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## ORIGINAL ARTICLE

Geriatrics

# Addition of the clinical frailty scale to triage tools and early warning scores improves mortality prognostication at 30 days: A prospective observational multicenter study

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Region Östergötland, Grant/Award Numbers: LIO-532001, LIO-700271, RÖ-979172; Lions Clubs International Sweden Abstract

**Objectives:** Frailty, assessed with clinical frailty scale (CFS), alone or in combination with aggregated vital signs, has been proposed as a measure to better predict mortality of older patients in the emergency department (ED), but the added predictive value to conventional triage is unclear.

Methods: This was a secondary analysis of a prospective observational study in three EDs in Sweden that evaluated the prognostic performance of the CFS alone or in combination with the national early warning score (NEWS), triage early warning score (TEWS) or the rapid emergency triage and treatment system (RETTS) triage tool using logistic regression. The primary outcome was 30-day mortality with 7- and 90-day mortality and admission as secondary outcomes reported as area under the receiver operating curve (AuROC) scores with 95% confidence intervals (CIs). The sensitivity, specificity, accuracy, predictive values, and likelihood ratios are reported for all models. Results: A total of 1832 patients were included with 17 (0.9%), 57 (3.1%), and 121 (6.6%) patients dying within 7, 30, and 90 days, respectively. The admission rate was 43% (795/1832). Frailty (CFS > 4) was significantly associated with 30-day mortality (odds ratio 6, 95% CI 3–12, p < 0.01). Prognostication of 30-day mortality was similar for all CFS-based models and better compared with models without CFS. The AuROC (95% CI) improved for RETTS from 0.67 (0.61–0.74) to 0.83 (0.79–0.88) (p = 0.008), for NEWS from 0.53 (0.45–0.61) to 0.82 (0.77–0.87) (p < 0.001), and for TEWS from 0.63 (0.55-0.71) to 0.82 (0.77-0.87) (p = 0.002).

**Conclusion:** Frailty measured with the CFS in combination with RETTS or structured vital sign assessment using NEWS or TEWS was better at prognosticating 30-day mortality compared to RETTS or early warnings score alone. Improved prognostication provides more realistic expectations and allows for informed discussions with patients and initiation of individualized treatment plans early in the ED process.

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## 1 | INTRODUCTION

### 1.1 | Background

Structured risk assessment in patients of older age in the emergency department (ED) is challenging. Initial risk stratification is conventionally done with a triage tool<sup>1,2</sup> to direct resource allocation and prioritization in the ED. Triage tools should indicate the need for urgent interventions in the ED but also serve as a prognostication tool to guide decision of care. The most commonly used triage tool in Sweden, the rapid emergency triage and treatment system (RETTS), was derived against 7-day mortality and hospital admission.<sup>3,4</sup> However, many triage tools have performed variably in patients of older age,<sup>5-9</sup> potentially due to altered physiology,<sup>10</sup> diminished physiological reserves, and atypical presentations,<sup>11</sup> which increase with advancing age.<sup>12</sup> As life expectancy increases, so do resource utilization and proportion of older patients in ED,<sup>13</sup> stressing the need for better risk stratification in this time- and resource-limited environment.

Frailty, a state of diminished physiological reserve<sup>14</sup> and a measure of functional, rather than chronological age<sup>15</sup> is a potential risk predictor in the ED,<sup>16</sup> although it is not commonly screened for.<sup>17</sup> Several frailty assessment tools exist, such as the clinical frailty scale (CFS), a nine-point scale with cutoff at five points for frailty, which has been suggested for use in an ED setting.<sup>18</sup> The CFS has been shown to prognosticate 30-day mortality in ED patients of older age.<sup>19-22</sup> When CFS was combined with aggregated vital signs based on the national early warning score (NEWS)<sup>23</sup> in the frailty-adjusted prognosis in ED tool (FaP-ED), Nissen et al could show improved prediction of 30-day mortality compared with NEWS or CFS alone.<sup>24</sup> However, this model was not compared with a triage tool and the results have not been replicated. The NEWS score has shown inferior performance in the ED compared to other early warning scores.<sup>25</sup> We hypothesized that the triage early warning score (TEWS)<sup>26</sup> may be more suitable for use in older patients in the ED. TEWS uses the same vital signs as NEWS but with slightly different score weights. Importantly, it also incorporates mobility, an independent predictor of prognosis in patients of older age.<sup>27,28</sup>

## 1.2 | Importance

Identifying frail patients early in the ED process may facilitate more appropriate resource allocation and discussions about goals of care based on mortality risk and patients' wishes, potentially reducing crowding, length of stay, and boarding, which are known to increase mortality in older patients.<sup>29,30</sup> The CFS has been suggested to be suitable for assessing frailty in triage.<sup>20</sup> There are two studies investigating CFS and triage tools. One study reported an improved 1-year mortality prognosis with the emergency severity index (ESI)<sup>31</sup> and other showed improved in-hospital mortality prognostication with the Taiwan triage score (TTS).<sup>32</sup> Both studies were single-center with different follow-up periods, limiting generalizability. The CFS has been studied most fre-

#### **The Bottom Line**

It is unknown if assessing frailty, a syndrome of increased vulnerability in the elderly, improves mortality prognostication in patients of older age compared to normal triage alone in the emergency department (ED). In this multicenter study from Sweden we found that frailty, measured by the Clinical Frailty Scale, improved prognostication of death at 7-, 30- and 90days after an ED visit compared to normal triage or vital signs alone. Results were consistent when considering age, triage acuity, sex and arrival by ambulance suggesting that frailty carries important information not captured by other prognostic information in the ED.

quently for 30-day mortality, including the derivation of the FaP-ED tool.

## **1.3** Goals of this investigation

The objective of this study was to evaluate the ability of frailty, as determined by the CFS, to predict 7-, 30-, and 90-day mortality, as well as admission rate, alone or in combination with a conventional triage tool and the NEWS and TEWS score. Secondarily, we also aimed to validate the previously proposed FaP-ED tool for risk assessment in patients of older age.

## 2 | METHODS

## 2.1 Study design and setting

This was a secondary analysis of a prospective observational study on outcomes of frail patients in the ED. The study was approved by the Swedish Ethical Review Authority (permit no. 2021-00875) and registered on ClinicalTrials.gov (identifier: NCT04877028, 2021-05-03). This study was carried out in accordance with the Declaration of Helsinki. The study is reported according to the TRIPOD guideline for prediction model validation.<sup>33</sup> The study enrolled a convenience sample of patients from the three EDs in Östergötland County in southeastern Sweden: one urban tertiary care center, one urban community hospital, and one rural community hospital with a combined census of around 125,000 visits per year, and approximately 720 patients >65 years of age per week. These EDs serve a population of approximately 465,000 inhabitants in a publicly funded unified healthcare system. Access to nursing homes is regulated by the municipalities in Sweden and granted for patients with the greatest needs, whereas the majority of older patients receive even relatively advanced care in their own homes. In 2022, about 16% of the population in Sweden was over the age of 65 years and this group accounted for approximately 45% of adult ED visits.<sup>34</sup> The admission rate in the included EDs was about 21% overall and around 40% in patients over 65 years of age.

## 2.2 | Selection of participants

Patients with Swedish citizenship over the age of 65 years who presented to any one of the EDs in the study were eligible for inclusion. The clinical staff included patients around the clock during 6 weeks at each ED. All visits by a patient over the age of 65 years were retrieved from the electronic health records (EHR) at the end of the study and visits with no case report form and no specified reason for exclusion were deemed as missed inclusion.

### 2.3 | Measurements

The CFS score (Figure S1) and mobility status were documented on paper-based case report form at assessment by a member of the care team (physician, registered nurse, or assistant nurse), which also does vital sign collection for the majority of patients at the study sites and then transcribed to a digital spreadsheet. Aside from the researchers, who were part of the care team for some of the patients as part of their clinical work, assessors were blinded to the hypothesis of this study. Prior to the study, CFS was introduced into clinical routine. As a part of continuing medical education, all staff members were encouraged to undergo a 30-min e-learning course based on the online training module developed by AIMS research group of Ottawa Hospital, Canada.<sup>35</sup> Outcome data, demographic data, acuity, and vital signs were exported from the EHR as comma-separated files.

## 2.4 | Outcomes

The primary outcome was 30-day mortality, with 7- and 90-day mortality and admission to hospital as secondary outcomes. Thirty-day mortality was chosen as primary outcome since effect size estimates for appropriate sample size calculation were known prior to initiation of the study. Mortality data were gathered from the EHR that links death dates from the national tax registry and captures all deaths in Sweden. The predictors were frailty, as assessed by the CFS, NEWS, TEWS, and FaP-ED scores. Patients with a score of 9 on the CFS were excluded from the analysis as described elsewhere<sup>19,24</sup> as these patients, by definition, are non-frail due to their high level of function and lack of limiting symptoms but have a life expectancy <6 months.<sup>36</sup> The NEWS scores each vital sign on a scale from 0 to 3, depending on the deviation from normal, and generates a total score (max 20) where higher score is worse. There are two versions of NEWS, NEWS and NEWS2 (version 2), where saturation is scored differently if the patient has a type II respiratory failure. We used version 1 of NEWS (Table S2) to replicate the methods by the FaP-ED investigators. TEWS is similar to NEWS but adds scores for mobility (0-2) and trauma (0-1) and

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does not score oxygen saturation (Table S3). We did not calculate the score from trauma in TEWS as this was not noted in the prospective data calculation and could not be assessed with certainty retrospectively (Table S3). Triage acuity was assessed with the RETTS triage tool, the most commonly used triage tool in Sweden,<sup>37</sup> on a scale from 1 (emergent) to 5 (non-urgent), which is based on vital signs and chief-complaint-specific questions. Triage is mandatory at all recruiting EDs and is done at first encounter with a provider. The RETTS triage tool allows providers to forgo vital signs assessment under certain circumstances, such as low acuity presentations, if deemed appropriate by the provider.

## 2.5 | Analysis

Based on CFS having an area under the receiver operating curve (AuROC) of 0.82,<sup>24</sup> a 30-day mortality of 4% and a 95% confidence interval (CI) width of 0.14 for a sample of 1163 patients were estimated for this secondary analysis.

A considerable proportion of patients had one or more missing vital sign data. A majority of these were missing all vital sign data. We did not exclude patients who were missing all vital sign data in the primary analysis as this is allowed by our triage tool. Prediction analysis was performed with the full dataset assuming normal vital signs for those missing vital signs and with sensitivity analysis where patients missing all vital sign data were excluded and remaining patients with missing data were imputed. Missing data were randomly distributed with an overweight of level on consciousness values. Mean-value imputation with random imputation order was done using the *IterativeImputer* in the scikit-learn package.

Patients with a CFS >4 were considered living with frailty, which is the conventional cutoff.<sup>36</sup> We combined triage scores of 4–5 (low acuity) as previously described<sup>38</sup> and inverted the scale in the regression analysis, with 1 being low acuity. In addition, we calculated NEWS and TEWS from the vital sign data and the FaP-ED score as described by Nissen et al., combining CFS 1–2 into one group.<sup>24</sup> The CFS and RETTS scores were treated as categorical variables and the early warning scores as numerical in the predictions analysis. We compared NEWS, 1 degree of freedom (df), and CFS (7 df) to the FaP-ED score (NEWS = 1 df, CFS = 6 df).

Descriptive data are reported as the means with standard deviations (SDs) or medians with interquartile range (IQR) as appropriate. Logistic regression was used to test model predictions, which are evaluated with the *roc\_auc\_score* and *accuracy\_score* functions in the scikit-learn statistical package for python.<sup>39</sup> The classification was reported as AuROC scores with 95% CIs and were compared using the deLong method.<sup>40</sup> Calibration was assessed using the *CalibrationDisplay* function in scikit-learn. We report the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), accuracy, precision, and likelihood ratios for all tested prediction models. A *p*-value less than 0.05 or a 95% CI not including 1 was considered statistically significant. Analysis was done using the Python (version 3.7) programming language.<sup>41</sup>

#### 



FIGURE 1 Flowchart of included patients.

## 3 | RESULTS

## 3.1 | Characteristics of study subjects

A total of 1840 patients were included in the study. After excluding eight (0.4%) patients with CFS 9, 1832 (99.6%) patients were included in the primary analysis (Figure 1). The mean age was 78.8 (SD 8) years and 55% were female (Table 1). The median CFS score was 4 (IQR 2–5) and 970 (53%) arrived via ambulance. The median scores were 0 (IQR 0–2), 1 (IQR 1–2), and 5 (IQR 3–7) for NEWS, TEWS, and FaP-ED, respectively. There were no vital sign data recorded for 532 (32%) patients (Table 1). Inclusion was carried out by clinical staff and an additional 2240 ED visits were deemed as potentially eligible but were missed inclusions in the study (Figure 1). The median age of the missed inclusion patients was 76 (71–82) and 51% were female.

A total of 17 (0.9%), 57 (3.1%), and 121 (6.6%) patients died within 7, 30, and 90 days, respectively, and the admission rate was 43% (795/1832) (Table 1). Mortality at 30 days was higher in patients living with frailty (CFS > 4) (7.7% [46/599] vs. 0.9% [11/1233]). Patients living with frailty (CFS > 4) had an increased risk of death at 30 days (odds ratio [OR] 6, 95% CI 3–12, p < 0.01) when adjusted for age (OR 1.04, 95% CI 1.01–1.08, p = 0.02), male sex (OR 1.53, 95% CI 0.89–2.63, p = 0.12), arrival by ambulance (OR 1.51, 95% CI 0.71–3.21, p = 0.28), and triage acuity (OR 1.91, 95% CI 1.32–2.76, p < 0.01).

## 3.2 | Main results

In general, models including frailty using the CFS scale, or the CFS scale alone, showed better classification ability according to the AuROC

scores compared to triage (RETTS) or vital signs alone (NEWS and TEWS) (Figure 2 and Table 2). AuROC improved for RETTS from 0.67 (95% CI 0.61–0.74) to 0.83 (95% CI 0.79–0.88) (p = 0.008), for NEWS from 0.53 (95% CI 0.45–0.61) to 0.82 (95% CI 0.77–0.87) (p < 0.001), and for TEWS from 0.63 (95% CI 0.55–0.71) to 0.82 (95% CI 0.77–0.87) (p = 0.002). The FaP-ED had an AuROC of 0.82 (95% CI 0.76–0.87). Calibration curves for 30-day mortality showed a slight overestimation in the low-risk groups and overestimation in the high-risk groups, similar in all models (Figure 2, Supporting Information). There were small increases in AuROC scores for the early warning scoring models when excluding patients without recorded vital signs with little or no difference in models including CFS and CFS alone (Table 3, Supporting Information). Multiple imputations had little effect on model performance.

The optimal cutoffs for each model were estimated based on the Youden index<sup>42</sup> and the diagnostic properties of the different models were calculated based on 30-day mortality (Table 3). Using the suggested cutoff for the FaP-ED model of NEWS = 3 and CFS = 5 resulted in a more specific and less sensitive model compared to the Youden-based cutoffs (Table 3). A patient with NEWS 3 and CFS 5 had a 9.8% probability of death within 30 days.

## 4 | LIMITATIONS

We did not have vital signs collected for all patients, which may have affected the performance of the scoring systems using vital signs, such as the NEWS and TEWS. Since vital signs are not mandated for all patients in the triage procedure of the RETTS system, we believe it is important to include these patients to investigate the validity of the triage process. However, the results of the sensitivity analysis, which excluded patients missing all vital sign data, were similar in terms of AuROC scores and we believe that this has little effect on our overall results and conclusions. We did not collect data on resource utilization, such as urgent need for interventions in the ED, and cannot speak to the utility of CFS in this aspect of ED operations.

## 5 | DISCUSSION

In this study, we showed improved prognostic performance for 30day mortality when adding frailty, measured with the CFS score, to structured vital sign assessment (NEWS or TEWS) or triage (RETTS triage tool). This is the first multicenter study evaluating the prognostic ability of the CFS combined with triage data or vital signs in the ED. Frailty was an independent prognosticator of 30-day mortality even when adjusting for several known confounders, such as age, sex, arrival by ambulance, and triage acuity. Furthermore, the AuROC scores for 7-day mortality were higher for all models based on the CFS compared to models without, including the RETTS triage tool, suggesting added value in short-term prognosis as well (Table 2). While frailty instruments, such as the CFS, have the potential to show an urgent TABLE 1 Descriptive data of included patients and calculated predictors with missing data.

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	Primary analysis ( $n = 1832$ )		Complete case analysis ( $n = 1250$ )		
		Missing		Missing	
Age (SD)	78.8 (8)	0 (0%)	78.4 (7.8)	0 (0%)	
Female (%)	55%	0 (0%)	53%	0 (0%)	
Respiratory rate	18.6 (4)	606 (33%)	18.6 (4)	24 (2%)	
Heart rate	84.8 (18.8)	614 (34%)	84.8 (18.8)	32 (3%)	
AVPU (IQR)	O (O-O)	889 (49%)	0 (0-0)	307 (25%)	
Temperature	36.8 (0.7)	625 (34%)	36.8 (0.7)	43 (3%)	
Saturation	97.1 (3)	605 (33%)	97.1 (3)	23 (2%)	
Systolic blood pressure	147.2 (25.1)	610 (33%)	147.2 (25.1)	28 (2%)	
Diastolic blood pressure	81 (15.6)	625 (34%)	81 (15.6)	43 (3%)	
CFS	4 (2–5)	0 (0%)	3 (2–5)	0 (0%)	
RETTS	2 (2–3)	0 (0%)	2 (2–3)	0 (0%)	
7-Day mortality (%)	0.9%	0 (0%)	0.6%	0 (0%)	
30-Day mortality (%)	3.1%	0 (0%)	2.6%	0 (0%)	
90-Day mortality (%)	6.6%	0 (0%)	6.0%	0 (0%)	
Admission (%)	43%	0 (0%)	43%	0 (0%)	
TEWS (median, IQR)	1 (1–2)	0 (0%)	2 (1–3)	0 (0%)	
NEWS (median, IQR)	0 (0–2)	0 (0%)	1 (0–3)	0 (0%)	
Fap-ED (median, IQR)	5 (3–7)	0 (0%)	5 (3–7)	0 (0%)	

Abbreviations: AVPU, alert = 0, verbal = 1, pain = 2, unconscious = 3; CFS, clinical frailty scale; FaP-ED, frailty-adjusted prognosis in emergency department tool; IQR, interquartile range; NEWS, national early warning score; RETTS, rapid emergency triage and treatment system; SD, standard deviation; TEWS, triage early warning score.

need of care in the ED,<sup>32</sup> they are likely better for short- to mediumterm prognostication<sup>19.24</sup> and should not replace conventional triage. Hence, assessment of frailty should be used in conjunction with, rather than instead of, a conventional triage tool.

Frailty assessment may influence ED workups by identifying potential mortality risk increases, guiding medical decisions, nursing care, and establishing care goals. In our study, the 30-day mortality rate was markedly higher in patients living with frailty in all triage categories. The proportion of preventable mortality is unknown and there are currently no investigations on whether interventions, guided by CFS assessment in the ED, affect length of stay or mortality. For some of these patients, one of the most important interventions may be to establish clear goals of care and a treatment plan,<sup>43</sup> whereas advanced procedures or treatments aiming at long-term extension of the lifespan may be unrealistic. Although time and resources are limited in the ED, the time frame to create and act on a treatment plan is short for a considerable part of our frail patients (7.7% 30-day mortality in our cohort), which may necessitate initiating a treatment plan in the ED.

The non-frail, robust patients, on the other hand, had a 30-day mortality rate that was lower than that of a Swedish general ED population (0.9% vs. 1.5% in a study of 2.4 million ED visits<sup>44</sup>), which confirms that age in general should not be a limiting factor when making treatment decisions in the ED.<sup>16</sup> In this context, frailty assessment may support further medical interventions that could otherwise be deemed futile based on the patient's age. Thus, we argue that frailty should be considered an independent prognosticator in the ED and a core component for patient-centered care where accurate risk-benefit prognostication is essential to guide informed discussions around the patients' goals of care.

This is the first external validation of the newly published FaP-ED score by Nissen et al.,<sup>24</sup> which showed improved prognostic ability, as measured by the AuROC score (0.86, 95% CI 0.83–0.90), compared to CFS (0.82, 95% CI 0.78–0.86) or NEWS alone (0.80, 95% CI 0.76–0.85). The FaP-ED score had a similar AuROC score in this dataset (0.84, 95% CI 0.77–0.91) for 30-day mortality, and it showed high accuracy and high PPV while still maintaining a high NPV (Table 3), suggesting better calibration compared to other models (Table 4, Supporting Information). Hence, the FaP-ED score holds external validity in this study.

In this multicenter study in Sweden, frailty measured by CFS alone, or in combination with the Swedish triage tool RETTS or structured vital sign assessment with NEWS or TEWS was better at predicting 30day mortality compared to RETTS or structured vital sign assessment alone. Further studies should expand on the implications of incorporating frailty into the decision making in the ED as well as the ability of interventions, based on frailty assessments in triage or the ED, to improve patient outcomes.



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**FIGURE 2** Area under the receiver operating curve (AuROC) curves for 30-day mortality models. CFS, clinical frailty scale; FaP-ED, frailty-adjusted prognosis in emergency department tool; NEWS, national early warning score; RETTS, rapid emergency triage and treatment system; TEWS, triage early warning score.

TABLE 2	Area under the receiver operating curve (AuROC) scores with 95% confidence intervals for each model and 7-, 30-, and 90-day
mortality and	d admission, respectively.

Model	7-Day mortality	30-Day mortality	90-Day mortality	Admission
TEWS	0.44 (0.31–0.58)	0.63 (0.55–0.71)	0.61 (0.56–0.67)	0.63 (0.60–0.65)
TEWS + CFS	0.82 (0.72–0.93)	0.82 (0.77–0.87)	0.79 (0.76–0.83)	0.68 (0.65–0.70)
RETTS	0.71 (0.60–0.82)	0.67 (0.61–0.74)	0.63 (0.58–0.68)	0.69 (0.67–0.71)
RETTS + CFS	0.87 (0.79–0.94)	0.83 (0.79–0.88)	0.80 (0.76–0.84)	0.73 (0.71–0.76)
CFS	0.83 (0.75–0.92)	0.82 (0.77–0.87)	0.79 (0.75–0.83)	0.64 (0.62–0.67)
NEWS	0.54 (0.41–0.67)	0.53 (0.45–0.61)	0.56 (0.51–0.61)	0.58 (0.55–0.60)
NEWS + CFS	0.83 (0.76–0.91)	0.82 (0.77 - 0.87)	0.80 (0.76–0.83)	0.66 (0.64–0.69)
FaP-ED	0.84 (0.77–0.91)	0.82 (0.76–0.87)	0.80 (0.76–0.83)	0.66 (0.64–0.69)

Abbreviations: CFS, clinical frailty scale; FaP-ED, frailty-adjusted prognosis in emergency department tool; NEWS, national early warning score; RETTS, rapid emergency triage and treatment system; TEWS, triage early warning score.

TABLE 3 Cutoff values for optimal sensitivity, specificity, likelihood ratios, and predictive values for each model.

Model	Sensitivity	Specificity	Accuracy	PPV	NPV	LR+	LR-
TEWS: 3	0.41	0.83	0.82	0.83	0.98	2.33	0.72
TEWS: 1; CFS: 5	0.72	0.74	0.74	0.74	0.99	2.73	0.38
RETTS: 3	0.63	0.67	0.67	0.67	0.99	1.89	0.56
RETTS: 2; CFS: 5	0.75	0.75	0.75	0.75	0.99	2.98	0.33
CFS: 5	0.75	0.72	0.72	0.72	0.99	2.68	0.35
NEWS: 3	0.56	0.69	0.69	0.69	0.98	1.83	0.63
NEWS: 1; CFS: 5	0.69	0.78	0.78	0.78	0.99	3.20	0.40
FaP-ED (NEWS: 1; CFS: 5) <sup>a</sup>	0.69	0.78	0.78	0.78	0.99	3.20	0.40
FaP-ED (NEWS: 3; CFS: 5)	0.50	0.88	0.87	0.88	0.99	4.17	0.57

Abbreviations: CFS, clinical frailty scale; FaP-ED, frailty-adjusted prognosis in emergency department tool; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NEWS, national early warning score; NPV, negative predictive value; PPV, positive predictive value; RETTS, rapid emergency triage and treatment system; TEWS, triage early warning score.

<sup>a</sup>Cutoffs suggested by Youden index.<sup>42</sup>

## AUTHOR CONTRIBUTIONS

Jens Wretborn and Daniel B. Wilhelms designed the study. Samia Munir-Ehrlington, Erika Hörlin, and Daniel B. Wilhelms acquired the ethical permit. All the authors facilitated the data collection. Jens Wretborn performed the analysis and wrote the draft of the manuscript. All the authors contributed to the final version of the manuscript. Jens Wretborn took responsibility for the study as a whole.

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### CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

#### DATA AVAILABILITY STATEMENT

The datasets generated during the current study are available from the corresponding author upon reasonable request.

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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