The diagnostic management of suspected pulmonary embolism in special patient populations

Stals, M.A.M.

7

Use of the National Early Warning Score for predicting deterioration of patients with acute pulmonary embolism: a post-hoc analysis of the YEARS study

Roisin Bavalia, Milou A.M. Stals, Frits I. Mulder, Ingrid M. Bistervels, Michiel Coppens, Laura M. Faber, Stephan V. Hendriks, Herman M.A. Hofstee, Menno V. Huisman, Tom van der Hulle, Albert T.A. Mairuhu, Marieke J.H.A. Kruip, Saskia Middeldorp, Frederikus A. Klok, Barbara A. Hutten, Frits Holleman

Emerg Med J. 2023 Jan;40(1):61-66

ABSTRACT

Background: The Pulmonary Embolism Severity Index (PESI) and the simplified PESI (sPESI) are validated scores for mortality prediction in patients with pulmonary embolism (PE). National Early Warning Score (NEWS) is a general prognostic risk score for multiple clinical settings. We investigated whether the NEWS had a comparable performance with the PESI and sPESI, for predicting intensive care unit (ICU) admission and death in patients with acute PE.

Methods: In haemodynamically stable patients with confirmed PE from the YEARS Study (2013–2015), we evaluated the performance of the NEWS, PESI and sPESI for predicting 7-day ICU admission and 30-day mortality. Receiver operating characteristic curves were plotted and the area under the curve (AUC) was calculated.

Results: Of 352 patients, 12 (3.4%) were admitted to the ICU and 5 (1.4%) died. The AUC of the NEWS for ICU admission was 0.80 (95% CI 0.66 to 0.94) and 0.92 (95% CI 0.82 to 1.00) for 30-day mortality. At a threshold of 3 points, NEWS yielded a sensitivity and specificity of 92% and 53% for ICU admission and 100% and 52% for 30-day mortality. The AUC of the PESI was 0.64 (95% CI 0.48 to 0.79) for ICU admission and 0.94 (95% CI 0.87 to 1.00) for mortality. At a threshold of 66 points, PESI yielded a sensitivity of 75% and a specificity of 38% for ICU admission. For mortality, these were 100% and 37%, respectively. The performance of the sPESI was similar to that of PESI.

Conclusion: In comparison with PESI and sPESI, NEWS adequately predicted 7-day ICU admission as well as 30-day mortality, supporting its potential relevance for clinical practice.

INTRODUCTION

In clinical practice, early warning scores (EWS) are important for recognising deterioration of patients over time and for enabling timely interventions that benefit the patients' outcome. Over the last decades, many scores have been developed for predicting prognostic outcomes of specific underlying diseases. Examples include the ADHERE algorithm for prediction of in-hospital mortality in patients with heart failure, and the TIMI risk score for patients with ST-elevation myocardial infarction. In the UK, the National Early Warning Score (NEWS), a derivative of the modified EWS, was implemented in 2012 to identify deteriorating patients in-hospital or in the ED at an early stage to improve clinical outcomes.[1] The NEWS has been validated in multiple medical settings and is a good discriminator for prognostic outcomes, regardless of the underlying disease.[2] In comparison with 33 other EWS, NEWS has a greater ability to discriminate patients at risk of unanticipated intensive care unit (ICU) admission or death within 24 hours, with area under the receiver operating characteristics (ROC) curve of 0.86 (95% CI 0.85 to 0.87) and 0.89 (95% CI 0.89 to 0.90), respectively.[3]

In patients with pulmonary embolism (PE), prognostic assessment is crucial as the clinical course varies between patients and ranges from fast recovery to haemodynamic compromise and death. While 30%–50% of haemodynamically stable patients with PE are eligible for home treatment, the other half require hospitalisation with or without haemodynamic monitoring.[4–6] The main indication for ICU admission in patients with PE is (impending) haemodynamic instability, sometimes with performing reperfusion therapy. This is in line with the 2019 European Society of Cardiology guidelines, which recommend that patients with intermediate-high to high-risk PE require monitoring.[6] Current guidelines advocate the use of the Pulmonary Embolism Severity Index (PESI) or its simplified version (sPESI) for risk stratification of patients with PE.[6]

In the acute care setting, the plethora of different prognostic scores for different diseases could be a source of confusion and poor adherence. A single, universal prognostic score, such as the NEWS, could help acute care physicians in making adequate decisions more rapidly. However, its prognostic performance in patients with acute PE has never been evaluated. Therefore, we investigated whether the NEWS had a comparable performance with the PESI and sPESI for predicting ICU admission and death in patients with acute PE.

METHODS

Study design and patient population

The study was a post-hoc analysis of the YEARS Study.[7,8] The YEARS Study was a multicentre, prospective cohort study in 12 Dutch hospitals conducted between October 2013 and July 2015 in haemodynamically stable patients with suspected acute PE, to validate the diagnostic YEARS algorithm. Patients were treated for their PE as per hospital protocol and were followed for 3 months. Clinical and PE-specific characteristics at inclusion were collected to assess the severity of the PE. For the present analysis, patients from seven Dutch hospitals participating in the YEARS Study diagnosed with radiologically confirmed acute PE at baseline were eligible for inclusion.[7] In these seven centres, variables needed to calculate the PESI, sPESI or NEWS were routinely collected while this was not the case for the other five hospitals from the YEARS Study consortium. Patients with an in-hospital PE were excluded from this analysis.

Prognostic scores

The three prognostic scores under evaluation were NEWS, PESI and sPESI. These risk scores were calculated as proposed in the original derivation studies (**Supplemental tables 1 and 2**).[3,9,10] The vital parameters used to calculate the NEWS, PESI and sPESI were the first measured parameters at presentation to the ED (**Supplemental table 3**). These data were collected for all seven included centres by four different authors (RB, MAMS, IMB, SVH). There was no overlap in data collection. Eventually, all items necessary for calculation of the three scores were available in our data set, except for the variable 'Alert Voice Pain Unresponsiveness' (AVPU) used in the NEWS. As a surrogate for the AVPU variable, we used the variable 'altered mental status'. Patients scored 0 points in the NEWS in case of no altered mental status and 3 points when they had an altered mental status.

The NEWS comprises seven variables (vital parameters) for which 0–3 points can be attributed per variable. The sum score ranges from 0 to 20 points, and directly predicts patients' deterioration.[3] The lower the NEWS, the lower the risk of deterioration.

The PESI is based on 11 routinely available patient characteristics and stratifies patients with PE into five severity classes: with 30-day mortality rates of 0%–1.6% in class I (PESI score 0–65), 1.7%–3.5% in class II (PESI score 66–85), 3.2%–7.1% in class III (PESI score 86–105), 4.0%–11.4% in class IV (PESI score 106–125) and 10.0%–24.5% in class V (PESI score ≥125).[9]

The sPESI is based on 6 of the 11 original PESI variables and stratifies patients with PE into two severity classes, with 30-day mortality rates of 1.1%, with 1.5% having recurrent thromboembolism or non-fatal bleeding (sPESI score 0 points), or mortality rates of 8.9% (sPESI score ≥1 points).[10]

Clinical outcomes

The outcomes were all-cause ICU admission within 7 days and all-cause mortality within 30 days after presentation. In a second analysis, we evaluated PE-related ICU admissions and PE-related mortality. All clinical outcomes had been collected prospectively during the YEARS Study. In the YEARS Study, deaths were classified as PE related if confirmed by autopsy, shown by objective testing before death or PE could not be ruled out as a cause of death.[7]

Statistical analysis

Demographic and clinical characteristics were described with standard descriptive statistics. Patients lost to follow-up were excluded. Multiple imputation by chained equations for the individual scoring items was used to account for missing data (**Supplemental table 3**). All scoring items of NEWS, PESI and sPESI, along with the clinical outcomes, were included in the imputation model to create five imputed data sets. After imputation of the scoring items, we calculated all risk scores for each individual. Differences between the risk scores for patients with and without the clinical outcome were calculated and tested for significance by performing the Mann-Whitney U test. The area under the ROC curve (AUC) was calculated separately for each imputed data set to evaluate the continuous predictive performance of the NEWS, PESI and sPESI for all outcomes. We hereafter pooled the AUCs of all imputed data sets to obtain summary estimates. The AUC represents the degree to which a risk score can distinguish between patients with and without one of the outcomes. We considered an AUC less than 0.60 as failing, 0.60–0.69 poor, 0.70–0.79 fair, 0.80–0.89 good, and more than or equal to 0.90 as excellent discrimination.[11] Estimates with SE were combined across the data set using Rubin's rules, to provide a summary estimate and its corresponding 95% CI.[12] Reclassification tables were created using all available thresholds, along with the sensitivity, specificity, and positive (PPV) and negative predictive value (NPV).

Data were analysed by the SPSS, V.26.0 and by R studio, V.3.6.3 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org), in particular using the 'mice' V.2.25 package for multiple imputation and the 'proc' package V.2.4.9 for the c-indices.

Patient and public involvement

Patients and the public were not involved in this research.

RESULTS

Study population

Of 456 patients enrolled in the YEARS Study and diagnosed with PE, we included 352 patients with an acute PE from seven centres for the current analysis (**Figure 1**). Mean age of the selected patients was 59 years (SD 17) and 186 (53%) patients were female (**Table 1**). In 75 (21%) patients, the anatomical extent of the PE was extensive, comprising central, segmental and subsegmental pulmonary arteries.[8] Because haemodynamically unstable patients were excluded from the YEARS Study, none required thrombolysis for the primary management.

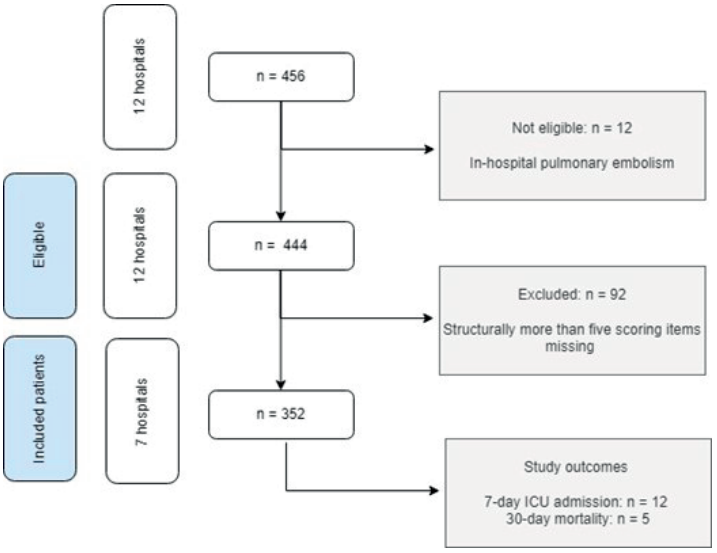

Figure 1. Flowchart of the study population
ICU: intensive care unit.

Detailed follow-up data were missing in six patients because of immediate transfer to another hospital. No other patients were lost to follow-up. Out of the remaining 346, 187 (54%) patients were admitted and 159 (46%) patients were treated at home. Twelve (3.4%) patients were admitted to the ICU within 7 days; 10 of these were PE related. Reasons for these PE-related admissions were haemodynamic and/or respiratory decompensation including respiratory shock requiring cardiopulmonary resuscitation. One of the non-PE-related ICU admissions was for additional monitoring due to a medical history of a thalamic haemorrhage and the other due to an intrathoracic haemorrhage. Detailed follow-up data on mortality were available for all 352 patients. Five (1.4%) died within 30 days, of whom one as a direct consequence of PE and two as a possible consequence of PE. One (0.3%) patient died of an intraparenchymal haemorrhage after

anticoagulation and another patient (0.3%) died by a euthanasia procedure in the setting of severe comorbidities. One patient who died had also been admitted to the ICU; all other (n=4) patients had not been admitted to the ICU.

Table 1. Demographic and clinical characteristics of the study population

	Patients with acute PE N=352
Age in years, mean (SD)	59 (17)
Female sex, n (%)	186 (53)
Smoking, n (%)	51 (15)
Renal impairment defined as e-GFR <30 mL/min, n (%)	3 (1)
Systolic BP in mm Hg, mean (SD)	137 (22)
HR in beats per minute, mean (SD)	91 (19)
RR in breaths per minute, mean (SD)	20 (5)
Peripheral oxygen saturation in percentage, mean (SD)	95 (5)
Temperature in degrees Centigrade, mean (SD)	37.0 (0.7)
Loss of consciousness, n (%)	6 (2)
PE location: central, segmental and subsegmental, n (%)*	75 (21)
Syncope before or during presentation at ED, n (%)	29 (8)
Comorbidity, n (%)	
Hypertension	85 (24)
Venous thromboembolism	84 (24)
Malignancy	46 (13)
Diabetes mellitus	29 (8)
Myocardial infarction	27 (8)
Chronic obstructive pulmonary disease	20 (6)
Stroke	20 (6)
Heart failure	10 (3)

Data on diabetes mellitus were missing in 12 patients, data on e-GFR were missing in 3 patients, data on hypertension were missing in 13 patients, data on PE location were missing in 88 patients, data on smoking were missing in 9 patients, data on stroke were missing in 11 patients, data on syncope were missing in 86 patients.
*This comprises patients, who had a PE at all three levels (subsegmental, segmental and central).
e-GFR, estimated glomerular filtration rate; n, number; PE, pulmonary embolism.

National Early Warning Score

Figure 2 shows the NEWS in patients who were admitted to the ICU (n=12) and in patients who were not (n=334). The pooled AUC for the NEWS for all-cause ICU admission was 0.80 (95% CI 0.66 to 0.94) (**Figure 3**). Out of 176 patients with a NEWS below 3, 1 of the 12 patients was misclassified as low risk and was ultimately admitted to the ICU. This corresponded to a sensitivity of 92%, a specificity of 53%, a NPV of 99% and a PPV of 6% (**Supplemental table 4**). At a NEWS of 7 points or higher, the sensitivity was 62% and the specificity 87%. The NPV and PPV were 98% and 14%, respectively (**Supplemental table 4**).

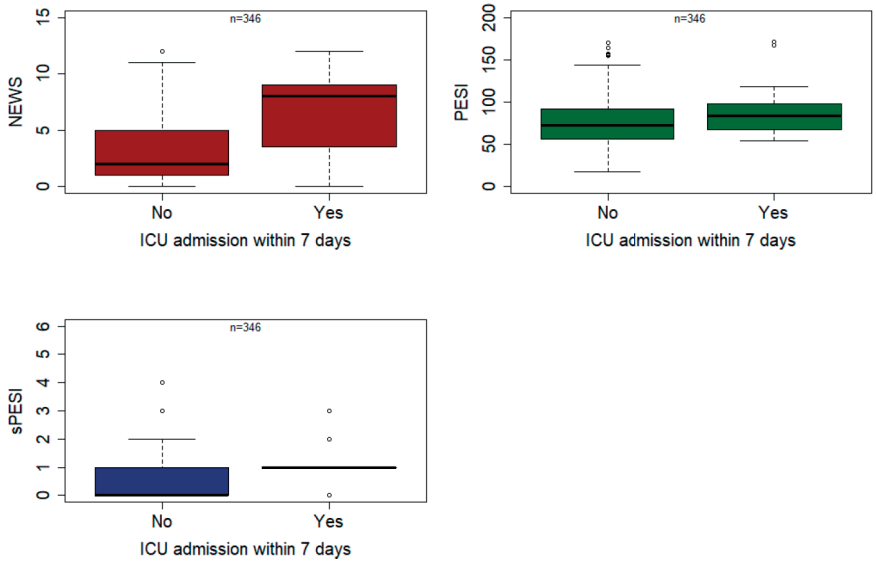

Figure 2. Differences in NEWS, PESI and sPESI scores between patients who were admitted to ICU and patients who were not, in the overall population (n=346)
The black horizontal line represents the median, the outer lines of the boxplot represent the first and third quartile range, the whiskers represent the 95% CI and the open circles represent the outliers. The range of the NEWS in this study varies from 0 to 15. The range of the PESI varies from 0 to 200. The range of the sPESI varies from 0 to 6. ICU, intensive care unit; NEWS, National Early Warning Score; PESI, Pulmonary Embolism Severity Index; sPESI, simplified PESI.

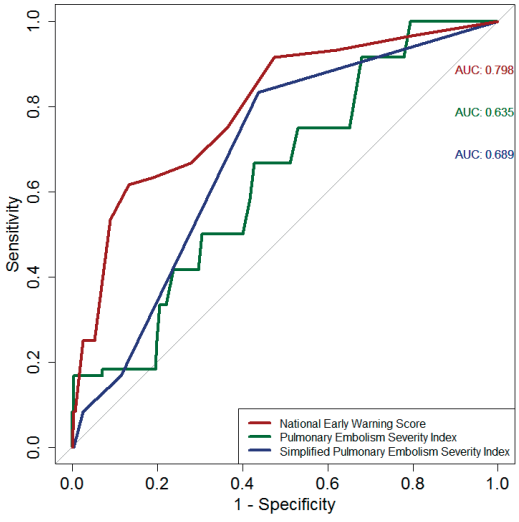

Figure 3. Area Under the Curve (AUC) for prediction of 7-day ICU admission for NEWS, PESI and sPESI in the overall population (n=346)
ICU, intensive care unit; NEWS, National Early Warning Score; PESI, Pulmonary Embolism Severity Index; sPESI, simplified PESI.

Figure 4 shows the NEWS in patients who died (n=5) and in patients who survived. The pooled AUC for 30-day all-cause mortality was 0.92 (95% CI 0.82 to 1.00) (**Figure 5**). In 179 patients with a NEWS lower than 3, zero patients were misclassified as low risk, as none of these died within 30 days. This yielded a sensitivity of 100%, a specificity of 37%, NPV 100% and PPV 2% (**Supplemental table 5**). At a NEWS of 7 points or higher, the sensitivity was 83% and the specificity was 85%. The NPV and PPV were 100% and 7%, respectively.

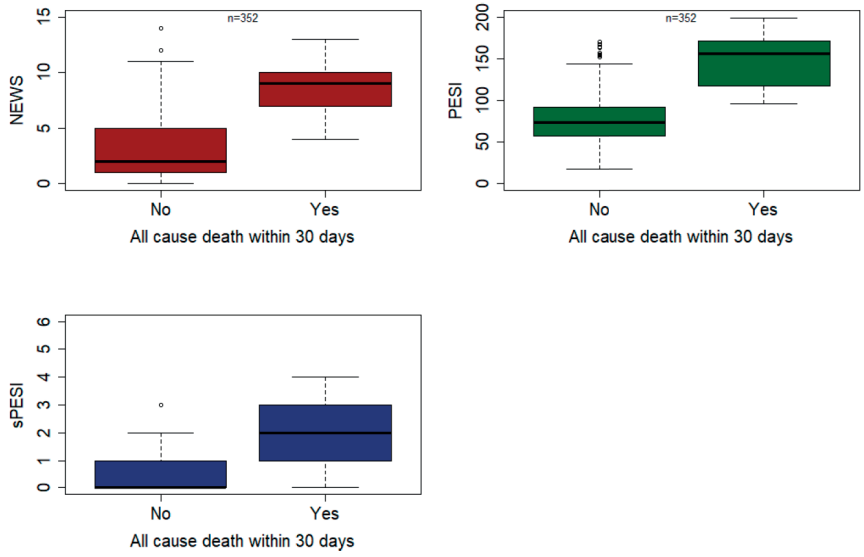

Figure 4. Difference in NEWS, PESI and sPESI scores between patients who survived and patients who died within 30 days, in the overall population (n=352)
The black horizontal line represents the median, the outer lines of the boxplot represent the first and third quartile range, the whiskers represent the 95% CI and the open circles represent the outliers. The range of the NEWS in this study varies from 0 to 15. The range of the PESI varies from 0 to 200. The range of the sPESI varies from 0 to 6. NEWS, National Early Warning Score; PESI, Pulmonary Embolism Severity Index; sPESI, simplified PESI.

The performance of the NEWS for predicting PE-related ICU admission and mortality was comparable with its performance for all-cause ICU admission and mortality (**Supplemental tables 6 and 7**).

PESI score

Figure 2 shows the PESI in patients who were admitted to the ICU (n=12) and in patients who were not. The overall pooled AUC for PESI for ICU admission was 0.64 (95% CI 0.48 to 0.79) (**Figure 3**). None of the PESI threshold values adequately discriminated patients

who were or were not admitted to the ICU, corresponding to low sensitivity and specificity values (**Supplemental table 4**).

In 129 patients with a PESI below 66, three patients were misclassified as low risk and were admitted to the ICU. This yielded a sensitivity of 75%, a specificity of 38%, a NPV of 98% and a PPV of 4%. At a PESI of 126 or higher, the sensitivity was 17% and the specificity was 95%. The NPV and PPV were 97% and 11%, respectively.

Figure 4 shows the PESI in patients who died and in patients who survived. The overall AUC for the PESI for 30-day all-cause mortality was 0.94 (95% CI 0.87 to 1.00), discriminating optimally with a maximal sensitivity at the threshold value of 86 points (**Supplemental table 5 and figure 5**). In 128 patients with a PESI below 66, zero were misclassified as low risk, as none of the patients died within 30 days. This corresponded to a sensitivity of 100% and a specificity of 37%. The NPV and PPV were 100% and 2%, respectively. At a PESI of 126 or higher, the sensitivity was 61% and the specificity was 95%. The NPV and PPV were 99% and 15%, respectively.

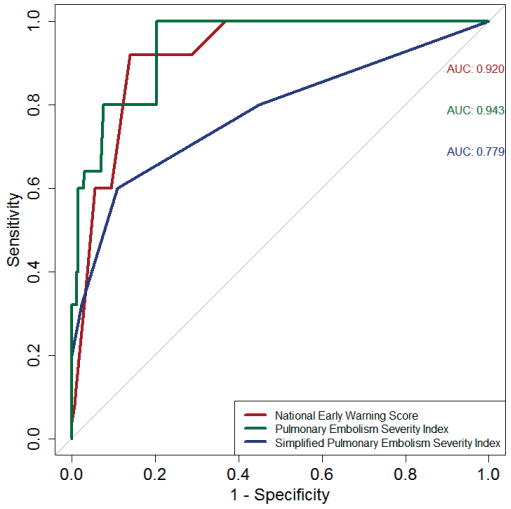

Figure 5. Area Under the Curve (AUC) for prediction of 30-day mortality for NEWS, PESI and sPESI in the overall population (n=352)
NEWS, National Early Warning Score; PESI, Pulmonary Embolism Severity Index; sPESI, simplified PESI.

The performance of the PESI for predicting PE-related ICU admission and mortality was comparable with its performance for all-cause ICU admission and mortality (**Supplemental tables 6 and 7**).

sPESI score

The overall median sPESI was 0 points (IQR 0–1). In patients who were admitted to hospital, the median sPESI was 1 point (IQR 0–1), compared with 0 points (IQR 0–1) in those who were treated at home (p <0.001). **Figure 2** shows the sPESI in patients who were admitted to the ICU (n=12) and in patients who were not admitted to the ICU. The overall AUC for the sPESI for all-cause ICU admission was 0.69 (95% CI 0.57 to 0.81). The threshold of 1 point misclassified two patients at low risk, who ultimately were admitted to the ICU, corresponding to a sensitivity of 83% and a specificity of 56%, and an NPV and PPV of 99% and 6%, respectively (**Supplemental table 4**).

Figure 4 shows the sPESI in patients who died within 30 days and in patients who survived. The overall AUC for the sPESI for all-cause 30-day mortality was 0.78 (95% CI 0.51 to 1.00). The threshold of 1 point misclassified one patient as low risk, who eventually died, corresponding to a sensitivity of 79%, a specificity of 55%, and a NPV and PPV of 99% and 2%, respectively (**Supplemental table 5**).

DISCUSSION

Our study demonstrates that NEWS has a comparable utility with PESI and sPESI in predicting 30-day mortality in haemodynamically stable patients with acute PE, and possibly better utility to predict 7-day ICU admission. The optimal cut-off value for NEWS was a score of 3 points—this yielded a sensitivity, specificity, NPV, and PPV of 92%, 53%, 99% and 6%, respectively, for ICU admission. Corresponding numbers for mortality were 100%, 52%, 100% and 3%. Our results suggest that the NEWS could have a good performance in predicting haemodynamic deterioration and death in patients with acute PE and may be an attractive alternative risk stratification score in this population.

However, the NEWS cannot adequately determine who should be admitted to the ICU, due to a large overestimation of patients at high risk. Of note, this overestimation would be expected to be lower if the NEWS was used in a population with a higher prevalence of haemodynamic compromise, that is, the patients excluded from the YEARS Study. For clinical purposes, the NEWS could therefore nonetheless help physicians in making decisions on the adequate care of these patients without the need for a more specialised score. Whether or not these patients are also eligible for home treatment cannot be concluded from our results as the patient group with a NEWS lower than 3 points consists of both patients treated at home and patients treated during hospital admission. Moreover, the NEWS does not include additional feasibility criteria for home treatment such as medical or social reasons for admission, which are incorporated in

the Hestia rule, a rule that was specifically developed to select candidates for safe home treatment.[13]

With high AUCs, the NEWS and the PESI both excellently discriminated between patients who survived and patients who died after presentation with acute PE. Our observed prognostic values of the NEWS and PESI for 30-day mortality are similar to those in many other studies evaluating the PESI, including studies which validated the PESI at the threshold of 86.[14,15] Our observed performance is substantially higher compared with studies evaluating the NEWS as a predictor for mortality in patients with other diseases at the ED.[16-18] Since haemodynamic instability is largely associated with mortality in patients with PE[19], and the NEWS is partially a surrogate for haemodynamic instability, this probably drives our finding of excellent performance of the NEWS in patients with PE.

The main strengths of this study are the prospective design of the original study and the fact that we were able to evaluate both scores, which are currently used in clinical practice in this population. The main limitation is that the data set was relatively small. In particular, the small number of observed clinical outcomes makes it challenging to draw firm conclusions from our findings. Nevertheless, the narrow CIs suggest that the study had a sufficient sample size. We deem the risk of bias possibly caused by our method of collection of vital parameters to be minimal, as these data were systematically filled out at the ED. The lack of overlap in data collection, however, remains a limitation of this multicentre study. In addition, we applied multiple imputation to account for missing data.[20] Unfortunately, our data set did not include any information on hypercapnic respiratory failure, so we were not able to evaluate the performance of the NEWS2. The results therefore need to be verified by other studies. Another limitation of this study was the surrogate 'altered mental status' that was used for the variable AVPU in the NEWS. This might have led to an overestimation of the NEWS in these patients as some of them might have had an altered mental state, but would have scored low on the AVPU. As only six of our included patients had an altered mental status, we suspect this overestimation did not substantially influence our results. In addition, the outcome 'ICU admission' is a relatively subjective outcome, prone to confounding by indication and criteria for ICU admission may have been different across the study sites. Consequently, our results may not represent the ICU management in patients with PE in other countries. We recommend validating this study in a prospective, independent and larger cohort. Such a study should investigate the optimal NEWS threshold for dedicated monitoring, the additive value of NEWS for risk stratification and the prognostic implications of changes in NEWS over time after treatment initiation.

In conclusion, the NEWS was able to identify patients with PE at low risk of haemodynamic deterioration in this study. A NEWS of lower than 3 accurately identified patients with a very low 30-day mortality risk and at low risk of 7-day ICU admission, making it an attractive clinical threshold to determine which patients presenting with an acute PE do not need intensive monitoring.

REFERENCES

1. Austen C, Patterson C, Poots A, Green S, Weldring T, Bell D. Using a local early warning scoring system as a model for the introduction of a national system. Acute Med 2012;11:66–73.
2. Kovacs C, Jarvis SW, Prytherch DR, et al. Comparison of the National Early Warning Score in non-elective medical and surgical patients. Br J Surg 2016;103:1385–93.
3. Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. Resuscitation 2013;84:465–70
4. Zondag W, Kooiman J, Klok FA, Dekkers OM, Huisman MV. Outpatient versus inpatient treatment in patients with pulmonary embolism: a meta-analysis. Eur Respir J 2013;42:134–44
5. van der Wall SJ, Hendriks SV, Huisman MV, Klok FA. Home treatment of acute pulmonary embolism: state of the art in 2018. Curr Opin Pulm Med 2018;24:425–31
6. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41:543–603
7. van der Hulle T, Cheung WY, Kooij S, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. Lancet 2017;390:289–97
8. Hendriks SV, Bavalia R, van Bemmel T, et al. Current practice patterns of outpatient management of acute pulmonary embolism: A post-hoc analysis of the YEARS study. Thromb Res 2020;193:60–5
9. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. Am J Respir Crit Care Med 2005;172:1041–6
10. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Archives of internal medicine. Arch Intern Med 2010;170:1383–9
11. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29–36
12. Rubin DB. Inference and Missing Data. Biometrika 1976;63:581–92
13. Zondag W, Mos IC, Creemers-Schild D, et al. Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. J Thromb Haemost 2011;9:1500–7
14. Zhou X-Y, Ben S-Q, Chen H-L, Ni S-S. The prognostic value of pulmonary embolism severity index in acute pulmonary embolism: a meta-analysis. Respir Res 2012;13:111
15. Donzé J, Le Gal G, Fine MJ, et al. Prospective validation of the Pulmonary Embolism Severity Index. A clinical prognostic model for pulmonary embolism. Thromb Haemost 2008;100:943–8
16. Alam N, Vegting IL, Houben E, et al. Exploring the performance of the National Early Warning Score (NEWS) in a European emergency department. Resuscitation 2015;90:111–5
17. Sbiti-Rohr D, Kutz A, Christ-Crain M, et al. 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. BMJ Open 2016;6:e011021
18. Ahn JH, Jung YK, Lee JR, et al. Predictive powers of the Modified Early Warning Score and the National Early Warning Score in general ward patients who activated the medical emergency team. PLoS One 2020;15:e0233078
19. Barco S, Ende-Verhaar YM, Becattini C, et al. Differential impact of syncope on the prognosis of patients with acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J 2018;39:4186–95

20. Kaji AH , Schriger D , Green S . Looking through the retrospectoscope: reducing bias in emergency medicine chart review studies. Ann Emerg Med 2014;64:292–8

SUPPLEMENTARY APPENDIX

Table S1. Parameters and scoring system of the NEWS

Physiological parameters	**3**	**2**	**1**	**0**	**1**	**2**	**3**
Respiration Rate (breaths per minute)	≤8	-	9–11	12–20	-	21–24	≥25
SpO2 (%)	≤91	92–93	94–95	≥96	-	-	-
Any supplemental oxygen?	-	Yes	-	No	-	-	-
Temperature (°C)	≤35.0	-	35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	-
Systolic BP (mmHg)	≤90	91–100	101–110	111–219	-	-	≥220
Heart/pulse rate (beats per minute)	≤40	-	41–50	51–90	91–110	111–130	≥131
Level of consciousness using the AVPU system	-	-	-	A	-	-	V, P or U

Top row is the amount of points assigned per vital parameter value. Maximum achievable NEWS is 20.
°C=degrees Centigrade; mmHg=millimeter mercury; AVPU=alert/voice/pain/unresponsive

Table S2. Parameters and scoring system of the PESI and sPESI

Parameter	**PESI**	**sPESI**
Age	Age in years	1 point (age >80 years)
Male sex	10 points	1 point
Cancer	30 points	1 point
Chronic pulmonary disease	10 points	1 point
Chronic heart failure	10 points	
Heart rate >110 beats per minute	20 points	1 point
Systolic blood pressure <100mm Hg	30 points	1 point
Respiratory rate >30 breaths per minute	20 points	-
Temperature <36 °C	20 points	-
Altered mental status	60 points	-
Arterial oxyhaemoglobin saturation <90%	20 points	1 point

Maximum achievable PESI is 230 + age. Maximum achievable sPESI is 6.
°C=degrees Celsius; mmHg=millimeter mercury;

Table S3. Overview missing variables before multiple imputation

Variable	Missing	
	Number	Percentage of 352
Hospital	0	0
Age	0	0
Gender	0	0
History of cancer	0	0
Heart rate	3	0,008523
Saturation	11	0,03125
Temperature	37	0,105114
Respiratory rate	70	0,198864
Systolic blood pressure	26	0,073864
Altered mental status	17	0,048295
History of COPD	0	0
History of heart failure	0	0
Hemodynamic instability	5	0,014205
Need for oxygen supply for more than 24 hours	11	0,03125
Death within 30 days	0	0
Transfer to ICU	6	0,017045
Hospital admission	6	0,017045

Additional to table S3. Number of missing data, stratified per center

	Heart rate	Saturation	Temperature	Respiratory rate	Systolic blood pressure	Altered mental status	hemodynamic instability	Need for oxygen supply
Leiden UMC	0	0	1	17	1	0	0	0
Amsterdam UMC	1	3	5	15	4	0	2	8
Erasmus MC	0	2	2	4	1	1	1	1
Red Cross Hospital	0	5	11	10	5	6	0	0
Haaglanden MC	0	0	3	8	0	0	0	0
Haga Teaching Hospital	0	1	6	7	6	1	7	0
Flevo Hospital	2	0	9	9	9	9	2	2

*MC = medical centre

Table S4. Diagnostic performance of the NEWS, PESI and sPESI for 7-day ICU admission at different thresholds

	Total n=346	No ICU admission n=334	ICU admission n=12	Sens	Spec	PPV	NPV
NEWS	AUC: 0.80 (95%CI 0.66-0.94)						
Low risk (<8)	310	304	6	0.53	0.91	0.18	0.98
High-risk (≥ 8)	36	30	6				
Low risk (<7)	294	289	5	0.62	0.87	0.14	0.98
High-risk (≥ 7)	52	45	7				
Low risk (<6)	274	270	4	0.63	0.81	0.11	0.98
High-risk (≥ 6)	72	64	8				
Low risk (<5)	245	241	4	0.67	0.72	0.08	0.98
High-risk (≥ 5)	101	93	8				
Low risk (<4)	215	212	3	0.75	0.64	0.07	0.99
High-risk (≥ 4)	131	122	9				
Low risk (<3)	176	175	1	0.92	0.53	0.06	0.99
High-risk (≥ 3)	170	159	11				
Low risk (<2)	128	127	1	0.93	0.38	0.05	0.99
High-risk (≥ 2)	218	207	11				
Low risk (<1)	67	67	0	0.97	0.20	0.04	0.99
High-risk (≥ 1)	279	267	12				

Table S4. Diagnostic performance of the NEWS, PESI and sPESI for 7-day ICU admission at different thresholds (*continued*)

	Total n=346	No ICU admission n=334	ICU admission n=12	Sens	Spec	PPV	NPV
PESI	AUC: 0.64 (95%CI 0.48-0.79)						
Low risk (<126)	328	318	10	0.17	0.95	0.11	0.97
High-risk (≥ 126)	18	16	2				
Low risk (<106)	300	290	10	0.18	0.87	0.05	0.97
High-risk (≥ 106)	46	44	2				
Low risk (<86)	229	223	6	0.50	0.67	0.05	0.97
High-risk (≥ 86)	117	111	6				
Low risk (<66)	129	126	3	0.75	0.38	0.04	0.98
High-risk (≥ 66)	217	208	9				
sPESI	AUC: 0.69 (95%CI 0.57-0.81)						
Low risk (<1)	190	188	2	0.83	0.56	0.06	0.99
High-risk (≥ 1)	156	146	10				

n=number, AUC=area under the Receiver Operating Characteristics curve, 95%CI=95%confidence interval, sens=sensitivity, spec=specificity, PPV=positive predictive value, NPV=negative predictive value. The test characteristics were performed after multiple imputation and therefore do not fully correspond with the 2x2 tables.

Table S5. Diagnostic performance of the NEWS, PESI and sPESI for 30-day mortality at different thresholds

	Total n=352	Patients who survived n=347	Patients who died n=5	Sens	Spec	PPV	NPV
NEWS	AUC: 0.92 (95%CI 0.82-1.00)						
Low risk (<8)	316	314	2	0.58	0.90	0.08	0.99
High-risk (≥ 8)	66	33	3				
Low risk (<7)	298	298	0	0.83	0.85	0.07	1
High-risk (≥ 7)	43	48	5				
Low risk (<6)	277	277	0	0.90	0.80	0.06	1
High-risk (≥ 6)	74	69	5				
Low risk (<5)	248	248	0	0.90	0.71	0.04	1
High-risk (≥ 5)	104	99	5				
Low risk (<4)	219	219	0	1	0.63	0.04	1
High-risk (≥ 4)	131	128	5				
Low risk (<3)	179	179	0	1	0.52	0.03	1
High-risk (≥ 3)	173	168	5				
Low risk (<2)	130	130	0	1	0.37	0.02	1
High-risk (≥ 2)	222	217	5				
Low risk (<1)	71	71	0	1	0.20	0.02	1
High-risk (≥ 1)	281	276	5				

Table S5. Diagnostic performance of the NEWS, PESI and sPESI for 30-day mortality at different thresholds (*continued*)

	Total n=352	Patients who survived n=347	Patients who died n=5	Sens	Spec	PPV	NPV
PESI	AUC: 0.94 (95%CI 0.87-1.00)						
Low risk (<126)	333	331	2	0.61	0.95	0.15	0.99
High-risk (≥ 126)	19	16	3				
Low risk (<106)	303	302	1	0.74	0.87	0.08	1
High-risk (≥ 106)	49	45	4				
Low risk (<86)	233	233	0	1	0.67	0.04	1
High-risk (≥ 86)	119	114	5				
Low risk (<66)	128	128	0	1	0.37	0.02	1
High-risk (≥ 66)	224	219	5				
sPESI	AUC: 0.78 (95%CI 0.51-1.00)						
Low risk (<1)	192	191	1	0.79	0.55	0.02	0.99
High risk (≥ 1)	160	156	4				

n=number, AUC=area under the Receiver Operating Characteristics curve, 95%CI=95%confidence interval, sens=sensitivity, spec=specificity, PPV=positive predictive value, NPV=negative predictive value. The test characteristics were performed after multiple imputation and therefore do not fully correspond with the 2x2 tables.

Table S6. Performance of all thresholds of the NEWS, PESI and sPESI for 7-day PE related ICU admission

PE related ICU 7 days	Total (n=346)	Patients without outcome, n (%)	Patients with outcome, n (%) (n=10)	Sens	Spec	PPV	NPV
NEWS	ROC 0.81 (0.65-0.96)						
Low risk (<8)	310	305	5	0.54	0.91	0.15	0.99
High-risk (≥ 8)	36	31	5				
Low risk (<7)	294	290	4	0.64	0.86	0.12	0.99
High-risk (≥ 7)	52	46	6				
Low risk (<6)	274	271	3	0.66	0.81	0.09	0.99
High-risk (≥ 6)	72	65	7				
Low risk (<5)	245	242	3	0.70	0.72	0.07	0.99
High-risk (≥ 5)	101	94	7				
Low risk (<4)	215	213	2	0.80	0.64	0.06	0.99
High-risk (≥ 4)	134	126	8				
Low risk (<3)	176	175	1	0.90	0.52	0.05	0.99
High-risk (≥ 3)	170	161	9				
Low risk (<2)	128	127	1	0.92	0.38	0.04	0.99
High-risk (≥ 2)	218	209	9				
Low risk (<1)	67	67	0	0.96	0.20	0.03	0.99
High-risk (≥ 1)	279	269	10				

Table S6. Performance of all thresholds of the NEWS, PESI and sPESI for 7-day PE related ICU admission (*continued*)

PE related ICU 7 days	Total (n=346)	Patients without outcome, n (%)	Patients with outcome, n (%) (n=10)	Sens	Spec	PPV	NPV
PESI	0.64 (0.46-0.83)						
Low risk (<126)	328	320	8	0.20	0.95	0.11	0.98
High-risk (≥ 126)	18	16	2				
Low risk (<106)	300	292	8	0.22	0.87	0.07	0.98
High-risk (≥ 106)	46	44	2				
Low risk (<86)	229	225	4	0.60	0.67	0.05	0.98
High-risk (≥ 86)	117	111	6				
Low risk (<66)	129	126	3	0.70	0.37	0.03	0.98
High-risk (≥ 66)	217	210	7				
sPESI	0.73 (0.61-0.85)						
Low risk (<1)	190	189	1	0.90	0.56	0.06	0.99
High risk (≥ 1)	156	147	9				

Table S7. Performance of all thresholds of the NEWS, PESI and sPESI for 30-day PE related mortality admission.

PE related mortality 30 days	Total (n=352)	Patients without outcome, n (%)	Patients with outcome, n (%) (n=3)	Sens	Spec	PPV	NPV
NEWS	ROC 0.94 (0.87-1.00)						
Low risk (<8)	316	315	1	0.58	0.90	0.05	1
High-risk (≥ 8)	36	34	2				
Low risk (<7)	299	299	0	0.94	0.85	0.05	1
High-risk (≥ 7)	53	50	3				
Low risk (<6)	278	278	0	1	0.80	0.04	1
High-risk (≥ 6)	74	71	3				
Low risk (<5)	248	248	0	1	0.71	0.03	1
High-risk (≥ 5)	104	101	3				
Low risk (<4)	219	219	0	1	0.63	0.02	1
High-risk (≥ 4)	133	130	3				
Low risk (<3)	179	179	0	1	0.52	0.02	1
High-risk (≥ 3)	173	170	3				
Low risk (<2)	130	130	0	1	0.38	0.01	1
High-risk (≥ 2)	222	219	3				
Low risk (<1)	71	71	0	1	0.20	0.01	1
High-risk (≥ 1)	281	278	3				

Table S7. Performance of all thresholds of the NEWS, PESI and sPESI for 30-day PE related mortality admission. (*continued*)

PE related mortality 30 days	Total (n=352)	Patients without outcome, n (%)	Patients with outcome, n (%) (n=3)	Sens	Spec	PPV	NPV
PESI	0.92 (0.79-1.00)						
Low risk (<126)	333	332	1	0.58	0.95	0.09	1
High-risk (≥ 126)	19	17	2				
Low risk (<106)	303	302	1	0.58	0.87	0.04	1
High-risk (≥ 106)	49	47	2				
Low risk (<86)	233	233	0	1	0.67	0.02	1
High-risk (≥ 86)	119	116	3				
Low risk (<66)	128	128	0	1	0.37	0.01	1
High-risk (≥ 66)	224	221	3				
sPESI	0.89 (0.72-1.00)						
Low risk (<1)	192	192	0	1	0.55	0.02	1
High risk (≥ 1)	160	157	3				