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qSOFA, SIRS, and early warning scores for detecting clinical deterioration in infected patients outside the ICU

Running title: Sepsis risk prediction outside the ICU

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At a Glance Commentary: Scientific Knowledge on the Subject: The quick Sepsis-related Organ Failure Assessment (qSOFA) score is a bedside tool that was recommended for use by the recent Third International Consensus Definitions Task Force to identify high-risk patients outside the ICU. qSOFA was found to be more accurate than the systemic inflammatory system criteria (SIRS) for predicting mortality and intensive care unit (ICU) transfer in patients outside the ICU. However, the qSOFA score has yet to be validated outside of the original publication and has not been compared to early warning scores already in widespread use.

What This Study Adds to the Field: We found that commonly used early warning scores are more accurate than the qSOFA score for predicting in-hospital mortality and ICU transfer among patients with suspected infection outside the ICU. These results suggest that the qSOFA score should not replace previously developed early warning scores already in use across the U.S. and Europe.

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ABSTRACT

Rationale: The 2016 definitions of sepsis included the quick Sepsis-related Organ Failure Assessment (qSOFA) score to identify high-risk patients outside the intensive care unit (ICU).

Objective: We sought to compare qSOFA to other commonly used early warning scores.

Methods: All admitted patients first meeting criteria for suspicion of infection in the emergency department (ED) or hospital wards from November 2008 until January 2016 were included. The qSOFA, Systemic Inflammatory Response Syndrome (SIRS), Modified Early Warning Score (MEWS), and the National Early Warning Score (NEWS) were compared for predicting death and ICU transfer.

Measurements and Main Results: Of the 30,677 included patients, 1,649 (5.4%) died and 7,385 (24%) experienced the composite outcome (death or ICU transfer). Sixty percent (n=18,523) first met the suspicion criteria in the ED. Discrimination for in-hospital mortality was highest for NEWS (AUC 0.77 [95% CI 0.76-0.79]), followed by MEWS (0.73 [0.71-0.74]), qSOFA (0.69 [0.67-0.70]), and SIRS (0.65 [0.63-0.66]) ($p < 0.01$ for all pairwise comparisons). Using a patient's highest non-ICU score, ≥2 SIRS had a sensitivity of 91% and specificity of 13% for the composite outcome compared to 54% and 67% for qSOFA ≥2, 59% and 70% for MEWS ≥5, and 67% and 66% for NEWS ≥8. Most patients met ≥2 SIRS criteria 17 hours before the combined outcome compared to 5 hours for ≥2 and 17 hours for ≥1 qSOFA criteria.

Conclusions: Commonly used early warning scores are more accurate than the qSOFA score for predicting death and ICU transfer in non-ICU patients. These results suggest that the qSOFA score should not replace general early warning scores when risk-stratifying patients with suspected infection.

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INTRODUCTION

Sepsis contributes to up to half of hospital deaths and is associated with more than $24 billion in costs in the U.S. annually (1, 2). Prior consensus definitions included the systemic inflammatory response syndrome (SIRS) criteria, consisting of temperature, white blood cell count, heart rate, and respiratory rate (3, 4). However, SIRS criteria have been criticized for their poor specificity, with 90% of intensive care unit (ICU) patients and 50% of general ward patients meeting the criteria at some point during their hospitalization (5-7). This led the authors of the 2016 sepsis guidelines to utilize a more data-driven approach to developing the definition of sepsis (8, 9).

Since most cases of sepsis present in the emergency department (ED) and on the wards, rather than the ICU (10), the 2016 guidelines included a new tool that was derived specifically to prompt clinicians to consider possible sepsis (9). This model, called the “quick Sepsis-related Organ Failure Assessment” (qSOFA), requires derangements in systolic blood pressure, mental status, and respiratory rate and was found to be more accurate than SIRS for predicting adverse events (9). Although supported by analyses of large datasets, the new definitions have been criticized because they identify patients too late in their course of illness (11). Further, qSOFA was not compared to risk stratification tools that are already commonly implemented in clinical practice outside the ICU, such as the Modified Early Warning Score (MEWS) (12) and the National Early Warning Score (NEWS) (13). There are substantial clinical and operational benefits to

using scores that are already in place if they have similar performance characteristics to novel scores. Therefore, the aim of this study was to compare the accuracy of qSOFA as an early warning score to SIRS, MEWS, and NEWS in patients with suspected infection on the wards and in the ED for predicting adverse outcomes.

METHODS

Study Population

All adult patients admitted to the University of Chicago, an urban tertiary care medical center with approximately 500 beds, from November 2008 until January 2016 were eligible for inclusion in this observational study. Patients without vital sign or laboratory data documented in the ED or ward were excluded. In addition, patients receiving mechanical ventilation or vasopressor medications prior to first suspicion of infection were excluded because a decision support tool would not offer additional value for these patients, as they would be admitted directly to the ICU. The protocol was approved by the University of Chicago Institutional Review Board (IRB #15-1705).

Data collection

All time- and location-stamped vital signs, laboratory, orders (e.g., blood cultures and medications) and demographic data from the electronic health record (EHR) for all admitted patients were collected by the University of Chicago's Clinical Research Data Warehouse, de-identified, and then made available on a secure

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SQL server for analysis. Non-physiologic values were changed to missing, as previously described (6).

Defining infection

The definition from the original qSOFA paper by Seymour and colleagues was used to define the time of initial suspicion of infection (9). Specifically, suspected infection was defined as either (1) any culture order followed by an intravenous (IV) antibiotic within 72 hours or (2) an IV antimicrobial followed by a culture order within 24 hours. The time of the culture order or IV antimicrobial administration was denoted as the time of suspicion of infection, whichever came first. Medications were reviewed by three of the authors (S.S., N.P., and X.H.) to exclude prophylactic antibiotics. In addition, we excluded oral medications from the definition of suspicion of infection because IV antibiotics are recommended as the initial treatment of sepsis (14). Only patients first meeting the suspicion of infection definition on the wards or ED were included in the study.

Outcomes

The primary outcome of the study was in-hospital mortality, and the secondary outcome was the composite of death or ICU stay at any point after a patient met the suspicion of infection criteria. A sensitivity analysis was performed by limiting the patient population to patients who met ICD-9-CM criteria for sepsis by the Angus criteria (15). A second sensitivity analysis was performed by calculating

accuracy for presumed septic shock, as defined by being both Angus-criteria-positive and receiving vasopressors after the time of suspicion of infection.

Sepsis-focused criteria and general early warning scores

The accuracy of two sepsis-focused criteria, SIRS and qSOFA, and two general early warning scores, MEWS and NEWS, were investigated in this study. SIRS criteria were defined as respiratory rate greater than 20 breaths per minute, temperature greater than 38° C or less than 36° C, heart rate greater than 90 beats per minute, and white blood cell count greater than 12,000/mm^3, less than 4,000/mm^3, or greater than 10% bands (4). The qSOFA criteria were defined as systolic blood pressure ≤100mm Hg, respiratory rate ≥22 breaths per minute, and altered mental status (defined as either a Glasgow Coma Scale score ≤13 or an Alert Voice Pain Unresponsive scale (AVPU) other than "Alert") (9). MEWS and NEWS were calculated based on previously published tables (12, 13). Of note, our hospital has been collecting GCS on ward patients since 2011, and prior to that period the components of AVPU were documented.

Statistical Analysis

Patient characteristics were compared between those first meeting the suspicion of infection definition on the wards vs. ED using t-tests, Wilcoxon rank sum tests, and chi-squared tests as necessary based on the distribution of the data. The highest value of each algorithm was calculated from the same contiguous non-ICU location segment (i.e., ED and ward) as when a patient first met the

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suspicion of infection definition. Previous values were pulled forward if they were missing, and if no prior values were available a median (normal) value was imputed, as per prior studies (9, 16, 17). Accuracy comparisons were performed using sensitivity, specificity, and the area under the receiver operating characteristic curve was used to compare algorithm discrimination. A two-tailed p-value <0.05 was considered statistically significant. Analyses were performed using Stata version 14.1 (StataCorps; College Station, Texas).

RESULTS

Study population

A total of 445,073 patient records were available during the study period, of which 150,288 admissions occurred that had vital signs or laboratory values documented in the ED or ward and were eligible for inclusion in the study. Of these patients, 59,078 (39%) had at least one culture order, and 54,367 (36%) received at least one dose of IV antibiotics (**Appendix Figure 1**). The final study cohort consisted of 30,677 patients meeting the definition of suspicion of infection outside the ICU, with both antibiotics and cultures within the pre-defined time window. Sixty percent (n=18,523) first met this definition in the ED and 40% (n=12,154) first met the definition on the wards. Compared to patients with first suspicion of infection in the ward, ED patients were more likely to be female (55% vs. 48%, p<0.001), black (73% vs. 36%; p<0.001), meet Angus sepsis criteria (29% vs. 28%, p<0.01), and be admitted to the ICU at any point during their hospitalization (26% vs. 20%, p<0.01). In addition, patients first meeting

suspicion criteria on the wards had higher in-hospital mortality (6% vs. 5%, p<0.01) and length of stay after suspicion of infection (8.3 vs. 6.8 days, p<0.01) (**Table 1**). A total of 1,649 (5.4%) patients died and 7,120 (23.2%) experienced an ICU stay after meeting suspicion of infection criteria. For those experiencing the composite outcome (death or ICU stay; n=7,385), the median time to the outcome after time of first suspicion of infection was 14 hours (IQR 6-66 hours), and 71% of patients who experienced the composite outcome did so within 48 hours.

Score distributions

Distributions of the highest SIRS criteria, qSOFA criteria, MEWS, and NEWS during the same contiguous non-ICU segment as when a patient met suspicion of infection criteria are shown in **Appendix Figures 2-5**. Eighty-eight percent (n=27,097) of patients met at least two SIRS criteria and 38% (n=11,729) met at least two qSOFA criteria during this time period. At the time of suspicion of infection, 51% of patients had met ≥2 SIRS, 9% had met ≥2 and 48% had met ≥1 qSOFA criteria at least once. The most common initial ≥2 qSOFA combination met by this time point was respiratory and blood pressure criteria 5,016 (42.8%), followed by respiratory rate and mental status criteria 3,249 (27.7%), blood pressure and mental status criteria 1,993 (17.0%), and all three criteria 1,471 (12.5%).

Accuracy comparisons

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Using each patient's highest score during their non-ICU stay, algorithm discrimination for in-hospital mortality in all non-ICU patients was highest for NEWS (AUC 0.77 [95% CI 0.76-0.79]), followed by MEWS (0.73 [0.71-0.74]), the qSOFA score (AUC 0.69 [0.67-0.70]) and lowest for SIRS (AUC 0.65 [0.63-0.66]) (p-value <0.01 for all pairwise comparisons). The relationship between the scores was consistent when comparing the ward and ED subgroups, with the AUCs being slightly lower on the wards (**Figure 1**). Furthermore, AUCs were similar but slightly lower for the composite outcome (**Appendix Figure 6**). Using a patient's highest non-ICU score, NEWS ≥9 had a 72% sensitivity for in-hospital mortality compared to 71% for MEWS ≥5, 69% for qSOFA ≥2, and 94% for ≥2 SIRS (**Table 2**). Positive and negative predictive values at different thresholds for each score are found in **Appendix Table 1**. Using the NEWS at a cut-off ≥9 would correctly reclassify 3% of patients who died and 9% of patients who did not die compared to using qSOFA ≥2. Furthermore, NEWS ≥8 would correctly reclassify 13% of patients who died or were transferred to the ICU compared to qSOFA ≥2 at a similar specificity. MEWS ≥5 would correctly reclassify 5% of patients who died or were transferred to the ICU and 3% of patients who did not experience the composite outcome compared to qSOFA ≥2. **Appendix Figure 7** and **Appendix Figure 8** show the percentage of positive screens in the study population as a function of sensitivity for each of the four tools for each outcome, demonstrating the relative efficiency of NEWS and lack of efficiency for SIRS across the continuum.

Using a patient's highest score up until the time of first suspicion of infection, ≥9 NEWS had a sensitivity of 18% for the combined outcome in all non-ICU patients compared to 26% for ≥5 MEWS, 17% for ≥2 qSOFA, 65% for ≥1 qSOFA, and 62% for ≥2 SIRS. The majority of patients met SIRS criteria 17 hours prior to ICU transfer or death, compared to 12 hours for NEWS ≥7, and 5 hours for ≥2 and 17 hours for ≥1 qSOFA criteria (**Figure 2**).

Sensitivity analyses

The ranking of the scores was similar in the cohort of patients meeting Angus ICD-9 criteria for sepsis (n=8,744), with an AUC for in-hospital mortality of 0.71 (95% CI 0.69-0.72) for NEWS, 0.66 (0.64-0.68) for MEWS, 0.63 (0.61-0.64) for qSOFA, and 0.60 (0.58-0.62) for SIRS ($p<0.01$ for all pairwise comparisons). In this population, NEWS ≥7 had a sensitivity of 82% for the composite outcome compared to a sensitivity of 63% for qSOFA ≥2 and 93% for ≥2 SIRS criteria. Accuracy was higher for the subset of patients who also received vasopressor drugs after the onset of infection, with a sensitivity of 87% for NEWS ≥7, 70% for ≥2 qSOFA, and 93% for ≥2 SIRS criteria for the composite outcome.

DISCUSSION

In this observational cohort study, we found that although qSOFA was more accurate than SIRS for predicting in-hospital mortality and ICU transfer in both ward and ED patients, it was less accurate than the general early warning scores. In fact, NEWS was the most accurate tool for predicting adverse

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outcomes in both ED and ward patients. This is important because early warning scores such as the MEWS are in widespread use in Europe and the United States, and the NEWS is now mandated in the U.K. as a tool to identify patients outside the ICU at high risk of clinical deterioration (13, 18-20).

The SIRS criteria have been part of the sepsis definition for over two decades, and have been criticized in the literature for almost as long (3, 5). In particular, they have been shown to have poor specificity, with up to 90% of ICU patients and almost half of ward patients meeting at least two of four criteria at some point in their stay (6, 7). These findings and others led to the recent update of the sepsis definitions in 2016 by the SCCM/ESICM task force (8). The qSOFA score was published with these updated sepsis definitions as a tool that could be used outside the ICU to prompt clinicians to consider possible sepsis (9). Although the new sepsis definitions were endorsed by several societies, other societies, including Chest and the American College of Emergency Physicians, did not endorse them (11). One criticism of these new criteria has been that they will identify patients too late in their course, after organ dysfunction has already occurred (11). Furthermore, some authors have questioned the use of qSOFA as a clinical decision tool given how it was developed (21).

We found that less than one in five patients who later go on to die or be transferred to the ICU will have met ≥2 qSOFA criteria by the time of infection suspicion, which illustrates the importance of score recalculation after the

initiation of therapy. Further, the majority of patients who experienced the composite outcome met ≥2 SIRS criteria over 17 hours prior to the composite outcome, compared to only 5 hours for ≥2 qSOFA, with almost half of patients still not meeting ≥2 qSOFA criteria at the time of the outcome. The prior paradigm using SIRS favored higher sensitivity at the cost of specificity while using a qSOFA score cut-off of ≥2 increases specificity at the cost of sensitivity. Interestingly, we found that using ≥1 qSOFA criteria had similar accuracy and timing compared to ≥2 SIRS criteria, which suggests that this lower threshold could be used if an earlier and more sensitive cut-off were desired.

Our study found that general early warning scores are more accurate than qSOFA for predicting adverse outcomes in the ED and on the wards. The MEWS, and its derivatives, such as the NEWS, which was endorsed by the Royal College of Physicians for standard use across the UK, are already utilized in many hospitals for Rapid Response System activation (13, 18, 19). We found NEWS to be the most accurate score we studied. qSOFA has the advantage of simplicity, and errors in manually calculating general early warning scores have been described (22). However, the NEWS and MEWS offer several more thresholds in order to vary sensitivity and specificity to resource availability. In addition, these early warning scores are increasingly becoming available for automated calculation within the EHR. Furthermore, data suggest that general early warning scores such as MEWS and the eCART model add useful predictive information to clinical judgment (23-25). Currently it is unknown whether using ≥2

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qSOFA criteria, which would identify a patient with both mental status changes and hypotension as a patient to pay more attention to, offers additional value above caregiver intuition. Overall, our study provides evidence that hospitals already utilizing the NEWS or MEWS would not benefit from switching to qSOFA for use as an early warning score given the costs and risks of retraining caregivers to use a new scoring system.

Our study has several limitations. First, this was a single-center investigation in an academic U.S. hospital so the results may not be generalizable to other settings. In addition, there is no gold standard to determine when a patient is infected so we may have excluded patients who were infected and included others who were not. However, we utilized the same definition as the original qSOFA paper and also included only IV medications, which should improve the validity of our results. Finally, we only studied two of the over 100 published early warning scores in the literature (26). Given that most of these scores are similar to the MEWS and NEWS and these are two of the most highly cited scores in common use we felt that these results would be of value for clinicians.

In conclusion, we found that general early warning scores were more accurate than the qSOFA score for predicting in-hospital mortality and ICU transfer in non-ICU patients with suspicion of infection, with the NEWS being the most accurate score in our study. These findings have important implications for clinicians at the

bedside, hospitals, and countries implementing these scoring systems in practice.

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AJRCCM Articles in Press. Published on 20-September-2016 as 10.1164/rccm.201604-0854OC

REFERENCES

1. Liu V, Escobar GJ, Greene JD, Soule J, Whippy A, Angus DC, Iwashyna TJ. Hospital deaths in patients with sepsis from 2 independent cohorts. *JAMA* 2014;312:90-92.

2. Lagu T, Rothberg MB, Shieh MS, Pekow PS, Steingrub JS, Lindenauer PK. Hospitalizations, costs, and outcomes of severe sepsis in the united states 2003 to 2007. *Crit Care Med* 2012;40:754-761.

3. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM consensus conference committee. American college of chest physicians/society of critical care medicine. *Chest* 1992;101:1644-1655.

4. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G, Sccm/Esicm/Accp/Ats/Sis. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Crit Care Med* 2003;31:1250-1256.

5. Vincent JL. Dear sirs, i'm sorry to say that i don't like you. *Crit Care Med* 1997;25:372-374.

6. Churpek MM, Zadravecz FJ, Winslow C, Howell MD, Edelson DP. Incidence and prognostic value of the systemic inflammatory response syndrome and organ dysfunctions in ward patients. *Am J Respir Crit Care Med* 2015;192:958-964.

7. Sprung CL, Sakr Y, Vincent JL, Le Gall JR, Reinhart K, Ranieri VM, Gerlach H, Fielden J, Groba CB, Payen D. An evaluation of systemic inflammatory response syndrome signs in the sepsis occurrence in acutely ill patients (SOAP) study. *Intensive Care Med* 2006;32:421-427.

8. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315:801-810.

9. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC. Assessment of clinical criteria for sepsis: For the third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315:762-774.

10. Levy MM, Rhodes A, Phillips GS, Townsend SR, Schorr CA, Beale R, Osborn T, Lemeshow S, Chiche JD, Artigas A, Dellinger RP. Surviving sepsis campaign: Association between performance metrics and outcomes in a 7.5-year study. *Crit Care Med* 2015;43:3-12.

11. Simpson SQ. New sepsis criteria: A change we should not make. *Chest* 2016;149:1117-1118.

12. Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified early warning score in medical admissions. *QJM : monthly journal of the Association of Physicians* 2001;94:521-526.

AJRCCM Articles in Press. Published on 20-September-2016 as 10.1164/rccm.201604-0854OC

13. 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;84:465-470.

14. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R, Surviving Sepsis Campaign Guidelines Committee. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580-637.

15. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the united states: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303-1310.

16. Churpek MM, Yuen TC, Winslow C, Robicsek AA, Meltzer DO, Gibbons RD, Edelson DP. Multicenter development and validation of a risk stratification tool for ward patients. *Am J Respir Crit Care Med* 2014;190:649-655.

17. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A, et al. The apache iii prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991;100:1619-1636.

18. Royal College of Physicians. National early warning score (NEWS): Standardising the assessment of acute illness severity in the NHS. *London: Royal College of Physicians* 2012.

19. Jones DA, DeVita MA, Bellomo R. Rapid-response teams. *N Engl J Med* 2011;365:139-146.

20. Smith ME, Chiovaro JC, O'Neil M, Kansagara D, Quinones AR, Freeman M, Motu'apuaka ML, Slatore CG. Early warning system scores for clinical deterioration in hospitalized patients: A systematic review. *Annals of the American Thoracic Society* 2014;11:1454-1465.

21. Moskowitz A, Andersen LW, Cocchi M, Donnino MW. The misapplication of severity-of-illness scores toward clinical decision making. *Am J Respir Crit Care Med* 2016.

22. Prytherch DR, Smith GB, Schmidt P, Featherstone PI, Stewart K, Knight D, Higgins B. Calculating early warning scores--a classroom comparison of pen and paper and hand-held computer methods. *Resuscitation* 2006;70:173-178.

23. Patel AR, Zadravecz FJ, Young RS, Williams MV, Churpek MM, Edelson DP. The value of clinical judgment in the detection of clinical deterioration. *JAMA internal medicine* 2015;175:456-458.

24. Fullerton JN, Price CL, Silvey NE, Brace SJ, Perkins GD. Is the modified early warning score (mews) superior to clinician judgement in detecting critical illness in the pre-hospital environment? *Resuscitation* 2012;83:557-562.

25. Kang MA, Churpek MM, Zadravecz FJ, Adhikari R, Twu NM, Edelson DP. Real-time risk prediction on the wards: A feasibility study. *Crit Care Med* 2016.

AJRCCM Articles in Press. Published on 20-September-2016 as 10.1164/rccm.201604-0854OC

26. Churpek MM, Yuen TC, Edelson DP. Risk stratification of hospitalized patients on the wards. *Chest* 2013;143:1758-1765.

Table 1: Patient characteristics

Characteristic	**All patients (n=30,677)**	**Ward patients (n=12,154)**	**ED patients (n=18,523)**	**P-value**
Age, mean (SD), years	58 (18.0)	57 (16.7)	58 (18.9)	<0.001
Female sex, n (%)	16,116 (53)	5,856 (48)	10,260 (55)	<0.001
Race, n (%)				<0.001
Black	17,813 (58)	4,384 (36)	13,429 (73)	
White	10,685 (35)	6,631 (55)	4,054 (22)	
Other	1,253 (4)	595 (5)	658 (4)	
Unknown	926 (3)	544 (4)	382 (2)	
LOS prior to time of suspicion, median (IQR), hours	2.9 (1.1-7.9)	7.4 (2.4-30.5)	1.9 (0.8-4.3)	<0.001
LOS after time of suspicion, median (IQR), days	7.3 (5.8-11.6)	8.3 (6.0-14.3)	6.8 (5.8-10.1)	<0.001
Met Angus sepsis criteria, n (%)	8,744 (29)	3,350 (28)	5,394 (29)	0.003
Ever ICU transfer, n (%)	7,258 (24)	2,390 (20)	4,868 (26)	<0.001
Ever received vasopressor, n (%)	2,724 (9)	1,113 (9)	1,611 (9)	0.166
In-hospital mortality, n (%)	1,649 (5)	729 (6)	920 (5)	<0.001
Composite outcome, n (%)	7,385 (24)	2,385 (20)	5,000 (27)	<0.001

Abbreviations: ED, emergency department; LOS, length of stay; ICU, intensive care unit

AJRCCM Articles in Press. Published on 20-September-2016 as 10.1164/rccm.201604-0854OC

Table 2: Accuracy for the outcomes across different score thresholds using each patient's highest non-ICU score*

Score	Threshold	Mortality		Mortality or ICU Transfer	
		Sensitivity	Specificity	Sensitivity	Specificity
SIRS	≥1	98.9%	1.2%	98.6%	1.1%
	≥2	93.8%	12.3%	91.0%	13.0%
	≥3	77.5%	43.8%	67.7%	45.9%
	≥4	36.8%	84.0%	26.1%	85.7%
qSOFA	≥1	95.2%	11.9%	92.9%	12.9%
	≥2	68.7%	63.5%	53.6%	66.7%
	≥3	19.0%	96.0%	10.4%	97.0%
MEWS	≥1	100.0%	0.0%	100.0%	0.0%
	≥2	96.2%	5.6%	96.2%	6.0%
	≥3	92.8%	20.3%	89.2%	22.3%
	≥4	84.7%	44.1%	76.1%	48.4%
	≥5	71.4%	65.0%	59.1%	70.1%
	≥6	52.7%	81.0%	40.2%	85.3%
	≥7	31.3%	91.6%	22.2%	94.4%
	≥8	17.5%	96.8%	11.1%	98.3%
	≥9	8.1%	99.1%	4.4%	99.7%
NEWS	≥1	97.0%	1.9%	98.4%	2.1%
	≥2	96.9%	2.9%	97.6%	3.0%
	≥3	96.5%	6.2%	96.2%	6.8%
	≥4	95.5%	13.2%	93.3%	14.7%

	≥5**	95.1%	15.0%	92.6%	16.7%
	≥5	93.6%	23.1%	89.2%	25.8%
	≥6	91.0%	34.6%	84.0%	38.7%
	≥7	86.6%	47.5%	76.5%	52.7%
	≥8	79.9%	60.0%	66.5%	65.6%
	≥9	71.9%	72.2%	54.4%	77.6%
	≥10	59.2%	82.3%	41.4%	86.9%
	≥11	46.7%	89.5%	29.7%	93.0%
	≥12	32.9%	94.2%	19.3%	96.6%
	≥13	21.6%	97.3%	11.0%	98.6%
	≥14	12.1%	98.8%	5.8%	99.5%
	≥15	6.3%	99.5%	2.7%	99.8%

*Commonly used cut-off thresholds are shown in bold font.

**NEWS total score ≥ 5 or at least one individual parameter score of 3

Abbreviations: SIRS, systemic inflammatory response syndrome; qSOFA, quick Sepsis-related Organ Failure Assessment; MEWS, Modified Early Warning Score; NEWS, National Early Warning Score

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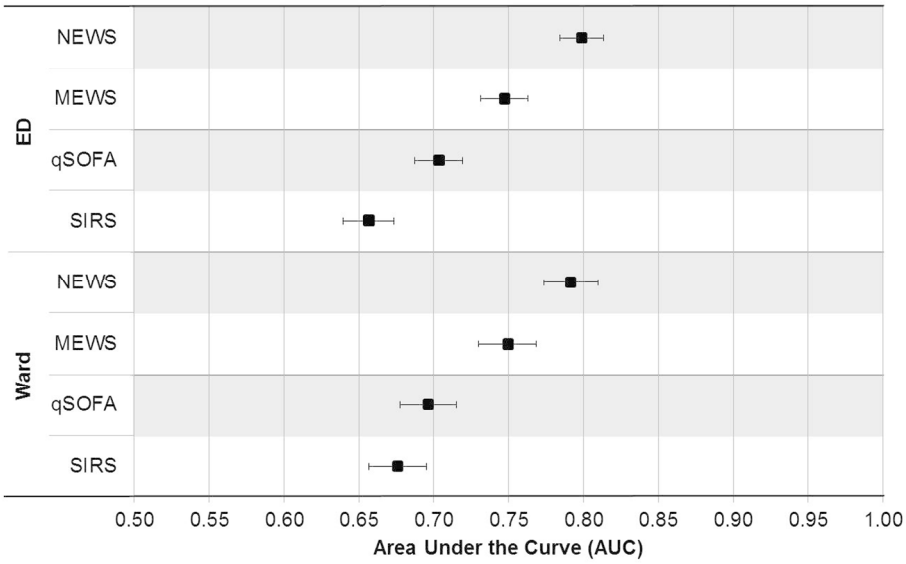
FIGURE LEGENDS

Figure 1: Discrimination of the different algorithms for predicting in-hospital mortality using each patient's highest score by location

Abbreviations: ED, emergency department; NEWS, National Early Warning Score; MEWS, Modified Early Warning Score; qSOFA, quick Sepsis-related Organ Failure Assessment; SIRS, systemic inflammatory response syndrome

Figure 2: Cumulative percentage of patients meeting ≥2 qSOFA criteria, ≥7 NEWS criteria, or ≥2 SIRS criteria in the 48 hours prior to the composite outcome



Discrimination of the different algorithms for predicting in-hospital mortality using each patient's highest score by location
Abbreviations: ED, emergency department; NEWS, National Early Warning Score; MEWS, Modified Early Warning Score; qSOFA, quick Sepsis-related Organ Failure Assessment; SIRS, systemic inflammatory response syndrome

Figure 1
243x154mm (150 x 150 DPI)

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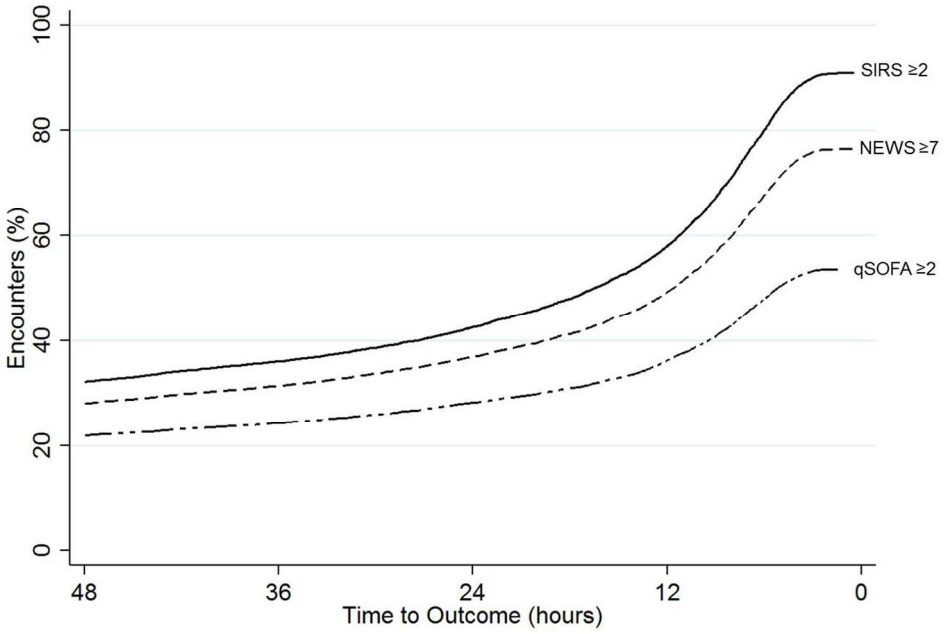

Cumulative percentage of patients meeting ≥2 qSOFA criteria, ≥7 NEWS criteria, or ≥2 SIRS criteria in the 48 hours prior to the composite outcome
Figure 2
234x150mm (150 x 150 DPI)

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ONLINE DATA SUPPLEMENT

qSOFA, SIRS, and early warning scores for detecting clinical deterioration in infected patients outside the intensive care unit

Running title: Sepsis risk prediction outside the ICU

Matthew M Churpek, MD, MPH, PhD; Ashley Snyder, MPH; Xuan Han, MD; Sarah Sokol, PharmD; Natasha Pettit, PharmD; Michael D. Howell, MD, MPH; Dana P Edelson, MD, MS

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Appendix Table 1: Positive and negative predictive values for the outcomes across different score thresholds using each patient's highest non-ICU score

Score	Threshold	Mortality		Mortality or ICU Transfer	
		PPV	NPV	PPV	NPV
SIRS	≥1	5.4%	94.6%	24.0%	71.4%
	≥2	5.7%	97.2%	24.9%	82.0%
	≥3	7.3%	97.2%	28.4%	81.7%
	≥4	11.5%	95.9%	36.7%	78.5%
qSOFA	≥1	5.8%	97.7%	25.3%	85.0%
	≥2	9.7%	97.3%	33.8%	81.9%
	≥3	21.3%	95.4%	52.2%	77.3%
MEWS	≥1	5.4%	100%	24.1%	100%
	≥2	5.5%	96.2%	24.5%	83.1%
	≥3	6.2%	98.0%	26.7%	86.7%
	≥4	7.9%	98.1%	31.9%	86.4%
	≥5	10.4%	97.6%	38.5%	84.4%
	≥6	13.6%	96.8%	46.5%	81.8%
	≥7	17.5%	95.9%	55.6%	79.3%
	≥8	23.6%	95.4%	67.1%	77.7%
	≥9	33.3%	95.0%	81.2%	76.7%
NEWS	≥1	5.3%	91.8%	24.2%	80.2%
	≥2	5.4%	94.1%	24.2%	79.7%

	≥3	5.5%	96.9%	24.7%	84.9%
	≥4	5.9%	98.1%	25.7%	87.3%
	≥5*	6.0%	98.2%	26.1%	87.7%
	≥5	6.5%	98.4%	27.6%	88.2%
	≥6	7.3%	98.5%	30.3%	88.4%
	≥7	8.6%	98.4%	33.9%	87.6%
	≥8	10.2%	98.1%	38.0%	86.1%
	≥9	12.8%	97.8%	43.5%	84.3%
	≥10	15.9%	97.3%	50.0%	82.4%
	≥11	20.1%	96.7%	57.3%	80.7%
	≥12	24.4%	96.1%	64.3%	79.1%
	≥13	31.3%	95.6%	71.2%	77.7%
	≥14	35.6%	95.2%	77.1%	76.9%
	≥15	41.0%	94.9%	79.3%	76.4%

*NEWS total score ≥ 5 or at least one individual parameter score of 3

Abbreviations: SIRS, systemic inflammatory response syndrome; qSOFA, quick Sepsis-related Organ Failure Assessment; MEWS, Modified Early Warning Score; NEWS, National Early Warning Score; PPV, Positive Predictive Value; NPV, Negative Predictive Value

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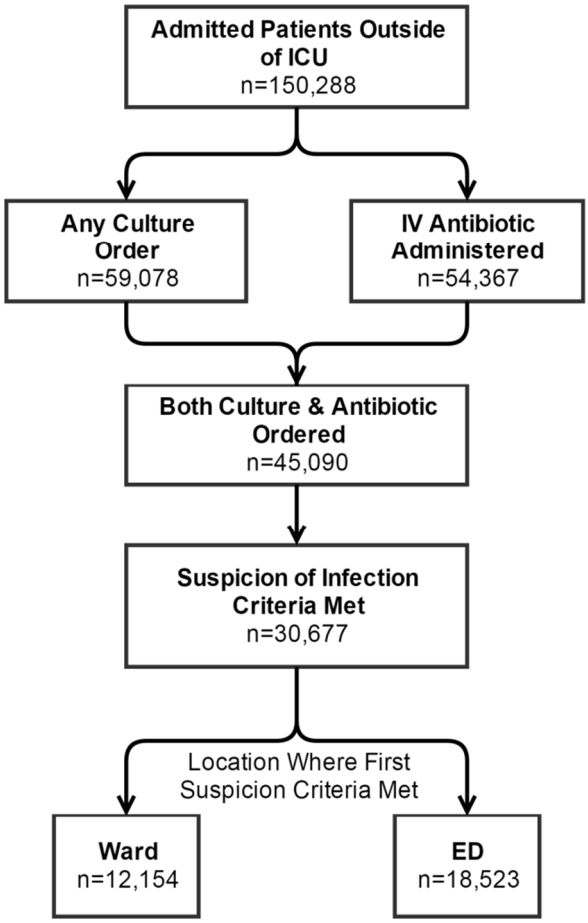
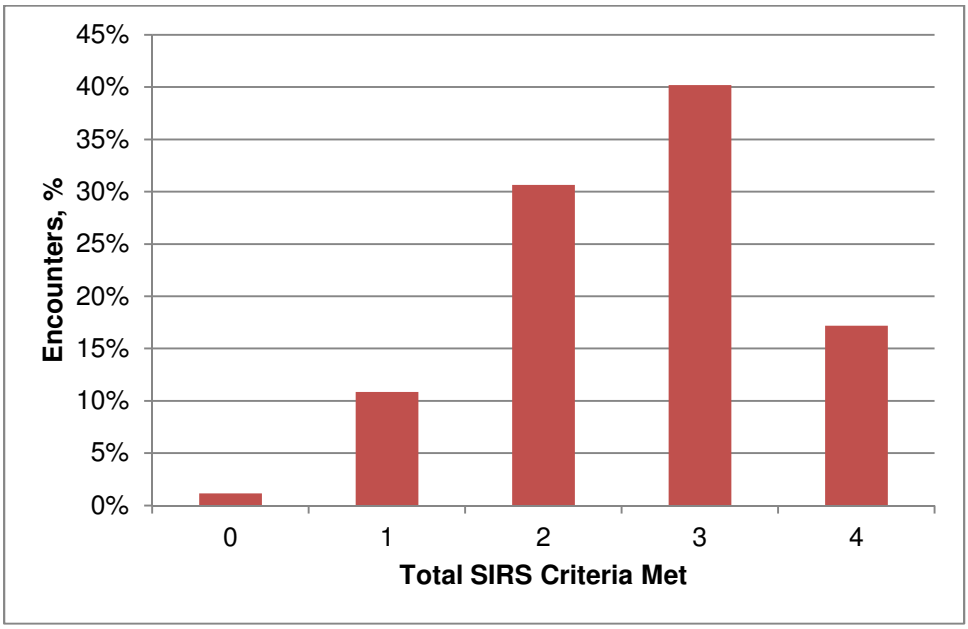
Appendix Figure 1: Flow diagram of study patients



Abbreviations: ICU = intensive care unit, ED = emergency department

Appendix Figure 2: Distribution of the highest number of SIRS criteria met during the same contiguous non-ICU segment as when a patient met suspicion of infection criteria



Abbreviations: SIRS = systemic inflammatory response syndrome

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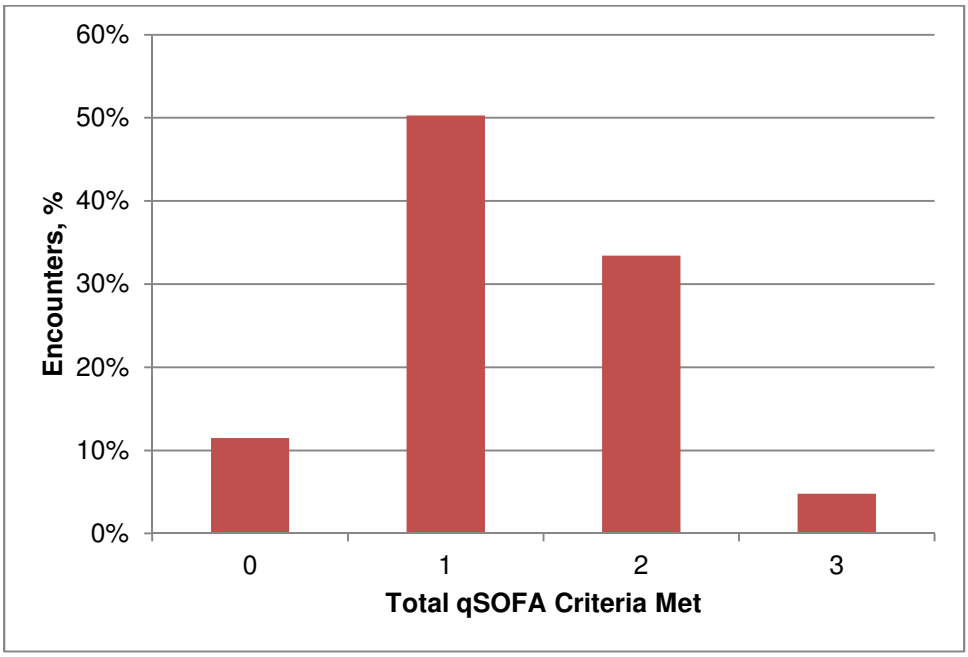
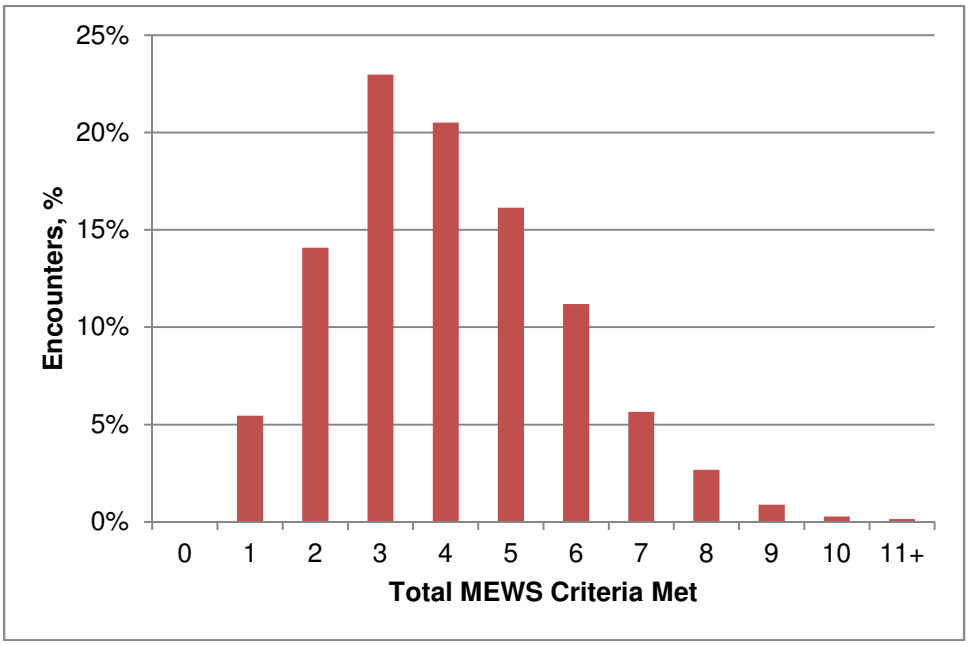
Appendix Figure 3: Distribution of the highest number of qSOFA criteria met during the same contiguous non-ICU segment as when a patient met suspicion of infection criteria



Abbreviations: qSOFA = quick Sepsis-related Organ Failure Assessment

Appendix Figure 4: Distribution of the highest MEWS during the same contiguous non-ICU segment as when a patient met suspicion of infection criteria



Abbreviations: MEWS = Modified Early Warning Score

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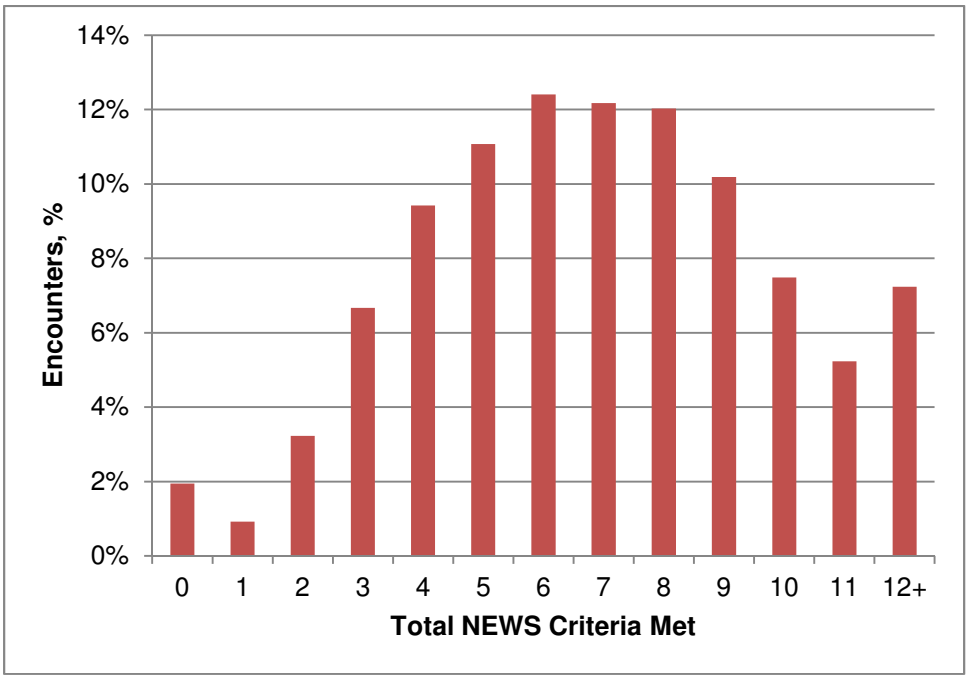
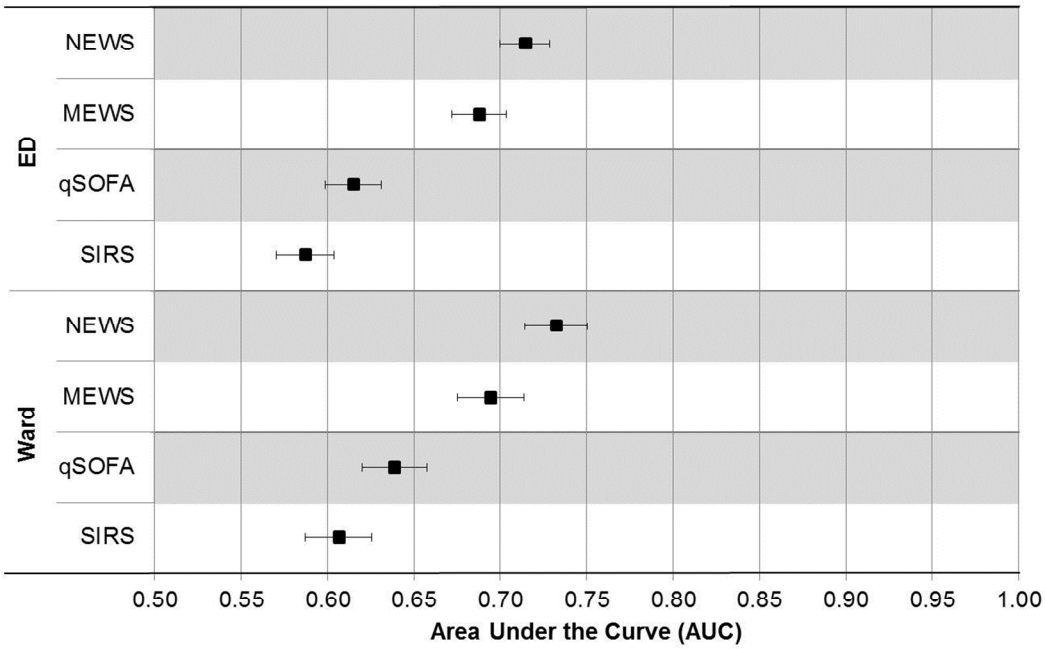
Appendix Figure 5: Distribution of the highest NEWS during the same contiguous non-ICU segment as when a patient met suspicion of infection criteria



Abbreviations: NEWS = National Early Warning Score

Appendix Figure 6: Accuracy of the different algorithms for predicting the combined outcome, by location



Abbreviations: ED, emergency department; NEWS, National Early Warning Score; MEWS, Modified Early Warning Score; qSOFA, quick Sepsis-related Organ Failure Assessment; SIRS, systemic inflammatory response syndrome

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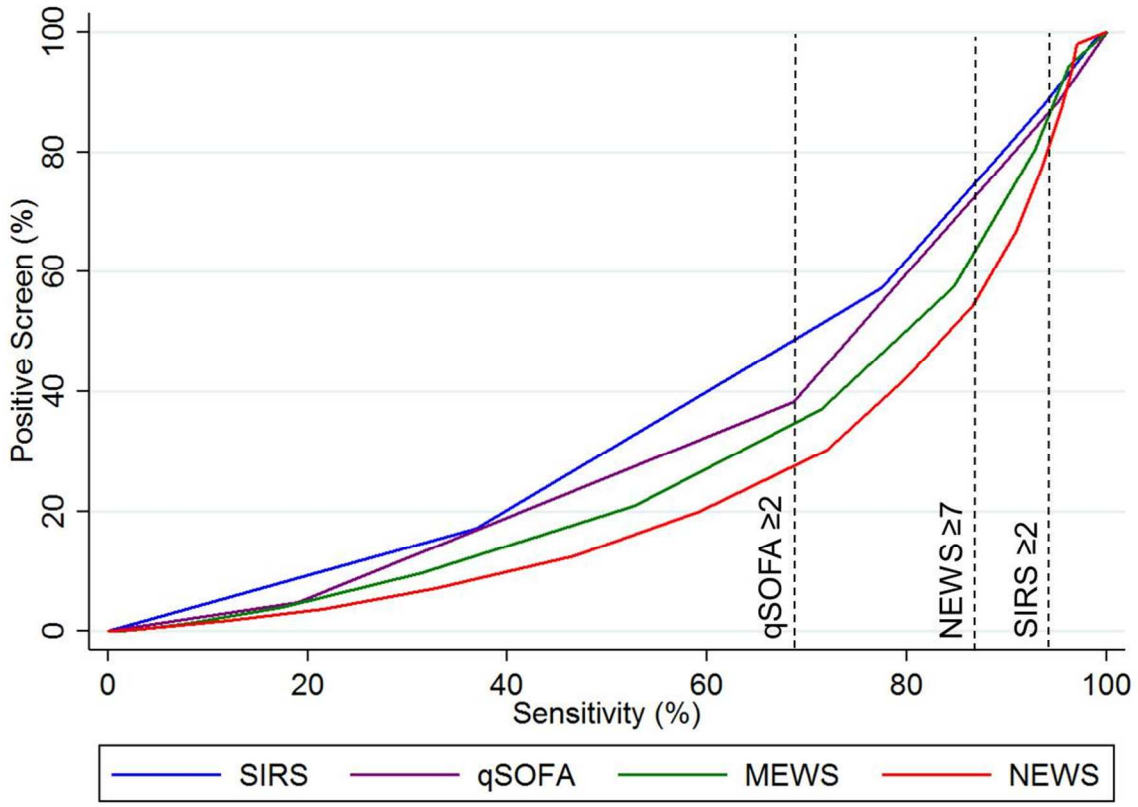
Appendix Figure 7: Efficiency curve for the different algorithms for in-hospital mortality



This graph shows model sensitivity on the x-axis by the percentage of patients that would need to be screened to achieve a given sensitivity on the y-axis. For example, the leftmost vertical black line shows the qSOFA ≥2 cut-point, which would require screening 38% of the non-ICU population at the time of suspicion of infection and had a sensitivity of 69%. The middle black line shows the NEWS ≥7 cut-off, which would require screening 54% of the non-ICU population and achieved a sensitivity of 87%. Finally, the rightmost black line shows the SIRS ≥2 cut-off, which would require screening 88% of the non-ICU population and achieved a sensitivity of 94%.

Abbreviations: ED = emergency department, NEWS = National Early Warning Score, MEWS = Modified Early Warning Score, qSOFA = quick Sepsis-related Organ Failure Assessment, SIRS = systemic inflammatory response syndrome

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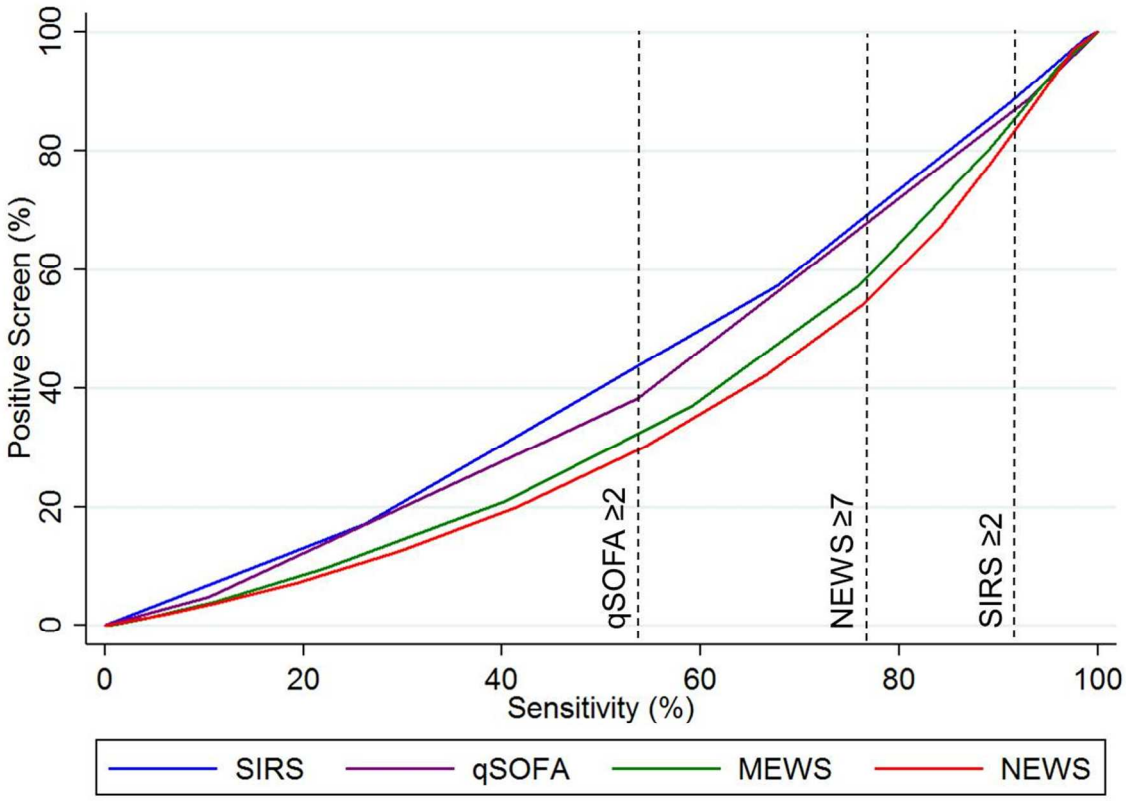
Appendix Figure 8: Efficiency curve for the different algorithms for the combined outcome



This graph shows model sensitivity on the x-axis by the percentage of patients that would need to be screened to achieve a given sensitivity on the y-axis. For example, the leftmost vertical black line shows the qSOFA ≥2 cut-point, which would require screening 38% of the non-ICU population at the time of suspicion of infection and had a sensitivity of 54%. The middle black line shows the NEWS ≥7 cut-off, which would require screening 54% of the non-ICU population and achieved a sensitivity of 77%. Finally, the rightmost black line shows the SIRS ≥2 cut-off, which would require screening 88% of the non-ICU population and achieved a sensitivity of 91%.

Abbreviations: ED = emergency department, NEWS = National Early Warning Score, MEWS = Modified Early Warning Score, qSOFA = quick Sepsis-related Organ Failure Assessment, SIRS = systemic inflammatory response syndrome