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The performance of screening tools for predicting mortality across multi-site international sepsis cohorts

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2
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2
3 **32 Abstract:**
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5 **33** Word count: 276
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7 **34 Objectives:** We evaluated the performance of commonly used sepsis screening tools across prospective
8
9 **35** sepsis cohorts in the United States, Cambodia, and Ghana.

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11 **36 Design:** Prospective cohort studies

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13 **37 Setting and participants:** From 2014 to 2021, participants with 2 or more SIRS (Systemic Inflammatory
14
15 **38** Response Syndrome) criteria and suspected infection were enrolled in emergency departments and
16
17 **39** medical wards at hospitals in the Cambodia and Ghana and hospitalized participants with suspected
18
19 **40** infection were enrolled in the United States. Cox proportional hazards regression was performed, and
20
21 **41** Harrell's C-statistic calculated to determine 28-day mortality prediction performance of the qSOFA score
22
23 **42** ≥ 2 , SIRS score ≥ 3 , NEWS ≥ 5 , MEWS ≥ 5 , or UVA score ≥ 2 . Screening tools were compared to baseline
24
25 **43** risk (age and sex) with the Wald test.
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27

28
29 **44 Results:** The cohorts included 567 participants (42.9% female) including 187 participants from Kumasi,
30
31 **45** Ghana, 200 participants from Takeo, Cambodia, and 180 participants from Durham, North Carolina in the
32
33 **46** United States. The pooled mortality was 16.4% at 28-days. The mortality prediction accuracy increased
34
35 **47** from baseline risk with the MEWS (C-statistic: 0.63, 95% CI: 0.58, 0.68; $p=0.002$), NEWS (C-statistic:
36
37 **48** 0.68; 95% confidence interval [CI]: 0.64, 0.73; $p<0.001$), qSOFA (C-statistic: 0.70, 95% CI: 0.64, 0.75;
38
39 **49** $p<0.001$), UVA score (C-statistic: 0.73, 95% CI: 0.69, 0.78; $p<0.001$), but not with SIRS (0.60; 95% CI:
40
41 **50** 0.54, 0.65; $p=0.13$). Within individual cohorts, only the UVA score in Ghana performed better than
42
43 **51** baseline risk (C-statistic: 0.77; 95% CI: 0.71, 0.83; $p<0.001$).
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45
46 **52 Conclusions:** Among the cohorts, MEWS, NEWS, qSOFA, and UVA scores performed better than
47
48 **53** baseline risk, largely driven by accuracy improvements in Ghana, while SIRS scores did not improve
49
50 **54** prognostication accuracy. Prognostication scores should be validated within the target population prior to
51
52 **55** clinical use.

53
54 **56** Keywords: Analysis, Survival; sepsis; Cohort Studies; Prognosis; Global Health
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3 **58 Strengths and limitations of this study:**
4

- 5 59 • While single-centre cohorts and retrospective analyses have been performed, the optimal sepsis
6 screening tool for prognostication in low- and middle-income countries is unknown. This study
7 60 includes two well-characterized sepsis cohorts in LMICs and a cohort in a high-resource setting
8 for comparison.
9 61
10 62
11 63 • Five sepsis screening tools (i.e., qSOFA score, SIRS score, NEWS, MEWS, and UVA score)
12 were evaluated across three international cohorts for one-month mortality prognostication,
13 providing comprehensive performance estimates in settings with disparate causes of sepsis.
14 64
15 65
16 66 • Diagnostic testing differed at each site and mortality specifically due to sepsis could not be
17 determined.
18 67
19 68 • Enrolment was by convenience sampling within the referral hospital catchment area and may not
20 be representative of the general population within these countries.
21 69
22 70 • While SIRS was identified as a tool with inferior prognostic performance, sample size limitations
23 in each of the cohorts may have led to decreased ability to identify differences between each
24 screening tool.
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75 **Narrative:**

76 Word count: 3,783
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78 **INTRODUCTION**

79 Sepsis, a syndrome resulting from a systemic dysregulated host response to an infection, is estimated to
80 cause six million deaths per year but is likely an underestimate due to limited information from low- and
81 middle-income countries (LMICs) where 87% of the world population live ¹. Despite declining age-

1
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3 82 standardized incidence and mortality, sepsis remains a major cause of health loss worldwide and has an
4
5 83 especially high health-related burden in LMICs².
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9 85 Clinical sepsis guidelines developed in the Western world may not be applicable in resource-limited settings
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11 86 and moreover can lead to detrimental effects on sepsis care and management when applied in these
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13 87 conditions due to decreased access to resources to manage iatrogenesis from fluid resuscitation ^{3 4}. In
14
15 88 contrast to the United States, pathogens that lead to directly lead to vascular injury are common causes of
16
17 89 acute febrile illness in Cambodia and Ghana such as dengue virus, malaria, or rickettsia and may alter
18
19 90 empiric treatment response ⁵. While early recognition and treatment of sepsis is critical, most sepsis scores
20
21 91 or early warning systems were derived from cohorts outside of LMICs. Differences in causes of sepsis,
22
23 92 available treatments, and available resources for supportive care should affect management strategies but
24
25 93 evidence is limited and optimal clinical scores or biomarkers for sepsis identification are unknown in these
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27 94 settings. Multi-site international sepsis studies are essential for evaluating current and future sepsis tools to
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29 95 ensure effectiveness in resource-limited settings and across populations.
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35 97 The most validated prognostication scores, SOFA (Sequential Organ Failure Assessment) and the
36
37 98 APACHE IV, have been developed for prognostication but require an arterial blood gas and multiple
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39 99 laboratory parameters ^{6 7} that are not widely available in low-resource settings. The qSOFA (quick SOFA)
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41 100 is an abbreviated score that does not require laboratory parameters. The qSOFA is one of the most widely
42
43 101 adopted sepsis screening tools and has largely replaced the SIRS (Systemic Inflammatory Response
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45 102 Syndrome) criteria as the standard abbreviated sepsis screening tool as part of the Sepsis-3 definition to
46
47 103 identify septic patients ⁸. While the qSOFA and other sepsis screening tools (i.e., Modified Early Warning
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49 104 Score [MEWS], National Early Warning Score [NEWS], and Universal Vital Assessment [UVA]) were
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51 105 developed to identify sepsis, these tools can be used rapidly in the clinical setting and have been studied for
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53 106 their ability to prognosticate mortality among those with suspected sepsis ⁹. Studies have evaluated these
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55 107 tools for predicting in-hospital mortality but the performance of these tools and the prevalence of 28-day
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3 108 mortality, a common metric of sepsis outcomes, have yet to be described across both high- and low-resource
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5 109 settings using similar methods ⁹⁻¹¹.

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9 111 We evaluated the performance of sepsis screening tools across prospective multi-site international cohorts
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11 112 that are part of the Austere environments Consortium for Enhanced Sepsis Outcomes (ACESO) consortium
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13 113 ¹². In contrast to APACHE IV and SOFA, these tools can be quickly performed with limited laboratory test
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15 114 results. We hypothesized that qSOFA may perform poorly in LMIC populations compared to the UVA
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17 115 score due to differences in causes of sepsis. We describe the diverse clinical characteristics, the aetiologies
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19 116 of suspected sepsis within these cohorts, and the performance of sepsis screening tools in current clinical
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21 117 use for predicting mortality at one month post enrolment.
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26 119 **METHODS**
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28 120 From May 2014 to November 2015, 200 participants were enrolled into a prospective observational study
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30 121 of sepsis at Takeo Provincial Hospital in Takeo Province Cambodia ¹³. This study was followed by a
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32 122 prospective study at Duke University Hospital in Durham, North Carolina, which enrolled 180 participants
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34 123 from December 2014 to March 2016. In Kumasi, Ghana, participants were enrolled at Komfo Anokye
35
36 124 Teaching Hospital from July 2016 to October 2017. Study protocols were approved by the Naval Medical
37
38 125 Research Center (NMRC) Institutional Review Board (IRB) (Cambodia sepsis study # NMRC.2013.0019;
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40 126 Ghana sepsis study # NMRC.2016.0004-GHA; Duke sepsis study Duke#PRO00054849) in compliance
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42 127 with all applicable Federal regulations governing the protection of human subjects as well as host country
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44 128 IRBs. The study protocol in Cambodia was approved by the Cambodian National Ethics Committee for
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46 129 Health Research (NECHR). The protocol in Ghana was approved by the Committee on Human Research,
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48 130 Publication and Ethics (CHRPE) at Kwame Nkrumah University of Science & Technology. All procedures
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50 131 were in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association.
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52 132 All patients, or their legally authorized representatives, provided written informed consent.
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3 133 Hospitalized patients ≥ 18 years of age whose attending physician judged them to have an active infection
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5 134 were considered for inclusion for each of the three cohorts. Additional inclusion and exclusion criteria
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7 135 were required in Cambodia and Ghana but not required in the United States protocol. In Cambodia and
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9 136 Ghana, participants were required to meet least two clinical criteria for systemic inflammatory response
10
11 137 syndrome (SIRS) during screening. In Cambodia and Ghana, patients were excluded if they had known
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13 138 malignancy, chronic renal/hepatic insufficiency, immunosuppressive conditions (except HIV) or systemic
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15 139 steroid usage that exceeded 20mg/day to prevent confounding in future biomarker studies. Patients were
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17 140 also excluded in Cambodia and Ghana if they had a history of organ transplant, hemodynamically
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19 141 significant gastrointestinal bleeding, anatomic or functional asplenia, acute cardiovascular disease,
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21 142 general anaesthesia, or surgery in the past week prior to enrolment, women who were pregnant, patients
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23 143 who had a haemoglobin less than 7 g/dL or weighed less than 35kg. Hospital physicians who deemed
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25 144 their patients too ill to participate could defer enrolment.
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29 145 Following informed consent, study team members conducted a detailed medical history, including prior
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31 146 medications, and physical exam. Responses were recorded on a standardized case report form and
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33 147 included demographics, medical history, physical exam findings, and admission diagnoses. Study specific
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35 148 procedures conducted in Cambodia were described in detail by Rozo et al ¹⁴. Similar enrolment and study
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37 149 procedures were followed in Kumasi, Ghana and in Durham, North Carolina, USA. Blood was collected
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39 150 at the time of enrolment, then at 6 hours later, and at 24 hours later. In Ghana and Cambodia, standardized
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41 151 clinical tests included a peripheral venous blood gas with lactate, complete blood count, complete
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43 152 metabolic panel, optional HIV screening with consent (Alere Determine HIV1/2, Abbott, OK, United
44
45 153 States), malaria rapid diagnostic tests (SD Bionline Ag. P.f./Pan, Abbott, OK, United States) and aerobic
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47 154 blood cultures (one aerobic bottle, Bactec 9050, BD, NJ, United States) as part of study procedures in
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49 155 Ghana and Cambodia. Microbiologic results were available if collected through routine clinical care
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51 156 across cohorts. Additional molecular testing and next generation sequencing for pathogens were also
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53 157 performed on blood samples in the Cambodia cohort as previously described ¹⁴. Participants were
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3 158 followed throughout their hospitalization and a record review performed at discharge. A follow-up
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5 159 interview was performed, and blood samples were collected at a 28-day follow-up visit across cohorts.
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7 160 When patients could not return in person, study team members attempted to conduct an interview with
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9 161 patients or a legally authorized representative by telephone. Fatal outcomes among each discharged
10
11 162 participant were also determined. Using clinical data from case report forms and microbiology diagnostic
12
13 163 information, clinical adjudication was performed by three physician reviewers (internal medicine or
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15 164 infectious diseases) to determine the source of infection by anatomic location and pathogen class. This
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17 165 was graded on a low, moderate, and high level of confidence by two independent reviewers and a third
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19 166 reviewer served as a tiebreaker for discordant conclusions. If the third reviewer did not agree with either
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21 167 adjudicator, then the decision was determined by committee. Microbiologic results presented include
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23 168 those adjudicated to be clinically relevant to participant's acute illness.
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27 28 170 *Patient and Public Involvement*

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30 171 Patients were not involved in recruitment, design, conduct, or dissemination plans of our research. Results
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32 172 of this study were disseminated to hospital and clinical leadership at Takeo Provincial Hospital and
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34 173 Komfo Anokye Teaching Hospital.
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39 175 Summary statistics were calculated for the cohorts individually and pooled, comparing baseline
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41 176 demographics (e.g., gender, age, ethnicity, selected medical comorbidities), baseline screening tool
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43 177 scores, physiologic parameters, baseline clinical laboratory values using either Chi-square (categorical
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45 178 values), Fishers exact (categorical values), or Mann-Whitney U tests (continuous values). Prevalence of
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47 179 diagnoses were described for each cohort by organ system and pathogen type (i.e., bacterial, viral,
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49 180 parasitic, or fungal aetiologies) and by anatomic site.
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53 182 After checking the proportional hazards assumption, Cox regression was performed with bivariable
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55 183 models to evaluate increased risk of death in each cohort by baseline demographics, comorbid conditions,
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3 184 physiologic parameters, and clinical laboratory parameters. Physiologic parameters and clinical laboratory
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5 185 parameters were modelled as dichotomous or ordinal parameters at clinically relevant cut offs. Screening
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7 186 tools were dichotomized according to current usage, including qSOFA score ≥ 2 (range, 0 [best] to 3
8
9 187 [worst] points), SIRS score ≥ 2 (range, 0 [best] to 4 [worst] points), MEWS ≥ 5 (range, 0 [best] to 13
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11 188 [worst] points), NEWS ≥ 5 (range, 0 [best] to 20 [worst] points), and UVA ≥ 2 (range, 0 [best] to 13
12
13 189 [worst])¹⁰ and were evaluated in Cox regression models unadjusted and adjusted for age and sex for risk
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15 190 of death⁹. Glasgow Coma Scale Score (GCS; range, 3 [worst] to 15 [best] points) of less than 15 was
16
17 191 used for estimation of the qSOFA score, and a GCS of ≤ 3 for unresponsiveness for NEWS, and GCS
18
19 192 score 3-15 for the “alert, verbal, pain, unresponsive” scale (AVPU; alert: GCS 13-15, voice: GCS 9-12;
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21 193 pain: GCS 4-8; unresponsiveness: GCS ≤ 3) score approximation for MEWS^{15 16}. Data was
22
23 194 administratively right censored past 28 days. The Harrell’s C-statistic was calculated for each screening
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25 195 tool for each cohort, the cohorts combined, and Cambodia and Ghana cohorts pooled¹⁷. This statistic is a
26
27 196 performance analogous to area under the receiver operating characteristic curve (AUROC) but accounts
28
29 197 for differences over time with survival outcomes. C-statistic confidence interval estimates were evaluated
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31 198 rather than a statistical test due to risk of type 1 error with that approach.¹⁸ The Cox regression Wald test
32
33 199 p-values were calculated for each score covariate was used adjusting for baseline risk estimated by age
34
35 200 and sex¹⁹. P-values < 0.002 were considered significant using a Bonferroni correction for multiple
36
37 201 comparisons. Cohort sample sizes were determined a priori through Monte Carlo simulation modelling
38
39 202 for prognostic biomarker identification. All statistical analyses were performed in SAS (Statistical
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41 203 Analytical Software, version 9.4), R version 4.0.2²⁰ or Stata (version 15.0; StataCorp LLC, College
42
43 204 Station, TX, USA)²¹.

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48 49 206 RESULTS

50 51 207 *Summary demographics, sepsis severity, and laboratory findings*

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53 208 There were 567 participants across the cohorts including 187 from Kumasi, Ghana, 200 from Takeo,
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55 209 Cambodia, and 180 from Durham, North Carolina, United States (**Figure 1**). The study population was

210 predominantly male (57.1% male), with more male participants enrolled in Cambodia than at other sites
 211 (68.0% vs 55.0% in the U.S. and 52.4% in Ghana). The overall median age was 50 years (interquartile
 212 range [IQR], 36 to 63), which was similar across cohorts (**Table 1**). Previously diagnosed comorbid
 213 conditions were most common at the U.S. site including a history of cardiovascular (65.6%; N=118),
 214 respiratory (42.2%; N=76), or gastrointestinal (36.7%; N=66) conditions.

Table 1. Baseline demographic characteristics stratified by sites.

Variable	Total	Takeo, Cambodia (n=200)	Durham, USA (n=180)	Kumasi, Ghana (n=187)
Female gender – no. (%)	243 (42.9%)	64 (32.0%)	81 (45.0%)	98 (52.4%)
Age – years, median (IQR)	50 (36 – 63)	50 (36 – 62)	52.5 (40 – 63)	46 (35 – 63)
Medical history* – no. (%)				
Cancer	44 (9.9%)	0 (0.0%)	44 (24.4%)	0 (0.0%)
Cardiovascular	202 (41.4%)	22 (18.2%)	118 (65.6%)	62 (33.2%)
Dermatologic	15 (3.1%)	1 (0.8%)	14 (7.8%)	0 (0.0%)
Endocrine	126 (25.8%)	6 (5.0%)	74 (41.1%)	46 (24.6%)
Gastrointestinal	76 (15.6%)	4 (3.3%)	66 (36.7%)	6 (3.2%)
Genitourinary or reproductive	34 (7.0%)	1 (0.8%)	33 (18.3%)	0 (0.0%)
HIV	26 (4.7%)	12 (6.2%)	8 (4.5%)	6 (3.2%)
Neurological	62 (12.7%)	1 (0.8%)	44 (24.4%)	17 (9.1%)
Other	206 (42.2%)	48 (39.7%)	151 (83.9%)	7 (3.7%)
Psychiatric	143 (29.3%)	41 (33.9%)	78 (43.3%)	24 (12.8%)
Renal	41 (8.4%)	0 (0.0%)	41 (22.8%)	0 (0.0%)
Respiratory	89 (18.2%)	7 (5.8%)	76 (42.2%)	6 (3.2%)
Rheumatologic	29 (5.9%)	1 (0.8%)	28 (15.6%)	0 (0.0%)
Surgery	27 (5.5%)	0 (0.0%)	22 (12.2%)	5 (2.7%)
Baseline scores – no. (%)				
MEWS (≥ 4)	315 (57.8%)	81 (40.7%)	105 (65.6%)	129 (69.3%)
NEWS score (≥ 5)	324 (61.6%)	90 (47.9%)	98 (64.5%)	136 (73.1%)
qSOFA (≥ 2)	139 (25.4%)	22 (11.1%)	48 (29.6%)	69 (37.1%)
SIRS (≥ 2)	447 (81.8%)	125 (68.3%)	157 (89.2%)	165 (88.2%)
UVA (≥ 2)	199 (37.8%)	47 (25.8%)	68 (42.8%)	84 (45.4%)

Table 1. Baseline demographic characteristics stratified by sites.

Variable	Total	Takeo, Cambodia (n=200)	Durham, USA (n=180)	Kumasi, Ghana (n=187)
Baseline scores (median [IQR])				
MEWS	4 (3-6)	3 (2-5)	1 (0-4)	1 (1-2)
NEWS	6 (3-8)	4 (2-7)	7 (3-9)	6 (4-8)
qSOFA	1 (1-2)	1 (0-1)	1 (0-2)	1 (1-2)
SIRS	2 (2-3)	2 (1-3)	3 (2-3)	3 (2-3)
UVA	1 (0-3)	1 (0-2)	1 (0-4)	1 (0-4)

215 Clinical physiologic and laboratory value abnormalities at enrolment were common with median
 216 respiratory rate at 24 (IQR: 20 to 30), the median white blood count elevated at 12.05×10^9 cells/L (IQR:
 217 8.13 to 16.6×10^9 cells/L), and median lactate elevated at 2.27 mmol/L (IQR: 1.66 to 3.09 mmol/L)
 218 (**Supplementary Table S1**). At enrolment, the proportion of an elevated qSOFA (≥ 2) at baseline was
 219 highest at the Ghana site with 44.4% (N=83) of participants compared to 26.0% (N=52) in Cambodia and
 220 22.2% (N=40) in the United States. The SIRS, MEWS, NEWS, and UVA screening tools were similarly
 221 higher in the Ghana cohort.

223 *Pathogens detected*

224 The most common positive microbiologic results overall included bacteraemia (N=83), respiratory culture
 225 growth (N=19), serum hepatitis B surface antigen (N=15), and malaria rapid diagnostic tests (N=11). A
 226 minority (121 of 567, 21.3%) of subjects had confirmed infections with complete adjudicator agreement
 227 using all available sources of clinical microbiologic results (with the notable addition of RNA sequencing
 228 of samples from Cambodia¹⁴) including 90 (15.9%) bacterial, 17 viral (3.0%), 20 malarial (3.5%), and 2
 229 (0.3%) fungal infections identified across all cohorts (**Supplementary Figure S1**).

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3 231 In Cambodia, the most common bacterial infections with complete adjudicator agreement were *B.*
4
5 232 *pseudomallei* (N=10, with blood or respiratory culture growth), presumptive *M. tuberculosis* (N=5, with
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7 233 acid fast positive smears), polymicrobial (N=5), and *O. tsutsugamushi* (N=4, determined by sequencing).
8
9 234 The most common causes of bacteraemia (17 total of 200 participants) were *B. pseudomallei* (N=8), *E.*
10
11 235 *coli* (N=3), and polymicrobial infections (N=3). Three participants had a positive malaria RDT. Fungal
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13 236 infections were uncommon with 1 participant with non-albicans Candidemia and 1 with cryptococcal
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15 237 meningitis. Two individuals had dengue fever (one PCR positive and one adjudicated IgM positive).
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20 239 In Ghana, the most common causes of bacteraemia (culture growth from 28 of 187 participants) were *E.*
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22 240 *coli* (N=6), *S. aureus* (N=6), *Salmonella spp.* (N=5), and *S. pneumoniae* (N=3). Nine participants had a
23
24 241 positive malaria RDT and 15 had a positive hepatitis B surface antigen.
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28 243 In the United States, the most common causes of bacteraemia (culture growth from 19 of 180
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30 244 participants) were *E.coli* (N=5), *K. pneumoniae* (N=3), polymicrobial (N=2), *Pseudomonas spp.* (N=2),
31
32 245 or *S. aureus* (N=2). Viral infections detected by PCR included rhinovirus (N=5), influenza A (N=4),
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34 246 respiratory syncytial virus (N=4), human immunodeficiency virus (N=3), and human metapneumovirus
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36 247 (N=3). There was one participant with *Aspergillus fumigatus* fungal pneumonia.
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41 249 *Diagnoses and Treatments*

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43 250 Across cohorts, the most common organ system sites of infection were lower respiratory tract infection
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45 251 (28.7%; N=163), multifocal or generalized source of infection (including malaria) (13.6%; N=77), and
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47 252 gastrointestinal (including hepatic) (12.7%; N=72) (**Figure S1a**). The most common antibiotics
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49 253 administered in United States, Ghana, and Cambodia were beta-lactam antibiotics (**Supplementary**
50
51 254 **Figure S2**), but antibiotic regimens varied widely among sites. The most common antibiotics classes used
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53 255 were other antibacterials (e.g., glycopeptide antibiotics, 58.9%), beta-lactam antibacterials, penicillins
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55 256 (51.7%), and cephalosporin and carbapenem antibacterials (44.4%) in the United States, cephalosporins

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3 257 and carbapenems (64.2%), macrolides, lincosamides and streptogramins (37.4%), and other antibacterials
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5 258 (33.7%) in Ghana, and cephalosporins and carbapenems (73.0%), beta-lactam antibacterials, penicillins
6
7 259 (46.5%) and aminoglycoside antibacterials (39.0%) in Cambodia.
8

9 260

11 261 *Survival*

13 262 Among all cohorts, 16.4% (N=93) of participants had died at one month, including 58 (31.0%) in Ghana,
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15 263 22 (11.0%) in Cambodia, and 13 (7.2%) in the U.S (**Figure 1**). Among those that died within one month,
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17 264 median time to death was 4 days (IQR: 1 to 11) in Ghana, 7 days (IQR: 3 to 16) in Cambodia, 10 (IQR: 5
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19 265 to 19) in the U.S., and 5 days (IQR: 2 to 13) overall. Parameters to calculate the qSOFA score and 28-day
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21 266 mortality were available for 96.4% participants. All screening tools were associated with an increased risk
22
23 267 of death (**Figure 2**) with the largest increase among those with an elevated UVA score (**Supplementary**
24
25 268 **Figure S3**). For individuals with a UVA ≥ 2 there was a 5.45 times increased risk of death (95% CI: 3.39
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27 269 to 8.76; C-statistic: 0.70) and those with a qSOFA ≥ 2 had a 4.11 times increased risk of death (95% CI:
28
29 270 2.71 to 6.22; C-statistic: 0.66). Those with an elevated SIRS had a 1.81 times increased risk of death
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31 271 (95% CI: 0.94 to 3.50; C-statistic:0.53). Elevated NEWS (HR: 4.03; 95% CI: 2.24 to 7.26; C-statistic:
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33 272 0.66) and MEWS (HR: 2.03; 95% CI: 1.28 to 3.23; C-statistic: 0.53) had similarly increased risks (**Figure**
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35 273 **3**).
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41 275 Accuracy in an adjusted Cox model was highest for UVA (0.73; 95% CI 0.68-0.78) followed by qSOFA
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43 276 (C-statistic: 0.70; 95% CI: 0.64 to 0.75) (**Table 2**). The sensitivity for predicting death was highest with
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45 277 SIRS (89%; 95% CI: 80 to 94%) but specificity was lowest (19%; 95% CI: 16 to 26%). The UVA score
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47 278 had a sensitivity of 74% and specificity of 70%. The qSOFA score had the lowest sensitivity (54%; 95%
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49 279 CI: 44 to 65%) but highest specificity (80%; 95% CI: 76 to 84%). We observed that the qSOFA
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51 280 discrimination for mortality was moderate with a C-statistic of 0.70 adjusting for age and sex (**Figure 3**).
52
53 281 There was similar qSOFA accuracy in individual cohorts from the United States (C-statistic 0.71; 95%
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55 282 CI: 0.54 to 0.89), Cambodia (C-statistic: 0.68; 95% CI: 0.59 to 0.77), or Ghana (C-statistic: 0.72; 95% CI:
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283 0.64 to 0.79) (**Figure 3**). Similarly, the UVA score had moderate accuracy with a C-statistics on 0.73
 284 (95% CI: 0.68 to 0.78). Other screening scores had similar moderate C-statistic values. The SIRS C-
 285 statistic was 0.60 (95% CI: 0.54 to 0.65). Among participants with a NEWS score of ≥ 5 (62% of the
 286 pooled cohort), the C-statistic was 0.68 (95% CI: 0.64 to 0.73) and among those with a MEWS score of
 287 ≥ 4 (58% of the pooled cohort), the C-statistic was 0.63 (95% CI: 0.58 to 0.68) for death. The qSOFA and
 288 UVA scores were significantly greater than baseline risk in Ghana in contrast to other scores or cohorts
 289 (Table 3). The qSOFA score increased prognostication accuracy in the United States cohort with a $p=0.02$
 290 but this was not significant after correcting for multiple comparisons. In Cambodia, while not significant

Table 2. Performance characteristics of sepsis score across cohorts for predicting 28-day mortality.

Score	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Unadjusted Bivariate Cox model C-statistic (95% CI)	Adjusted* Cox model C-statistic (95% CI)	p-value (Wald test)
Age and sex	–	–	–	–	–	0.59 (0.53,0.64)	
MEWS $\geq 4^*$	0.73 (0.63, 0.82)	0.45 (0.40, 0.49)	0.21 (0.16, 0.26)	0.89 (0.85, 0.93)	0.59 (0.54, 0.63)	0.63 (0.58,0.68)	0.002**
NEWS $\geq 5^*$	0.86 (0.77,0.93)	0.43 (0.38,0.48)	0.25 (0.23,0.28)	0.93 (0.89, 0.95)	0.65 (0.64, 0.67)	0.68 (0.64,0.73)	<0.001**
qSOFA $\geq 2^*$	0.54 (0.44, 0.65)	0.80 (0.76, 0.84)	0.35 (0.27, 0.44)	0.90 (0.87, 0.93)	0.66 (0.61, 0.71)	0.70 (0.64,0.75)	<0.001**
SIRS $\geq 2^*$	0.89 (0.80, 0.94)	0.19 (0.16, 0.23)	0.17 (0.14, 0.21)	0.90 (0.82, 0.95)	0.53 (0.50, 0.57)	0.60 (0.54,0.65)	0.134
UVA $\geq 2^*$	0.74 (0.64, 0.83)	0.70 (0.65, 0.74)	0.33 (0.27, 0.40)	0.93 (0.90,0.95)	0.70 (0.65, 0.74)	0.73 (0.68,0.78)	<0.001**

*Adjusted Cox model C-statistic is adjusted for age and gender. Note: p-value are from Wald test of the adjusted Cox regression model.

**Significant at $p < 0.002$

291 after correction, NEWS ($p=0.01$) and UVA ($p=0.01$) scores increased accuracy greater than baseline risk.
 292 When pooling LMIC cohorts (i.e., Ghana and Cambodia), after adjustment for age and sex, the qSOFA
 293 (C-statistic: 0.71; 95% CI: 0.66 to 0.77) and UVA scores (C-statistic: 0.76; 95% CI: 0.71 to 0.81) had

Table 3. Performance characteristics of sepsis score across cohorts for predicting 28-day mortality stratified by site.

Model	Takeo, Cambodia		Durham, USA		Kumasi, Ghana	
	C-statistic (95% CI)	p-value	C-statistic (95% CI)	p-value	C-statistic (95% CI)	p-value
Age and Sex	0.68 (0.59, 0.78)	–	0.68 (0.54,0.81)	–	0.57 (0.49, 0.64)	–
MEWS	0.68 (0.59, 0.78)	0.2102	0.68 (0.57, 0.79)	0.4991	0.63 (0.56, 0.70)	0.0097
NEWS	0.73 (0.63, 0.83)	0.0106	0.71 (0.59, 0.84)	0.2557	0.64 (0.57, 0.70)	0.0022
qSOFA	0.68 (0.59, 0.77)	0.5101	0.71 (0.54, 0.89)	0.0365	0.72 (0.64, 0.79)	< 0.001*
SIRS	0.69 (0.60, 0.78)	0.5020	0.69 (0.55, 0.83)	0.5831	0.58 (0.51, 0.65)	0.1882
UVA	0.71 (0.60, 0.83)	0.0109	0.70 (0.55, 0.85)	0.4753	0.77 (0.71,0.83)	< 0.001*

Note: p-value are from Wald test of the adjusted Cox regression model. Each model is adjusted for age and sex. *Significant at p<0.002

294 higher accuracy compared with MEWS (C-statistic: 0.66 (95% CI 0.61 to 0.72), NEWS (C-statistic: 0.70
 295 (95% CI: 0.65 to 0.76), and SIRS (C-statistic: 0.61; 95% CI: 0.55 to 0.67). In contrast, in the United
 296 States cohort, NEWS, MEWS, SIRS, qSOFA, and UVA scores after age and sex adjustment each had
 297 similar accuracy with C-statistics ranging from 0.66 to 0.71 (**Table 3 and Supplementary Table S3**).

299 DISCUSSION

300 In pooled prospective international cohorts in Cambodia, Ghana, and the United States, the UVA score
 301 and Sepsis-3 (qSOFA) performed well with a C-statistic around 0.7 for predicting 28-day mortality.
 302 However, this improvement was largely identified in the cohort in Ghana and the accuracy was no
 303 different than baseline risk in the Cambodia cohort. There was a trend towards improving prognostication
 304 accuracy with the NEWS and UVA score in Cambodia and only with the qSOFA score in the United
 305 States. These results suggest that widely used sepsis screening tools may have varying performance for
 306 prognostication in diverse settings with different treatment regimens and aetiologies of sepsis. Therefore,
 307 screening tools should be selected after validation within populations prior to widespread adoption.

309 Current sepsis screening tools have had variable performance when applied for prognostication. SOFA or
 310 APACHE scores have been developed specifically for prognostication but required parameters including

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3 311 arterial blood oxygen saturation are often not available⁹. Performance of qSOFA and SIRS for mortality
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5 312 have performed poorly (SIRS, area under the receiving operator curve [AUROC], 0.61; qSOFA:
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7 313 AUROC, 0.61) for prognostication in high-resource settings intensive care unit (ICU) settings¹¹ and in
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9 314 diverse LMICs (adjusted SIRS: AUROC, 0.59; adjusted qSOFA: AUROC, 0.70)⁹ in prior studies for
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11 315 mortality prognostication. While qSOFA is generally more specific than other screening tools, it is less
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13 316 sensitive than SIRS, MEWS, and NEWS, which is consistent with our data²². When applied to sepsis
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15 317 identification, Surviving Sepsis 2021 guidelines recommend against solely using qSOFA,²³ due to being
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17 318 a more specific rather than sensitive screening test. Additionally, qSOFA has been found to be inferior to
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19 319 MEWS, and NEWS but more accurate and specific than SIRS for predicting in-hospital mortality and
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21 320 ICU transfer in a large retrospective cohort of over 30 thousand patients in the United States (NEWS:
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23 321 AUROC, 0.77; MEWS: AUROC, 0.73; qSOFA: AUROC, 0.69; SIRS: AUROC, 0.65)²². Different
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25 322 screening scores have been evaluated in prospective cohorts in sub-Saharan Africa (sSA) previously in
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27 323 Tanzania (qSOFA: AUROC, 0.57; MEWS: AUROC, 0.49)²⁴ and Rwanda²⁵ (MEWS: AUROC, 0.69;
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29 324 UVA: AUROC, 0.71; qSOFA: AUROC, 0.65) and in Gabon²⁶ (UVA: AUROC, 0.90; qSOFA: AUROC,
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31 325 0.77; MEWS: AUROC, 0.72; SIRS: AUROC, 0.70). Given the performance variability that has been
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33 326 previously observed and was observed in this study, it is prudent to evaluate prediction scores within the
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35 327 populations they serve prior to widespread promotion.
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41 329 The UVA score performed better than baseline risk in the Ghana cohort. Our results externally validated
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43 330 the UVA score for use prognostication of hospitalized patients with suspected sepsis in Kumasi, Ghana
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45 331 and potentially in the region when demographics are similar. The superiority of the UVA score in the
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47 332 Ghana cohort could be related to similarities in infectious causes of illness with other countries in sub-
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49 333 Saharan Africa (sSA) populations from which the UVA score was derived²⁷. In contrast to the score
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51 334 derivation study²⁷, UVA score performed similarly to qSOFA in Ghana. The accuracy of the UVA scores
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53 335 was not greater than baseline risk in the cohort in Cambodia after adjustment for multiple comparisons.
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55 336 While conclusions may be limited by sample size, sepsis scores derived from the regions of the world
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3 337 with more similar infectious aetiologies may perform better. Our results highlight the importance of
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5 338 validating scores in new patient populations prior to widespread use.
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9 340 This study had multiple limitations. First, exclusion criteria of immunocompromising conditions except
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11 341 HIV may have led to a skewed populations from Ghana and Cambodia. These exclusion criteria were
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13 342 created to decrease the effect of comorbid conditions or medications on immune biomarkers. However, in
14
15 343 Cambodia and Ghana, immunosuppressive medications or diagnoses of chronic liver or kidney disease
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17 344 may be less common in the general population due to limited access to specialists or specialized
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19 345 medications. Additionally, while there were differences in the baseline severity between cohorts, study
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21 346 processes including inclusion criteria were largely standardized across sites improving the comparability
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23 347 of the cohorts in diverse settings. Diagnostic testing differed at each site and mortality specifically due to
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25 348 sepsis could not be determined. Enrolment was by convenience sampling within the referral hospital
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27 349 catchment area and may not be representative of the general population within these countries.
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30 350 Approximation of the mental status for the MEWS scoring using GCS may not be generalizable to the use
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32 351 of GCS at other sites. However, similar MEWS and NEWS performance was observed across sites.
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34 352 Lastly, due to the limited sample size in each of the cohorts, smaller improvements in accuracy may not
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36 353 have been identified in the Cambodia and United States cohorts that had less deaths compared to the
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38 354 Ghana cohort.
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43 356 Inexpensive and readily available tools are needed for triage in resource-limited areas in the world to help
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45 357 identify patients that need escalation and possible transfer to higher levels of care. Current widely used
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47 358 sepsis screening tools represent a clinical benchmark for the development of future triage tools. Research
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49 359 is ongoing to assess point-of-care diagnostics within our sepsis cohort research network. Assays with
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51 360 portable and low-cost inflammation biomarkers tests, molecular diagnostics, or point-of-care ultrasound
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53 361 (POCUS) have the potential to augment the performance of clinical screening tools towards a more
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55 362 personalized approach to sepsis recognition and triage.
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364 CONCLUSION

365 Sepsis screening tools that are widely used during clinical care had sub-optimal performance for risk

366 stratification in three international cohorts with increased performance of the UVA and qSOFA scores in

367 Ghana compared to baseline risk. There remains a need for reliable, low-cost, and scalable

368 prognostication methods that are validated in diverse settings.

369

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377

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3 388 TV, AO, DA, and GO were involved in protocol development and data generation. LM, MS, WH, SK, were
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5 389 involved in research operations. AL, KLS, CWW, DF, ELT, CB, DVC, and PWB were involved in
6
7 390 manuscript revisions. All authors reviewed and approved of this manuscript.
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10 391 **Data sharing statement:** De-identified data may be made available upon reasonable request to the
11
12 392 corresponding author.
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3 **478 Figure Legends**

4 479 Figure 1. Enrolment flow diagram across cohorts.

5 480 Figure 2. Kaplan-Meier survival plot of 28-day mortality stratified by site.

6 481 Figure 3. The C-statistic by score overall and by cohort (adjusted for age and sex).

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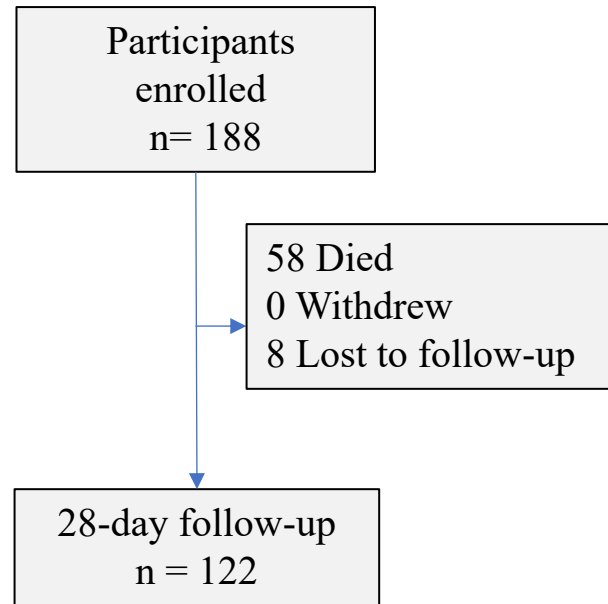
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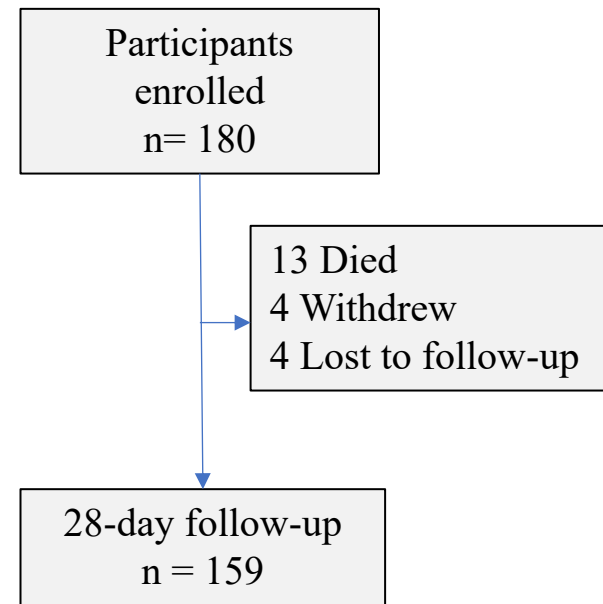
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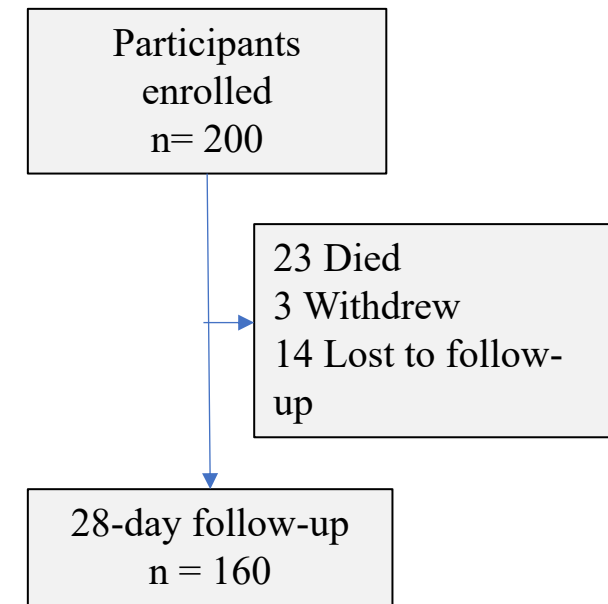
Kumasi, Ghana

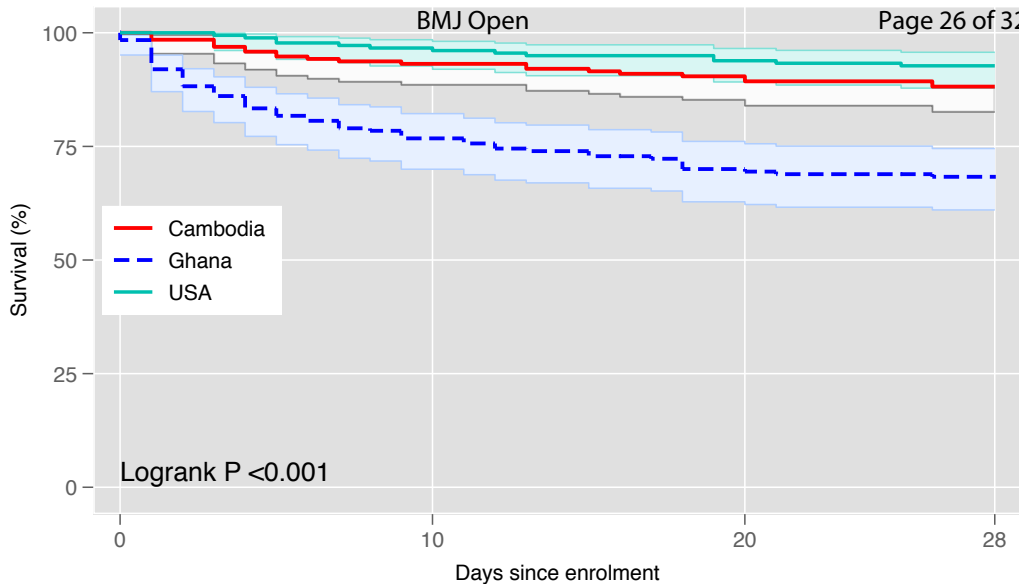


Durham, United States



Takeo, Cambodia





No. at Risk:

Cambodia	200	(13)	171	(5)	164	(4)	148
Ghana	187	(43)	137	(12)	124	(3)	118
USA	180	(6)	173	(5)	168	(2)	166

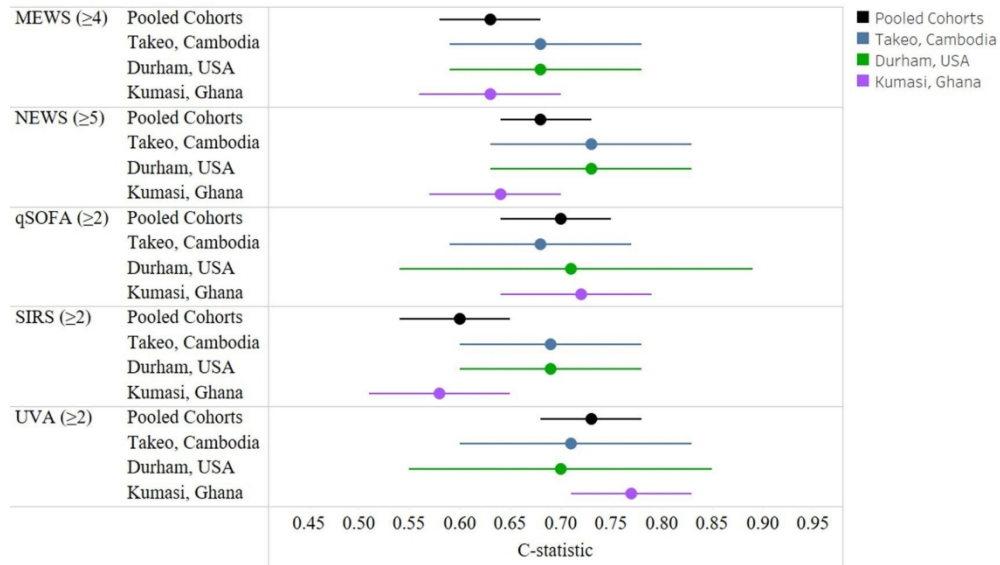


Figure 3. The C-statistic by score overall and by cohort (adjusted for age and sex).

165x96mm (600 x 600 DPI)

Table S1. Baseline physiologic and clinical laboratory parameters by site at enrollment.

Parameter	Total Median (IQR)	Takeo, Cambodia Median (IQR)	Durham, USA Median (IQR)	Kumasi, Ghana Median (IQR)
Physiologic parameters				
Respiratory rate (breaths per minute)	24 (20, 30)	24 (20, 28)	24 (20, 31)	26 (22, 30)
Systolic blood pressure (mmHg)	120 (100, 130)	110 (100, 130)	113 (96, 129)	127.5 (110, 140)
Diastolic blood pressure (mmHg)	70 (60, 80)	70 (70, 80)	64 (56, 75)	80 (60, 90)
Oxygen saturation (%)	97 (94, 98)	98 (96, 98)	95 (92, 97.5)	97 (95, 98)
Temperature (°C)	37.9 (37, 38.7)	37.5 (37, 38.5)	38.1 (36.9, 38.89)	38.2 (37.4, 38.8)
Heart rate (beats per minute)	105 (94, 118)	96 (86.5, 105.5)	111 (99.5, 124)	111 (99, 118)
Clinical laboratory parameters				
White blood cells (x10 ⁹ cells/L)	12.05 (8.13, 16.6)	11.9 (8.2, 16.6)	13.35 (9.7, 17.6)	10.76 (7.68, 15.41)
Platelets (x10 ⁹ cells/L)	222 (152.5, 321.5)	262 (169, 366)	236.5 (160, 291)	193 (137, 284)
Sodium (mEq/L)	135 (132, 138)	135 (131, 138)	137 (134, 139)	134 (130, 138)
Potassium (mEq/L)	3.7 (3.3, 4.2)	3.7 (3.2, 4.1)	3.9 (3.5, 4.3)	3.6 (3.2, 4)
Sodium Bicarbonate (mmol/L)	24 (21, 26)	24 (22, 27)	25 (22, 27)	22 (19, 25)
Glucose (mg/dL)	6.56 (5.4, 10)	6.44 (5.39, 8.28)	6.69 (5.67, 10.06)	6.65 (5.2, 12)
Blood Urea Nitrogen (mg/dL)	5 (3.57, 7.9)	4.29 (3.21, 5.71)	5.71 (3.57, 10)	5.4 (3.5, 9.4)
Creatinine (mg/dL)	88.42 (66, 130)	79.58 (53.05, 88.42)	106.1 (70.74, 150.31)	91 (70, 135)
Alkaline Phosphatase (U/L)	86.5 (65, 132)	98.5 (72, 172)	80 (63, 106)	85 (63, 125)
Alanine Transaminase (U/L)	32 (22, 58)	46 (27, 86)	22 (18, 40)	29 (22, 48)
Aspartate Aminotransferase (U/L)	42 (27, 76)	61 (38, 117)	29 (21, 45)	35.5 (25, 65)
Bilirubin (mg/dL)	15 (10.26, 21)	13.68 (10.26, 20.52)	15.39 (10.26, 20.52)	15 (11, 23)

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Parameter	Total Median (IQR)	Takeo, Cambodia Median (IQR)	Durham, USA Median (IQR)	Kumasi, Ghana Median (IQR)
Albumin (g/dL)	3.0 (2.5, 3.5)	2.9 (2.5, 3.4)	3.0 (2.5, 3.5)	3.0 (2.3, 3.6)
Total protein (g/dL)	73 (65, 79)	74 (68, 79.5)	67 (57, 72)	75 (69, 83)
Lactate (mmol/L)	2.27 (1.66, 3.09)	2.33 (1.79, 3.03)	1.5 (1, 2.4)	2.54 (1.8, 3.42)

**All variables are presented as median, interquartile range*

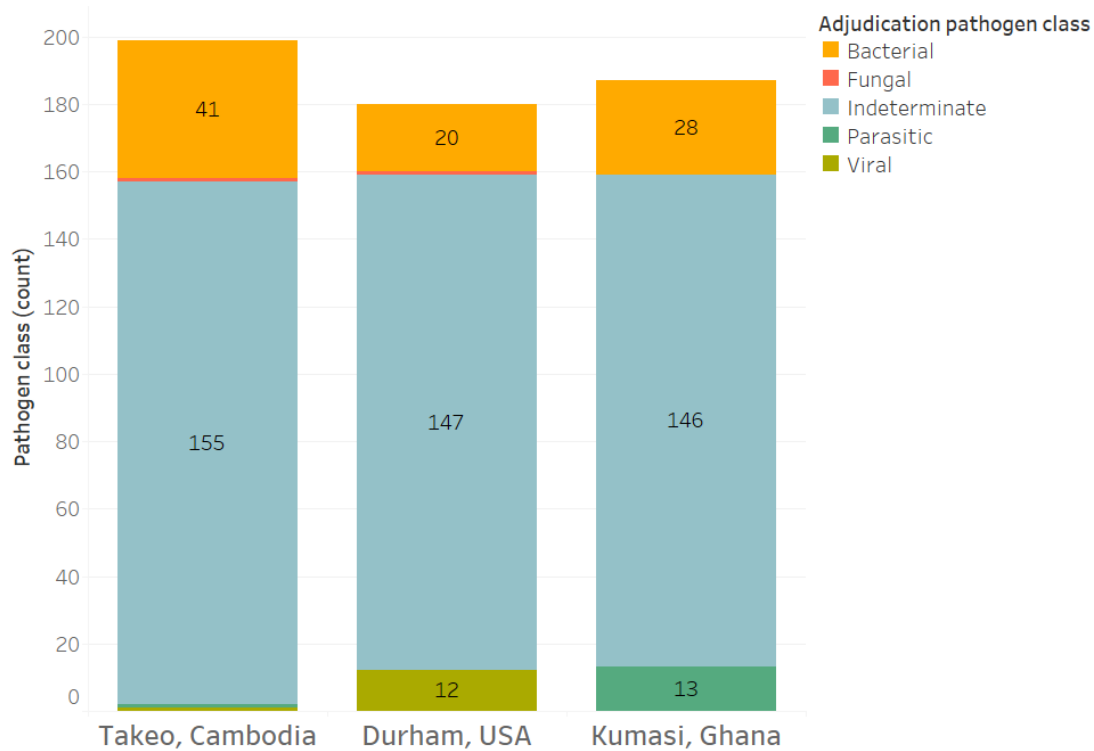
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Table S2. Performance characteristics of sepsis score across Cambodia and Ghana sites combined for predicting 28-day mortality.

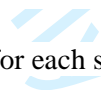
Score	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Unadjusted Bivariate Cox model C-statistic (95% CI)	Adjusted* Cox model C-statistic (95% CI)	p-value
Baseline						0.60 (0.54 – 0.66)	
MEWS ≥ 4	0.74 (0.64 – 0.84)	0.50 (0.44–0.56)	0.28 (0.25 – 0.32)	0.88 (0.84 – 0.92)	0.62 (0.57 – 0.66)	0.66 (0.61 – 0.72)	<0.001
NEWS ≥ 5	0.85 (0.75–0.92)	0.46 (0.38–0.52)	0.33 (0.29–0.36)	0.91 (0.85 – 0.94)	0.65 (0.62 – 0.70)	0.70 (0.65 – 0.76)	0.001
qSOFA ≥ 2	0.54 (0.42 – 0.65)	0.84 (0.80 – 0.88)	0.47 (0.39 – 0.55)	0.87 (0.84 – 0.90)	0.67 (0.62 – 0.73)	0.71 (0.66–0.77)	<0.001
SIRS ≥ 2	0.88 (0.78 – 0.94)	0.24 (0.19 (0.30)	0.23 (0.21 – 0.24)	0.89 (0.81 – 0.94)	0.55 (0.51 – 0.59)	0.61 (0.55 – 0.67)	0.066
UVA ≥ 2	0.75 (0.65 – 0.84)	0.74 (0.70 – 0.80)	0.45 (0.40 – 0.52)	0.92 (0.88 – 0.94)	0.73 (0.68 – 0.77)	0.76 (0.71–0.81)	<0.001

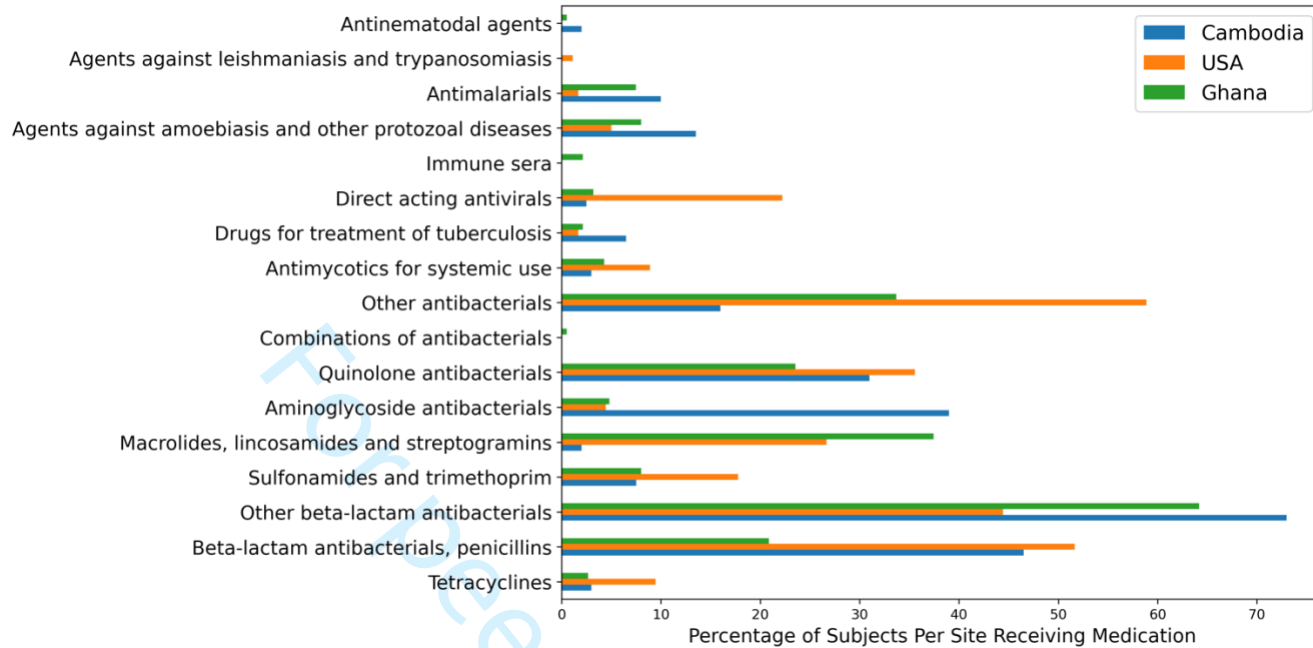
Table S3. Performance characteristics of sepsis score across the United States site for predicting 28-day mortality.

Score	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Unadjusted Bivariate Cox model C-statistic (95% CI)	Adjusted* Cox model C-statistic (95% CI)	p-value
Baseline (age +sex)						0.61 (0.52 – 0.66)	
MEWS\geq4	0.60 (0.26- 0.87)	0.33 (0.26 –0.41)	0.05 (0.03 –0.09)	0.92 (0.85 –0.96)	0.53 (0.38 – 0.67)	0.68 (0.57 – 0.79)	0.743
NEWS\geq5	0.90 (0.56 – 0.99)	0.37 (0.29 –0.45)	0.09 (0.07 –0.11)	0.98 (0.89- 0.99)	0.63 (0.54 - 0.71)	0.71 (0.59- 0.84)	0.256
qSOFA \geq2	0.60 (0.26 - 87)	0.72 (0.65 –0.79)	0.13 (0.08 - 0.20)	0.96 (0.93 –0.98)	0.66 (0.51 – 0.81)	0.71 (0.54 – 0.89)	0.019
SIRS \geq2	0.92 (0.64 - 0.99)	0.11 (0.07 –0.16)	0.08 (0.07 –0.09)	0.94 (0.72 –0.99)	0.51 (0.45 – 0.58)	0.66 (0.54 – 0.82)	0.694
UVA\geq2	0.60 (0.26 – 0.88)	0.58 (0.50 –0.66)	0.09 (0.05 -0.14)	0.95 (0.90 -0.98)	0.59 (0.44 – 0.73)	0.70 (0.50 – 0.87)	0.281

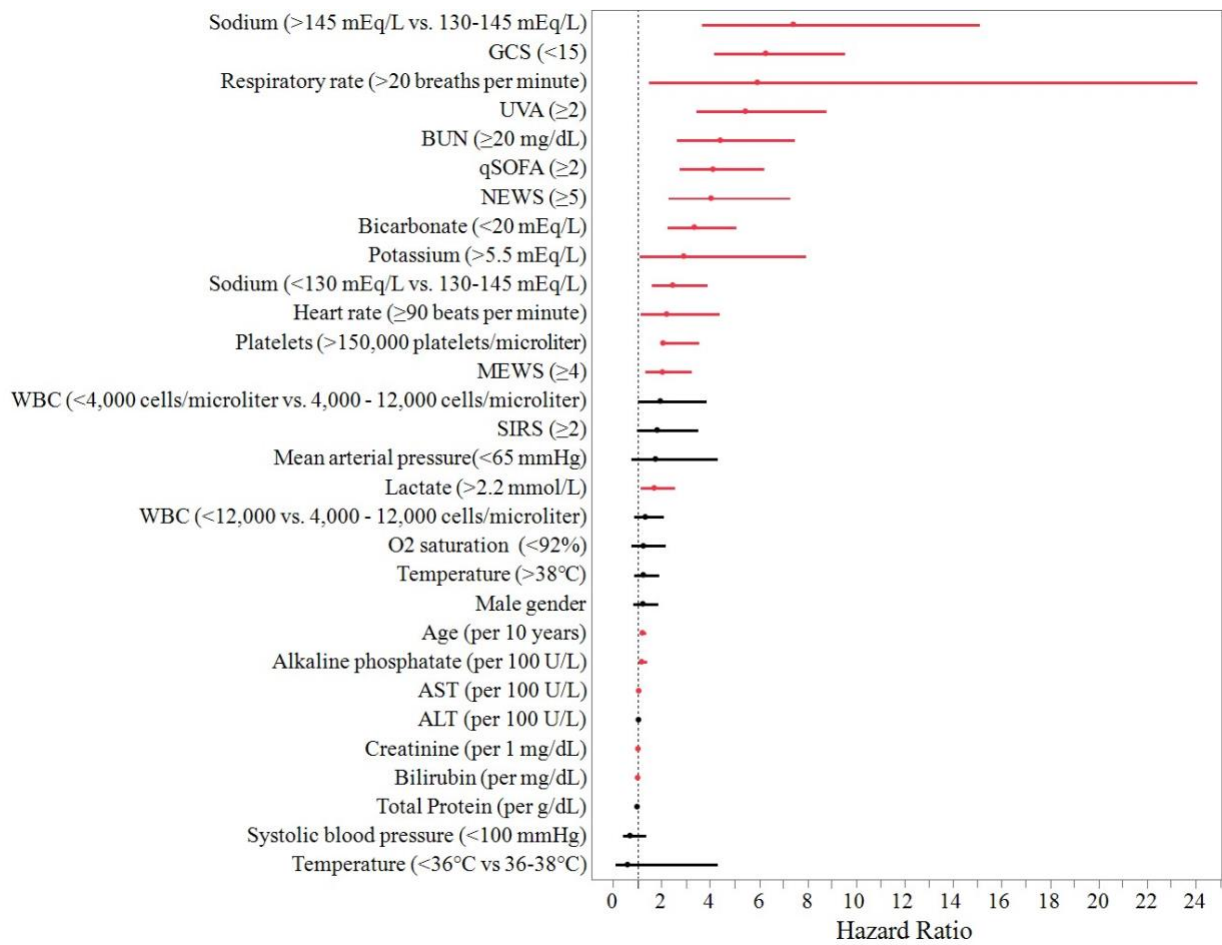


Supplementary Figure S1. Distribution of adjudicated pathogen class for each site.





Supplementary Figure S2. Prevalence of antibiotics received per site.



Supplementary Figure S3. Forest plot of hazard ratios from bivariate Cox regression models for risk of death at 28-day for sepsis scores, physiologic parameters, and clinical laboratory parameters.

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Validation of screening tools for predicting mortality across multi-site international sepsis cohorts

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3 **32 Abstract:**
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5 **33** Word count: 276
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7 **34 Objectives:** We evaluated the performance of commonly used sepsis screening tools across prospective
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9 **35** sepsis cohorts in the United States, Cambodia, and Ghana.
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11 **36 Design:** Prospective cohort studies
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13 **37 Setting and participants:** From 2014 to 2021, participants with 2 or more SIRS (Systemic Inflammatory
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15 **38** Response Syndrome) criteria and suspected infection were enrolled in emergency departments and
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17 **39** medical wards at hospitals in the Cambodia and Ghana and hospitalized participants with suspected
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19 **40** infection were enrolled in the United States. Cox proportional hazards regression was performed, and
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21 **41** Harrell's C-statistic calculated to determine 28-day mortality prediction performance of the qSOFA score
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23 **42** ≥ 2 , SIRS score ≥ 3 , NEWS ≥ 5 , MEWS ≥ 5 , or UVA score ≥ 2 . Screening tools were compared to baseline
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25 **43** risk (age and sex) with the Wald test.
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28 **44 Results:** The cohorts included 567 participants (42.9% female) including 187 participants from Kumasi,
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30 **45** Ghana, 200 participants from Takeo, Cambodia, and 180 participants from Durham, North Carolina in the
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32 **46** United States. The pooled mortality was 16.4% at 28-days. The mortality prediction accuracy increased
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34 **47** from baseline risk with the MEWS (C-statistic: 0.63, 95% CI: 0.58, 0.68; $p=0.002$), NEWS (C-statistic:
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36 **48** 0.68; 95% confidence interval [CI]: 0.64, 0.73; $p<0.001$), qSOFA (C-statistic: 0.70, 95% CI: 0.64, 0.75;
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38 **49** $p<0.001$), UVA score (C-statistic: 0.73, 95% CI: 0.69, 0.78; $p<0.001$), but not with SIRS (0.60; 95% CI:
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40 **50** 0.54, 0.65; $p=0.13$). Within individual cohorts, only the UVA score in Ghana performed better than
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42 **51** baseline risk (C-statistic: 0.77; 95% CI: 0.71, 0.83; $p<0.001$).
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45 **52 Conclusions:** Among the cohorts, MEWS, NEWS, qSOFA, and UVA scores performed better than
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47 **53** baseline risk, largely driven by accuracy improvements in Ghana, while SIRS scores did not improve
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49 **54** prognostication accuracy. Prognostication scores should be validated within the target population prior to
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51 **55** clinical use.
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53 **56** Keywords: Analysis, Survival; sepsis; Cohort Studies; Prognosis; Global Health
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3 **58 Strengths and limitations of this study:**
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- 5 **59** • While single-centre cohorts and retrospective analyses have been performed, the optimal sepsis
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7 **60** screening tool for prognostication in low- and middle-income countries is unknown. This study
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9 **61** includes two well-characterized sepsis cohorts in LMICs and a cohort in a high-resource setting
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11 **62** for comparison.
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14 **63** • Five sepsis screening tools (i.e., qSOFA score, SIRS score, NEWS, MEWS, and UVA score)
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16 **64** were evaluated across three international cohorts for one-month mortality prognostication,
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18 **65** providing comprehensive performance estimates in settings with disparate causes of sepsis.
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20 **66** • Diagnostic testing differed at each site and mortality specifically due to sepsis could not be
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22 **67** determined.
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24 **68** • Enrolment was by convenience sampling within the referral hospital catchment area and may not
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26 **69** be representative of the general population within these countries.
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29 **70** • While SIRS was identified as a tool with inferior prognostic performance, sample size limitations
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31 **71** in each of the cohorts may have led to decreased ability to identify differences between each
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33 **72** screening tool.
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39 **75 Narrative:**

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41 **76** Word count: 3,783
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45 **78 INTRODUCTION**

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47 **79** Sepsis, a syndrome resulting from a systemic dysregulated host response to an infection, is estimated to
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49 **80** cause six million deaths per year but is likely an underestimate due to limited information from low- and
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51 **81** middle-income countries (LMICs) where 87% of the world population live [1]. Despite declining age-
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3 82 standardized incidence and mortality, sepsis remains a major cause of health loss worldwide and has an
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5 83 especially high health-related burden in LMICs[2].
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9 85 Clinical sepsis guidelines developed in the Western world may not be applicable in resource-limited settings
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11 86 and moreover can lead to detrimental effects on sepsis care and management when applied in these
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13 87 conditions due to decreased access to resources to manage iatrogenesis from fluid resuscitation [3, 4]. In
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15 88 contrast to the United States, pathogens that lead to directly lead to vascular injury are common causes of
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17 89 acute febrile illness in Cambodia and Ghana such as dengue virus, malaria, or rickettsia and may alter
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19 90 empiric treatment response [5]. While early recognition and treatment of sepsis is critical, most sepsis scores
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21 91 or early warning systems were derived from cohorts outside of LMICs. Differences in causes of sepsis,
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23 92 available treatments, and available resources for supportive care should affect management strategies but
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25 93 evidence is limited and optimal clinical scores or biomarkers for sepsis identification are unknown in these
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27 94 settings. Multi-site international sepsis studies are essential for evaluating current and future sepsis tools to
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29 95 ensure effectiveness in resource-limited settings and across populations.
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34 97 The most validated prognostication scores, SOFA (Sequential Organ Failure Assessment) and the
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36 98 APACHE IV, have been developed for prognostication but require an arterial blood gas and multiple
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38 99 laboratory parameters [6, 7] that are not widely available in low-resource settings. The qSOFA (quick
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40 100 SOFA) is an abbreviated score that does not require laboratory parameters. The qSOFA is one of the most
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42 101 widely adopted sepsis screening tools and has largely replaced the SIRS (Systemic Inflammatory Response
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44 102 Syndrome) criteria as the standard abbreviated sepsis screening tool as part of the Sepsis-3 definition to
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46 103 identify septic patients [8]. The qSOFA and other sepsis screening tools (i.e., Modified Early Warning
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48 104 Score [MEWS], National Early Warning Score [NEWS], and Universal Vital Assessment [UVA]) are often
49
50 105 used clinically to identify those at risk of sepsis, but these tools have been studied for their ability to
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52 106 prognosticate mortality or poor composite outcomes among hospitalized adults[9-12]. Studies have
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54 107 evaluated these tools for predicting in-hospital mortality but the performance of these tools and the
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3 108 prevalence of 28-day mortality, a common metric of sepsis outcomes, have yet to be described across both
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5 109 high- and low-resource settings using similar methods [9, 13, 14].
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9 111 We used prospective multi-site international cohorts that are part of the Austere environments Consortium
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11 112 for Enhanced Sepsis Outcomes (ACESO) consortium to validate commonly used sepsis screening tools
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13 113 [15]. In contrast to APACHE IV and SOFA, these tools can be quickly performed with limited laboratory
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15 114 test results. We hypothesized that qSOFA may perform poorly in LMIC populations compared to the UVA
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17 115 score due to differences in causes of sepsis. We describe the diverse clinical characteristics, the aetiologies
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19 116 of suspected sepsis within these cohorts, and the performance of sepsis screening tools in current clinical
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21 117 use for predicting mortality at one month post enrolment.
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26 119 **METHODS**
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28 120 From May 2014 to November 2015, 200 participants were enrolled into a prospective observational study
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30 121 of sepsis at Takeo Provincial Hospital in Takeo Province Cambodia [16] (Figure 1). This study was
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32 122 followed by a prospective study at Duke University Hospital in Durham, North Carolina, which enrolled
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34 123 180 participants from December 2014 to March 2016. In Kumasi, Ghana, 187 participants were enrolled at
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36 124 Komfo Anokye Teaching Hospital from July 2016 to October 2017.
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40 125 Hospitalized patients ≥ 18 years of age whose attending physician judged them to have an active infection
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42 126 were considered for inclusion for each of the three cohorts. Additional inclusion and exclusion criteria
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44 127 were required in Cambodia and Ghana but not required in the United States protocol. In Cambodia and
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46 128 Ghana, participants were required to meet least two clinical criteria for systemic inflammatory response
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48 129 syndrome (SIRS) during screening. In Cambodia and Ghana, patients were excluded if they had known
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50 130 malignancy, chronic renal/hepatic insufficiency, immunosuppressive conditions (except HIV) or systemic
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52 131 steroid usage that exceeded 20mg/day to prevent confounding in future biomarker studies. Patients were
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54 132 also excluded in Cambodia and Ghana if they had a history of organ transplant, hemodynamically
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3 133 significant gastrointestinal bleeding, anatomic or functional asplenia, acute cardiovascular disease,
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5 134 general anaesthesia, or surgery in the past week prior to enrolment, women who were pregnant, patients
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7 135 who had a haemoglobin less than 7 g/dL or weighed less than 35kg. Hospital physicians who deemed
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9 136 their patients too ill to participate could defer enrolment.
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13 137 *Study procedures*

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15 138 Following informed consent, study team members conducted a detailed medical history, including prior
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17 139 medications, and physical exam. Responses were recorded on a standardized case report form and
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19 140 included demographics, medical history, physical exam findings, and admission diagnoses. Study specific
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21 141 procedures conducted in Cambodia were described in detail by Rozo et al [17]. Similar enrolment and
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23 142 study procedures were followed in Kumasi, Ghana and in Durham, North Carolina, USA. Blood was
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25 143 collected at the time of enrolment, then at 6 hours later, and at 24 hours later. In Ghana and Cambodia,
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27 144 standardized clinical tests included a peripheral venous blood gas with lactate, complete blood count,
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29 145 complete metabolic panel, optional HIV screening with consent (Alere Determine HIV1/2, Abbott, OK,
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31 146 United States), malaria rapid diagnostic tests (SD Bioline Ag. P.f./Pan, Abbott, OK, United States) and
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33 147 aerobic blood cultures (one aerobic bottle, Bactec 9050, BD, NJ, United States) as part of study
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36 148 procedures in Ghana and Cambodia. Microbiologic results were available if collected through routine
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38 149 clinical care across cohorts. Additional molecular testing and next generation sequencing for pathogens
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40 150 were also performed on blood samples in the Cambodia cohort as previously described [17]. Participants
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42 151 were followed throughout their hospitalization and a record review performed at discharge.
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45 152 An interview was performed, and blood samples were collected at a 28-day follow-up visit across cohorts.
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47 153 When patients could not return in person, study team members attempted to conduct an interview with
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49 154 patients or a legally authorized representative by telephone. Fatal outcomes among each discharged
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51 155 participant were also determined.
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3 156 Using clinical data from case report forms and microbiology diagnostic information, clinical adjudication
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5 157 was performed by three physician reviewers (internal medicine or infectious diseases) to determine the
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7 158 source of infection by anatomic location and pathogen class (i.e., bacterial, parasitic, viral, or fungal).
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9 159 This was graded on a low, moderate, and high level of confidence by two independent reviewers and a
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11 160 third reviewer served as a tiebreaker for discordant conclusions. If the third reviewer did not agree with
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13 161 either adjudicator, then the decision was determined by committee. Microbiologic results presented
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15 162 include those adjudicated to be clinically relevant to participant's acute illness.
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19 163 *Patient and Public Involvement*

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21 164 Patients were not involved in recruitment, design, conduct, or dissemination plans of our research. Results
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23 165 of this study were disseminated to hospital and clinical leadership at Takeo Provincial Hospital and
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25 166 Komfo Anokye Teaching Hospital.
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29 168 *Statistical analysis*

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31 169 Summary statistics were calculated for the cohorts individually and pooled, comparing baseline
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33 170 demographics (e.g., gender, age, ethnicity, selected medical comorbidities), baseline screening tool
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35 171 scores, physiologic parameters, baseline clinical laboratory values using either Chi-square (categorical
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37 172 values), Fishers exact (categorical values), or Kruskal-Wallis (continuous values) tests. Prevalence of
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39 173 diagnoses were described for each cohort by organ system and pathogen type and by anatomic site.
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43 175 After checking the proportional hazards assumption, Cox regression was performed with bivariate models
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45 176 to evaluate increased risk of death in each cohort by baseline demographics, comorbid conditions,
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47 177 physiologic parameters, and clinical laboratory parameters. Physiologic parameters and clinical laboratory
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49 178 parameters were modelled as dichotomous or ordinal parameters at clinically relevant abnormal range cut
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51 179 offs (e.g., blood urea nitrogen ≥ 20 mg/dL) to explore associations with increased risk of death and for
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53 180 clinical inference. Screening tools were dichotomized according to current usage, including qSOFA score
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3 181 ≥ 2 (range, 0 [best] to 3 [worst] points), SIRS score ≥ 2 (range, 0 [best] to 4 [worst] points), MEWS ≥ 5
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5 182 (range, 0 [best] to 13 [worst] points), NEWS ≥ 5 (range, 0 [best] to 20 [worst] points), and UVA ≥ 2
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7 183 (range, 0 [best] to 13 [worst])[13] and were evaluated in Cox regression models unadjusted and adjusted
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9 184 for age and sex for risk of death [9]. Glasgow Coma Scale Score (GCS; range, 3 [worst] to 15 [best]
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11 185 points) of less than 15 was used for estimation of the qSOFA score, and a GCS of ≤ 3 for
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13 186 unresponsiveness for NEWS, and GCS score 3-15 for the “alert, verbal, pain, unresponsive” scale
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15 187 (AVPU; alert: GCS 13-15, voice: GCS 9-12; pain: GCS 4-8; unresponsiveness: GCS ≤ 3) score
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17 188 approximation for MEWS [18, 19]. Data was administratively right censored past 28 days. The Harrell’s
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19 189 C-statistic was calculated for each screening tool for each cohort, the cohorts combined, and Cambodia
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21 190 and Ghana cohorts pooled [20]. This statistic is a performance analogous to area under the receiver
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23 191 operating characteristic curve (AUROC) but accounts for differences over time with survival outcomes.
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25 192 C-statistic confidence interval estimates were determined.[21] The Cox regression Wald test p-values
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27 193 were calculated for each score covariate adjusting for baseline risk estimated by age and sex [22]. P-
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29 194 values < 0.002 were considered significant using a Bonferroni correction for multiple comparisons. Cohort
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31 195 sample sizes were determined a priori through Monte Carlo simulation modelling for prognostic
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33 196 biomarker identification. All statistical analyses were performed in SAS (Statistical Analytical Software,
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35 197 version 9.4), R version 4.0.2 [23] or Stata (version 15.0; StataCorp LLC, College Station, TX, USA) [24].
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41 199 RESULTS

42 200 *Summary demographics, sepsis severity, and laboratory findings*

43 201 There were 567 participants across the cohorts including 187 from Kumasi, Ghana, 200 from Takeo,
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45 202 Cambodia, and 180 from Durham, North Carolina, United States (**Figure 1**). The study population was
46
47 203 predominantly male (57.1% male), with more male participants enrolled in Cambodia than at other sites
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49 204 (68.0% vs 55.0% in the U.S. and 52.4% in Ghana). The overall median age was 50 years (interquartile
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51 205 range [IQR], 36 to 63), which was similar across cohorts (**Table 1**). Previously diagnosed comorbid
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206 conditions were most common at the U.S. site including a history of cardiovascular (65.6%; N=118),
 207 respiratory (42.2%; N=76), or gastrointestinal (36.7%; N=66) conditions.

Table 1. Baseline demographic characteristics stratified by sites.

Characteristic	Total (n=567)	Takeo, Cambodia (n=200)	Durham, USA (n=180)	Kumasi, Ghana (n=187)	p-value**
Female gender – no. (%)	243 (42.9%)	64 (32.0%)	81 (45.0%)	98 (52.4%)	< 0.001
Age – years, median (IQR)	50 (36 – 63)	50 (36 – 62)	52.5 (40 – 63)	46 (35 – 63)	0.151
Medical history* – no. (%)					
Cancer	44 (9.9%)	0 (0.0%)	44 (24.4%)	0 (0.0%)	< 0.001
Cardiovascular	202 (41.4%)	22 (18.2%)	118 (65.6%)	62 (33.2%)	< 0.001
Dermatologic	15 (3.1%)	1 (0.8%)	14 (7.8%)	0 (0.0%)	< 0.001
Endocrine	126 (25.8%)	6 (5.0%)	74 (41.1%)	46 (24.6%)	< 0.001
Gastrointestinal	76 (15.6%)	4 (3.3%)	66 (36.7%)	6 (3.2%)	< 0.001
Genitourinary or reproductive	34 (7.0%)	1 (0.8%)	33 (18.3%)	0 (0.0%)	< 0.001
HIV	26 (4.7%)	12 (6.2%)	8 (4.5%)	6 (3.2%)	0.388
Neurological	62 (12.7%)	1 (0.8%)	44 (24.4%)	17 (9.1%)	< 0.001
Other	206 (42.2%)	48 (39.7%)	151 (83.9%)	7 (3.7%)	< 0.001
Psychiatric	143 (29.3%)	41 (33.9%)	78 (43.3%)	24 (12.8%)	< 0.001
Renal	41 (8.4%)	0 (0.0%)	41 (22.8%)	0 (0.0%)	< 0.001
Respiratory	89 (18.2%)	7 (5.8%)	76 (42.2%)	6 (3.2%)	< 0.001
Rheumatologic	29 (5.9%)	1 (0.8%)	28 (15.6%)	0 (0.0%)	< 0.001
Surgery	27 (5.5%)	0 (0.0%)	22 (12.2%)	5 (2.7%)	< 0.001
Baseline scores – no. (%)					
MEWS (≥ 4)	315 (57.8%)	81 (40.7%)	105 (65.6%)	129 (69.3%)	< 0.001
NEWS score (≥ 5)	324 (61.6%)	90 (47.9%)	98 (64.5%)	136 (73.1%)	< 0.001
qSOFA (≥ 2)	139 (25.4%)	22 (11.1%)	48 (29.6%)	69 (37.1%)	< 0.001
SIRS (≥ 2)	447 (81.8%)	125 (68.3%)	157 (89.2%)	165 (88.2%)	< 0.001
UVA (≥ 2)	199 (37.8%)	47 (25.8%)	68 (42.8%)	84 (45.4%)	< 0.001
Baseline scores (median [IQR])					
MEWS	4 (3-6)	3 (2-5)	1 (0-4)	1 (1-2)	< 0.001

Table 1. Baseline demographic characteristics stratified by sites.

Characteristic	Total (n=567)	Takeo, Cambodia (n=200)	Durham, USA (n=180)	Kumasi, Ghana (n=187)	p-value**
NEWS	6 (3-8)	4 (2-7)	7 (3-9)	6 (4-8)	< 0.001
qSOFA	1 (1-2)	1 (0-1)	1 (0-2)	1 (1-2)	< 0.001
SIRS	2 (2-3)	2 (1-3)	3 (2-3)	3 (2-3)	< 0.001
UVA	1 (0-3)	1 (0-2)	1 (0-4)	1 (0-4)	< 0.001

*There were 79 subjects without comorbidity information in the Cambodia cohort. **Categorical parameters compared with chi-squared test and numeric parameters compared with Kruskal-Wallis test.

208 Clinical physiologic and laboratory value abnormalities at enrolment were common with median
 209 respiratory rate at 24 (IQR: 20 to 30), the median white blood count elevated at 12.05×10^9 cells/L (IQR:
 210 8.13 to 16.6×10^9 cells/L), and median lactate elevated at 2.27 mmol/L (IQR: 1.66 to 3.09 mmol/L)
 211 (**Supplementary Table S1**). At enrolment, the proportion of an elevated qSOFA (≥ 2) at baseline was
 212 highest at the Ghana site with 44.4% (N=83) of participants compared to 26.0% (N=52) in Cambodia and
 213 22.2% (N=40) in the United States. The SIRS, MEWS, NEWS, and UVA screening tools were similarly
 214 higher in the Ghana cohort.

215

216 *Pathogens detected*

217 The most common positive microbiologic results overall included bacteraemia (N=83), respiratory culture
 218 growth (N=19), serum hepatitis B surface antigen (N=15), and malaria rapid diagnostic tests (N=11). A
 219 minority (121 of 567, 21.3%) of subjects had confirmed infections with complete adjudicator agreement
 220 using all available sources of clinical microbiologic results (with the notable addition of RNA sequencing
 221 of samples from Cambodia[17]) including 90 (15.9%) bacterial, 17 viral (3.0%), 20 malarial (3.5%), and
 222 2 (0.3%) fungal infections identified across all cohorts (**Supplementary Figure S1**). These infection
 223 classes were different among sites (chi-squared test $p < 0.001$).

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3 225 In Cambodia, the most common bacterial infections with complete adjudicator agreement were *B.*
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5 226 *pseudomallei* (N=10, with blood or respiratory culture growth), presumptive *M. tuberculosis* (N=5, with
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7 227 acid fast positive smears), polymicrobial (N=5), and *O. tsutsugamushi* (N=4, determined by sequencing).
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9 228 The most common causes of bacteraemia (17 total of 200 participants) were *B. pseudomallei* (N=8), *E.*
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11 229 *coli* (N=3), and polymicrobial infections (N=3). Three participants had a positive malaria RDT. Fungal
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13 230 infections were uncommon with 1 participant with non-albicans Candidemia and 1 with cryptococcal
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15 231 meningitis. Two individuals had dengue fever (one PCR positive and one adjudicated IgM positive).
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19 233 In Ghana, the most common causes of bacteraemia (culture growth from 28 of 187 participants) were *E.*
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21 234 *coli* (N=6), *S. aureus* (N=6), *Salmonella spp.* (N=5), and *S. pneumoniae* (N=3). Nine participants had a
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23 235 positive malaria RDT and 15 had a positive hepatitis B surface antigen.
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28 237 In the United States, the most common causes of bacteraemia (culture growth from 19 of 180
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30 238 participants) were *E.coli* (N=5), *K. pneumoniae* (N=3), polymicrobial (N=2), *Pseudomonas spp.* (N=2),
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32 239 or *S. aureus* (N=2). Viral infections detected by PCR included rhinovirus (N=5), influenza A (N=4),
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34 240 respiratory syncytial virus (N=4), human immunodeficiency virus (N=3), and human metapneumovirus
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36 241 (N=3). There was one participant with *Aspergillus fumigatus* fungal pneumonia.
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41 243 *Diagnoses and Treatments*

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43 244 Across cohorts, the most common organ system sites of infection were lower respiratory tract infection
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45 245 (28.7%; N=163), multifocal or generalized source of infection (including malaria) (13.6%; N=77), and
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47 246 gastrointestinal (including hepatic) (12.7%; N=72) (**Figure S1a**). The most common antibiotics
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49 247 administered in United States, Ghana, and Cambodia were beta-lactam antibiotics (**Supplementary**
50
51 248 **Figure S2**), but antibiotic regimens varied widely among sites. The most common antibiotics classes used
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53 249 were other antibacterials (e.g., glycopeptide antibiotics, 58.9%), beta-lactam antibacterials, penicillins
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55 250 (51.7%), and cephalosporin and carbapenem antibacterials (44.4%) in the United States, cephalosporins
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3 251 and carbapenems (64.2%), macrolides, lincosamides and streptogramins (37.4%), and other antibacterials
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5 252 (33.7%) in Ghana, and cephalosporins and carbapenems (73.0%), beta-lactam antibacterials, penicillins
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7 253 (46.5%) and aminoglycoside antibacterials (39.0%) in Cambodia.
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11 255 *Survival*

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13 256 Among all cohorts, 16.4% (N=93) of participants had died at one month, including 58 (31.0%) in Ghana,
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15 257 22 (11.0%) in Cambodia, and 13 (7.2%) in the U.S (**Figure 1**). Among those that died within one month,
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17 258 median time to death was 4 days (IQR: 1 to 11) in Ghana, 7 days (IQR: 3 to 16) in Cambodia, 10 (IQR: 5
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19 259 to 19) in the U.S., and 5 days (IQR: 2 to 13) overall. Parameters to calculate the qSOFA score and 28-day
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21 260 mortality were available for 96.4% participants. Hyponatremia (>145 mEq/L) had the highest unadjusted
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23 261 risk of death (hazard ratio 6.89, 95% CI: 3.43, 13.85) among parameters tested in bivariate models
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25 262 (**Supplementary Figure S3**). All screening tools were associated with an increased risk of death (**Figure**
26
27 263 **2**) with the largest increase among those with an elevated UVA score (**Supplementary Figure S3**). For
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29 264 individuals with a UVA ≥ 2 there was a 5.45 times increased risk of death (95% CI: 3.39 to 8.76; C-
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31 265 statistic: 0.70) and those with a qSOFA ≥ 2 had a 4.11 times increased risk of death (95% CI: 2.71 to 6.22;
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33 266 C-statistic: 0.66). Those with an elevated SIRS had a 1.81 times increased risk of death (95% CI: 0.94 to
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35 267 3.50; C-statistic:0.53). Elevated NEWS (HR: 4.03; 95% CI: 2.24 to 7.26; C-statistic: 0.66) and MEWS
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37 268 (HR: 2.03; 95% CI: 1.28 to 3.23; C-statistic: 0.53) had similarly increased risks (**Figure 3**).
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43 270 Accuracy in an adjusted Cox model was highest for UVA (0.73; 95% CI 0.68-0.78) followed by qSOFA
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45 271 (C-statistic: 0.70; 95% CI: 0.64 to 0.75) (**Table 2**). The sensitivity for predicting death was highest with
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47 272 SIRS (89%; 95% CI: 80 to 94%) but specificity was lowest (19%; 95% CI: 16 to 26%). The UVA score
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49 273 had a sensitivity of 74% and specificity of 70%. The qSOFA score had the lowest sensitivity (54%; 95%
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51 274 CI: 44 to 65%) but highest specificity (80%; 95% CI: 76 to 84%). We observed that the qSOFA
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53 275 discrimination for mortality was moderate with a C-statistic of 0.70 adjusting for age and sex (**Figure 3**).
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55 276 There was similar qSOFA accuracy in individual cohorts from the United States (C-statistic 0.71; 95%
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277 CI: 0.54 to 0.89), Cambodia (C-statistic: 0.68; 95% CI: 0.59 to 0.77), or Ghana (C-statistic: 0.72; 95% CI:
 278 0.64 to 0.79) (**Figure 3**). Similarly, the UVA score had moderate accuracy with a C-statistics on 0.73
 279 (95% CI: 0.68 to 0.78). Other screening scores had similar moderate C-statistic values. The SIRS C-
 280 statistic was 0.60 (95% CI: 0.54 to 0.65). Among participants with a NEWS score of ≥ 5 (62% of the
 281 pooled cohort), the C-statistic was 0.68 (95% CI: 0.64 to 0.73) and among those with a MEWS score of
 282 ≥ 4 (58% of the pooled cohort), the C-statistic was 0.63 (95% CI: 0.58 to 0.68) for death. The qSOFA and
 283 UVA scores were significantly greater than baseline risk in Ghana in contrast to other scores or cohorts
 284 (Table 3). The qSOFA score increased prognostication accuracy in the United States cohort with a $p=0.02$
 285 but this was not significant after correcting for multiple comparisons. In Cambodia, while not significant

Table 2. Performance characteristics of sepsis score across cohorts for predicting 28-day mortality.

Score	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Unadjusted Bivariate Cox model C-statistic (95% CI)	Adjusted* Cox model C-statistic (95% CI)	p-value (Wald test)
Age and sex	–	–	–	–	–	0.59 (0.53,0.64)	
MEWS ≥ 4 *	0.73 (0.63, 0.82)	0.45 (0.40, 0.49)	0.21 (0.16, 0.26)	0.89 (0.85, 0.93)	0.59 (0.54, 0.63)	0.63 (0.58,0.68)	0.002**
NEWS ≥ 5 *	0.86 (0.77,0.93)	0.43 (0.38,0.48)	0.25 (0.23,0.28)	0.93 (0.89, 0.95)	0.65 (0.64, 0.67)	0.68 (0.64,0.73)	<0.001**
qSOFA ≥ 2 *	0.54 (0.44, 0.65)	0.80 (0.76, 0.84)	0.35 (0.27, 0.44)	0.90 (0.87, 0.93)	0.66 (0.61, 0.71)	0.70 (0.64,0.75)	<0.001**
SIRS ≥ 2 *	0.89 (0.80, 0.94)	0.19 (0.16, 0.23)	0.17 (0.14, 0.21)	0.90 (0.82, 0.95)	0.53 (0.50, 0.57)	0.60 (0.54,0.65)	0.134
UVA ≥ 2 *	0.74 (0.64, 0.83)	0.70 (0.65, 0.74)	0.33 (0.27, 0.40)	0.93 (0.90,0.95)	0.70 (0.65, 0.74)	0.73 (0.68,0.78)	<0.001**

*Adjusted Cox model C-statistic is adjusted for age and gender. Note: p-value are from Wald test of the adjusted Cox regression model.

**Significant at $p < 0.002$

286 after correction, NEWS ($p=0.01$) and UVA ($p=0.01$) scores increased accuracy greater than baseline risk.
 287 When pooling LMIC cohorts (i.e., Ghana and Cambodia), after adjustment for age and sex, the qSOFA
 288 (C-statistic: 0.71; 95% CI: 0.66 to 0.77) and UVA scores (C-statistic: 0.76; 95% CI: 0.71 to 0.81) had

Table 3. Performance characteristics of sepsis score across cohorts for predicting 28-day mortality stratified by site.

Model	Takeo, Cambodia		Durham, USA		Kumasi, Ghana	
	C-statistic (95% CI)	p-value	C-statistic (95% CI)	p-value	C-statistic (95% CI)	p-value
Age and Sex	0.68 (0.59, 0.78)	–	0.68 (0.54, 0.81)	–	0.57 (0.49, 0.64)	–
MEWS	0.68 (0.59, 0.78)	0.2102	0.68 (0.57, 0.79)	0.4991	0.63 (0.56, 0.70)	0.0097
NEWS	0.73 (0.63, 0.83)	0.0106	0.71 (0.59, 0.84)	0.2557	0.64 (0.57, 0.70)	0.0022
qSOFA	0.68 (0.59, 0.77)	0.5101	0.71 (0.54, 0.89)	0.0365	0.72 (0.64, 0.79)	<0.001*
SIRS	0.69 (0.60, 0.78)	0.5020	0.69 (0.55, 0.83)	0.5831	0.58 (0.51, 0.65)	0.1882
UVA	0.71 (0.60, 0.83)	0.0109	0.70 (0.55, 0.85)	0.4753	0.77 (0.71, 0.83)	<0.001*

Note: p-value are from Wald test of the adjusted Cox regression model. Each model is adjusted for age and sex. *Significant at p<0.002

289 higher accuracy compared with MEWS (C-statistic: 0.66 (95% CI 0.61 to 0.72), NEWS (C-statistic: 0.70
 290 (95% CI: 0.65 to 0.76), and SIRS (C-statistic: 0.61; 95% CI: 0.55 to 0.67) (**Supplementary Table S2**). In
 291 contrast, in the United States cohort, NEWS, MEWS, SIRS, qSOFA, and UVA scores after age and sex
 292 adjustment each had similar accuracy with C-statistics ranging from 0.66 to 0.71 (**Table 3 and**
 293 **Supplementary Table S3**).

295 DISCUSSION

296 In pooled prospective international cohorts in Cambodia, Ghana, and the United States, the UVA score
 297 and Sepsis-3 (qSOFA) performed well with a C-statistic around 0.7 for predicting 28-day mortality.
 298 However, this improvement was largely identified in the cohort in Ghana and the accuracy was no
 299 different than baseline risk in the Cambodia cohort. There was a trend towards improving prognostication
 300 accuracy with the NEWS and UVA score in Cambodia and only with the qSOFA score in the United
 301 States. These results suggest that widely used sepsis screening tools may have varying performance for
 302 prognostication in diverse settings with different treatment regimens and aetiologies of sepsis. Therefore,
 303 screening tools should be selected after validation within populations prior to widespread adoption.

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3 305 Current sepsis screening tools have had variable performance when applied for prognostication. SOFA or
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5 306 APACHE scores have been developed specifically for prognostication but required parameters including
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7 307 arterial blood oxygen saturation are often not available [9]. Performance of qSOFA and SIRS for
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9 308 mortality have performed poorly (SIRS, area under the receiving operator curve [AUROC], 0.61; qSOFA:
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11 309 AUROC, 0.61) for prognostication in high-resource settings intensive care unit (ICU) settings [14] and in
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13 310 diverse LMICs (adjusted SIRS: AUROC, 0.59; adjusted qSOFA: AUROC, 0.70) [9] in prior studies for
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15 311 mortality prognostication. While qSOFA is generally more specific than other screening tools, it is less
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17 312 sensitive than SIRS, MEWS, and NEWS, which is consistent with our data[25]. When applied to sepsis
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19 313 identification, Surviving Sepsis 2021 guidelines recommend against solely using qSOFA, [26] due to
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21 314 being a more specific rather than sensitive screening test. Additionally, qSOFA has been found to be
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23 315 inferior to MEWS, and NEWS but more accurate and specific than SIRS for predicting in-hospital
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25 316 mortality and ICU transfer in a large retrospective cohort of over 30 thousand patients in the United States
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27 317 (NEWS: AUROC, 0.77; MEWS: AUROC, 0.73; qSOFA: AUROC, 0.69; SIRS: AUROC, 0.65) [25].
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29 318 Different screening scores have been evaluated in prospective cohorts in sub-Saharan Africa (sSA)
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31 319 previously in Tanzania (qSOFA: AUROC, 0.57; MEWS: AUROC, 0.49) [27] and Rwanda [28] (MEWS:
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33 320 AUROC, 0.69; UVA: AUROC, 0.71; qSOFA: AUROC, 0.65) and in Gabon [29] (UVA: AUROC, 0.90;
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35 321 qSOFA: AUROC, 0.77; MEWS: AUROC, 0.72; SIRS: AUROC, 0.70). Given the performance variability
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37 322 that has been previously observed and was observed in this study, it is prudent to evaluate prediction
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39 323 scores within the populations they serve prior to widespread promotion.
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45 325 The UVA score performed better than baseline risk in the Ghana cohort. Our results externally validated
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47 326 the UVA score for use prognostication of hospitalized patients with suspected sepsis in Kumasi, Ghana
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49 327 and potentially in the region when demographics are similar. The superiority of the UVA score in the
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51 328 Ghana cohort could be related to similarities in infectious causes of illness with other countries in sub-
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53 329 Saharan Africa (sSA) populations from which the UVA score was derived[12]. In contrast to the score
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55 330 derivation study[12], UVA score performed similarly to qSOFA in Ghana. The accuracy of the UVA
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3 331 scores was not greater than baseline risk in the cohort in Cambodia after adjustment for multiple
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5 332 comparisons. While conclusions may be limited by sample size, sepsis scores derived from the regions of
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7 333 the world with more similar infectious aetiologies may perform better. Our results highlight the
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9 334 importance of validating scores in new patient populations prior to widespread use.
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13 336 This study had multiple limitations. First, exclusion criteria of immunocompromising conditions except
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15 337 HIV may have led to a skewed populations from Ghana and Cambodia. These exclusion criteria were
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17 338 created to decrease the effect of comorbid conditions or medications on immune biomarkers. However, in
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19 339 Cambodia and Ghana, immunosuppressive medications or diagnoses of chronic liver or kidney disease
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21 340 may be less common in the general population due to limited access to specialists or specialized
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23 341 medications. Additionally, while there were differences in the baseline severity between cohorts, study
24
25 342 processes including inclusion criteria were largely standardized across sites improving the comparability
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27 343 of the cohorts in diverse settings. Diagnostic testing differed at each site and mortality specifically due to
28
29 344 sepsis could not be determined. Enrolment was by convenience sampling within the referral hospital
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31 345 catchment area and may not be representative of the general population within these countries.
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33 346 Approximation of the mental status for the MEWS scoring using GCS may not be generalizable to the use
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35 347 of GCS at other sites. However, similar MEWS and NEWS performance was observed across sites.
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37 348 Lastly, due to the limited sample size in each of the cohorts, smaller improvements in accuracy may not
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39 349 have been identified in the Cambodia and United States cohorts that had less deaths compared to the
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41 350 Ghana cohort.
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45 352 Inexpensive and readily available tools are needed for triage in resource-limited areas in the world to help
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47 353 identify patients that need escalation and possible transfer to higher levels of care. Current widely used
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49 354 sepsis screening tools represent a clinical benchmark for the development of future triage tools. Research
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51 355 is ongoing to assess point-of-care diagnostics within our sepsis cohort research network. Assays with
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53 356 portable and low-cost inflammation biomarkers tests, molecular diagnostics, or point-of-care ultrasound
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3 357 (POCUS) have the potential to augment the performance of clinical screening tools towards a more
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5 358 personalized approach to sepsis recognition and triage.
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9 360 CONCLUSION

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11 361 Sepsis screening tools that are widely used during clinical care had sub-optimal performance for risk
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13 362 stratification in three international cohorts with increased performance of the UVA and qSOFA scores in
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15 363 Ghana compared to baseline risk. There remains a need for reliable, low-cost, and scalable
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17 364 prognostication methods that are validated in diverse settings.
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22 366 **Funding:** Defense Threat Reduction Agency (JSTO-CBA) to Naval Medical Research Center (NMRC)
23
24 367 (HDTRA1516108), Defense Health Bureau of Medicine & Surgery to NMRC for Combating Antibiotic
25
26 368 Resistance Bacteria (FY1819 0130.1832), Naval Medical Logistics Command Cooperative Agreement
27
28 369 (N626451920001).
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35
36 372 of Danaher Diagnostics. All other authors declared no competing interests.
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41 374 **Ethics approval:** Study protocols were approved by the Naval Medical Research Center (NMRC)
42
43 375 Institutional Review Board (IRB) (Cambodia sepsis study # NMRC.2013.0019; Ghana sepsis study #
44
45 376 NMRC.2016.0004-GHA; Duke sepsis study Duke#PRO00054849) in compliance with all applicable
46
47 377 Federal regulations governing the protection of human subjects as well as host country IRBs. The study
48
49 378 protocol in Cambodia was approved by the Cambodian National Ethics Committee for Health Research
50
51 379 (NECHR). The protocol in Ghana was approved by the Committee on Human Research, Publication and
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53 380 Ethics (CHRPE) at Kwame Nkrumah University of Science & Technology. All procedures were in
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3 381 accordance with the ethical standards of the Helsinki Declaration of the World Medical Association. All
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5 382 patients, or their legally authorized representatives, provided written informed consent.
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9
10 384 **Disclaimer:** K.L.S. is an employee of the US government, and C.B, N.A., C.D., M.P., and A.L. are military
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12 385 service members. This work was prepared as a part of official duties. Title 17 U.S.C. 105 provides that
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14 386 ‘Copyright protection under this title is not available for any work of the United States Government.’ Title
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16 387 17 U.S.C. 101 defines a U.S. Government work as a work prepared by a military service member or
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18 388 employee of the U.S. Government as part of a person’s official duties. The views expressed reflect the
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20 389 results of research conducted by the authors and do not necessarily reflect the official policy or position of
21
22 390 the Department of the Navy, Department of Defense, nor the United States Government.
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27 392 **Contributorship Statement:** PWB, RM, JB, LM, DAS, REM performed data curation and analyses. PWB,
28
29 393 KLS, and DVC developed the manuscript concept. DVC and KLS provided resources for research
30
31 394 development. AL, KLS, CO, JC, TS, ERK, ELT, CB, CWW, AF, AL, DF, JVL, MP, MR, NA, CD, MGG,
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33 395 TV, AO, DA, and GO were involved in protocol development and data generation. LM, MS, WH, SK, were
34
35 396 involved in research operations. AL, KLS, CWW, DF, ELT, CB, DVC, and PWB were involved in
36
37 397 manuscript revisions. All authors reviewed and approved of this manuscript.
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43 399 **Data sharing statement:** De-identified data may be made available upon reasonable request to the
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45 400 corresponding author.
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492 Figure Legends

493 Figure 1. Enrolment flow diagram across cohorts.

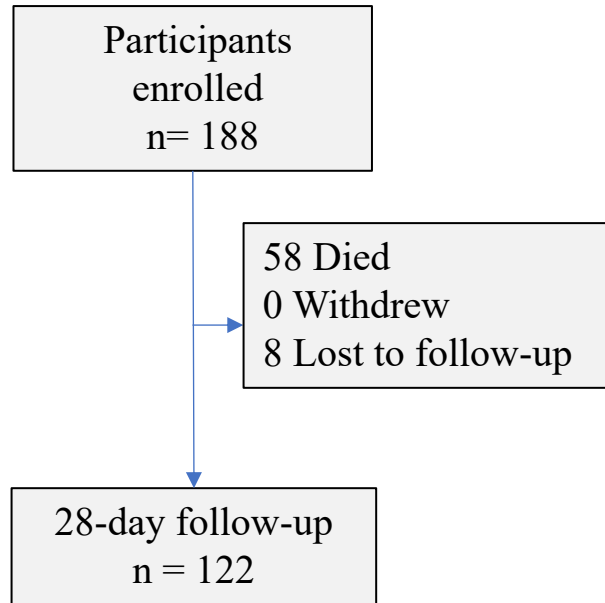
494 Figure 2. Kaplan-Meier survival plot of 28-day mortality stratified by site.

495 Figure 3. The C-statistic by score overall and by cohort (adjusted for age and sex).

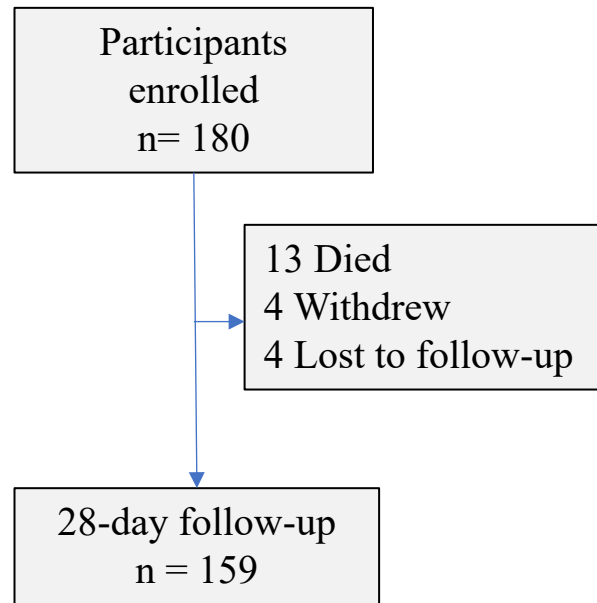
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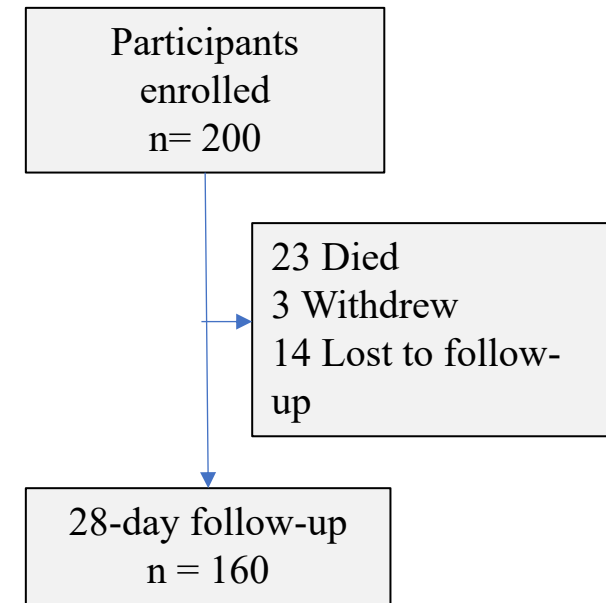
Kumasi, Ghana



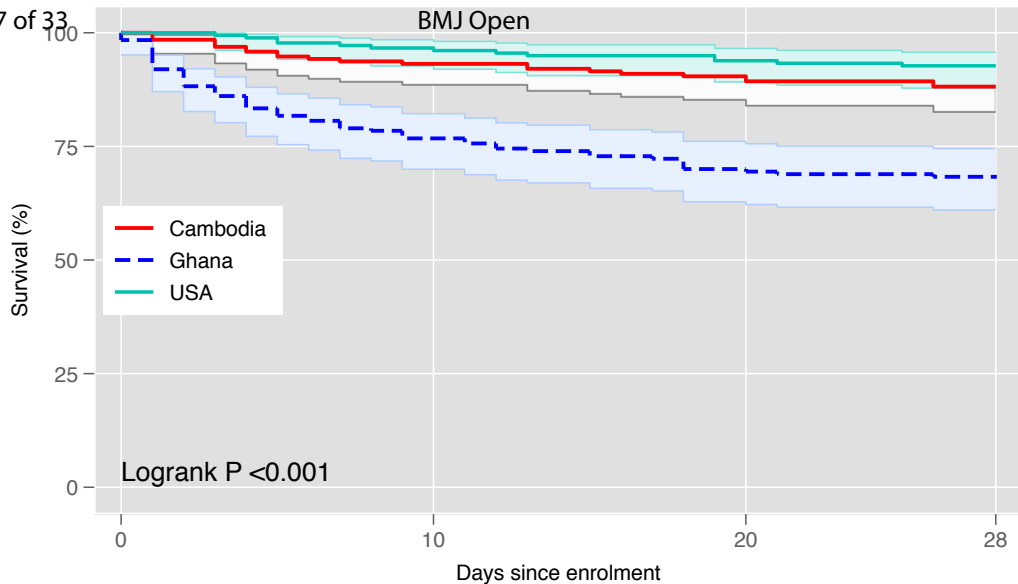
Durham, United States



Takeo, Cambodia



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No. at Risk:

	0	5	10	15	20	25	28
Cambodia	200	(13)	171	(5)	164	(4)	148
Ghana	187	(43)	137	(12)	124	(3)	118
USA	180	(6)	173	(5)	168	(2)	166

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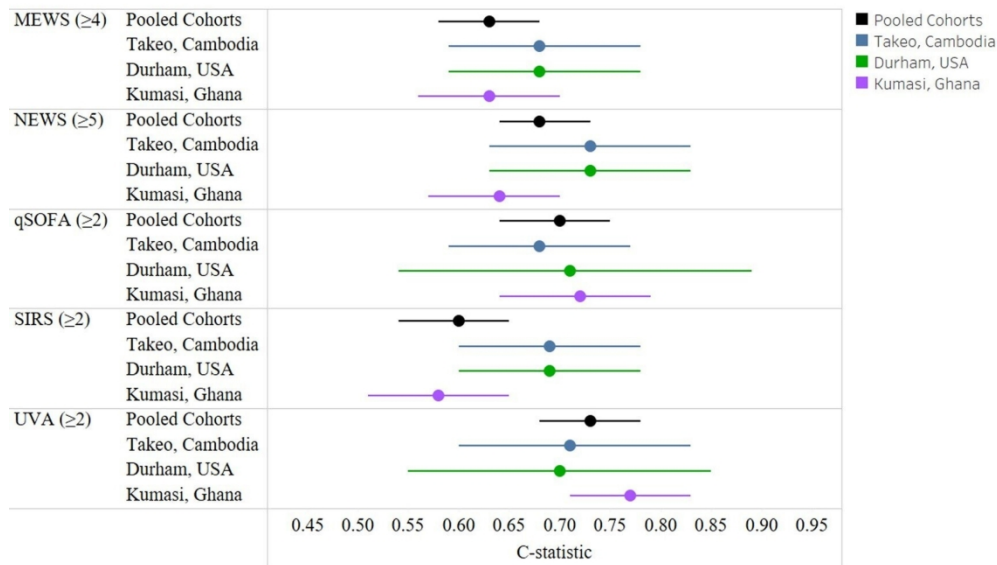


Figure 3. The C-statistic by score overall and by cohort (adjusted for age and sex).

165x96mm (800 x 800 DPI)

Table S1. Baseline physiologic and clinical laboratory parameters by site at enrollment.

Parameter	Total Median (IQR)	Takeo, Cambodia Median (IQR)	Durham, USA Median (IQR)	Kumasi, Ghana Median (IQR)
Physiologic parameters				
Respiratory rate (breaths per minute)	24 (20, 30)	24 (20, 28)	24 (20, 31)	26 (22, 30)
Systolic blood pressure (mmHg)	120 (100, 130)	110 (100, 130)	113 (96, 129)	127.5 (110, 140)
Diastolic blood pressure (mmHg)	70 (60, 80)	70 (70, 80)	64 (56, 75)	80 (60, 90)
Oxygen saturation (%)	97 (94, 98)	98 (96, 98)	95 (92, 97.5)	97 (95, 98)
Temperature (°C)	37.9 (37, 38.7)	37.5 (37, 38.5)	38.1 (36.9, 38.89)	38.2 (37.4, 38.8)
Heart rate (beats per minute)	105 (94, 118)	96 (86.5, 105.5)	111 (99.5, 124)	111 (99, 118)
Clinical laboratory parameters				
White blood cells (x10 ⁹ cells/L)	12.05 (8.13, 16.6)	11.9 (8.2, 16.6)	13.35 (9.7, 17.6)	10.76 (7.68, 15.41)
Platelets (x10 ⁹ cells/L)	222 (152.5, 321.5)	262 (169, 366)	236.5 (160, 291)	193 (137, 284)
Sodium (mEq/L)	135 (132, 138)	135 (131, 138)	137 (134, 139)	134 (130, 138)
Potassium (mEq/L)	3.7 (3.3, 4.2)	3.7 (3.2, 4.1)	3.9 (3.5, 4.3)	3.6 (3.2, 4)
Sodium Bicarbonate (mmol/L)	24 (21, 26)	24 (22, 27)	25 (22, 27)	22 (19, 25)
Glucose (mg/dL)	6.56 (5.4, 10)	6.44 (5.39, 8.28)	6.69 (5.67, 10.06)	6.65 (5.2, 12)
Blood Urea Nitrogen (mg/dL)	5 (3.57, 7.9)	4.29 (3.21, 5.71)	5.71 (3.57, 10)	5.4 (3.5, 9.4)
Creatinine (mg/dL)	88.42 (66, 130)	79.58 (53.05, 88.42)	106.1 (70.74, 150.31)	91 (70, 135)
Alkaline Phosphatase (U/L)	86.5 (65, 132)	98.5 (72, 172)	80 (63, 106)	85 (63, 125)
Alanine Transaminase (U/L)	32 (22, 58)	46 (27, 86)	22 (18, 40)	29 (22, 48)
Aspartate Aminotransferase (U/L)	42 (27, 76)	61 (38, 117)	29 (21, 45)	35.5 (25, 65)
Bilirubin (mg/dL)	15 (10.26, 21)	13.68 (10.26, 20.52)	15.39 (10.26, 20.52)	15 (11, 23)

Parameter	Total Median (IQR)	Takeo, Cambodia Median (IQR)	Durham, USA Median (IQR)	Kumasi, Ghana Median (IQR)
Albumin (g/dL)	3.0 (2.5, 3.5)	2.9 (2.5, 3.4)	3.0 (2.5, 3.5)	3.0 (2.3, 3.6)
Total protein (g/dL)	73 (65, 79)	74 (68, 79.5)	67 (57, 72)	75 (69, 83)
Lactate (mmol/L)	2.27 (1.66, 3.09)	2.33 (1.79, 3.03)	1.5 (1, 2.4)	2.54 (1.8, 3.42)

**All variables are presented as median, interquartile range*

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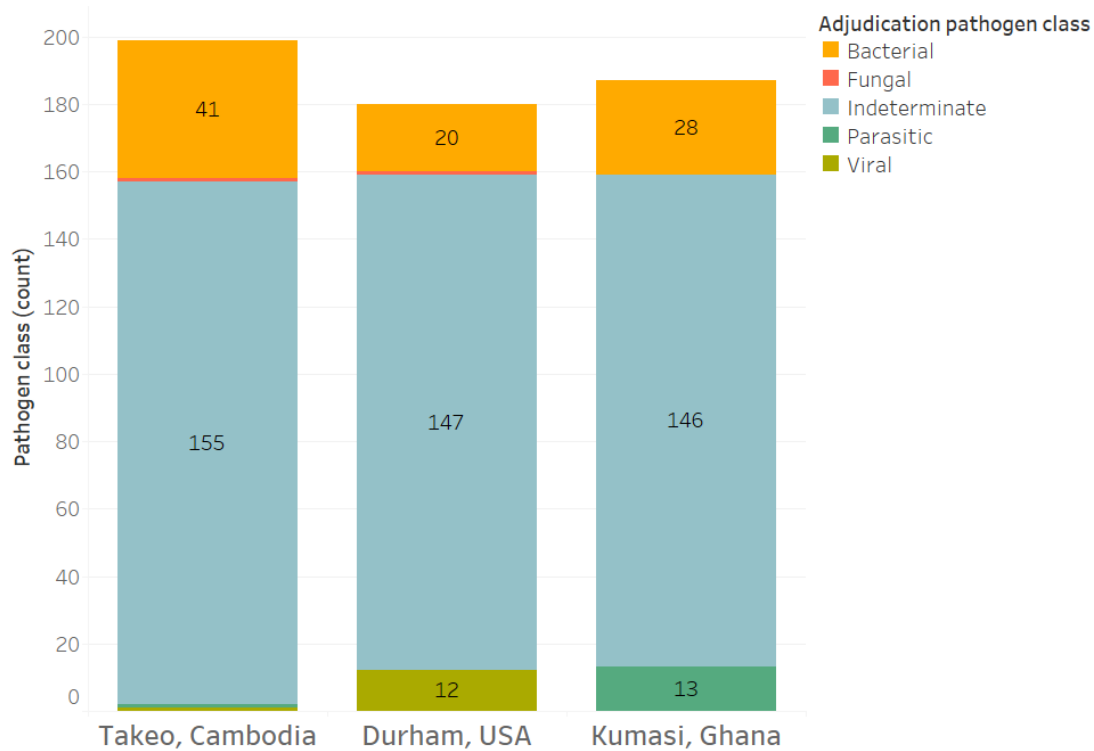
Table S2. Performance characteristics of sepsis score across Cambodia and Ghana sites combined for predicting 28-day mortality.

Score	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Unadjusted Bivariate Cox model C-statistic (95% CI)	Adjusted* Cox model C-statistic (95% CI)	p-value
Baseline						0.60 (0.54 – 0.66)	
MEWS ≥ 4	0.74 (0.64 – 0.84)	0.50 (0.44 – 0.56)	0.28 (0.25 – 0.32)	0.88 (0.84 – 0.92)	0.62 (0.57 – 0.66)	0.66 (0.61 – 0.72)	<0.001
NEWS ≥ 5	0.85 (0.75– 0.92)	0.46 (0.38– 0.52)	0.33 (0.29– 0.36)	0.91 (0.85 – 0.94)	0.65 (0.62 – 0.70)	0.70 (0.65 – 0.76)	0.001
qSOFA ≥ 2	0.54 (0.42 – 0.65)	0.84 (0.80 – 0.88)	0.47 (0.39 – 0.55)	0.87 (0.84 – 0.90)	0.67 (0.62 – 0.73)	0.71 (0.66– 0.77)	<0.001
SIRS ≥ 2	0.88 (0.78 = 0.94)	0.24 (0.19 (0.30)	0.23 (0.21 – 0.24)	0.89 (0.81 – 0.94)	0.55 (0.51 – 0.59)	0.61 (0.55 – 0.67)	0.066
UVA ≥ 2	0.75 (0.65 – 0.84)	0.74 (0.70 – 0.80)	0.45 (0.40 – 0.52)	0.92 (0.88 – 0.94)	0.73 (0.68 – 0.77)	0.76 (0.71– 0.81)	<0.001

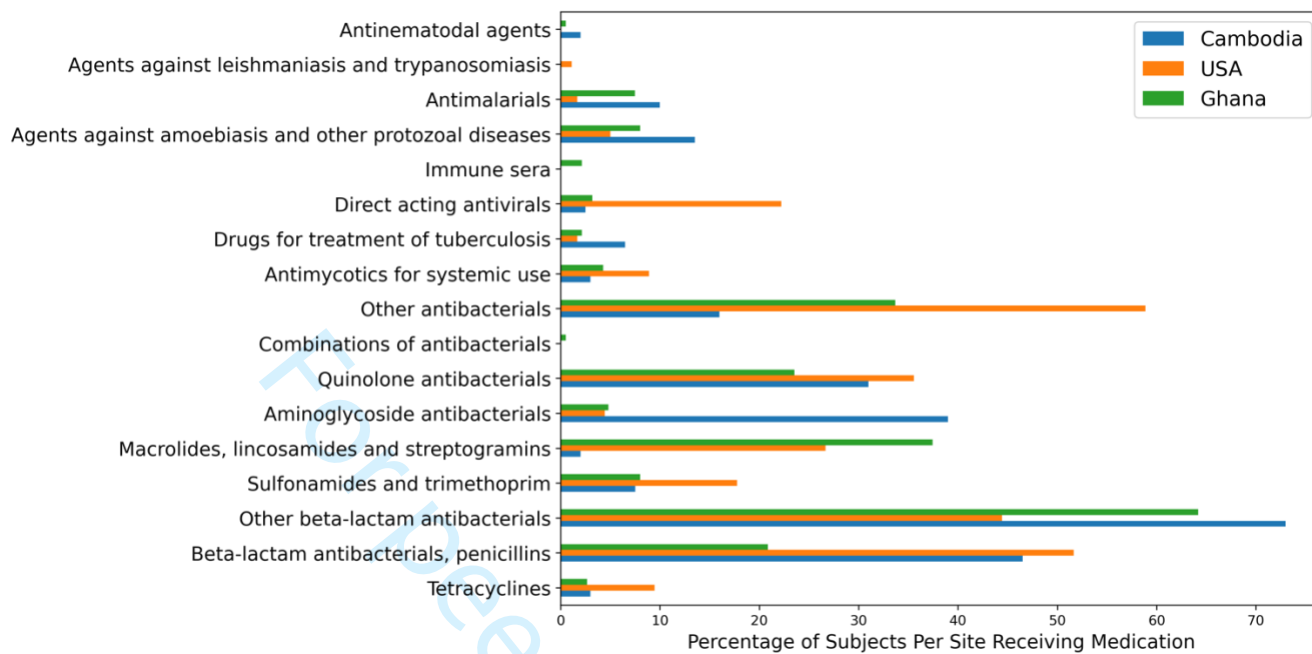
Table S3. Performance characteristics of sepsis score across the United States site for predicting 28-day mortality.

Score	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Unadjusted Bivariate Cox model C-statistic (95% CI)	Adjusted* Cox model C-statistic (95% CI)	p-value
Baseline (age +sex)						0.61 (0.52 – 0.66)	
MEWS\geq4	0.60 (0.26- 0.87)	0.33 (0.26 –0.41)	0.05 (0.03 –0.09)	0.92 (0.85 –0.96)	0.53 (0.38 – 0.67)	0.68 (0.57 – 0.79)	0.743
NEWS\geq5	0.90 (0.56 – 0.99)	0.37 (0.29 –0.45)	0.09 (0.07 –0.11)	0.98 (0.89- 0.99)	0.63 (0.54 - 0.71)	0.71 (0.59- 0.84)	0.256
qSOFA \geq2	0.60 (0.26 - 87)	0.72 (0.65 –0.79)	0.13 (0.08 - 0.20)	0.96 (0.93 –0.98)	0.66 (0.51 – 0.81)	0.71 (0.54 – 0.89)	0.019
SIRS \geq2	0.92 (0.64 - 0.99)	0.11 (0.07 –0.16)	0.08 (0.07 –0.09)	0.94 (0.72 –0.99)	0.51 (0.45 – 0.58)	0.66 (0.54 – 0.82)	0.694
UVA\geq2	0.60 (0.26 – 0.88)	0.58 (0.50 –0.66)	0.09 (0.05 -0.14)	0.95 (0.90 -0.98)	0.59 (0.44 – 0.73)	0.70 (0.50 – 0.87)	0.281

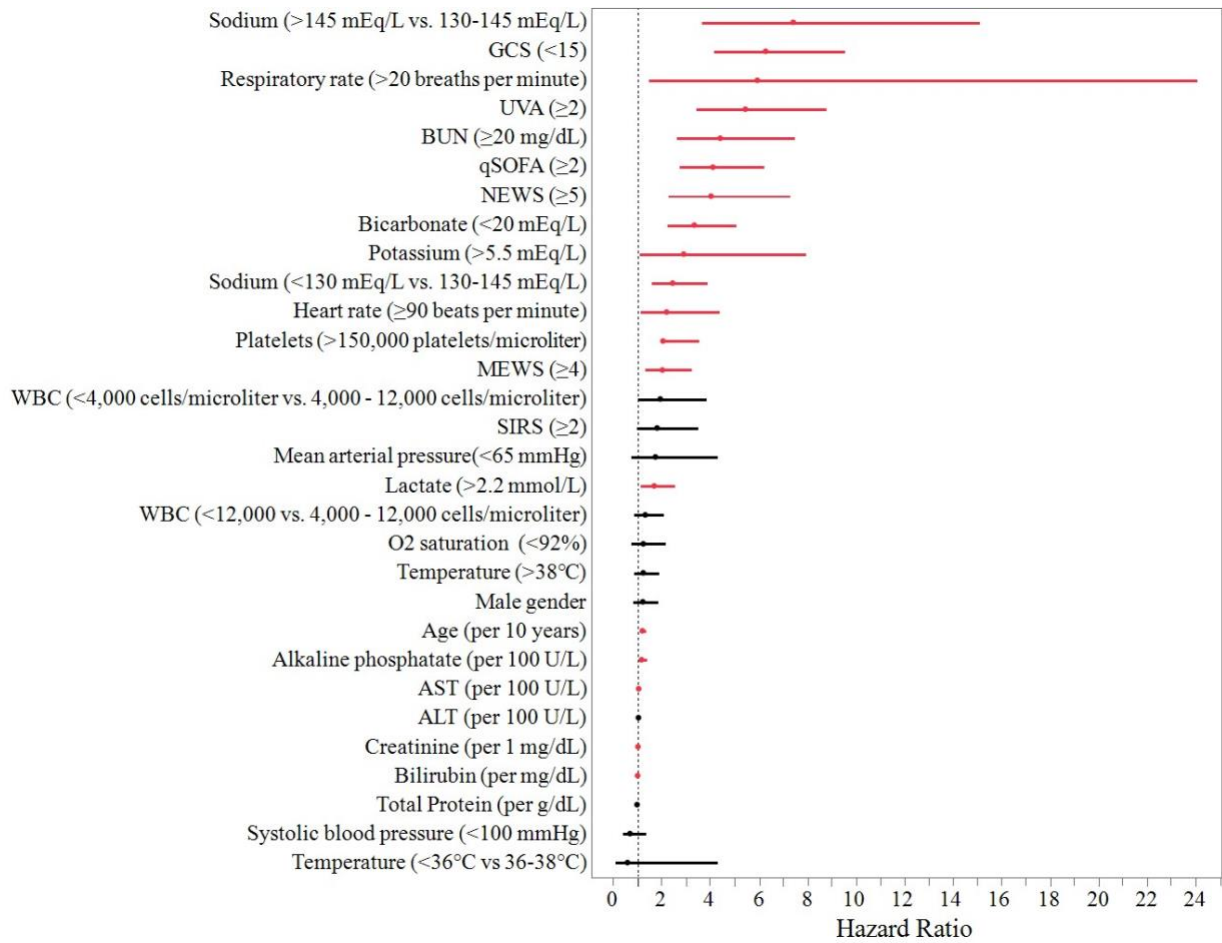
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Supplementary Figure S1. Distribution of adjudicated pathogen class for each site.



Supplementary Figure S2. Prevalence of antibiotics received per site.



Supplementary Figure S3. Forest plot of hazard ratios from bivariate Cox regression models for risk of death at 28-day for sepsis scores, physiologic parameters, and clinical laboratory parameters.

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Screening tools for predicting mortality of adults with suspected sepsis: an international sepsis cohort validation study

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2
3 1 **Title:** Screening tools for predicting mortality of adults with suspected sepsis: an international sepsis
4 cohort validation study

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Abstract:

Word count: 276

Objectives: We evaluated the performance of commonly used sepsis screening tools across prospective sepsis cohorts in the United States, Cambodia, and Ghana.

Design: Prospective cohort studies

Setting and participants: From 2014 to 2021, participants with 2 or more SIRS (Systemic Inflammatory Response Syndrome) criteria and suspected infection were enrolled in emergency departments and medical wards at hospitals in the Cambodia and Ghana and hospitalized participants with suspected infection were enrolled in the United States. Cox proportional hazards regression was performed, and Harrell's C-statistic calculated to determine 28-day mortality prediction performance of the qSOFA score ≥ 2 , SIRS score ≥ 3 , NEWS ≥ 5 , MEWS ≥ 5 , or UVA score ≥ 2 . Screening tools were compared to baseline risk (age and sex) with the Wald test.

Results: The cohorts included 567 participants (42.9% female) including 187 participants from Kumasi, Ghana, 200 participants from Takeo, Cambodia, and 180 participants from Durham, North Carolina in the United States. The pooled mortality was 16.4% at 28-days. The mortality prediction accuracy increased from baseline risk with the MEWS (C-statistic: 0.63, 95% CI: 0.58, 0.68; $p=0.002$), NEWS (C-statistic: 0.68; 95% confidence interval [CI]: 0.64, 0.73; $p<0.001$), qSOFA (C-statistic: 0.70, 95% CI: 0.64, 0.75; $p<0.001$), UVA score (C-statistic: 0.73, 95% CI: 0.69, 0.78; $p<0.001$), but not with SIRS (0.60; 95% CI: 0.54, 0.65; $p=0.13$). Within individual cohorts, only the UVA score in Ghana performed better than baseline risk (C-statistic: 0.77; 95% CI: 0.71, 0.83; $p<0.001$).

Conclusions: Among the cohorts, MEWS, NEWS, qSOFA, and UVA scores performed better than baseline risk, largely driven by accuracy improvements in Ghana, while SIRS scores did not improve prognostication accuracy. Prognostication scores should be validated within the target population prior to clinical use.

Keywords: Analysis, Survival; sepsis; Cohort Studies; Prognosis; Global Health

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45 59 **Strengths and limitations of this study:**
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- 7 60 • This study includes two well-characterized sepsis cohorts in low- and middle-income countries
8 (LMICs) and a cohort in a high-resource setting for comparison.
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12 62 • The performance characteristics of five commonly used sepsis screening tools for predicting 28-
13 day death was compared to baseline risk after adjustment for multiple comparisons.
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16 64 • Diagnostic testing differed at each site and mortality specifically due to sepsis could not be
17 determined.
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20 66 • Enrolment was by convenience sampling within the referral hospital catchment area and may not
21 be representative of the general population within these countries.
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24 68 • Sample size limitations in each of the cohorts may have led to decreased ability to identify
25 differences between each screening tool.
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33 72 **Narrative:**
3435 73 Word count: 3,883
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37 74
3839 75 INTRODUCTION
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41 76 Sepsis, a syndrome resulting from a systemic dysregulated host response to an infection, is estimated to
42 cause six million deaths per year but is likely an underestimate due to limited information from low- and
43 middle-income countries (LMICs) where 87% of the world population live [1]. Despite declining age-
44 standardized incidence and mortality, sepsis remains a major cause of health loss worldwide and has an
45 especially high health-related burden in LMICs[2].
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3 82 Clinical sepsis guidelines developed in the Western world may not be applicable in resource-limited settings
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5 83 and moreover can lead to detrimental effects on sepsis care and management when applied in these
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7 84 conditions due to decreased access to resources to manage iatrogenesis from fluid resuscitation [3, 4]. In
8
9 85 contrast to the United States, pathogens that lead to directly lead to vascular injury are common causes of
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11 86 acute febrile illness in Cambodia and Ghana such as dengue virus, malaria, or rickettsia and may alter
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13 87 empiric treatment response [5]. While early recognition and treatment of sepsis is critical, most sepsis scores
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15 88 or early warning systems were derived from cohorts outside of LMICs. Differences in causes of sepsis,
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17 89 available treatments, and available resources for supportive care should affect management strategies but
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19 90 evidence is limited and optimal clinical scores or biomarkers for sepsis identification are unknown in these
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21 91 settings. Multi-site international sepsis studies are essential for evaluating current and future sepsis tools to
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23 92 ensure effectiveness in resource-limited settings and across populations.
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28 94 The most validated prognostication scores, SOFA (Sequential Organ Failure Assessment) and the
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30 95 APACHE IV, have been developed for prognostication but require an arterial blood gas and multiple
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32 96 laboratory parameters [6, 7] that are not widely available in low-resource settings. The qSOFA (quick
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34 97 SOFA) is an abbreviated score that does not require laboratory parameters. The qSOFA is one of the most
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36 98 widely adopted sepsis screening tools and has largely replaced the SIRS (Systemic Inflammatory Response
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38 99 Syndrome) criteria as the standard abbreviated sepsis screening tool as part of the Sepsis-3 definition to
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40 100 identify septic patients [8]. The qSOFA and other sepsis screening tools (i.e., Modified Early Warning
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42 101 Score [MEWS], National Early Warning Score [NEWS], and Universal Vital Assessment [UVA]) are often
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44 102 used clinically to identify those at risk of sepsis, but these tools have been studied for their ability to
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46 103 prognosticate mortality or poor composite outcomes among hospitalized adults[9-12]. Studies have
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48 104 evaluated these tools for predicting in-hospital mortality but the performance of these tools and the
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50 105 prevalence of 28-day mortality, a common metric of sepsis outcomes, have yet to be described across both
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52 106 high- and low-resource settings using similar methods [9, 13, 14].
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3 108 We used prospective multi-site international cohorts that are part of the Austere environments Consortium
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5 109 for Enhanced Sepsis Outcomes (ACESO) consortium to validate commonly used sepsis screening tools
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7 110 [15]. In contrast to APACHE IV and SOFA, these tools can be quickly performed with limited laboratory
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9 111 test results. We hypothesized that qSOFA may perform poorly in LMIC populations compared to the UVA
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11 112 score due to differences in causes of sepsis. We describe the diverse clinical characteristics, the aetiologies
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13 113 of suspected sepsis within these cohorts, and the performance of sepsis screening tools in current clinical
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15 114 use for predicting mortality at one month post enrolment.
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19 20 116 METHODS

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22 117 From May 2014 to November 2015, 200 participants were enrolled into a prospective observational study
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24 118 of sepsis at Takeo Provincial Hospital in Takeo Province Cambodia [16] (Figure 1). This study was
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26 119 followed by a prospective study at Duke University Hospital in Durham, North Carolina, which enrolled
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28 120 180 participants from December 2014 to March 2016. In Kumasi, Ghana, 187 participants were enrolled at
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30 121 Komfo Anokye Teaching Hospital from July 2016 to October 2017.
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34 122 Hospitalized patients ≥ 18 years of age whose attending physician judged them to have an active infection
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36 123 were considered for inclusion for each of the three cohorts. Additional inclusion and exclusion criteria
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38 124 were required in Cambodia and Ghana but not required in the United States protocol. In Cambodia and
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40 125 Ghana, participants were required to meet least two clinical criteria for systemic inflammatory response
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42 126 syndrome (SIRS) during screening. In Cambodia and Ghana, patients were excluded if they had known
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44 127 malignancy, chronic renal/hepatic insufficiency, immunosuppressive conditions (except HIV) or systemic
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46 128 steroid usage that exceeded 20mg/day to prevent confounding in future biomarker studies. Patients were
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48 129 also excluded in Cambodia and Ghana if they had a history of organ transplant, hemodynamically
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50 130 significant gastrointestinal bleeding, anatomic or functional asplenia, acute cardiovascular disease,
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52 131 general anaesthesia, or surgery in the past week prior to enrolment, women who were pregnant, patients
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3 132 who had a haemoglobin less than 7 g/dL or weighed less than 35kg. Hospital physicians who deemed
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5 133 their patients too ill to participate could defer enrolment.
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8 134 *Study procedures*
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10 135 Following informed consent, study team members conducted a detailed medical history, including prior
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12 136 medications, and physical exam. Responses were recorded on a standardized case report form and
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14 137 included demographics, medical history, physical exam findings, and admission diagnoses. Study specific
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16 138 procedures conducted in Cambodia were described in detail by Rozo et al [17]. Similar enrolment and
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18 139 study procedures were followed in Kumasi, Ghana and in Durham, North Carolina, USA. Blood was
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20 140 collected at the time of enrolment, then at 6 hours later, and at 24 hours later. In Ghana and Cambodia,
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22 141 standardized clinical tests included a peripheral venous blood gas with lactate, complete blood count,
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24 142 complete metabolic panel, optional HIV screening with consent (Alere Determine HIV1/2, Abbott, OK,
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26 143 United States), malaria rapid diagnostic tests (SD Bioline Ag. P.f./Pan, Abbott, OK, United States) and
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28 144 aerobic blood cultures (one aerobic bottle, Bactec 9050, BD, NJ, United States) as part of study
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30 145 procedures in Ghana and Cambodia. Microbiologic results were available if collected through routine
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32 146 clinical care across cohorts. Additional molecular testing and next generation sequencing for pathogens
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34 147 were also performed on blood samples in the Cambodia cohort as previously described [17]. Participants
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36 148 were followed throughout their hospitalization and a record review performed at discharge.
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41 149 An interview was performed, and blood samples were collected at a 28-day follow-up visit across cohorts.
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43 150 When patients could not return in person, study team members attempted to conduct an interview with
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45 151 patients or a legally authorized representative by telephone. Fatal outcomes among each discharged
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47 152 participant were also determined.
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51 153 Using clinical data from case report forms and microbiology diagnostic information, clinical adjudication
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53 154 was performed by three physician reviewers (internal medicine or infectious diseases) to determine the
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55 155 source of infection by anatomic location and pathogen class (i.e., bacterial, parasitic, viral, or fungal).
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3 156 This was graded on a low, moderate, and high level of confidence by two independent reviewers and a
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5 157 third reviewer served as a tiebreaker for discordant conclusions. If the third reviewer did not agree with
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7 158 either adjudicator, then the decision was determined by committee. Microbiologic results presented
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9 159 include those adjudicated to be clinically relevant to participant's acute illness.
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12 160 *Patient and Public Involvement*

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15 161 Patients were not involved in recruitment, design, conduct, or dissemination plans of our research. Results
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17 162 of this study were disseminated to hospital and clinical leadership at Takeo Provincial Hospital and
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19 163 Komfo Anokye Teaching Hospital.
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22 23 165 *Statistical analysis*

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25 166 Summary statistics were calculated for the cohorts individually and pooled, comparing baseline
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27 167 demographics (e.g., gender, age, ethnicity, selected medical comorbidities), baseline screening tool
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29 168 scores, physiologic parameters, baseline clinical laboratory values using either Chi-square (categorical
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31 169 values), Fishers exact (categorical values), or Kruskal-Wallis (continuous values) tests. Prevalence of
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33 170 diagnoses were described for each cohort by organ system and pathogen type and by anatomic site.
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38 172 After checking the proportional hazards assumption, Cox regression was performed with bivariate models
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40 173 to evaluate increased risk of death in each cohort by baseline demographics, comorbid conditions,
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42 174 physiologic parameters, and clinical laboratory parameters. Physiologic parameters and clinical laboratory
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44 175 parameters were modelled as dichotomous or ordinal parameters at clinically relevant abnormal range cut
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46 176 offs (e.g., blood urea nitrogen ≥ 20 mg/dL) to explore associations with increased risk of death and for
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48 177 clinical inference. Screening tools were dichotomized according to current usage, including qSOFA score
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50 178 ≥ 2 (range, 0 [best] to 3 [worst] points), SIRS score ≥ 2 (range, 0 [best] to 4 [worst] points), MEWS ≥ 5
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52 179 (range, 0 [best] to 13 [worst] points), NEWS ≥ 5 (range, 0 [best] to 20 [worst] points), and UVA ≥ 2
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54 180 (range, 0 [best] to 13 [worst])[13] and were evaluated in Cox regression models unadjusted and adjusted
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3 181 for age and sex for risk of death [9]. Glasgow Coma Scale Score (GCS; range, 3 [worst] to 15 [best]
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5 182 points) of less than 15 was used for estimation of the qSOFA score, and a GCS of ≤ 3 for
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7 183 unresponsiveness for NEWS, and GCS score 3-15 for the “alert, verbal, pain, unresponsive” scale
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9 184 (AVPU; alert: GCS 13-15, voice: GCS 9-12; pain: GCS 4-8; unresponsiveness: GCS ≤ 3) score
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11 185 approximation for MEWS [18, 19]. Data was administratively right censored past 28 days. The Harrell’s
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13 186 C-statistic was calculated for each screening tool for each cohort, the cohorts combined, and Cambodia
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15 187 and Ghana cohorts pooled [20]. This statistic is a performance analogous to area under the receiver
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17 188 operating characteristic curve (AUROC) but accounts for differences over time with survival outcomes.
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19 189 C-statistic confidence interval estimates were determined.[21] The Cox regression Wald test p-values
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21 190 were calculated for each score covariate adjusting for baseline risk estimated by age and sex to determine
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23 191 if scores improved model accuracy above baseline risk [9, 22]. P-values < 0.002 were considered
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25 192 significant using a Bonferroni correction for multiple comparisons. Cohort sample sizes were determined
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27 193 a priori through Monte Carlo simulation modelling for prognostic biomarker identification. All statistical
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29 194 analyses were performed in SAS (Statistical Analytical Software, version 9.4), R version 4.0.2 [23] or
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31 195 Stata (version 15.0; StataCorp LLC, College Station, TX, USA) [24].
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37 196 38 197 RESULTS

39 198 *Summary demographics, sepsis severity, and laboratory findings*

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41 199 There were 567 participants across the cohorts including 187 from Kumasi, Ghana, 200 from Takeo,
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43 200 Cambodia, and 180 from Durham, North Carolina, United States (**Figure 1**). The study population was
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45 201 predominantly male (57.1% male), with more male participants enrolled in Cambodia than at other sites
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47 202 (68.0% vs 55.0% in the U.S. and 52.4% in Ghana). The overall median age was 50 years (interquartile
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49 203 range [IQR], 36 to 63), which was similar across cohorts (**Table 1**). Previously diagnosed comorbid
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51 204 conditions were most common at the U.S. site including a history of cardiovascular (65.6%; N=118),
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53 205 respiratory (42.2%; N=76), or gastrointestinal (36.7%; N=66) conditions.
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Table 1. Baseline demographic characteristics stratified by sites.

Characteristic	Total (n=567)	Takeo, Cambodia (n=200)	Durham, USA (n=180)	Kumasi, Ghana (n=187)	p-value**
Female gender – no. (%)	243 (42.9%)	64 (32.0%)	81 (45.0%)	98 (52.4%)	< 0.001
Age – years, median (IQR)	50 (36 – 63)	50 (36 – 62)	52.5 (40 – 63)	46 (35 – 63)	0.151
Medical history* – no. (%)					
Cancer	44 (9.9%)	0 (0.0%)	44 (24.4%)	0 (0.0%)	< 0.001
Cardiovascular	202 (41.4%)	22 (18.2%)	118 (65.6%)	62 (33.2%)	< 0.001
Dermatologic	15 (3.1%)	1 (0.8%)	14 (7.8%)	0 (0.0%)	< 0.001
Endocrine	126 (25.8%)	6 (5.0%)	74 (41.1%)	46 (24.6%)	< 0.001
Gastrointestinal	76 (15.6%)	4 (3.3%)	66 (36.7%)	6 (3.2%)	< 0.001
Genitourinary or reproductive	34 (7.0%)	1 (0.8%)	33 (18.3%)	0 (0.0%)	< 0.001
HIV	26 (4.7%)	12 (6.2%)	8 (4.5%)	6 (3.2%)	0.388
Neurological	62 (12.7%)	1 (0.8%)	44 (24.4%)	17 (9.1%)	< 0.001
Other	206 (42.2%)	48 (39.7%)	151 (83.9%)	7 (3.7%)	< 0.001
Psychiatric	143 (29.3%)	41 (33.9%)	78 (43.3%)	24 (12.8%)	< 0.001
Renal	41 (8.4%)	0 (0.0%)	41 (22.8%)	0 (0.0%)	< 0.001
Respiratory	89 (18.2%)	7 (5.8%)	76 (42.2%)	6 (3.2%)	< 0.001
Rheumatologic	29 (5.9%)	1 (0.8%)	28 (15.6%)	0 (0.0%)	< 0.001
Surgery	27 (5.5%)	0 (0.0%)	22 (12.2%)	5 (2.7%)	< 0.001
Baseline scores – no. (%)					
MEWS (≥ 4)	315 (57.8%)	81 (40.7%)	105 (65.6%)	129 (69.3%)	< 0.001
NEWS score (≥ 5)	324 (61.6%)	90 (47.9%)	98 (64.5%)	136 (73.1%)	< 0.001
qSOFA (≥ 2)	139 (25.4%)	22 (11.1%)	48 (29.6%)	69 (37.1%)	< 0.001
SIRS (≥ 2)	447 (81.8%)	125 (68.3%)	157 (89.2%)	165 (88.2%)	< 0.001
UVA (≥ 2)	199 (37.8%)	47 (25.8%)	68 (42.8%)	84 (45.4%)	< 0.001
Baseline scores (median [IQR])					
MEWS	4 (3-6)	3 (2-5)	1 (0-4)	1 (1-2)	< 0.001
NEWS	6 (3-8)	4 (2-7)	7 (3-9)	6 (4-8)	< 0.001
qSOFA	1 (1-2)	1 (0-1)	1 (0-2)	1 (1-2)	< 0.001
SIRS	2 (2-3)	2 (1-3)	3 (2-3)	3 (2-3)	< 0.001

Table 1. Baseline demographic characteristics stratified by sites.

Characteristic	Total (n=567)	Takeo, Cambodia (n=200)	Durham, USA (n=180)	Kumasi, Ghana (n=187)	p-value**
UVA	1 (0-3)	1 (0-2)	1 (0-4)	1 (0-4)	< 0.001

*There were 79 subjects without comorbidity information in the Cambodia cohort. **Categorical parameters compared with chi-squared test and numeric parameters compared with Kruskal-Wallis test. Not adjusted for multiple comparisons.

206 Clinical physiologic and laboratory value abnormalities at enrolment were common with median

207 respiratory rate at 24 (IQR: 20 to 30), the median white blood count elevated at 12.05×10^9 cells/L (IQR:

208 8.13 to 16.6×10^9 cells/L), and median lactate elevated at 2.27 mmol/L (IQR: 1.66 to 3.09 mmol/L)

209 (**Supplementary Table S1**). At enrolment, the proportion of an elevated qSOFA (≥ 2) at baseline was

210 highest at the Ghana site with 44.4% (N=83) of participants compared to 26.0% (N=52) in Cambodia and

211 22.2% (N=40) in the United States. The SIRS, MEWS, NEWS, and UVA screening tools were similarly

212 higher in the Ghana cohort.

213

214 *Pathogens detected*

215 The most common positive microbiologic results overall included bacteraemia (N=83), respiratory culture

216 growth (N=19), serum hepatitis B surface antigen (N=15), and malaria rapid diagnostic tests (N=11). A

217 minority (121 of 567, 21.3%) of subjects had confirmed infections with complete adjudicator agreement

218 using all available sources of clinical microbiologic results (with the notable addition of RNA sequencing

219 of samples from Cambodia[17]) including 90 (15.9%) bacterial, 17 viral (3.0%), 20 malarial (3.5%), and

220 2 (0.3%) fungal infections identified across all cohorts (**Supplementary Figure S1**). These infection

221 classes were different among sites (chi-squared test $p < 0.001$).

222

223 In Cambodia, the most common bacterial infections with complete adjudicator agreement were *B.*

224 *pseudomallei* (N=10, with blood or respiratory culture growth), presumptive *M. tuberculosis* (N=5, with

225 acid fast positive smears), polymicrobial (N=5), and *O. tsutsugamushi* (N=4, determined by sequencing).

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3 226 The most common causes of bacteraemia (17 total of 200 participants) were *B. pseudomallei* (N=8), *E.*
4 227 *coli* (N=3), and polymicrobial infections (N=3). Three participants had a positive malaria RDT. Fungal
5 228 infections were uncommon with 1 participant with non-albicans Candidemia and 1 with cryptococcal
6 229 meningitis. Two individuals had dengue fever (one PCR positive and one adjudicated IgM positive).
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11 230
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13 231 In Ghana, the most common causes of bacteraemia (culture growth from 28 of 187 participants) were *E.*
14 232 *coli* (N=6), *S. aureus* (N=6), *Salmonella spp.* (N=5), and *S. pneumoniae* (N=3). Nine participants had a
15
16 233 positive malaria RDT and 15 had a positive hepatitis B surface antigen.
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22 235 In the United States, the most common causes of bacteraemia (culture growth from 19 of 180
23
24 236 participants) were *E.coli* (N=5), *K. pneumoniae* (N=3), polymicrobial (N=2), *Pseudomonas spp.* (N=2),
25
26 237 or *S. aureus* (N=2). Viral infections detected by PCR included rhinovirus (N=5), influenza A (N=4),
27
28 238 respiratory syncytial virus (N=4), human immunodeficiency virus (N=3), and human metapneumovirus
29
30 239 (N=3). There was one participant with *Aspergillus fumigatus* fungal pneumonia.
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34 241 *Diagnoses and Treatments*

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36 242 Across cohorts, the most common organ system sites of infection were lower respiratory tract infection
37
38 243 (28.7%; N=163), multifocal or generalized source of infection (including malaria) (13.6%; N=77), and
39
40 244 gastrointestinal (including hepatic) (12.7%; N=72) (**Figure S1a**). The most common antibiotics
41
42 245 administered in United States, Ghana, and Cambodia were beta-lactam antibiotics (**Supplementary**
43
44 246 **Figure S2**), but antibiotic regimens varied widely among sites. The most common antibiotics classes used
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46 247 were other antibacterials (e.g., glycopeptide antibiotics, 58.9%), beta-lactam antibacterials, penicillins
47
48 248 (51.7%), and cephalosporin and carbapenem antibacterials (44.4%) in the United States, cephalosporins
49
50 249 and carbapenems (64.2%), macrolides, lincosamides and streptogramins (37.4%), and other antibacterials
51
52 250 (33.7%) in Ghana, and cephalosporins and carbapenems (73.0%), beta-lactam antibacterials, penicillins
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54 251 (46.5%) and aminoglycoside antibacterials (39.0%) in Cambodia.
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252

253 *Survival*

254 Among all cohorts, 16.4% (N=93) of participants had died at one month, including 58 (31.0%) in Ghana,
255 22 (11.0%) in Cambodia, and 13 (7.2%) in the U.S (**Figure 1**). Among those that died within one month,
256 median time to death was 4 days (IQR: 1 to 11) in Ghana, 7 days (IQR: 3 to 16) in Cambodia, 10 (IQR: 5
257 to 19) in the U.S., and 5 days (IQR: 2 to 13) overall. Parameters to calculate the qSOFA score and 28-day
258 mortality were available for 96.4% participants. Hypernatremia (>145 mEq/L) had the highest unadjusted
259 risk of death (hazard ratio 6.89, 95% CI: 3.43, 13.85) among parameters tested in bivariate models
260 (**Supplementary Figure S3**). All screening tools were associated with an increased risk of death (**Figure**
261 **2**) with the largest increase among those with an elevated UVA score (**Supplementary Figure S3**). For
262 individuals with a UVA ≥ 2 there was a 5.45 times increased risk of death (95% CI: 3.39 to 8.76; C-
263 statistic: 0.70) and those with a qSOFA ≥ 2 had a 4.11 times increased risk of death (95% CI: 2.71 to 6.22;
264 C-statistic: 0.66). Those with an elevated SIRS had a 1.81 times increased risk of death (95% CI: 0.94 to
265 3.50; C-statistic:0.53). Elevated NEWS (HR: 4.03; 95% CI: 2.24 to 7.26; C-statistic: 0.66) and MEWS
266 (HR: 2.03; 95% CI: 1.28 to 3.23; C-statistic: 0.53) had similarly increased risks (**Figure 3**).

267

268 Accuracy in an adjusted Cox model was highest for UVA (0.73; 95% CI 0.68-0.78) followed by qSOFA
269 (C-statistic: 0.70; 95% CI: 0.64 to 0.75) (**Table 2**). The sensitivity for predicting death was highest with
270 SIRS (89%; 95% CI: 80 to 94%) but specificity was lowest (19%; 95% CI: 16 to 26%). The UVA score
271 had a sensitivity of 74% and specificity of 70%. The qSOFA score had the lowest sensitivity (54%; 95%
272 CI: 44 to 65%) but highest specificity (80%; 95% CI: 76 to 84%). We observed that the qSOFA
273 discrimination for mortality was moderate with a C-statistic of 0.70 adjusting for age and sex (**Figure 3**).
274 There was similar qSOFA accuracy in individual cohorts from the United States (C-statistic 0.71; 95%
275 CI: 0.54 to 0.89), Cambodia (C-statistic: 0.68; 95% CI: 0.59 to 0.77), or Ghana (C-statistic: 0.72; 95% CI:
276 0.64 to 0.79) (**Figure 3**). Similarly, the UVA score had moderate accuracy with a C-statistics on 0.73
277 (95% CI: 0.68 to 0.78). Other screening scores had similar moderate C-statistic values. The SIRS C-

278 statistic was 0.60 (95% CI: 0.54 to 0.65). Among participants with a NEWS score of ≥ 5 (62% of the
 279 pooled cohort), the C-statistic was 0.68 (95% CI: 0.64 to 0.73) and among those with a MEWS score of
 280 ≥ 4 (58% of the pooled cohort), the C-statistic was 0.63 (95% CI: 0.58 to 0.68) for death. The qSOFA and
 281 UVA scores were significantly greater than baseline risk in Ghana in contrast to other scores or cohorts
 282 (Table 3). The qSOFA score increased prognostication accuracy in the United States cohort with a $p=0.02$
 283 but this was not significant after correcting for multiple comparisons. In Cambodia, while not significant

Table 2. Performance characteristics of sepsis score across cohorts for predicting 28-day mortality.

Score	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Unadjusted Bivariate Cox model C-statistic (95% CI)	Adjusted* Cox model C-statistic (95% CI)	p-value (Wald test)
Age and sex	–	–	–	–	–	0.59 (0.53,0.64)	
MEWS $\geq 4^*$	0.73 (0.63, 0.82)	0.45 (0.40, 0.49)	0.21 (0.16, 0.26)	0.89 (0.85, 0.93)	0.59 (0.54, 0.63)	0.63 (0.58,0.68)	0.002**
NEWS $\geq 5^*$	0.86 (0.77,0.93)	0.43 (0.38,0.48)	0.25 (0.23,0.28)	0.93 (0.89, 0.95)	0.65 (0.64, 0.67)	0.68 (0.64,0.73)	<0.001**
qSOFA $\geq 2^*$	0.54 (0.44, 0.65)	0.80 (0.76, 0.84)	0.35 (0.27, 0.44)	0.90 (0.87, 0.93)	0.66 (0.61, 0.71)	0.70 (0.64,0.75)	<0.001**
SIRS $\geq 2^*$	0.89 (0.80, 0.94)	0.19 (0.16, 0.23)	0.17 (0.14, 0.21)	0.90 (0.82, 0.95)	0.53 (0.50, 0.57)	0.60 (0.54,0.65)	0.134
UVA $\geq 2^*$	0.74 (0.64, 0.83)	0.70 (0.65, 0.74)	0.33 (0.27, 0.40)	0.93 (0.90,0.95)	0.70 (0.65, 0.74)	0.73 (0.68,0.78)	<0.001**

*Adjusted Cox model C-statistic is adjusted for age and gender. Note: p-value are from Wald test of the adjusted Cox regression model.

**Significant at $p<0.002$

284 after correction, NEWS ($p=0.01$) and UVA ($p=0.01$) scores increased accuracy greater than baseline risk.
 285 When pooling LMIC cohorts (i.e., Ghana and Cambodia), after adjustment for age and sex, the qSOFA
 286 (C-statistic: 0.71; 95% CI: 0.66 to 0.77) and UVA scores (C-statistic: 0.76; 95% CI: 0.71 to 0.81) had

Table 3. Performance characteristics of sepsis score across cohorts for predicting 28-day mortality stratified by site.

Model	Takeo, Cambodia		Durham, USA		Kumasi, Ghana	
	C-statistic (95% CI)	p-value	C-statistic (95% CI)	p-value	C-statistic (95% CI)	p-value
Age and Sex	0.68 (0.59, 0.78)	–	0.68 (0.54,0.81)	–	0.57 (0.49, 0.64)	–

MEWS	0.68 (0.59, 0.78)	0.2102	0.68 (0.57, 0.79)	0.4991	0.63 (0.56, 0.70)	0.0097
NEWS	0.73 (0.63, 0.83)	0.0106	0.71 (0.59, 0.84)	0.2557	0.64 (0.57, 0.70)	0.0022
qSOFA	0.68 (0.59, 0.77)	0.5101	0.71 (0.54, 0.89)	0.0365	0.72 (0.64, 0.79)	<0.001*
SIRS	0.69 (0.60, 0.78)	0.5020	0.69 (0.55, 0.83)	0.5831	0.58 (0.51, 0.65)	0.1882
UVA	0.71 (0.60, 0.83)	0.0109	0.70 (0.55, 0.85)	0.4753	0.77 (0.71,0.83)	<0.001*

*Note: p-value are from Wald test of the adjusted Cox regression model. Each model is adjusted for age and sex. *Significant at p<0.002*

287 higher accuracy compared with MEWS (C-statistic: 0.66 (95% CI 0.61 to 0.72), NEWS (C-statistic: 0.70
 288 (95% CI: 0.65 to 0.76), and SIRS (C-statistic: 0.61; 95% CI: 0.55 to 0.67) (**Supplementary Table S2**). In
 289 contrast, in the United States cohort, NEWS, MEWS, SIRS, qSOFA, and UVA scores after age and sex
 290 adjustment each had similar accuracy with C-statistics ranging from 0.66 to 0.71 (**Table 3 and**
 291 **Supplementary Table S3**).

293 DISCUSSION

294 In pooled prospective international cohorts in Cambodia, Ghana, and the United States, the UVA score
 295 and Sepsis-3 (qSOFA) performed well with a C-statistic around 0.7 for predicting 28-day mortality.
 296 However, this improvement was largely identified in the cohort in Ghana and the accuracy was no
 297 different than baseline risk in the Cambodia cohort. There was a trend towards improving prognostication
 298 accuracy with the NEWS and UVA score in Cambodia and only with the qSOFA score in the United
 299 States. These results suggest that widely used sepsis screening tools may have varying performance for
 300 prognostication in diverse settings with different treatment regimens and aetiologies of sepsis. Therefore,
 301 screening tools should be selected after validation within populations prior to widespread adoption.

302
 303 High sodium (hyponatremia) was associated with the highest risk of 28-day death among individual
 304 clinical parameters. Hyponatremia during critical illness has been previously associated with mortality in
 305 large observational studies from high resource settings [25, 26]. Hyponatremia can occur in sepsis due to
 306 intravascular fluid loss due to breakdown of vascular cell junctions, insensible fluid losses, or dehydration

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3 307 from the disease process [27]. There can also be an iatrogenic contribution from diuretics, sodium from
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5 308 intravenous fluids, or with inadequate fluid resuscitation. Ultimately, there is not data available to
6
7 309 precisely determine the causes of hypernatremia among the participants in our cohorts. However, our
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9 310 results highlight the universal risk of death among those with hypernatremia among those with sepsis and
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11 311 emphasize the need for close management of fluid and electrolytes across critical care settings.
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16 313 Current sepsis screening tools have had variable performance when applied for prognostication. SOFA or
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18 314 APACHE scores have been developed specifically for prognostication but required parameters including
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20 315 arterial blood oxygen saturation are often not available [9]. Performance of qSOFA and SIRS for
21
22 316 mortality have performed poorly (SIRS, area under the receiving operator curve [AUROC], 0.61; qSOFA:
23
24 317 AUROC, 0.61) for prognostication in high-resource settings intensive care unit (ICU) settings [14] and in
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26 318 diverse LMICs (adjusted SIRS: AUROC, 0.59; adjusted qSOFA: AUROC, 0.70) [9] in prior studies for
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28 319 mortality prognostication. While qSOFA is generally more specific than other screening tools, it is less
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30 320 sensitive than SIRS, MEWS, and NEWS, which is consistent with our data[28]. When applied to sepsis
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32 321 identification, Surviving Sepsis 2021 guidelines recommend against solely using qSOFA, [29] due to
33
34 322 being a more specific rather than sensitive screening test. Additionally, qSOFA has been found to be
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36 323 inferior to MEWS, and NEWS but more accurate and specific than SIRS for predicting in-hospital
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38 324 mortality and ICU transfer in a large retrospective cohort of over 30 thousand patients in the United States
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40 325 (NEWS: AUROC, 0.77; MEWS: AUROC, 0.73; qSOFA: AUROC, 0.69; SIRS: AUROC, 0.65) [28].
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42 326 Different screening scores have been evaluated in prospective cohorts in sub-Saharan Africa (SSA)
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44 327 previously in Tanzania (qSOFA: AUROC, 0.57; MEWS: AUROC, 0.49) [30] and Rwanda [31] (MEWS:
45
46 328 AUROC, 0.69; UVA: AUROC, 0.71; qSOFA: AUROC, 0.65) and in Gabon [32] (UVA: AUROC, 0.90;
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48 329 qSOFA: AUROC, 0.77; MEWS: AUROC, 0.72; SIRS: AUROC, 0.70). Given the performance variability
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50 330 that has been previously observed and was observed in this study, it is prudent to evaluate prediction
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52 331 scores within the populations they serve prior to widespread promotion.
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3 333 The UVA score performed better than baseline risk in the Ghana cohort. Our results externally validated
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5 334 the UVA score for use prognostication of hospitalized patients with suspected sepsis in Kumasi, Ghana
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7 335 and potentially in the region when demographics are similar. The superiority of the UVA score in the
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9 336 Ghana cohort could be related to similarities in infectious causes of illness with other countries in SSA
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11 337 populations from which the UVA score was derived[12]. In contrast to the score derivation study[12],
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13 338 UVA score performed similarly to qSOFA in Ghana. The accuracy of the UVA scores was not greater
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15 339 than baseline risk in the cohort in Cambodia after adjustment for multiple comparisons. While
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17 340 conclusions may be limited by sample size, sepsis scores derived from the regions of the world with more
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19 341 similar infectious aetiologies may perform better. Our results highlight the importance of validating
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21 342 scores in new patient populations prior to widespread use.
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25
26 344 This study had multiple limitations. First, exclusion criteria of immunocompromising conditions except
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28 345 HIV may have led to a skewed populations from Ghana and Cambodia. These exclusion criteria were
29
30 346 created to decrease the effect of comorbid conditions or medications on immune biomarkers. However, in
31
32 347 Cambodia and Ghana, immunosuppressive medications or diagnoses of chronic liver or kidney disease
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34 348 may be less common in the general population due to limited access to specialists or specialized
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36 349 medications. Additionally, while there were differences in the baseline severity between cohorts, study
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38 350 processes including inclusion criteria were largely standardized across sites improving the comparability
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40 351 of the cohorts in diverse settings and baseline risk was adjusted in models using age and sex. Diagnostic
41
42 352 testing differed at each site and mortality specifically due to sepsis could not be determined. Enrolment
43
44 353 was by convenience sampling within the referral hospital catchment area and may not be representative of
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46 354 the general population within these countries. Approximation of the mental status for the MEWS scoring
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48 355 using GCS may not be generalizable to the use of GCS at other sites. However, similar MEWS and
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50 356 NEWS performance was observed across sites. Lastly, due to the limited sample size in each of the
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52 357 cohorts, smaller improvements in accuracy may not have been identified in the Cambodia and United
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54 358 States cohorts that had less deaths compared to the Ghana cohort.
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5 360 Inexpensive and readily available tools are needed for triage in resource-limited areas in the world to help
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7 361 identify patients that need escalation and possible transfer to higher levels of care. Current widely used
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9 362 sepsis screening tools represent a clinical benchmark for the development of future triage tools. Research
10
11 363 is ongoing to assess point-of-care diagnostics within our sepsis cohort research network. Assays with
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13 364 portable and low-cost inflammation biomarkers tests, molecular diagnostics, or point-of-care ultrasound
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15 365 (POCUS) have the potential to augment the performance of clinical screening tools towards a more
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17 366 personalized approach to sepsis recognition and triage.
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21 22 368 CONCLUSION

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24 369 Sepsis screening tools that are widely used during clinical care had sub-optimal performance for risk
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26 370 stratification in three international cohorts with increased performance of the UVA and qSOFA scores in
27
28 371 Ghana compared to baseline risk. There remains a need for reliable, low-cost, and scalable
29
30 372 prognostication methods that are validated in diverse settings.
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40
41 377 (N626451920001).
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48
49 380 of Danaher Diagnostics. All other authors declared no competing interests.
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3 382 **Ethics approval:** Study protocols were approved by the Naval Medical Research Center (NMRC)
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5 383 Institutional Review Board (IRB) (Cambodia sepsis study # NMRC.2013.0019; Ghana sepsis study #
6
7 384 NMRC.2016.0004-GHA; Duke sepsis study Duke#PRO00054849) in compliance with all applicable
8
9 385 Federal regulations governing the protection of human subjects as well as host country IRBs. The study
10
11 386 protocol in Cambodia was approved by the Cambodian National Ethics Committee for Health Research
12
13 387 (NECHR). The protocol in Ghana was approved by the Committee on Human Research, Publication and
14
15 388 Ethics (CHRPE) at Kwame Nkrumah University of Science & Technology. All procedures were in
16
17 389 accordance with the ethical standards of the Helsinki Declaration of the World Medical Association. All
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19 390 patients, or their legally authorized representatives, provided written informed consent.
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26
27 393 service members. This work was prepared as a part of official duties. Title 17 U.S.C. 105 provides that
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29 394 ‘Copyright protection under this title is not available for any work of the United States Government.’ Title
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31 395 17 U.S.C. 101 defines a U.S. Government work as a work prepared by a military service member or
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34
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44
45 401 KLS, and DVC developed the manuscript concept. DVC and KLS provided resources for research
46
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49 403 TV, AO, DA, and GO were involved in protocol development and data generation. LM, MS, WH, SK, were
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51 404 involved in research operations. AL, KLS, CWW, DF, ELT, CB, DVC, and PWB were involved in
52
53 405 manuscript revisions. All authors reviewed and approved of this manuscript.
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3 407 **Data sharing statement:** De-identified data may be made available upon reasonable request to the
4
5 408 corresponding author.
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10 410 **References**

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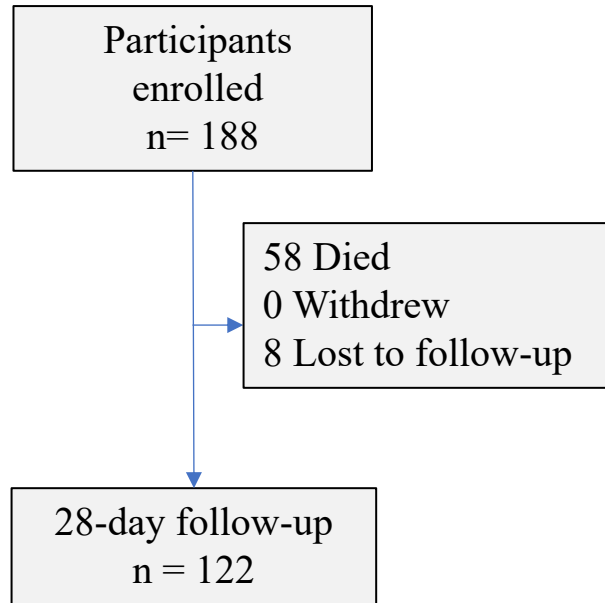
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490 Figure Legends

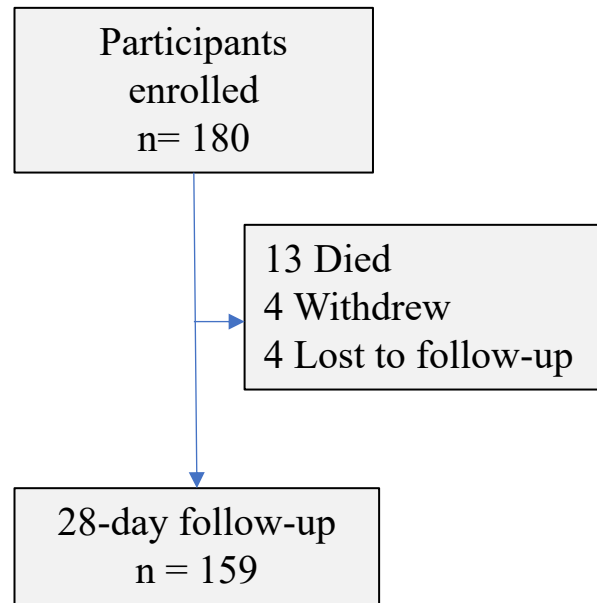
- 491 Figure 1. Enrolment flow diagram across cohorts.
- 492 Figure 2. Kaplan-Meier survival plot of 28-day mortality stratified by site.
- 493 Figure 3. The C-statistic by score overall and by cohort (adjusted for age and sex).
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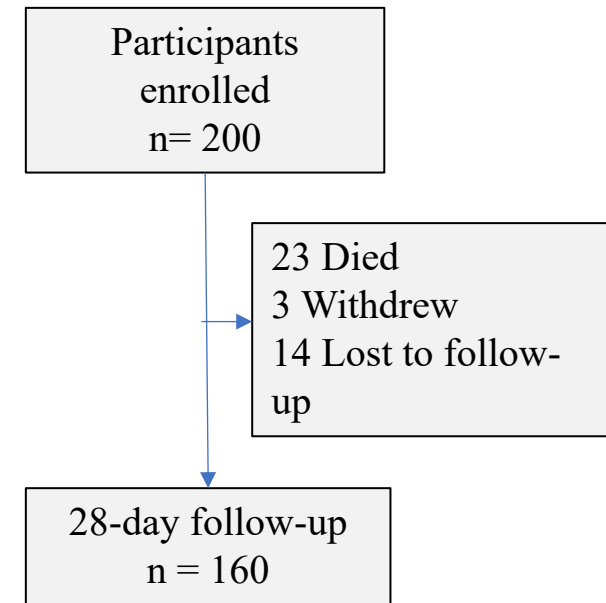
Kumasi, Ghana



Durham, United States



Takeo, Cambodia



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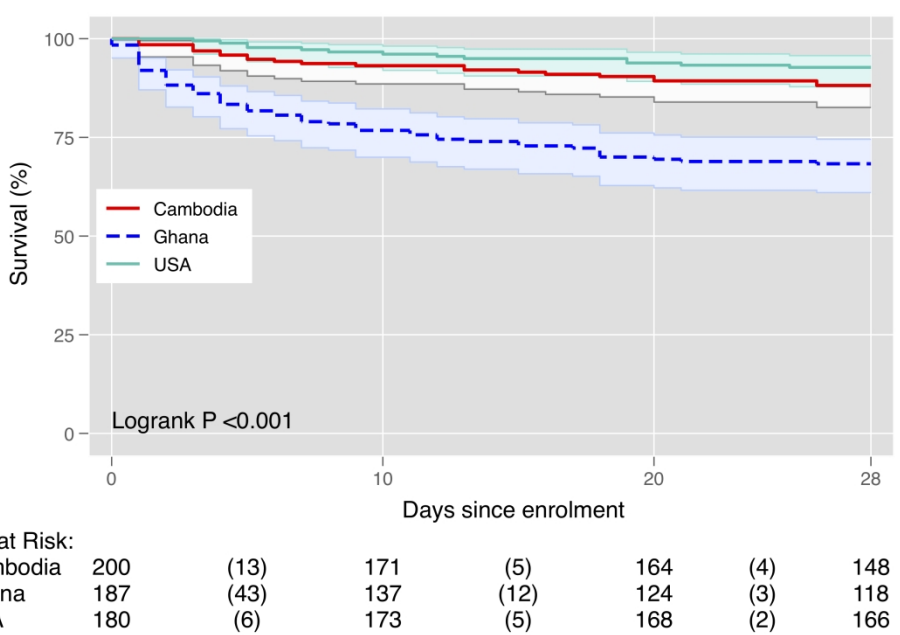


Figure 2. Kaplan-Meier survival plot of 28-day mortality stratified by site.

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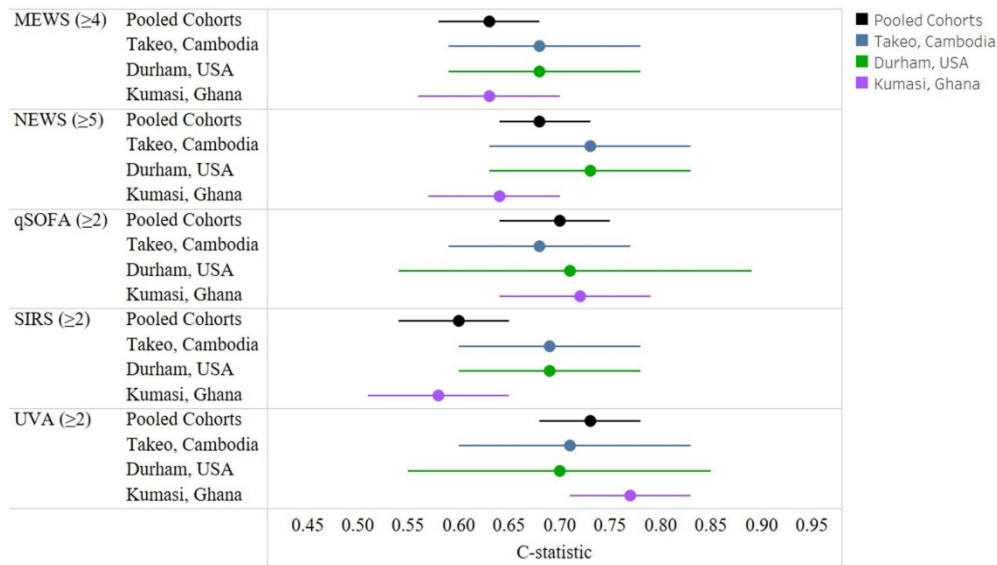


Figure 3. The C-statistic by score overall and by cohort (adjusted for age and sex).

165x96mm (800 x 800 DPI)

Table S1. Baseline physiologic and clinical laboratory parameters by site at enrollment.

Parameter	Total Median (IQR)	Takeo, Cambodia Median (IQR)	Durham, USA Median (IQR)	Kumasi, Ghana Median (IQR)
Physiologic parameters				
Respiratory rate (breaths per minute)	24 (20, 30)	24 (20, 28)	24 (20, 31)	26 (22, 30)
Systolic blood pressure (mmHg)	120 (100, 130)	110 (100, 130)	113 (96, 129)	127.5 (110, 140)
Diastolic blood pressure (mmHg)	70 (60, 80)	70 (70, 80)	64 (56, 75)	80 (60, 90)
Oxygen saturation (%)	97 (94, 98)	98 (96, 98)	95 (92, 97.5)	97 (95, 98)
Temperature (°C)	37.9 (37, 38.7)	37.5 (37, 38.5)	38.1 (36.9, 38.89)	38.2 (37.4, 38.8)
Heart rate (beats per minute)	105 (94, 118)	96 (86.5, 105.5)	111 (99.5, 124)	111 (99, 118)
Clinical laboratory parameters				
White blood cells (x10 ⁹ cells/L)	12.05 (8.13, 16.6)	11.9 (8.2, 16.6)	13.35 (9.7, 17.6)	10.76 (7.68, 15.41)
Platelets (x10 ⁹ cells/L)	222 (152.5, 321.5)	262 (169, 366)	236.5 (160, 291)	193 (137, 284)
Sodium (mEq/L)	135 (132, 138)	135 (131, 138)	137 (134, 139)	134 (130, 138)
Potassium (mEq/L)	3.7 (3.3, 4.2)	3.7 (3.2, 4.1)	3.9 (3.5, 4.3)	3.6 (3.2, 4)
Sodium Bicarbonate (mmol/L)	24 (21, 26)	24 (22, 27)	25 (22, 27)	22 (19, 25)
Glucose (mg/dL)	6.56 (5.4, 10)	6.44 (5.39, 8.28)	6.69 (5.67, 10.06)	6.65 (5.2, 12)
Blood Urea Nitrogen (mg/dL)	5 (3.57, 7.9)	4.29 (3.21, 5.71)	5.71 (3.57, 10)	5.4 (3.5, 9.4)
Creatinine (mg/dL)	88.42 (66, 130)	79.58 (53.05, 88.42)	106.1 (70.74, 150.31)	91 (70, 135)
Alkaline Phosphatase (U/L)	86.5 (65, 132)	98.5 (72, 172)	80 (63, 106)	85 (63, 125)
Alanine Transaminase (U/L)	32 (22, 58)	46 (27, 86)	22 (18, 40)	29 (22, 48)
Aspartate Aminotransferase (U/L)	42 (27, 76)	61 (38, 117)	29 (21, 45)	35.5 (25, 65)
Bilirubin (mg/dL)	15 (10.26, 21)	13.68 (10.26, 20.52)	15.39 (10.26, 20.52)	15 (11, 23)

Parameter	Total Median (IQR)	Takeo, Cambodia Median (IQR)	Durham, USA Median (IQR)	Kumasi, Ghana Median (IQR)
Albumin (g/dL)	3.0 (2.5, 3.5)	2.9 (2.5, 3.4)	3.0 (2.5, 3.5)	3.0 (2.3, 3.6)
Total protein (g/dL)	73 (65, 79)	74 (68, 79.5)	67 (57, 72)	75 (69, 83)
Lactate (mmol/L)	2.27 (1.66, 3.09)	2.33 (1.79, 3.03)	1.5 (1, 2.4)	2.54 (1.8, 3.42)

**All variables are presented as median, interquartile range*

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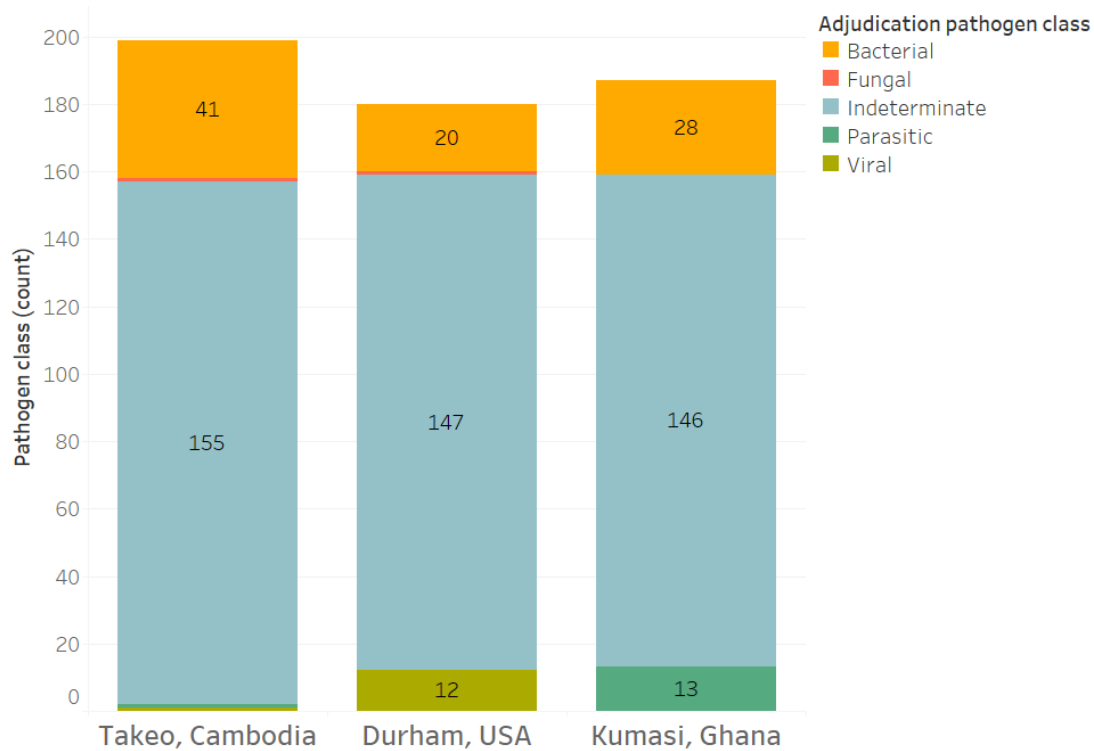
Table S2. Performance characteristics of sepsis score across Cambodia and Ghana sites combined for predicting 28-day mortality.

Score	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Unadjusted Bivariate Cox model C-statistic (95% CI)	Adjusted* Cox model C-statistic (95% CI)	p-value
Baseline						0.60 (0.54 – 0.66)	
MEWS ≥ 4	0.74 (0.64 – 0.84)	0.50 (0.44 – 0.56)	0.28 (0.25 – 0.32)	0.88 (0.84 – 0.92)	0.62 (0.57 – 0.66)	0.66 (0.61 – 0.72)	<0.001
NEWS ≥ 5	0.85 (0.75– 0.92)	0.46 (0.38– 0.52)	0.33 (0.29– 0.36)	0.91 (0.85 – 0.94)	0.65 (0.62 – 0.70)	0.70 (0.65 – 0.76)	0.001
qSOFA ≥ 2	0.54 (0.42 – 0.65)	0.84 (0.80 – 0.88)	0.47 (0.39 – 0.55)	0.87 (0.84 – 0.90)	0.67 (0.62 – 0.73)	0.71 (0.66– 0.77)	<0.001
SIRS ≥ 2	0.88 (0.78 = 0.94)	0.24 (0.19 (0.30)	0.23 (0.21 – 24)	0.89 (0.81 – 0.94)	0.55 (0.51 – 0.59)	0.61 (0.55 – 0.67)	0.066
UVA ≥ 2	0.75 (0.65 – 0.84)	0.74 (0.70 – 0.80)	0.45 (0.40 - 0.52)	0.92 (0.88 - 0.94)	0.73 (0.68 – 0.77)	0.76 (0.71– 0.81)	<0.001

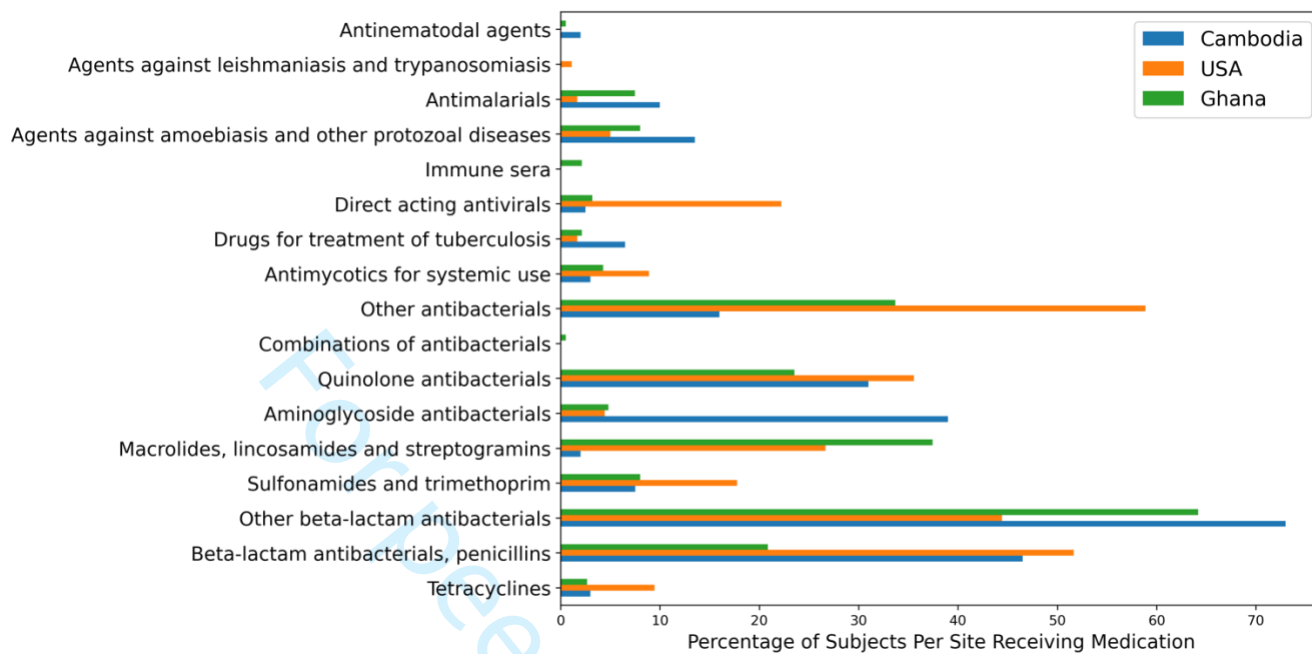
Table S3. Performance characteristics of sepsis score across the United States site for predicting 28-day mortality.

Score	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Unadjusted Bivariate Cox model C-statistic (95% CI)	Adjusted* Cox model C-statistic (95% CI)	p-value
Baseline (age +sex)						0.61 (0.52 – 0.66)	
MEWS\geq4	0.60 (0.26- 0.87)	0.33 (0.26 –0.41)	0.05 (0.03 –0.09)	0.92 (0.85 –0.96)	0.53 (0.38 – 0.67)	0.68 (0.57 – 0.79)	0.743
NEWS\geq5	0.90 (0.56 – 0.99)	0.37 (0.29 –0.45)	0.09 (0.07 –0.11)	0.98 (0.89- 0.99)	0.63 (0.54 - 0.71)	0.71 (0.59- 0.84)	0.256
qSOFA \geq2	0.60 (0.26 - 87)	0.72 (0.65 –0.79)	0.13 (0.08 - 0.20)	0.96 (0.93 –0.98)	0.66 (0.51 – 0.81)	0.71 (0.54 – 0.89)	0.019
SIRS \geq2	0.92 (0.64 - 0.99)	0.11 (0.07 –0.16)	0.08 (0.07 –0.09)	0.94 (0.72 –0.99)	0.51 (0.45 – 0.58)	0.66 (0.54 – 0.82)	0.694
UVA\geq2	0.60 (0.26 – 0.88)	0.58 (0.50 –0.66)	0.09 (0.05 -0.14)	0.95 (0.90 -0.98)	0.59 (0.44 – 0.73)	0.70 (0.50 – 0.87)	0.281

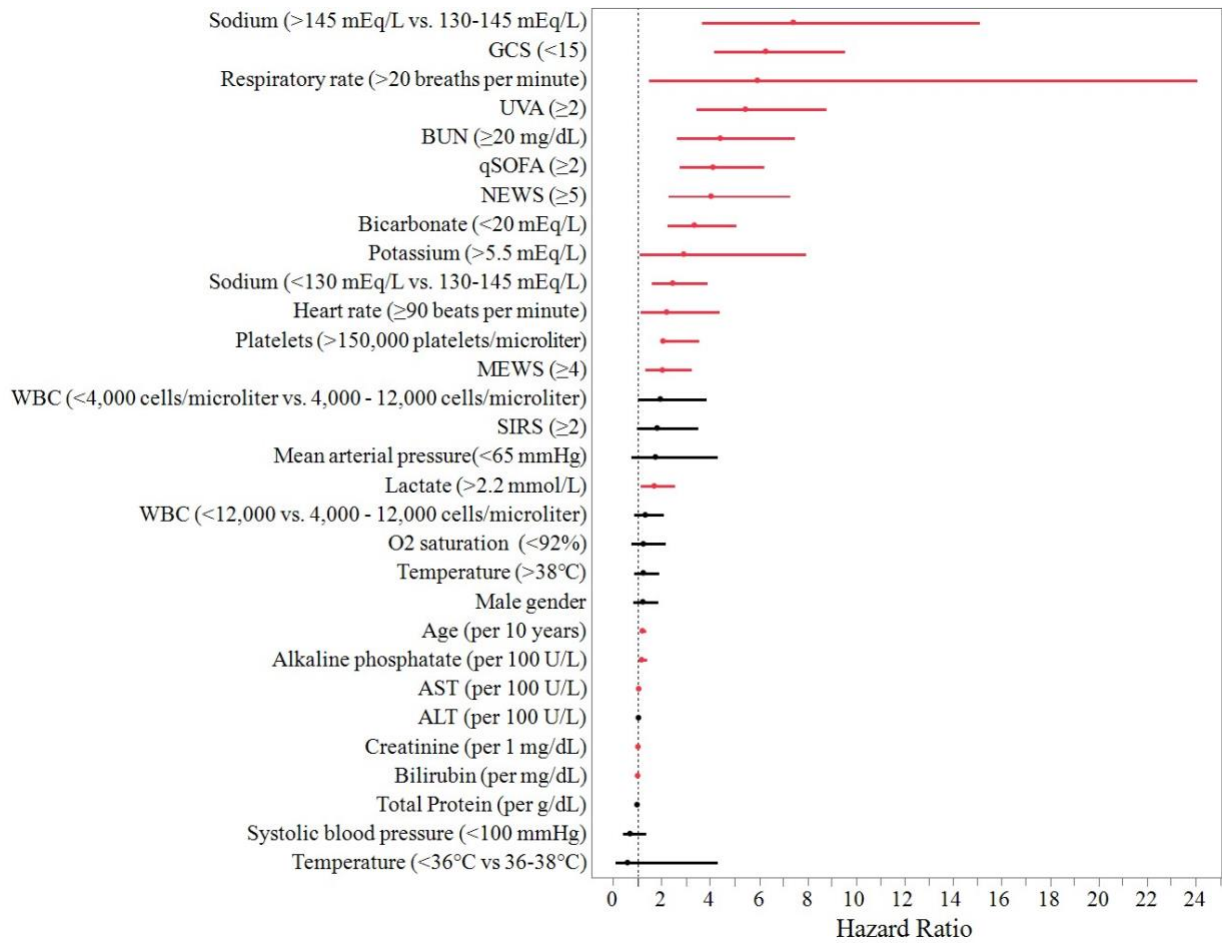
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Supplementary Figure S1. Distribution of adjudicated pathogen class for each site.



Supplementary Figure S2. Prevalence of antibiotics received per site.



Supplementary Figure S3. Forest plot of hazard ratios from bivariate Cox regression models for risk of death at 28-day for sepsis scores, physiologic parameters, and clinical laboratory parameters.

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Screening tools for predicting mortality of adults with suspected sepsis: an international sepsis cohort validation study

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1
2
3 1 **Title:** Screening tools for predicting mortality of adults with suspected sepsis: an international sepsis
4 cohort validation study

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Abstract:

Word count: 276

Objectives: We evaluated the performance of commonly used sepsis screening tools across prospective sepsis cohorts in the United States, Cambodia, and Ghana.

Design: Prospective cohort studies

Setting and participants: From 2014 to 2021, participants with 2 or more SIRS (Systemic Inflammatory Response Syndrome) criteria and suspected infection were enrolled in emergency departments and medical wards at hospitals in the Cambodia and Ghana and hospitalized participants with suspected infection were enrolled in the United States. Cox proportional hazards regression was performed, and Harrell's C-statistic calculated to determine 28-day mortality prediction performance of the qSOFA score ≥ 2 , SIRS score ≥ 3 , NEWS ≥ 5 , MEWS ≥ 5 , or UVA score ≥ 2 . Screening tools were compared to baseline risk (age and sex) with the Wald test.

Results: The cohorts included 567 participants (42.9% female) including 187 participants from Kumasi, Ghana, 200 participants from Takeo, Cambodia, and 180 participants from Durham, North Carolina in the United States. The pooled mortality was 16.4% at 28-days. The mortality prediction accuracy increased from baseline risk with the MEWS (C-statistic: 0.63, 95% CI: 0.58, 0.68; $p=0.002$), NEWS (C-statistic: 0.68; 95% confidence interval [CI]: 0.64, 0.73; $p<0.001$), qSOFA (C-statistic: 0.70, 95% CI: 0.64, 0.75; $p<0.001$), UVA score (C-statistic: 0.73, 95% CI: 0.69, 0.78; $p<0.001$), but not with SIRS (0.60; 95% CI: 0.54, 0.65; $p=0.13$). Within individual cohorts, only the UVA score in Ghana performed better than baseline risk (C-statistic: 0.77; 95% CI: 0.71, 0.83; $p<0.001$).

Conclusions: Among the cohorts, MEWS, NEWS, qSOFA, and UVA scores performed better than baseline risk, largely driven by accuracy improvements in Ghana, while SIRS scores did not improve prognostication accuracy. Prognostication scores should be validated within the target population prior to clinical use.

Keywords: Analysis, Survival; sepsis; Cohort Studies; Prognosis; Global Health

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3 58
45 59 **Strengths and limitations of this study:**
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- 7 60 • This study includes two well-characterized sepsis cohorts in low- and middle-income countries
8 (LMICs) and a cohort in a high-resource setting for comparison.
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12 62 • The performance characteristics of five commonly used sepsis screening tools for predicting 28-
13 day death was compared to baseline risk after adjustment for multiple comparisons.
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16 64 • Diagnostic testing differed at each site and mortality specifically due to sepsis could not be
17 determined.
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20 66 • Enrolment was by convenience sampling within the referral hospital catchment area and may not
21 be representative of the general population within these countries.
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24 68 • Sample size limitations in each of the cohorts may have led to decreased ability to identify
25 differences between each screening tool.
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33 72 **Narrative:**
3435 73 Word count: 3,883
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3839 75 INTRODUCTION
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41 76 Sepsis, a syndrome resulting from a systemic dysregulated host response to an infection, is estimated to
42 cause six million deaths per year but is likely an underestimate due to limited information from low- and
43 middle-income countries (LMICs) where 87% of the world population live [1]. Despite declining age-
44 standardized incidence and mortality, sepsis remains a major cause of health loss worldwide and has an
45 especially high health-related burden in LMICs[2].
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3 82 Clinical sepsis guidelines developed in the Western world may not be applicable in resource-limited settings
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5 83 and moreover can lead to detrimental effects on sepsis care and management when applied in these
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7 84 conditions due to decreased access to resources to manage iatrogenesis from fluid resuscitation [3, 4]. In
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9 85 contrast to the United States, pathogens that lead to directly lead to vascular injury are common causes of
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11 86 acute febrile illness in Cambodia and Ghana such as dengue virus, malaria, or rickettsia and may alter
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13 87 empiric treatment response [5]. While early recognition and treatment of sepsis is critical, most sepsis scores
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15 88 or early warning systems were derived from cohorts outside of LMICs. Differences in causes of sepsis,
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17 89 available treatments, and available resources for supportive care should affect management strategies but
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19 90 evidence is limited and optimal clinical scores or biomarkers for sepsis identification are unknown in these
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21 91 settings. Multi-site international sepsis studies are essential for evaluating current and future sepsis tools to
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23 92 ensure effectiveness in resource-limited settings and across populations.
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28 94 The most validated prognostication scores, SOFA (Sequential Organ Failure Assessment) and the
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30 95 APACHE IV, have been developed for prognostication but require an arterial blood gas and multiple
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32 96 laboratory parameters [6, 7] that are not widely available in low-resource settings. The qSOFA (quick
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34 97 SOFA) is an abbreviated score that does not require laboratory parameters. The qSOFA is one of the most
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36 98 widely adopted sepsis screening tools and has largely replaced the SIRS (Systemic Inflammatory Response
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38 99 Syndrome) criteria as the standard abbreviated sepsis screening tool as part of the Sepsis-3 definition to
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40 100 identify septic patients [8]. The qSOFA and other sepsis screening tools (i.e., Modified Early Warning
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42 101 Score [MEWS], National Early Warning Score [NEWS], and Universal Vital Assessment [UVA]) are often
43
44 102 used clinically to identify those at risk of sepsis, but these tools have been studied for their ability to
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46 103 prognosticate mortality or poor composite outcomes among hospitalized adults[9-12]. Studies have
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48 104 evaluated these tools for predicting in-hospital mortality but the performance of these tools and the
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50 105 prevalence of 28-day mortality, a common metric of sepsis outcomes, have yet to be described across both
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52 106 high- and low-resource settings using similar methods [9, 13, 14].
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3 108 We used prospective multi-site international cohorts that are part of the Austere environments Consortium
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5 109 for Enhanced Sepsis Outcomes (ACESO) consortium to validate commonly used sepsis screening tools
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7 110 [15]. In contrast to APACHE IV and SOFA, these tools can be quickly performed with limited laboratory
8
9 111 test results. We hypothesized that qSOFA may perform poorly in LMIC populations compared to the UVA
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11 112 score due to differences in causes of sepsis. We describe the diverse clinical characteristics, the aetiologies
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13 113 of suspected sepsis within these cohorts, and the performance of sepsis screening tools in current clinical
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15 114 use for predicting mortality at one month post enrolment.
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19 20 116 METHODS

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22 117 From May 2014 to November 2015, 200 participants were enrolled into a prospective observational study
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24 118 of sepsis at Takeo Provincial Hospital in Takeo Province Cambodia [16] (Figure 1). This study was
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26 119 followed by a prospective study at Duke University Hospital in Durham, North Carolina, which enrolled
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28 120 180 participants from December 2014 to March 2016. In Kumasi, Ghana, 187 participants were enrolled at
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30 121 Komfo Anokye Teaching Hospital from July 2016 to October 2017.
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34 122 Hospitalized patients ≥ 18 years of age whose attending physician judged them to have an active infection
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36 123 were considered for inclusion for each of the three cohorts. Additional inclusion and exclusion criteria
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38 124 were required in Cambodia and Ghana but not required in the United States protocol. In Cambodia and
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40 125 Ghana, participants were required to meet least two clinical criteria for systemic inflammatory response
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42 126 syndrome (SIRS) during screening. In Cambodia and Ghana, patients were excluded if they had known
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44 127 malignancy, chronic renal/hepatic insufficiency, immunosuppressive conditions (except HIV) or systemic
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46 128 steroid usage that exceeded 20mg/day to prevent confounding in future biomarker studies. Patients were
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48 129 also excluded in Cambodia and Ghana if they had a history of organ transplant, hemodynamically
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50 130 significant gastrointestinal bleeding, anatomic or functional asplenia, acute cardiovascular disease,
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52 131 general anaesthesia, or surgery in the past week prior to enrolment, women who were pregnant, patients
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3 132 who had a haemoglobin less than 7 g/dL or weighed less than 35kg. Hospital physicians who deemed
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5 133 their patients too ill to participate could defer enrolment.
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8 134 *Study procedures*
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10 135 Following informed consent, study team members conducted a detailed medical history, including prior
11
12 136 medications, and physical exam. Responses were recorded on a standardized case report form and
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14 137 included demographics, medical history, physical exam findings, and admission diagnoses. Study specific
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16 138 procedures conducted in Cambodia were described in detail by Rozo et al [17]. Similar enrolment and
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18 139 study procedures were followed in Kumasi, Ghana and in Durham, North Carolina, USA. Blood was
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20 140 collected at the time of enrolment, then at 6 hours later, and at 24 hours later. In Ghana and Cambodia,
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22 141 standardized clinical tests included a peripheral venous blood gas with lactate, complete blood count,
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24 142 complete metabolic panel, optional HIV screening with consent (Alere Determine HIV1/2, Abbott, OK,
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26 143 United States), malaria rapid diagnostic tests (SD Bioline Ag. P.f./Pan, Abbott, OK, United States) and
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28 144 aerobic blood cultures (one aerobic bottle, Bactec 9050, BD, NJ, United States) as part of study
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30 145 procedures in Ghana and Cambodia. Microbiologic results were available if collected through routine
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32 146 clinical care across cohorts. Additional molecular testing and next generation sequencing for pathogens
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34 147 were also performed on blood samples in the Cambodia cohort as previously described [17]. Participants
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36 148 were followed throughout their hospitalization and a record review performed at discharge.
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41 149 An interview was performed, and blood samples were collected at a 28-day follow-up visit across cohorts.
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43 150 When patients could not return in person, study team members attempted to conduct an interview with
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45 151 patients or a legally authorized representative by telephone. Fatal outcomes among each discharged
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47 152 participant were also determined.
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51 153 Using clinical data from case report forms and microbiology diagnostic information, clinical adjudication
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53 154 was performed by three physician reviewers (internal medicine or infectious diseases) to determine the
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55 155 source of infection by anatomic location and pathogen class (i.e., bacterial, parasitic, viral, or fungal).
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3 156 This was graded on a low, moderate, and high level of confidence by two independent reviewers and a
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5 157 third reviewer served as a tiebreaker for discordant conclusions. If the third reviewer did not agree with
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7 158 either adjudicator, then the decision was determined by committee. Microbiologic results presented
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9 159 include those adjudicated to be clinically relevant to participant's acute illness.
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12 160 *Patient and Public Involvement*

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15 161 Patients were not involved in recruitment, design, conduct, or dissemination plans of our research. Results
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17 162 of this study were disseminated to hospital and clinical leadership at Takeo Provincial Hospital and
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19 163 Komfo Anokye Teaching Hospital.
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22 23 165 *Statistical analysis*

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25 166 Summary statistics were calculated for the cohorts individually and pooled, comparing baseline
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27 167 demographics (e.g., gender, age, ethnicity, selected medical comorbidities), baseline screening tool
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29 168 scores, physiologic parameters, baseline clinical laboratory values using either Chi-square (categorical
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31 169 values), Fishers exact (categorical values), or Kruskal-Wallis (continuous values) tests. Prevalence of
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33 170 diagnoses were described for each cohort by organ system and pathogen type and by anatomic site.
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38 172 After checking the proportional hazards assumption, Cox regression was performed with bivariate models
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40 173 to evaluate increased risk of death in each cohort by baseline demographics, comorbid conditions,
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42 174 physiologic parameters, and clinical laboratory parameters. Physiologic parameters and clinical laboratory
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44 175 parameters were modelled as dichotomous or ordinal parameters at clinically relevant abnormal range cut
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46 176 offs (e.g., blood urea nitrogen ≥ 20 mg/dL) to explore associations with increased risk of death and for
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48 177 clinical inference. Screening tools were dichotomized according to current usage, including qSOFA score
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50 178 ≥ 2 (range, 0 [best] to 3 [worst] points), SIRS score ≥ 2 (range, 0 [best] to 4 [worst] points), MEWS ≥ 5
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52 179 (range, 0 [best] to 13 [worst] points), NEWS ≥ 5 (range, 0 [best] to 20 [worst] points), and UVA ≥ 2
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54 180 (range, 0 [best] to 13 [worst])[13] and were evaluated in Cox regression models unadjusted and adjusted
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3 181 for age and sex for risk of death [9]. Glasgow Coma Scale Score (GCS; range, 3 [worst] to 15 [best]
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5 182 points) of less than 15 was used for estimation of the qSOFA score, and a GCS of ≤ 3 for
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7 183 unresponsiveness for NEWS, and GCS score 3-15 for the “alert, verbal, pain, unresponsive” scale
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9 184 (AVPU; alert: GCS 13-15, voice: GCS 9-12; pain: GCS 4-8; unresponsiveness: GCS ≤ 3) score
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11 185 approximation for MEWS [18, 19]. Data was administratively right censored past 28 days. The Harrell’s
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13 186 C-statistic was calculated for each screening tool for each cohort, the cohorts combined, and Cambodia
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15 187 and Ghana cohorts pooled [20]. This statistic is a performance analogous to area under the receiver
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17 188 operating characteristic curve (AUROC) but accounts for differences over time with survival outcomes.
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19 189 C-statistic confidence interval estimates were determined.[21] The Cox regression Wald test p-values
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21 190 were calculated for each score covariate adjusting for baseline risk estimated by age and sex to determine
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23 191 if scores improved model accuracy above baseline risk [9, 22]. Adjustment was limited to age and sex
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25 192 covariates to avoid introducing confounding (e.g., ascertainment bias from past medical history), type I
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27 193 error from multiple comparisons, or overfitting. P-values < 0.002 were considered significant using a
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29 194 Bonferroni correction for multiple comparisons. Cohort sample sizes were determined a priori through
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31 195 Monte Carlo simulation modelling for prognostic biomarker identification. All statistical analyses were
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33 196 performed in SAS (Statistical Analytical Software, version 9.4), R version 4.0.2 [23] or Stata (version
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35 197 15.0; StataCorp LLC, College Station, TX, USA) [24].
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41 199 RESULTS

42 200 *Summary demographics, sepsis severity, and laboratory findings*

43 201 There were 567 participants across the cohorts including 187 from Kumasi, Ghana, 200 from Takeo,
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45 202 Cambodia, and 180 from Durham, North Carolina, United States (**Figure 1**). The study population was
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47 203 predominantly male (57.1% male), with more male participants enrolled in Cambodia than at other sites
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49 204 (68.0% vs 55.0% in the U.S. and 52.4% in Ghana). The overall median age was 50 years (interquartile
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51 205 range [IQR], 36 to 63), which was similar across cohorts (**Table 1**). Previously diagnosed comorbid
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206 conditions were most common at the U.S. site including a history of cardiovascular (65.6%; N=118),
 207 respiratory (42.2%; N=76), or gastrointestinal (36.7%; N=66) conditions.

Table 1. Baseline demographic characteristics stratified by sites.

Characteristic	Total (n=567)	Takeo, Cambodia (n=200)	Durham, USA (n=180)	Kumasi, Ghana (n=187)	p-value**
Female gender – no. (%)	243 (42.9%)	64 (32.0%)	81 (45.0%)	98 (52.4%)	< 0.001
Age – years, median (IQR)	50 (36 – 63)	50 (36 – 62)	52.5 (40 – 63)	46 (35 – 63)	0.151
Medical history* – no. (%)					
Cancer	44 (9.9%)	0 (0.0%)	44 (24.4%)	0 (0.0%)	< 0.001
Cardiovascular	202 (41.4%)	22 (18.2%)	118 (65.6%)	62 (33.2%)	< 0.001
Dermatologic	15 (3.1%)	1 (0.8%)	14 (7.8%)	0 (0.0%)	< 0.001
Endocrine	126 (25.8%)	6 (5.0%)	74 (41.1%)	46 (24.6%)	< 0.001
Gastrointestinal	76 (15.6%)	4 (3.3%)	66 (36.7%)	6 (3.2%)	< 0.001
Genitourinary or reproductive	34 (7.0%)	1 (0.8%)	33 (18.3%)	0 (0.0%)	< 0.001
HIV	26 (4.7%)	12 (6.2%)	8 (4.5%)	6 (3.2%)	0.388
Neurological	62 (12.7%)	1 (0.8%)	44 (24.4%)	17 (9.1%)	< 0.001
Other	206 (42.2%)	48 (39.7%)	151 (83.9%)	7 (3.7%)	< 0.001
Psychiatric	143 (29.3%)	41 (33.9%)	78 (43.3%)	24 (12.8%)	< 0.001
Renal	41 (8.4%)	0 (0.0%)	41 (22.8%)	0 (0.0%)	< 0.001
Respiratory	89 (18.2%)	7 (5.8%)	76 (42.2%)	6 (3.2%)	< 0.001
Rheumatologic	29 (5.9%)	1 (0.8%)	28 (15.6%)	0 (0.0%)	< 0.001
Surgery	27 (5.5%)	0 (0.0%)	22 (12.2%)	5 (2.7%)	< 0.001
Baseline scores – no. (%)					
MEWS (≥ 4)	315 (57.8%)	81 (40.7%)	105 (65.6%)	129 (69.3%)	< 0.001
NEWS score (≥ 5)	324 (61.6%)	90 (47.9%)	98 (64.5%)	136 (73.1%)	< 0.001
qSOFA (≥ 2)	139 (25.4%)	22 (11.1%)	48 (29.6%)	69 (37.1%)	< 0.001
SIRS (≥ 2)	447 (81.8%)	125 (68.3%)	157 (89.2%)	165 (88.2%)	< 0.001
UVA (≥ 2)	199 (37.8%)	47 (25.8%)	68 (42.8%)	84 (45.4%)	< 0.001
Baseline scores (median [IQR])					
MEWS	4 (3-6)	3 (2-5)	1 (0-4)	1 (1-2)	< 0.001

Table 1. Baseline demographic characteristics stratified by sites.

Characteristic	Total (n=567)	Takeo, Cambodia (n=200)	Durham, USA (n=180)	Kumasi, Ghana (n=187)	p-value**
NEWS	6 (3-8)	4 (2-7)	7 (3-9)	6 (4-8)	< 0.001
qSOFA	1 (1-2)	1 (0-1)	1 (0-2)	1 (1-2)	< 0.001
SIRS	2 (2-3)	2 (1-3)	3 (2-3)	3 (2-3)	< 0.001
UVA	1 (0-3)	1 (0-2)	1 (0-4)	1 (0-4)	< 0.001

*There were 79 subjects without comorbidity information in the Cambodia cohort. **Categorical parameters compared with chi-squared test and numeric parameters compared with Kruskal-Wallis test. Not adjusted for multiple comparisons.

208 Clinical physiologic and laboratory value abnormalities at enrolment were common with median
 209 respiratory rate at 24 (IQR: 20 to 30), the median white blood count elevated at 12.05×10^9 cells/L (IQR:
 210 8.13 to 16.6×10^9 cells/L), and median lactate elevated at 2.27 mmol/L (IQR: 1.66 to 3.09 mmol/L)
 211 (**Supplementary Table S1**). At enrolment, the proportion of an elevated qSOFA (≥ 2) at baseline was
 212 highest at the Ghana site with 44.4% (N=83) of participants compared to 26.0% (N=52) in Cambodia and
 213 22.2% (N=40) in the United States. The SIRS, MEWS, NEWS, and UVA screening tools were similarly
 214 higher in the Ghana cohort.

215 216 *Pathogens detected*

217 The most common positive microbiologic results overall included bacteraemia (N=83), respiratory culture
 218 growth (N=19), serum hepatitis B surface antigen (N=15), and malaria rapid diagnostic tests (N=11). A
 219 minority (121 of 567, 21.3%) of subjects had confirmed infections with complete adjudicator agreement
 220 using all available sources of clinical microbiologic results (with the notable addition of RNA sequencing
 221 of samples from Cambodia[17]) including 90 (15.9%) bacterial, 17 viral (3.0%), 20 malarial (3.5%), and
 222 2 (0.3%) fungal infections identified across all cohorts (**Supplementary Figure S1**). These infection
 223 classes were different among sites (chi-squared test $p < 0.001$).

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3 225 In Cambodia, the most common bacterial infections with complete adjudicator agreement were *B.*
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5 226 *pseudomallei* (N=10, with blood or respiratory culture growth), presumptive *M. tuberculosis* (N=5, with
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7 227 acid fast positive smears), polymicrobial (N=5), and *O. tsutsugamushi* (N=4, determined by sequencing).
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9 228 The most common causes of bacteraemia (17 total of 200 participants) were *B. pseudomallei* (N=8), *E.*
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11 229 *coli* (N=3), and polymicrobial infections (N=3). Three participants had a positive malaria RDT. Fungal
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13 230 infections were uncommon with 1 participant with non-albicans Candidemia and 1 with cryptococcal
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15 231 meningitis. Two individuals had dengue fever (one PCR positive and one adjudicated IgM positive).
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19 233 In Ghana, the most common causes of bacteraemia (culture growth from 28 of 187 participants) were *E.*
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21 234 *coli* (N=6), *S. aureus* (N=6), *Salmonella spp.* (N=5), and *S. pneumoniae* (N=3). Nine participants had a
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23 235 positive malaria RDT and 15 had a positive hepatitis B surface antigen.
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28 237 In the United States, the most common causes of bacteraemia (culture growth from 19 of 180
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30 238 participants) were *E. coli* (N=5), *K. pneumoniae* (N=3), polymicrobial (N=2), *Pseudomonas spp.* (N=2),
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32 239 or *S. aureus* (N=2). Viral infections detected by PCR included rhinovirus (N=5), influenza A (N=4),
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34 240 respiratory syncytial virus (N=4), human immunodeficiency virus (N=3), and human metapneumovirus
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36 241 (N=3). There was one participant with *Aspergillus fumigatus* fungal pneumonia.
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41 243 *Diagnoses and Treatments*

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43 244 Across cohorts, the most common organ system sites of infection were lower respiratory tract infection
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45 245 (28.7%; N=163), multifocal or generalized source of infection (including malaria) (13.6%; N=77), and
46
47 246 gastrointestinal (including hepatic) (12.7%; N=72) (**Figure S1a**). The most common antibiotics
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49 247 administered in United States, Ghana, and Cambodia were beta-lactam antibiotics (**Supplementary**
50
51 248 **Figure S2**), but antibiotic regimens varied widely among sites. The most common antibiotics classes used
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53 249 were other antibacterials (e.g., glycopeptide antibiotics, 58.9%), beta-lactam antibacterials, penicillins
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55 250 (51.7%), and cephalosporin and carbapenem antibacterials (44.4%) in the United States, cephalosporins
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3 251 and carbapenems (64.2%), macrolides, lincosamides and streptogramins (37.4%), and other antibacterials
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5 252 (33.7%) in Ghana, and cephalosporins and carbapenems (73.0%), beta-lactam antibacterials, penicillins
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7 253 (46.5%) and aminoglycoside antibacterials (39.0%) in Cambodia.
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11 255 *Survival*

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13 256 Among all cohorts, 16.4% (N=93) of participants had died at one month, including 58 (31.0%) in Ghana,
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15 257 22 (11.0%) in Cambodia, and 13 (7.2%) in the U.S (**Figure 1**). Among those that died within one month,
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17 258 median time to death was 4 days (IQR: 1 to 11) in Ghana, 7 days (IQR: 3 to 16) in Cambodia, 10 (IQR: 5
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19 259 to 19) in the U.S., and 5 days (IQR: 2 to 13) overall. Parameters to calculate the qSOFA score and 28-day
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21 260 mortality were available for 96.4% participants. Hyponatremia (>145 mEq/L) had the highest unadjusted
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23 261 risk of death (hazard ratio 6.89, 95% CI: 3.43, 13.85) among parameters tested in bivariate models
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25 262 (**Supplementary Figure S3**). All screening tools were associated with an increased risk of death (**Figure**
26
27 263 **2**) with the largest increase among those with an elevated UVA score (**Supplementary Figure S3**). For
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29 264 individuals with a UVA ≥ 2 there was a 5.45 times increased risk of death (95% CI: 3.39 to 8.76; C-
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31 265 statistic: 0.70) and those with a qSOFA ≥ 2 had a 4.11 times increased risk of death (95% CI: 2.71 to 6.22;
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33 266 C-statistic: 0.66). Those with an elevated SIRS had a 1.81 times increased risk of death (95% CI: 0.94 to
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35 267 3.50; C-statistic:0.53). Elevated NEWS (HR: 4.03; 95% CI: 2.24 to 7.26; C-statistic: 0.66) and MEWS
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37 268 (HR: 2.03; 95% CI: 1.28 to 3.23; C-statistic: 0.53) had similarly increased risks (**Figure 3**).
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43 270 Accuracy in an adjusted Cox model was highest for UVA (0.73; 95% CI 0.68-0.78) followed by qSOFA
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45 271 (C-statistic: 0.70; 95% CI: 0.64 to 0.75) (**Table 2**). The sensitivity for predicting death was highest with
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47 272 SIRS (89%; 95% CI: 80 to 94%) but specificity was lowest (19%; 95% CI: 16 to 26%). The UVA score
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49 273 had a sensitivity of 74% and specificity of 70%. The qSOFA score had the lowest sensitivity (54%; 95%
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51 274 CI: 44 to 65%) but highest specificity (80%; 95% CI: 76 to 84%). We observed that the qSOFA
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53 275 discrimination for mortality was moderate with a C-statistic of 0.70 adjusting for age and sex (**Figure 3**).
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55 276 There was similar qSOFA accuracy in individual cohorts from the United States (C-statistic 0.71; 95%
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277 CI: 0.54 to 0.89), Cambodia (C-statistic: 0.68; 95% CI: 0.59 to 0.77), or Ghana (C-statistic: 0.72; 95% CI:
 278 0.64 to 0.79) (**Figure 3**). Similarly, the UVA score had moderate accuracy with a C-statistics on 0.73
 279 (95% CI: 0.68 to 0.78). Other screening scores had similar moderate C-statistic values. The SIRS C-
 280 statistic was 0.60 (95% CI: 0.54 to 0.65). Among participants with a NEWS score of ≥ 5 (62% of the
 281 pooled cohort), the C-statistic was 0.68 (95% CI: 0.64 to 0.73) and among those with a MEWS score of
 282 ≥ 4 (58% of the pooled cohort), the C-statistic was 0.63 (95% CI: 0.58 to 0.68) for death. The qSOFA and
 283 UVA scores were significantly greater than baseline risk in Ghana in contrast to other scores or cohorts
 284 (Table 3). The qSOFA score increased prognostication accuracy in the United States cohort with a $p=0.02$
 285 but this was not significant after correcting for multiple comparisons. In Cambodia, while not significant

Table 2. Performance characteristics of sepsis score across cohorts for predicting 28-day mortality.

Score	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Unadjusted Bivariate Cox model C-statistic (95% CI)	Adjusted* Cox model C-statistic (95% CI)	p-value (Wald test)
Age and sex	–	–	–	–	–	0.59 (0.53,0.64)	
MEWS ≥ 4 *	0.73 (0.63, 0.82)	0.45 (0.40, 0.49)	0.21 (0.16, 0.26)	0.89 (0.85, 0.93)	0.59 (0.54, 0.63)	0.63 (0.58,0.68)	0.002**
NEWS ≥ 5 *	0.86 (0.77,0.93)	0.43 (0.38,0.48)	0.25 (0.23,0.28)	0.93 (0.89, 0.95)	0.65 (0.64, 0.67)	0.68 (0.64,0.73)	<0.001**
qSOFA ≥ 2 *	0.54 (0.44, 0.65)	0.80 (0.76, 0.84)	0.35 (0.27, 0.44)	0.90 (0.87, 0.93)	0.66 (0.61, 0.71)	0.70 (0.64,0.75)	<0.001**
SIRS ≥ 2 *	0.89 (0.80, 0.94)	0.19 (0.16, 0.23)	0.17 (0.14, 0.21)	0.90 (0.82, 0.95)	0.53 (0.50, 0.57)	0.60 (0.54,0.65)	0.134
UVA ≥ 2 *	0.74 (0.64, 0.83)	0.70 (0.65, 0.74)	0.33 (0.27, 0.40)	0.93 (0.90,0.95)	0.70 (0.65, 0.74)	0.73 (0.68,0.78)	<0.001**

*Adjusted Cox model C-statistic is adjusted for age and gender. Note: p-value are from Wald test of the adjusted Cox regression model.

**Significant at $p < 0.002$

286 after correction, NEWS ($p=0.01$) and UVA ($p=0.01$) scores increased accuracy greater than baseline risk.
 287 When pooling LMIC cohorts (i.e., Ghana and Cambodia), after adjustment for age and sex, the qSOFA
 288 (C-statistic: 0.71; 95% CI: 0.66 to 0.77) and UVA scores (C-statistic: 0.76; 95% CI: 0.71 to 0.81) had

Table 3. Performance characteristics of sepsis score across cohorts for predicting 28-day mortality stratified by site.

Model	Takeo, Cambodia		Durham, USA		Kumasi, Ghana	
	C-statistic (95% CI)	p-value	C-statistic (95% CI)	p-value	C-statistic (95% CI)	p-value
Age and Sex	0.68 (0.59, 0.78)	–	0.68 (0.54, 0.81)	–	0.57 (0.49, 0.64)	–
MEWS	0.68 (0.59, 0.78)	0.2102	0.68 (0.57, 0.79)	0.4991	0.63 (0.56, 0.70)	0.0097
NEWS	0.73 (0.63, 0.83)	0.0106	0.71 (0.59, 0.84)	0.2557	0.64 (0.57, 0.70)	0.0022
qSOFA	0.68 (0.59, 0.77)	0.5101	0.71 (0.54, 0.89)	0.0365	0.72 (0.64, 0.79)	<0.001*
SIRS	0.69 (0.60, 0.78)	0.5020	0.69 (0.55, 0.83)	0.5831	0.58 (0.51, 0.65)	0.1882
UVA	0.71 (0.60, 0.83)	0.0109	0.70 (0.55, 0.85)	0.4753	0.77 (0.71, 0.83)	<0.001*

Note: p-value are from Wald test of the adjusted Cox regression model. Each model is adjusted for age and sex. *Significant at p<0.002

289 higher accuracy compared with MEWS (C-statistic: 0.66 (95% CI 0.61 to 0.72), NEWS (C-statistic: 0.70
 290 (95% CI: 0.65 to 0.76), and SIRS (C-statistic: 0.61; 95% CI: 0.55 to 0.67) (**Supplementary Table S2**). In
 291 contrast, in the United States cohort, NEWS, MEWS, SIRS, qSOFA, and UVA scores after age and sex
 292 adjustment each had similar accuracy with C-statistics ranging from 0.66 to 0.71 (**Table 3 and**
 293 **Supplementary Table S3**).

295 DISCUSSION

296 In pooled prospective international cohorts in Cambodia, Ghana, and the United States, the UVA score
 297 and Sepsis-3 (qSOFA) performed well with a C-statistic around 0.7 for predicting 28-day mortality.
 298 However, this improvement was largely identified in the cohort in Ghana and the accuracy was no
 299 different than baseline risk in the Cambodia cohort. There was a trend towards improving prognostication
 300 accuracy with the NEWS and UVA score in Cambodia and only with the qSOFA score in the United
 301 States. These results suggest that widely used sepsis screening tools may have varying performance for
 302 prognostication in diverse settings with different treatment regimens and aetiologies of sepsis. Therefore,
 303 screening tools should be selected after validation within populations prior to widespread adoption.

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3 305 High sodium (hypernatremia) was associated with the highest risk of 28-day death among individual
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5 306 clinical parameters. Hypernatremia during critical illness has been previously associated with mortality in
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7 307 large observational studies from high resource settings [25, 26]. Hypernatremia can occur in sepsis due to
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9 308 intravascular fluid loss due to breakdown of vascular cell junctions, insensible fluid losses, or dehydration
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11 309 from the disease process [27]. There can also be an iatrogenic contribution from diuretics, sodium from
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13 310 intravenous fluids, or with inadequate fluid resuscitation. Ultimately, there is not data available to
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15 311 precisely determine the causes of hypernatremia among the participants in our cohorts. However, our
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17 312 results highlight the universal risk of death among those with hypernatremia among those with sepsis and
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19 313 emphasize the need for close management of fluid and electrolytes across critical care settings.
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24 315 Current sepsis screening tools have had variable performance when applied for prognostication. SOFA or
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26 316 APACHE scores have been developed specifically for prognostication but required parameters including
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28 317 arterial blood oxygen saturation are often not available [9]. Performance of qSOFA and SIRS for
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30 318 mortality have performed poorly (SIRS, area under the receiving operator curve [AUROC], 0.61; qSOFA:
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32 319 AUROC, 0.61) for prognostication in high-resource settings intensive care unit (ICU) settings [14] and in
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34 320 diverse LMICs (adjusted SIRS: AUROC, 0.59; adjusted qSOFA: AUROC, 0.70) [9] in prior studies for
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36 321 mortality prognostication. While qSOFA is generally more specific than other screening tools, it is less
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38 322 sensitive than SIRS, MEWS, and NEWS, which is consistent with our data[28]. When applied to sepsis
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40 323 identification, Surviving Sepsis 2021 guidelines recommend against solely using qSOFA, [29] due to
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42 324 being a more specific rather than sensitive screening test. Additionally, qSOFA has been found to be
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44 325 inferior to MEWS, and NEWS but more accurate and specific than SIRS for predicting in-hospital
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46 326 mortality and ICU transfer in a large retrospective cohort of over 30 thousand patients in the United States
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48 327 (NEWS: AUROC, 0.77; MEWS: AUROC, 0.73; qSOFA: AUROC, 0.69; SIRS: AUROC, 0.65) [28].
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50 328 Different screening scores have been evaluated in prospective cohorts in sub-Saharan Africa (SSA)
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52 329 previously in Tanzania (qSOFA: AUROC, 0.57; MEWS: AUROC, 0.49) [30] and Rwanda [31] (MEWS:
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54 330 AUROC, 0.69; UVA: AUROC, 0.71; qSOFA: AUROC, 0.65) and in Gabon [32] (UVA: AUROC, 0.90;
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3 331 qSOFA: AUROC, 0.77; MEWS: AUROC, 0.72; SIRS: AUROC, 0.70). Given the performance variability
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5 332 that has been previously observed and was observed in this study, it is prudent to evaluate prediction
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7 333 scores within the populations they serve prior to widespread promotion.
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11 335 The UVA score performed better than baseline risk in the Ghana cohort. Our results externally validated
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13 336 the UVA score for use prognostication of hospitalized patients with suspected sepsis in Kumasi, Ghana
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15 337 and potentially in the region when demographics are similar. The superiority of the UVA score in the
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17 338 Ghana cohort could be related to similarities in infectious causes of illness with other countries in SSA
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19 339 populations from which the UVA score was derived[12]. In contrast to the score derivation study[12],
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21 340 UVA score performed similarly to qSOFA in Ghana. The accuracy of the UVA scores was not greater
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23 341 than baseline risk in the cohort in Cambodia after adjustment for multiple comparisons. While
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25 342 conclusions may be limited by sample size, sepsis scores derived from the regions of the world with more
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27 343 similar infectious aetiologies may perform better. Our results highlight the importance of validating
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29 344 scores in new patient populations prior to widespread use.
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35 346 This study had multiple limitations. First, exclusion criteria of immunocompromising conditions except
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37 347 HIV may have led to a skewed populations from Ghana and Cambodia. These exclusion criteria were
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39 348 created to decrease the effect of comorbid conditions or medications on immune biomarkers. However, in
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41 349 Cambodia and Ghana, immunosuppressive medications or diagnoses of chronic liver or kidney disease
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43 350 may be less common in the general population due to limited access to specialists or specialized
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45 351 medications. Additionally, while there were differences in the baseline severity between cohorts, study
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47 352 processes including inclusion criteria were largely standardized across sites improving the comparability
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49 353 of the cohorts in diverse settings and baseline risk was adjusted in models using age and sex. Diagnostic
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51 354 testing differed at each site and mortality specifically due to sepsis could not be determined. Enrolment
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53 355 was by convenience sampling within the referral hospital catchment area and may not be representative of
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55 356 the general population within these countries. Approximation of the mental status for the MEWS scoring
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3 357 using GCS may not be generalizable to the use of GCS at other sites. However, similar MEWS and
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5 358 NEWS performance was observed across sites. Lastly, due to the limited sample size in each of the
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7 359 cohorts, smaller improvements in accuracy may not have been identified in the Cambodia and United
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9 360 States cohorts that had less deaths compared to the Ghana cohort.

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13 362 Inexpensive and readily available tools are needed for triage in resource-limited areas in the world to help
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15 363 identify patients that need escalation and possible transfer to higher levels of care. Current widely used
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17 364 sepsis screening tools represent a clinical benchmark for the development of future triage tools. Research
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19 365 is ongoing to assess point-of-care diagnostics within our sepsis cohort research network. Assays with
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21 366 portable and low-cost inflammation biomarkers tests, molecular diagnostics, or point-of-care ultrasound
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23 367 (POCUS) have the potential to augment the performance of clinical screening tools towards a more
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25 368 personalized approach to sepsis recognition and triage.

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30 370 CONCLUSION
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32 371 Sepsis screening tools that are widely used during clinical care had sub-optimal performance for risk
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34 372 stratification in three international cohorts with increased performance of the UVA and qSOFA scores in
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36 373 Ghana compared to baseline risk. There remains a need for reliable, low-cost, and scalable
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38 374 prognostication methods that are validated in diverse settings.

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49 379 (N626451920001).

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3 381 **Conflicts of Interest:** ELT has held equity and consulted for Predigen and Biomeme, and he is an employee
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5 382 of Danaher Diagnostics. All other authors declared no competing interests.
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9
10 384 **Ethics approval:** Study protocols were approved by the Naval Medical Research Center (NMRC)
11
12 385 Institutional Review Board (IRB) (Cambodia sepsis study # NMRC.2013.0019; Ghana sepsis study #
13
14 386 NMRC.2016.0004-GHA; Duke sepsis study Duke#PRO00054849) in compliance with all applicable
15
16 387 Federal regulations governing the protection of human subjects as well as host country IRBs. The study
17
18 388 protocol in Cambodia was approved by the Cambodian National Ethics Committee for Health Research
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20 389 (NECHR). The protocol in Ghana was approved by the Committee on Human Research, Publication and
21
22 390 Ethics (CHRPE) at Kwame Nkrumah University of Science & Technology. All procedures were in
23
24 391 accordance with the ethical standards of the Helsinki Declaration of the World Medical Association. All
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26 392 patients, or their legally authorized representatives, provided written informed consent.
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31
32 394 **Disclaimer:** K.L.S. is an employee of the US government, and C.B, N.A., C.D., M.P., and A.L. are military
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34 395 service members. This work was prepared as a part of official duties. Title 17 U.S.C. 105 provides that
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36 396 ‘Copyright protection under this title is not available for any work of the United States Government.’ Title
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40 398 employee of the U.S. Government as part of a person’s official duties. The views expressed reflect the
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42 399 results of research conducted by the authors and do not necessarily reflect the official policy or position of
43
44 400 the Department of the Navy, Department of Defense, nor the United States Government.
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49 402 **Contributorship Statement:** PWB, RM, JB, LM, DAS, REM performed data curation and analyses. PWB,
50
51 403 KLS, and DVC developed the manuscript concept. DVC and KLS provided resources for research
52
53 404 development. AL, KLS, CO, JC, TS, ERK, ELT, CB, CWW, AF, AL, DF, JVL, MP, MR, NA, CD, MGG,
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3 405 TV, AO, DA, and GO were involved in protocol development and data generation. LM, MS, WH, SK, were
4
5 406 involved in research operations. AL, KLS, CWW, DF, ELT, CB, DVC, and PWB were involved in
6
7 407 manuscript revisions. All authors reviewed and approved of this manuscript.
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12 409 **Data sharing statement:** De-identified data may be made available upon reasonable request to the
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14 410 corresponding author.
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19 412 **References**
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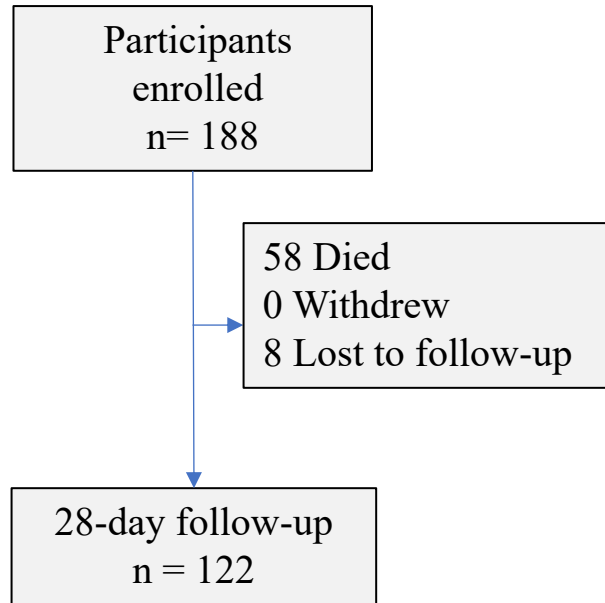
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492 Figure Legends

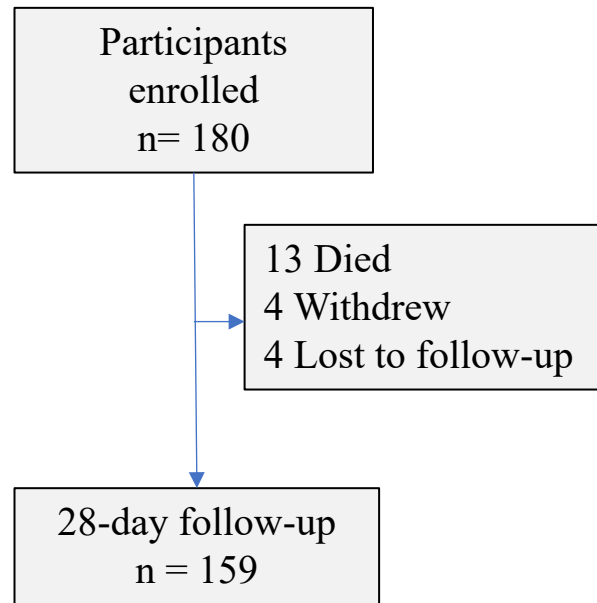
- 493 Figure 1. Enrolment flow diagram across cohorts.
- 494 Figure 2. Kaplan-Meier survival plot of 28-day mortality stratified by site.
- 495 Figure 3. The C-statistic by score overall and by cohort (adjusted for age and sex).
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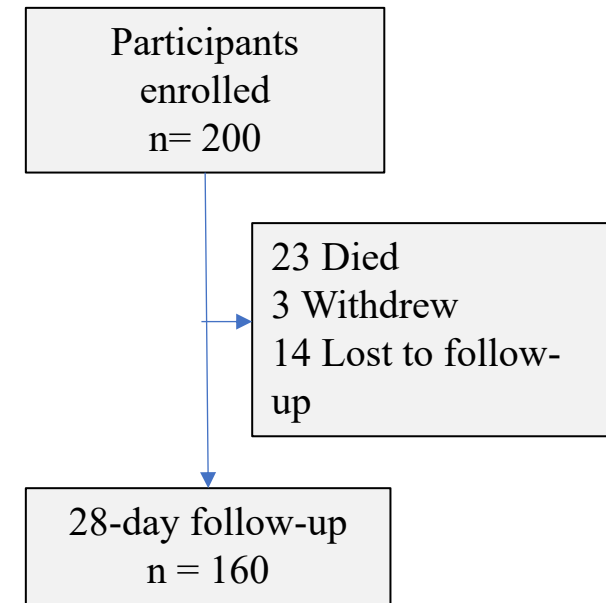
Kumasi, Ghana



Durham, United States



Takeo, Cambodia



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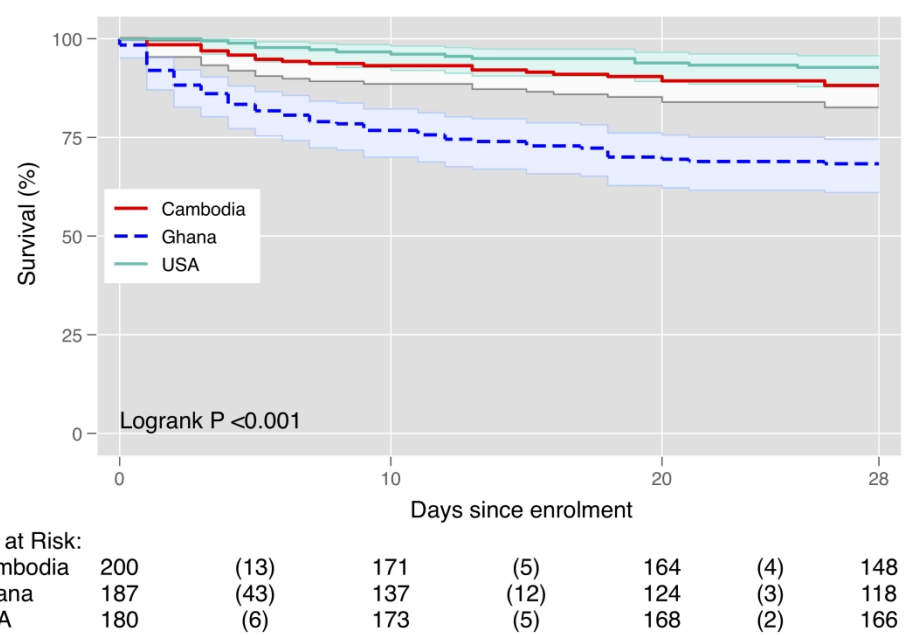


Figure 2. Kaplan-Meier survival plot of 28-day mortality stratified by site.

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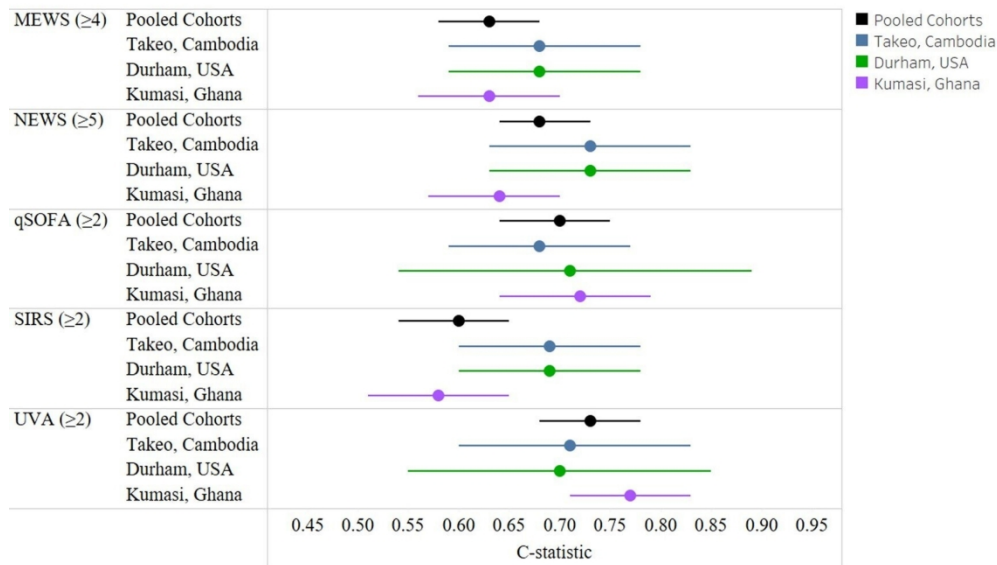


Figure 3. The C-statistic by score overall and by cohort (adjusted for age and sex).

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Table S1. Baseline physiologic and clinical laboratory parameters by site at enrollment.

Parameter	Total Median (IQR)	Takeo, Cambodia Median (IQR)	Durham, USA Median (IQR)	Kumasi, Ghana Median (IQR)
Physiologic parameters				
Respiratory rate (breaths per minute)	24 (20, 30)	24 (20, 28)	24 (20, 31)	26 (22, 30)
Systolic blood pressure (mmHg)	120 (100, 130)	110 (100, 130)	113 (96, 129)	127.5 (110, 140)
Diastolic blood pressure (mmHg)	70 (60, 80)	70 (70, 80)	64 (56, 75)	80 (60, 90)
Oxygen saturation (%)	97 (94, 98)	98 (96, 98)	95 (92, 97.5)	97 (95, 98)
Temperature (°C)	37.9 (37, 38.7)	37.5 (37, 38.5)	38.1 (36.9, 38.89)	38.2 (37.4, 38.8)
Heart rate (beats per minute)	105 (94, 118)	96 (86.5, 105.5)	111 (99.5, 124)	111 (99, 118)
Clinical laboratory parameters				
White blood cells (x10 ⁹ cells/L)	12.05 (8.13, 16.6)	11.9 (8.2, 16.6)	13.35 (9.7, 17.6)	10.76 (7.68, 15.41)
Platelets (x10 ⁹ cells/L)	222 (152.5, 321.5)	262 (169, 366)	236.5 (160, 291)	193 (137, 284)
Sodium (mEq/L)	135 (132, 138)	135 (131, 138)	137 (134, 139)	134 (130, 138)
Potassium (mEq/L)	3.7 (3.3, 4.2)	3.7 (3.2, 4.1)	3.9 (3.5, 4.3)	3.6 (3.2, 4)
Sodium Bicarbonate (mmol/L)	24 (21, 26)	24 (22, 27)	25 (22, 27)	22 (19, 25)
Glucose (mg/dL)	6.56 (5.4, 10)	6.44 (5.39, 8.28)	6.69 (5.67, 10.06)	6.65 (5.2, 12)
Blood Urea Nitrogen (mg/dL)	5 (3.57, 7.9)	4.29 (3.21, 5.71)	5.71 (3.57, 10)	5.4 (3.5, 9.4)
Creatinine (mg/dL)	88.42 (66, 130)	79.58 (53.05, 88.42)	106.1 (70.74, 150.31)	91 (70, 135)
Alkaline Phosphatase (U/L)	86.5 (65, 132)	98.5 (72, 172)	80 (63, 106)	85 (63, 125)
Alanine Transaminase (U/L)	32 (22, 58)	46 (27, 86)	22 (18, 40)	29 (22, 48)
Aspartate Aminotransferase (U/L)	42 (27, 76)	61 (38, 117)	29 (21, 45)	35.5 (25, 65)
Bilirubin (mg/dL)	15 (10.26, 21)	13.68 (10.26, 20.52)	15.39 (10.26, 20.52)	15 (11, 23)

Parameter	Total Median (IQR)	Takeo, Cambodia Median (IQR)	Durham, USA Median (IQR)	Kumasi, Ghana Median (IQR)
Albumin (g/dL)	3.0 (2.5, 3.5)	2.9 (2.5, 3.4)	3.0 (2.5, 3.5)	3.0 (2.3, 3.6)
Total protein (g/dL)	73 (65, 79)	74 (68, 79.5)	67 (57, 72)	75 (69, 83)
Lactate (mmol/L)	2.27 (1.66, 3.09)	2.33 (1.79, 3.03)	1.5 (1, 2.4)	2.54 (1.8, 3.42)

**All variables are presented as median, interquartile range*

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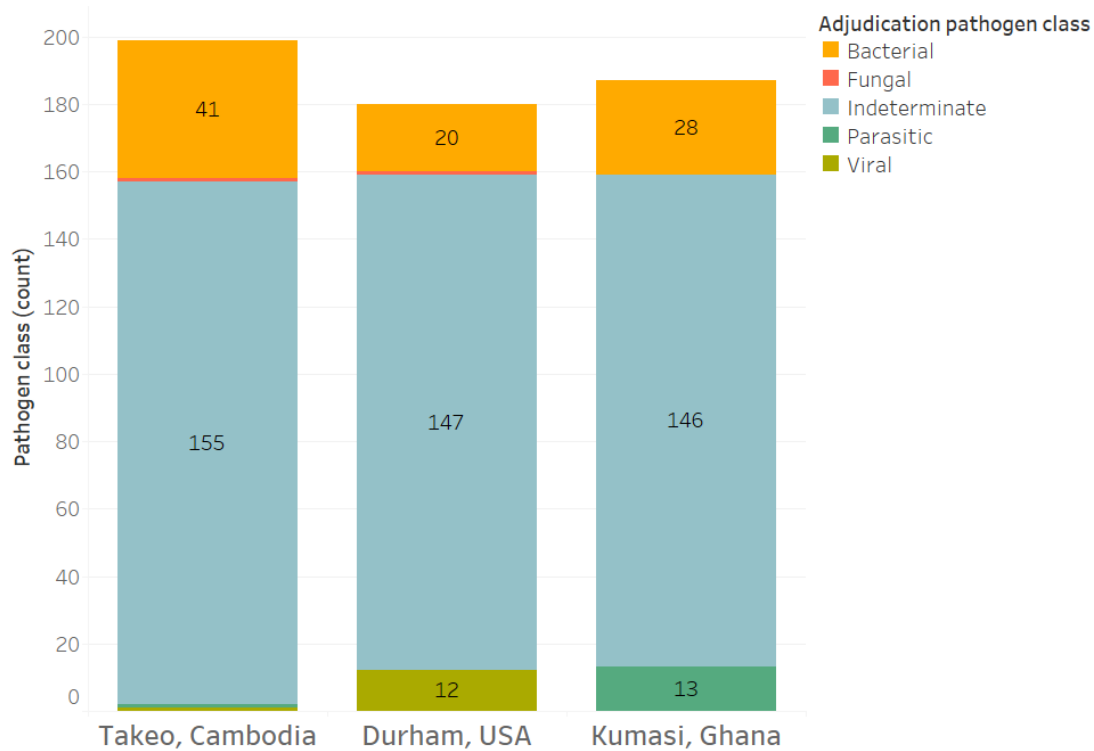
Table S2. Performance characteristics of sepsis score across Cambodia and Ghana sites combined for predicting 28-day mortality.

Score	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Unadjusted Bivariate Cox model C-statistic (95% CI)	Adjusted* Cox model C-statistic (95% CI)	p-value
Baseline						0.60 (0.54 – 0.66)	
MEWS ≥ 4	0.74 (0.64 – 0.84)	0.50 (0.44 – 0.56)	0.28 (0.25 – 0.32)	0.88 (0.84 – 0.92)	0.62 (0.57 – 0.66)	0.66 (0.61 – 0.72)	<0.001
NEWS ≥ 5	0.85 (0.75– 0.92)	0.46 (0.38– 0.52)	0.33 (0.29– 0.36)	0.91 (0.85 – 0.94)	0.65 (0.62 – 0.70)	0.70 (0.65 – 0.76)	0.001
qSOFA ≥ 2	0.54 (0.42 – 0.65)	0.84 (0.80 – 0.88)	0.47 (0.39 – 0.55)	0.87 (0.84 – 0.90)	0.67 (0.62 – 0.73)	0.71 (0.66– 0.77)	<0.001
SIRS ≥ 2	0.88 (0.78 = 0.94)	0.24 (0.19 (0.30)	0.23 (0.21 – 24)	0.89 (0.81 – 0.94)	0.55 (0.51 – 0.59)	0.61 (0.55 – 0.67)	0.066
UVA ≥ 2	0.75 (0.65 – 0.84)	0.74 (0.70 – 0.80)	0.45 (0.40 - 0.52)	0.92 (0.88 - 0.94)	0.73 (0.68 – 0.77)	0.76 (0.71– 0.81)	<0.001

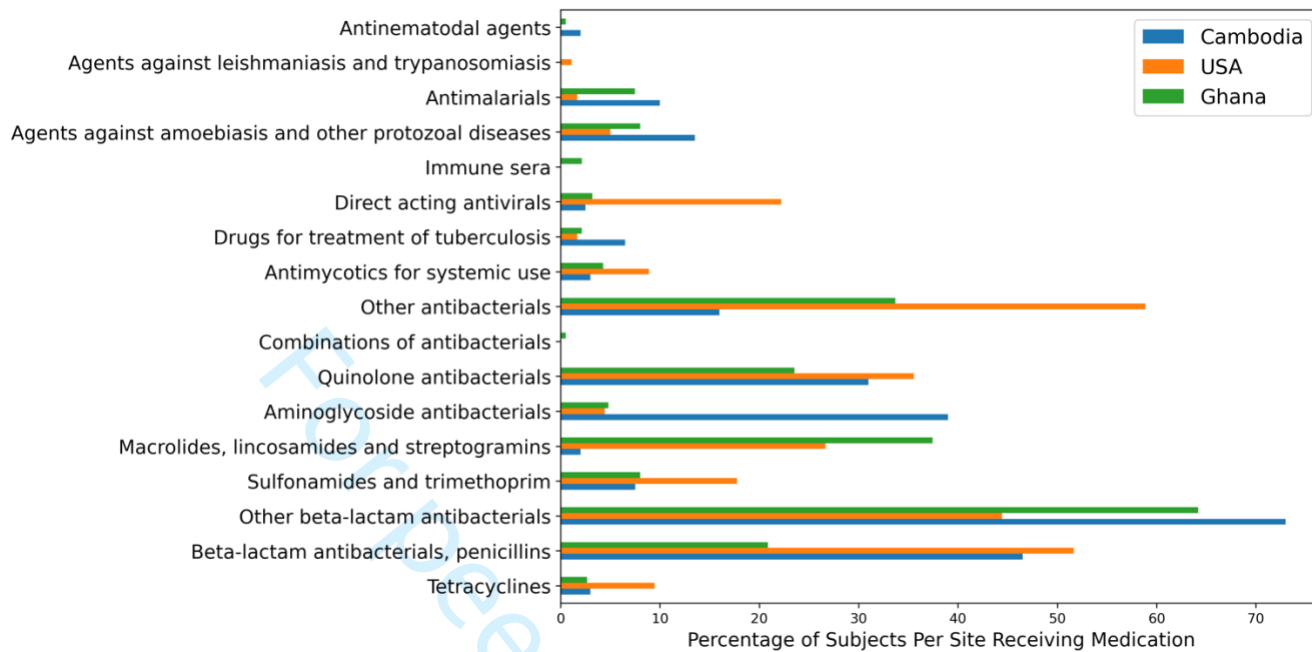
Table S3. Performance characteristics of sepsis score across the United States site for predicting 28-day mortality.

Score	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Unadjusted Bivariate Cox model C-statistic (95% CI)	Adjusted* Cox model C-statistic (95% CI)	p-value
Baseline (age +sex)						0.61 (0.52 – 0.66)	
MEWS\geq4	0.60 (0.26- 0.87)	0.33 (0.26 –0.41)	0.05 (0.03 –0.09)	0.92 (0.85 –0.96)	0.53 (0.38 – 0.67)	0.68 (0.57 – 0.79)	0.743
NEWS\geq5	0.90 (0.56 – 0.99)	0.37 (0.29 –0.45)	0.09 (0.07 –0.11)	0.98 (0.89- 0.99)	0.63 (0.54 - 0.71)	0.71 (0.59- 0.84)	0.256
qSOFA \geq2	0.60 (0.26 - 87)	0.72 (0.65 –0.79)	0.13 (0.08 - 0.20)	0.96 (0.93 –0.98)	0.66 (0.51 – 0.81)	0.71 (0.54 – 0.89)	0.019
SIRS \geq2	0.92 (0.64 - 0.99)	0.11 (0.07 –0.16)	0.08 (0.07 –0.09)	0.94 (0.72 –0.99)	0.51 (0.45 – 0.58)	0.66 (0.54 – 0.82)	0.694
UVA\geq2	0.60 (0.26 – 0.88)	0.58 (0.50 –0.66)	0.09 (0.05 -0.14)	0.95 (0.90 -0.98)	0.59 (0.44 – 0.73)	0.70 (0.50 – 0.87)	0.281

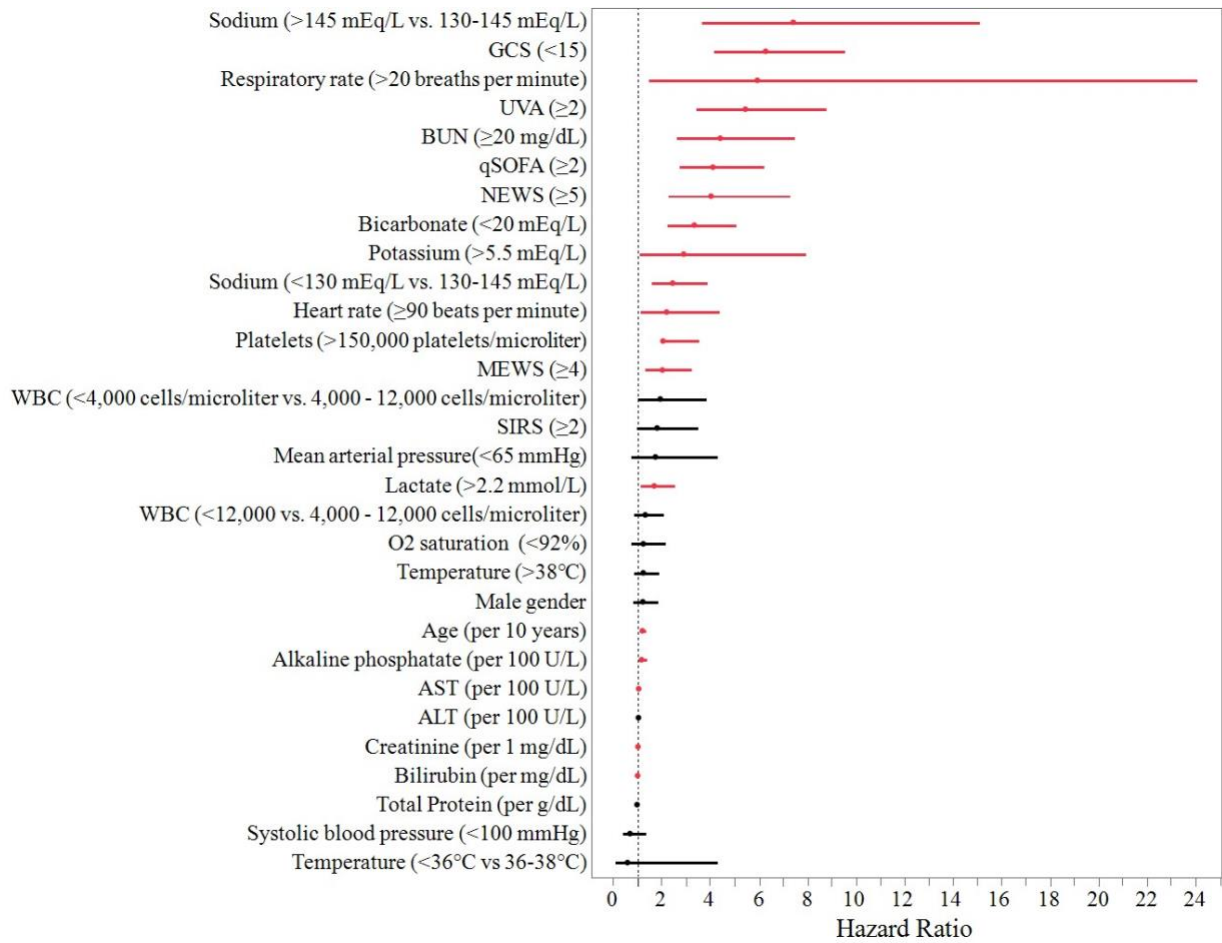
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Supplementary Figure S1. Distribution of adjudicated pathogen class for each site.



Supplementary Figure S2. Prevalence of antibiotics received per site.



Supplementary Figure S3. Forest plot of hazard ratios from bivariate Cox regression models for risk of death at 28-day for sepsis scores, physiologic parameters, and clinical laboratory parameters.