Derivation and validation of an international clinical prognostication model for 28-day sepsis mortality

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Background

Survival prediction models have largely been derived and validated only in high-resource Western countries or in single center studies. We sought to create a prediction model for 28-day mortality using laboratory and physiologic parameters from 3 international sepsis cohorts and externally validated the model.

Methods

- During 2014 to 2021, adult hospitalized patients with suspected infection were enrolled in Durham, United States (N=180) and those with suspected infection and ≥2 SIRS (Systemic Inflammatory Response Syndrome) criteria in Takeo, Cambodia (N=200), and Kumasi, Ghana (N=187).
- In Ghana and Cambodia, standardized clinical tests included a peripheral venous blood gas with lactate, complete blood count, complete metabolic panel, optional HIV screening with consent (Alere Determine HIV1/2, Abbott, OK, United States), malaria rapid diagnostic tests (SD Bioline Ag. P.f./Pan, Abbott, OK, United States) and aerobic blood cultures (one aerobic bottle, Bactec 9050, BD, NJ, United States) as part of study procedures in Ghana and Cambodia. Microbiologic results were available if collected through routine clinical care across cohorts. Additional molecular testing and next generation sequencing for pathogens were also performed on blood samples in the Cambodia cohort .
- Twenty-five clinical laboratory and physiologic parameters were candidate covariates and sepsis screening scores included as comparators.
- First, bivariate Cox regression models were performed to determine risk of individual parameters.
- Then, a 10-fold cross-validated forward stepwise model selection technique was used to eliminate nonsignificant variables using a p-value <0.10 and the cross-validated C-statistic was estimated.
- For comparison, five sepsis screening tools (i.e., qSOFA score, SIRS score, NEWS, MEWS, and UVA score) were evaluated across three international cohorts for one-month mortality prognostication, providing comprehensive performance estimates in settings with disparate causes of sepsis.
- Lastly, the stepwise selected model was applied to an external cohort of hospitalized adults with suspected infection and ≥2 SIRS in Fort Portal, Uganda (N=331 with 9.3% 28-day mortality).

Results

- There were 567 participants across the cohorts including 187 from Kumasi, Ghana, 200 from Takeo, Cambodia, and 180 from Durham, North Carolina, United States (Figure 1).
- At enrollment, the proportion of an elevated qSOFA (≥2) at baseline was highest at the Ghana site with 44.4% (N=83) of participants compared to 26.0% (N=52) in Cambodia and 22.2% (N=40) in the United States (Table 1).
- The most common antibiotics administered in United States, Ghana, and Cambodia were beta-lactam antibiotics, but antibiotic regimens varied widely among sites. The most common antibiotics classes used were "other" antibacterials (e.g., glycopeptide antibiotics, 58.9%), beta-lactam antibacterials, penicillins (51.7%), and cephalosporin and carbapenem antibacterials (44.4%) in the United States, cephalosporins and carbapenems (64.2%), macrolides, lincosamides and streptogramins (37.4%), and other antibacterials (33.7%) in Ghana, and cephalosporins and carbapenems (73.0%), beta-lactam antibacterials, penicillins (46.5%) and aminoglycoside antibacterials (39.0%) in Cambodia (Figure 2).
- The most common positive microbiologic results overall included bacteremia (N=83), respiratory culture growth (N=19), serum hepatitis B surface antigen (N=15), and malaria rapid diagnostic tests (N=11). A minority (121 of 567, 21.3%) of subjects had confirmed infections with complete adjudicator agreement using all available sources of clinical microbiologic results (with the notable addition of RNA sequencing of samples from Cambodia) including 90 (15.9%) bacterial, 17 viral (3.0%), 20 malarial (3.5%), and 2 (0.3%) fungal infections identified across all cohorts (Figure 3).

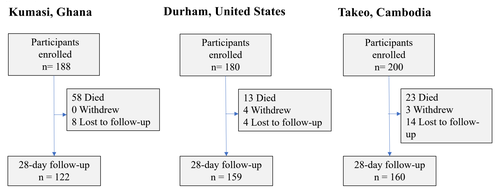

Figure 1. Flow diagram (derivation sepsis cohorts)

Results

Table 1. Baseline demographic characteristics stratified by derivation cohort 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)
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)

*There were 79 subjects without comorbidity information in the Cambodia cohort.

Table 2. Baseline clinical features in Uganda sepsis validation cohort.

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)
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)

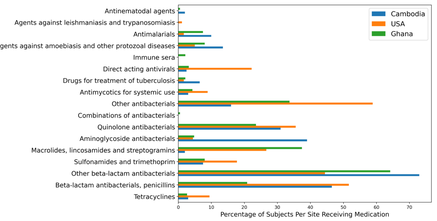

Figure 2. Antibiotics per derivation cohort site.

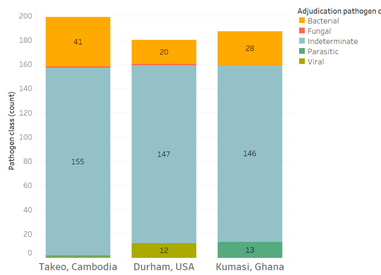

Figure 3. Distribution of adjudicated pathogen class for each site.

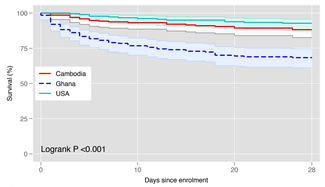

Figure 4. Survival by derivation cohort site.

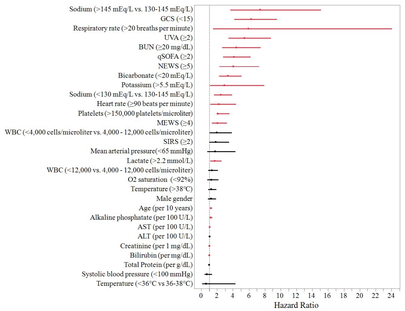

Figure 5. Forest plot for bivariate analyses for one month survival across United States, Cambodia, and Ghana cohorts.

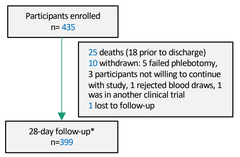

Figure 6. Flow diagram (Uganda validation cohort)

Table 3. Baseline demographics for Uganda validation cohort

Characteristic	Total (N=435)	HIV-negative (N=309)	HIV-positive (N=126)
Female sex – no. (%)	257 (59.1)	178 (57.6)	79 (62.7)
Age, yrs. – median (IQR)	42.0 (28.0, 57.0)	45.0 (28.0, 60.0)	39.0 (29.0, 46.0)
Past medical history – no. (%)			
Diabetes mellitus	25 (5.7)	24 (7.8)	1 (0.8)
Heart failure	6 (1.4)	5 (1.6)	1 (0.8)
Hypertension	51 (11.7)	46 (14.9)	5 (4.0)
Liver disease	3 (0.7)	3 (1.0)	0 (0.0)
Lung disease	6 (1.4)	6 (1.9)	0 (0.0)
Malignancy	3 (0.7)	3 (1.0)	0 (0.0)
Tobacco use – no. (%)			
Current	19 (4.4)	14 (4.6)	5 (4.0)
Prior	48 (11.1)	31 (10.1)	17 (13.5)
Physiologic parameters – median (IQR)			
Heart rate (beats per minute)	100.0 (89.0, 111.0)	99.0 (89.3, 111.0)	101.0 (89.3, 112.8)
Temperature (degrees Centigrade)	37.300 (36.7, 38.0)	37.400 (36.7, 38.0)	37.100 (36.6, 37.9)
Mean arterial pressure (mmHg)	87.7 (79.0, 97.1)	88.3 (80.3, 97.6)	85.9 (75.850, 94.8)
Respiratory rate (breaths per minute)	28.0 (24.0, 32.0)	28.0 (24.0, 32.0)	28.0 (24.0, 33.5)
Oxygen saturation (%)	95.0 (92.0, 96.3)	95.0 (92.0, 96.8)	95.0 (93.0, 96.0)
Supplemental oxygen requirements – no. (%)			
None	397 (91.7)	275 (89.6)	122 (96.8)
Face mask	6 (1.4)	5 (1.6)	1 (0.8)
Nasal cannula	29 (6.7)	26 (8.5)	3 (2.4)
Non-rebreather	1 (0.2)	1 (0.3)	0 (0.0)
Glasgow coma scale – median (IQR)	15.0 (15.0, 15.0)	15.0 (15.0, 15.0)	15.0 (15.0, 15.0)
qSOFA score – median (IQR)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 2.0)
qSOFA score ≥2 – no. (%)	91 (21.1)	53 (17.4%)	38 (30.2)

Results

Table 4. 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)
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)
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)
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)
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)
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)

Adjusted Cox model C-statistic is adjusted for age and gender.

Table 5. Prediction model for 28-day mortality identified by stepwise selection Cox regression using 10-fold cross validation (C-statistic of 0.80).

Parameter	HR (95% CI)	p-value
Sodium <130 mEq/L (low) vs 130-145 mEq/L (normal)	2.64 (1.65 – 4.23)	<0.001
Sodium >145 mEq/L (high) vs 130-145 mEq/L (normal)	2.09 (0.95 – 4.59)	0.066
Mean Arterial Pressure <65 mmHg (low) versus >65 mmHg (high)	3.34 (1.04 – 10.72)	0.043
Lactate >2.2 mmol/L (high) vs ≤2.2 (low)	1.67 (1.08 – 2.58)	0.022
BUN ≥ 20 mg/dL (high) vs <20 mg/dL (low)	2.40 (1.29 – 4.49)	0.006
Glasgow Coma Score <15	6.18 (3.92 – 9.72)	<0.001

Prediction model results

- Among all cohorts, 16.4% (N=93) of participants had died at one month, including 58 (31.0%) in Ghana, 22 (11.0%) in Cambodia, and 13 (7.2%) in the U.S. Among those that died within one month, median time to death was 4 days (IQR: 1 to 11) in Ghana, 7 days (IQR: 3 to 16) in Cambodia, 10 (IQR: 5 to 19) in the U.S., and 5 days (IQR: 2 to 13) overall.
- Bivariate analyses identified hypernatremia (>145 mEq/L) being associated with the highest risk of death (hazard ratio: 7.42; 95% CI: 3.65 to 15.10; Figure 5).
- On multivariable analysis, a 28-day mortality model including mean arterial pressure, Glasgow Coma score, blood sodium, lactate, and blood urea nitrogen (Table 5) resulted in a 10-fold cross-validated C-statistic of 0.80 (95% CI: 0.61 to 0.88).
- This model predicted mortality accurately in the validation cohort with a C-statistic of 0.74 (95% CI: 0.69 to 0.79).

Conclusions

- Diverse antibiotic regiments were used at each site. Confirmation of sepsis source was uncommon.
- All clinical scores (i.e., NEWS, MEWS, qSOFA, and UVA) were associated with increased mortality except SIRS.
- Hypotension, altered mental status, serum sodium, serum BUN, and plasma lactate accurately identified risk of death by 28-days among those with suspected sepsis in 3 international derivation cohorts and in a validation cohort in Uganda.
- Our findings emphasize the importance of clinical laboratory results for sepsis risk stratification.

Limitations

- Diagnostic testing differed at each site and mortality specifically due to sepsis could not be determined.
- Enrolment was by convenience sampling within the referral hospital catchment area and may not be representative of the general population within these countries.

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Ethics declaration: Study protocols were approved by the Naval Medical Research Center (NMRC) Institutional Review Board (IRB) (Cambodia sepsis study # NMRC.2013.0019; Ghana sepsis study # NMRC.2016.0004-GHA; Duke sepsis study Duke#PRO00054849) in compliance with all applicable Federal regulations governing the protection of human subjects as well as host country IRBs.

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