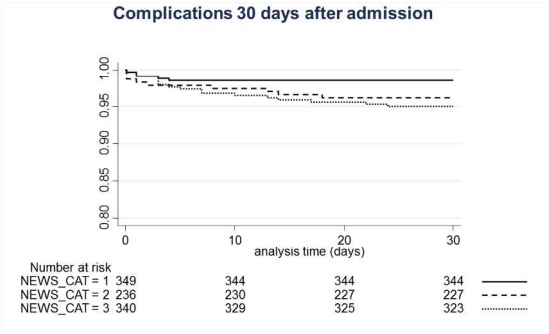


Figure 1 Kaplan-Meier plots showing the association between mortality outcomes and NEWS categories

138x299mm (300 x 300 DPI)





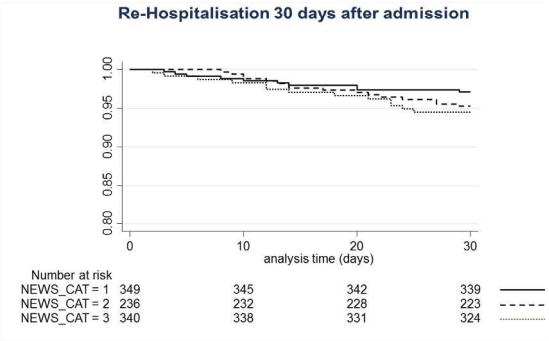


Figure 2 Kaplan-Meier plots showing the association between adverse outcomes and NEWS categories

138x299mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1/2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ~~*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls~~ ~~*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants~~	5/6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed ~~*Case-control study*—For matched studies, give matching criteria and the number of controls per case~~	n.a.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6/7/8
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	n.a.
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5/6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	n.a.
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed ~~*Case-control study*—If applicable, explain how matching of cases and controls was addressed~~ ~~*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy~~	6
		(*e*) Describe any sensitivity analyses	n.a.

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	5
		(b) Give reasons for non-participation at each stage	5
		(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	5
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11
		~~*Case-control study*—Report numbers in each exposure category, or summary measures of exposure~~	
		~~*Cross-sectional study*—Report numbers of outcome events or summary measures~~	
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	11-14
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*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	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15/16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
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	21

*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

The National Early Warning Score (NEWS) for outcome prediction in emergency department patients with community-acquired pneumonia: Results from a 6 year prospective cohort study

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The National Early Warning Score (NEWS) for outcome prediction in emergency department patients with community-acquired pneumonia: *Results from a 6 year prospective cohort study*

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Key words: National Early Warning Score (NEWS), community-acquired pneumonia (CAP), Pneumonia Severity Index (PSI), CURB-65, ICU-admission

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ABSTRACT

Objective: To investigate the accuracy of NEWS to predict mortality and adverse clinical outcomes for patients with community acquired pneumonia compared to standard risk scores such as the pneumonia severity index (PSI) and CURB-65.

Design: Secondary analysis of patients included in a previous randomized-controlled trial with a median follow-up of 6.1 years.

Settings: Patients with community acquired pneumonia included upon admission to emergency departments of six tertiary care hospitals in Switzerland.

Participants: A total of 925 patients with confirmed community acquired pneumonia were included. NEWS, PSI and CURB-65 scores were calculated upon admission to the emergency department based on admission data.

Main outcome measure: Our primary outcome was all-cause mortality within 6 years of follow-up. Secondary outcomes were adverse clinical outcome defined as intensive care unit (ICU) admission, empyema and unplanned hospital readmission all occurring within 30 days after admission. We used regression models to study associations of baseline risk scores and outcomes with the area under the receiver operating curve (AUC) as a measure of discrimination.

Results: Six-year overall mortality was 45.1% (n=417) with a step-wise increase with higher NEWS categories. For 30-days and 6-year mortality prediction, NEWS showed only low discrimination (AUC 0.65 and 0.60) inferior compared to PSI and CURB-65. For prediction of ICU admission, NEWS showed moderate discrimination (AUC 0.73) and improved the prognostic accuracy of a regression model including PSI (AUC from 0.66 to 0.74, p=0.001) and CURB-65 (AUC from 0.64 to 0.73,

p=0.015). NEWS was also superior to PSI and CURB-65 for prediction of empyema, but did not well predict rehospitalisation.

Conclusion: NEWS provides additional prognostic information in regard to risk of ICU admission and complications and thereby improves traditional clinical risk scores in the management of community-acquired pneumonia patients in the emergency department setting.

Trial registration: ISRCTN 95122877

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

- This is the first large-scale study with a long-term follow up investigating the association of NEWS and adverse outcome in community-acquired pneumonia patients
- In the emergency department setting, NEWS was an adequate tool for risk stratification in regard to ICU admission and clinical empyema

Limitations

- The study was observational and it remains unclear whether NEWS will improve patient management
- This study was limited to Swiss, predominantly Caucasian patients, limiting the generalizability of results

INTRODUCTION

Current guidelines recommend that clinical decisions regarding patient management in the emergency department (ED) setting are supported by objective risk scores [1-3]. In patients with community-acquired pneumonia (CAP), risk scores support practitioners to decide whether a patient is at higher risk for mortality and, thus, may need inpatient treatment [4-7]. Several risk scores have been developed and validated for predicting 30-day mortality in patients with CAP [8-12]. To date, the Pneumonia severity index (PSI) and CURB-65 are recommended by most international guidelines for this purpose [2] [13]. The CURB-65 is a five point score that is predominantly used in Europe. The PSI is mostly used in the US and has been validated in several studies [9] [14-19]. As a limitation, both scores have their main focus on 30-day mortality prediction, but other outcomes such as disease severity (e.g. requiring intensive care unit (ICU) admission) are not well predicted [20]. This raises the question whether these scores can be improved by combination with other instruments focusing on the initial severity of disease, such as generalized early warning scores (EWS).

Among different EWS, the National Early Warning Score (NEWS), that was derived in the UK by the National Early Warning Score Development and Implementation Group (NEWSDIG) on behalf of the Royal College of Physicians, has been well established [21]. Its purpose was to introduce a standardised trigger-system to identify acutely ill patients throughout hospitalisation. NEWS consists of six physiological measurements classifying the patients into three risk-categories (low, moderate, high). Several studies found NEWS to be superior compared to other risk stratification tools [22-25] and a valid tool in different settings (ED, prehospital setting) [26-

[28]. Yet, there is currently no study investigating how well NEWS predicts severity and adverse clinical outcome in patients with CAP upon admission to the ED.

Our hypothesis was that NEWS would show an association with short and long-term adverse outcome in patients with CAP and possibly improve risk prediction as compared to established CAP scores. The aim of our study was thus to compare the accuracy of NEWS with PSI and CURB-65 to predict mortality and adverse clinical outcomes in a well characterised cohort of CAP patients from a previous randomized-controlled trial.

METHODS

Study design

This is a secondary analysis using data of 925 patients included in a previous randomized-controlled non-inferiority trial with a 6 year follow-up. The initial trial enrolled patients from October 2006 to March 2008 at six Swiss secondary or tertiary care, academic or non-academic hospitals [29]. The aim of the initial trial was to examine whether procalcitonin (PCT) could reduce antibiotic use without compromising the safety of patients [30]. All local ethical committees approved the initial trial protocol, and gave permission to do a 6-year follow-up study. All patients gave written informed consent to the initial study and the follow-up analysis including the current analysis. The study was also registered in the "Current Controlled Trial Database" (ISRCTN 95122877) at http://www.controlled-trials.com and a study protocol was published previously [30].

Study procedures

Consecutive adults (age ≥ 18 years) with a diagnosis of CAP presenting from the community or a nursing home to the emergency department of one of the participating hospitals were included. All patients fulfilling the following CAP criteria based on the American Thoracic Society guidelines [2] were eligible: at least one symptom of cough, sputum production, dyspnoea, tachypnoea or pleuritic pain in addition to one finding during auscultation (rales or crepitation) or one infectious sign (core body temperature > 38.0°C, shivering or white blood cell count > 10 or < 4 cells x 10^9/L). The diagnosis of CAP was confirmed in all patients by a new or increasing lung infiltrate on chest X-ray. Inpatients and outpatients were eligible for the study. As previously reported, we included 1381 out of from 1825 screened patients in the study of which 925 had a confirmed diagnosis of CAP and were used for the current analysis [29].

The exclusion criteria were defined as follows: language restriction or dementia precluding informed consent, intravenous drug abuse, severe immunosuppression other than corticosteroids, chronic antibiotic therapy, medical comorbidities with imminent risk of death, hospital acquired pneumonia (defined as newly appearing pulmonary infiltrate ≥ 48h postindex admission or during hospitalization within 2 weeks before enrolment).

Assessment of vital status and score assignment

Patients were clinically and biochemically evaluated upon admission and throughout the hospital stay. Data on demographics, comorbidities, medication, laboratory variables and imaging as well as vital signs were collected.

Vital status was ascertained by trained medical students by means of phone interviews at days 30, 180 and 540 as well as 6 years after discharge. Patients or their household members were contacted first, if not attainable, the primary care physicians were called. In cases of missing vital status, patients were categorized as survivors and the latest hospital discharge date derived from medical records was used to calculate survival time. The decision for ICU transfer was up to the discretion of the treating physicians who were not aware of the NEWS score. We recorded all patients with empyema diagnosed by their treating physicians by ultrasound and laboratory examinations.

For all patients, PSI and CURB-65 scores were calculated upon admission to the emergency department as part of the routine [9 10 21]. The PSI includes 20 variables resulting in a point score and classifies the patients with CAP into five risk classes whereas the CURB-65 score uses a five point system (Confusion, Urea, Respiratory rate, Blood Pressure, Age > 65 years) classifying the patients into three risk classes. NEWS was calculated retrospectively on admission data based on the following six physiological parameters: respiratory rate, oxygen saturation, temperature, systolic blood pressure, pulse rate and level of consciousness. Every continuous variable scores a maximum of 3 points, whereas the need for supplemental oxygen and the level of consciousness are binary coded with zero points if absent/normal and 2 or 3 points if present/altered respectively. The resulting aggregate divides the patients into three categories with low (0-4 points), medium (5-6 points) or high (≥ 7 points) risk. As an exception, a single physiological parameter scoring 3 points categorizes a patient at medium risk instead of low risk, denominated as RED score.

Statistical analyses

For the statistical analysis we used STATA 12.1 (Stata Corp, College Station, TX, USA). Statistical significance was defined as a p-value < 0.05; two-tailed tests were used.

The categorical variables are presented as percentages (numbers) and the continuous variables as medians (interquartile range [IQRs]) with 95% confidence intervals (CIs), wherever applicable. Frequency comparison was estimated by chi-square (Wald) test and two-group comparisons by Mann-Whitney U-test.

The primary endpoint of this study was mortality within 6 years. Mortality was reported at short term (day 30), and long term (day 180 and six years). Secondary outcomes were adverse clinical outcomes including ICU-admission, empyema and re-hospitalisation, all occurring within 30 days after randomisation admission.

We used univariate and multivariate regression analyses to assess the association between the prognostic scores and the different outcomes. We report hazard ratio (HR) for all time to event analyses, and odds ratios (ORs) for all logistic regression analyses. We calculated different multivariate regression models including age and gender (model 1) and age, gender and main comorbidities (chronic obstructive pulmonary disease [COPD], congestive heart failure, neoplastic disease, diabetes mellitus, coronary artery disease, cerebrovascular disease, peripheral artery occlusive disease [PAOD], chronic renal failure) (model 2). Discrimination was assessed by means of the area under the receiver operating characteristics (ROC)

curve (AUC) with the 95% CI. For further illustration, we generated Kaplan-Meier plots for mortality and adverse outcomes by NEWS category. For this time-to-event analysis, censoring occurred at the time of death or at the last contact for patients lost to follow-up.

Finally, we also investigated whether NEWS adds prognostic information to PSI and CURB-65 in regard to discrimination. For this purpose, we compared the AUC of a regression model limited to the PSI score with a binary regression model including PSI and NEWS. The same was done for CURB-65.

RESULTS

Patient population

Overall, we included 925 CAP patients and the median follow- up was 6.1 year. Baseline characteristics overall and according to NEWS categories (low (0-4 points), medium (5-6 points) or high (≥ 7 points)) risk are presented in **Table 1.** The study population showed a considerably burden of comorbidities (e.g. COPD, chronic renal failure, coronary artery disease), with higher frequency in higher NEWS categories. Most patients were treated as inpatients with 8.8% of patients being treated on an outpatient basis.

Table 1 Baseline characteristics and outcomes of the study population

Characteristics	Entire cohort (n=925)	NEWS categories			
		low(n=349)	moderate (n=236)	high (n=340)	p value
Demographic characteristics					
Age	73 (59-82)	67 (50-82)	74 (62-83)	75 (63-82)	<0.001
Male	544 (58.8%)	195 (55.9%)	131 (55.5%)	218 (64.1%)	0.044
Comorbidities					
Congestive heart failure	159 (17.2%)	38 (10.9%)	44 (18.6%)	77 (22.6%)	<0.001
Chronic renal failure	206 (22.3%)	56 (16.0%)	59 (25.0%)	91 (26.8%)	0.002
Diabetes mellitus	162 (17.5%)	51 (14.6%)	45 (19.1%)	66 (19.4%)	0.19
COPD	282 (30.5%)	75 (21.5%)	73 (30.9%)	134 (39.4%)	<0.001
Neoplastic disease	118 (12.8%)	42 (12.0%)	31 (13.1%)	45 (13.2%)	0.88
Cerebrovascular disease	82 (8.9%)	18 (5.2%)	23 (9.7%)	41 (12.1%)	0.005
Coronary artery disease	183 (19.8%)	46 (13.2%)	53 (22.5%)	84 (24.7%)	<0.001
PAOD	47 (5.1%)	13 (3.7%)	16 (6.8%)	18 (5.3%)	0.25
Clinical history and risk factors					
Chills	301 (32.5%)	108 (35.3%)	80 (39.6%)	113 (37.8%)	0.71
Fever	618 (67.2%)	240 (68.8%)	152 (65.2%)	226 (67.1%)	0.67
Average Smoking (pack-years)	40 (20-50)	30 (12-50)	35 (15-50)	40 (30-60)	0.001
Clinical findings					
Confusion	74 (8.8%)	0 (0.0%)	22 (10.3%)	52 (17.0%)	<0.001
Body temperature, °C	38.1 (37.2-38.9)	37.8 (37.1-38.6)	37.8 (37.1-38.7)	38.5 (37.6-39.1)	<0.001
Systolic blood pressure, mmHg	132 (119-148)	134 (120-150)	133 (120-148)	130 (110-148)	0.001
Peripheral oxgen saturation	95 (92-97)	96.0 (94.0-97.0)	96.0 (92.5-97.0)	94.0 (92.0-96.0)	0.041
Respiratory rate	20 (16-25)	17 (15-20)	20 (16-24)	25 (22-31)	<0.001
Oxygen therapy, non invasive	460 (49.7%)	81 (23.2%)	113 (47.9%)	266 (78.2%)	<0.001
Scores					
PSI class I	104 (11.2%)	73 (20.9%)	17 (7.2%)	14 (4.1%)	<0.001
PSI class II	139 (15.0%)	74 (21.2%)	31 (13.1%)	34 (10.0%)	
PSI class III	180 (19.5%)	76 (21.8%)	53 (22.5%)	51 (15.0%)	
PSI class IV	351 (37.9%)	97 (27.8%)	96 (40.7%)	158 (46.5%)	
PSI class V	151 (16.3%)	29 (8.3%)	39 (16.5%)	83 (24.4%)	
CURB-65 class 0	206 (22.3%)	124 (35.5%)	45 (19.1%)	37 (10.9%)	<0.001
CURB-65 class 1	253 (27.4%)	109 (31.2%)	71 (30.1%)	73 (21.5%)	
CURB-65 class 2	306 (33.1%)	102 (29.2%)	82 (34.7%)	122 (35.9%)	
CURB-65 class 3	134 (14.5%)	14 (4.0%)	35 (14.8%)	85 (25.0%)	
CURB-65 class 4	25 (2.7%)	0 (0.0%)	3 (1.3%)	22 (6.5%)	
CURB-65 class 5	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	
Outcomes					
30-day mortality	50 (5.4%)	7 (2.0%)	16 (6.8%)	27 (7.9%)	0.001
180-day mortality	106 (11.5%)	22 (6.3%)	30 (12.7%)	54 (15.9%)	<0.001
6-year mortality	417 (45.1%)	118 (33.8%)	115 (48.7%)	184 (54.1%)	<0.001
ICU admission	83 (9.0%)	7 (2.0%)	21 (8.9%)	55 (16.2%)	<0.001
Empyema	31 (3.4%)	5 (1.4%)	9 (3.8%)	17 (5.0%)	0.031
Relapse / Rehospitalisation	39 (4.2%)	10 (2.9%)	13 (5.5%)	16 (4.7%)	0.25
Lenght of stay, days	8 (5-12)	6.0 (3.0-10.0)	8.0 (6.0-12.0)	10.0 (6.0-14.5)	<0.001

Data are presented as percentage (n) or median (interquartile range). COPD: chronic obstructive pulmonary disease; PAOD : peripheral artery occlusive disease ; NEWS: National Early Warning Score ; PSI: Pneumonia Severity Index, CURB-65: confusion, urea > 7mmol/L^{-1}, respiratory frequency ≥ 30 breaths/min^{-1}, low blood pressure (systolic value < 90 mmHg or diastolic value ≤ 60 mmHg) and age ≥ 65 yrs ; ICU : intensive care unit. NEWS categories refers to low (0-4 points), medium (5-6 points) or high (≥ 7 points).

NEWS and mortality outcomes

The overall 30-day mortality was 5.4% and increased to 45.1% after 6 years. 30-day mortality was significantly higher in NEWS category 3 compared to category 1 and 2 as presented in Kaplan-Meier survival curves (**Figure 1)**.

Table 2 shows the unadjusted and adjusted regression analyses assessing the association of NEWS with all-cause mortality at 30 days, 180 days and 6 years. For 30-day mortality, an increase in NEWS category was associated with a 16% increase in odds for reaching the event (OR 1.16, 95% 1.07 to 1.27), p=0.001). These results were similar for longer term mortality and also after rigorous adjustment in the different models. Yet, mortality discrimination analysis shows only low results for NEWS with AUCs of 0.65, 0.62 and 0.60 after 30-days, 180-days and 6 years. In contrast, PSI and CURB-65 showed better mortality discrimination with AUC between 0.76 and 0.80 for PSI and 0.69 and 0.73 for CURB-65. Combining NEWS with PSI or CURB-65 score in a statistical model did not improve the predictive value of these established scores in regard to mortality compared to the scores alone.

Table 2 ***NEWS as a mortality predictor compared to the PSI and CURB-65 scores***

	Mortality 30 days	Mortality 180 days	Mortality 6 years
Unadjusted OR	1.16 (1.07 to 1.27), p=0.001	1.13 (1.06 to 1.20), p<0.001	1.13 (95%CI 1.08 to 1.17), p<0.001
Adjusted OR (model 1)*	1.15 (1.05 to 1.25), p=0.003	1.11 (1.04 to 1.18), p=0.002	1.10 (95%CI 1.05 to 1.16), p<0.001
Adjusted OR (model 2)**	1.10 (1.01 to 1.21), p=0.035	1.07 (1.00 to 1.15), p=0.038	1.08 (95%CI 1.02 to 1.13), p=0.007
Discrimination			
AUC NEWS	0.65 (0.58 to 0.72)	0.62 (0.57 to 0.67)	0.60 (95%CI 0.57 to 0.64)
AUC PSI	0.80 (0.76 to 0.84)	0.76 (0.72 to 0.80)	0.79 (95%CI 0.76 to 0.81)
p value (NEWS vs PSI)	*<0.001*	*<0.001*	*<0.001*
AUC NEWS and PSI	0.82 (0.77 to 0.86)	0.77 (0.73 to 0.81)	0.79 (95%CI 0.76 to 0.82)
p value (NEWS & PSI vs PSI)	*0.084*	*0.074*	*0.911*
AUC CURB-65	0.72 (0.65 to 0.78)	0.69 (0.64 to 0.74)	0.73 (95%CI 0.69 to 0.76)
p value (NEWS vs CURB-65)	*0.076*	*0.015*	*<0.001*
AUC NEWS and CURB-65	0.73 (0.67 to 0.79)	0.70 (0.66 to 0.75)	0.73 (95%CI 0.70 to 0.76)
p value (NEWS & CURB-65 vs CURB-65)	*0.178*	*0.091*	*0.29*

Data from univariate and multivariate analysis are given as odds ratio (95%CI) per point increase, p value. Data from the ROC analysis are given as AUC (95%CI) or p value. OR: odds ratio; AUC: area under the curve; NEWS: National Early Warning Score; PSI: Pneumonia Severity Index; CURB-65: confusion, urea > 7mmol/L^{-1}, respiratory frequency ≥ 30 breaths/min^{-1}, low blood pressure (systolic value < 90 mmHg or diastolic value ≤ 60 mmHg) and age ≥ 65 yrs ;

**** adjusted for age, gender***

***** adjusted for age, gender, comorbidities (COPD, congestive heart failure, neoplastic disease, diabetes mellitus, coronary artery disease, cerebrovascular disease, PAOD, chronic renal failure)***

NEWS and adverse clinical outcomes

The risk for ICU admission and empyema significantly increased with increasing NEWS categories. **Figure 2** shows a significant separation in time to ICU admission with increasing NEWS categories.

Table 3 shows the unadjusted and adjusted regression analysis investigating the association of NEWS with adverse clinical outcomes, namely ICU-admission, empyema and re-hospitalisation. The results were statistically significant for NEWS as a predictor for ICU-admission (OR 1.29 [1.2, 1.39]) and empyema (OR 1.16 [1.04, 1.29]) within 30 days after admission. This was also true after adjustment for age, gender and comorbidities ($p<0.01$, each). Concerning re-hospitalization, no significant association was found.

In regard to discrimination, NEWS showed the highest AUC for all three outcomes compared to PSI and CURB-65. For ICU admission, NEWS significantly improved PSI (from AUC 0.66 to 0.74, p=*0.001*) and CURB-65 (from AUC 0.64 to 0.73, p=*0.002*). For empyema, NEWS also tended to improve PSI (from AUC 0.50 to 0.64, p=0.086) and significantly improved CURB-65 (from AUC 0.50 to 0.65, p=*0.025*). For re-hospitalization, no significant improvement was found.

Patients that were misclassified by the PSI score as low risk (PSI class 1 or 2) but correctly identified by NEWS had a younger age (median age 49 years vs 74 years), less comorbidities (heart and renal failure, coronary heart disease) and more frequent deterioration (chills, oxygenation) of vital signs compared to patients that were correctly identified by both scores.

Table 3 ***NEWS as adverse outcome predictor compared to the PSI and CURB-65 scores***

	ICU-Admission within 30 days	**Empyema** within 30 days	**Re-Hospitalisation** within 30 days
Unadjusted OR	1.29 (1.20 to 1.39), p<0.001	1.16 (1.04 to 1.29), p=0.007	1.08 (0.98 to 1.18), p=0.143
Adjusted OR (model 1)*	1.30 (1.20 to 1.40), p<0.001	1.18 (1.06 to 1.32), p=0.003	1.08 (0.98 to 1.20), p=0.106
Adjusted OR (model 2)**	1.27 (1.18 to 1.37), p<0.001	1.17 (1.05 to 1.30), p=0.005	1.07 (0.97 to 1.18), p=0.184
Discrimination			
AUC NEWS	0.73 (0.67 to 0.78)	0.64 (0.54 to 0.73)	0.58 (0.49 to 0.66)
AUC PSI	0.66 (0.60 to 0.72)	0.50 (0.40 to 0.60)	0.53 (0.43 to 0.63)
p value (NEWS vs PSI)	*0.072*	*0.042*	*0.358*
AUC NEWS and PSI	0.74 (0.69 to 0.79)	0.64 (0.54 to 0.73)	0.58 (0.49 to 0.66)
p value (NEWS & PSI vs PSI)	*0.001*	*0.086*	*0.414*
AUC CURB-65	0.64 (0.58 to 0.70)	0.50 (0.40 to 0.59)	0.50 (0.41 to 0.59)
p value (NEWS vs CURB-65)	*0.015*	*0.011*	*0.118*
AUC NEWS and CURB-65	0.73 (0.68 to 0.79)	0.65 (0.55 to 0.74)	0.58 (0.49 to 0.67)
p value (NEWS & CURB-65 vs CURB-65)	*0.002*	*0.025*	*0.246*

Data from univariate and multivariate analysis are given as odds ratio (95%CI) per point increase. Data from the ROC analysis are given as AUC (95%CI) or p value. OR: odds ratio; AUC: area under the curve; NEWS: National Early Warning Score; PSI: Pneumonia Severity Index; CURB-65: confusion, urea > 7mmol/L^{-1}, respiratory frequency ≥ 30 breaths/min^{-1}, low blood pressure (systolic value < 90 mmHg or diastolic value ≤ 60 mmHg) and age ≥ 65 yrs ; ICU : intensive care unit

**** adjusted for age, gender***

***** adjusted for age, gender, comorbidities (COPD, congestive heart failure, neoplastic disease, diabetes mellitus, coronary artery disease, cerebrovascular disease, PAOD, chronic renal failure)***

DISCUSSION

This first study evaluating NEWS in a large population with CAP from a multicentre study with a 6 year follow-up has three key findings. First, NEWS is a moderate predictor for adverse clinical outcomes particularly ICU admission and to a lesser degree for empyema in patients presenting with CAP to the ED. Second, NEWS improves the PSI and CURB-65 for prediction of ICU admission. Third, although NEWS is associated with mortality, this score has a lower prognostic performance compared to standard CAP scores and did not improve their performance.

NEWS has been originally established and validated as a track-and-trigger system for acute illness. A first study showed its superiority comparing it to other EWS [21 22]. Most subsequent research validated the superior performance of NEWS compared to other algorithms [23-25 27]. Also the different parameters included in NEWS were well validated [31-33]. Yet, performance of NEWS within specific patient subpopulations has not well been studied, with some exceptions such as patients with severe sepsis or septic shock [28]. Most validation studies were single-centre studies with short follow-up of patients. Thus, external validity and long-term predictive ability of NEWS remains unknown today.

Reflecting the data of our clinical findings [see **Table 1**], mortality and adverse clinical outcomes occurred more frequently in higher NEWS categories, confirming the basic utility of NEWS as a severity indicator. However, a majority of the clinical trials were performed in a heterogeneous patient population with diverse principal morbidities [22 25-28 31-33]. Our study focused on patients with CAP, a disease with a relatively high short-term mortality [4 34]. Therefore, early recognition of severity is crucial for the further patient management and the use of predictive tools is currently recommended by American and European guidelines [2 13]. Our analyses reveal a moderate

predictive value for 30-day ICU-admission and empyema using NEWS. Despite the rather aged patient population with a high burden of comorbidities, results remained significant after adjustment for these factors. This main finding supports the routine use of NEWS in CAP patients. Interestingly, the PSI contains similar physiological parameters as used for NEWS calculation. Still, NEWS was superior for adverse outcome prediction but inferior in regard to mortality prediction. This may be explained by the fact that PSI is age-dominated and while age is a good predictor for mortality, aged people at the end of life may be less often admitted to the ICU. NEWS sets the main focus on the acute condition (e.g. need for supplemental oxygen or altered level of consciousness) allowing better evaluation for the eventual of need for ICU-admission. Interestingly, in line with this, we found that younger patients with lower burden of comorbidities and more severe deterioration of vital signs were at higher risk for being misclassified as “low risk” with PSI but correctly identified with NEWS. This patient population may thus show the most benefit of combination of both scores.

Further, we found that combining NEWS with established CAP-specific scores in a joint regression model improves the prognostic accuracy regarding 30-day ICU-admission. The application of the PSI in patients with CAP is widespread in the US, whereas the CURB-65 is mostly used in Europe. Our data support the calculation of both scores upon admission to the ED in the CAP patient population. Although, this may increase resource use, EWS as well as CAP scores are routinely calculated in many hospitals. Indeed, further studies should be done to compare patient management based on these combined scores to routine care to ultimately understand the benefit for patients.

Most of the previous studies analysed and proved association between NEWS and short-term mortality at maximal 30 days [22 23 25]. In our regression models for mortality outcomes, we could show an association of NEWS with 30-day, 180-day and 6-year mortality. However, PSI and CURB-65 were superior as mortality predictors. Probably this is due to the simple six point system of basic physiological parameter reflecting the very acute condition of a patient and thus the trigger and track nature of the NEWS. Whereas the PSI and CURB-65 scores include more variables taking into consideration the all-over morbidity of the patient (e.g. age, comorbidities, laboratory parameters), giving them an advantage about mortality prediction beyond the emergency setting.

The strength of our study is the considerable patient number originating from a multicentre setting with well-defined CAP criteria and a consistent distribution to the three NEWS categories. Further, the long follow-up of 6 years with repeated telephone interviews allows the investigation of short and long-term outcomes, while most previous studies focused on short-term data. There are, however, several limitations to this report. Despite the multicentre character, the study was conducted exclusively in Switzerland with predominantly Caucasian patients limiting generalizability. Furthermore, this was a secondary analysis of a previous trial which had some exclusion criteria inducing potential confounding. NEWS has been primarily recommended to be used as a trigger score for patient deterioration during hospital stay and not in the initial setting[21]. Because parameters for calculation of NEWS were only collected upon admission to the ED, no follow-up analyses were done.

CONCLUSION

We found NEWS to provide additional prognostic information in regard to risk of ICU admission and empyema thereby improving traditional clinical CAP risk scores in the management of patients in the ED setting.

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DATA SHARING STATEMENT

No additional data available.

AUTHOR CONTRIBUTIONS

All authors made substantive intellectual contributions to this study. DS, AK, PS and BM had the idea for and conducted statistical analyses and drafted the first manuscript. MCC, RT, WZ, CHo, and CHe were in charge of the acquisition of patient data during the trial, and provided individual patient data from their hospitals. For this manuscript they have made substantial contributions to conception and design, and have taken an active part in acquisition, analysis and interpretation of data. All authors contributed to the interpretation of data and to the revising of the manuscript critically for important intellectual content. All authors approved the final version of the manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

COMPETING INTEREST

AK, MCC, BM, and PS received support from B·R·A·H·M·S/Thermo Scientific Biomarkers and BioMerieux to attend meetings and fulfill speaking engagements. PS and BM received unrestricted research grants from, and BM has served as a consultant to these firms. All other authors have no relationships to industry relevant to this paper.

LIST OF ETHICAL BODIES

EKBB, Ethikkommission beider Basel

Kantonale Ethikkommission Aargau/Solothurn

Ethikkommission des Kantons Luzern

Ethikkommission des Kantons Thurgau

CONFLICT OF INTEREST STATEMENT

All authors confirm that they do not have a conflict of interest associated with this manuscript.

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LIST OF ABBREVIATIONS

NEWS – National Early Warning Score

CAP – community-acquired pneumonia

PSI – Pneumonia Severity Index

CURB-65 – new-onset confusion, urea >7 mmol L-1, respiratory rate ≥30 breaths per min, systolic or diastolic blood pressure <90mmHg or ≤60mmHg, respectively, age ≥65 years (pneumonia risk scoring system)

ICU – Intensive Care Unit

AUC – area under the receiver operating characteristic curve

ED – emergency department

EWS – Early Warning Score

PCT – Procalcitonin

IQR – interquartile range

CI – confidence interval

OR – Odds Ratio

ROC – Receiver Operating Characteristics

COPD – chronic obstructive pulmonary disease

PAOD – peripheral artery occlusive disease

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LEGENDS

Figure 1 *Kaplan-Meier plots showing the association between mortality outcomes and NEWS categories*

Figure 2 *Kaplan-Meier plots showing the association between adverse outcomes and NEWS categories*

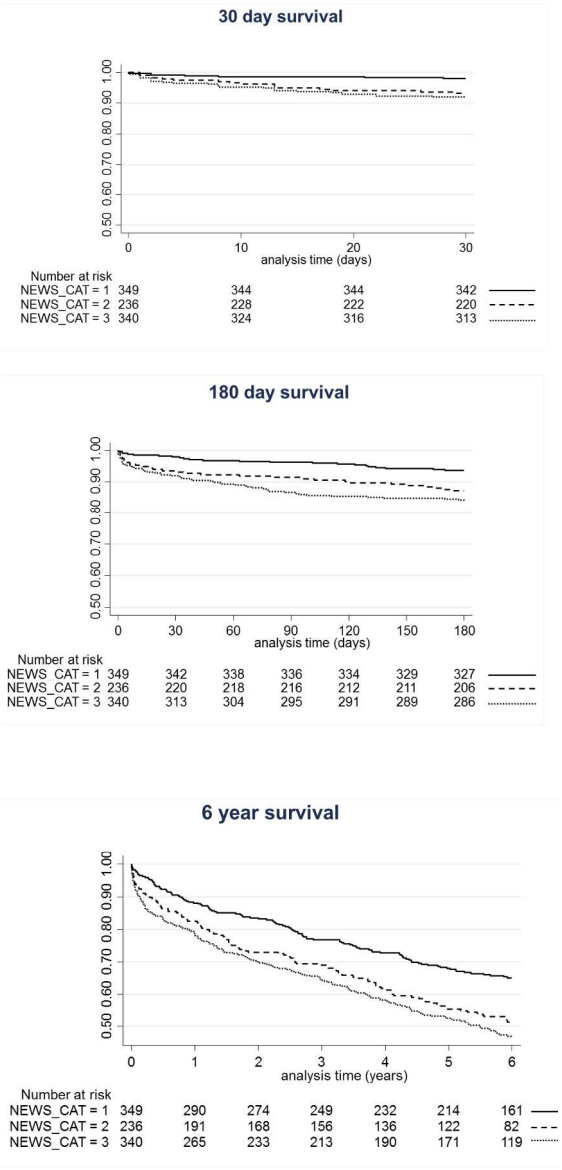
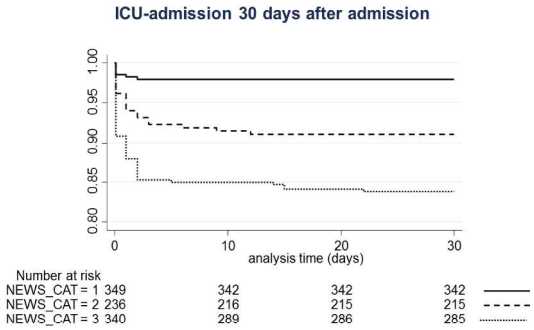
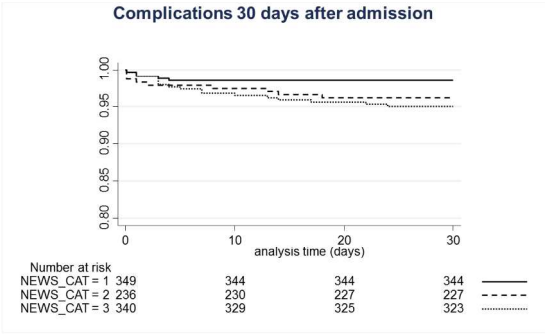


Figure 1 Kaplan-Meier plots showing the association between mortality outcomes and NEWS categories

138x299mm (300 x 300 DPI)





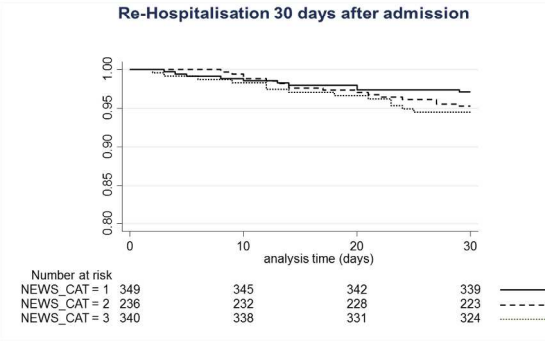


Figure 2 Kaplan-Meier plots showing the association between adverse outcomes and NEWS categories

138x299mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1/2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ~~*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls~~ ~~*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants~~	5/6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed ~~*Case-control study*—For matched studies, give matching criteria and the number of controls per case~~	n.a.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6/7/8
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	n.a.
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5/6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	n.a.
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed ~~*Case-control study*—If applicable, explain how matching of cases and controls was addressed~~ ~~*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy~~	6
		(*e*) Describe any sensitivity analyses	n.a.

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	5
		(b) Give reasons for non-participation at each stage	5
		(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	5
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11
		~~*Case-control study*—Report numbers in each exposure category, or summary measures of exposure~~	
		~~*Cross-sectional study*—Report numbers of outcome events or summary measures~~	
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	11-14
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*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	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15/16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
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	21

*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.