

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040361
Article Type:	Original research
Date Submitted by the Author:	12-May-2020
Complete List of Authors:	Klinger, Amanda; Beth Israel Deaconess Medical Center Mueller, Ariel; Beth Israel Deaconess Medical Center, Anesthesia; Harvard Medical School Sutherland, Tori; Beth Israel Deaconess Medical Center Mpirimbanyi, Christophe; University of Rwanda - Kigali Campus Nziyomaze, Elie; University of Rwanda College of Medicine and Health Sciences Niyomugabo, Jean-Paul ; University of Rwanda College of Medicine and Health Sciences Niyonsenga , Zack; University of Rwanda College of Medicine and Health Sciences Rickard, Jennifer; University of Minnesota Talmor, Daniel; Beth Israel Deaconess Medical Center, Anesthesiology Riviello, Elisabeth; Harvard University,
Keywords:	International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Authors: Amanda Klinger MD¹, Ariel Mueller MA², Tori Sutherland MD², Christophe Mpirimbanyi MD³, Elie Nziyomaze MD³, Jean-Paul Niyomugabo MD³, Zack Niyonsenga MD³, Jennifer Rickard MD^{3,4}, Daniel Talmor MD², Elisabeth D Riviello MD MPH⁵

Affiliations

1. Department of Medicine, Beth Israel Deaconess Medical Center (BIDMC), Harvard Medical School, Boston, USA
2. Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center (BIDMC), Harvard Medical School, Boston, USA
3. Department of Surgery, Kigali University Teaching Hospital, University of Rwanda, College of Medicine and Health Sciences, School of Medicine and Pharmacy, Kigali, Rwanda
4. Department of Surgery, University of Minnesota, Minneapolis, USA
5. Division of Pulmonary, Critical Care and Sleep Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA

Corresponding author: Elisabeth D. Riviello, beth_riviello@post.harvard.edu, ORCID: 0000-0002-9443-3928

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: 3,061

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

Funding statement: This work was supported by The Beth Israel Anesthesia Foundation and the University of Minnesota Department of Surgery.

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

1
2
3 **ABSTRACT** (word count: 287)
4

5 **Rationale:** Mortality prediction scores are increasingly being evaluated in low and middle income
6 countries (LMICs) for research comparisons, quality improvement, and clinical decision-making. The
7 modified early warning score (MEWS), quick Sequential (Sepsis-Related) Organ Failure Assessment
8 (qSOFA), and Universal Vital Assessment Score (UVA) use variables that are feasible to obtain, and
9 have demonstrated potential to predict mortality in LMIC cohorts.
10
11
12
13
14
15
16
17

18
19
20 **Objective:** To determine the predictive capacity of adapted MEWS, qSOFA and UVA in a Rwandan
21 hospital.
22
23
24
25
26
27

28 **Design, setting, participants, and outcome measures:** We prospectively collected data on all adult
29 patients admitted to a tertiary hospital in Rwanda with suspected infection over seven months. We
30 calculated an adapted MEWS, qSOFA, and UVA score for each participant. The predictive capacity of
31 each score was assessed including sensitivity, specificity, positive and negative predictive value, odds
32 ratio, area under the receiver operating curve (AUROC), and performance by underlying risk quartile.
33
34
35
36
37
38
39
40
41
42

43 **Results:** We screened 19,178 patient-days, and enrolled 647 unique patients. Median age was 35 years,
44 and in-hospital mortality was 18.1%. The proportion of data missing for each variable ranged from
45 0% to 11.7%. The sensitivities and specificities of the scores were: adapted MEWS ≥ 4 , 50.4% and
46 74.9%, respectively; qSOFA ≥ 2 , 24.8% and 90.4% respectively; and UVA ≥ 4 , 28.2% and 91.1%
47 respectively. The scores as continuous variables demonstrated the following AUROCs: adapted
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 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);
4
5
6 there was no statistically significant difference between the scores' discriminative capacities.
7
8
9

10 **Conclusions:** Three scores demonstrated modest ability to predict mortality in a prospective study of
11
12 inpatients with suspected infection at a Rwandan tertiary hospital. Careful consideration must be
13
14 given to their adequacy before using them in research comparisons, quality improvement, or clinical
15
16 decision-making.
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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].

1
2
3 All three scores use accessible bedside clinical measures and are therefore appealing for LMIC
4
5 settings where laboratory values and detailed comorbidity histories are often not available. All three
6
7 scores have also been developed for hospital ward patients, which is relevant to LMICs, where
8
9 critically ill patients often remain in general wards due to the scarcity of ICU beds.
10
11

12
13 We prospectively collected data on all adult hospitalized patients with suspected infection
14
15 over a seven month period in a study of antimicrobial resistance patterns in a tertiary referral hospital
16
17 in Rwanda [24]. The current study was planned as part of the original study design, and is a
18
19 secondary analysis of this data evaluating the predictive capacity of adapted MEWS, qSOFA, and
20
21 UVA scores for in-hospital mortality in this population.
22
23
24
25
26
27

28 **METHODS**

29 **Study oversight**

30
31
32
33 The Institutional Review Board of the University of Rwanda, College of Medicine and Health
34
35 Sciences in Kigali, Rwanda and the Committee on Clinical Investigations at Beth Israel Deaconess
36
37 Medical Center (BIDMC) in Boston, Massachusetts approved the study. Verbal consent for
38
39 participation was obtained using a script in the participant's primary language.
40
41
42
43
44

45 **Patient and public involvement**

46
47 This research was performed without explicit patient feedback on the design or
48
49 implementation. Results will be available to the public through open access publication.
50
51
52
53
54

55 **Setting**

1
2
3 The study took place at the University Teaching Hospital of Kigali. The hospital is a public
4
5 academic tertiary referral hospital in Kigali, Rwanda. It is one of three public referral hospitals in a
6
7 country of approximately twelve million people, with 560 total beds including a 35-bed adult
8
9 Emergency Department, a seven-bed intensive care unit, a four-bed step-down unit, and
10
11 approximately 12,000 admissions each year.
12
13
14
15
16
17

18 **Inclusion criteria and data collection**

19
20 We prospectively enrolled all hospitalized adult patients (age \geq 15 years, the hospital's cutoff
21
22 for adult hospital ward admission) with suspected infection between January 25 and August 14, 2017
23
24 as part of a study examining antimicrobial resistance patterns [24]. All hospitalized patients were
25
26 screened for inclusion criteria each day of their hospitalization. Patients were included if they had
27
28 temperature \leq 35.0° C or \geq 38.0° C and suspected infection, underwent surgery for an infectious
29
30 process, or had a positive microbial culture collected by the clinical team. For those who met inclusion
31
32 criteria, demographic and clinical data needed for each of the scores were collected at one time point
33
34 from each participant's chart by study research assistants. Vital sign and mental status data to include
35
36 in the models were collected at the time of fever or hypothermia, the time of surgery, or the time of
37
38 culture sample collection, depending on the inclusion criteria met for each participant. Participants
39
40 were followed through hospital discharge to determine length of stay and in-hospital mortality. All
41
42 coded data were entered into a secure online database, REDCap (Research Electronic Data Capture;
43
44 Vanderbilt University, Nashville, TN), which was hosted by BIDMC.
45
46
47
48
49
50
51
52
53
54

55 **Definitions**

1
2
3 MEWS includes five variables, with scores between 0-3 assigned for each variable [20] (Table
4
5
6 1). It yields a maximum score of 14, with a score >4 considered to be high risk for mortality in prior
7
8 studies [20]. Because we collected altered mental status as a binary variable (present or not), we
9
10 adapted this variable in the MEWS score to be 0 for normal mental status and 2 for any altered mental
11
12 status, rather than a range of severity of altered mental statuses from 0-3. qSOFA includes three
13
14 variables, with one point given to each abnormal value, a maximum score of three, and ≥ 2 considered
15
16 high risk [15]. UVA includes seven variables, with variable points given for each abnormality. It
17
18 yields a maximum score of 13, with >4 considered high risk based on its derivation study [13].
19
20
21
22

23 To replicate the methods for predictive validity in the original qSOFA and qSOFA LMIC
24
25 validation studies [15, 25], we also calculated a baseline risk model to stratify the population, using
26
27 the same variables used in these studies: age, sex, HIV status, and hospital transfer status (whether
28
29 the patient had been transferred from another facility).
30
31
32
33
34

35 **Data Analysis**

36
37 The primary outcome of interest was in-hospital mortality. The sample size was determined
38
39 based on adequate power for the antimicrobial resistance study from which this cohort was taken,
40
41 and is described in the methods of that study [24]. Adapted MEWS, qSOFA, and UVA scores were
42
43 calculated for all enrolled participants. Missing data were assumed to be within normal range, with
44
45 no additional points assigned. Data are presented as median (interquartile range, IQR) or frequency
46
47 (proportion) depending on variable type. Normality was assessed with the Shapiro-Wilk
48
49 test. Demographic differences between survivors and non-survivors were assessed with a Wilcoxon
50
51 rank-sum test, chi-square or Fisher's Exact test, as appropriate. Sensitivity, specificity, positive and
52
53
54
55
56
57
58
59
60

1
2
3 negative predictive values for the previously-reported cutoffs for each score are reported. Separate
4
5 unadjusted logistic regression models were used to generate odds ratios (OR) and 95% confidence
6
7 intervals (CI) for adapted MEWS, qSOFA, and UVA. Multivariable logistic regression models using
8
9 the four variables noted above were calculated for the baseline risk model.
10
11

12
13 We used the predicted probabilities from our baseline risk model to stratify our results into
14
15 risk quartiles, presenting ORs and 95% CIs for adapted MEWS, qSOFA and UVA with their
16
17 previously-defined cutoffs separately, as was done in the original LMIC cohort qSOFA study [15]. We
18
19 calculated the discriminative ability of adapted MEWS, qSOFA, and UVA as continuous variables and
20
21 found the area under the receiver operating characteristic (AUROC) curves for each of these
22
23 models. We also calculated the discriminative ability of the three scores as continuous variables in
24
25 models with baseline risk adjustment.
26
27
28

29
30 Data analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC) with two-sided p-
31
32 values < 0.05 considered statistically significant.
33
34
35
36
37

38 RESULTS

39
40 We screened every patient in the hospital for suspected infection each day of the study period,
41
42 for a total of 19,178 patient-days screened. We enrolled 647 unique patients with suspected infection;
43
44 only one patient who met study criteria declined enrollment. Within this study population, the
45
46 median age was 35 years (IQR 27, 51) and 53.6% of participants were male (Table 2). Known pre-
47
48 existing comorbidities were present in 22.1% of participants, and 10.5% of participants were known to
49
50 be HIV positive. A positive bacterial culture result was identified in 42.2% of participants.
51
52
53
54
55
56
57
58
59

1
2
3 In the full cohort, the in-hospital mortality rate was 18.1%. An adapted MEWS score of >4 was
4 present in 192 (29.7%) cases, qSOFA score of ≥ 2 was present in 81 (12.5%) cases, while a UVA score >4
5 was present in 80 (12.4%) cases (Table 2). The full distribution for each score is shown in Figure 1,
6 with adapted MEWS range 0-10, median 3, IQR 2,5; qSOFA range 0-3, median 0, IQR 0,1; and UVA
7 range 0-8, median 2, IQR 0,4. The proportion of data that was missing for the components of the
8 scores ranged from 0% to 11.7% (Supplemental Table 1).
9
10
11
12
13
14
15
16
17

18 The sensitivity and specificity of the adapted MEWS score with cutoff value >4 to predict in-
19 hospital mortality were 50.4% and 74.9%, respectively (Table 3). The sensitivity and specificity of
20 qSOFA with cutoff value ≥ 2 were 24.8% and 90.4%, respectively. For the UVA score with cutoff value
21 >4 , the sensitivity and specificity were 28.2% and 91.1%, respectively. The unadjusted ORs for
22 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
23 4.04 (95% CI 2.44, 6.67), respectively. The OR for hospital mortality was most often >1 for each binary
24 score within each quartile of baseline risk, though the 95% CI for the OR crossed one for qSOFA and
25 UVA in quartile 4, and for adapted MEWS in quartile 1 (Supplemental Figure 1).
26
27
28
29
30
31
32
33
34
35
36
37

38 Overall, increasing scores for adapted MEWS, qSOFA and UVA corresponded with increasing
39 mortality, though this was not true for every one-point increase in adapted MEWS (Figure 1). For
40 each one point increase in score as a continuous variable, the unadjusted odds ratios were: adapted
41 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)
42 (Supplemental Table 2).
43
44
45
46
47
48
49

50 The area under the receiver operating curve (AUROC) for each score as a continuous variable
51 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
52 0.66, 0.76) (Figure 2, Supplemental Table 2). There was no statistically significant difference between
53
54
55
56
57
58
59
60

1
2
3 the AUROCs for the three scores as pairwise comparisons: UVA versus adapted MEWS $p=0.57$; UVA
4 versus qSOFA $p=0.09$; and adapted MEWS versus qSOFA $p=0.26$).

5
6
7
8 The AUROC for the baseline risk model was 0.57 (95% CI 0.52, 0.63). Adding adapted MEWS,
9
10 qSOFA and UVA as continuous variables to the baseline risk model changed the AUROC to 0.72
11
12 (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
13
14 Figure 2, Supplemental Table 3.)
15

16 17 18 19 20 **DISCUSSION**

21
22
23 In a prospective study of 647 patients with suspected infection in a Rwandan tertiary referral
24
25 hospital, we found that the adapted MEWS, qSOFA, and UVA scores had modest ability to predict
26
27 mortality. Using previously defined cutoffs for each of the scores, adapted MEWS had sensitivity
28
29 and specificity of 50% and 75% respectively, while qSOFA and UVA were less sensitive but had
30
31 higher specificity (25% and 90% respectively for qSOFA and 28% and 91% respectively for UVA).
32
33 AUROCs for the continuous scores ranged from 0.65 to 0.71, with no continuous score's AUROC
34
35 demonstrating statistically significant superiority to another.
36
37

38
39
40 We presented the performance of the three scores using the continuous scores, continuous
41
42 scores in addition to a baseline risk model, and binary scores using previously defined cutoff values.
43
44 Depending on the intended use of the scores, any of these might be appropriate in understanding the
45
46 adequacy of the score. For quality improvement and research comparisons, the AUROC is a useful
47
48 single value in deciding whether a model can help determine differences in severity of illness
49
50 between cohorts [13]. For determining the predictive validity of a definition of sepsis, assessing
51
52 mortality risk above baseline risk may be most appropriate [15]. For deciding who needs escalation of
53
54
55
56
57
58
59
60

1
2
3 care, the sensitivity and specificity with a particular cutoff value is likely to be more important in
4
5 judging the adequacy of the model [11]. Particularly in the latter example, which is the most oft-cited
6
7 use for scores in LMICs, care must be taken in how the scores are used for individual clinical decision-
8
9 making since low sensitivity could lead to patients who need additional care being missed and low
10
11 specificity could lead to attempts at using scarce resources for a relatively large population [11, 26,
12
13 27].
14
15
16

17
18 Our study has several strengths. We looked at adult patients across the entire hospital rather
19
20 than the ICU alone [1, 2, 7, 10, 16, 17], which is particularly important in settings where many
21
22 critically ill patients remain outside the ICU due to limited ICU capacity [13]. We also analyzed the
23
24 score performances in multiple ways: as continuous scores, continuous scores added to baseline risk,
25
26 and as dichotomous values. In addition, the retrospective multi-site LMIC qSOFA validation included
27
28 a cohort from the emergency department of our hospital [15]; our cohort and that cohort showed
29
30 similarly modest predictive capacity for the continuous qSOFA score without baseline model,
31
32 providing criterion validity to our results (AUROC 0.55 in the multisite study and 0.65 in this study).
33
34 Finally, other than one small study confined to emergency department patients and with a low (5%)
35
36 mortality rate [23], our study is the first to assess the UVA score outside of its LMIC derivation cohort
37
38 [13].
39
40
41
42
43
44

45 Our study also has several limitations. We conducted it in a single tertiary care hospital in sub-
46
47 Saharan Africa, so its results may not be generalizable. Even more complex severity of illness scores
48
49 derived from much larger populations, such as the APACHE score for ICU patients in HICs, have
50
51 quite variable performance, requiring recalibration for different populations and over time in the
52
53 same population [12, 28, 29]. Of note, in the retrospective study of qSOFA in nine LMIC cohorts, the
54
55
56
57
58
59
60

1
2
3 AUROC for all combined sites without the baseline model was 0.69, but the AUROC range for
4
5 individual sites was wide, from 0.55 to 0.81 [15]. Second, the variables used to calculate the scores for
6
7 patients in our study were recorded from different time points (time of fever, operation, or culture
8
9 sample retrieval) depending on the inclusion criteria each participant met for the study. While this
10
11 variability likely diminishes the capacity of the scores to predict mortality, it also simulates how the
12
13 scores might be used in practice. Nonetheless, it is possible the scores would perform better with
14
15 more consistent data collection time points. Third, oxygen saturation was included as a variable,
16
17 without oxygen delivery; this was a feature of the UVA score design, but it nonetheless seems likely
18
19 that oxygen saturation without oxygen delivery will be more limited in its predictive power. Fourth,
20
21 we had some missing data, up to 11.7% for oxygen saturation, for which we assumed normal values;
22
23 however, the missingness was relatively low compared to many other LMIC studies [1, 12] and
24
25 reflects reasonable real-world data availability. Finally, we were unable to evaluate the original
26
27 MEWS score since we did not have detailed mental status data; we used an adapted MEWS with a
28
29 binary version of the mental status variable.
30
31
32
33
34
35
36
37
38
39

40 CONCLUSIONS

41
42
43 Our study found modest predictive power of adjusted MEWS, qSOFA, and UVA scores in our
44
45 cohort of inpatients with suspected infection at a Rwandan tertiary hospital. These modest predictive
46
47 performances must be acknowledged if these scores are to be considered for use in research
48
49 comparisons, quality improvement, or clinical decision-making.
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Acknowledgments: We thank Claude Mambo Muvunyi, Theoneste Nkubana, Emile Musoni, and Jean-Paul Mvukiyehe for their excellent research assistance.

For peer review only

References

1. Haniffa R, Isaam I, De Silva AP, Dondorp AM, De Keizer NF, (2018) Performance of critical care prognostic scoring systems in low and middle-income countries: a systematic review. *Critical care (London, England)* 22: 18
2. Lalani HS, Waweru-Siika W, Mwogi T, Kituyi P, Egger JR, Park LP, Kussin PS, (2018) Intensive Care Outcomes and Mortality Prediction at a National Referral Hospital in Western Kenya. *Annals of the American Thoracic Society* 15: 1336-1343
3. Opio MO, Nansubuga G, Kellett J, (2013) Validation of the VitalPAC Early Warning Score (ViEWS) in acutely ill medical patients attending a resource-poor hospital in sub-Saharan Africa. *Resuscitation* 84: 743-746
4. Aluisio AR, Garbern S, Wiskel T, Mutabazi ZA, Umuhire O, Ch'ng CC, Rudd KE, D'Arc Nyinawankusi J, Byiringiro JC, Levine AC, (2018) Mortality outcomes based on ED qSOFA score and HIV status in a developing low income country. *The American journal of emergency medicine* 36: 2010-2019
5. Khwannimit B, Bhurayanontachai R, Vattanavanit V, (2018) Comparison of the performance of SOFA, qSOFA and SIRS for predicting mortality and organ failure among sepsis patients admitted to the intensive care unit in a middle-income country. *Journal of critical care* 44: 156-160
6. Boillat-Blanco N, Mbarack Z, Samaka J, Mlaganile T, Mamin A, Genton B, Kaiser L, Calandra T, D'Acremont V, (2018) Prognostic value of quickSOFA as a predictor of 28-day mortality among febrile adult patients presenting to emergency departments in Dar es Salaam, Tanzania. *PloS one* 13: e0197982

- 1
2
3 7. Sendagire C, Lipnick MS, Kizito S, Kruisselbrink R, Obua D, Ejoku J, Ssemogerere L,
4 Nakibuuka J, Kwizera A, (2017) Feasibility of the modified sequential organ function
5 assessment score in a resource-constrained setting: a prospective observational study. BMC
6 anesthesiology 17: 12
7
8
9
10
11
12
- 13 8. Carugati M, Zhang HL, Kilonzo KG, Maze MJ, Maro VP, Rubach MP, Crump JA, (2018)
14 Predicting Mortality for Adolescent and Adult Patients with Fever in Resource-Limited
15 Settings. The American journal of tropical medicine and hygiene 99: 1246-1254
16
17
18
19
- 20 9. Baig MA, Sheikh S, Hussain E, Bakhtawar S, Subhan Khan M, Mujtaba S, Waheed S, (2018)
21 Comparison of qSOFA and SOFA score for predicting mortality in severe sepsis and septic
22 shock patients in the emergency department of a low middle income country. Turkish journal
23 of emergency medicine 18: 148-151
24
25
26
27
28
29
- 30 10. Prin M, Pan S, Kadyaudzu C, Li G, Charles A, (2018) Development of a Malawi Intensive care
31 Mortality risk Evaluation (MIME) model, a prospective cohort study. International journal of
32 surgery (London, England) 60: 60-66
33
34
35
36
37
- 38 11. Machado FR, Cavalcanti AB, Monteiro MB, Sousa JL, Bossa A, Bafi AT, Dal-Pizzol F, Freitas
39 FGR, Lisboa T, Westphal GA, Japiassu AM, Azevedo LC, (2020) Predictive Accuracy of the
40 Quick Sepsis-Related Organ Failure Assessment Score in Brazil: A Prospective Multicenter
41 Study. American journal of respiratory and critical care medicine
42
43
44
45
46
47
- 48 12. Beane A, De Silva AP, De Silva N, Sujeewa JA, Rathnayake RMD, Sigera PC, Athapattu PL,
49 Mahipala PG, Rashan A, Munasinghe SB, Jayasinghe KSA, Dondorp AM, Haniffa R, (2018)
50 Evaluation of the feasibility and performance of early warning scores to identify patients at
51 risk of adverse outcomes in a low-middle income country setting. BMJ open 8: e019387
52
53
54
55
56
57
58
59
60

- 1
2
3 13. Moore CC, Hazard R, Saulters KJ, Ainsworth J, Adakun SA, Amir A, Andrews B, Auma M,
4 Baker T, Banura P, Crump JA, Grobusch MP, Huson MAM, Jacob ST, Jarrett OD, Kellett J,
5 Lakhi S, Majwala A, Opio M, Rubach MP, Rylance J, Michael Scheld W, Schieffelin J,
6 Ssekitoleko R, Wheeler I, Barnes LE, (2017) Derivation and validation of a universal vital
7 assessment (UVA) score: a tool for predicting mortality in adult hospitalised patients in sub-
8 Saharan Africa. *BMJ global health* 2: e000344
9
10
11
12
13
14
15
16
17
18 14. Baker T, Schell CO, Lugazia E, Blixt J, Mulungu M, Castegren M, Eriksen J, Konrad D, (2015)
19 Vital Signs Directed Therapy: Improving Care in an Intensive Care Unit in a Low-Income
20 Country. *PloS one* 10: e0144801
21
22
23
24
25
26 15. Rudd KE, Seymour CW, Aluisio AR, Augustin ME, Bagenda DS, Beane A, Byiringiro JC,
27 Chang CH, Colas LN, Day NPJ, De Silva AP, Dondorp AM, Dunser MW, Faiz MA, Grant DS,
28 Haniffa R, Van Hao N, Kennedy JN, Levine AC, Limmathurotsakul D, Mohanty S, Nosten F,
29 Papali A, Patterson AJ, Schieffelin JS, Shaffer JG, Thuy DB, Thwaites CL, Urayeneza O, White
30 NJ, West TE, Angus DC, (2018) Association of the Quick Sequential (Sepsis-Related) Organ
31 Failure Assessment (qSOFA) Score With Excess Hospital Mortality in Adults With Suspected
32 Infection in Low- and Middle-Income Countries. *Jama* 319: 2202-2211
33
34
35
36
37
38
39
40
41
42
43 16. Haniffa R, Mukaka M, Munasinghe SB, De Silva AP, Jayasinghe KSA, Beane A, de Keizer N,
44 Dondorp AM, (2017) Simplified prognostic model for critically ill patients in resource limited
45 settings in South Asia. *Critical care (London, England)* 21: 250
46
47
48
49
50
51 17. Riviello ED, Kiviri W, Fowler RA, Mueller A, Novack V, Banner-Goodspeed VM, Weinkauff JL,
52 Talmor DS, Twagirumugabe T, (2016) Predicting Mortality in Low-Income Country ICUs: The
53 Rwanda Mortality Probability Model (R-MPM). *PloS one* 11: e0155858
54
55
56
57
58
59
60

- 1
2
3 18. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L,
4
5 Slutsky AS, (2012) Acute respiratory distress syndrome: the Berlin Definition. *Jama* 307: 2526-
6
7 2533
8
9
10 19. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R,
11
12 Bernard GR, Chiche JD, Cooper-Smith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS,
13
14 Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC, (2016) The Third International
15
16 Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama* 315: 801-810
17
18
19
20 20. Subbe CP, Kruger M, Rutherford P, Gemmel L, (2001) Validation of a modified Early Warning
21
22 Score in medical admissions. *QJM : monthly journal of the Association of Physicians* 94: 521-
23
24 526
25
26
27
28 21. Morgan RJM WF, Wright MM, (1997) An Early Warning Scoring System for detecting
29
30 developing critical illness. *Clinical Intensive Care: International Journal of Critical & Coronary*
31
32 *Care Medicine* 8: 100
33
34
35 22. Kruisselbrink R, Kwizera A, Crowther M, Fox-Robichaud A, O'Shea T, Nakibuuka J,
36
37 Ssinabulya I, Nalyazi J, Bonner A, Devji T, Wong J, Cook D, (2016) Modified Early Warning
38
39 Score (MEWS) Identifies Critical Illness among Ward Patients in a Resource Restricted Setting
40
41 in Kampala, Uganda: A Prospective Observational Study. *PloS one* 11: e0151408
42
43
44
45 23. Schmedding M, Adegbite BR, Gould S, Beyeme JO, Adegnika AA, Grobusch MP, Huson
46
47 MAM, (2019) A Prospective Comparison of Quick Sequential Organ Failure Assessment,
48
49 Systemic Inflammatory Response Syndrome Criteria, Universal Vital Assessment, and
50
51 Modified Early Warning Score to Predict Mortality in Patients with Suspected Infection in
52
53 Gabon. *The American journal of tropical medicine and hygiene* 100: 202-208
54
55
56
57
58
59
60

- 1
2
3 24. Sutherland T, Mpirimbanyi C, Nziyomaze E, Niyomugabo JP, Niyonsenga Z, Muvunyi CM,
4
5 Mueller A, Bebell LM, Nkubana T, Musoni E, Talmor D, Rickard J, Riviello ED, (2019)
6
7 Widespread antimicrobial resistance among bacterial infections in a Rwandan referral
8
9 hospital. PloS one 14: e0221121
10
11
12
13 25. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn
14
15 JM, Shankar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC, (2016) Assessment of
16
17 Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and
18
19 Septic Shock (Sepsis-3). Jama 315: 762-774
20
21
22
23 26. Sinuff T, Adhikari NK, Cook DJ, Schunemann HJ, Griffith LE, Rocker G, Walter SD, (2006)
24
25 Mortality predictions in the intensive care unit: comparing physicians with scoring systems.
26
27 Critical care medicine 34: 878-885
28
29
30 27. Aoyama K, D'Souza R, Pinto R, Ray JG, Hill A, Scales DC, Lapinsky SE, Seaward GR,
31
32 Hladunewich M, Shah PS, Fowler RA, (2018) Risk prediction models for maternal mortality: A
33
34 systematic review and meta-analysis. PloS one 13: e0208563
35
36
37
38 28. Salluh JI, Soares M, (2014) ICU severity of illness scores: APACHE, SAPS and MPM. Current
39
40 opinion in critical care 20: 557-565
41
42
43 29. Haniffa R, Beane A, Baker T, Riviello ED, Schell CO, Dondorp AM, (2018) Development and
44
45 internal validation of the Simplified Mortality Score for the Intensive Care Unit (SMS-ICU).
46
47 Acta anaesthesiologica Scandinavica 62: 407-408
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Figure Legends**
4
5
6

7 **Figure 1.** Distribution of Patients (A) and Observed Mortality (B) with standard errors by adapted
8 Modified Early Warning Score (MEWS), Quick Sequential (Sepsis-Related) Organ Failure Assessment
9 (qSOFA) Score and Universal Vital Assessment (UVA) Among Patients With Suspected Infection
10
11

12
13
14 **Figure 2.** Receiver Operating Characteristic Curves for adapted MEWS, qSOFA, or UVA Criteria as
15 Continuous Variables
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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, <i>beats/minute</i>				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, <i>mmHg</i>				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, <i>beats/minute</i>				< 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

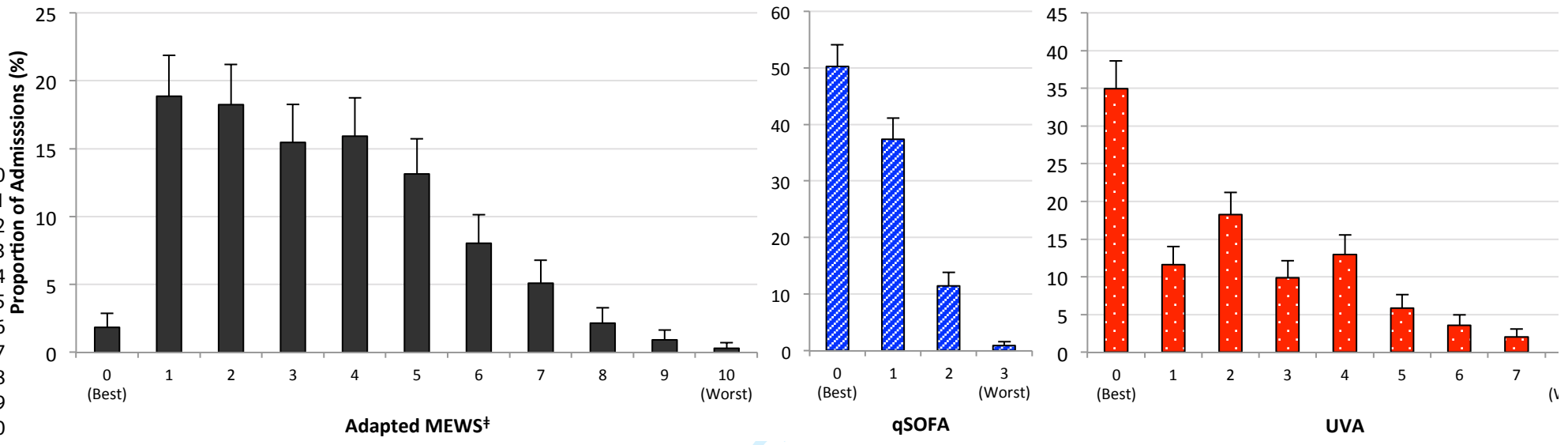
* Includes patients who had any of the following documented co-morbidities: diabetes, hypertension, tuberculosis, cancer, and/or severe malnutrition.

† 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.

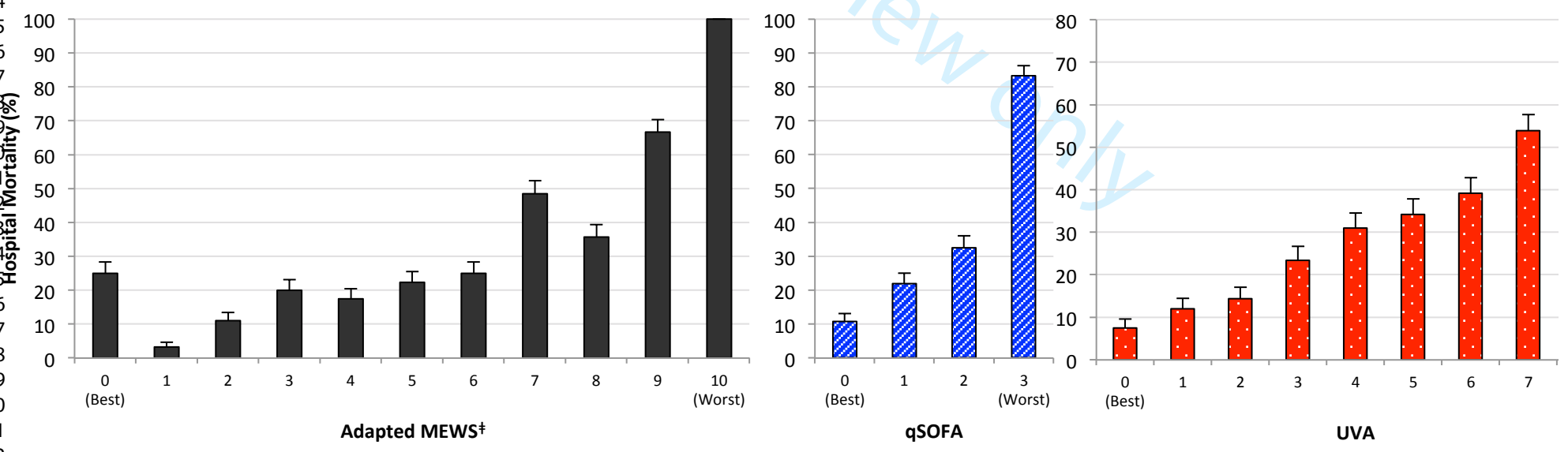
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

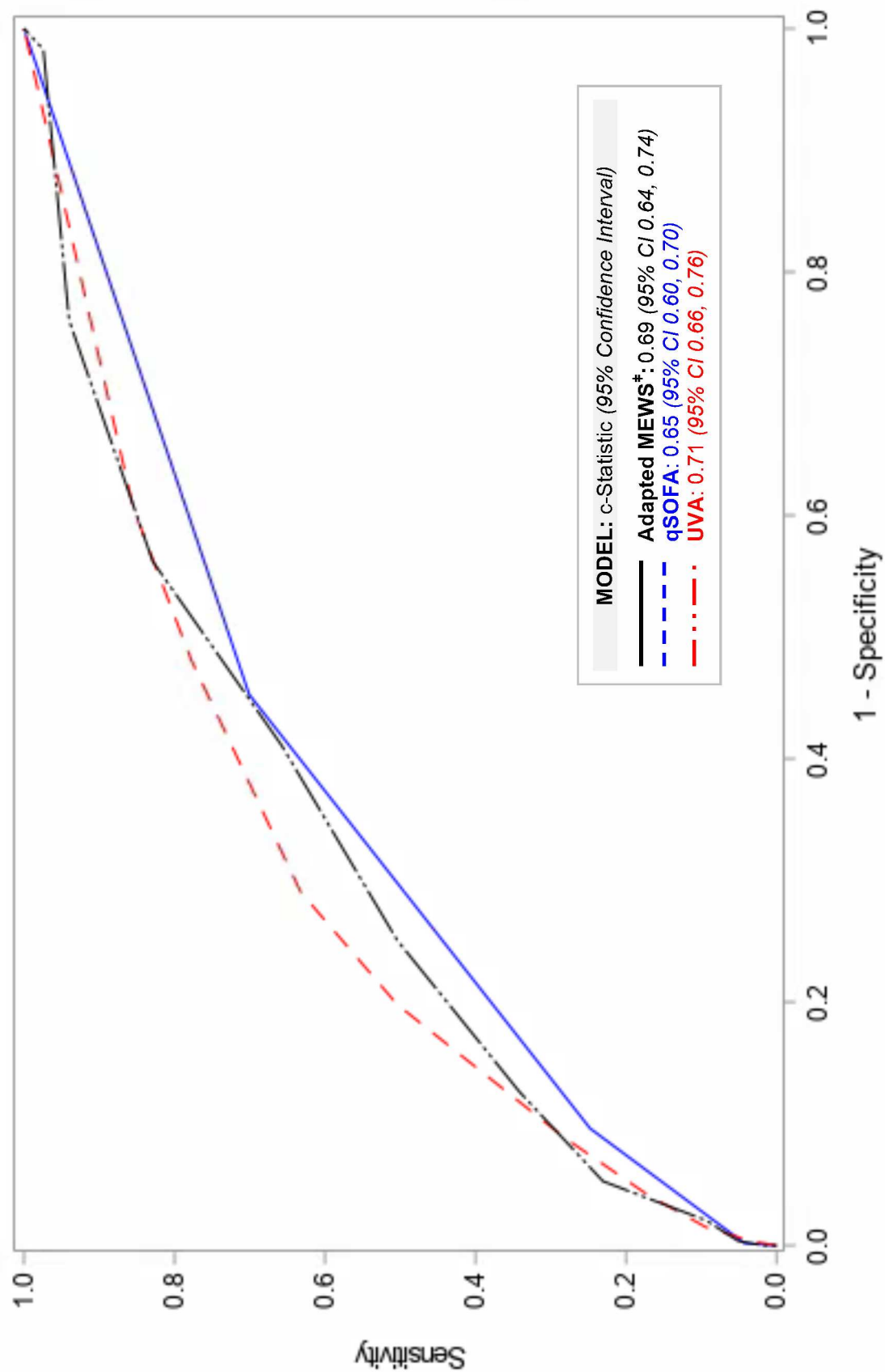
	Adapted MEWS[†] > 4	qSOFA ≥ 2	UVA > 4
Unadjusted			
Sensitivity	50.43	24.79	28.21
Specificity	74.91	90.38	91.13
Positive predictive value	30.73	36.25	41.25
Negative predictive value	87.25	84.48	85.19
OR (95% Confidence Interval)	3.04 (2.01, 4.59)	3.10 (1.86, 5.15)	4.04 (2.44, 6.67)
[†] The adaptation 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.			

[A] Distribution of Patients (n=647)



[B] Observed Mortality

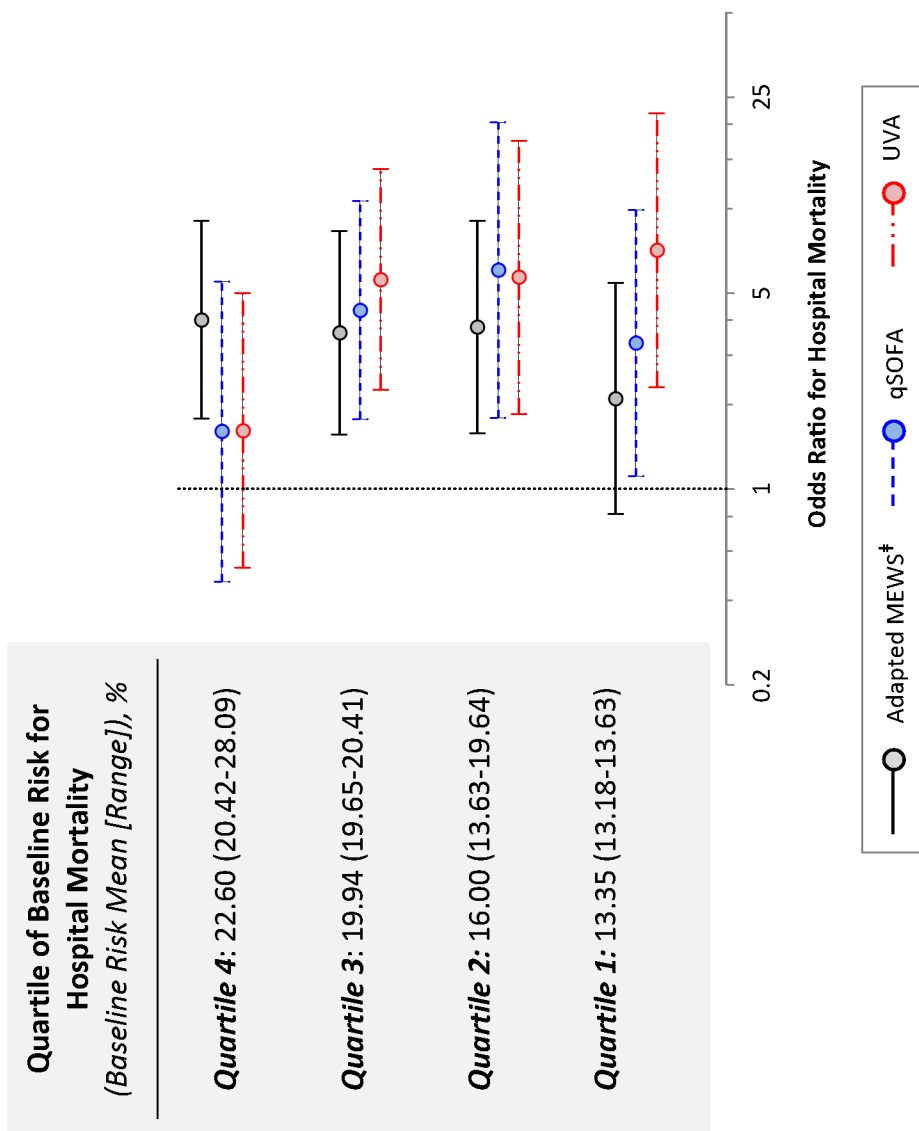




1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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.



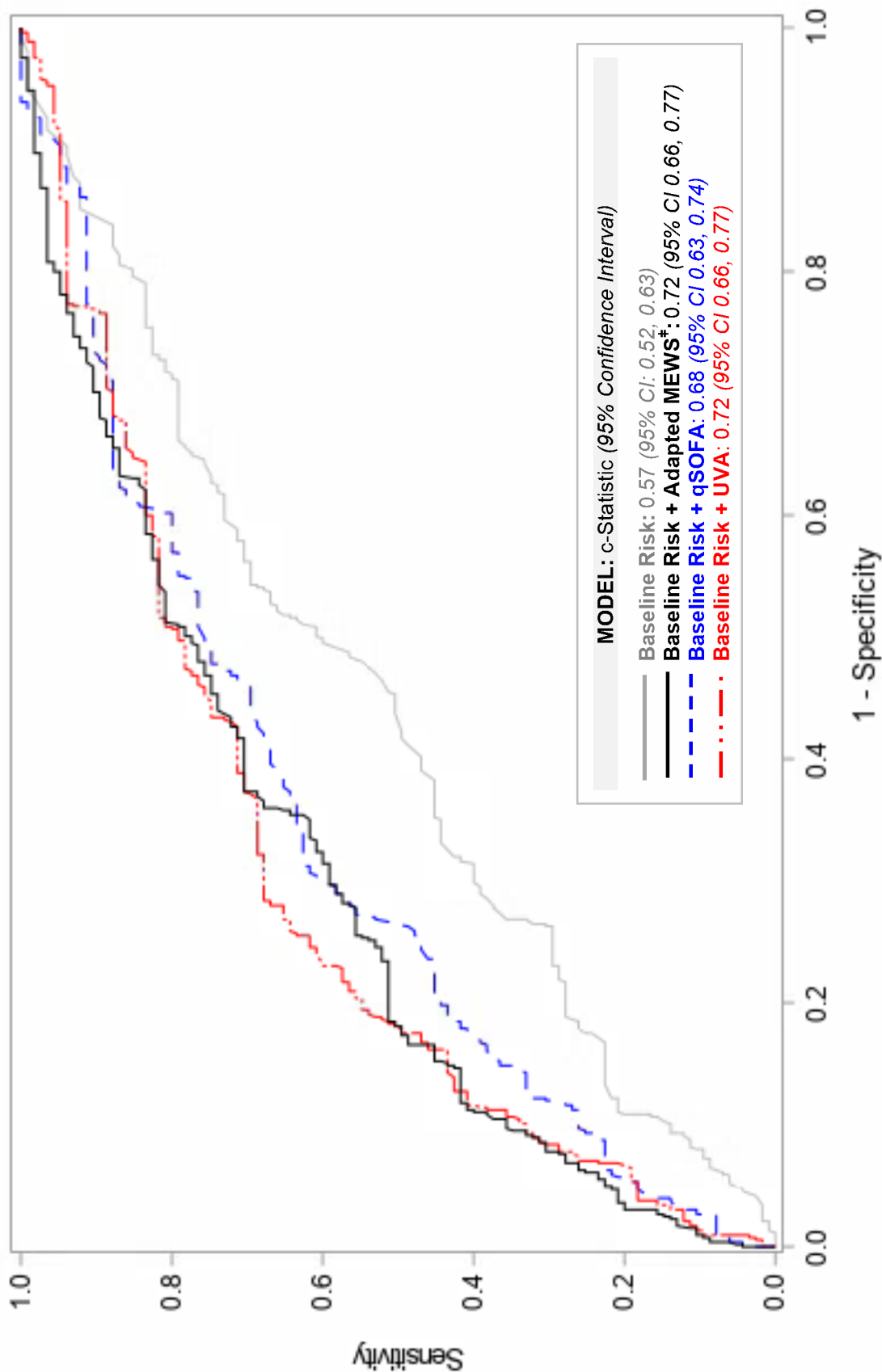
Odds ratio for hospital mortality (log-scale) comparing encounters with > 4 vs ≤ 4 adapted MEWS, ≥2 vs <2 qSOFA points, and >4 vs ≤ 4 UVA, and criteria among patients with suspected infection by quartile of baseline risk for hospital mortality. Baseline risk is calculated using age, gender, HIV status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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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 (<i>per 1 point increase</i>)	0.3445	0.0515	1.411 (1.276, 1.561)	<0.0001
MODEL 2 - qSOFA				
Intercept	-2.1088	0.1597	---	<0.0001
qSOFA (<i>per 1 point increase</i>)	0.7891	0.1372	2.201 (1.682, 2.880)	<0.0001
MODEL 3 - UVA				
Intercept	-2.4477	0.1832	---	<0.0001
UVA (<i>per 1 point increase</i>)	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, <i>per year</i>	0.000945	0.00624	1.001 (0.989, 1.013)	0.88
	Gender (<i>Male vs Female</i>)	0.2349	0.1070	1.600 (1.052, 2.433)	0.03
	HIV (<i>Yes vs No</i>)	0.1595	0.1576	1.376 (0.742, 2.552)	0.31
	Transfer (<i>Yes vs No</i>)	-0.0534	0.1078	0.899 (0.589, 1.371)	0.62
MODEL 2 – adapted MEWS					
	Intercept	-3.1376	0.4087	---	<0.0001
	Age, <i>per year</i>	0.00506	0.00664	1.005 (0.992, 1.018)	0.45
	Gender (<i>Male vs Female</i>)	0.2819	0.1127	1.757 (1.130, 2.734)	0.01
	HIV (<i>Yes vs No</i>)	0.0696	0.1667	1.149 (0.598, 2.210)	0.68
	Transfer (<i>Yes vs No</i>)	-0.1503	0.1147	0.740 (0.472, 1.160)	0.19
	MEWS (<i>per 1 point increase</i>)	0.3797	0.0537	1.462 (1.316, 1.624)	<0.0001
MODEL 3 - qSOFA					
	Intercept	-2.1031	0.3311	---	<.0001
	Age, <i>per year</i>	0.00131	0.00647	1.001 (0.989, 1.014)	0.84
	Gender (<i>Male vs Female</i>)	0.2440	0.1105	1.629 (1.056, 2.513)	0.03
	HIV (<i>Yes vs No</i>)	0.1264	0.1630	1.288 (0.680, 2.439)	0.44
	Transfer (<i>Yes vs No</i>)	-0.1345	0.1127	0.764 (0.491, 1.188)	0.23
	qSOFA (<i>per 1 point increase</i>)	0.8381	0.1412	2.312 (1.753, 3.049)	<0.0001
MODEL 4 - UVA					
	Intercept	-2.4523	0.3442	---	<0.0001
	Age, <i>per year</i>	-0.00074	0.00658	0.999 (0.986, 1.012)	0.91
	Gender (<i>Male vs Female</i>)	0.1395	0.1128	1.322 (0.849, 2.057)	0.22
	HIV (<i>Yes vs No</i>)	-0.0493	0.1655	0.906 (0.474, 1.733)	0.77
	Transfer (<i>Yes vs No</i>)	-0.0988	0.1142	0.821 (0.525, 1.284)	0.39
	UVA (<i>per 1 point increase</i>)	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

1	8	Main 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		
2				(b) Report category boundaries when continuous variables were categorized		
3				(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
4						
5						
6						
7						
8						
9		Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8	
10						
11		Discussion				
12						
13		Key results	18	Summarise key results with reference to study objectives	9	
14		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	
15						
16		Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10	
17						
18		Generalisability	21	Discuss the generalisability (external validity) of the study results	10	
19						
20		Other information				
21						
22		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	
23						
24						

*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>.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040361.R1
Article Type:	Original research
Date Submitted by the Author:	19-Oct-2020
Complete List of Authors:	Klinger, Amanda; Beth Israel Deaconess Medical Center Mueller, Ariel; Beth Israel Deaconess Medical Center, Anesthesia; Harvard Medical School Sutherland, Tori; Beth Israel Deaconess Medical Center Mpirimbanyi, Christophe; University of Rwanda - Kigali Campus Nziyomaze, Elie; University of Rwanda College of Medicine and Health Sciences Niyomugabo, Jean-Paul ; University of Rwanda College of Medicine and Health Sciences Niyonsenga , Zack; University of Rwanda College of Medicine and Health Sciences Rickard, Jennifer; University of Minnesota Talmor, Daniel; Beth Israel Deaconess Medical Center, Anesthesiology Riviello, Elisabeth; Harvard University,
Primary Subject Heading:	Global health
Secondary Subject Heading:	Intensive care
Keywords:	International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Authors: Amanda Klinger MD¹, Ariel Mueller MA², Tori Sutherland MD², Christophe Mpirimbanyi MD³, Elie Nziyomaze MD³, Jean-Paul Niyomugabo MD³, Zack Niyonsenga MD³, Jennifer Rickard MD^{3,4}, Daniel Talmor MD², Elisabeth D Riviello MD MPH⁵

Affiliations

1. Department of Medicine, Beth Israel Deaconess Medical Center (BIDMC), Harvard Medical School, Boston, USA
2. Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center (BIDMC), Harvard Medical School, Boston, USA
3. Department of Surgery, Kigali University Teaching Hospital, University of Rwanda, College of Medicine and Health Sciences, School of Medicine and Pharmacy, Kigali, Rwanda
4. Department of Surgery, University of Minnesota, Minneapolis, USA
5. Division of Pulmonary, Critical Care and Sleep Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA

Corresponding author: Elisabeth D. Riviello,
beth_riviello@post.harvard.edu, ORCID: 0000-0002-9443-3928

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

Funding statement: This work was supported by The Beth Israel Anesthesia Foundation and the University of Minnesota Department of Surgery.

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

1
2
3 **ABSTRACT** (word count: 287)
4

5 **Rationale:** Mortality prediction scores are increasingly being evaluated in
6 low and middle income countries (LMICs) for research comparisons, quality
7 improvement, and clinical decision-making. The modified early warning score
8 (MEWS), quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA),
9 and Universal Vital Assessment Score (UVA) use variables that are feasible
10 to obtain, and have demonstrated potential to predict mortality in LMIC
11 cohorts.
12
13
14
15
16
17
18

19
20
21 **Objective:** To determine the predictive capacity of adapted MEWS, qSOFA and
22 UVA in a Rwandan hospital.
23
24
25
26
27

28 **Design, setting, participants, and outcome measures:** We prospectively
29 collected data on all adult patients admitted to a tertiary hospital in
30 Rwanda with suspected infection over seven months. We calculated an adapted
31 MEWS, qSOFA, and UVA score for each participant. The predictive capacity of
32 each score was assessed including sensitivity, specificity, positive and
33 negative predictive value, odds ratio, area under the receiver operating
34 curve (AUROC), and performance by underlying risk quartile.
35
36
37
38
39
40
41
42
43
44

45 **Results:** We screened 19,178 patient-days, and enrolled 647 unique patients.
46 Median age was 35 years, and in-hospital mortality was 18.1%. The
47 proportion of data missing for each variable ranged from 0% to 11.7%. The
48 sensitivities and specificities of the scores were: adapted MEWS >4, 50.4%
49 and 74.9%, respectively; qSOFA_≥2, 24.8% and 90.4% respectively; and UVA >4,
50 28.2% and 91.1% respectively. The scores as continuous variables
51
52
53
54
55
56
57
58
59
60

1
2
3 demonstrated the following AUROCs: adapted MEWS 0.69 (95% CI 0.64, 0.74),
4
5 qSOFA 0.65 (95% CI 0.60, 0.70), and UVA 0.71 (95% CI 0.66, 0.76); there was
6
7 no statistically significant difference between the scores' discriminative
8
9 capacities.
10

11
12
13 **Conclusions:** Three scores demonstrated modest ability to predict mortality
14
15 in a prospective study of inpatients with suspected infection at a Rwandan
16
17 tertiary hospital. Careful consideration must be given to their adequacy
18
19 before using them in research comparisons, quality improvement, or clinical
20
21 decision-making.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 across the entire derivation population, with no reporting on its
4 performance in the individual cohorts [13]. It has only been assessed in
5 one small emergency department cohort outside the initial derivation
6 population [23].
7
8
9

10
11 All three scores use accessible bedside clinical measures and are
12 therefore appealing for LMIC settings where laboratory values and detailed
13 comorbidity histories are often not available. All three scores have also
14 been developed for hospital ward patients, which is relevant to LMICs,
15 where critically ill patients often remain in general wards due to the
16 scarcity of ICU beds.
17
18
19
20
21
22

23
24 We prospectively collected data on all adult hospitalized patients
25 with suspected infection over a seven month period in a study of
26 antimicrobial resistance patterns in a tertiary referral hospital in Rwanda
27 [24]. The current study was planned as part of the original study design,
28 and is a secondary analysis of this data evaluating the predictive capacity
29 of adapted MEWS, qSOFA, and UVA scores for in-hospital mortality in this
30 population.
31
32
33
34
35
36
37
38
39

40 **METHODS**

41 **Study oversight**

42
43 The Institutional Review Board of the University of Rwanda, College
44 of Medicine and Health Sciences in Kigali, Rwanda and the Committee on
45 Clinical Investigations at Beth Israel Deaconess Medical Center (BIDMC) in
46 Boston, Massachusetts approved the study. Verbal consent for participation
47 was obtained using a script in the participant's primary language.
48
49
50
51
52
53
54
55
56
57
58
59

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 \geq 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 \leq 35.0° C or \geq 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

1
2
3 each of the scores were collected at one time point from each participant's
4 chart by study research assistants. Vital sign and mental status data to
5 include in the models were collected at the time of fever or hypothermia,
6 the time of surgery, or the time of culture sample collection, depending on
7 the inclusion criteria met for each participant. For patients who met more
8 than one inclusion criteria, the time point for clinical data collection
9 was based on the first inclusion criteria met. Participants were followed
10 through hospital discharge to determine length of stay and in-hospital
11 mortality. All coded data were entered into a secure online database,
12 REDCap (Research Electronic Data Capture; Vanderbilt University, Nashville,
13 TN), which was hosted by BIDMC.
14
15
16
17
18
19
20
21
22
23
24
25
26
27

28 **Definitions**

29
30 MEWS includes five variables, with scores between 0-3 assigned for
31 each variable [20] (Table 1). It yields a maximum score of 14, with a score
32 >4 considered to be high risk for mortality in prior studies [20]. Because
33 we collected altered mental status as a binary variable (present or not),
34 we adapted this variable in the MEWS score to be 0 for normal mental status
35 and 2 for any altered mental status, rather than a range of severity of
36 altered mental statuses from 0-3. qSOFA includes three variables, with one
37 point given to each abnormal value, a maximum score of three, and ≥ 2
38 considered high risk [15]. UVA includes seven variables, with variable
39 points given for each abnormality. It yields a maximum score of 13, with >4
40 considered high risk based on its derivation study [13].
41
42
43
44
45
46
47
48
49
50
51
52

53 To replicate the methods for predictive validity in the original
54 qSOFA and qSOFA LMIC validation studies [15, 25], we also calculated a
55
56
57
58
59
60

1
2
3 baseline risk model to stratify the population, using the same variables
4 used in these studies: age, sex, HIV status, and hospital transfer status
5 (whether the patient had been transferred from another facility).
6
7
8
9

10 11 **Data Analysis**

12
13 The primary outcome of interest was in-hospital mortality. The sample
14 size was determined based on adequate power for the antimicrobial
15 resistance study from which this cohort was taken, and is described in the
16 methods of that study [24]. Adapted MEWS, qSOFA, and UVA scores were
17 calculated for all enrolled participants. Missing data were assumed to be
18 within normal range, with no additional points assigned. Data are presented
19 as median (interquartile range, IQR) or frequency (proportion) depending on
20 variable type. Normality was assessed with the Shapiro-Wilk
21 test. Demographic differences between survivors and non-survivors were
22 assessed with a Wilcoxon rank-sum test, chi-square or Fisher's Exact test,
23 as appropriate. Sensitivity, specificity, positive and negative predictive
24 values for the previously-reported cutoffs for each score are reported.
25 Separate unadjusted logistic regression models were used to generate odds
26 ratios (OR) and 95% confidence intervals (CI) for adapted MEWS, qSOFA, and
27 UVA. Multivariable logistic regression models using the four variables
28 noted above were calculated for the baseline risk model.
29

30
31 We used the predicted probabilities from our baseline risk model to
32 stratify our results into risk quartiles, presenting ORs and 95% CIs for
33 adapted MEWS, qSOFA and UVA with their previously-defined cutoffs
34 separately, as was done in the original LMIC cohort qSOFA study [15]. We
35 calculated the discriminative ability of adapted MEWS, qSOFA, and UVA as
36
37
38
39
40
41
42
43
44
45
46

1
2
3 continuous variables and found the area under the receiver operating
4 characteristic (AUROC) curves for each of these models. We also calculated
5 the discriminative ability of the three scores as continuous variables in
6 models with baseline risk adjustment.
7
8
9

10
11 Data analysis was performed using SAS 9.4 (SAS Institute Inc., Cary,
12 NC) with two-sided p-values < 0.05 considered statistically significant.
13
14
15

16 17 **RESULTS**

18
19 We screened every patient in the hospital for suspected infection
20 each day of the study period, for a total of 19,178 patient-days screened.
21 We enrolled 647 of the 648 unique patients who met our criteria for
22 suspected infection; the only exclusion was one patient who met study
23 criteria but declined enrollment. Within this study population, the median
24 age was 35 years (IQR 27, 51) and 347 (53.6%) of participants were male
25 (Table 2). Known pre-existing comorbidities were present in 143 (22.1%) of
26 participants, and 68 (10.5%) of participants were known to be HIV positive.
27 A positive bacterial culture result was identified in 273 (42.2%) of
28 participants.
29
30
31
32
33
34
35
36
37
38
39

40 In the full cohort, the in-hospital mortality rate was 18.1% (117 of
41 647 participants). An adapted MEWS score of >4 was present in 29.7%
42 (192/647) of cases, qSOFA score of ≥ 2 was present in 12.5% (81/647) of
43 cases, while a UVA score >4 was present in 12.4% (80/647) of cases (Table
44 2). The full distribution for each score is shown in Figure 1, with adapted
45 MEWS range 0-10, median 3, IQR 2,5; qSOFA range 0-3, median 0, IQR 0,1; and
46 UVA range 0-8, median 2, IQR 0,4. The proportion of data that was missing
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 for the components of the scores ranged from 0% to 11.7% (Supplemental
4
5 Table 1).

6
7 The sensitivity and specificity of the adapted MEWS score with cutoff
8
9 value >4 to predict in-hospital mortality were 50.4% and 74.9%,
10
11 respectively (Table 3). The sensitivity and specificity of qSOFA with
12
13 cutoff value ≥ 2 were 24.8% and 90.4%, respectively. For the UVA score with
14
15 cutoff value >4 , the sensitivity and specificity were 28.2% and 91.1%,
16
17 respectively. The sensitivity, specificity, positive predictive value, and
18
19 negative predictive value for each score using the full range of possible
20
21 cutoff values are presented in Supplemental Table 2. The unadjusted ORs for
22
23 adapted MEWS >4 , qSOFA ≥ 2 and UVA >4 were 3.04 (95% CI 2.01, 4.59), 3.10
24
25 (95% CI 1.86, 5.15) and 4.04 (95% CI 2.44, 6.67), respectively. The OR for
26
27 hospital mortality was most often >1 for each binary score within each
28
29 quartile of baseline risk, though the 95% CI for the OR crossed one for
30
31 qSOFA and UVA in quartile 4, and for adapted MEWS in quartile 1
32
33 (Supplemental Figure 1).
34
35

36 Overall, increasing scores for adapted MEWS, qSOFA and UVA
37
38 corresponded with increasing mortality, though this was not true for every
39
40 one-point increase in adapted MEWS (Figure 1). For each one point increase
41
42 in score as a continuous variable, the unadjusted odds ratios were: adapted
43
44 MEWS 1.41 (95% CI 1.28, 1.56), qSOFA 2.20 (95% CI 1.68, 2.88), and UVA
45
46 1.46 (1.32, 1.61) (Supplemental Table 3).
47
48

49 The area under the receiver operating curve (AUROC) for each score as
50
51 a continuous variable was: adapted MEWS 0.69 (95% CI 0.64, 0.74), qSOFA
52
53 0.65 (95% CI 0.60, 0.70), and UVA 0.71 (95% CI 0.66, 0.76) (Figure 2,
54
55 Supplemental Table 3). There was no statistically significant difference
56
57
58
59
60

1
2
3 between the AUROCs for the three scores as pairwise comparisons: UVA versus
4 adapted MEWS $p=0.57$; UVA versus qSOFA $p=0.09$; and adapted MEWS versus qSOFA
5 $p=0.26$).

6
7
8
9 The AUROC for the baseline risk model was 0.57 (95% CI 0.52, 0.63).
10 Adding adapted MEWS, qSOFA and UVA as continuous variables to the baseline
11 risk model changed the AUROC to 0.72 (95% CI 0.66, 0.77), 0.68 (95% CI
12 0.63, 0.74), and 0.72 (95% CI 0.66, 0.77), respectively (Supplemental
13 Figure 2, Supplemental Table 4.)

14 15 16 17 18 19 20 21 22 **DISCUSSION**

23
24 In a prospective study of 647 patients with suspected infection in a
25 Rwandan tertiary referral hospital, we found that the adapted MEWS, qSOFA,
26 and UVA scores had modest ability to predict mortality. Using previously
27 defined cutoffs for the each of the scores, adapted MEWS had sensitivity
28 and specificity of 50% and 75% respectively, while qSOFA and UVA were less
29 sensitive but had higher specificity (25% and 90% respectively for qSOFA
30 and 28% and 91% respectively for UVA). AUROCs for the continuous scores
31 ranged from 0.65 to 0.71, with no continuous score's AUROC demonstrating
32 statistically significant superiority to another.

33
34
35
36
37
38
39
40
41
42 We presented the performance of the three scores using the continuous
43 scores, continuous scores in addition to a baseline risk model, and binary
44 scores using previously defined cutoff values. Depending on the intended
45 use of the scores, any of these might be appropriate in understanding the
46 adequacy of the score. For quality improvement and research comparisons,
47 the AUROC is a useful single value in deciding whether a model can help
48 determine differences in severity of illness between cohorts [13]. For
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 determining the predictive validity of a definition of sepsis, assessing
4 mortality risk above baseline risk may be most appropriate [15]. For
5 deciding who needs escalation of care, the sensitivity and specificity with
6 a particular cutoff value is likely to be more important in judging the
7 adequacy of the model [11]. Particularly in the latter example, which is
8 the most oft-cited use for scores in LMICs, care must be taken in how the
9 scores are used for individual clinical decision-making since low
10 sensitivity could lead to patients who need additional care being missed
11 and low specificity could lead to attempts at using scarce resources for a
12 relatively large population [11, 26, 27].

13
14 Our study has several strengths. We looked at adult patients across
15 the entire hospital rather than the ICU alone [1, 2, 7, 10, 16, 17], which
16 is particularly important in settings where many critically ill patients
17 remain outside the ICU due to limited ICU capacity [13]. We also analyzed
18 the score performances in multiple ways: as continuous scores, continuous
19 scores added to baseline risk, and as dichotomous values. In addition, the
20 retrospective multi-site LMIC qSOFA validation included a cohort from the
21 emergency department of our hospital [15]; our cohort and that cohort
22 showed similarly modest predictive capacity for the continuous qSOFA score
23 without baseline model, providing criterion validity to our results (AUROC
24 0.55 in the multisite study and 0.65 in this study). Finally, other than
25 one small study confined to emergency department patients and with a low
26 (5%) mortality rate [23], our study is the first to assess the UVA score
27 outside of its LMIC derivation cohort [13].

28
29 Our study also has several limitations. We conducted it in a single
30 tertiary care hospital in sub-Saharan Africa, so its results may not be

1
2
3 generalizable. Even more complex severity of illness scores derived from
4 much larger populations, such as the APACHE score for ICU patients in HICs,
5 have quite variable performance, requiring recalibration for different
6 populations and over time in the same population [12, 28, 29]. It is
7 reasonable to expect that variations in patient characteristics, management
8 systems, and resources across hospitals would translate to different
9 predictive capacities of scores across hospitals. Of note, in the
10 retrospective study of qSOFA in nine LMIC cohorts, the AUROC for all
11 combined sites without the baseline model was 0.69, but the AUROC range for
12 individual sites was wide, from 0.55 to 0.81 [15]. Second, the variables
13 used to calculate the scores for patients in our study were recorded from
14 different time points (time of fever, operation, or culture sample
15 retrieval) depending on the inclusion criteria each participant met for the
16 study. This likely simulates how the scores might be used in practice;
17 however, it is certainly possible the scores would perform better with more
18 consistent data collection time points. We may also have a survivor bias of
19 unknown direction since patients who died rapidly after admission to the
20 hospital before they could be screened, or who died before infection was
21 suspected, were not included. Third, oxygen saturation was included as a
22 variable, without oxygen delivery; this was a feature of the UVA score
23 design, but it nonetheless seems likely that oxygen saturation without
24 oxygen delivery will be more limited in its predictive power. Fourth, we
25 had some missing data, up to 11.7% for oxygen saturation, for which we
26 assumed normal values; however, the missingness was relatively low compared
27 to many other LMIC studies [1, 12] and reflects reasonable real-world data
28 availability. Fifth, our positive culture rate of 42.2% in this population
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 is likely artificially high given that one of the inclusion criteria for
4 the study was a positive culture. Finally, we were unable to evaluate the
5 original MEWS score since we did not have detailed mental status data. We
6 used an adapted MEWS with a binary version of the mental status variable
7 without prior validation of this adaptation; these scores could have been
8 over- or under-estimated and therefore impacted the score's capacity to
9 differentiate participants.
10
11
12
13
14
15
16
17
18
19

20 **CONCLUSIONS**

21
22 Our study found modest predictive power of adjusted MEWS, qSOFA, and
23 UVA scores in our cohort of inpatients with suspected infection at a
24 Rwandan tertiary hospital. These modest predictive performances must be
25 acknowledged if these scores are to be considered for use in research
26 comparisons, quality improvement, or clinical decision-making.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Acknowledgments: We thank Claude Mambo Muvunyi, Theoneste Nkubana, Emile Musoni, and Jean-Paul Mvukiyeha for their excellent research assistance.

For peer review only

References

1. Haniffa R, Isaam I, De Silva AP, Dondorp AM, De Keizer NF, (2018) Performance of critical care prognostic scoring systems in low and middle-income countries: a systematic review. *Critical care* (London, England) 22: 18
2. Lalani HS, Waweru-Siika W, Mwogi T, Kituyi P, Egger JR, Park LP, Kussin PS, (2018) Intensive Care Outcomes and Mortality Prediction at a National Referral Hospital in Western Kenya. *Annals of the American Thoracic Society* 15: 1336-1343
3. Opio MO, Nansubuga G, Kellett J, (2013) Validation of the VitalPAC Early Warning Score (ViEWS) in acutely ill medical patients attending a resource-poor hospital in sub-Saharan Africa. *Resuscitation* 84: 743-746
4. Aluisio AR, Garbern S, Wiskel T, Mutabazi ZA, Umuhire O, Ch'ng CC, Rudd KE, D'Arc Nyinawankusi J, Byiringiro JC, Levine AC, (2018) Mortality outcomes based on ED qSOFA score and HIV status in a developing low income country. *The American journal of emergency medicine* 36: 2010-2019
5. Khwannimit B, Bhurayanontachai R, Vattanavanit V, (2018) Comparison of the performance of SOFA, qSOFA and SIRS for predicting mortality and organ failure among sepsis patients admitted to the intensive care unit in a middle-income country. *Journal of critical care* 44: 156-160
6. Boillat-Blanco N, Mbarack Z, Samaka J, Mlaganile T, Mamin A, Genton B, Kaiser L, Calandra T, D'Acremont V, (2018) Prognostic value of quickSOFA as a predictor of 28-day mortality among febrile adult

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

patients presenting to emergency departments in Dar es Salaam, Tanzania. PloS one 13: e0197982

7. Sendagire C, Lipnick MS, Kizito S, Kruisselbrink R, Obua D, Ejoku J, Ssemogerere L, Nakibuuka J, Kwizera A, (2017) Feasibility of the modified sequential organ function assessment score in a resource-constrained setting: a prospective observational study. BMC anesthesiology 17: 12
8. Carugati M, Zhang HL, Kilonzo KG, Maze MJ, Maro VP, Rubach MP, Crump JA, (2018) Predicting Mortality for Adolescent and Adult Patients with Fever in Resource-Limited Settings. The American journal of tropical medicine and hygiene 99: 1246-1254
9. Baig MA, Sheikh S, Hussain E, Bakhtawar S, Subhan Khan M, Mujtaba S, Waheed S, (2018) Comparison of qSOFA and SOFA score for predicting mortality in severe sepsis and septic shock patients in the emergency department of a low middle income country. Turkish journal of emergency medicine 18: 148-151
10. Prin M, Pan S, Kadyaudzu C, Li G, Charles A, (2018) Development of a Malawi Intensive care Mortality risk Evaluation (MIME) model, a prospective cohort study. International journal of surgery (London, England) 60: 60-66
11. Machado FR, Cavalcanti AB, Monteiro MB, Sousa JL, Bossa A, Bafi AT, Dal-Pizzol F, Freitas FGR, Lisboa T, Westphal GA, Japiassu AM, Azevedo LC, (2020) Predictive Accuracy of the Quick Sepsis-Related Organ Failure Assessment Score in Brazil: A Prospective Multicenter Study. American journal of respiratory and critical care medicine

- 1
2
3 12. Beane A, De Silva AP, De Silva N, Sujeewa JA, Rathnayake RMD, Sigera
4 PC, Athapattu PL, Mahipala PG, Rashan A, Munasinghe SB, Jayasinghe
5 KSA, Dondorp AM, Haniffa R, (2018) Evaluation of the feasibility and
6 performance of early warning scores to identify patients at risk of
7 adverse outcomes in a low-middle income country setting. *BMJ open* 8:
8 e019387
9
10
11
12
13
14
15 13. Moore CC, Hazard R, Saulters KJ, Ainsworth J, Adakun SA, Amir A,
16 Andrews B, Auma M, Baker T, Banura P, Crump JA, Grobusch MP, Huson
17 MAM, Jacob ST, Jarrett OD, Kellett J, Lakhi S, Majwala A, Opio M,
18 Rubach MP, Rylance J, Michael Scheld W, Schieffelin J, Ssekitoleko R,
19 Wheeler I, Barnes LE, (2017) Derivation and validation of a universal
20 vital assessment (UVA) score: a tool for predicting mortality in
21 adult hospitalised patients in sub-Saharan Africa. *BMJ global health*
22 2: e000344
23
24
25
26
27
28
29
30
31
32 14. Baker T, Schell CO, Lugazia E, Blixt J, Mulungu M, Castegren M,
33 Eriksen J, Konrad D, (2015) Vital Signs Directed Therapy: Improving
34 Care in an Intensive Care Unit in a Low-Income Country. *PloS one* 10:
35 e0144801
36
37
38
39
40 15. Rudd KE, Seymour CW, Aluisio AR, Augustin ME, Bagenda DS, Beane A,
41 Byiringiro JC, Chang CH, Colas LN, Day NPJ, De Silva AP, Dondorp AM,
42 Dunser MW, Faiz MA, Grant DS, Haniffa R, Van Hao N, Kennedy JN,
43 Levine AC, Limmathurotsakul D, Mohanty S, Nosten F, Papali A,
44 Patterson AJ, Schieffelin JS, Shaffer JG, Thuy DB, Thwaites CL,
45 Urayeneza O, White NJ, West TE, Angus DC, (2018) Association of the
46 Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA)
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 Score With Excess Hospital Mortality in Adults With Suspected
4
5 Infection in Low- and Middle-Income Countries. *Jama* 319: 2202-2211
6
7 16. Haniffa R, Mukaka M, Munasinghe SB, De Silva AP, Jayasinghe KSA,
8
9 Beane A, de Keizer N, Dondorp AM, (2017) Simplified prognostic model
10
11 for critically ill patients in resource limited settings in South
12
13 Asia. *Critical care (London, England)* 21: 250
14
15 17. Riviello ED, Kiviri W, Fowler RA, Mueller A, Novack V, Banner-
16
17 Goodspeed VM, Weinkauff JL, Talmor DS, Twagirimugabe T, (2016)
18
19 Predicting Mortality in Low-Income Country ICUs: The Rwanda Mortality
20
21 Probability Model (R-MPM). *PloS one* 11: e0155858
22
23 18. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan
24
25 E, Camporota L, Slutsky AS, (2012) Acute respiratory distress
26
27 syndrome: the Berlin Definition. *Jama* 307: 2526-2533
28
29
30 19. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer
31
32 M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS,
33
34 Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll
35
36 T, Vincent JL, Angus DC, (2016) The Third International Consensus
37
38 Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama* 315: 801-810
39
40 20. Subbe CP, Kruger M, Rutherford P, Gemmel L, (2001) Validation of a
41
42 modified Early Warning Score in medical admissions. *QJM : monthly*
43
44 *journal of the Association of Physicians* 94: 521-526
45
46 21. Morgan RJM WF, Wright MM, (1997) An Early Warning Scoring System for
47
48 detecting developing critical illness. *Clinical Intensive Care:*
49
50 *International Journal of Critical & Coronary Care Medicine* 8: 100
51
52
53 22. Kruisselbrink R, Kwizera A, Crowther M, Fox-Robichaud A, O'Shea T,
54
55 Nakibuuka J, Ssinabulya I, Nalyazi J, Bonner A, Devji T, Wong J, Cook
56
57
58
59
60

- 1
2
3 D, (2016) Modified Early Warning Score (MEWS) Identifies Critical
4
5 Illness among Ward Patients in a Resource Restricted Setting in
6
7 Kampala, Uganda: A Prospective Observational Study. PloS one 11:
8
9 e0151408
10
- 11 23. Schmedding M, Adegbite BR, Gould S, Beyeme JO, Adegnika AA, Grobusch
12
13 MP, Huson MAM, (2019) A Prospective Comparison of Quick Sequential
14
15 Organ Failure Assessment, Systemic Inflammatory Response Syndrome
16
17 Criteria, Universal Vital Assessment, and Modified Early Warning
18
19 Score to Predict Mortality in Patients with Suspected Infection in
20
21 Gabon. The American journal of tropical medicine and hygiene 100:
22
23 202-208
24
- 25 24. Sutherland T, Mpirimbanyi C, Nziyomaze E, Niyomugabo JP, Niyonsenga
26
27 Z, Muvunyi CM, Mueller A, Bebell LM, Nkubana T, Musoni E, Talmor D,
28
29 Rickard J, Riviello ED, (2019) Widespread antimicrobial resistance
30
31 among bacterial infections in a Rwandan referral hospital. PloS one
32
33 14: e0221121
34
- 35 25. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A,
36
37 Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS,
38
39 Escobar GJ, Angus DC, (2016) Assessment of Clinical Criteria for
40
41 Sepsis: For the Third International Consensus Definitions for Sepsis
42
43 and Septic Shock (Sepsis-3). Jama 315: 762-774
44
- 45 26. Sinuff T, Adhikari NK, Cook DJ, Schunemann HJ, Griffith LE, Rocker G,
46
47 Walter SD, (2006) Mortality predictions in the intensive care unit:
48
49 comparing physicians with scoring systems. Critical care medicine 34:
50
51 878-885
52
53
54
55
56
57
58
59
60

- 1
2
3 27. Aoyama K, D'Souza R, Pinto R, Ray JG, Hill A, Scales DC, Lapinsky SE,
4 Seaward GR, Hladunewich M, Shah PS, Fowler RA, (2018) Risk prediction
5 models for maternal mortality: A systematic review and meta-analysis.
6 PloS one 13: e0208563
7
8
9
10
11 28. Salluh JI, Soares M, (2014) ICU severity of illness scores: APACHE,
12 SAPS and MPM. Current opinion in critical care 20: 557-565
13
14
15 29. Haniffa R, Beane A, Baker T, Riviello ED, Schell CO, Dondorp AM,
16 (2018) Development and internal validation of the Simplified
17 Mortality Score for the Intensive Care Unit (SMS-ICU). Acta
18 anaesthesiologica Scandinavica 62: 407-408
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Figure Legends**
4
5

6 **Figure 1.** Distribution of Patients (A) and Observed Mortality (B) with
7 standard errors by adapted Modified Early Warning Score (MEWS), Quick
8 Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Score and
9 Universal Vital Assessment (UVA) Among Patients With Suspected Infection
10
11
12
13

14 **Figure 2.** Receiver Operating Characteristic Curves for adapted MEWS, qSOFA,
15 or UVA Criteria as Continuous Variables
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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, <i>beats/minute</i>				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, <i>mmHg</i>				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, <i>beats/minute</i>				< 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

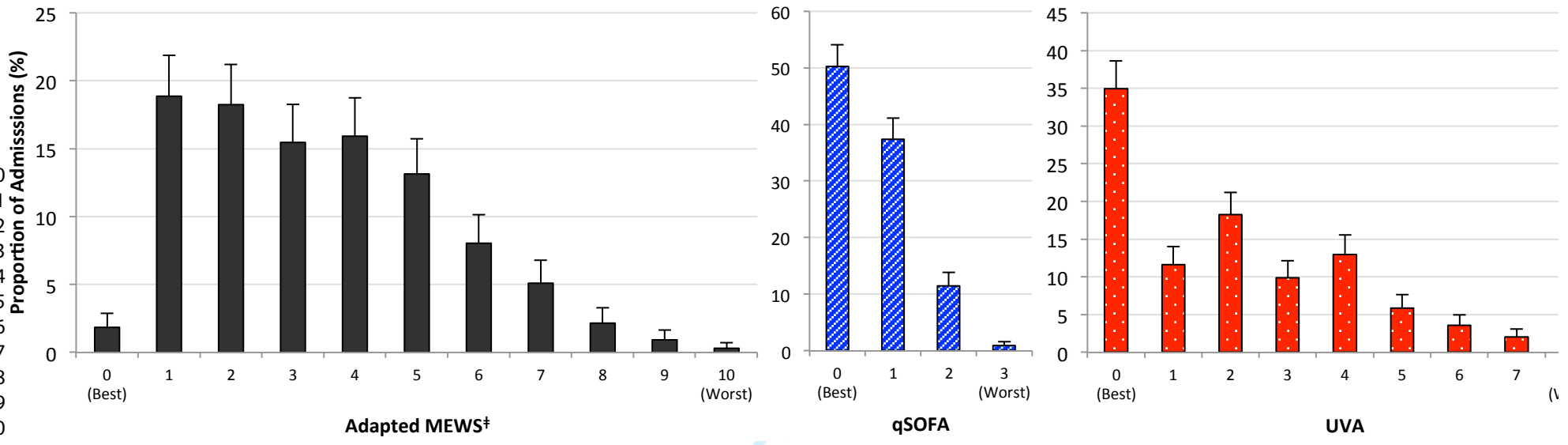
*Includes patients who had any of the following documented co-morbidities: diabetes, hypertension, tuberculosis, cancer, and/or severe malnutrition. *The adaption to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they 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.

For peer review only

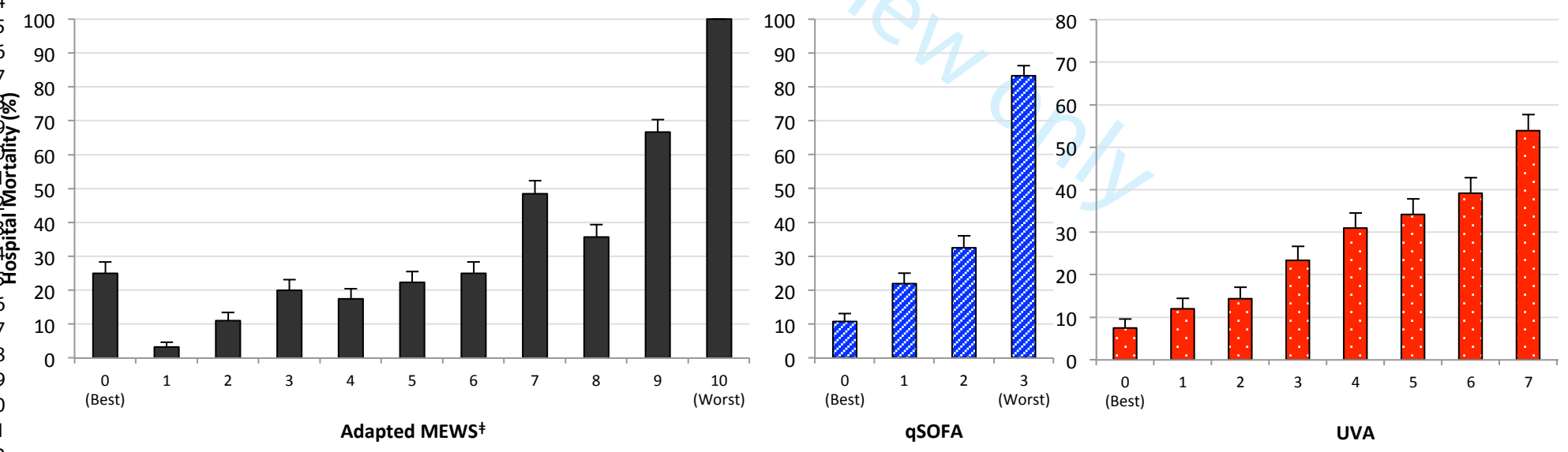
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

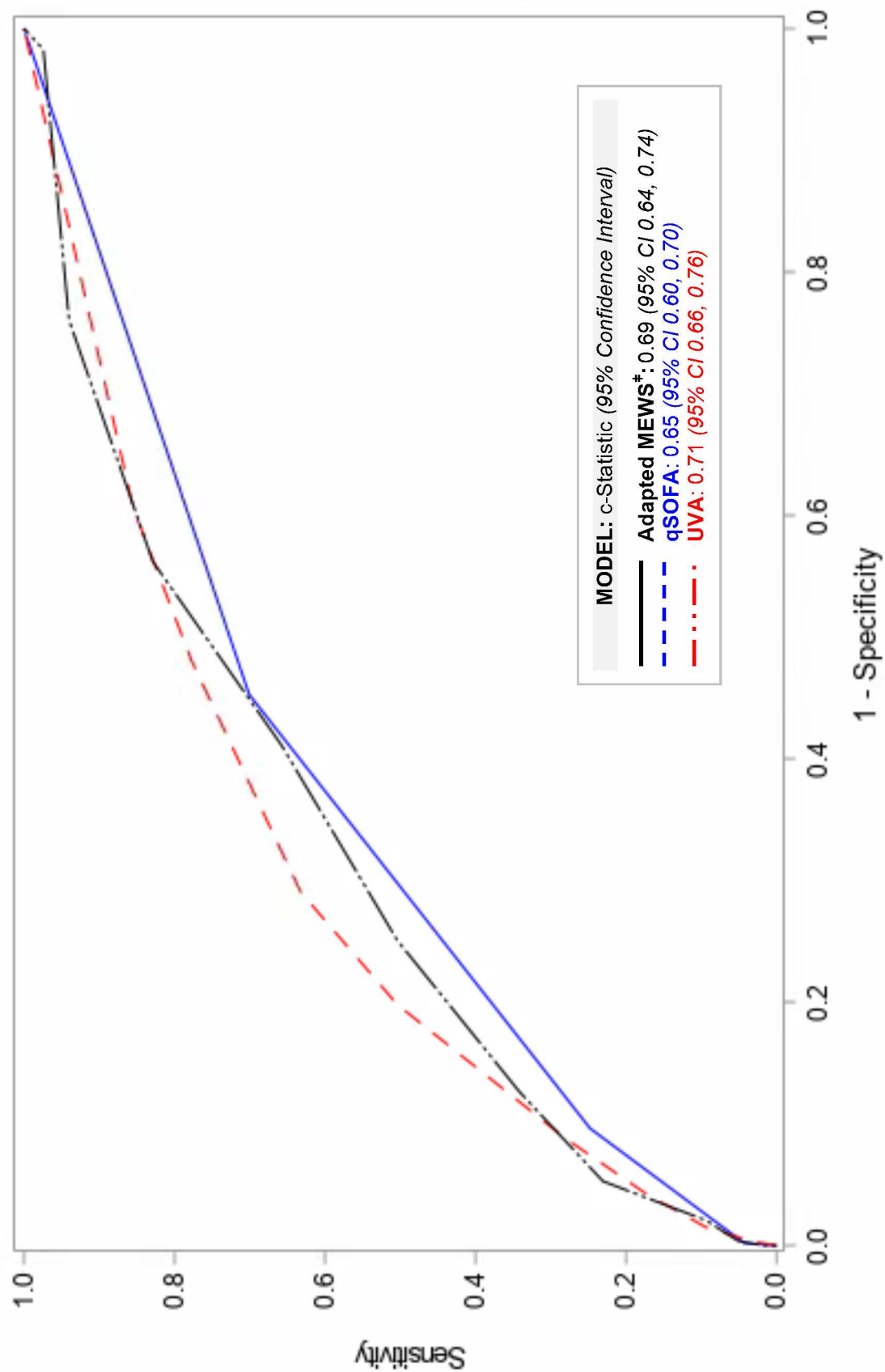
	Adapted MEWS[†] > 4	qSOFA ≥ 2	UVA > 4
Unadjusted			
Sensitivity	50.43	24.79	28.21
Specificity	74.91	90.38	91.13
Positive predictive value	30.73	36.25	41.25
Negative predictive value	87.25	84.48	85.19
OR (95% Confidence Interval)	3.04 (2.01, 4.59)	3.10 (1.86, 5.15)	4.04 (2.44, 6.67)
[†] The adaptation 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.			

[A] Distribution of Patients (n=647)



[B] Observed Mortality





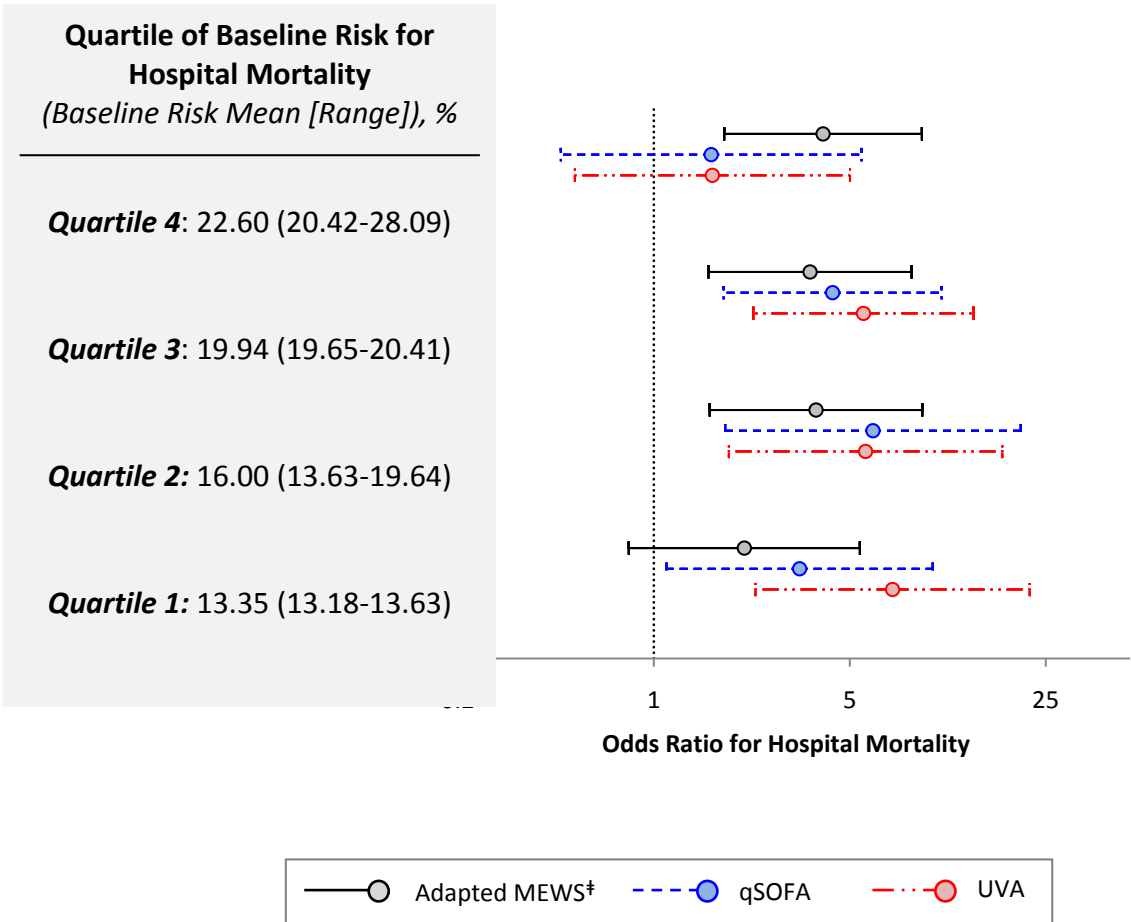
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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.	

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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
<p>*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.</p> <p>Abbreviations: PPV = positive predictive values; NPV = negative predictive value;</p>				

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.

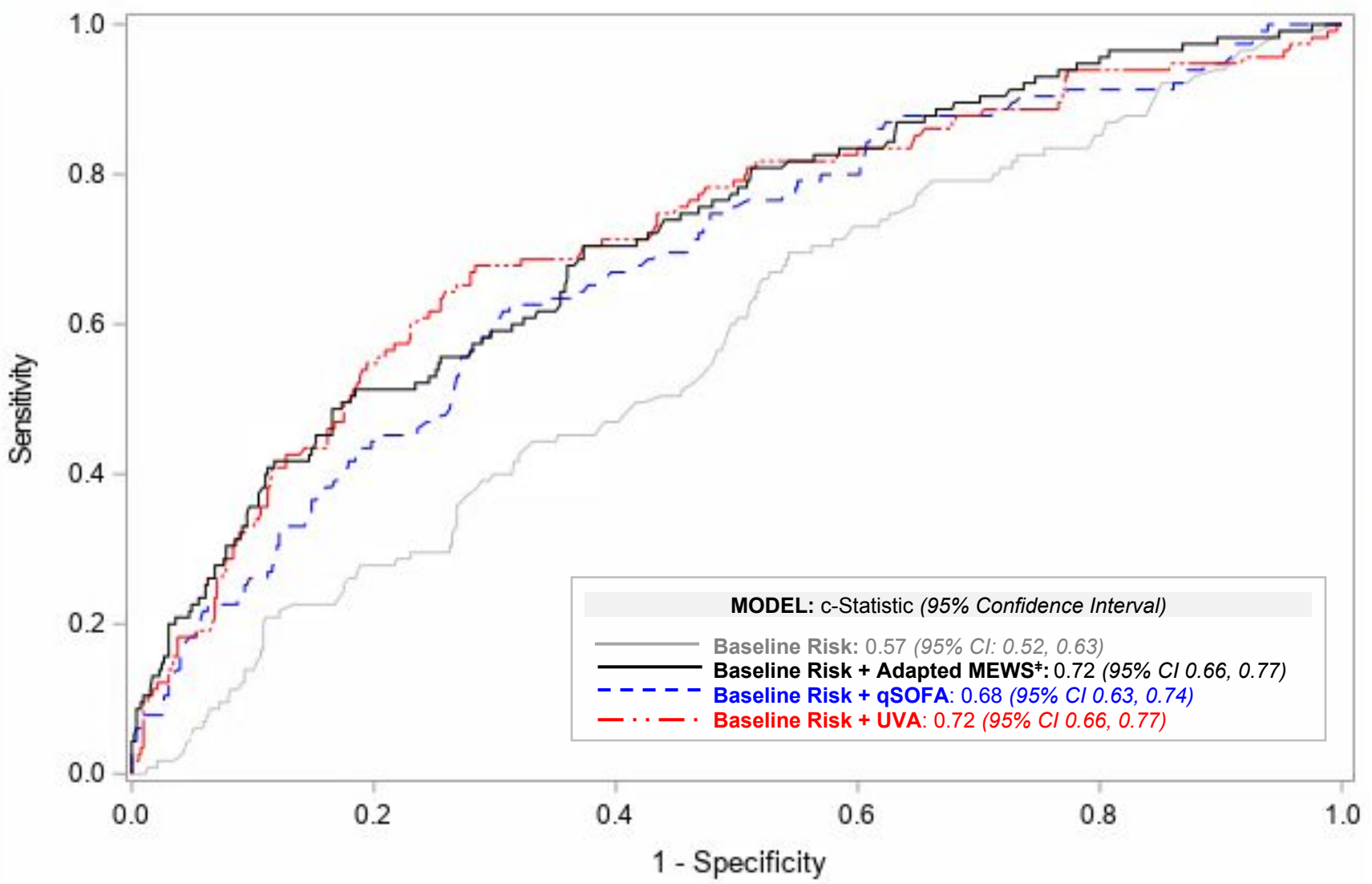
[†]The adaption to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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 (<i>per 1 point increase</i>)	0.3445	0.0515	1.411 (1.276, 1.561)	<0.0001
MODEL 2 - qSOFA					
	Intercept	-2.1088	0.1597	---	<0.0001
	qSOFA (<i>per 1 point increase</i>)	0.7891	0.1372	2.201 (1.682, 2.880)	<0.0001
MODEL 3 - UVA					
	Intercept	-2.4477	0.1832	---	<0.0001
	UVA (<i>per 1 point increase</i>)	0.3769	0.0511	1.458 (1.319, 1.611)	<0.0001

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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

1	8	Main 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		
2				(b) Report category boundaries when continuous variables were categorized		
3				(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
4						
5						
6						
7						
8						
9		Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8	
10						
11		Discussion				
12						
13		Key results	18	Summarise key results with reference to study objectives	9	
14		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	
15						
16		Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10	
17						
18		Generalisability	21	Discuss the generalisability (external validity) of the study results	10	
19						
20		Other information				
21						
22		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	
23						
24						

*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>.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040361.R2
Article Type:	Original research
Date Submitted by the Author:	20-Nov-2020
Complete List of Authors:	Klinger, Amanda; Beth Israel Deaconess Medical Center Mueller, Ariel; Beth Israel Deaconess Medical Center, Anesthesia; Harvard Medical School Sutherland, Tori; Beth Israel Deaconess Medical Center Mpirimbanyi, Christophe; University of Rwanda - Kigali Campus Nziyomaze, Elie; University of Rwanda College of Medicine and Health Sciences Niyomugabo, Jean-Paul ; University of Rwanda College of Medicine and Health Sciences Niyonsenga , Zack; University of Rwanda College of Medicine and Health Sciences Rickard, Jennifer; University of Minnesota Talmor, Daniel; Beth Israel Deaconess Medical Center, Anesthesiology Riviello, Elisabeth; Harvard University,
Primary Subject Heading:	Global health
Secondary Subject Heading:	Intensive care
Keywords:	International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Authors: Amanda Klinger MD¹, Ariel Mueller MA², Tori Sutherland MD², Christophe Mpirimbanyi MD³, Elie Nziyomaze MD³, Jean-Paul Niyomugabo MD³, Zack Niyonsenga MD³, Jennifer Rickard MD^{3,4}, Daniel Talmor MD², Elisabeth D Riviello MD MPH⁵

Affiliations

1. Department of Medicine, Beth Israel Deaconess Medical Center (BIDMC), Harvard Medical School, Boston, USA
2. Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center (BIDMC), Harvard Medical School, Boston, USA
3. Department of Surgery, Kigali University Teaching Hospital, University of Rwanda, College of Medicine and Health Sciences, School of Medicine and Pharmacy, Kigali, Rwanda
4. Department of Surgery, University of Minnesota, Minneapolis, USA
5. Division of Pulmonary, Critical Care and Sleep Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA

Corresponding author: Elisabeth D. Riviello,
beth_riviello@post.harvard.edu, ORCID: 0000-0002-9443-3928

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

Funding statement: This work was supported by The Beth Israel Anesthesia Foundation and the University of Minnesota Department of Surgery.

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

1
2
3 **ABSTRACT** (word count: 287)
4

5 **Rationale:** Mortality prediction scores are increasingly being evaluated in
6 low and middle income countries (LMICs) for research comparisons, quality
7 improvement, and clinical decision-making. The modified early warning score
8 (MEWS), quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA),
9 and Universal Vital Assessment Score (UVA) use variables that are feasible
10 to obtain, and have demonstrated potential to predict mortality in LMIC
11 cohorts.
12
13
14
15
16
17
18

19
20
21
22 **Objective:** To determine the predictive capacity of adapted MEWS, qSOFA and
23 UVA in a Rwandan hospital.
24
25
26
27

28 **Design, setting, participants, and outcome measures:** We prospectively
29 collected data on all adult patients admitted to a tertiary hospital in
30 Rwanda with suspected infection over seven months. We calculated an adapted
31 MEWS, qSOFA, and UVA score for each participant. The predictive capacity of
32 each score was assessed including sensitivity, specificity, positive and
33 negative predictive value, odds ratio, area under the receiver operating
34 curve (AUROC), and performance by underlying risk quartile.
35
36
37
38
39
40
41
42
43
44

45 **Results:** We screened 19,178 patient-days, and enrolled 647 unique patients.
46 Median age was 35 years, and in-hospital mortality was 18.1%. The
47 proportion of data missing for each variable ranged from 0% to 11.7%. The
48 sensitivities and specificities of the scores were: adapted MEWS >4, 50.4%
49 and 74.9%, respectively; qSOFA_≥2, 24.8% and 90.4% respectively; and UVA >4,
50 28.2% and 91.1% respectively. The scores as continuous variables
51
52
53
54
55
56
57
58
59
60

1
2
3 demonstrated the following AUROCs: adapted MEWS 0.69 (95% CI 0.64, 0.74),
4
5 qSOFA 0.65 (95% CI 0.60, 0.70), and UVA 0.71 (95% CI 0.66, 0.76); there was
6
7 no statistically significant difference between the scores' discriminative
8
9 capacities.
10

11
12
13 **Conclusions:** Three scores demonstrated modest ability to predict mortality
14
15 in a prospective study of inpatients with suspected infection at a Rwandan
16
17 tertiary hospital. Careful consideration must be given to their adequacy
18
19 before using them in research comparisons, quality improvement, or clinical
20
21 decision-making.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 across the entire derivation population, with no reporting on its
4 performance in the individual cohorts [13]. It has only been assessed in
5 one small emergency department cohort outside the initial derivation
6 population [23].
7
8
9

10
11 All three scores use accessible bedside clinical measures and are
12 therefore appealing for LMIC settings where laboratory values and detailed
13 comorbidity histories are often not available. All three scores have also
14 been developed for hospital ward patients, which is relevant to LMICs,
15 where critically ill patients often remain in general wards due to the
16 scarcity of ICU beds.
17
18
19
20
21
22
23

24 We prospectively collected data on all adult hospitalized patients
25 with suspected infection over a seven month period in a study of
26 antimicrobial resistance patterns in a tertiary referral hospital in Rwanda
27 [24]. The current study was planned as part of the original study design,
28 and is a secondary analysis of this data evaluating the predictive capacity
29 of adapted MEWS, qSOFA, and UVA scores for in-hospital mortality in this
30 population.
31
32
33
34
35
36
37
38
39

40 **METHODS**

41 **Study oversight**

42
43 The Institutional Review Board of the University of Rwanda, College
44 of Medicine and Health Sciences in Kigali, Rwanda and the Committee on
45 Clinical Investigations at Beth Israel Deaconess Medical Center (BIDMC) in
46 Boston, Massachusetts approved the study. Verbal consent for participation
47 was obtained using a script in the participant's primary language.
48
49
50
51
52
53
54
55
56
57
58
59
60

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 \geq 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 \leq 35.0° C or \geq 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

1
2
3 each of the scores were collected at one time point from each participant's
4 chart by study research assistants. Vital sign and mental status data to
5 include in the models were collected at the time of fever or hypothermia,
6 the time of surgery, or the time of culture sample collection, depending on
7 the inclusion criteria met for each participant. For patients who met more
8 than one inclusion criteria, the time point for clinical data collection
9 was based on the first inclusion criteria met. Participants were followed
10 through hospital discharge to determine length of stay and in-hospital
11 mortality. All coded data were entered into a secure online database,
12 REDCap (Research Electronic Data Capture; Vanderbilt University, Nashville,
13 TN), which was hosted by BIDMC.
14
15
16
17
18
19
20
21
22
23
24
25
26
27

28 **Definitions**

29
30 MEWS includes five variables, with scores between 0-3 assigned for
31 each variable [20] (Table 1). It yields a maximum score of 14, with a score
32 >4 considered to be high risk for mortality in prior studies [20]. Because
33 we collected altered mental status as a binary variable (present or not),
34 we adapted this variable in the MEWS score to be 0 for normal mental status
35 and 2 for any altered mental status, rather than a range of severity of
36 altered mental statuses from 0-3. qSOFA includes three variables, with one
37 point given to each abnormal value, a maximum score of three, and ≥ 2
38 considered high risk [15]. UVA includes seven variables, with variable
39 points given for each abnormality. It yields a maximum score of 13, with >4
40 considered high risk based on its derivation study [13].
41
42
43
44
45
46
47
48
49
50
51
52

53 To replicate the methods for predictive validity in the original
54 qSOFA and qSOFA LMIC validation studies [15, 25], we also calculated a
55
56
57
58
59
60

1
2
3 baseline risk model to stratify the population, using the same variables
4 used in these studies: age, sex, HIV status, and hospital transfer status
5 (whether the patient had been transferred from another facility).
6
7
8
9

11 **Data Analysis**

13 The primary outcome of interest was in-hospital mortality. The sample
14 size was determined based on adequate power for the antimicrobial
15 resistance study from which this cohort was taken, and is described in the
16 methods of that study [24]. Adapted MEWS, qSOFA, and UVA scores were
17 calculated for all enrolled participants. Missing data were assumed to be
18 within normal range, with no additional points assigned. Data are presented
19 as median (interquartile range, IQR) or frequency (proportion) depending on
20 variable type. Normality was assessed with the Shapiro-Wilk
21 test. Demographic differences between survivors and non-survivors were
22 assessed with a Wilcoxon rank-sum test, chi-square or Fisher's Exact test,
23 as appropriate. Sensitivity, specificity, positive and negative predictive
24 values for the previously-reported cutoffs for each score are reported.
25 Separate unadjusted logistic regression models were used to generate odds
26 ratios (OR) and 95% confidence intervals (CI) for adapted MEWS, qSOFA, and
27 UVA. Multivariable logistic regression models using the four variables
28 noted above were calculated for the baseline risk model.
29

30 We used the predicted probabilities from our baseline risk model to
31 stratify our results into risk quartiles, presenting ORs and 95% CIs for
32 adapted MEWS, qSOFA and UVA with their previously-defined cutoffs
33 separately, as was done in the original LMIC cohort qSOFA study [15]. We
34 calculated the discriminative ability of adapted MEWS, qSOFA, and UVA as
35
36
37
38
39
40
41
42
43
44
45

1
2
3 continuous variables and found the area under the receiver operating
4 characteristic (AUROC) curves for each of these models. We also calculated
5 the discriminative ability of the three scores as continuous variables in
6 models with baseline risk adjustment.
7
8
9

10
11 Data analysis was performed using SAS 9.4 (SAS Institute Inc., Cary,
12 NC) with two-sided p-values < 0.05 considered statistically significant.
13
14
15

16 17 **RESULTS**

18
19 We screened every patient in the hospital for suspected infection
20 each day of the study period, for a total of 19,178 patient-days screened.
21 We enrolled 647 of the 648 unique patients who met our criteria for
22 suspected infection; the only exclusion was one patient who met study
23 criteria but declined enrollment. Within this study population, 497
24 participants (76.8%) had hypo or hyperthermia and suspected infection, 308
25 participants (47.6%) underwent surgery for an infectious process, and 273
26 participants (42.2%) had a positive microbial culture (Supplemental Figure
27 1). The median age was 35 years (IQR 27, 51) and 347 (53.6%) of
28 participants were male (Table 2). Known pre-existing comorbidities were
29 present in 143 (22.1%) of participants, and 68 (10.5%) of participants were
30 known to be HIV positive.
31
32
33
34
35
36
37
38
39
40
41
42
43

44 In the full cohort, the in-hospital mortality rate was 18.1% (117 of
45 647 participants). An adapted MEWS score of >4 was present in 29.7%
46 (192/647) of cases, qSOFA score of ≥ 2 was present in 12.5% (81/647) of
47 cases, while a UVA score >4 was present in 12.4% (80/647) of cases (Table
48 2). The full distribution for each score is shown in Figure 1, with adapted
49 MEWS range 0-10, median 3, IQR 2,5; qSOFA range 0-3, median 0, IQR 0,1; and
50
51
52
53
54
55
56
57
58
59

1
2
3 UVA range 0-8, median 2, IQR 0,4. The proportion of data that was missing
4 for the components of the scores ranged from 0% to 11.7% (Supplemental
5 Table 1).
6
7

8
9 The sensitivity and specificity of the adapted MEWS score with cutoff
10 value >4 to predict in-hospital mortality were 50.4% (59/117) and 74.9%
11 (397/530), respectively (Table 3). The sensitivity and specificity of qSOFA
12 with cutoff value ≥ 2 were 24.8% (29/117) and 90.4% (479/530), respectively.
13 For the UVA score with cutoff value >4, the sensitivity and specificity
14 were 28.2% (33/117) and 91.1% (483/530), respectively. The sensitivity,
15 specificity, positive predictive value, and negative predictive value for
16 each score using the full range of possible cutoff values are presented in
17 Supplemental Table 2. The unadjusted ORs for adapted MEWS>4, qSOFA ≥ 2 and
18 UVA >4 were 3.04 (95% CI 2.01, 4.59), 3.10 (95% CI 1.86, 5.15) and 4.04
19 (95% CI 2.44, 6.67), respectively. The OR for hospital mortality was most
20 often >1 for each binary score within each quartile of baseline risk,
21 though the 95% CI for the OR crossed one for qSOFA and UVA in quartile 4,
22 and for adapted MEWS in quartile 1 (Supplemental Figure 2).
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37

38 Overall, increasing scores for adapted MEWS, qSOFA and UVA
39 corresponded with increasing mortality, though this was not true for every
40 one-point increase in adapted MEWS (Figure 1). For each one point increase
41 in score as a continuous variable, the unadjusted odds ratios were: adapted
42 MEWS 1.41 (95% CI 1.28, 1.56), qSOFA 2.20 (95% CI 1.68, 2.88), and UVA
43 1.46 (1.32, 1.61) (Supplemental Table 3).
44
45
46
47
48
49
50

51 The area under the receiver operating curve (AUROC) for each score as
52 a continuous variable was: adapted MEWS 0.69 (95% CI 0.64, 0.74), qSOFA
53 0.65 (95% CI 0.60, 0.70), and UVA 0.71 (95% CI 0.66, 0.76) (Figure 2,
54
55
56
57
58
59
60

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

1
2
3 determine differences in severity of illness between cohorts [13]. For
4 determining the predictive validity of a definition of sepsis, assessing
5 mortality risk above baseline risk may be most appropriate [15]. For
6 deciding who needs escalation of care, the sensitivity and specificity with
7 a particular cutoff value is likely to be more important in judging the
8 adequacy of the model [11]. Particularly in the latter example, which is
9 the most oft-cited use for scores in LMICs, care must be taken in how the
10 scores are used for individual clinical decision-making since low
11 sensitivity could lead to patients who need additional care being missed
12 and low specificity could lead to attempts at using scarce resources for a
13 relatively large population [11, 26, 27].

14
15 Our study has several strengths. We looked at adult patients across
16 the entire hospital rather than the ICU alone [1, 2, 7, 10, 16, 17], which
17 is particularly important in settings where many critically ill patients
18 remain outside the ICU due to limited ICU capacity [13]. We also analyzed
19 the score performances in multiple ways: as continuous scores, continuous
20 scores added to baseline risk, and as dichotomous values. In addition, the
21 retrospective multi-site LMIC qSOFA validation included a cohort from the
22 emergency department of our hospital [15]; our cohort and that cohort
23 showed similarly modest predictive capacity for the continuous qSOFA score
24 without baseline model, providing criterion validity to our results (AUROC
25 0.55 in the multisite study and 0.65 in this study). Finally, other than
26 one small study confined to emergency department patients and with a low
27 (5%) mortality rate [23], our study is the first to assess the UVA score
28 outside of its LMIC derivation cohort [13].
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Our study also has several limitations. We conducted it in a single
4 tertiary care hospital in sub-Saharan Africa, so its results may not be
5 generalizable. Even more complex severity of illness scores derived from
6 much larger populations, such as the APACHE score for ICU patients in HICs,
7 have quite variable performance, requiring recalibration for different
8 populations and over time in the same population [12, 28, 29]. It is
9 reasonable to expect that variations in patient characteristics, management
10 systems, and resources across hospitals would translate to different
11 predictive capacities of scores across hospitals. Of note, in the
12 retrospective study of qSOFA in nine LMIC cohorts, the AUROC for all
13 combined sites without the baseline model was 0.69, but the AUROC range for
14 individual sites was wide, from 0.55 to 0.81 [15]. Second, the variables
15 used to calculate the scores for patients in our study were recorded from
16 different time points (time of fever, operation, or culture sample
17 retrieval) depending on the inclusion criteria each participant met for the
18 study. This likely simulates how the scores might be used in practice;
19 however, it is certainly possible the scores would perform better with more
20 consistent data collection time points. We may also have a survivor bias of
21 unknown direction since patients who died rapidly after admission to the
22 hospital before they could be screened, or who died before infection was
23 suspected, were not included. Third, oxygen saturation was included as a
24 variable, without oxygen delivery; this was a feature of the UVA score
25 design, but it nonetheless seems likely that oxygen saturation without
26 oxygen delivery will be more limited in its predictive power. Fourth, we
27 had some missing data, up to 11.7% for oxygen saturation, for which we
28 assumed normal values; however, the missingness was relatively low compared
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 to many other LMIC studies [1, 12] and reflects reasonable real-world data
4 availability. Fifth, our positive culture rate of 42.2% in this population
5 is likely artificially high given that one of the inclusion criteria for
6 the study was a positive culture. Finally, we were unable to evaluate the
7 original MEWS score since we did not have detailed mental status data. We
8 used an adapted MEWS with a binary version of the mental status variable
9 without prior validation of this adaptation; these scores could have been
10 over- or under-estimated and therefore impacted the score's capacity to
11 differentiate participants.
12
13
14
15
16
17
18
19
20
21
22
23

24 **CONCLUSIONS**

25
26 Our study found modest predictive power of adjusted MEWS, qSOFA, and
27 UVA scores in our cohort of inpatients with suspected infection at a
28 Rwandan tertiary hospital. These modest predictive performances must be
29 acknowledged if these scores are to be considered for use in research
30 comparisons, quality improvement, or clinical decision-making.
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Acknowledgments: We thank Claude Mambo Muvunyi, Theoneste Nkubana, Emile Musoni, and Jean-Paul Mvukiyehé for their excellent research assistance.

For peer review only

References

1. Haniffa R, Isaam I, De Silva AP, Dondorp AM, De Keizer NF, (2018) Performance of critical care prognostic scoring systems in low and middle-income countries: a systematic review. *Critical care* (London, England) 22: 18
2. Lalani HS, Waweru-Siika W, Mwogi T, Kituyi P, Egger JR, Park LP, Kussin PS, (2018) Intensive Care Outcomes and Mortality Prediction at a National Referral Hospital in Western Kenya. *Annals of the American Thoracic Society* 15: 1336-1343
3. Opio MO, Nansubuga G, Kellett J, (2013) Validation of the VitalPAC Early Warning Score (ViEWS) in acutely ill medical patients attending a resource-poor hospital in sub-Saharan Africa. *Resuscitation* 84: 743-746
4. Aluisio AR, Garbern S, Wiskel T, Mutabazi ZA, Umuhire O, Ch'ng CC, Rudd KE, D'Arc Nyinawankusi J, Byiringiro JC, Levine AC, (2018) Mortality outcomes based on ED qSOFA score and HIV status in a developing low income country. *The American journal of emergency medicine* 36: 2010-2019
5. Khwannimit B, Bhurayanontachai R, Vattanavanit V, (2018) Comparison of the performance of SOFA, qSOFA and SIRS for predicting mortality and organ failure among sepsis patients admitted to the intensive care unit in a middle-income country. *Journal of critical care* 44: 156-160
6. Boillat-Blanco N, Mbarack Z, Samaka J, Mlaganile T, Mamin A, Genton B, Kaiser L, Calandra T, D'Acremont V, (2018) Prognostic value of quickSOFA as a predictor of 28-day mortality among febrile adult

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

patients presenting to emergency departments in Dar es Salaam, Tanzania. PloS one 13: e0197982

7. Sendagire C, Lipnick MS, Kizito S, Kruisselbrink R, Obua D, Ejoku J, Ssemogerere L, Nakibuuka J, Kwizera A, (2017) Feasibility of the modified sequential organ function assessment score in a resource-constrained setting: a prospective observational study. BMC anesthesiology 17: 12
8. Carugati M, Zhang HL, Kilonzo KG, Maze MJ, Maro VP, Rubach MP, Crump JA, (2018) Predicting Mortality for Adolescent and Adult Patients with Fever in Resource-Limited Settings. The American journal of tropical medicine and hygiene 99: 1246-1254
9. Baig MA, Sheikh S, Hussain E, Bakhtawar S, Subhan Khan M, Mujtaba S, Waheed S, (2018) Comparison of qSOFA and SOFA score for predicting mortality in severe sepsis and septic shock patients in the emergency department of a low middle income country. Turkish journal of emergency medicine 18: 148-151
10. Prin M, Pan S, Kadyaudzu C, Li G, Charles A, (2018) Development of a Malawi Intensive care Mortality risk Evaluation (MIME) model, a prospective cohort study. International journal of surgery (London, England) 60: 60-66
11. Machado FR, Cavalcanti AB, Monteiro MB, Sousa JL, Bossa A, Bafi AT, Dal-Pizzol F, Freitas FGR, Lisboa T, Westphal GA, Japiassu AM, Azevedo LC, (2020) Predictive Accuracy of the Quick Sepsis-Related Organ Failure Assessment Score in Brazil: A Prospective Multicenter Study. American journal of respiratory and critical care medicine

- 1
2
3 12. Beane A, De Silva AP, De Silva N, Sujeewa JA, Rathnayake RMD, Sigera
4 PC, Athapattu PL, Mahipala PG, Rashan A, Munasinghe SB, Jayasinghe
5 KSA, Dondorp AM, Haniffa R, (2018) Evaluation of the feasibility and
6 performance of early warning scores to identify patients at risk of
7 adverse outcomes in a low-middle income country setting. *BMJ open* 8:
8 e019387
9
10
11
12
13
14
15 13. Moore CC, Hazard R, Saulters KJ, Ainsworth J, Adakun SA, Amir A,
16 Andrews B, Auma M, Baker T, Banura P, Crump JA, Grobusch MP, Huson
17 MAM, Jacob ST, Jarrett OD, Kellett J, Lakhi S, Majwala A, Opio M,
18 Rubach MP, Rylance J, Michael Scheld W, Schieffelin J, Ssekitoleko R,
19 Wheeler I, Barnes LE, (2017) Derivation and validation of a universal
20 vital assessment (UVA) score: a tool for predicting mortality in
21 adult hospitalised patients in sub-Saharan Africa. *BMJ global health*
22 2: e000344
23
24
25
26
27
28
29
30
31
32 14. Baker T, Schell CO, Lugazia E, Blixt J, Mulungu M, Castegren M,
33 Eriksen J, Konrad D, (2015) Vital Signs Directed Therapy: Improving
34 Care in an Intensive Care Unit in a Low-Income Country. *PloS one* 10:
35 e0144801
36
37
38
39
40 15. Rudd KE, Seymour CW, Aluisio AR, Augustin ME, Bagenda DS, Beane A,
41 Byiringiro JC, Chang CH, Colas LN, Day NPJ, De Silva AP, Dondorp AM,
42 Dunser MW, Faiz MA, Grant DS, Haniffa R, Van Hao N, Kennedy JN,
43 Levine AC, Limmathurotsakul D, Mohanty S, Nosten F, Papali A,
44 Patterson AJ, Schieffelin JS, Shaffer JG, Thuy DB, Thwaites CL,
45 Urayeneza O, White NJ, West TE, Angus DC, (2018) Association of the
46 Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA)
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 Score With Excess Hospital Mortality in Adults With Suspected
4
5 Infection in Low- and Middle-Income Countries. *Jama* 319: 2202-2211
6
7 16. Haniffa R, Mukaka M, Munasinghe SB, De Silva AP, Jayasinghe KSA,
8
9 Beane A, de Keizer N, Dondorp AM, (2017) Simplified prognostic model
10
11 for critically ill patients in resource limited settings in South
12
13 Asia. *Critical care (London, England)* 21: 250
14
15 17. Riviello ED, Kiviri W, Fowler RA, Mueller A, Novack V, Banner-
16
17 Goodspeed VM, Weinkauff JL, Talmor DS, Twagirimugabe T, (2016)
18
19 Predicting Mortality in Low-Income Country ICUs: The Rwanda Mortality
20
21 Probability Model (R-MPM). *PloS one* 11: e0155858
22
23 18. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan
24
25 E, Camporota L, Slutsky AS, (2012) Acute respiratory distress
26
27 syndrome: the Berlin Definition. *Jama* 307: 2526-2533
28
29
30 19. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer
31
32 M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS,
33
34 Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll
35
36 T, Vincent JL, Angus DC, (2016) The Third International Consensus
37
38 Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama* 315: 801-810
39
40 20. Subbe CP, Kruger M, Rutherford P, Gemmel L, (2001) Validation of a
41
42 modified Early Warning Score in medical admissions. *QJM : monthly*
43
44 *journal of the Association of Physicians* 94: 521-526
45
46 21. Morgan RJM WF, Wright MM, (1997) An Early Warning Scoring System for
47
48 detecting developing critical illness. *Clinical Intensive Care:*
49
50 *International Journal of Critical & Coronary Care Medicine* 8: 100
51
52
53 22. Kruisselbrink R, Kwizera A, Crowther M, Fox-Robichaud A, O'Shea T,
54
55 Nakibuuka J, Ssinabulya I, Nalyazi J, Bonner A, Devji T, Wong J, Cook
56
57
58
59
60

- 1
2
3 D, (2016) Modified Early Warning Score (MEWS) Identifies Critical
4
5 Illness among Ward Patients in a Resource Restricted Setting in
6
7 Kampala, Uganda: A Prospective Observational Study. PloS one 11:
8
9 e0151408
10
- 11 23. Schmedding M, Adegbite BR, Gould S, Beyeme JO, Adegnika AA, Grobusch
12
13 MP, Huson MAM, (2019) A Prospective Comparison of Quick Sequential
14
15 Organ Failure Assessment, Systemic Inflammatory Response Syndrome
16
17 Criteria, Universal Vital Assessment, and Modified Early Warning
18
19 Score to Predict Mortality in Patients with Suspected Infection in
20
21 Gabon. The American journal of tropical medicine and hygiene 100:
22
23 202-208
24
- 25 24. Sutherland T, Mpirimbanyi C, Nziyomaze E, Niyomugabo JP, Niyonsenga
26
27 Z, Muvunyi CM, Mueller A, Bebell LM, Nkubana T, Musoni E, Talmor D,
28
29 Rickard J, Riviello ED, (2019) Widespread antimicrobial resistance
30
31 among bacterial infections in a Rwandan referral hospital. PloS one
32
33 14: e0221121
34
35
- 36 25. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A,
37
38 Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS,
39
40 Escobar GJ, Angus DC, (2016) Assessment of Clinical Criteria for
41
42 Sepsis: For the Third International Consensus Definitions for Sepsis
43
44 and Septic Shock (Sepsis-3). Jama 315: 762-774
45
- 46 26. Sinuff T, Adhikari NK, Cook DJ, Schunemann HJ, Griffith LE, Rocker G,
47
48 Walter SD, (2006) Mortality predictions in the intensive care unit:
49
50 comparing physicians with scoring systems. Critical care medicine 34:
51
52 878-885
53
54
55
56
57
58
59
60

- 1
2
3 27. Aoyama K, D'Souza R, Pinto R, Ray JG, Hill A, Scales DC, Lapinsky SE,
4 Seaward GR, Hladunewich M, Shah PS, Fowler RA, (2018) Risk prediction
5 models for maternal mortality: A systematic review and meta-analysis.
6 PloS one 13: e0208563
7
8
9
10
11 28. Salluh JI, Soares M, (2014) ICU severity of illness scores: APACHE,
12 SAPS and MPM. Current opinion in critical care 20: 557-565
13
14
15 29. Haniffa R, Beane A, Baker T, Riviello ED, Schell CO, Dondorp AM,
16 (2018) Development and internal validation of the Simplified
17 Mortality Score for the Intensive Care Unit (SMS-ICU). Acta
18 anaesthesiologica Scandinavica 62: 407-408
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Figure Legends**
4
5

6 **Figure 1.** Distribution of Patients (A) and Observed Mortality (B) with
7 standard errors by adapted Modified Early Warning Score (MEWS), Quick
8 Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Score and
9 Universal Vital Assessment (UVA) Among Patients With Suspected Infection
10
11
12
13

14 **Figure 2.** Receiver Operating Characteristic Curves for adapted MEWS, qSOFA,
15 or UVA Criteria as Continuous Variables
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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, <i>beats/minute</i>				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, <i>mmHg</i>				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, <i>beats/minute</i>				< 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

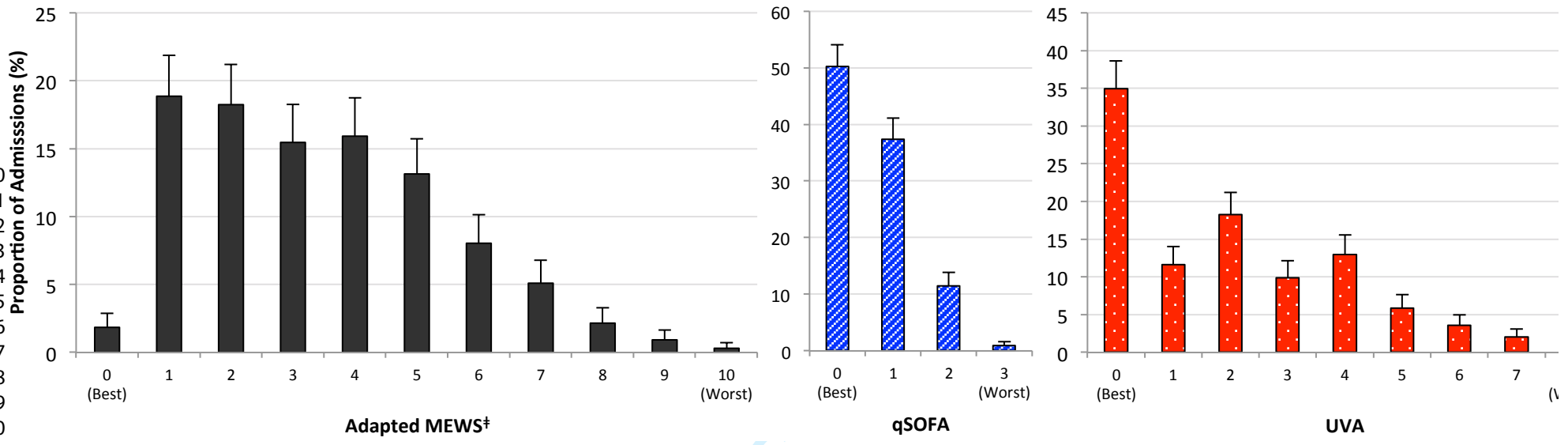
1
2 *Includes patients who had any of the following documented co-morbidities: diabetes, hypertension, tuberculosis, cancer,
3 and/or severe malnutrition. *The adaption to the MEWS score pertains to the altered mental status score. In the original
4 MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were
5 unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points for a patient with any altered
6 mental status.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

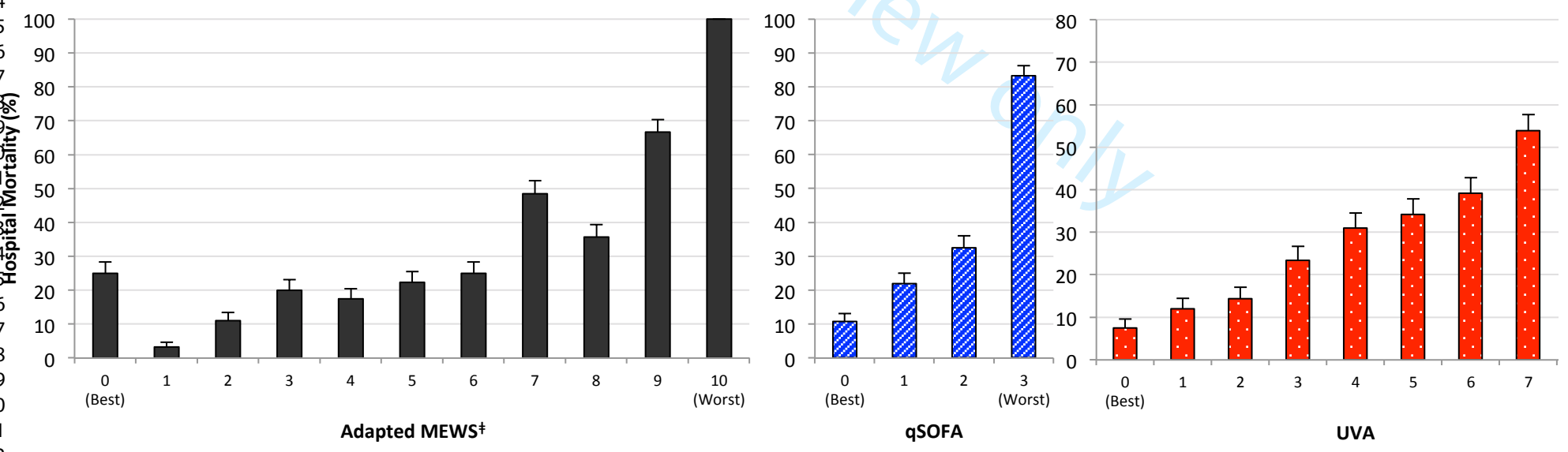
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

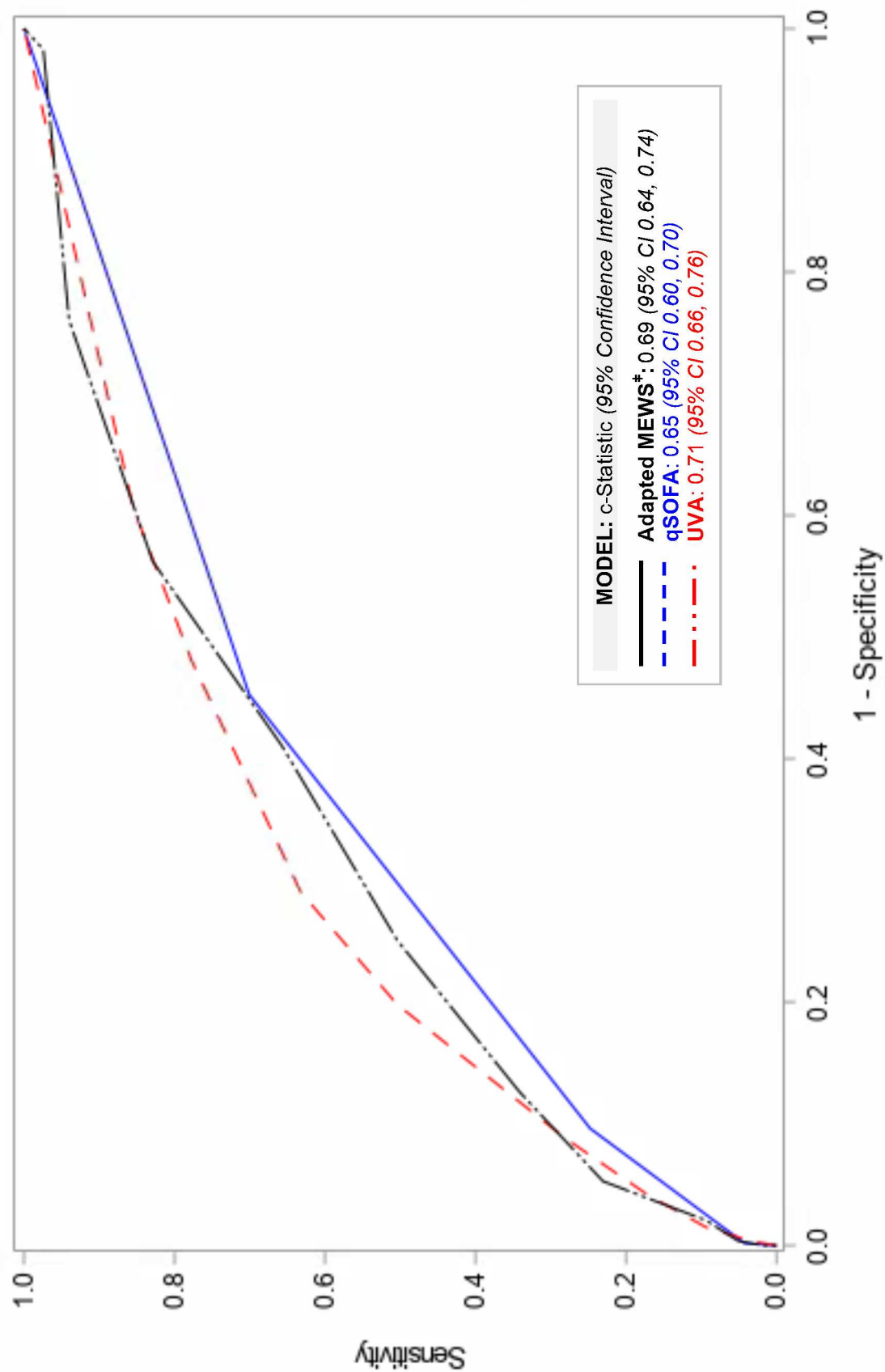
	Adapted MEWS[†] > 4	qSOFA ≥ 2	UVA > 4
Unadjusted			
Sensitivity	50.4	24.8	28.2
Specificity	74.9	90.4	91.1
Positive predictive value	30.7	36.2	41.2
Negative predictive value	87.2	84.5	85.2
OR (95% Confidence Interval)	3.04 (2.01, 4.59)	3.10 (1.86, 5.15)	4.04 (2.44, 6.67)
[†] The adaptation to the MEWS 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.			

[A] Distribution of Patients (n=647)

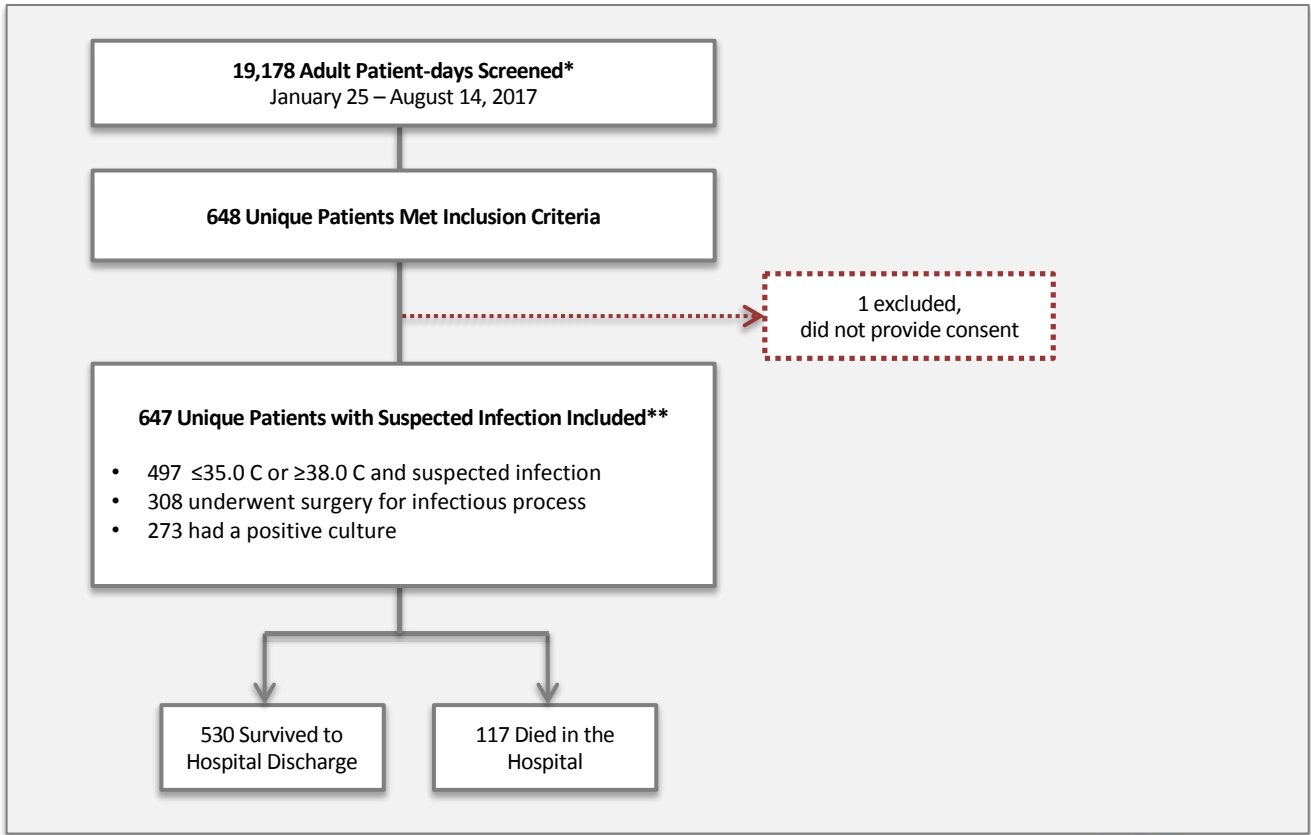


[B] Observed Mortality





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.

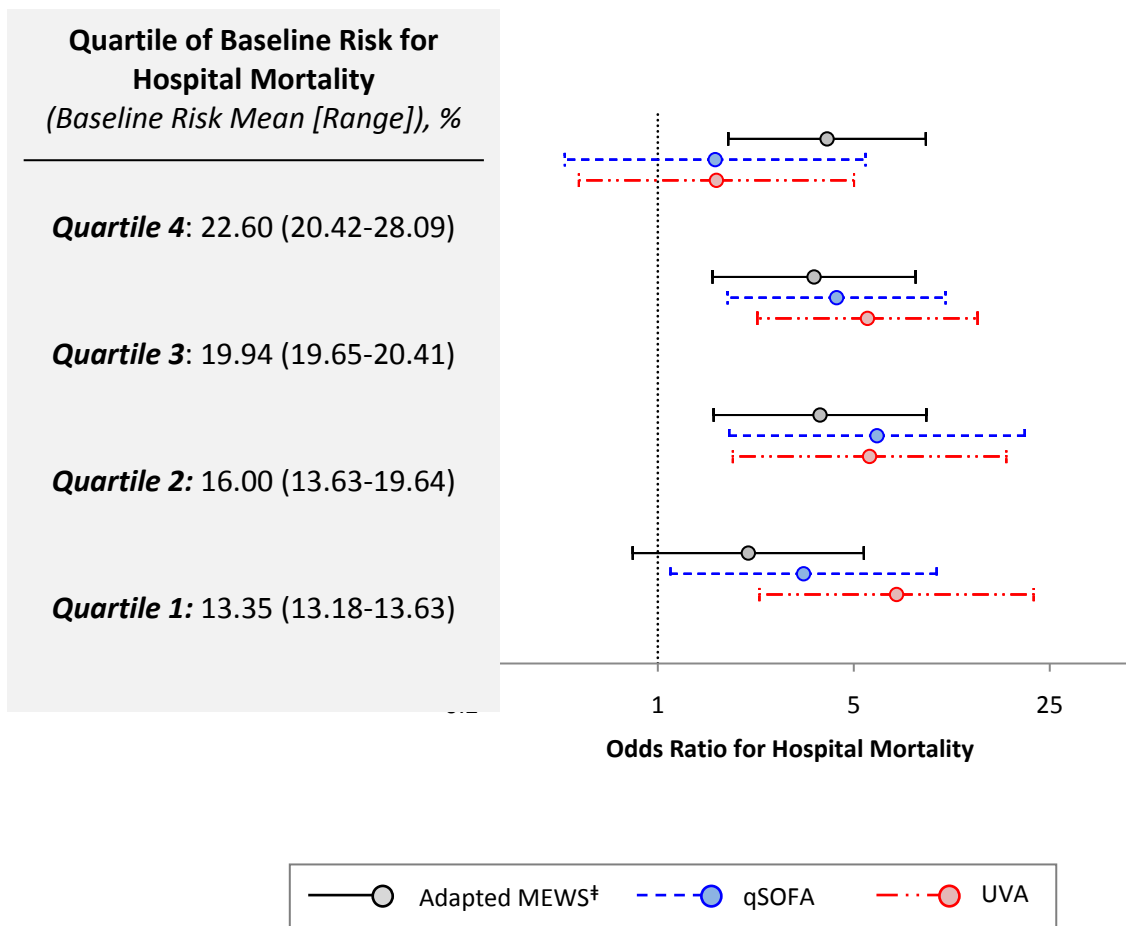
**Non-exclusive categories.
For patients who met more than one inclusion criteria, clinical data were recorded based on the first inclusion criteria met: at the time of fever or hypothermia, the time of surgery, or the time of culture sample collection, depending on the inclusion criteria met first for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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

Supplemental Table 1. Number and proportion of missing values for each variable	
	Total <i>N</i> = 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
<p>*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.</p> <p><i>Abbreviations: PPV = positive predictive values; NPV = negative predictive value;</i></p>				

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.

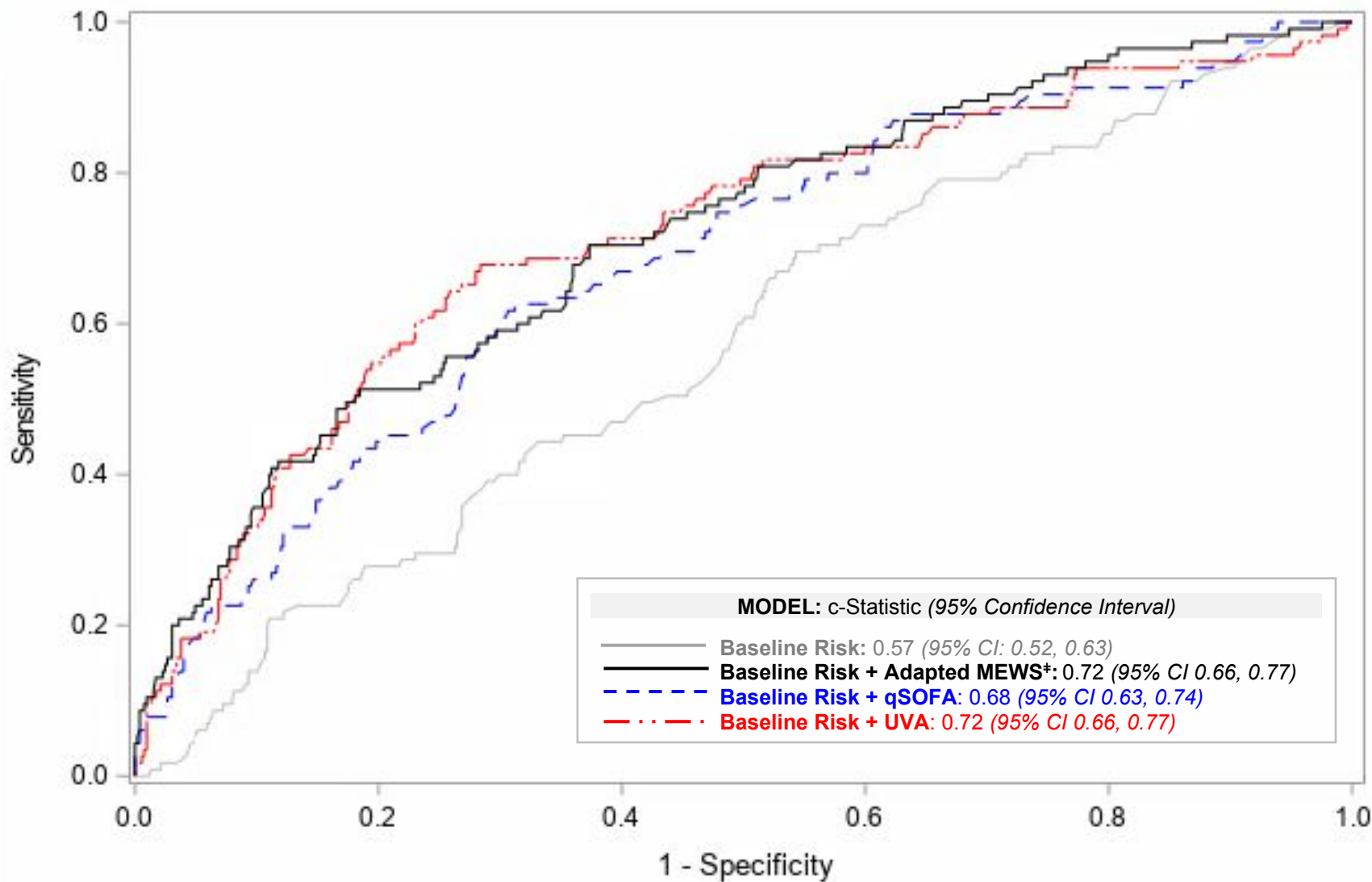
[†]The adaption to the MEWS score pertains to the altered mental status score. In the original MEWS, 0 points were assigned for alert patients, 1 if they reacted to voice, 2 if they reacted to pain, and 3 if they were unresponsive. In our adapted MEWS, we assign 0 points for an alert patient and 2 points 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 (<i>per 1 point increase</i>)	0.3445	0.0515	1.411 (1.276, 1.561)	<0.0001
MODEL 2 - qSOFA				
Intercept	-2.1088	0.1597	---	<0.0001
qSOFA (<i>per 1 point increase</i>)	0.7891	0.1372	2.201 (1.682, 2.880)	<0.0001
MODEL 3 - UVA				
Intercept	-2.4477	0.1832	---	<0.0001
UVA (<i>per 1 point increase</i>)	0.3769	0.0511	1.458 (1.319, 1.611)	<0.0001

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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

1	8	Main 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		
2				(b) Report category boundaries when continuous variables were categorized		
3				(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
4						
5						
6						
7						
8						
9		Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8	
10						
11		Discussion				
12						
13		Key results	18	Summarise key results with reference to study objectives	9	
14		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	
15						
16		Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10	
17						
18		Generalisability	21	Discuss the generalisability (external validity) of the study results	10	
19						
20		Other information				
21						
22		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	
23						
24						

*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>.