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The Use of Different Sepsis Risk Stratification Tools on the Wards and in Emergency Departments Uncovers Different Mortality Risks: Results of the Three Welsh National Multicenter Point-Prevalence Studies

OBJECTIVES: To compare the performance of Sequential Organ Failure Assessment, systemic inflammatory response syndrome, Red Flag Sepsis, and National Institute of Clinical Excellence sepsis risk stratification tools in the identification of patients at greatest risk of mortality from sepsis in nonintensive care environments.

DESIGN: Secondary analysis of three annual 24-hour point-prevalence study periods.

SETTING: The general wards and emergency departments of 14 acute hospitals across Wales. Studies were conducted on the third Wednesday of October in 2017, 2018, and 2019.

PATIENTS: We screened all patients presenting to the emergency department and on the general wards.

MEASUREMENTS AND MAIN RESULTS: We recruited 1,271 patients, of which 724 (56.9%) had systemic inflammatory response syndrome greater than or equal to 2, 679 (53.4%) had Sequential Organ Failure Assessment greater than or equal to 2, and 977 (76.9%) had Red Flag Sepsis. When stratified according to National Institute of Clinical Excellence guidelines, 450 patients (35.4%) were in the “High risk” category in comparison with 665 (52.3%) in “Moderate to High risk” and 156 (12.3%) in “Low risk” category. In a planned sensitivity analysis, we found that none of the tools accurately predicted mortality at 90 days, and Sequential Organ Failure Assessment and National Institute of Clinical Excellence tools showed only moderate discriminatory power for mortality at 7 and 14 days. Furthermore, we could not find any significant correlation with any of the tools at any of the mortality time points.

CONCLUSIONS: Our data suggest that the sepsis risk stratification tools currently utilized in emergency departments and on the general wards do not predict mortality adequately. This is illustrated by the disparity in mortality risk of the populations captured by each instrument, as well as the weak concordance between them. We propose that future studies on the development of sepsis identification tools should focus on identifying predictor values of both the short- and long-term outcomes of sepsis.

KEY WORDS: mortality; National Institute of Clinical Excellence; red flag; sepsis; Sequential Organ Failure Assessment; systemic inflammatory response syndrome

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Sepsis needs early diagnosis and urgent care to decrease patient mortality (1). Thus, in the last decade, there have been significant attempts to enhance the recognition of its presenting and defining features (2, 3).

Previously, sepsis definitions sought primarily to identify patients at risk of poor outcomes within ICUs (4, 5). However, it is now understood that the vast majority of patients with sepsis appear in emergency departments (EDs) and general wards (6, 7). Thus, there is pressing need to develop robust methods for the risk stratification of sepsis outside of the ICU. Crucially, by highlighting those patients most at risk, such tools will enable clinical management plans to focus and prompt the initiation of timely interventions, such as resuscitation bundles. However, very little U.K. data currently exist regarding the impact risk stratification tools have on sepsis care beyond the ICU.

The 2016 SEPSIS-3 definitions proposed using the Sequential Organ Failure Assessment (SOFA) to help clinicians identify those most at risk from sepsis; however, this has been considered awkward and probably undeliverable outside the critical care environment. The simple quick SOFA tool developed for risk stratification has also been criticized for a perceived lack of sensitivity and specificity (8, 9). Other tools have been repurposed, such as the National Early Warning Score (NEWS) and the Pediatric Early Warning Score or developed without significant external validation: the Red Flag Sepsis tool by the U.K. Sepsis Trust and the Sepsis Risk Stratification tool by the National Institute of Clinical Excellence (NICE) (10, 11). We have previously demonstrated that none of the proposed tools captures the at-risk population entirely, though SOFA score has consistently performed well (12, 13).

Since the publication of the SEPSIS-3 definitions 5 years ago, the publicity (and controversy) around these tools has likely increased awareness of the condition and engagement with efforts in the National Health Service to improve outcomes. However, the most robust and readily applicable tool for risk stratifying sepsis, once infection is suspected, in a general hospital setting is yet to be identified and implemented effectively. Using 3 years' data from our all Wales point-prevalence studies, the aim of our investigation was to compare the performance of the SOFA tool, underpinning the SEPSIS-3 definition, the systemic inflammatory response syndrome (SIRS) tool, used in the SEPSIS-1 definition, and the Red Flag Sepsis and the NICE risk stratification tool in the identification of patients at the greatest risk of mortality from sepsis outside the critical care environment.

MATERIALS AND METHODS

Study Design and Participants

We performed a secondary analysis of the Defining Sepsis on the Wards (DESEPTiW) study, on the patient populations recruited into three annual multicenter 24-hour point-prevalence studies conducted on the third Wednesday of October from 2017 to 2019. Ethical approval was granted by the South Wales Regional Ethics Committee (16/WA/0071), and patients or legal representatives gave written informed consent. The DESEPTiW study was prospectively registered with an international trial registry (ISRCTN86502304).

Patients were recruited from 14 acute hospitals across Wales, all of which had 24-hour consultant cover in the ED and nonselective intake. We screened all patients presenting to the ED and on the general wards. At the start of the study days at 08:00, data collectors systematically screened every patient on the acute inpatient wards within 4 hours, then continued screening for any potential new participants until 07:59 the next morning. In each hospital, dedicated data collectors were stationed in the ED during the 24-hour periods. We approached all patients with NEWS greater than or equal to 3 in whom the treating clinical teams had a high degree of clinical suspicion of an infection (documented as such in the medical or nursing notes), and following the patients or their proxy, in cases of patients lacking capacity, gave written informed consent, and were recruited to the study (14). Patients under 18 and those cared for in critical care or mental health units were excluded.

We collected data from medical and nursing records using a specifically developed digital platform. Further description of the methodology and performance of this platform is outlined in previous publications (12, 13, 15). We collected data on preadmission patient characteristics, comorbidities, and physiologic and laboratory values. Missing variables were imputed as normal, as default. Frailty was evaluated on the Clinical Frailty Scale. We recorded management actions such as the completion of the 'Sepsis Six' bundle and involvement of critical care outreach. We conducted follow-up at 30 and 90 days. Our primary outcome was all-cause mortality at 90 days.

Statistical Analysis

Categorical variables are described as proportions and are compared using chi-square test. Continuous variables are described as median and interquartile range (IQR) and compared using Kruskal-Wallis test. To assess the performances of the SOFA, SIRS, Red Flag Sepsis, and NICE Sepsis Risk tools to predict the primary end point, we constructed a receiver operating characteristic (ROC) curve and calculated the corresponding area under the ROC curve. As physiologic variables are likely to perform better predicting short-term outcomes, we have performed a sensitivity analysis in order to assess the ability of these tools to predict 7-, 14-, 21-, and 28-day mortality.

We plotted Kaplan-Meier survival curves and compared time-to-event data using log-rank testing. We estimated the respective hazard ratios for the primary outcome within 90 days with a Cox proportional hazards model after adjustment for measured confounders. A two-tailed p value less than 0.05 was considered statistically significant. All statistical tests were calculated using SPSS 25.0 (SPSS, Chicago, IL).

Data visualization was performed in R (Version 3.6.2) with the following packages utilized: UpSetR (Version 1.5.0), SunburstR (Version 2.1.5), ComplexHeatmap (Version 2.7.8.1000), GGally (Version 2.1.0), pROC (Version 1.17.0.1), dplyr (Version 1.0.5), and ggplot2 (Version 3.3.3) (16, 17).

RESULTS

Patient Characteristics

Over the three annual 24-hour point-prevalence study periods, we screened a total of 21,525 patients, of whom 1,271 met inclusion criteria and were subsequently recruited and followed to 90 days (Fig. 1).

Patient demographics and clinical characteristics for each year of study are shown in Table 1. The median age (IQR [range]) of participants was 73 years (60–82 [18–103]), and more females 652 (51.3%) than males 619 (48.7%) were recruited. The median (IQR) score on the Clinical Frailty Scale was 5 (3–6). Age, gender, and frailty of participants did not vary between years; 90-day survival was significantly better in 2018 and 2019 compared with baseline. Further details about the ward and ED cohort are provided in Supplementary Table 1 (<http://links.lww.com/CCX/A821>).

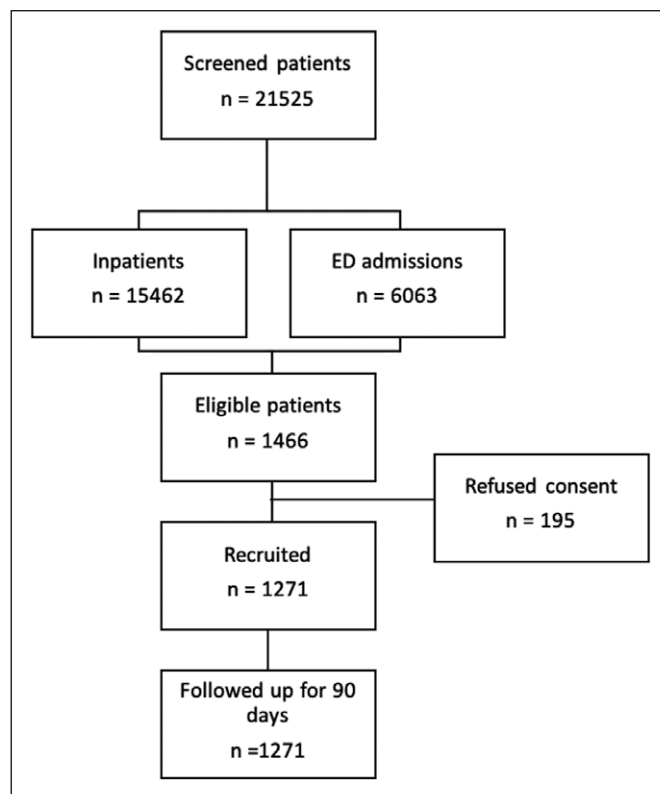


Figure 1. Study flow diagram and eventual study sample. ED = emergency department.

Risk Stratification Tools

Within the study population, 724 (56.9%) had SIRS greater than or equal to 2, 679 (53.4%) had SOFA greater than or equal to 2, and 977 (76.9%) had Red Flag Sepsis (Fig. 2; and Supplementary Fig. 1, <http://links.lww.com/CCX/A821>). We also stratified patients according to NICE guidelines: 450 patients (35.4%) were in the “High risk” category in comparison with 665 (52.3%) in “Moderate-to-High-risk” and 156 (12.3%) in “Low-risk” category. Data completeness for SOFA calculation is described in Supplementary Table 2 (<http://links.lww.com/CCX/A821>).

Sepsis management

In comparison with those not scoring, the “Sepsis Six” bundle was completed on a significantly higher number of occasions for SIRS greater than or equal to 2 ($p = 0.03$) and SOFA greater than or equal to 2 ($p < 0.0001$) (Table 2). Neither Red Flag sepsis nor NICE risk criteria were associated with a higher likelihood of “Sepsis Six” completion. Blood cultures were obtained from 595 patients (46.8%), of which 75

TABLE 1.
Demographics and Clinical Characteristic Survival of Patients in Each Year of Study

Variables	Year				p
	2017 (n = 459)	2018 (n = 413)	2019 (n = 399)	All Years (n = 1,271)	
Patient demographics					
Age: median years	73 (62–84 [18–103])	73 (59–81 [19–99])	73 (60–81 [19–99])	73 (60–82 [18–103])	0.40
Sex: male	231 (50.3%)	213 (51.6%)	175 (43.9%)	619 (48.7%)	0.06
Survival to 90 d	325 (70.8%)	311 (75.3%)	313 (78.4%)	949 (74.7%)	0.04
Mean survival days	71.9 (68.9–74.7)	74.1 (71.1–77.1)	74.6 (71.6–77.5)	73.4 (71.7–75.1)	0.054
Clinical characteristics					
Chronic obstructive pulmonary disease	118 (26.2%)	117 (30.1%)	135 (34.8%)	370 (29.1%)	0.03
Diabetes	98 (21.8%)	89 (22.9%)	71 (18.3%)	258 (20.3%)	0.26
Drugs of abuse	8 (1.8%)	11 (2.8%)	7 (1.8%)	26 (2.0%)	0.50
Heart failure	49 (10.9%)	50 (12.9%)	39 (10.1%)	138 (10.9%)	0.44
Hypertension	165 (36.7%)	145 (37.3%)	140 (36.1%)	450 (35.4%)	0.94
Ischemic heart disease	82 (18.2%)	65 (16.7%)	67 (17.3%)	214 (16.8%)	0.84
Liver disease	13 (2.9%)	19 (4.9%)	16 (4.1%)	48 (3.8%)	0.32
Neuromuscular disease	16 (3.6%)	11 (2.8%)	12 (3.1%)	39 (3.1%)	0.83
Recent chemotherapy	21 (4.7%)	15 (3.9%)	24 (6.2%)	60 (4.7%)	0.31
Clinical Frailty Scale ^a	5 (3–6)	4 (3–6)	5 (3–6)	5 (3–6)	0.14
Do-not-attempt cardiopulmonary resuscitation order	123 (27.5%)	92 (24.5%)	109 (27.9%)	324 (25.5%)	0.50

^aClinical Frailty Scale range was 1 (very fit) to 9 (terminally ill) in all years. Values are median (IQR [range]), number (proportion), or mean (95% CI).

(12.6%) were positive for growth. Of the sepsis risk tools examined, only SIRS greater than or equal to 2 was associated with higher likelihood of obtaining blood cultures (Table 2).

Survival Analysis

Mortality at 90 days was 203/724 (28.0%) for patients who scored SIRS greater than or equal to 2, 201/679 (29.6%) who scored SOFA greater than or equal to 2, 247/977 (25.3%) who had Red Flag sepsis, and 140/450 (31.1%), 153/665 (23.0%), and 29/156 (18.6%) who had High, Moderate to High, and Low risk of sepsis as per NICE criteria, respectively. The survival plots are presented in **Figure 3**.

None of the tools were able to predict mortality reliably at 90 days (**Fig. 4**). In a planned sensitivity analysis, we have found that SOFA and NICE sepsis criteria had moderate discriminatory power for mortality at 7 and

14 days (**Supplementary Fig. 2A and B**, <http://links.lww.com/CCX/A821>), which disappeared by days 21 and 28 (**Supplementary Fig. 2C and D**, <http://links.lww.com/CCX/A821>). Furthermore, we could not find any significant correlation with any of the tools at any of the mortality time points (**Supplementary Fig. 3**, <http://links.lww.com/CCX/A821>).

DISCUSSION

We found that the risk of mortality from sepsis on the wards is unlikely to be captured entirely with any of the tools examined. Sepsis episodes stratified by SIRS, SOFA, and NICE tools had significantly worse outcomes; however, the Red Flag Sepsis tool was unable to capture a population at higher risk. None of the tools were able to differentiate reliably between patients who would survive at 90 days versus those who would not. The tools that are designed to predict in-hospital

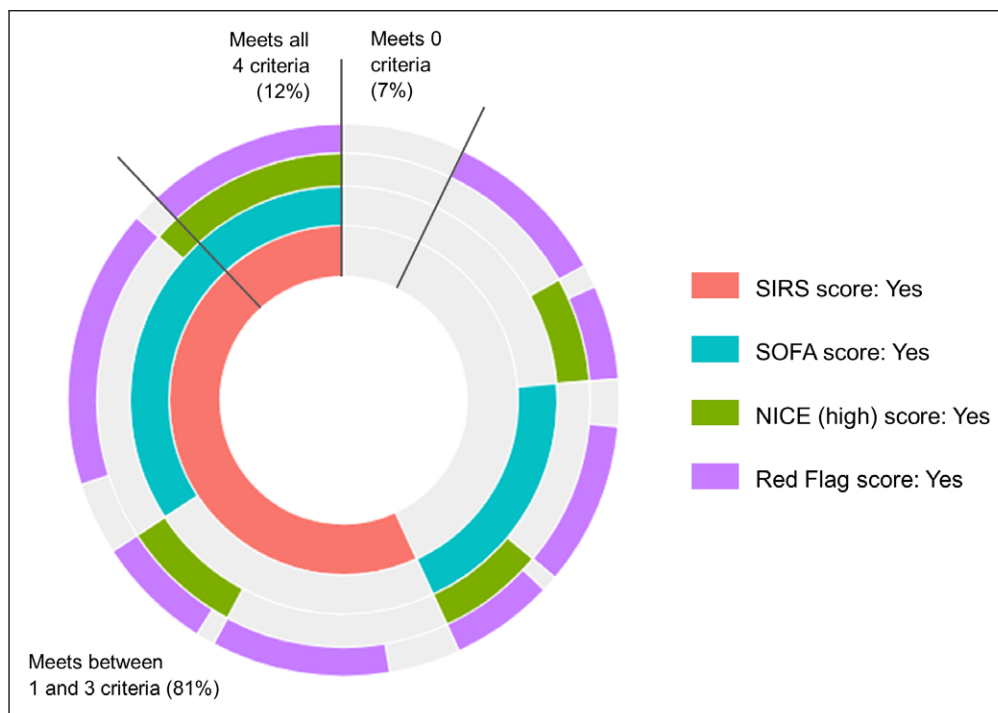


Figure 2. A sunburst plot illustrating the frequency of fulfilling each sepsis criteria. The colored areas denote the percentage of the events where the sepsis criteria is met, and the gray areas denote where patients did not score on the criteria. Working from the center, the frequency of each combination of sepsis tool is illustrated. NICE = National Institute for Health and Care Excellence, Red Flag = fulfilling Red Flag sepsis criteria, SIRS = systemic inflammatory response syndrome, SOFA = Sequential Organ Failure Assessment.

mortality from sepsis based on measuring acute physiologic disturbance had moderate ability to differentiate at ultrashort-term outcomes of mortality at 7 and 14 days. The four different approaches had little concordance, further highlighting the need for better risk stratification tools for sepsis on the wards.

The current results confirm and add incremental knowledge to our previous studies, in which we evaluated the predictive abilities of SIRS-, SOFA-, and Red Flag Sepsis-based definitions (12, 13). To our knowledge, our study is the first to evaluate the predictive capabilities of the NICE guidance criteria that are advocated to be used in the ward setting in the United Kingdom to direct therapeutic response to sepsis (12). Our data indicate that only SOFA- and SIRS-based criteria are associated with better response in terms of diagnostic workup and delivery of the “Sepsis Six” bundle.

Since the publication of the SEPSIS-3 definition and the proposal for using SOFA score 2 or above in the presence of infection to diagnose sepsis, there has been an intense debate as to whether this approach would lead to better characterization of the high-risk population (3,

18–23). Although SOFA outperformed SIRS in predicting mortality in a non-ICU setting in a large 6-year retrospective analysis of 7,193 non-ICU patients by Kovach et al (24) and also corroborated by U.K.-wide critical care data from the Intensive Care National Audit and Research Centre (18), surprisingly there is hardly any data available on the predictive validity of the NICE criteria or Red Flag Sepsis (10, 11).

Criticism regarding the use of SOFA outside of the ICU stems from its complexity and unfamiliarity among noncritical care practitioners (25). Further obstacles to using SOFA on the general wards and ED include the need for laboratory test results for

platelets, bilirubin, and creatinine, which creates delay in the diagnosis of sepsis (26). A recent retrospective cohort study of 16,612 patients outside of the ICU with suspicion of sepsis by Prasad et al (27) observed that time to identification of sepsis according to SOFA score was much longer than that for SIRS. However, they also found that an SIRS-based tool performed inadequately, as it was seen to miss sepsis presentations with organ dysfunction (27). Importantly, in our dataset, the majority of bilirubin and creatinine values were available at the first instance of patient presenting with sepsis, and this should, therefore, not be seen as a barrier to use SOFA in the U.K. hospital setting. Although SOFA and SIRS were developed initially for use in a critically ill population, the Red Flag Sepsis and NICE tools (which do not include laboratory values) were created with a more general patient population in mind. Analyzing shorter time-scales, only SOFA reached moderate performance; furthermore, risk stratification tools based on vital signs and clinical symptoms could not be used as reliable predictors of longer term outcome—a finding supported by previous critical care studies (28, 29).

TABLE 2.**Contingency Table of the Effect of the Presence of Management Actions on the Number of Patients in Each Group**

Variables	Chosen Tool Scores Positive for Sepsis	Chosen Tool Scores Negative for Sepsis	<i>p</i>
Blood cultures obtained			
SIRS	370 (51.1%)	197 (36.0%)	< 0.0001
SOFA	331 (48.7%)	211 (35.6%)	0.35
Red Flag	466 (47.7%)	129 (43.9%)	0.73
NICE–high risk	219 (48.7%)	376 (45.8%)	0.52
NICE–moderate risk	320 (48.1%)	275 (45.4%)	0.80
“Sepsis six” bundle compliant			
SIRS	114 (15.7%)	55 (10.1%)	0.03
SOFA	117 (17.2%)	44 (7.4%)	< 0.0001
Red flag	140 (14.3%)	39 (13.3%)	0.91
NICE–high risk	72 (16.0%)	107 (13.0%)	0.19
NICE–moderate risk	92 (13.8%)	87 (14.4%)	0.56
	Seen by Critical Care Outreach	Not Seen by Critical Care Outreach	
Complete “sepsis six”	44 (32.1%)	126 (11.1%)	< 0.0001
Antibiotics	117 (85.4%)	657 (57.9%)	< 0.0001

NICE = National Institute for Health and Care Excellence, SIRS = systemic inflammatory response syndrome, SOFA = Sequential Organ Failure Assessment.

Values are number/total number (proportion).

SIRS and SOFA classed as positive for sepsis with score of greater than or equal to 2.

Critical Care outreach represents nurse-led, physician-supported team offering intensive care skills to patients at risk of critical illness outside of the ICU.

Overall, the tools that had been developed using less than robust, nondata-driven frameworks performed worse. Consequently, this should prompt researchers and organizations to adopt the current best practice recommendations while developing and reporting new scores, to avoid the pitfalls experienced previously (30).

The tools utilized in this study were all based on physiologic, routine laboratory, and clinical symptom variables. These signs and derangements could signal presence of infection but can also change in the same direction in other inflammatory etiologies (5, 10). Applying the tools only in patients with proven infections is likely to change their performance (10). The significant overlap of the tools in our dataset further suggests that any new scores developed should be supported by host response biomarker and even transcriptomics data to improve sensitivity and specificity (31, 32).

It has been repeatedly shown that a dedicated “effector arm” of the sepsis response in the form of rapid

response, medical emergency, critical care outreach, or sepsis response team can significantly improve care processes and likely to affect outcome (20, 33–35). Our current results support this notion as we have observed significantly better care process and completion of “Sepsis Six” among the patients who have been seen by critical care outreach; however, the compliance with this bundle was very low both in the ED and on the wards (36). We have previously reported that antimicrobial treatment, arguably one of the most important elements of “Sepsis Six,” was similarly disorganized in this patient group (37).

Our study is not without limitations. The dataset collected was a balance between having a comprehensive list of clinical and laboratory data and being small enough to preserve reliability. The data were collected by medical students at various levels of training, which may have introduced bias. To mitigate this, we held extensive online and in-person training and implemented

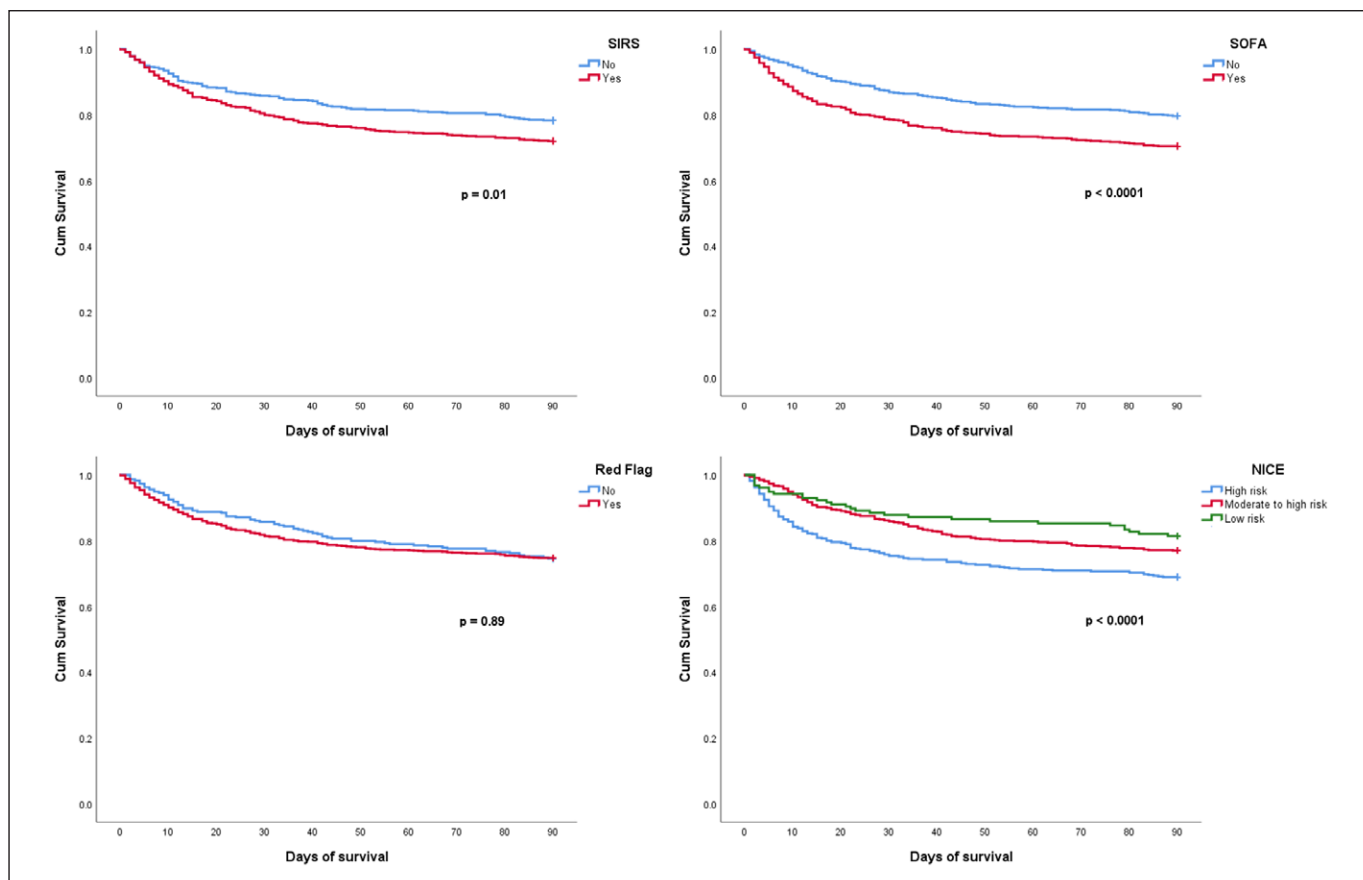


Figure 3. Survival difference of patients using different sepsis identification tools of sepsis. NICE = National Institute for Health and Care Excellence, Red Flag = fulfilling Red Flag sepsis criteria, SIRS = systemic inflammatory response syndrome, SOFA = Sequential Organ Failure Assessment.

a student leadership structure based on previous experience within the study while keeping the same primary clinical leads each year of the study. Although NEWS has a high sensitivity, its specificity for sepsis is reported as varying from 77% to as low as 6% (8, 9, 14). Thus, our use of NEWS cutoff of 3 when selecting patients creates the possibility of missing some septic patients while including some who were not septic. Recent data suggest that our applied cutoff may be the optimal trigger to screen patients for sepsis in the ED, and the same is recommended as an escalation trigger by NICE and used in the Sepsis Trust's Red Flag Sepsis pathways (11, 14).

Missing laboratory data (bilirubin and creatinine) to calculate the full SOFA score was frequent in our cohort, which could have led to underestimate the number of patients scoring positive on this risk tool and affecting predictive performance. Consistent with previous studies, we assumed missing parameters being normal (22, 24).

In terms of elements that may anticipate longer term mortality, our study did not look to distinguish any

individual predictor values. However, we and others have previously shown that acute illness severity has less of an impact on longer term outcome; therefore, we propose that future research should examine factors, such as comorbidity and frailty, in conjunction with the clinical tools investigated (7, 21, 38–41). The association between higher compliance with resuscitation bundles and patients scores using SOFA and SIRS poses an interesting question regarding a potential confounding effect on mortality; for example, components of these tools could be identifying patients in these settings who visibly look more unwell in comparison with other tools. In turn, this could lead to earlier recognition and more aggressive management including the completion of “Sepsis Six”; however, overall, the bundle completion rates within our study are very low, making any conclusions difficult to draw (37). Examining the user perception and acceptance of different scoring tools should be a priority in any future study as they might influence healthcare provider behavior and treatment processes.

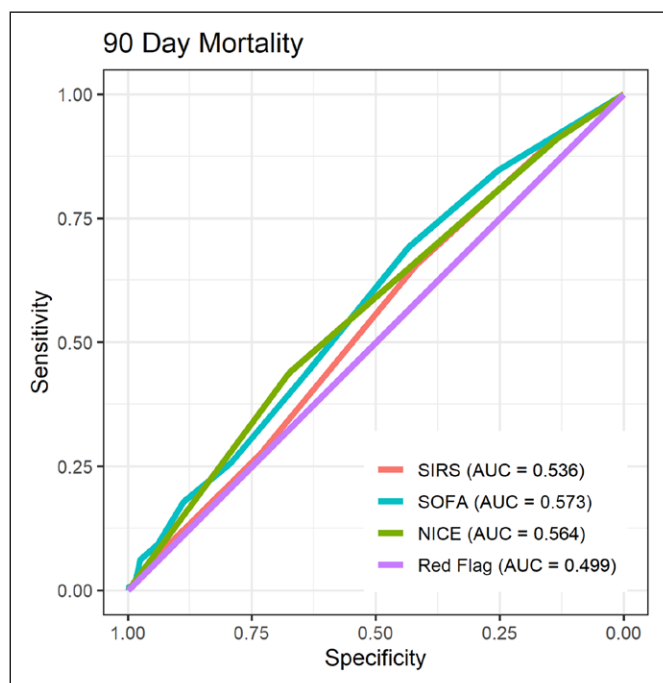


Figure 4. Receiver operating curve (ROC) and area under ROC (AUC) for sepsis tools used for prediction of mortality at 90 d. NICE = National Institute for Health and Care Excellence sepsis criteria, Red Flag = fulfilling Red Flag sepsis criteria, SIRS = systemic inflammatory response syndrome, SOFA = Sequential Organ Failure Assessment.

CONCLUSION

In summary, our data suggest that the sepsis identification tools currently utilized in EDs and on the general wards do not predict mortality adequately. This is illustrated by the disparity in mortality risk of the populations captured by each instrument and the fairly weak concordance between them. Identifying the risks associated with sepsis in both the acute phase and long term, therefore, remains challenging. We suggest that future studies should focus on identifying predictor values of both the short- and long-term outcomes of sepsis.

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