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Title: Predicting mortality in adults with infection in a Rwandan hospital: an evaluation of the adapted MEWS, qSOFA, and UVA scores

Running head: Predicting mortality in a Rwandan hospital

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ABTRACT (word count: 287)

Rationale: Mortality prediction scores are increasingly being evaluated in low and middle income countries (LMICs) for research comparisons, quality improvement, and clinical decision-making. The modified early warning score (MEWS), quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA), and Universal Vital Assessment Score (UVA) use variables that are feasible to obtain, and have demonstrated potential to predict mortality in LMIC cohorts.

Objective: To determine the predictive capacity of adapted MEWS, qSOFA and UVA in a Rwandan hospital.

Design, setting, participants, and outcome measures: We prospectively collected data on all adult patients admitted to a tertiary hospital in Rwanda with suspected infection over seven months. We calculated an adapted MEWS, qSOFA, and UVA score for each participant. The predictive capacity of each score was assessed including sensitivity, specificity, positive and negative predictive value, odds ratio, area under the receiver operating curve (AUROC), and performance by underlying risk quartile.

Results: We screened 19,178 patient-days, and enrolled 647 unique patients. Median age was 35 years, and in-hospital mortality was 18.1%. The proportion of data missing for each variable ranged from 0% to 11.7%. The sensitivities and specificities of the scores were: adapted MEWS >4, 50.4% and 74.9%, respectively; qSOFA≥2, 24.8% and 90.4% respectively; and UVA >4, 28.2% and 91.1% respectively. The scores as continuous variables demonstrated the following AUROCs: adapted

MEWS 0.69 (95% CI 0.64, 0.74), qSOFA 0.65 (95% CI 0.60, 0.70), and UVA 0.71 (95% CI 0.66, 0.76); there was no statistically significant difference between the scores' discriminative capacities.

Conclusions: Three scores demonstrated modest ability to predict mortality in a prospective study of inpatients with suspected infection at a Rwandan tertiary hospital. Careful consideration must be given to their adequacy before using them in research comparisons, quality improvement, or clinical decision-making.

Strengths and limitations of this study

- We evaluated the three severity of illness (SOI) scores in the literature that are most likely to be feasible and predictive in LMIC settings; this includes the first hospital-wide evaluation of UVA, the only score that was developed using LMIC cohorts.
- Many SOI scores are developed and tested in ICU populations while our analysis also includes hospitalized patients outside the ICU; this is important because many critically ill patients in LMICs remain outside the ICU due to resource constraints.
- We analyzed the predictive capacity of the SOI models as both continuous and dichotomous scores and using multiple metrics, including sensitivity, specificity, positive and negative predictive value, odds ratio, area under the receiver operating curve, and performance by underlying risk quartile.
- Vital signs used in the scores were collected at different times in the participants' hospitalizations, depending on how they met inclusion criteria for the study (time of fever, operation, or culture sample retrieval); while this may decrease the predictive capacity of the scores, it also mirrors how the scores might be used in practice.
- The results from this single-center study among adults with suspected infection may not be generalizable to other populations; this variability in predictive capacity is a known challenge in using SOI scores and the reason it is important to validate a score in a particular site before using it.

INTRODUCTION

Multiple mortality prediction models have been developed or validated in low and middle income countries (LMICs) over the last five years [1-11]. The proposed uses of these models include identifying patients at acute risk for deterioration in order to trigger increased levels of care [3, 11-15], more informed allocation of scarce resources [13, 15], benchmarking for quality assessment and quality improvement [1], and controlling for severity of illness in future trials [13, 16, 17]. In addition, updates to definitions of critical illness syndromes, most notably sepsis and acute respiratory distress syndrome (ARDS), have increasingly emphasized definitions that have predictive validity [18, 19].

The modified early warning score (MEWS) was first reported describing 709 medical patients in a district hospital in the United Kingdom in 2001 [20], and was based on an early warning score (EWS) developed and published in an abstract in 1997 [21]. It was created by assigning weighted scores to each vital sign based on severity of the vital sign abnormality, and it has since been tested in multiple LMIC sites [8, 12, 22, 23]. The quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) score was developed as part of an international re-defining of sepsis, using high income country (HIC) hospital administrative data [19] and retrospectively tested in nine sites in low and middle income countries (LMICs); it demonstrated variable predictive capability across these sites [15]. qSOFA was also prospectively tested in a study from an upper middle income country with multiple sites [11]. The Universal Vital Assessment Score (UVA) was recently developed using linear regression in fifteen in-hospital cohorts from six African countries, and showed good predictive capability across the entire derivation population, with no reporting on its performance in the individual cohorts [13]. It has only been assessed in one small emergency department cohort outside the initial derivation population [23].

All three scores use accessible bedside clinical measures and are therefore appealing for LMIC settings where laboratory values and detailed comorbidity histories are often not available. All three scores have also been developed for hospital ward patients, which is relevant to LMICs, where critically ill patients often remain in general wards due to the scarcity of ICU beds.

We prospectively collected data on all adult hospitalized patients with suspected infection over a seven month period in a study of antimicrobial resistance patterns in a tertiary referral hospital in Rwanda [24]. The current study was planned as part of the original study design, and is a secondary analysis of this data evaluating the predictive capacity of adapted MEWS, qSOFA, and UVA scores for in-hospital mortality in this population.

METHODS

Study oversight

The Institutional Review Board of the University of Rwanda, College of Medicine and Health Sciences in Kigali, Rwanda and the Committee on Clinical Investigations at Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts approved the study. Verbal consent for participation was obtained using a script in the participant's primary language.

Patient and public involvement

This research was performed without explicit patient feedback on the design or implementation. Results will be available to the public through open access publication.

Setting

The study took place at the University Teaching Hospital of Kigali. The hospital is a public academic tertiary referral hospital in Kigali, Rwanda. It is one of three public referral hospitals in a country of approximately twelve million people, with 560 total beds including a 35-bed adult Emergency Department, a seven-bed intensive care unit, a four-bed step-down unit, and approximately 12,000 admissions each year.

Inclusion criteria and data collection

We prospectively enrolled all hospitalized adult patients (age≥15 years, the hospital's cutoff for adult hospital ward admission) with suspected infection between January 25 and August 14, 2017 as part of a study examining antimicrobial resistance patterns [24]. All hospitalized patients were screened for inclusion criteria each day of their hospitalization. Patients were included if they had temperature ≤35.0° C or ≥38.0° C and suspected infection, underwent surgery for an infectious process, or had a positive microbial culture collected by the clinical team. For those who met inclusion criteria, demographic and clinical data needed for each of the scores were collected at one time point from each participant's chart by study research assistants. Vital sign and mental status data to include in the models were collected at the time of fever or hypothermia, the time of surgery, or the time of culture sample collection, depending on the inclusion criteria met for each participant. Participants were followed through hospital discharge to determine length of stay and in-hospital mortality. All coded data were entered into a secure online database, REDCap (Research Electronic Data Capture; Vanderbilt University, Nashville, TN), which was hosted by BIDMC.

Definitions

MEWS includes five variables, with scores between 0-3 assigned for each variable [20] (Table 1). It yields a maximum score of 14, with a score >4 considered to be high risk for mortality in prior studies [20]. Because we collected altered mental status as a binary variable (present or not), we adapted this variable in the MEWS score to be 0 for normal mental status and 2 for any altered mental status, rather than a range of severity of altered mental statuses from 0-3. qSOFA includes three variables, with one point given to each abnormal value, a maximum score of three, and ≥2 considered high risk [15]. UVA includes seven variables, with variable points given for each abnormality. It yields a maximum score of 13, with >4 considered high risk based on its derivation study [13].

To replicate the methods for predictive validity in the original qSOFA and qSOFA LMIC validation studies [15, 25], we also calculated a baseline risk model to stratify the population, using the same variables used in these studies: age, sex, HIV status, and hospital transfer status (whether the patient had been transferred from another facility).

Data Analysis

The primary outcome of interest was in-hospital mortality. The sample size was determined based on adequate power for the antimicrobial resistance study from which this cohort was taken, and is described in the methods of that study [24]. Adapted MEWS, qSOFA, and UVA scores were calculated for all enrolled participants. Missing data were assumed to be within normal range, with no additional points assigned. Data are presented as median (interquartile range, IQR) or frequency (proportion) depending on variable type. Normality was assessed with the Shapiro-Wilk test. Demographic differences between survivors and non-survivors were assessed with a Wilcoxon rank-sum test, chi-square or Fisher's Exact test, as appropriate. Sensitivity, specificity, positive and

negative predictive values for the previously-reported cutoffs for each score are reported. Separate unadjusted logistic regression models were used to generate odds ratios (OR) and 95% confidence intervals (CI) for adapted MEWS, qSOFA, and UVA. Multivariable logistic regression models using the four variables noted above were calculated for the baseline risk model.

We used the predicted probabilities from our baseline risk model to stratify our results into risk quartiles, presenting ORs and 95% CIs for adapted MEWS, qSOFA and UVA with their previously-defined cutoffs separately, as was done in the original LMIC cohort qSOFA study [15]. We calculated the discriminative ability of adapted MEWS, qSOFA, and UVA as continuous variables and found the area under the receiver operating characteristic (AUROC) curves for each of these models. We also calculated the discriminative ability of the three scores as continuous variables in models with baseline risk adjustment.

Data analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC) with two-sided p-values < 0·05 considered statistically significant.

RESULTS

We screened every patient in the hospital for suspected infection each day of the study period, for a total of 19,178 patient-days screened. We enrolled 647 unique patients with suspected infection; only one patient who met study criteria declined enrollment. Within this study population, the median age was 35 years (IQR 27, 51) and 53.6% of participants were male (Table 2). Known pre-existing comorbidities were present in 22.1% of participants, and 10.5% of participants were known to be HIV positive. A positive bacterial culture result was identified in 42.2% of participants.

In the full cohort, the in-hospital mortality rate was 18.1%. An adapted MEWS score of >4 was present in 192 (29.7%) cases, qSOFA score of ≥2 was present in 81 (12.5%) cases, while a UVA score >4 was present in 80 (12.4%) cases (Table 2). The full distribution for each score is shown in Figure 1, with adapted MEWS range 0-10, median 3, IQR 2,5; qSOFA range 0-3, median 0, IQR 0,1; and UVA range 0-8, median 2, IQR 0,4. The proportion of data that was missing for the components of the scores ranged from 0% to 11.7% (Supplemental Table 1).

The sensitivity and specificity of the adapted MEWS score with cutoff value >4 to predict in-hospital mortality were 50.4% and 74.9%, respectively (Table 3). The sensitivity and specificity of qSOFA with cutoff value ≥2 were 24.8% and 90.4%, respectively. For the UVA score with cutoff value >4, the sensitivity and specificity were 28.2% and 91.1%, respectively. The unadjusted ORs for adapted MEWS>4, qSOFA ≥2 and UVA >4 were 3.04 (95% CI 2.01, 4.59), 3.10 (95% CI 1.86, 5.15) and 4.04 (95% CI 2.44, 6.67), respectively. The OR for hospital mortality was most often >1 for each binary score within each quartile of baseline risk, though the 95% CI for the OR crossed one for qSOFA and UVA in quartile 4, and for adapted MEWS in quartile 1 (Supplemental Figure 1).

Overall, increasing scores for adapted MEWS, qSOFA and UVA corresponded with increasing mortality, though this was not true for every one-point increase in adapted MEWS (Figure 1). For each one point increase in score as a continuous variable, the unadjusted odds ratios were: adapted MEWS 1.41 (95% CI 1.28, 1.56), qSOFA 2.20 (95% CI 1.68, 2.88), and UVA 1.46 (1.32, 1.61) (Supplemental Table 2).

The area under the receiver operating curve (AUROC) for each score as a continuous variable was: adapted MEWS 0.69 (95% CI 0.64, 0.74), qSOFA 0.65 (95% CI 0.60, 0.70), and UVA 0.71 (95% CI 0.66, 0.76) (Figure 2, Supplemental Table 2). There was no statistically significant difference between

the AUROCs for the three scores as pairwise comparisons: UVA versus adapted MEWS p=0.57; UVA versus qSOFA p=0.09; and adapted MEWS versus qSOFA p=0.26).

The AUROC for the baseline risk model was 0.57 (95% CI 0.52, 0.63). Adding adapted MEWS, qSOFA and UVA as continuous variables to the baseline risk model changed the AUROC to 0.72 (95% CI 0.66, 0.77), 0.68 (95% CI 0.63, 0.74), and 0.72 (95% CI 0.66, 0.77), respectively (Supplemental Figure 2, Supplemental Table 3.)

DISCUSSION

In a prospective study of 647 patients with suspected infection in a Rwandan tertiary referral hospital, we found that the adapted MEWS, qSOFA, and UVA scores had modest ability to predict mortality. Using previously defined cutoffs for the each of the scores, adapted MEWS had sensitivity and specificity of 50% and 75% respectively, while qSOFA and UVA were less sensitive but had higher specificity (25% and 90% respectively for qSOFA and 28% and 91% respectively for UVA). AUROCs for the continuous scores ranged from 0.65 to 0.71, with no continuous score's AUROC demonstrating statistically significant superiority to another.

We presented the performance of the three scores using the continuous scores, continuous scores in addition to a baseline risk model, and binary scores using previously defined cutoff values. Depending on the intended use of the scores, any of these might be appropriate in understanding the adequacy of the score. For quality improvement and research comparisons, the AUROC is a useful single value in deciding whether a model can help determine differences in severity of illness between cohorts [13]. For determining the predictive validity of a definition of sepsis, assessing mortality risk above baseline risk may be most appropriate [15]. For deciding who needs escalation of

care, the sensitivity and specificity with a particular cutoff value is likely to be more important in judging the adequacy of the model [11]. Particularly in the latter example, which is the most oft-cited use for scores in LMICs, care must be taken in how the scores are used for individual clinical decision-making since low sensitivity could lead to patients who need additional care being missed and low specificity could lead to attempts at using scarce resources for a relatively large population [11, 26, 27].

Our study has several strengths. We looked at adult patients across the entire hospital rather than the ICU alone [1, 2, 7, 10, 16, 17], which is particularly important in settings where many critically ill patients remain outside the ICU due to limited ICU capacity [13]. We also analyzed the score performances in multiple ways: as continuous scores, continuous scores added to baseline risk, and as dichotomous values. In addition, the retrospective multi-site LMIC qSOFA validation included a cohort from the emergency department of our hospital [15]; our cohort and that cohort showed similarly modest predictive capacity for the continuous qSOFA score without baseline model, providing criterion validity to our results (AUROC 0.55 in the multisite study and 0.65 in this study). Finally, other than one small study confined to emergency department patients and with a low (5%) mortality rate [23], our study is the first to assess the UVA score outside of its LMIC derivation cohort [13].

Our study also has several limitations. We conducted it in a single tertiary care hospital in sub-Saharan Africa, so its results may not be generalizable. Even more complex severity of illness scores derived from much larger populations, such as the APACHE score for ICU patients in HICs, have quite variable performance, requiring recalibration for different populations and over time in the same population [12, 28, 29]. Of note, in the retrospective study of qSOFA in nine LMIC cohorts, the

AUROC for all combined sites without the baseline model was 0.69, but the AUROC range for individual sites was wide, from 0.55 to 0.81 [15]. Second, the variables used to calculate the scores for patients in our study were recorded from different time points (time of fever, operation, or culture sample retrieval) depending on the inclusion criteria each participant met for the study. While this variability likely diminishes the capacity of the scores to predict mortality, it also simulates how the scores might be used in practice. Nonetheless, it is possible the scores would perform better with more consistent data collection time points. Third, oxygen saturation was included as a variable, without oxygen delivery; this was a feature of the UVA score design, but it nonetheless seems likely that oxygen saturation without oxygen delivery will be more limited in its predictive power. Fourth, we had some missing data, up to 11.7% for oxygen saturation, for which we assumed normal values; however, the missingness was relatively low compared to many other LMIC studies [1, 12] and reflects reasonable real-world data availability. Finally, we were unable to evaluate the original MEWS score since we did not have detailed mental status data; we used an adapted MEWS with a binary version of the mental status variable.

CONCLUSIONS

Our study found modest predictive power of adjusted MEWS, qSOFA, and UVA scores in our cohort of inpatients with suspected infection at a Rwandan tertiary hospital. These modest predictive performances must be acknowledged if these scores are to be considered for use in research comparisons, quality improvement, or clinical decision-making.

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Figure Legends

Figure 1. Distribution of Patients (A) and Observed Mortality (B) with standard errors by adapted Modified Early Warning Score (MEWS), Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Score and Universal Vital Assessment (UVA) Among Patients With Suspected Infection

Figure 2. Receiver Operating Characteristic Curves for adapted MEWS, qSOFA, or UVA Criteria as Continuous Variables

Table 1. Variables and values in adapted MEWS, qSOFA, and UVA scores

	Adapted MEWS‡		qSOFA		UVA	
	Cutoff	*Points*	*Cutoff*	*Points*	*Cutoff*	*Points*
Respiratory rate *(*breaths per minute)	15-20	1	≥ 22	1	≥ 30	1
	21-29 or < 9	2				
	≥ 30	3				
Altered mental status (GCS<15)	Present	2	Present	1	Present	4
Systolic blood pressure (mmHg)	81–100	1	≤ 100	1	< 90	1
	71–80 or ≥ 200	2				
	≤ 70	3				
Temperature (°C)	≥ 38.5	1			< 36	2
	< 35	2				
Heart rate (beats per minute)	101-110 or 41-50	1			≥ 120	1
	111-129 or < 40	2				
	≥ 130	3				
Oxygen saturation (%)					< 92	2
HIV seropositivity					Present	2

‡The adaptation to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points for a patient with any altered mental status

Table 2. Characteristics of hospital patients with suspected infection

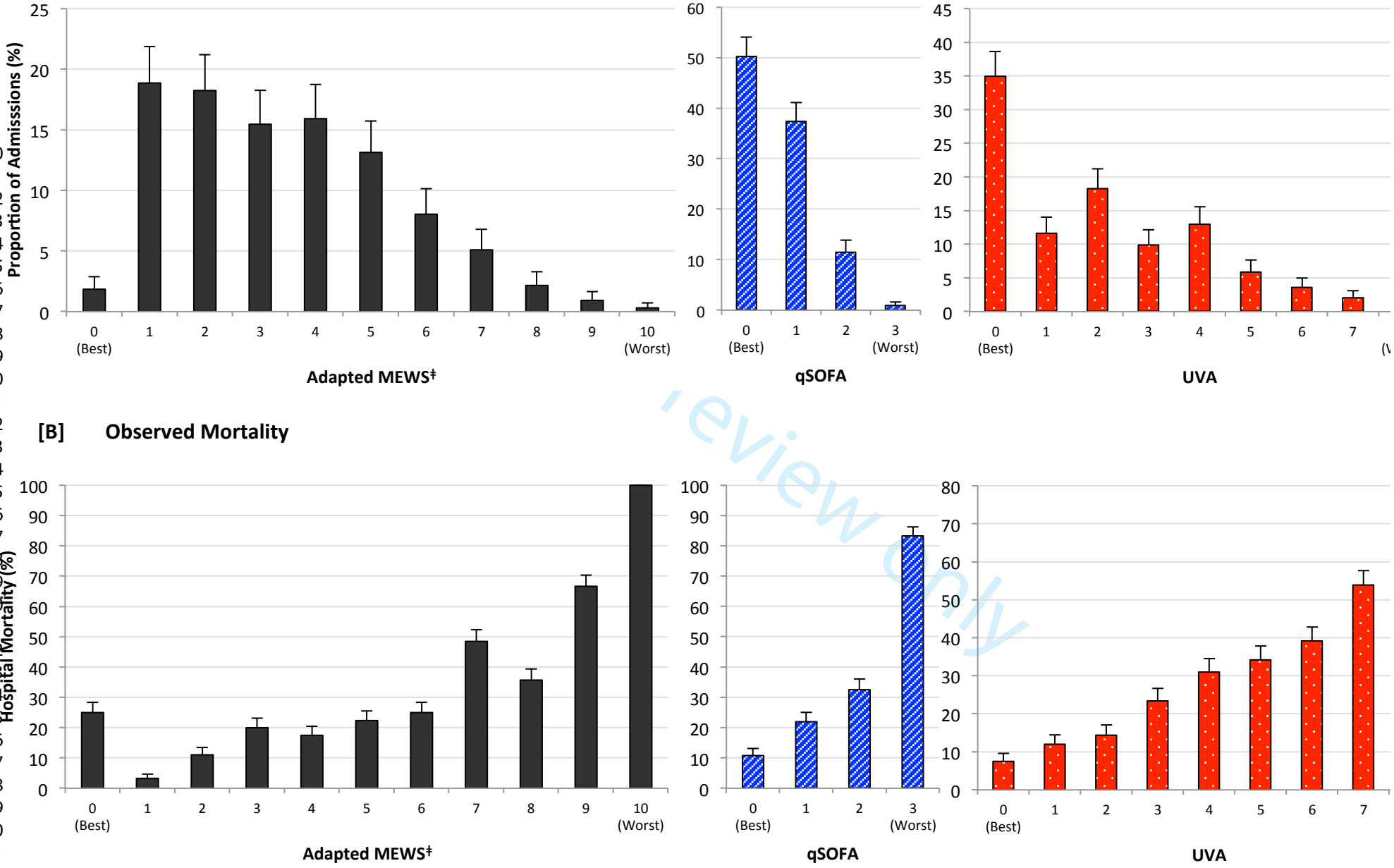
	Total *N = 647*	Survivors *N = 530*	Non-survivors *N = 117*	P-value
Demographics				
Age, median (IQR)	35.0 (27.0, 51.0)	35.0 (27.0, 51.0)	36.0 (27.0, 56.0)	0.46
Male Sex, n (%)	347 (53.63)	273 (51.51)	74 (63.25)	0.02
HIV positive, n (%)	68 (10.51)	52 (9.81)	16 (13.68)	0.22
Other known pre-existing co-morbidity*, n (%)	143 (22.10)	106 (20.00)	37 (31.62)	0.01
Any positive bacterial culture, n (%)	273 (42.19)	223 (42.08)	50 (42.74)	0.90
Transferred from an outside hospital	414 (63.99)	342 (64.53)	72 (61.54)	0.54
Adapted‡ MEWS Components				
Respiratory Rate, *beats/minute*				0.0002
15-20	417 (64.45)	361 (68.11)	56 (47.86)	
21-29 or < 9	122 (18.86)	94 (17.74)	28 (23.93)	
≥ 30	36 (5.56)	24 (4.53)	12 (10.26)	
Altered Mental Status	150 (23.18)	92 (17.36)	58 (49.57)	< 0.0001
Systolic Blood Pressure, *mmHg*				0.13
81–100	97 (14.99)	81 (15.28)	16 (13.68)	
71–80 or ≥ 200	12 (1.85)	10 (1.89)	2 (1.71)	
≤ 70	5 (0.77)	2 (0.38)	3 (2.56)	
Temperature				
≥ 38.5°C	309 (47.76)	238 (44.91)	71 (60.68)	0.002
< 35°C	0 (0)	0 (0)	0 (0)	---
Heart Rate, *beats/minute*				< 0.0001
101-110 or 41-50	98 (15.15)	76 (14.34)	22 (18.80)	
111-129 or < 40	177 (27.36)	136 (25.66)	41 (35.04)	
≥ 130	86 (13.29)	61 (11.51)	25 (21.37)	
Adapted MEWS > 4	192 (29.68)	133 (25.09)	59 (50.43)	< 0.0001
qSOFA Components				
Altered Mental Status	150 (23.18)	92 (17.36)	58 (49.57)	< 0.0001
Systolic Blood Pressure ≤ 100	112 (17.31)	91 (17.17)	21 (17.95)	0.84
Respiratory Rate ≥ 22	147 (22.72)	110 (20.75)	37 (31.62)	0.01
qSOFA ≥ 2	81 (12.52)	52 (9.81)	29 (24.79)	< 0.0001
UVA Components				
Temperature < 36°C	12 (1.85)	12 (2.26)	0 (0)	0.10
Heart Rate ≥ 120	175 (27.05)	129 (24.34)	46 (39.32)	0.001
Respiratory Rate ≥ 30	37 (5.72)	25 (4.72)	12 (10.26)	0.02
Systolic Blood Pressure < 90 mmHg	37 (5.72)	29 (5.47)	8 (6.84)	0.56
Oxygen Saturation < 92%	149 (23.03)	118 (22.26)	31 (26.50)	0.33
Altered Mental Status	150 (23.18)	92 (17.36)	58 (49.57)	< 0.0001
HIV positive	68 (10.51)	52 (9.81)	16 (13.68)	0.22
UVA > 4	80 (12.36)	47 (8.87)	33 (28.21)	< 0.0001

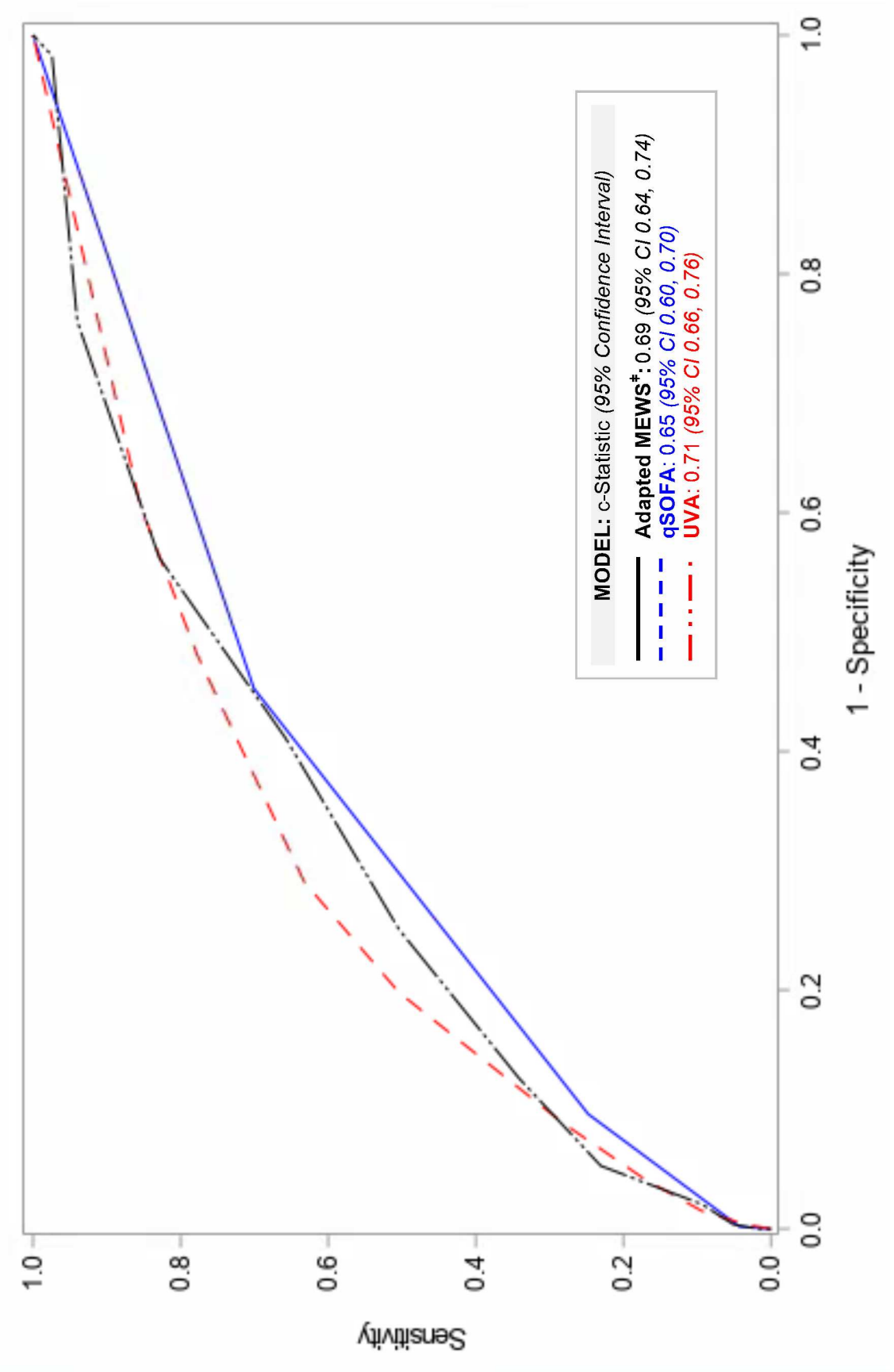
* Includes patients who had any of the following documented co-morbidities: diabetes, hypertension, tuberculosis, cancer, and/or severe malnutrition.

‡ The adaptation to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points for a patient with any altered mental status.

Table 3. Predictive capacity of apted MEWS, qSOFA and UVA scores			
	Adapted MEWS‡ > 4	**qSOFA ≥ 2**	**UVA > 4**
Unadjusted			
Sensitivity	50.43	24.79	28.21
Specificity	74.91	90.38	91.13
Positive predictive value	30.73	36.25	41.25
Negative predictive value	87.25	84.48	85.19
OR (95% Confidence Interval)	3.04 (2.01, 4.59)	3.10 (1.86, 5.15)	4.04 (2.44, 6.67)

‡The adaptation to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points for a patient with any altered mental status.

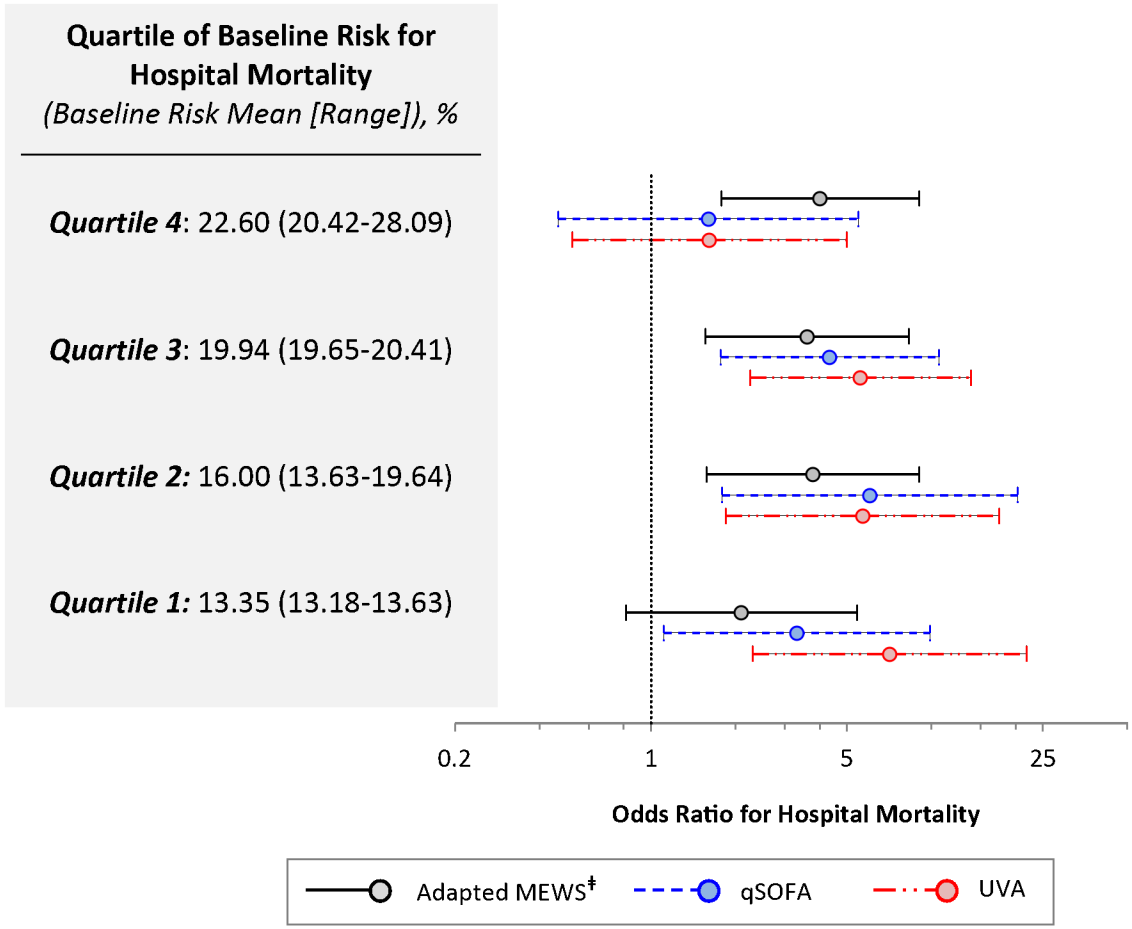



MODEL: c-Statistic (95% Confidence Interval)
Adapted MEWS*: 0.69 (95% CI 0.64, 0.74)
qSOFA: 0.65 (95% CI 0.60, 0.70)
UVA: 0.71 (95% CI 0.66, 0.76)
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0

Supplemental Table 1. Number and proportion of missing values for each variable	
	Total *N = 647*
Variable	
Age, years	7 (1.08)
Male Sex	0 (0)
HIV positive	0 (0)
Other known pre-existing co-morbidity*	0 (0)
Any positive bacterial culture	0 (0)
Respiratory Rate, breaths/minute	58 (8.96)
Altered Mental Status	0 (0)
Systolic Blood Pressure, mmHg	15 (2.32)
Temperature, °C	2 (0.31)
Heart Rate, beats/minute	17 (2.63)
Oxygen Saturation, %	76 (11.75)
Transfer Status	10 (1.55)

Data is reported as the frequency and proportion of missing data.
* Includes patients who had any of the following documented co-morbidities: diabetes, hypertension, tuberculosis, cancer, and/or severe malnutrition.

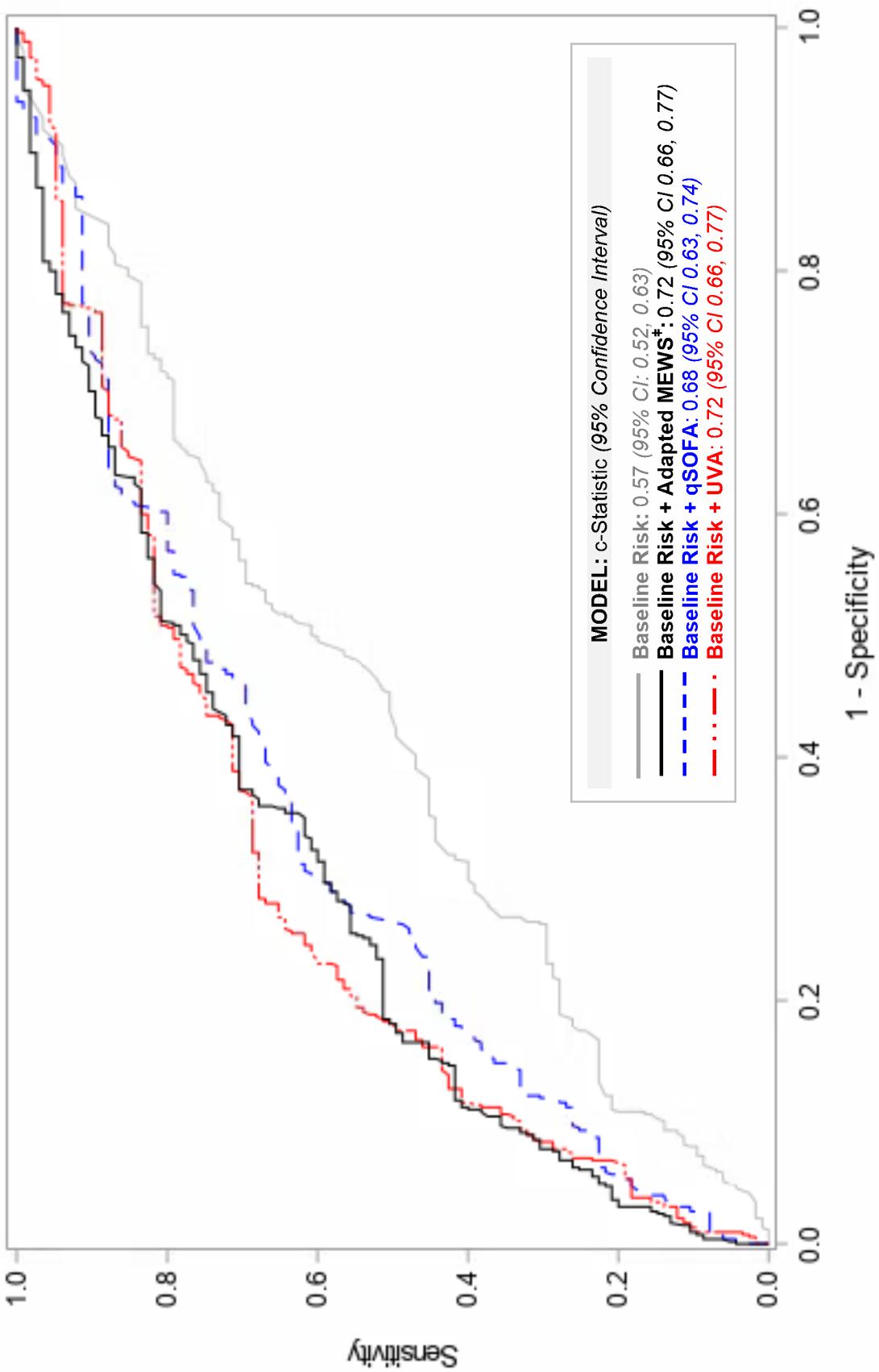
Supplemental Figure 1. Odds Ratios for Hospital Mortality.



Odds ratio for hospital mortality (log-scale) comparing encounters with > 4 vs ≤ 4 adapted MEWS, ≥2 vs <2 qSOFA points, and >4 vs ≤ 4 UVA, and criteria among patients with suspected infection by quartile of baseline risk for hospital mortality. Baseline risk is calculated using age, gender, HIV status and transfer status. Error bars indicate 95% CIs.

‡The adaption to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points for a patient with any altered mental status.

Supplemental Table 2. Model Estimates from Figure 2 (Receiver Operating Characteristic Curves for adapted MEWS, qSOFA, or UVA Criteria as Continuous Variables)				
	Parameter	**Standard Error**	**Odds Ratio (95% CI)**	**P-Value**
MODEL 1 – adapted MEWS				
Intercept	-2.8458	0.2443	---	<0.0001
MEWS *(per 1 point increase)*	0.3445	0.0515	1.411 (1.276, 1.561)	<0.0001
MODEL 2 - qSOFA				
Intercept	-2.1088	0.1597	---	<0.0001
qSOFA *(per 1 point increase)*	0.7891	0.1372	2.201 (1.682, 2.880)	<0.0001
MODEL 3 - UVA				
Intercept	-2.4477	0.1832	---	<0.0001
UVA *(per 1 point increase)*	0.3769	0.0511	1.458 (1.319, 1.611)	<0.0001



Supplemental Figure 2. Receiver Operating Characteristic Curves for adapted MEWS, qSOFA, or UVA Criteria Added to Baseline Risk Model for Hospital Mortality Among Patients With Suspected Infection. Baseline risk is calculated using age, gender, HIV status and transfer status.

Supplemental Table 3. Model Estimates From Supplemental Figure 2 (Receiver Operating Characteristic Curves for adapted MEWS, qSOFA, or UVA Criteria as continuous variables added to Baseline Risk Model)				
	Parameter	**Standard Error**	**Odds Ratio (95% CI)**	**P-Value**
MODEL 1 - baseline				
Intercept	-1.4512	0.2946	---	<0.0001
Age, *per year*	0.000945	0.00624	1.001 (0.989, 1.013)	0.88
Gender *(Male vs Female)*	0.2349	0.1070	1.600 (1.052, 2.433)	0.03
HIV *(Yes vs No)*	0.1595	0.1576	1.376 (0.742, 2.552)	0.31
Transfer *(Yes vs No)*	-0.0534	0.1078	0.899 (0.589, 1.371)	0.62
MODEL 2 – adapted MEWS				
Intercept	-3.1376	0.4087	---	<0.0001
Age, *per year*	0.00506	0.00664	1.005 (0.992, 1.018)	0.45
Gender *(Male vs Female)*	0.2819	0.1127	1.757 (1.130, 2.734)	0.01
HIV *(Yes vs No)*	0.0696	0.1667	1.149 (0.598, 2.210)	0.68
Transfer *(Yes vs No)*	-0.1503	0.1147	0.740 (0.472, 1.160)	0.19
MEWS *(per 1 point increase)*	0.3797	0.0537	1.462 (1.316, 1.624)	<0.0001
MODEL 3 - qSOFA				
Intercept	-2.1031	0.3311	---	<.0001
Age, *per year*	0.00131	0.00647	1.001 (0.989, 1.014)	0.84
Gender *(Male vs Female)*	0.2440	0.1105	1.629 (1.056, 2.513)	0.03
HIV *(Yes vs No)*	0.1264	0.1630	1.288 (0.680, 2.439)	0.44
Transfer *(Yes vs No)*	-0.1345	0.1127	0.764 (0.491, 1.188)	0.23
qSOFA *(per 1 point increase)*	0.8381	0.1412	2.312 (1.753, 3.049)	<0.0001
MODEL 4 - UVA				
Intercept	-2.4523	0.3442	---	<0.0001
Age, *per year*	-0.00074	0.00658	0.999 (0.986, 1.012)	0.91
Gender *(Male vs Female)*	0.1395	0.1128	1.322 (0.849, 2.057)	0.22
HIV *(Yes vs No)*	-0.0493	0.1655	0.906 (0.474, 1.733)	0.77
Transfer *(Yes vs No)*	-0.0988	0.1142	0.821 (0.525, 1.284)	0.39
UVA *(per 1 point increase)*	0.3776	0.0524	1.459 (1.316, 1.617)	<0.0001

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6-7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7-8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

8Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Predicting mortality in adults with suspected infection in a Rwandan hospital: an evaluation of the adapted MEWS, qSOFA, and UVA scores

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Title: Predicting mortality in adults with suspected infection in a Rwandan hospital: an evaluation of the adapted MEWS, qSOFA, and UVA scores

Running head: Predicting mortality in a Rwandan hospital

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Competing interests: The authors have no conflicts of interest.

Author contributions: AK, AM, TS, CM, JR, DT, and EDR contributed to study conception and design including methodology. Data acquisition was performed by TS, CM, EN, JPN, ZN, and JR. Analysis was performed by AM and EDR. The first draft of the manuscript was written by AK and EDR, and all authors commented on drafts of the manuscript. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work including accuracy and integrity of the data and analysis.

Word count including abstract: 3,267

Keywords: severity of illness scores, mortality prediction, critical care, low-income country, resource poor settings, Rwanda

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Data sharing: De-identified data is available from the authors upon request.

ABTRACT (word count: 287)

Rationale: Mortality prediction scores are increasingly being evaluated in low and middle income countries (LMICs) for research comparisons, quality improvement, and clinical decision-making. The modified early warning score (MEWS), quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA), and Universal Vital Assessment Score (UVA) use variables that are feasible to obtain, and have demonstrated potential to predict mortality in LMIC cohorts.

Objective: To determine the predictive capacity of adapted MEWS, qSOFA and UVA in a Rwandan hospital.

Design, setting, participants, and outcome measures: We prospectively collected data on all adult patients admitted to a tertiary hospital in Rwanda with suspected infection over seven months. We calculated an adapted MEWS, qSOFA, and UVA score for each participant. The predictive capacity of each score was assessed including sensitivity, specificity, positive and negative predictive value, odds ratio, area under the receiver operating curve (AUROC), and performance by underlying risk quartile.

Results: We screened 19,178 patient-days, and enrolled 647 unique patients. Median age was 35 years, and in-hospital mortality was 18.1%. The proportion of data missing for each variable ranged from 0% to 11.7%. The sensitivities and specificities of the scores were: adapted MEWS >4, 50.4% and 74.9%, respectively; qSOFA≥2, 24.8% and 90.4% respectively; and UVA >4, 28.2% and 91.1% respectively. The scores as continuous variables

demonstrated the following AUROCs: adapted MEWS 0.69 (95% CI 0.64, 0.74), qSOFA 0.65 (95% CI 0.60, 0.70), and UVA 0.71 (95% CI 0.66, 0.76); there was no statistically significant difference between the scores' discriminative capacities.

Conclusions: Three scores demonstrated modest ability to predict mortality in a prospective study of inpatients with suspected infection at a Rwandan tertiary hospital. Careful consideration must be given to their adequacy before using them in research comparisons, quality improvement, or clinical decision-making.

Strengths and limitations of this study

- We evaluated the three severity of illness (SOI) scores in the literature that are most likely to be feasible and predictive in LMIC settings; this includes the first hospital-wide evaluation of UVA, the only score that was developed using LMIC cohorts.
- Many SOI scores are developed and tested in ICU populations while our analysis also includes hospitalized patients outside the ICU; this is important because many critically ill patients in LMICs remain outside the ICU due to resource constraints.
- We analyzed the predictive capacity of the SOI models as both continuous and dichotomous scores and using multiple metrics, including sensitivity, specificity, positive and negative predictive value, odds ratio, area under the receiver operating curve, and performance by underlying risk quartile.
- Vital signs used in the scores were collected at different times in the participants' hospitalizations, depending on how they met inclusion criteria for the study (time of fever, operation, or culture sample retrieval); while this may decrease the predictive capacity of the scores, it also mirrors how the scores might be used in practice.
- The results from this single-center study among adults with suspected infection may not be generalizable to other populations; this variability in predictive capacity is a known challenge in using SOI scores and the reason it is important to validate a score in a particular site before using it.

INTRODUCTION

Multiple mortality prediction models have been developed or validated in low and middle income countries (LMICs) over the last five years [1-11]. The proposed uses of these models include identifying patients at acute risk for deterioration in order to trigger increased levels of care [3, 11-15], more informed allocation of scarce resources [13, 15], benchmarking for quality assessment and quality improvement [1], and controlling for severity of illness in future trials [13, 16, 17]. In addition, updates to definitions of critical illness syndromes, most notably sepsis and acute respiratory distress syndrome (ARDS), have increasingly emphasized definitions that have predictive validity [18, 19].

The modified early warning score (MEWS) was first reported describing 709 medical patients in a district hospital in the United Kingdom in 2001 [20], and was based on an early warning score (EWS) developed and published in an abstract in 1997 [21]. It was created by assigning weighted scores to each vital sign based on severity of the vital sign abnormality, and it has since been tested in multiple LMIC sites [8, 12, 22, 23]. The quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) score was developed as part of an international re-defining of sepsis, using high income country (HIC) hospital administrative data [19] and retrospectively tested in nine sites in low and middle income countries (LMICs); it demonstrated variable predictive capability across these sites [15]. qSOFA was also prospectively tested in a study from an upper middle income country with multiple sites [11]. The Universal Vital Assessment Score (UVA) was recently developed using linear regression in fifteen in-hospital cohorts from six African countries, and showed good predictive capability

across the entire derivation population, with no reporting on its performance in the individual cohorts [13]. It has only been assessed in one small emergency department cohort outside the initial derivation population [23].

All three scores use accessible bedside clinical measures and are therefore appealing for LMIC settings where laboratory values and detailed comorbidity histories are often not available. All three scores have also been developed for hospital ward patients, which is relevant to LMICs, where critically ill patients often remain in general wards due to the scarcity of ICU beds.

We prospectively collected data on all adult hospitalized patients with suspected infection over a seven month period in a study of antimicrobial resistance patterns in a tertiary referral hospital in Rwanda [24]. The current study was planned as part of the original study design, and is a secondary analysis of this data evaluating the predictive capacity of adapted MEWS, qSOFA, and UVA scores for in-hospital mortality in this population.

METHODS

Study oversight

The Institutional Review Board of the University of Rwanda, College of Medicine and Health Sciences in Kigali, Rwanda and the Committee on Clinical Investigations at Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts approved the study. Verbal consent for participation was obtained using a script in the participant's primary language.

Patient and public involvement

This research was performed without explicit patient feedback on the design or implementation. Results will be available to the public through open access publication.

Setting

The study took place at the University Teaching Hospital of Kigali. The hospital is a public academic tertiary referral hospital in Kigali, Rwanda. It is one of three public referral hospitals in a country of approximately twelve million people, with 560 total beds including a 35-bed adult Emergency Department, a seven-bed intensive care unit, a four-bed step-down unit, and approximately 12,000 admissions each year.

Inclusion criteria and data collection

We prospectively enrolled all hospitalized adult patients (age≥15 years, the hospital's cutoff for adult hospital ward admission) with suspected infection between January 25 and August 14, 2017 as part of a study examining antimicrobial resistance patterns [24]. All hospitalized patients were screened for inclusion criteria each day of their hospitalization. We recorded the number of patients screened each day in each area of the hospital; we did not record the number of unique patients screened over the entire study period. Patients met inclusion criteria if they had temperature ≤35.0° C or ≥38.0° C and suspected infection, underwent surgery for an infectious process, or had a positive microbial culture collected by the clinical team. For those who met inclusion criteria and provided consent, demographic and clinical data needed for

each of the scores were collected at one time point from each participant's chart by study research assistants. Vital sign and mental status data to include in the models were collected at the time of fever or hypothermia, the time of surgery, or the time of culture sample collection, depending on the inclusion criteria met for each participant. For patients who met more than one inclusion criteria, the time point for clinical data collection was based on the first inclusion criteria met. Participants were followed through hospital discharge to determine length of stay and in-hospital mortality. All coded data were entered into a secure online database, REDCap (Research Electronic Data Capture; Vanderbilt University, Nashville, TN), which was hosted by BIDMC.

Definitions

MEWS includes five variables, with scores between 0-3 assigned for each variable [20] (Table 1). It yields a maximum score of 14, with a score >4 considered to be high risk for mortality in prior studies [20]. Because we collected altered mental status as a binary variable (present or not), we adapted this variable in the MEWS score to be 0 for normal mental status and 2 for any altered mental status, rather than a range of severity of altered mental statuses from 0-3. qSOFA includes three variables, with one point given to each abnormal value, a maximum score of three, and ≥2 considered high risk [15]. UVA includes seven variables, with variable points given for each abnormality. It yields a maximum score of 13, with >4 considered high risk based on its derivation study [13].

To replicate the methods for predictive validity in the original qSOFA and qSOFA LMIC validation studies [15, 25], we also calculated a

baseline risk model to stratify the population, using the same variables used in these studies: age, sex, HIV status, and hospital transfer status (whether the patient had been transferred from another facility).

Data Analysis

The primary outcome of interest was in-hospital mortality. The sample size was determined based on adequate power for the antimicrobial resistance study from which this cohort was taken, and is described in the methods of that study [24]. Adapted MEWS, qSOFA, and UVA scores were calculated for all enrolled participants. Missing data were assumed to be within normal range, with no additional points assigned. Data are presented as median (interquartile range, IQR) or frequency (proportion) depending on variable type. Normality was assessed with the Shapiro-Wilk test. Demographic differences between survivors and non-survivors were assessed with a Wilcoxon rank-sum test, chi-square or Fisher's Exact test, as appropriate. Sensitivity, specificity, positive and negative predictive values for the previously-reported cutoffs for each score are reported. Separate unadjusted logistic regression models were used to generate odds ratios (OR) and 95% confidence intervals (CI) for adapted MEWS, qSOFA, and UVA. Multivariable logistic regression models using the four variables noted above were calculated for the baseline risk model.

We used the predicted probabilities from our baseline risk model to stratify our results into risk quartiles, presenting ORs and 95% CIs for adapted MEWS, qSOFA and UVA with their previously-defined cutoffs separately, as was done in the original LMIC cohort qSOFA study [15]. We calculated the discriminative ability of adapted MEWS, qSOFA, and UVA as

continuous variables and found the area under the receiver operating characteristic (AUROC) curves for each of these models. We also calculated the discriminative ability of the three scores as continuous variables in models with baseline risk adjustment.

Data analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC) with two-sided p-values < 0.05 considered statistically significant.

RESULTS

We screened every patient in the hospital for suspected infection each day of the study period, for a total of 19,178 patient-days screened. We enrolled 647 of the 648 unique patients who met our criteria for suspected infection; the only exclusion was one patient who met study criteria but declined enrollment. Within this study population, the median age was 35 years (IQR 27, 51) and 347 (53.6%) of participants were male (Table 2). Known pre-existing comorbidities were present in 143 (22.1%) of participants, and 68 (10.5%) of participants were known to be HIV positive. A positive bacterial culture result was identified in 273 (42.2%) of participants.

In the full cohort, the in-hospital mortality rate was 18.1% (117 of 647 participants). An adapted MEWS score of >4 was present in 29.7% (192/647) of cases, qSOFA score of ≥2 was present in 12.5% (81/647) of cases, while a UVA score >4 was present in 12.4% (80/647) of cases (Table 2). The full distribution for each score is shown in Figure 1, with adapted MEWS range 0-10, median 3, IQR 2,5; qSOFA range 0-3, median 0, IQR 0,1; and UVA range 0-8, median 2, IQR 0,4. The proportion of data that was missing

for the components of the scores ranged from 0% to 11.7% (Supplemental Table 1).

The sensitivity and specificity of the adapted MEWS score with cutoff value >4 to predict in-hospital mortality were 50.4% and 74.9%, respectively (Table 3). The sensitivity and specificity of qSOFA with cutoff value ≥2 were 24.8% and 90.4%, respectively. For the UVA score with cutoff value >4, the sensitivity and specificity were 28.2% and 91.1%, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value for each score using the full range of possible cutoff values are presented in Supplemental Table 2. The unadjusted ORs for adapted MEWS>4, qSOFA ≥2 and UVA >4 were 3.04 (95% CI 2.01, 4.59), 3.10 (95% CI 1.86, 5.15) and 4.04 (95% CI 2.44, 6.67), respectively. The OR for hospital mortality was most often >1 for each binary score within each quartile of baseline risk, though the 95% CI for the OR crossed one for qSOFA and UVA in quartile 4, and for adapted MEWS in quartile 1 (Supplemental Figure 1).

Overall, increasing scores for adapted MEWS, qSOFA and UVA corresponded with increasing mortality, though this was not true for every one-point increase in adapted MEWS (Figure 1). For each one point increase in score as a continuous variable, the unadjusted odds ratios were: adapted MEWS 1.41 (95% CI 1.28, 1.56), qSOFA 2.20 (95% CI 1.68, 2.88), and UVA 1.46 (1.32, 1.61) (Supplemental Table 3).

The area under the receiver operating curve (AUROC) for each score as a continuous variable was: adapted MEWS 0.69 (95% CI 0.64, 0.74), qSOFA 0.65 (95% CI 0.60, 0.70), and UVA 0.71 (95% CI 0.66, 0.76) (Figure 2, Supplemental Table 3). There was no statistically significant difference

between the AUROCs for the three scores as pairwise comparisons: UVA versus adapted MEWS p=0.57; UVA versus qSOFA p=0.09; and adapted MEWS versus qSOFA p=0.26).

The AUROC for the baseline risk model was 0.57 (95% CI 0.52, 0.63). Adding adapted MEWS, qSOFA and UVA as continuous variables to the baseline risk model changed the AUROC to 0.72 (95% CI 0.66, 0.77), 0.68 (95% CI 0.63, 0.74), and 0.72 (95% CI 0.66, 0.77), respectively (Supplemental Figure 2, Supplemental Table 4.)

DISCUSSION

In a prospective study of 647 patients with suspected infection in a Rwandan tertiary referral hospital, we found that the adapted MEWS, qSOFA, and UVA scores had modest ability to predict mortality. Using previously defined cutoffs for the each of the scores, adapted MEWS had sensitivity and specificity of 50% and 75% respectively, while qSOFA and UVA were less sensitive but had higher specificity (25% and 90% respectively for qSOFA and 28% and 91% respectively for UVA). AUROCs for the continuous scores ranged from 0.65 to 0.71, with no continuous score's AUROC demonstrating statistically significant superiority to another.

We presented the performance of the three scores using the continuous scores, continuous scores in addition to a baseline risk model, and binary scores using previously defined cutoff values. Depending on the intended use of the scores, any of these might be appropriate in understanding the adequacy of the score. For quality improvement and research comparisons, the AUROC is a useful single value in deciding whether a model can help determine differences in severity of illness between cohorts [13]. For

determining the predictive validity of a definition of sepsis, assessing mortality risk above baseline risk may be most appropriate [15]. For deciding who needs escalation of care, the sensitivity and specificity with a particular cutoff value is likely to be more important in judging the adequacy of the model [11]. Particularly in the latter example, which is the most oft-cited use for scores in LMICs, care must be taken in how the scores are used for individual clinical decision-making since low sensitivity could lead to patients who need additional care being missed and low specificity could lead to attempts at using scarce resources for a relatively large population [11, 26, 27].

Our study has several strengths. We looked at adult patients across the entire hospital rather than the ICU alone [1, 2, 7, 10, 16, 17], which is particularly important in settings where many critically ill patients remain outside the ICU due to limited ICU capacity [13]. We also analyzed the score performances in multiple ways: as continuous scores, continuous scores added to baseline risk, and as dichotomous values. In addition, the retrospective multi-site LMIC qSOFA validation included a cohort from the emergency department of our hospital [15]; our cohort and that cohort showed similarly modest predictive capacity for the continuous qSOFA score without baseline model, providing criterion validity to our results (AUROC 0.55 in the multisite study and 0.65 in this study). Finally, other than one small study confined to emergency department patients and with a low (5%) mortality rate [23], our study is the first to assess the UVA score outside of its LMIC derivation cohort [13].

Our study also has several limitations. We conducted it in a single tertiary care hospital in sub-Saharan Africa, so its results may not be

generalizable. Even more complex severity of illness scores derived from much larger populations, such as the APACHE score for ICU patients in HICs, have quite variable performance, requiring recalibration for different populations and over time in the same population [12, 28, 29]. It is reasonable to expect that variations in patient characteristics, management systems, and resources across hospitals would translate to different predictive capacities of scores across hospitals. Of note, in the retrospective study of qSOFA in nine LMIC cohorts, the AUROC for all combined sites without the baseline model was 0.69, but the AUROC range for individual sites was wide, from 0.55 to 0.81 [15]. Second, the variables used to calculate the scores for patients in our study were recorded from different time points (time of fever, operation, or culture sample retrieval) depending on the inclusion criteria each participant met for the study. This likely simulates how the scores might be used in practice; however, it is certainly possible the scores would perform better with more consistent data collection time points. We may also have a survivor bias of unknown direction since patients who died rapidly after admission to the hospital before they could be screened, or who died before infection was suspected, were not included. Third, oxygen saturation was included as a variable, without oxygen delivery; this was a feature of the UVA score design, but it nonetheless seems likely that oxygen saturation without oxygen delivery will be more limited in its predictive power. Fourth, we had some missing data, up to 11.7% for oxygen saturation, for which we assumed normal values; however, the missingness was relatively low compared to many other LMIC studies [1, 12] and reflects reasonable real-world data availability. Fifth, our positive culture rate of 42.2% in this population

is likely artificially high given that one of the inclusion criteria for the study was a positive culture. Finally, we were unable to evaluate the original MEWS score since we did not have detailed mental status data. We used an adapted MEWS with a binary version of the mental status variable without prior validation of this adaptation; these scores could have been over- or under-estimated and therefore impacted the score's capacity to differentiate participants.

CONCLUSIONS

Our study found modest predictive power of adjusted MEWS, qSOFA, and UVA scores in our cohort of inpatients with suspected infection at a Rwandan tertiary hospital. These modest predictive performances must be acknowledged if these scores are to be considered for use in research comparisons, quality improvement, or clinical decision-making.

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Figure Legends

Figure 1. Distribution of Patients (A) and Observed Mortality (B) with standard errors by adapted Modified Early Warning Score (MEWS), Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Score and Universal Vital Assessment (UVA) Among Patients With Suspected Infection

Figure 2. Receiver Operating Characteristic Curves for adapted MEWS, qSOFA, or UVA Criteria as Continuous Variables

Table 1. Variables and values in adapted MEWS, qSOFA, and UVA scores

	Adapted MEWS‡		qSOFA		UVA	
	Cutoff	*Points*	*Cutoff*	*Points*	*Cutoff*	*Points*
Respiratory rate (breaths per minute)	15-20	1	≥ 22	1	≥ 30	1
	21-29 or < 9	2				
	≥ 30	3				
Altered mental status (GCS<15)	Present	2	Present	1	Present	4
Systolic blood pressure (mmHg)	81–100	1	≤ 100	1	< 90	1
	71–80 or ≥ 200	2				
	≤ 70	3				
Temperature (°C)	≥ 38.5	1			< 36	2
	< 35	2				
Heart rate (beats per minute)	101-110 or 41-50	1			≥ 120	1
	111-129 or < 40	2				
	≥ 130	3				
Oxygen saturation (%)					< 92	2
HIV seropositivity					Present	2

‡The adaptation to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points for a patient with any altered mental status

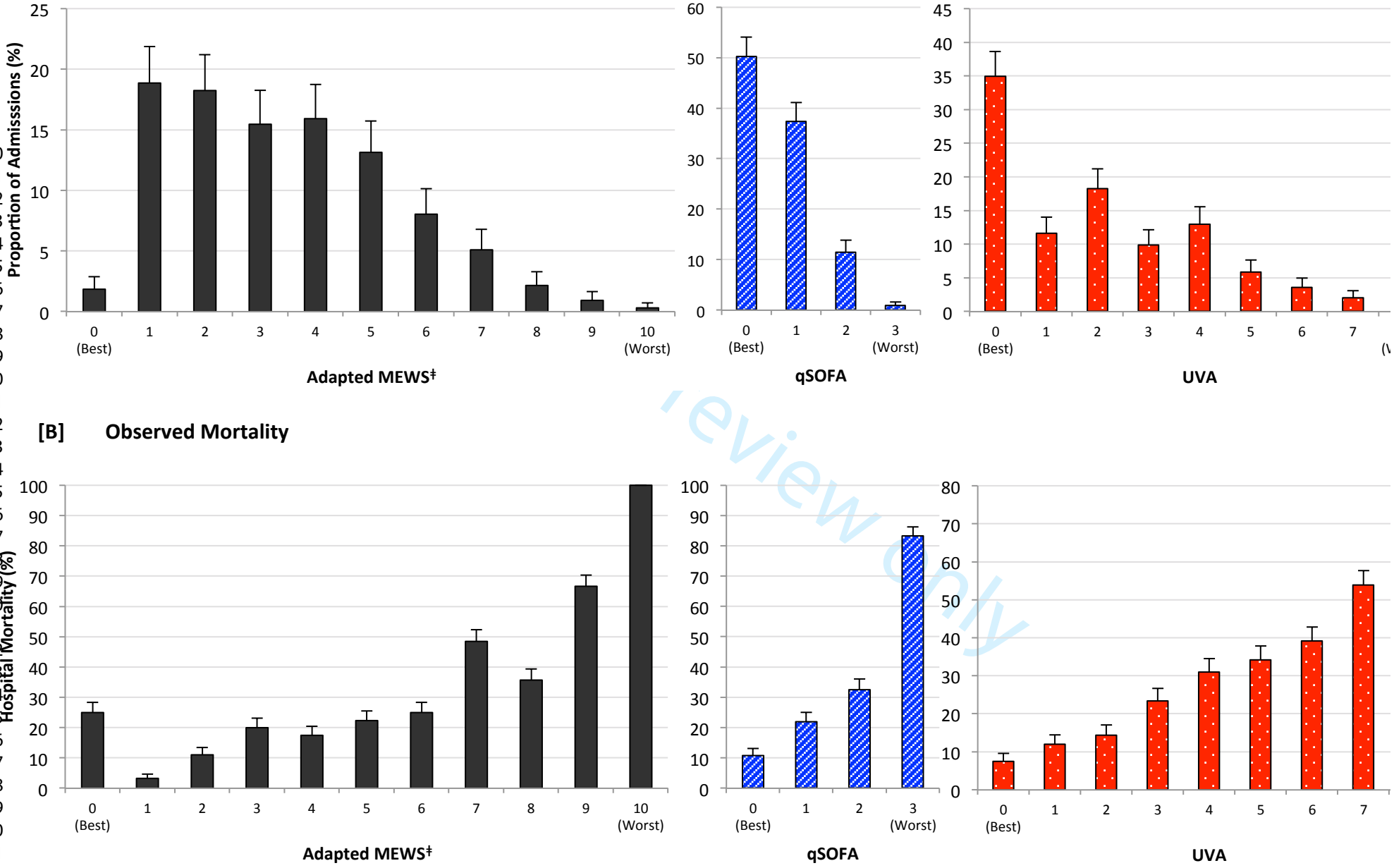
Table 2. Baseline characteristics of patients admitted with suspected infection

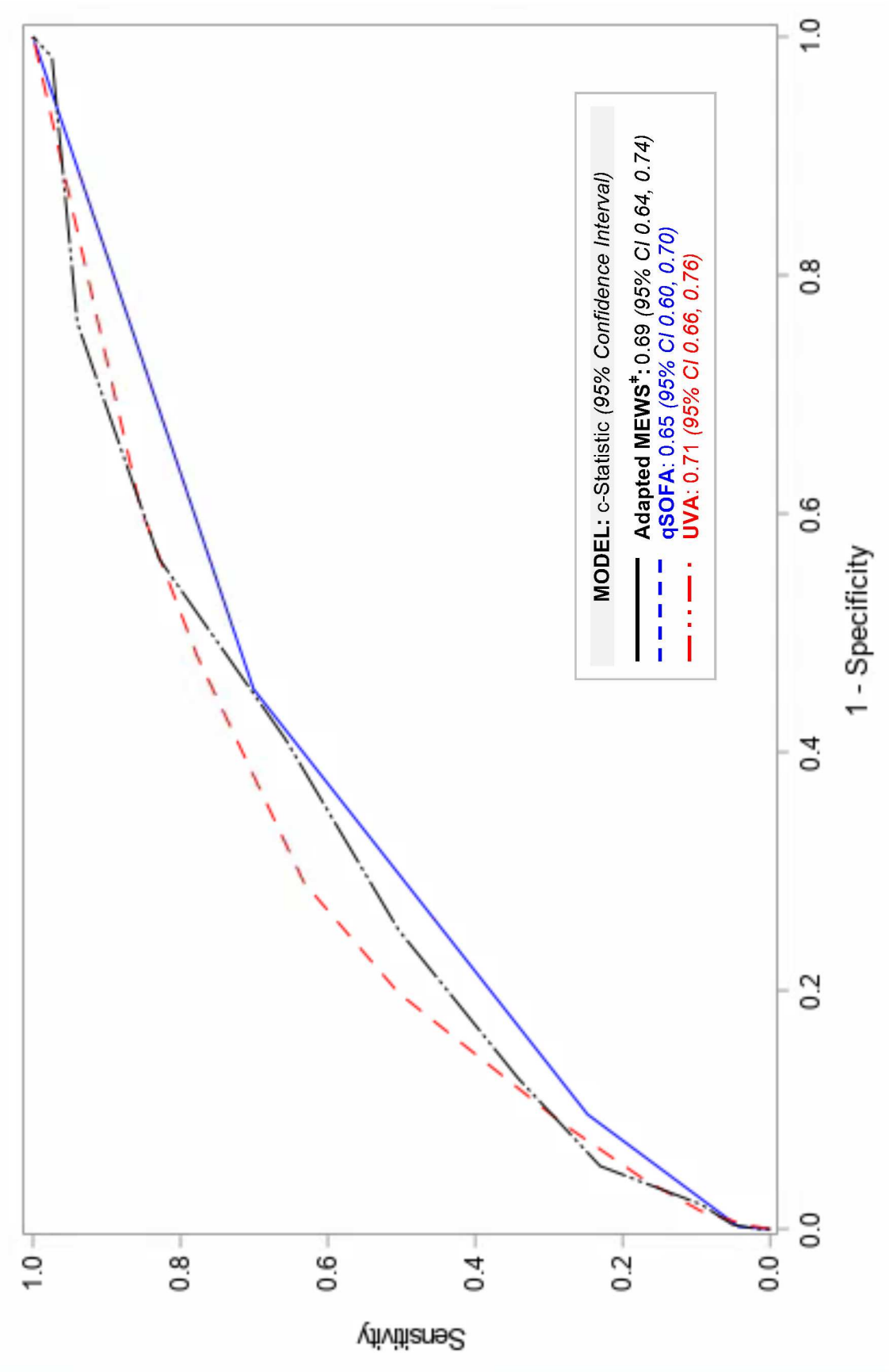
	Total *N = 647*	Survivors *N = 530*	Non-survivors *N = 117*	P-value
Demographics				
Age, median (IQR)	35.0 (27.0, 51.0)	35.0 (27.0, 51.0)	36.0 (27.0, 56.0)	0.46
Male Sex, n (%)	347 (53.63)	273 (51.51)	74 (63.25)	0.02
HIV positive, n (%)	68 (10.51)	52 (9.81)	16 (13.68)	0.22
Other known pre-existing co-morbidity*, n (%)	143 (22.10)	106 (20.00)	37 (31.62)	0.01
Any positive bacterial culture, n (%)	273 (42.19)	223 (42.08)	50 (42.74)	0.90
Transferred from an outside hospital	414 (63.99)	342 (64.53)	72 (61.54)	0.54
Adapted* MEWS Components				
Respiratory Rate, *beats/minute*				0.0002
9-14	72 (11.13)	51 (9.62)	21 (17.95)	
15-20	417 (64.45)	361 (68.11)	56 (47.86)	
21-29 or < 9	122 (18.86)	94 (17.74)	28 (23.93)	
≥ 30	36 (5.56)	24 (4.53)	12 (10.26)	
Altered Mental Status	150 (23.18)	92 (17.36)	58 (49.57)	< 0.0001
Systolic Blood Pressure, *mmHg*				0.13
100-199	533 (82.38)	437 (82.45)	96 (82.05)	
81–100	97 (14.99)	81 (15.28)	16 (13.68)	
71–80 or ≥ 200	12 (1.85)	10 (1.89)	2 (1.71)	
≤ 70	5 (0.77)	2 (0.38)	3 (2.56)	
Temperature				0.002
≥ 38.5°C	309 (47.76)	238 (44.91)	71 (60.68)	
35-38.4°C	338 (52.24)	292 (55.09)	46 (39.32)	
< 35°C	0 (0)	0 (0)	0 (0)	
Heart Rate, *beats/minute*				< 0.0001
51-100	286 (44.20)	257 (48.49)	29 (24.79)	
101-110 or 41-50	98 (15.15)	76 (14.34)	22 (18.80)	
111-129 or < 40	177 (27.36)	136 (25.66)	41 (35.04)	
≥ 130	86 (13.29)	61 (11.51)	25 (21.37)	
Adapted MEWS > 4	192 (29.68)	133 (25.09)	59 (50.43)	< 0.0001
qSOFA Components				
Altered Mental Status	150 (23.18)	92 (17.36)	58 (49.57)	< 0.0001
Systolic Blood Pressure ≤ 100	112 (17.31)	91 (17.17)	21 (17.95)	0.84
Respiratory Rate ≥ 22	147 (22.72)	110 (20.75)	37 (31.62)	0.01
qSOFA ≥ 2	81 (12.52)	52 (9.81)	29 (24.79)	< 0.0001
UVA Components				
Temperature < 36°C	12 (1.85)	12 (2.26)	0 (0)	0.10
Heart Rate ≥ 120	175 (27.05)	129 (24.34)	46 (39.32)	0.001
Respiratory Rate ≥ 30	37 (5.72)	25 (4.72)	12 (10.26)	0.02
Systolic Blood Pressure < 90 mmHg	37 (5.72)	29 (5.47)	8 (6.84)	0.56
Oxygen Saturation < 92%	149 (23.03)	118 (22.26)	31 (26.50)	0.33
Altered Mental Status	150 (23.18)	92 (17.36)	58 (49.57)	< 0.0001
HIV positive	68 (10.51)	52 (9.81)	16 (13.68)	0.22
UVA > 4	80 (12.36)	47 (8.87)	33 (28.21)	< 0.0001

*Includes patients who had any of the following documented co-morbidities: diabetes, hypertension, tuberculosis, cancer, and/or severe malnutrition. ‡The adaption to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points for a patient with any altered mental status.

Table 3. Predictive capacity of adapted MEWS, qSOFA and UVA scores			
	Adapted MEWS[‡] > 4	**qSOFA ≥ 2**	**UVA > 4**
Unadjusted			
Sensitivity	50.43	24.79	28.21
Specificity	74.91	90.38	91.13
Positive predictive value	30.73	36.25	41.25
Negative predictive value	87.25	84.48	85.19
OR (95% Confidence Interval)	3.04 (2.01, 4.59)	3.10 (1.86, 5.15)	4.04 (2.44, 6.67)

[‡]The adaptation to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points for a patient with any altered mental status.




MODEL: c-Statistic (95% Confidence Interval)
Adapted MEWS*: 0.69 (95% CI 0.64, 0.74)
qSOFA: 0.65 (95% CI 0.60, 0.70)
UVA: 0.71 (95% CI 0.66, 0.76)
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0

Supplemental Table 1. Number and proportion of missing values for each variable	
	Total *N = 647*
Variable	
Age, years	7 (1.08)
Male Sex	0 (0)
HIV positive	0 (0)
Other known pre-existing co-morbidity*	0 (0)
Any positive bacterial culture	0 (0)
Respiratory Rate, breaths/minute	58 (8.96)
Altered Mental Status	0 (0)
Systolic Blood Pressure, mmHg	15 (2.32)
Temperature, °C	2 (0.31)
Heart Rate, beats/minute	17 (2.63)
Oxygen Saturation, %	76 (11.75)
Transfer Status	10 (1.55)

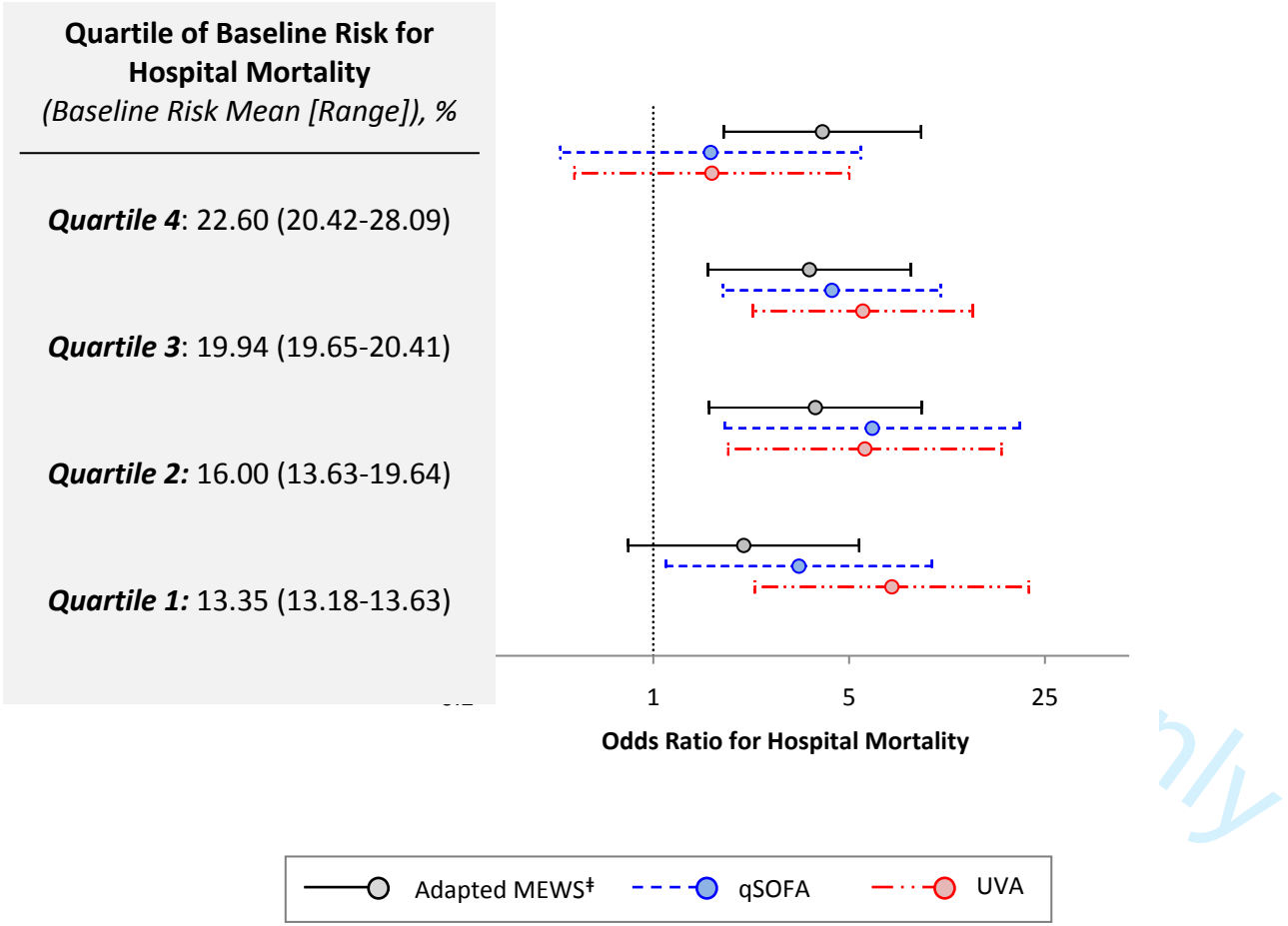
Data is reported as the frequency and proportion of missing data.
* Includes patients who had any of the following documented co-morbidities: diabetes, hypertension, tuberculosis, cancer, and/or severe malnutrition.

Supplemental Table 2. Predictive capacity of differing cutoffs for adapted MEWS, qSOFA and UVA scores

	Sensitivity	Specificity	PPV	NPV
Adapted MEWS‡ Cutoff Values				
Adapted MEWS‡ > 0	97.44	1.70	17.95	75.00
Adapted MEWS‡ > 1	94.02	23.96	21.44	94.78
Adapted MEWS‡ > 2	82.91	43.77	24.56	92.06
Adapted MEWS‡ > 3	65.81	58.87	26.10	88.64
Adapted MEWS‡ > 4	50.43	74.91	30.73	87.25
Adapted MEWS‡ > 5	34.19	87.36	37.38	85.74
Adapted MEWS‡ > 6	23.08	94.72	49.09	84.80
Adapted MEWS‡ > 7	9.40	97.92	50.00	83.04
Adapted MEWS‡ > 8	5.13	99.62	75.00	82.63
Adapted MEWS‡ > 9	1.71	100.00	100.00	82.17
qSOFA Cutoff Values				
qSOFA ≥ 1	70.09	54.72	25.47	89.23
qSOFA ≥ 2	24.79	90.38	36.25	84.48
qSOFA ≥ 3	4.27	99.81	83.33	82.53
UVA Cutoff Values				
UVA > 1	77.78	51.89	26.30	91.36
UVA > 2	63.25	70.94	32.46	89.74
UVA > 3	50.43	80.19	35.98	87.99
UVA > 4	28.21	91.13	41.25	85.19
UVA > 5	17.09	95.85	47.62	83.97
UVA > 6	9.40	98.49	57.89	83.12

‡The adaption to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points for a patient with any altered mental status.
Abbreviations: PPV = positive predictive values; NPV = negative predictive value;

Supplemental Figure 1. Odds Ratios for Hospital Mortality.

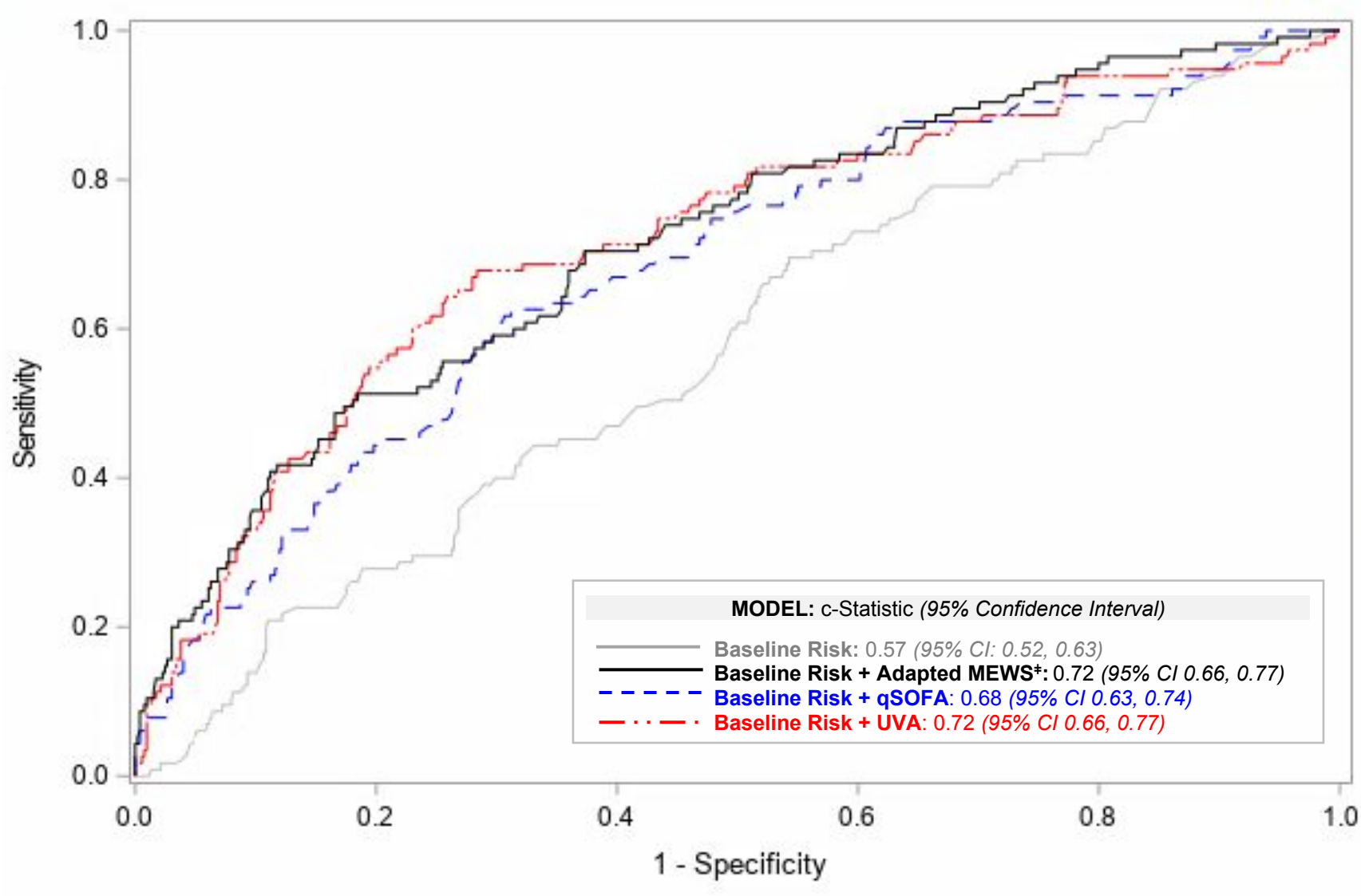


Odds ratio for hospital mortality (log-scale) comparing encounters with > 4 vs ≤ 4 adapted MEWS, ≥2 vs <2 qSOFA points, and >4 vs ≤ 4 UVA, and criteria among patients with suspected infection by quartile of baseline risk for hospital mortality. Baseline risk is calculated using age, gender, HIV status and transfer status. Error bars indicate 95% CIs.

‡The adaption to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points for a patient with any altered mental status.

Supplemental Table 3. Model Estimates from Figure 2 (Receiver Operating Characteristic Curves for adapted MEWS, qSOFA, or UVA Criteria as Continuous Variables)				
	Parameter	**Standard Error**	**Odds Ratio (95% CI)**	**P-Value**
MODEL 1 – adapted MEWS				
Intercept	-2.8458	0.2443	---	<0.0001
MEWS *(per 1 point increase)*	0.3445	0.0515	1.411 (1.276, 1.561)	<0.0001
MODEL 2 - qSOFA				
Intercept	-2.1088	0.1597	---	<0.0001
qSOFA *(per 1 point increase)*	0.7891	0.1372	2.201 (1.682, 2.880)	<0.0001
MODEL 3 - UVA				
Intercept	-2.4477	0.1832	---	<0.0001
UVA *(per 1 point increase)*	0.3769	0.0511	1.458 (1.319, 1.611)	<0.0001

Supplemental Figure 2. Receiver Operating Characteristic Curves for adapted MEWS, qSOFA, or UVA Criteria Added to Baseline Risk Model for Hospital Mortality Among Patients With Suspected Infection. Baseline risk is calculated using age, gender, HIV status and transfer status.



Supplemental Table 4. Model Estimates From Supplemental Figure 2 (Receiver Operating Characteristic Curves for adapted MEWS, qSOFA, or UVA Criteria as continuous variables added to Baseline Risk Model)

	Parameter	Standard Error	Odds Ratio (95% CI)	P-Value
MODEL 1 - baseline				
Intercept	-1.4512	0.2946	---	<0.0001
Age, *per year*	0.000945	0.00624	1.001 (0.989, 1.013)	0.88
Gender *(Male vs Female)*	0.2349	0.1070	1.600 (1.052, 2.433)	0.03
HIV *(Yes vs No)*	0.1595	0.1576	1.376 (0.742, 2.552)	0.31
Transfer *(Yes vs No)*	-0.0534	0.1078	0.899 (0.589, 1.371)	0.62
MODEL 2 – adapted MEWS				
Intercept	-3.1376	0.4087	---	<0.0001
Age, *per year*	0.00506	0.00664	1.005 (0.992, 1.018)	0.45
Gender *(Male vs Female)*	0.2819	0.1127	1.757 (1.130, 2.734)	0.01
HIV *(Yes vs No)*	0.0696	0.1667	1.149 (0.598, 2.210)	0.68
Transfer *(Yes vs No)*	-0.1503	0.1147	0.740 (0.472, 1.160)	0.19
MEWS *(per 1 point increase)*	0.3797	0.0537	1.462 (1.316, 1.624)	<0.0001
MODEL 3 - qSOFA				
Intercept	-2.1031	0.3311	---	<.0001
Age, *per year*	0.00131	0.00647	1.001 (0.989, 1.014)	0.84
Gender *(Male vs Female)*	0.2440	0.1105	1.629 (1.056, 2.513)	0.03
HIV *(Yes vs No)*	0.1264	0.1630	1.288 (0.680, 2.439)	0.44
Transfer *(Yes vs No)*	-0.1345	0.1127	0.764 (0.491, 1.188)	0.23
qSOFA *(per 1 point increase)*	0.8381	0.1412	2.312 (1.753, 3.049)	<0.0001
MODEL 4 - UVA				
Intercept	-2.4523	0.3442	---	<0.0001
Age, *per year*	-0.00074	0.00658	0.999 (0.986, 1.012)	0.91
Gender *(Male vs Female)*	0.1395	0.1128	1.322 (0.849, 2.057)	0.22
HIV *(Yes vs No)*	-0.0493	0.1655	0.906 (0.474, 1.733)	0.77
Transfer *(Yes vs No)*	-0.0988	0.1142	0.821 (0.525, 1.284)	0.39
UVA *(per 1 point increase)*	0.3776	0.0524	1.459 (1.316, 1.617)	<0.0001

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6-7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7-8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

8Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Predicting mortality in adults with suspected infection in a Rwandan hospital: an evaluation of the adapted MEWS, qSOFA, and UVA scores

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Title: Predicting mortality in adults with suspected infection in a Rwandan hospital: an evaluation of the adapted MEWS, qSOFA, and UVA scores

Running head: Predicting mortality in a Rwandan hospital

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Competing interests: The authors have no conflicts of interest.

Author contributions: AK, AM, TS, CM, JR, DT, and EDR contributed to study conception and design including methodology. Data acquisition was performed by TS, CM, EN, JPN, ZN, and JR. Analysis was performed by AM and EDR. The first draft of the manuscript was written by AK and EDR, and all authors commented on drafts of the manuscript. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work including accuracy and integrity of the data and analysis.

Word count including abstract: 3,292

Keywords: severity of illness scores, mortality prediction, critical care, low-income country, resource poor settings, Rwanda

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Data sharing: De-identified data is available from the authors upon request.

ABTRACT (word count: 287)

Rationale: Mortality prediction scores are increasingly being evaluated in low and middle income countries (LMICs) for research comparisons, quality improvement, and clinical decision-making. The modified early warning score (MEWS), quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA), and Universal Vital Assessment Score (UVA) use variables that are feasible to obtain, and have demonstrated potential to predict mortality in LMIC cohorts.

Objective: To determine the predictive capacity of adapted MEWS, qSOFA and UVA in a Rwandan hospital.

Design, setting, participants, and outcome measures: We prospectively collected data on all adult patients admitted to a tertiary hospital in Rwanda with suspected infection over seven months. We calculated an adapted MEWS, qSOFA, and UVA score for each participant. The predictive capacity of each score was assessed including sensitivity, specificity, positive and negative predictive value, odds ratio, area under the receiver operating curve (AUROC), and performance by underlying risk quartile.

Results: We screened 19,178 patient-days, and enrolled 647 unique patients. Median age was 35 years, and in-hospital mortality was 18.1%. The proportion of data missing for each variable ranged from 0% to 11.7%. The sensitivities and specificities of the scores were: adapted MEWS >4, 50.4% and 74.9%, respectively; qSOFA≥2, 24.8% and 90.4% respectively; and UVA >4, 28.2% and 91.1% respectively. The scores as continuous variables

demonstrated the following AUROCs: adapted MEWS 0.69 (95% CI 0.64, 0.74), qSOFA 0.65 (95% CI 0.60, 0.70), and UVA 0.71 (95% CI 0.66, 0.76); there was no statistically significant difference between the scores' discriminative capacities.

Conclusions: Three scores demonstrated modest ability to predict mortality in a prospective study of inpatients with suspected infection at a Rwandan tertiary hospital. Careful consideration must be given to their adequacy before using them in research comparisons, quality improvement, or clinical decision-making.

Strengths and limitations of this study

- We evaluated the three severity of illness (SOI) scores in the literature that are most likely to be feasible and predictive in LMIC settings; this includes the first hospital-wide evaluation of UVA, the only score that was developed using LMIC cohorts.
- Many SOI scores are developed and tested in ICU populations while our analysis also includes hospitalized patients outside the ICU; this is important because many critically ill patients in LMICs remain outside the ICU due to resource constraints.
- We analyzed the predictive capacity of the SOI models as both continuous and dichotomous scores and using multiple metrics, including sensitivity, specificity, positive and negative predictive value, odds ratio, area under the receiver operating curve, and performance by underlying risk quartile.
- Vital signs used in the scores were collected at different times in the participants' hospitalizations, depending on how they met inclusion criteria for the study (time of fever, operation, or culture sample retrieval); while this may decrease the predictive capacity of the scores, it also mirrors how the scores might be used in practice.
- The results from this single-center study among adults with suspected infection may not be generalizable to other populations; this variability in predictive capacity is a known challenge in using SOI scores and the reason it is important to validate a score in a particular site before using it.

INTRODUCTION

Multiple mortality prediction models have been developed or validated in low and middle income countries (LMICs) over the last five years [1-11]. The proposed uses of these models include identifying patients at acute risk for deterioration in order to trigger increased levels of care [3, 11-15], more informed allocation of scarce resources [13, 15], benchmarking for quality assessment and quality improvement [1], and controlling for severity of illness in future trials [13, 16, 17]. In addition, updates to definitions of critical illness syndromes, most notably sepsis and acute respiratory distress syndrome (ARDS), have increasingly emphasized definitions that have predictive validity [18, 19].

The modified early warning score (MEWS) was first reported describing 709 medical patients in a district hospital in the United Kingdom in 2001 [20], and was based on an early warning score (EWS) developed and published in an abstract in 1997 [21]. It was created by assigning weighted scores to each vital sign based on severity of the vital sign abnormality, and it has since been tested in multiple LMIC sites [8, 12, 22, 23]. The quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) score was developed as part of an international re-defining of sepsis, using high income country (HIC) hospital administrative data [19] and retrospectively tested in nine sites in low and middle income countries (LMICs); it demonstrated variable predictive capability across these sites [15]. qSOFA was also prospectively tested in a study from an upper middle income country with multiple sites [11]. The Universal Vital Assessment Score (UVA) was recently developed using linear regression in fifteen in-hospital cohorts from six African countries, and showed good predictive capability

across the entire derivation population, with no reporting on its performance in the individual cohorts [13]. It has only been assessed in one small emergency department cohort outside the initial derivation population [23].

All three scores use accessible bedside clinical measures and are therefore appealing for LMIC settings where laboratory values and detailed comorbidity histories are often not available. All three scores have also been developed for hospital ward patients, which is relevant to LMICs, where critically ill patients often remain in general wards due to the scarcity of ICU beds.

We prospectively collected data on all adult hospitalized patients with suspected infection over a seven month period in a study of antimicrobial resistance patterns in a tertiary referral hospital in Rwanda [24]. The current study was planned as part of the original study design, and is a secondary analysis of this data evaluating the predictive capacity of adapted MEWS, qSOFA, and UVA scores for in-hospital mortality in this population.

METHODS

Study oversight

The Institutional Review Board of the University of Rwanda, College of Medicine and Health Sciences in Kigali, Rwanda and the Committee on Clinical Investigations at Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts approved the study. Verbal consent for participation was obtained using a script in the participant's primary language.

Patient and public involvement

This research was performed without explicit patient feedback on the design or implementation. Results will be available to the public through open access publication.

Setting

The study took place at the University Teaching Hospital of Kigali. The hospital is a public academic tertiary referral hospital in Kigali, Rwanda. It is one of three public referral hospitals in a country of approximately twelve million people, with 560 total beds including a 35-bed adult Emergency Department, a seven-bed intensive care unit, a four-bed step-down unit, and approximately 12,000 admissions each year.

Inclusion criteria and data collection

We prospectively enrolled all hospitalized adult patients (age≥15 years, the hospital's cutoff for adult hospital ward admission) with suspected infection between January 25 and August 14, 2017 as part of a study examining antimicrobial resistance patterns [24]. All hospitalized patients were screened for inclusion criteria each day of their hospitalization. We recorded the number of patients screened each day in each area of the hospital; we did not record the number of unique patients screened over the entire study period. Patients met inclusion criteria if they had temperature ≤35.0° C or ≥38.0° C and suspected infection, underwent surgery for an infectious process, or had a positive microbial culture collected by the clinical team. For those who met inclusion criteria and provided consent, demographic and clinical data needed for

each of the scores were collected at one time point from each participant's chart by study research assistants. Vital sign and mental status data to include in the models were collected at the time of fever or hypothermia, the time of surgery, or the time of culture sample collection, depending on the inclusion criteria met for each participant. For patients who met more than one inclusion criteria, the time point for clinical data collection was based on the first inclusion criteria met. Participants were followed through hospital discharge to determine length of stay and in-hospital mortality. All coded data were entered into a secure online database, REDCap (Research Electronic Data Capture; Vanderbilt University, Nashville, TN), which was hosted by BIDMC.

Definitions

MEWS includes five variables, with scores between 0-3 assigned for each variable [20] (Table 1). It yields a maximum score of 14, with a score >4 considered to be high risk for mortality in prior studies [20]. Because we collected altered mental status as a binary variable (present or not), we adapted this variable in the MEWS score to be 0 for normal mental status and 2 for any altered mental status, rather than a range of severity of altered mental statuses from 0-3. qSOFA includes three variables, with one point given to each abnormal value, a maximum score of three, and ≥2 considered high risk [15]. UVA includes seven variables, with variable points given for each abnormality. It yields a maximum score of 13, with >4 considered high risk based on its derivation study [13].

To replicate the methods for predictive validity in the original qSOFA and qSOFA LMIC validation studies [15, 25], we also calculated a

baseline risk model to stratify the population, using the same variables used in these studies: age, sex, HIV status, and hospital transfer status (whether the patient had been transferred from another facility).

Data Analysis

The primary outcome of interest was in-hospital mortality. The sample size was determined based on adequate power for the antimicrobial resistance study from which this cohort was taken, and is described in the methods of that study [24]. Adapted MEWS, qSOFA, and UVA scores were calculated for all enrolled participants. Missing data were assumed to be within normal range, with no additional points assigned. Data are presented as median (interquartile range, IQR) or frequency (proportion) depending on variable type. Normality was assessed with the Shapiro-Wilk test. Demographic differences between survivors and non-survivors were assessed with a Wilcoxon rank-sum test, chi-square or Fisher's Exact test, as appropriate. Sensitivity, specificity, positive and negative predictive values for the previously-reported cutoffs for each score are reported. Separate unadjusted logistic regression models were used to generate odds ratios (OR) and 95% confidence intervals (CI) for adapted MEWS, qSOFA, and UVA. Multivariable logistic regression models using the four variables noted above were calculated for the baseline risk model.

We used the predicted probabilities from our baseline risk model to stratify our results into risk quartiles, presenting ORs and 95% CIs for adapted MEWS, qSOFA and UVA with their previously-defined cutoffs separately, as was done in the original LMIC cohort qSOFA study [15]. We calculated the discriminative ability of adapted MEWS, qSOFA, and UVA as

continuous variables and found the area under the receiver operating characteristic (AUROC) curves for each of these models. We also calculated the discriminative ability of the three scores as continuous variables in models with baseline risk adjustment.

Data analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC) with two-sided p-values < 0.05 considered statistically significant.

RESULTS

We screened every patient in the hospital for suspected infection each day of the study period, for a total of 19,178 patient-days screened. We enrolled 647 of the 648 unique patients who met our criteria for suspected infection; the only exclusion was one patient who met study criteria but declined enrollment. Within this study population, 497 participants (76.8%) had hypo or hyperthermia and suspected infection, 308 participants (47.6%) underwent surgery for an infectious process, and 273 participants (42.2%) had a positive microbial culture (Supplemental Figure 1). The median age was 35 years (IQR 27, 51) and 347 (53.6%) of participants were male (Table 2). Known pre-existing comorbidities were present in 143 (22.1%) of participants, and 68 (10.5%) of participants were known to be HIV positive.

In the full cohort, the in-hospital mortality rate was 18.1% (117 of 647 participants). An adapted MEWS score of >4 was present in 29.7% (192/647) of cases, qSOFA score of ≥2 was present in 12.5% (81/647) of cases, while a UVA score >4 was present in 12.4% (80/647) of cases (Table 2). The full distribution for each score is shown in Figure 1, with adapted MEWS range 0-10, median 3, IQR 2,5; qSOFA range 0-3, median 0, IQR 0,1; and

UVA range 0-8, median 2, IQR 0,4. The proportion of data that was missing for the components of the scores ranged from 0% to 11.7% (Supplemental Table 1).

The sensitivity and specificity of the adapted MEWS score with cutoff value >4 to predict in-hospital mortality were 50.4% (59/117) and 74.9% (397/530), respectively (Table 3). The sensitivity and specificity of qSOFA with cutoff value ≥2 were 24.8% (29/117) and 90.4% (479/530), respectively. For the UVA score with cutoff value >4, the sensitivity and specificity were 28.2% (33/117) and 91.1% (483/530), respectively. The sensitivity, specificity, positive predictive value, and negative predictive value for each score using the full range of possible cutoff values are presented in Supplemental Table 2. The unadjusted ORs for adapted MEWS>4, qSOFA ≥2 and UVA >4 were 3.04 (95% CI 2.01, 4.59), 3.10 (95% CI 1.86, 5.15) and 4.04 (95% CI 2.44, 6.67), respectively. The OR for hospital mortality was most often >1 for each binary score within each quartile of baseline risk, though the 95% CI for the OR crossed one for qSOFA and UVA in quartile 4, and for adapted MEWS in quartile 1 (Supplemental Figure 2).

Overall, increasing scores for adapted MEWS, qSOFA and UVA corresponded with increasing mortality, though this was not true for every one-point increase in adapted MEWS (Figure 1). For each one point increase in score as a continuous variable, the unadjusted odds ratios were: adapted MEWS 1.41 (95% CI 1.28, 1.56), qSOFA 2.20 (95% CI 1.68, 2.88), and UVA 1.46 (1.32, 1.61) (Supplemental Table 3).

The area under the receiver operating curve (AUROC) for each score as a continuous variable was: adapted MEWS 0.69 (95% CI 0.64, 0.74), qSOFA 0.65 (95% CI 0.60, 0.70), and UVA 0.71 (95% CI 0.66, 0.76) (Figure 2,

Supplemental Table 3). There was no statistically significant difference between the AUROCs for the three scores as pairwise comparisons: UVA versus adapted MEWS p=0.57; UVA versus qSOFA p=0.09; and adapted MEWS versus qSOFA p=0.26).

The AUROC for the baseline risk model was 0.57 (95% CI 0.52, 0.63). Adding adapted MEWS, qSOFA and UVA as continuous variables to the baseline risk model changed the AUROC to 0.72 (95% CI 0.66, 0.77), 0.68 (95% CI 0.63, 0.74), and 0.72 (95% CI 0.66, 0.77), respectively (Supplemental Figure 3, Supplemental Table 4.)

DISCUSSION

In a prospective study of 647 patients with suspected infection in a Rwandan tertiary referral hospital, we found that the adapted MEWS, qSOFA, and UVA scores had modest ability to predict mortality. Using previously defined cutoffs for the each of the scores, adapted MEWS had sensitivity and specificity of 50% and 75% respectively, while qSOFA and UVA were less sensitive but had higher specificity (25% and 90% respectively for qSOFA and 28% and 91% respectively for UVA). AUROCs for the continuous scores ranged from 0.65 to 0.71, with no continuous score's AUROC demonstrating statistically significant superiority to another.

We presented the performance of the three scores using the continuous scores, continuous scores in addition to a baseline risk model, and binary scores using previously defined cutoff values. Depending on the intended use of the scores, any of these might be appropriate in understanding the adequacy of the score. For quality improvement and research comparisons, the AUROC is a useful single value in deciding whether a model can help

determine differences in severity of illness between cohorts [13]. For determining the predictive validity of a definition of sepsis, assessing mortality risk above baseline risk may be most appropriate [15]. For deciding who needs escalation of care, the sensitivity and specificity with a particular cutoff value is likely to be more important in judging the adequacy of the model [11]. Particularly in the latter example, which is the most oft-cited use for scores in LMICs, care must be taken in how the scores are used for individual clinical decision-making since low sensitivity could lead to patients who need additional care being missed and low specificity could lead to attempts at using scarce resources for a relatively large population [11, 26, 27].

Our study has several strengths. We looked at adult patients across the entire hospital rather than the ICU alone [1, 2, 7, 10, 16, 17], which is particularly important in settings where many critically ill patients remain outside the ICU due to limited ICU capacity [13]. We also analyzed the score performances in multiple ways: as continuous scores, continuous scores added to baseline risk, and as dichotomous values. In addition, the retrospective multi-site LMIC qSOFA validation included a cohort from the emergency department of our hospital [15]; our cohort and that cohort showed similarly modest predictive capacity for the continuous qSOFA score without baseline model, providing criterion validity to our results (AUROC 0.55 in the multisite study and 0.65 in this study). Finally, other than one small study confined to emergency department patients and with a low (5%) mortality rate [23], our study is the first to assess the UVA score outside of its LMIC derivation cohort [13].

Our study also has several limitations. We conducted it in a single tertiary care hospital in sub-Saharan Africa, so its results may not be generalizable. Even more complex severity of illness scores derived from much larger populations, such as the APACHE score for ICU patients in HICs, have quite variable performance, requiring recalibration for different populations and over time in the same population [12, 28, 29]. It is reasonable to expect that variations in patient characteristics, management systems, and resources across hospitals would translate to different predictive capacities of scores across hospitals. Of note, in the retrospective study of qSOFA in nine LMIC cohorts, the AUROC for all combined sites without the baseline model was 0.69, but the AUROC range for individual sites was wide, from 0.55 to 0.81 [15]. Second, the variables used to calculate the scores for patients in our study were recorded from different time points (time of fever, operation, or culture sample retrieval) depending on the inclusion criteria each participant met for the study. This likely simulates how the scores might be used in practice; however, it is certainly possible the scores would perform better with more consistent data collection time points. We may also have a survivor bias of unknown direction since patients who died rapidly after admission to the hospital before they could be screened, or who died before infection was suspected, were not included. Third, oxygen saturation was included as a variable, without oxygen delivery; this was a feature of the UVA score design, but it nonetheless seems likely that oxygen saturation without oxygen delivery will be more limited in its predictive power. Fourth, we had some missing data, up to 11.7% for oxygen saturation, for which we assumed normal values; however, the missingness was relatively low compared

to many other LMIC studies [1, 12] and reflects reasonable real-world data availability. Fifth, our positive culture rate of 42.2% in this population is likely artificially high given that one of the inclusion criteria for the study was a positive culture. Finally, we were unable to evaluate the original MEWS score since we did not have detailed mental status data. We used an adapted MEWS with a binary version of the mental status variable without prior validation of this adaptation; these scores could have been over- or under-estimated and therefore impacted the score's capacity to differentiate participants.

CONCLUSIONS

Our study found modest predictive power of adjusted MEWS, qSOFA, and UVA scores in our cohort of inpatients with suspected infection at a Rwandan tertiary hospital. These modest predictive performances must be acknowledged if these scores are to be considered for use in research comparisons, quality improvement, or clinical decision-making.

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Figure Legends

Figure 1. Distribution of Patients (A) and Observed Mortality (B) with standard errors by adapted Modified Early Warning Score (MEWS), Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Score and Universal Vital Assessment (UVA) Among Patients With Suspected Infection

Figure 2. Receiver Operating Characteristic Curves for adapted MEWS, qSOFA, or UVA Criteria as Continuous Variables

Table 1. Variables and values in adapted MEWS, qSOFA, and UVA scores

	Adapted MEWS‡		qSOFA		UVA	
	Cutoff	*Points*	*Cutoff*	*Points*	*Cutoff*	*Points*
Respiratory rate (breaths per minute)	15-20	1	≥ 22	1	≥ 30	1
	21-29 or < 9	2				
	≥ 30	3				
Altered mental status (GCS<15)	Present	2	Present	1	Present	4
Systolic blood pressure (mmHg)	81–100	1	≤ 100	1	< 90	1
	71–80 or ≥ 200	2				
	≤ 70	3				
Temperature (°C)	≥ 38.5	1			< 36	2
	< 35	2				
Heart rate (beats per minute)	101-110 or 41-50	1			≥ 120	1
	111-129 or < 40	2				
	≥ 130	3				
Oxygen saturation (%)					< 92	2
HIV seropositivity					Present	2

‡The adaptation to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points for a patient with any altered mental status

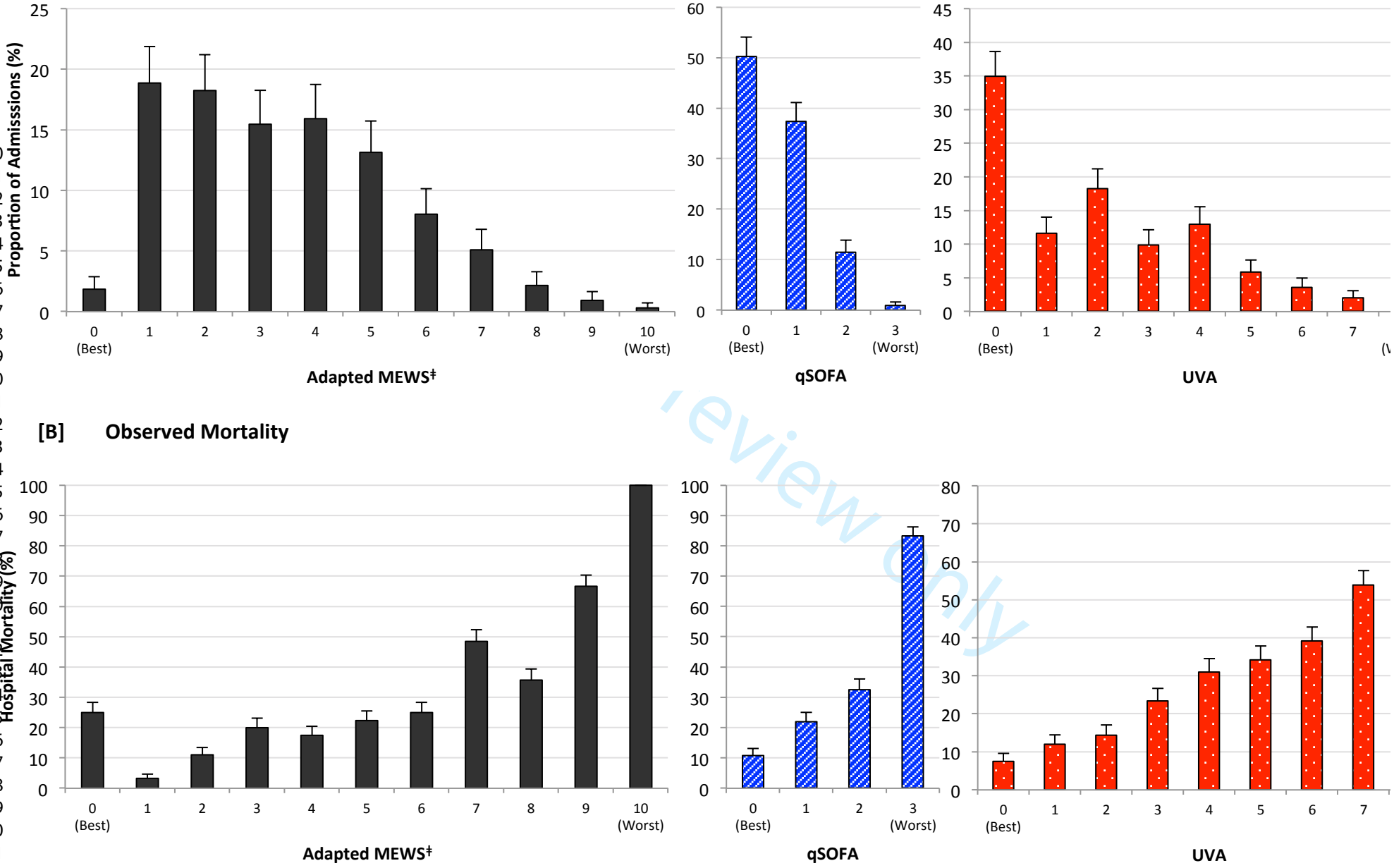
Table 2. Baseline characteristics of patients admitted with suspected infection

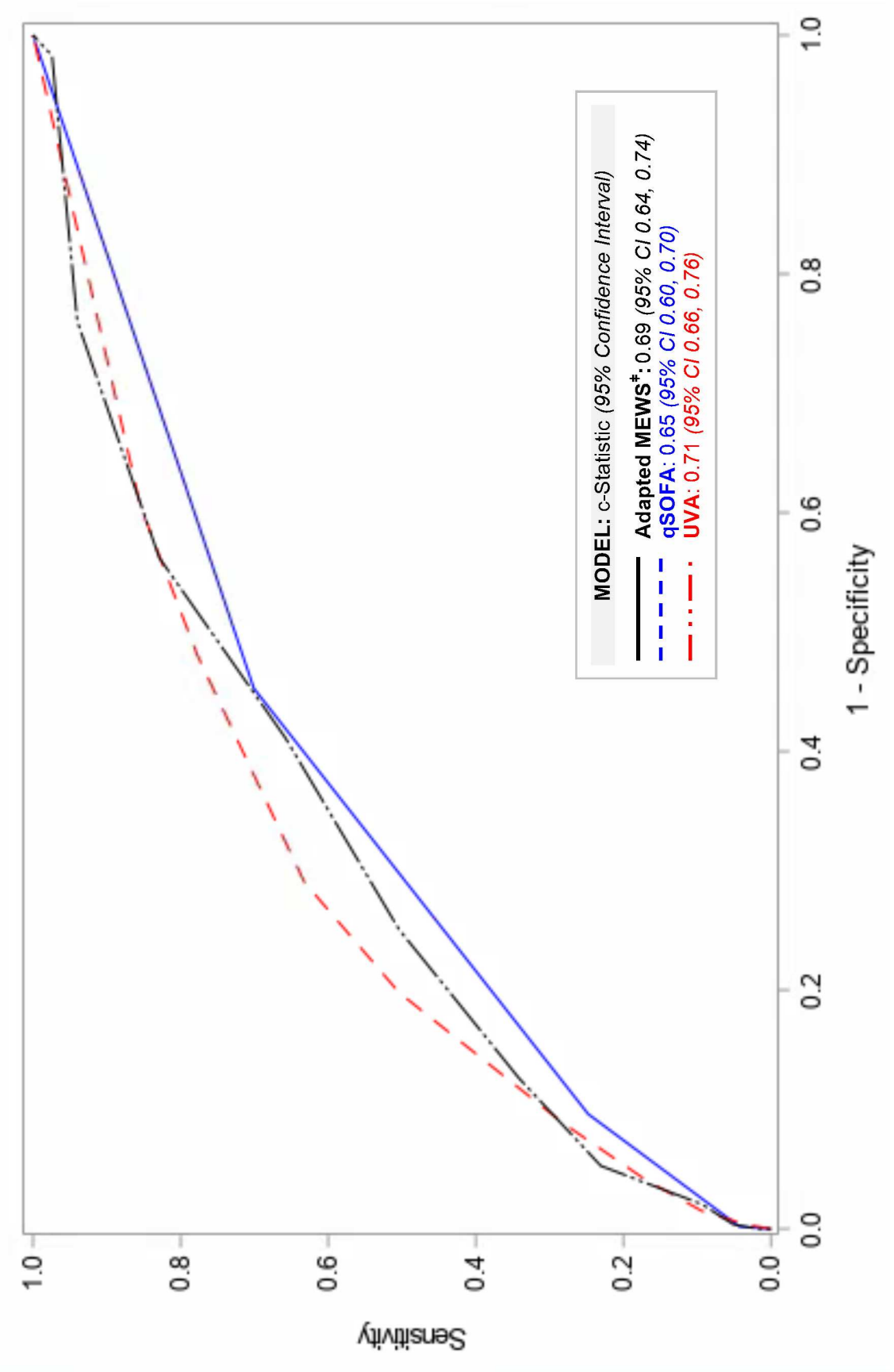
	Total *N = 647*	Survivors *N = 530*	Non-survivors *N = 117*	P-value
Demographics				
Age, median (IQR)	35.0 (27.0, 51.0)	35.0 (27.0, 51.0)	36.0 (27.0, 56.0)	0.46
Male Sex, n (%)	347 (53.6)	273 (51.5)	74 (63.2)	0.02
HIV positive, n (%)	68 (10.5)	52 (9.8)	16 (13.7)	0.22
Other known pre-existing co-morbidity*, n (%)	143 (22.1)	106 (20.0)	37 (31.6)	0.01
Any positive bacterial culture, n (%)	273 (42.2)	223 (42.1)	50 (42.7)	0.90
Transferred from an outside hospital	414 (64.0)	342 (64.5)	72 (61.5)	0.54
Adapted* MEWS Components				
Respiratory Rate, *beats/minute*				0.0002
9-14	72 (11.1)	51 (9.6)	21 (17.9)	
15-20	417 (64.4)	361 (68.1)	56 (47.9)	
21-29 or < 9	122 (18.9)	94 (17.7)	28 (23.9)	
≥ 30	36 (5.6)	24 (4.5)	12 (10.3)	
Altered Mental Status	150 (23.2)	92 (17.4)	58 (49.6)	< 0.0001
Systolic Blood Pressure, *mmHg*				0.13
100-199	533 (82.4)	437 (82.4)	96 (82.0)	
81–100	97 (15.0)	81 (15.3)	16 (13.7)	
71–80 or ≥ 200	12 (1.8)	10 (1.9)	2 (1.7)	
≤ 70	5 (0.8)	2 (0.4)	3 (2.6)	
Temperature				0.002
≥ 38.5°C	309 (47.8)	238 (44.9)	71 (60.7)	
35-38.4°C	338 (52.2)	292 (55.1)	46 (39.3)	
< 35°C	0 (0)	0 (0)	0 (0)	
Heart Rate, *beats/minute*				< 0.0001
51-100	286 (44.2)	257 (48.5)	29 (24.8)	
101-110 or 41-50	98 (15.1)	76 (14.3)	22 (18.8)	
111-129 or < 40	177 (27.4)	136 (25.7)	41 (35.0)	
≥ 130	86 (13.3)	61 (11.5)	25 (21.4)	
Adapted MEWS > 4	192 (29.7)	133 (25.1)	59 (50.4)	< 0.0001
qSOFA Components				
Altered Mental Status	150 (23.2)	92 (17.4)	58 (49.6)	< 0.0001
Systolic Blood Pressure ≤ 100	112 (17.3)	91 (17.2)	21 (17.9)	0.84
Respiratory Rate ≥ 22	147 (22.7)	110 (20.7)	37 (31.6)	0.01
qSOFA ≥ 2	81 (12.5)	52 (9.8)	29 (24.8)	< 0.0001
UVA Components				
Temperature < 36°C	12 (1.8)	12 (2.3)	0 (0)	0.10
Heart Rate ≥ 120	175 (27.0)	129 (24.3)	46 (39.3)	0.001
Respiratory Rate ≥ 30	37 (5.7)	25 (4.7)	12 (10.3)	0.02
Systolic Blood Pressure < 90 mmHg	37 (5.7)	29 (5.5)	8 (6.8)	0.56
Oxygen Saturation < 92%	149 (23.0)	118 (22.3)	31 (26.5)	0.33
Altered Mental Status	150 (23.2)	92 (17.4)	58 (49.6)	< 0.0001
HIV positive	68 (10.5)	52 (9.8)	16 (13.7)	0.22
UVA > 4	80 (12.4)	47 (8.9)	33 (28.2)	< 0.0001

*Includes patients who had any of the following documented co-morbidities: diabetes, hypertension, tuberculosis, cancer, and/or severe malnutrition. ‡The adaption to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points for a patient with any altered mental status.

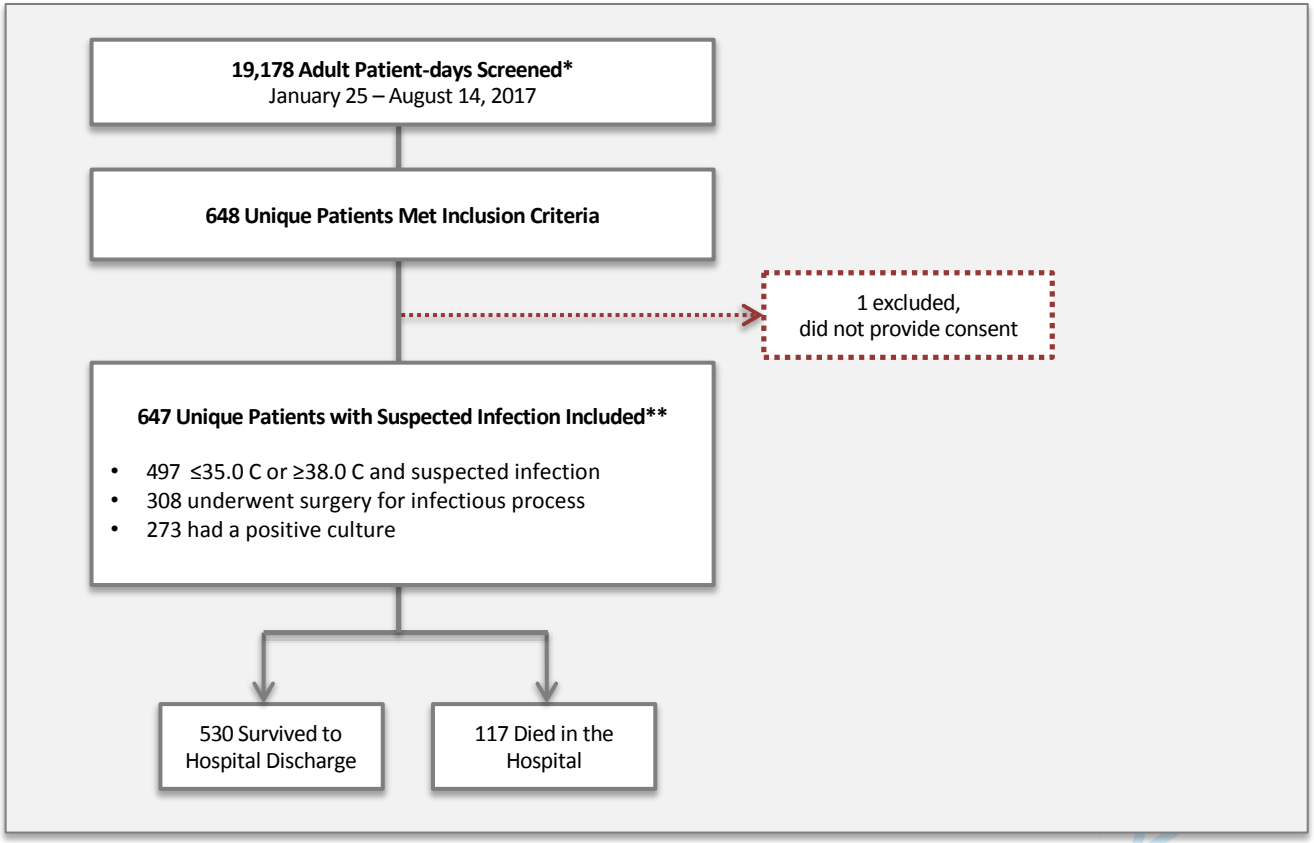
Table 3. Predictive capacity of adapted MEWS, qSOFA and UVA scores			
	Adapted MEWS‡ > 4	**qSOFA ≥ 2**	**UVA > 4**
Unadjusted			
Sensitivity	50.4	24.8	28.2
Specificity	74.9	90.4	91.1
Positive predictive value	30.7	36.2	41.2
Negative predictive value	87.2	84.5	85.2
OR (95% Confidence Interval)	3.04 (2.01, 4.59)	3.10 (1.86, 5.15)	4.04 (2.44, 6.67)

‡The adaptation to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points for a patient with any altered mental status.




MODEL: c-Statistic (95% Confidence Interval)
Adapted MEWS*: 0.69 (95% CI 0.64, 0.74)
qSOFA: 0.65 (95% CI 0.60, 0.70)
UVA: 0.71 (95% CI 0.66, 0.76)
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0

Supplemental Figure 1. The study cohort.



*We screened every adult inpatient each day, and documented the number screened each day. We collected detailed data on patients included in the study with suspected infection. We did not track the number of *unique* patients screened.

**Non-exclusive categories.
For patients who met more than one inclusion criteria, clinical data were recorded based on the first inclusion criteria met: at the time of fever or hypothermia, the time of surgery, or the time of culture sample collection, depending on the inclusion criteria met first for each participant.

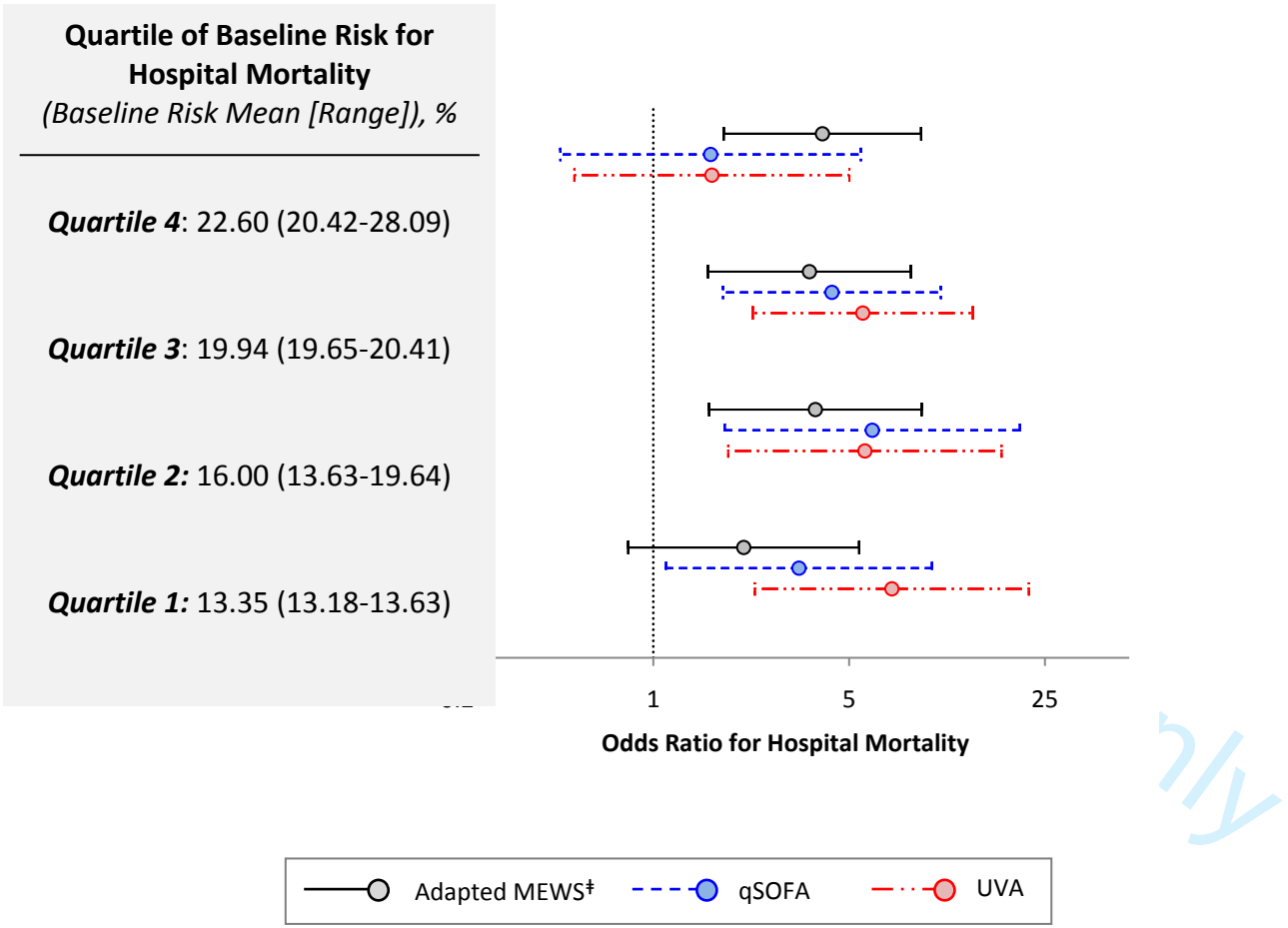
Supplemental Table 1. Number and proportion of missing values for each variable	
	Total *N = 647*
Variable	
Age, years	7 (1.08)
Male Sex	0 (0)
HIV positive	0 (0)
Other known pre-existing co-morbidity*	0 (0)
Any positive bacterial culture	0 (0)
Respiratory Rate, breaths/minute	58 (8.96)
Altered Mental Status	0 (0)
Systolic Blood Pressure, mmHg	15 (2.32)
Temperature, °C	2 (0.31)
Heart Rate, beats/minute	17 (2.63)
Oxygen Saturation, %	76 (11.75)
Transfer Status	10 (1.55)

Data is reported as the frequency and proportion of missing data.
* Includes patients who had any of the following documented co-morbidities: diabetes, hypertension, tuberculosis, cancer, and/or severe malnutrition.

Supplemental Table 2. Predictive capacity of differing cutoffs for adapted MEWS, qSOFA and UVA scores				
	Sensitivity	**Specificity**	**PPV**	**NPV**
Adapted MEWS‡ Cutoff Values				
Adapted MEWS‡ > 0	97.44	1.70	17.95	75.00
Adapted MEWS‡ > 1	94.02	23.96	21.44	94.78
Adapted MEWS‡ > 2	82.91	43.77	24.56	92.06
Adapted MEWS‡ > 3	65.81	58.87	26.10	88.64
Adapted MEWS‡ > 4	50.43	74.91	30.73	87.25
Adapted MEWS‡ > 5	34.19	87.36	37.38	85.74
Adapted MEWS‡ > 6	23.08	94.72	49.09	84.80
Adapted MEWS‡ > 7	9.40	97.92	50.00	83.04
Adapted MEWS‡ > 8	5.13	99.62	75.00	82.63
Adapted MEWS‡ > 9	1.71	100.00	100.00	82.17
qSOFA Cutoff Values				
qSOFA ≥ 1	70.09	54.72	25.47	89.23
qSOFA ≥ 2	24.79	90.38	36.25	84.48
qSOFA ≥ 3	4.27	99.81	83.33	82.53
UVA Cutoff Values				
UVA > 1	77.78	51.89	26.30	91.36
UVA > 2	63.25	70.94	32.46	89.74
UVA > 3	50.43	80.19	35.98	87.99
UVA > 4	28.21	91.13	41.25	85.19
UVA > 5	17.09	95.85	47.62	83.97
UVA > 6	9.40	98.49	57.89	83.12

‡The adaption to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points for a patient with any altered mental status.
Abbreviations: PPV = positive predictive values; NPV = negative predictive value;

Supplemental Figure 2. Odds Ratios for Hospital Mortality.



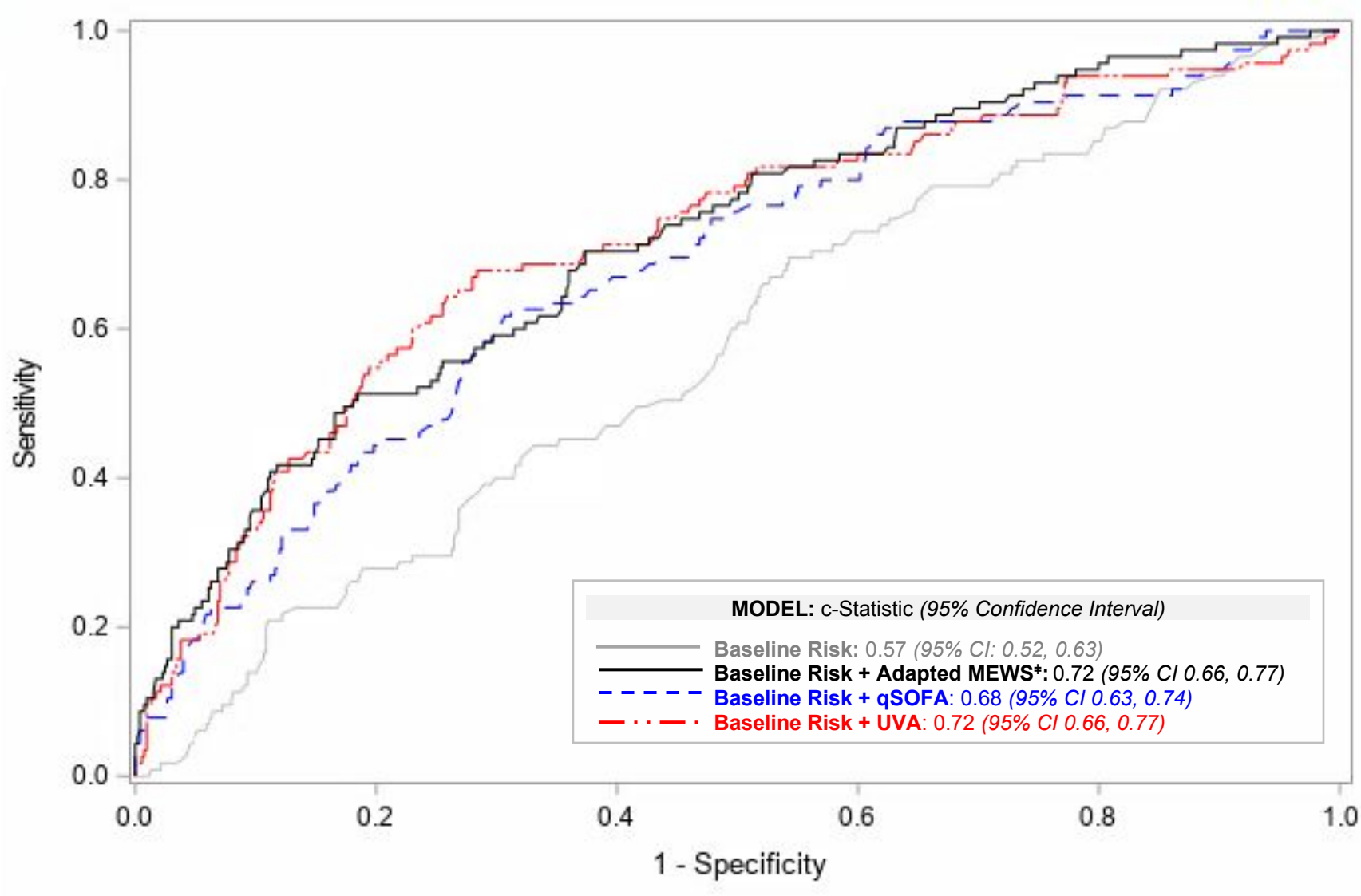
Odds ratio for hospital mortality (log-scale) comparing encounters with > 4 vs ≤ 4 adapted MEWS, ≥2 vs <2 qSOFA points, and >4 vs ≤ 4 UVA, and criteria among patients with suspected infection by quartile of baseline risk for hospital mortality. Baseline risk is calculated using age, gender, HIV status and transfer status. Error bars indicate 95% CIs.

‡The adaption to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points for a patient with any altered mental status.

Supplemental Table 3. Model Estimates from Figure 2 (Receiver Operating Characteristic Curves for adapted MEWS, qSOFA, or UVA Criteria as Continuous Variables)

	Parameter	Standard Error	Odds Ratio (95% CI)	P-Value
MODEL 1 – adapted MEWS				
Intercept	-2.8458	0.2443	---	<0.0001
MEWS *(per 1 point increase)*	0.3445	0.0515	1.411 (1.276, 1.561)	<0.0001
MODEL 2 - qSOFA				
Intercept	-2.1088	0.1597	---	<0.0001
qSOFA *(per 1 point increase)*	0.7891	0.1372	2.201 (1.682, 2.880)	<0.0001
MODEL 3 - UVA				
Intercept	-2.4477	0.1832	---	<0.0001
UVA *(per 1 point increase)*	0.3769	0.0511	1.458 (1.319, 1.611)	<0.0001

Supplemental Figure 3. Receiver Operating Characteristic Curves for adapted MEWS, qSOFA, or UVA Criteria Added to Baseline Risk Model for Hospital Mortality Among Patients With Suspected Infection. Baseline risk is calculated using age, gender, HIV status and transfer status.



Supplemental Table 4. Model Estimates From Supplemental Figure 2 (Receiver Operating Characteristic Curves for adapted MEWS, qSOFA, or UVA Criteria as continuous variables added to Baseline Risk Model)

	Parameter	Standard Error	Odds Ratio (95% CI)	P-Value
MODEL 1 - baseline				
Intercept	-1.4512	0.2946	---	<0.0001
Age, *per year*	0.000945	0.00624	1.001 (0.989, 1.013)	0.88
Gender *(Male vs Female)*	0.2349	0.1070	1.600 (1.052, 2.433)	0.03
HIV *(Yes vs No)*	0.1595	0.1576	1.376 (0.742, 2.552)	0.31
Transfer *(Yes vs No)*	-0.0534	0.1078	0.899 (0.589, 1.371)	0.62
MODEL 2 – adapted MEWS				
Intercept	-3.1376	0.4087	---	<0.0001
Age, *per year*	0.00506	0.00664	1.005 (0.992, 1.018)	0.45
Gender *(Male vs Female)*	0.2819	0.1127	1.757 (1.130, 2.734)	0.01
HIV *(Yes vs No)*	0.0696	0.1667	1.149 (0.598, 2.210)	0.68
Transfer *(Yes vs No)*	-0.1503	0.1147	0.740 (0.472, 1.160)	0.19
MEWS *(per 1 point increase)*	0.3797	0.0537	1.462 (1.316, 1.624)	<0.0001
MODEL 3 - qSOFA				
Intercept	-2.1031	0.3311	---	<.0001
Age, *per year*	0.00131	0.00647	1.001 (0.989, 1.014)	0.84
Gender *(Male vs Female)*	0.2440	0.1105	1.629 (1.056, 2.513)	0.03
HIV *(Yes vs No)*	0.1264	0.1630	1.288 (0.680, 2.439)	0.44
Transfer *(Yes vs No)*	-0.1345	0.1127	0.764 (0.491, 1.188)	0.23
qSOFA *(per 1 point increase)*	0.8381	0.1412	2.312 (1.753, 3.049)	<0.0001
MODEL 4 - UVA				
Intercept	-2.4523	0.3442	---	<0.0001
Age, *per year*	-0.00074	0.00658	0.999 (0.986, 1.012)	0.91
Gender *(Male vs Female)*	0.1395	0.1128	1.322 (0.849, 2.057)	0.22
HIV *(Yes vs No)*	-0.0493	0.1655	0.906 (0.474, 1.733)	0.77
Transfer *(Yes vs No)*	-0.0988	0.1142	0.821 (0.525, 1.284)	0.39
UVA *(per 1 point increase)*	0.3776	0.0524	1.459 (1.316, 1.617)	<0.0001

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6-7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7-8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

8Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.