Predicting Mortality for Adolescent and Adult Patients with Fever in Resource-Limited Settings

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Abstract. Febrile illnesses are a major cause of mortality in sub-Saharan Africa. Early identification of patients at increased risk of death may avert adverse outcomes. We aimed to independently evaluate the performance of the Modified Early Warning Score, quick Sequential Organ Failure Assessment (qSOFA) score, and Integrated Management of Adolescent and Adult Illness (IMAI) emergency signs and severity criteria to predict in-hospital mortality among a prospective cohort of febrile patients in Tanzania. We evaluated 419 patients aged ≥ 10 years in the period 2007–2008. Of the 44 patients who died, 31 (70.5%) were human immunodeficiency virus (HIV) infected. On univariate analysis, in-hospital mortality was associated with HIV infection, oxygen saturation $< 90\%$, respiratory distress, Glasgow Coma Scale < 15 , neck stiffness, unconsciousness, convulsions, hemoglobin < 9 g/dL, absence of a systemic syndrome, and neurologic syndrome. A qSOFA score ≥ 2 , the presence of at least one, two, or three IMAI emergency signs, and IMAI severe respiratory distress syndrome without shock were significantly associated with in-hospital mortality. The criterion “presence of at least one IMAI emergency sign” showed a good diagnostic accuracy, as highlighted by the high sensitivity, low negative likelihood ratio, and wide area under the receiver operating characteristics curve. The remaining scores showed a poor performance in predicting fatal outcomes in our study population. Further studies are needed to validate our findings and to derive early warning scores that have good clinical performance in settings throughout sub-Saharan Africa.

INTRODUCTION

Febrile illness remains a common cause of mortality in low-resource countries.^{1,2} In such settings, limited laboratory and radiologic capacity often require that febrile patients be managed empirically using syndrome-based approaches.^{3,4} Rapid and easy-to-perform triage protocols can be powerful tools in low-resource countries to direct early intervention, such as antimicrobial therapy and fluid resuscitation, to those with critical illness.^{5–7}

Several prognostic indices have been developed to risk-stratify acutely ill patients. Among scoring systems developed in well-resourced settings, those based on routinely available parameters (i.e., vital signs, peripheral oxygen saturation, and level of consciousness) include the modified Early Warning Score (MEWS) and the quick Sequential Organ Failure Assessment (qSOFA) score.^{7–9} A limited number of studies applying the MEWS or the qSOFA scores to resource-limited settings suggests some utility of these scoring systems in mortality prediction, although findings have not been uniform.^{10–14} The World Health Organization (WHO) provides clinical triage criteria to identify life-threatening syndromes among pediatric and adult populations in resource-limited settings through the Integrated Management of Childhood Illness (IMCI) and Integrated Management of Adolescent and Adult Illness (IMAI) guidelines, respectively.^{15,16} Although good performance of IMCI clinical signs and syndromes has been previously reported,^{17,18} the prognostic value of WHO syndrome classifications for adults remains unknown. In this study, we evaluate the performance of the IMAI severity criteria and emergency signs as well as of the MEWS and qSOFA score, scores predicting in-hospital mortality among febrile adolescents and adults in northern Tanzania.

MATERIALS AND METHODS

Study design. We performed a secondary analysis of data from a prospective cohort study enrolling febrile patients admitted to Kilimanjaro Christian Medical Center (KCMC) and Mawenzi Regional Referral Hospital (MRRH), Moshi, Tanzania, from September 17, 2007, through August 31, 2008.

Study setting. Moshi (population 184,000) is the administrative center of the Kilimanjaro region (population 1.6 million) in northern Tanzania.¹⁹ Malaria endemicity in the region is low.²⁰ In 2007–2008, the estimated prevalence of human immunodeficiency virus (HIV) infection in northern Tanzania among men and women aged 15–45 years was 1.8% and 3.2%, respectively.²¹ Kilimanjaro Christian Medical Center is a 458-bed hospital, which serves as the consultant referral hospital for northern Tanzania. Mawenzi Regional Referral Hospital is a 300-bed hospital, which serves as the regional hospital of the Kilimanjaro Region. Together, KCMC and MRRH provide the most of the hospital care in Moshi.

Study population. Consistent with the IMAI definition of adolescents and adults,¹⁵ febrile patients ≥ 10 years of age were included in this secondary analysis. The methods of the parent study are described in detail elsewhere.^{22,23} In brief, patients with oral temperature $\geq 38.0^\circ\text{C}$ were eligible to participate. Among consenting participants, at admission, the following information was collected by trained study team clinical officers: standardized clinical history and physical examination, including vital signs. Venous blood sample for blood cultures, complete blood count, parasite examination, serologic investigations, and HIV antibody testing was collected from all participants. CD4-positive T-lymphocyte count (CD4 count) was measured among participants with positive HIV serology. Chest radiography was also performed. At time of discharge, a form was completed to document in-hospital management, provisional diagnoses as determined by the hospital clinical team, discharge diagnoses, and whether the patient had died in-hospital.

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TABLE 1
Demographic, clinical, and laboratory characteristics at admission of febrile inpatients by outcome, Kilimanjaro Christian Medical Center and Mawenzi Regional Referral Hospital, 2007–2008.
Univariate analysis

	HIV-uninfected and uninfected population				HIV-infected population				HIV-uninfected population			
	Survivors (N = 375)	Decedents (N = 44)	OR (95% CI)		Survivors (N = 129)	Decedents (N = 31)	OR (95% CI)		Survivors (N = 242)	Decedents (N = 12)	OR (95% CI)	
Baseline data												
Age (years), median (IQR)	37.3 (35.7–39.0)	40.7 (37.0–44.3)	–		38.9 (36.9–40.8)	41.4 (37.8–15.0)	–		31.1 (22.3–49.1)	35.7 (27.0–53.8)	–	
Male gender	202 (53.9)	23 (52.3)	0.9 (0.5–1.8)		81 (62.8)	17 (54.8)	0.7 (0.3–1.6)		120 (49.6)	5 (41.7)	0.7 (0.2–2.4)	
HIV infection	129 (34.8)	31 (72.1)	5.0 (2.5–10.0)		–	–	–		–	–	–	
Vital signs												
Systolic blood pressure (mmHg), median (IQR)	114.2 (112.4–116.0)	112.9 (107.6–118.3)	–		108.7 (106.1–111.4)	111.0 (104.0–118.1)	–		117.0 (105.0–126.0)	117.5 (103.2–128.0)	–	
Mean arterial pressure (mmHg), median (IQR)	85.4 (83.8–86.9)	86.4 (82.0–90.8)	–		81.4 (79.1–83.8)	84.6 (79.5–89.7)	–		86.7 (78.0–96.2)	91.7 (75.5–103.0)	–	
Systolic blood pressure ≤ 100 mmHg	86 (23.0)	10 (22.7)	1.0 (0.5–2.1)		42 (32.6)	8 (25.8)	0.7 (0.3–1.7)		42 (17.4)	2 (16.7)	0.9 (0.2–4.4)	
Systolic blood pressure < 90 mmHg	22 (5.9)	4 (9.1)	1.6 (0.5–4.9)		10 (7.8)	4 (12.9)	1.8 (0.5–6.0)		12 (5.0)	0 (0.0)	–	
Heart rate (beats/minute), median (IQR)	101.2 (99.2–103.2)	106.3 (99.6–113.1)	–		107.7 (104.3–111.1)	104.7 (96.8–112.6)	–		98.0 (86.0–110.0)	104.0 (92.0–136.0)	–	
Heart rate > 100 beats/minute	185 (49.5)	24 (54.5)	1.2 (0.7–2.3)		83 (64.3)	17 (54.8)	0.7 (0.3–1.5)		101 (41.9)	6 (50.0)	1.4 (0.4–4.4)	
Respiratory rate ≥ 22 breaths/minute, median (Q1–Q3)	28.2 (27.0–29.4)	26.8 (24.8–28.9)	–		29.9 (27.5–32.2)	26.8 (24.5–29.1)	–		24.0 (22.0–28.0)	24.0 (20.0–30.0)	–	
Respiratory rate ≥ 24 breaths/minute	304 (81.7)	33 (76.7)	0.7 (0.3–1.6)		113 (88.3)	25 (80.6)	0.5 (0.2–1.6)		187 (77.9)	7 (63.6)	0.5 (0.1–1.7)	
Respiratory rate > 30 breaths/minute	196 (52.7)	26 (60.5)	1.4 (0.7–2.6)		78 (60.9)	21 (67.7)	1.3 (0.6–3.1)		116 (48.3)	4 (36.4)	0.6 (0.2–2.1)	
Respiratory rate > 30 breaths/minute	68 (18.3)	6 (14.0)	0.7 (0.3–1.8)		31 (24.2)	4 (12.9)	0.5 (0.2–1.4)		36 (15.0)	1 (9.1)	0.6 (0.1–4.6)	
Peripheral oxygen saturation, median (IQR)	94.9 (94.5–95.4)	91.7 (89.7–93.7)	–		94.3 (93.4–95.1)	91.3 (88.8–93.7)	–		96.0 (94.0–98.0)	94.5 (92.0–97.7)	–	
Peripheral oxygen saturation < 90%	30 (8.1)	11 (25.0)	3.8 (1.7–8.3)		15 (11.7)	9 (29.0)	3.1 (1.2–7.9)		14 (5.8)	2 (16.7)	3.2 (0.6–16.2)	
Respiratory rate > 30 breaths/minute or peripheral oxygen saturation < 90%	86 (23.0)	15 (34.1)	1.7 (0.9–3.4)		39 (30.2)	12 (38.7)	1.5 (0.6–3.3)		46 (19.1)	2 (16.7)	0.8 (0.2–4.0)	
Tympanic temperature > 38°C or < 36°C	301 (81.1)	32 (72.7)	0.6 (0.3–1.3)		112 (87.5)	21 (67.7)	0.3 (0.1–0.8)		188 (78.7)	11 (91.7)	2.9 (0.4–23.7)	
Glasgow Coma Scale, median (IQR)	14.8 (14.7–14.9)	12.6 (11.4–13.8)	–		15 (15–15)	15 (13–15)	–		15.0 (15.0–15.0)	15.0 (4.0–15.0)	–	
Glasgow Coma Scale < 15	16 (4.5)	15 (34.9)	11.4 (5.1–25.3)		6 (4.8)	9 (29.0)	8.0 (2.6–24.9)		9 (3.9)	5 (45.5)	3.1 (0.9–10.7)	
Laboratory evaluations												
Hemoglobin (g/dL), median (IQR)	11.2 (10.9–11.5)	9.5 (8.6–10.5)	–		9.8 (9.3–10.3)	9.2 (8.3–10.1)	–		12.2 (10.5–13.8)	10.5 (7.3–13.2)	–	
Hemoglobin < 9 g/dL	76 (20.4)	23 (52.3)	4.3 (2.2–8.1)		42 (32.8)	18 (58.1)	2.8 (1.3–6.3)		34 (14.0)	4 (33.3)	3.1 (0.9–1.1)	
Platelets (10 ³ /μL), median (IQR)	216.4 (203.5–229.4)	220.1 (171.4–268.8)	–		214.1 (193.7–234.5)	207.7 (157.9–257.4)	–		198.5 (129.8–270.5)	186.5 (55.5–419.0)	–	
White blood cells (10 ³ /μL), median (IQR)	8.9 (8.1–9.6)	10.8 (6.2–15.4)	–		7.5 (6.7–8.2)	7.2 (5.4–9.0)	–		6.9 (4.5–12.1)	10.8 (7.8–18.9)	–	
CD4 ⁺ cells count (cells/μL), median (IQR)	–	–	–		175.4 (141.4–209.4)	81.2 (42.2–120.2)	–		–	–	–	
CD4 ⁺ count < 200 cells/μL	–	–	–		82 (66.1)	27 (93.1)	6.9 (1.6–30.5)		–	–	–	
CD4 ⁺ count < 350 cells/μL	–	–	–		107 (86.3)	28 (96.6)	4.4 (0.5–34.9)		–	–	–	
Blood smear positive for malaria, median (IQR)	14 (3.8)	0 (0.0)	–		0 (0.0)	0 (0.0)	–		14 (5.8)	0 (0.0)	–	
Bacteremia or fungemia												
Bacteremia or fungemia	77 (20.5)	11 (25.0)	1.3 (0.6–2.7)		27 (20.9)	10 (32.3)	1.8 (0.8–4.2)		50 (20.7)	0 (0.0)	–	
Clinical presentation												
Gastrointestinal syndrome	41 (10.9)	3 (6.8)	0.6 (0.2–2.0)		12 (9.3)	2 (6.5)	0.7 (0.1–3.2)		29 (12.0)	1 (8.3)	0.7 (0.1–5.4)	
Genitourinary syndrome	20 (5.3)	1 (2.3)	0.4 (0.1–3.2)		8 (6.2)	1 (3.2)	0.5 (0.1–4.2)		11 (4.5)	0 (0.0)	–	
Neurologic syndrome	22 (5.9)	12 (27.3)	6.0 (2.7–13.3)		7 (5.4)	7 (22.6)	5.1 (1.6–15.8)		14 (5.8)	4 (33.3)	8.1 (2.2–30.4)	
Respiratory syndrome	124 (33.1)	19 (43.2)	1.5 (0.8–2.9)		61 (47.3)	14 (45.6)	0.9 (0.4–2.0)		62 (25.6)	5 (41.7)	2.1 (0.6–8.8)	
Systemic syndrome	168 (44.8)	9 (20.5)	0.3 (0.1–0.6)		41 (31.8)	7 (22.6)	0.6 (0.3–1.6)		126 (52.1)	2 (16.7)	0.2 (0.1–0.9)	

CI = confidence interval; HIV = human immunodeficiency virus; IMAI = Integrated Management of Adolescent and Adult Illness; IQR = interquartile range; OR = odds ratio; qSOFA = quick Sequential Organ Failure Assessment. Human immunodeficiency virus status was unknown for five of the 419 patients included in the study. Continuous variables are presented as medians with IQRs. Categorical variables are presented as frequencies and percentages of the specified group with the corresponding OR estimates. Systolic blood pressure ≤ 100 mmHg is a qSOFA score variable, whereas systolic blood pressure < 90 mmHg is an IMAI severe sepsis or septic shock variable. Respiratory rate ≥ 22 breaths/minute is a qSOFA variable, respiratory rate > 24 breaths/minute is an IMAI severe sepsis or septic shock variable, whereas respiratory rate > 30 breaths/minute is part of IMAI severe respiratory distress without shock and IMAI severe pneumonia scores. Statistically significant values are in bold.

Definitions. Illness severity scores were calculated as originally described. Specifically, MEWS assigns a value from 0 to 3 for each of five parameters: systolic blood pressure, heart rate, respiratory rate, temperature, and AVPU score ('A' for alert, 'V' for reacting to voice, 'P' for reacting to pain, and 'U' for unresponsive). A composite score ≥ 5 defined a "critical score."⁸ quick Sequential Organ Failure Assessment score assigns one point for each of three criteria: respiratory rate ≥ 22 breaths per minute, altered mentation, and systolic blood pressure ≤ 100 mmHg. A cutoff value ≥ 2 was used to define individuals with suspected infection likely to have poor outcomes.⁹ Severe sepsis or septic shock was defined by the IMAI guidelines as a condition characterized by suspicion of infection, systolic blood pressure < 90 mm of Hg, and one or more of the following parameters: pulse rate > 100 beats per minute, respiratory rate > 24 breaths per minute, and abnormal body temperature (either $> 38^\circ\text{C}$ or $< 36^\circ\text{C}$). Severe respiratory distress without shock was defined by the IMAI guidelines as a respiratory rate > 30 breaths per minute or peripheral oxygen saturation (SpO_2) $< 90\%$, systolic blood pressure > 90 mm of Hg, and suspected pneumonia or acute lung injury in the absence of heart failure. Severe pneumonia was defined by the IMAI guidelines as the presence of fever or suspected infection, cough, respiratory rate > 30 breaths per minute, severe respiratory distress, and peripheral oxygen saturation $< 90\%$. The following were considered as IMAI emergency signs: neck stiffness, lethargy, unconsciousness, convulsions, severe abdominal pain, and respiratory distress.¹⁵ We were not able to assess the presence of the IMAI severity sign "weakness/inability to stand" because of the lack of this variable in the parent study.

Based on their clinical presentation at enrollment, patients were categorized in the following groups: neurologic syndrome, gastrointestinal syndrome, genitourinary syndrome,

respiratory syndrome, and systemic syndrome.^{24–26} Specifically, the following classification criteria were adopted: 1) neurologic syndrome—convulsions or Glasgow Coma Scale (GCS) < 15 in association with either neck stiffness or headache; 2) respiratory syndrome—dyspnea or respiratory rate > 30 breaths/minute or peripheral oxygen saturation $< 90\%$ and hemoptysis or cough or radiologic evidence of pneumonia; 3) gastrointestinal syndrome—diarrhea or vomiting and abdominal tenderness; 4) genitourinary syndrome—dysuria; and 5) systemic syndrome—if none of the above. In the event criteria for more than one syndrome were fulfilled, an infectious disease expert assessed the case and attributed the case to one of the five clinical categories.

Statistical analysis. Continuous variables are presented as medians with interquartile ranges. Categorical variables are presented as frequencies and percentages of the specified group. Comparisons of baseline characteristics of patients who did or did not die were made with the Fisher's exact test, Mann-Whitney test, or Kruskal-Wallis test as appropriate. To assess the diagnostic accuracy of the warning scores when applied to the overall study population and when limited to the HIV-infected study population, sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and areas under the receiver operating characteristics (AUROC) curve were calculated. Because the literature provides limited data regarding the most appropriate cutoff values for the MEWS, a sensitivity analysis was performed and the diagnostic performance of this score was assessed using different cutoff values. To evaluate the ability of warning scores to predict in-hospital mortality, clinical variables found to be associated with in-hospital mortality at univariate analysis were entered into a logistic regression model. All the variables significant in the crude model were tested in subsequent multivariable models, according to the best candidate model selection procedure.

TABLE 2

IMAI emergency signs and severity scores at admission in febrile inpatients by outcome, Kilimanjaro Christian Medical Center and Mawenzi Regional Referral Hospital, 2007–2008. Univariate analysis

	HIV-infected and uninfected population			HIV-infected population			HIV-uninfected population		
	Survivors (N = 375)	Decedents (N = 44)	OR (95% CI)	Survivors (N = 129)	Decedents (N = 31)	OR (95% CI)	Survivors (N = 242)	Decedents (N = 12)	OR (95% CI)
IMAI emergency signs									
Neck stiffness	15 (4.1)	8 (18.2)	5.2 (2.1–13.2)	5 (3.9)	7 (22.6)	7.2 (2.1–24.7)	8 (3.4)	1 (8.3)	2.6 (0.3–22.6)
Lethargy	1 (0.3)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	1 (0.4)	0 (0.0)	–
Unconsciousness	28 (7.5)	17 (38.6)	7.8 (3.8–15.9)	5 (3.9)	11 (35.5)	13.6 (4.3–43.4)	21 (8.7)	6 (50.0)	10.5 (3.1–35.4)
Convulsions	18 (5.0)	8 (18.2)	4.2 (1.7–10.4)	5 (4.0)	5 (16.1)	4.6 (1.2–17.1)	11 (4.7)	3 (25.0)	6.7 (1.6–28.4)
Severe abdominal pain	46 (13.2)	7 (16.7)	1.3 (0.5–3.1)	18 (14.8)	6 (20.0)	1.4 (0.5–4.0)	28 (12.6)	1 (9.1)	0.7 (0.1–5.6)
Respiratory distress	126 (34.1)	23 (53.5)	2.2 (1.2–4.2)	54 (42.5)	16 (53.3)	1.5 (0.7–3.4)	71 (29.8)	7 (58.3)	3.3 (1.1–10.7)
At least one IMAI emergency sign	181 (48.3)	38 (86.4)	6.8 (2.8–16.4)	71 (55.0)	27 (87.1)	5.5 (1.8–16.7)	107 (44.2)	11 (91.7)	13.9 (1.8–109.2)
At least two IMAI emergency signs	43 (11.5)	18 (40.9)	5.3 (2.7–10.5)	12 (9.3)	12 (38.7)	6.2 (2.4–15.7)	29 (12.0)	6 (50.0)	7.3 (2.2–24.3)
At least three IMAI emergency signs	8 (2.1)	7 (15.9)	8.7 (3.0–25.3)	3 (2.3)	6 (19.4)	10.1 (2.4–43.0)	3 (1.2)	1 (8.3)	7.2 (0.7–75.4)
Severity scores									
MEWS ≥ 5	49 (13.5)	10 (23.3)	1.9 (0.9–4.2)	31 (24.4)	7 (22.6)	0.9 (0.4–2.3)	17 (7.3)	3 (27.3)	4.8 (1.2–19.6)
qSOFA ≥ 2	85 (23.5)	18 (41.9)	2.3 (1.2–4.5)	42 (33.1)	14 (45.2)	1.7 (0.8–3.7)	40 (17.3)	3 (27.3)	1.8 (0.5–7.0)
IMAI severe sepsis or septic shock	21 (5.6)	4 (9.1)	1.7 (0.5–5.1)	10 (7.8)	4 (12.9)	1.8 (0.5–6.0)	11 (4.6)	0 (0.0)	–
IMAI severe respiratory distress without shock	28 (8.2)	9 (22.5)	3.2 (1.4–7.5)	18 (15.0)	8 (27.6)	2.1 (0.8–5.6)	10 (4.6)	1 (9.1)	2.1 (0.2–17.8)
IMAI severe pneumonia	10 (2.7)	2 (4.7)	1.7 (0.4–8.2)	6 (4.7)	1 (3.3)	0.7 (0.1–6.0)	3 (1.3)	1 (8.3)	7.1 (0.7–73.8)

CI = confidence interval; HIV = human immunodeficiency virus; IMAIs = Integrated Management of Adolescent and Adult Illness; MEWS = Modified Early Warning Score; OR = odds ratio; qSOFA = quick Sequential Organ Failure Assessment. Human immunodeficiency virus status was unknown for five of the 419 patients included in the study. Variables are presented as frequencies and percentages of the specified group. Statistically significant values are in bold.

TABLE 3

	HIV-infected and uninfected population (N = 419)				HIV-infected population (N = 160)				HIV-uninfected population (N = 254)						
	Sensitivity (%)	Specificity (%)	LR+	AUROC	Sensitivity (%)	Specificity (%)	LR+	AUROC	Sensitivity (%)	Specificity (%)	LR+	AUROC			
MEWS ≥ 5	23.3	86.5	1.7	0.9	0.55 (0.44–0.65)	22.6	75.6	0.9	1.0	0.49 (0.37–0.61)	27.3	92.7	3.7	0.8	0.57 (0.37–0.77)
qSOFA ≥ 2	41.9	76.5	1.8	0.8	0.60 (0.50–0.70)	45.2	66.9	1.4	0.8	0.57 (0.45–0.70)	27.3	82.7	1.6	0.9	0.57 (0.38–0.77)
IMAI severe sepsis or septic shock	9.1	94.4	1.6	1.0	0.52 (0.42–0.62)	12.9	92.2	1.7	0.9	0.53 (0.41–0.65)	0.0	95.4	0.0	1.0	0.48 (0.30–0.65)
IMAI severe respiratory distress without shock	22.5	91.8	2.7	0.8	0.58 (0.47–0.68)	27.6	85.0	1.8	0.9	0.57 (0.44–0.69)	9.1	95.4	2.0	1.0	0.53 (0.34–0.72)
IMAI severe pneumonia	4.7	97.3	1.7	1.0	0.52 (0.42–0.62)	3.3	95.3	0.7	1.0	0.49 (0.37–0.61)	8.3	98.7	6.4	0.9	0.55 (0.35–0.75)
At least one IMAI emergency sign	86.4	51.7	1.8	0.2	0.71 (0.64–0.78)	87.1	45.0	1.6	0.3	0.67 (0.57–0.77)	91.7	55.8	2.1	0.1	0.74 (0.61–0.87)
At least two IMAI emergency signs	40.9	88.5	3.6	0.7	0.65 (0.55–0.76)	38.7	90.7	4.2	0.7	0.65 (0.52–0.77)	50.0	88.0	4.2	0.6	0.69 (0.50–0.88)
At least three IMAI emergency signs	15.9	97.9	7.6	0.9	0.57 (0.47–0.67)	19.4	97.7	8.4	0.8	0.58 (0.45–0.70)	8.3	98.8	6.9	0.9	0.55 (0.35–0.74)

AUROC = area under receiver operating characteristics; IMAI = Integrated Management of Adolescent and Adult Illness; LR+ = positive likelihood ratio; LR– = negative likelihood ratio; MEWS = Modified Early Warning Score; qSOFA = quick Sequential Organ Failure Assessment.

Research ethics. This study was approved by the KCMC Research Ethics Committee (#295), the Tanzania National Institute for Medical Research National Ethics Coordinating Committee (NIMR1HQ/R.8cNo1. 11/283), and the Institutional Review Board of Duke University Medical Center (IRB #Pro00016134). All study participants provided written informed consent. Parents or guardians provided written informed consent for their children.

RESULTS

Study population. Of the 870 febrile patients hospitalized with febrile illness at KCMC and MRRH, Moshi, Tanzania, in the period 2007–2008 and enrolled in the parent study, 419 were ≥ 10 years old and were included in this secondary analysis. Of 419 participants, 44 (10.5%) died during the hospital stay. Of the patients who died, 31 (70.5%) were HIV infected. Of the 44 who died, 19 (43.2%) had respiratory tract infection and 12 (27.3%) had central nervous system infection. Of the 375 participants who survived, 124 (33.1%) had respiratory tract infection and 168 (44.8%) had systemic infection (Table 1).

Univariate analysis. On univariate analysis, in-hospital mortality was significantly associated with HIV infection, peripheral oxygen saturation < 90%, respiratory distress, Glasgow Coma Scale < 15, neck stiffness, unconsciousness, convulsions, hemoglobin < 9 g/dL, and neurologic syndrome. A systemic syndrome was associated with a reduced risk of in-hospital mortality. The presence of at least one, two, or three IMAI emergency signs, and IMAI severe respiratory distress syndrome without shock were significantly associated with in-hospital mortality, as was qSOFA score ≥ 2 . When the analysis was limited to the HIV-infected population, the following factors were significantly associated with in-hospital mortality: peripheral oxygen saturation < 90%, tympanic temperature > 38°C or < 36°C, Glasgow Coma Scale < 15, neck stiffness, unconsciousness, convulsions, hemoglobin < 9 g/dL, CD4 count < 200 cells/ μ L, neurologic syndrome, the presence of at least one IMAI emergency sign, the presence of at least two IMAI emergency signs, and the presence of at least three IMAI emergency signs. Finally, the following factors were significantly associated with in-hospital mortality among HIV-uninfected patients: Glasgow Coma Scale < 15, high

FIGURE 1. Receiver operating characteristics curves of severity scores applied to HIV-infected and uninfected febrile inpatients, Kilimanjaro Christian Medical Center and Mawenzi Regional Referral Hospital, 2007–2008. IMAI = Integrated Management of Adolescent and Adult Illness; MEWS = Modified Early Warning Score; qSOFA = quick Sequential Organ Failure Assessment. This figure appears in color at www.ajtmh.org.

leukocyte count, and neurologic syndrome. A systemic syndrome was associated with a reduced risk of in-hospital mortality. The presence of at least one or two IMAI emergency signs and a MEWS ≥ 5 were significantly associated with in-hospital mortality. Malaria, bacteremia, and fungemia were similarly distributed among patients who did and did not die (Tables 1 and 2).

Diagnostic accuracy of severity scores. The diagnostic accuracy of the included scores, IMAI emergency signs, and IMAI syndromes in identifying patients likely to die during the hospital stay are shown in Table 3. Specificity and positive likelihood ratios ranged from 51.7% to 97.9% and from 1.7 to 7.6, respectively. The presence of at least one IMAI emergency sign was characterized by the following diagnostic performance parameters: sensitivity 86.4%, negative likelihood ratio 0.2, and AUROC of 0.71 (0.64–0.78) (Table 3 and Figure 1). When limiting the analysis to HIV-infected febrile inpatients, the discriminatory power of “presence of at least one IMAI emergency sign” was similar: sensitivity 87.1%, negative likelihood ratio 0.3, and AUROC of 0.67 (0.57–0.77) (Table 3). The analysis of the HIV-uninfected subgroup of patients led to similar results (Table 3). The performance of IMAI severe respiratory distress without shock and IMAI severe pneumonia was tested among HIV-infected and uninfected febrile inpatients presenting with a respiratory syndrome: the AUROC curves were 0.63 (0.48–0.78) and 0.52 (0.37–0.68), respectively (Table 4). We also tested the diagnostic accuracy of various cutoff values for the MEWS: the negative

likelihood ratio ranged from 0.8 to 1.2 (Table 5). Finally, we performed an exploratory analysis of the diagnostic performance of three other scores, namely Asiimwe, Rapid Acute Physiology Score (RAPS), and Rapid Emergency Medicine Score (REMS) score^{28–30}; the results of this analysis are shown in Supplemental Table 1.

Logistic regression analysis. A unique logistic regression model for each warning score was generated to assess the association between scores and in-hospital mortality. To account for confounders, variables significantly associated to in-hospital mortality in the crude model (Table 6) were tested in multivariable models according to the best candidate model selection procedure. Age, heart rate, and tympanic

TABLE 4

Sensitivity and specificity of severity scores for mortality applied to febrile inpatients presenting with a respiratory syndrome based on measurements at admission, Kilimanjaro Christian Medical Center and Mawenzi Regional Referral Hospital, 2007–2008

	Respiratory syndrome population (N = 143)				
	Sensitivity (%)	Specificity (%)	LR+	LR–	AUROC
IMAI severe respiratory distress without shock	52.9	72.3	1.9	0.7	0.63 (0.48–0.78)
IMAI severe pneumonia	10.9	91.9	1.3	1.0	0.52 (0.37–0.68)

AUROC = area under receiver operating characteristics; IMAI = Integrated Management of Adolescent and Adult Illness; LR+ = positive likelihood ratio; LR– = negative likelihood ratio.

TABLE 5
Diagnostic performance of MEWS severity score applying different cutoff values to febrile inpatients, Kilimanjaro Christian Medical Center and Mawenzi Regional Referral Hospital, 2007–2008.
Sensitivity analysis

	HIV-infected and uninfected population (N = 419)					HIV-infected population (N = 160)					HIV-uninfected population (N = 254)				
	Sensitivity (%)	Specificity (%)	LR+	LR-	AUROC	Sensitivity (%)	Specificity (%)	LR+	LR-	AUROC	Sensitivity (%)	Specificity (%)	LR+	LR-	AUROC
MEWS ≥ 2	77.3	28.8	1.1	0.8	0.54 (0.44–0.63)	80.6	20.3	1.0	1.0	0.52 (0.40–0.64)	66.7	32.6	1.0	1.0	0.48 (0.29–0.66)
MEWS ≥ 3	50.0	55.5	1.1	0.9	0.53 (0.43–0.63)	48.4	42.5	0.8	1.2	0.47 (0.35–0.59)	50.0	62.1	1.3	0.8	0.53 (0.34–0.71)
MEWS ≥ 4	39.5	73.5	1.5	0.8	0.56 (0.46–0.66)	35.5	58.3	0.9	1.1	0.48 (0.36–0.60)	45.5	81.8	2.5	0.7	0.61 (0.42–0.81)

AUROC = area under receiver operating characteristics; HIV = human immunodeficiency virus; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; MEWS = Modified Early Warning Score.

temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$ were forced in the final models because of their clinical relevance. When HIV-infected and uninfected febrile patients were analyzed, the following variables were retained in the final multivariable model: GCS < 15 , Hb < 9 g/dL, unconsciousness, respiratory distress, and HIV infection. None of the scores showed a statistically significant association with in-hospital mortality among HIV-infected and uninfected febrile inpatients. Specifically, the significant crude associations between IMAI severe respiratory distress, qSOFA ≥ 2 , and in-hospital mortality vanished after adjustment for confounders (Table 6). When only HIV-infected febrile patients were evaluated, peripheral oxygen saturation $< 90\%$, Hb < 9 g/dL, unconsciousness, and CD4⁺ coun < 200 cells/ μL were retained in the final multivariable model. We found no association, crude or adjusted, between the severity scores analyzed and in-hospital mortality (Table 6). Logistic regression analysis was not performed in the HIV-uninfected population because of the low number of deaths in this subgroup of patients.

DISCUSSION

Our study showed that in-hospital mortality among febrile adolescents and adults in northern Tanzania in the period 2007–2008 was significantly associated with HIV infection, peripheral oxygen saturation $< 90\%$, respiratory distress, hemoglobin < 9 g/dL, GCS < 15 , unconsciousness, neck stiffness, convulsions, and neurologic syndrome. A qSOFA ≥ 2 ; the presence of at least one, two, or three IMAI emergency signs; and the fulfillment of the IMAI severe respiratory distress without shock criteria were all significantly associated with increased odds of death. After adjustment for confounders, none of the scores was significantly associated with in-hospital mortality. The criterion “presence of at least one IMAI emergency sign” was characterized by a very good diagnostic accuracy, as highlighted by the high sensitivity, low negative likelihood ratio, and wide area under the receiver operating characteristics curve. The remaining scores showed a poor performance in predicting fatal outcomes in our study population.

To our knowledge, this is the first study to assess the ability of IMAI emergency signs and IMAI severity criteria to predict in-hospital mortality among febrile adolescents and adults in resource-constrained settings. The IMAI emergency signs showed a significant correlation with in-hospital mortality in univariate analysis, and the presence of at least one IMAI emergency sign showed good discriminatory power to identify patients likely to have a poor outcome. With high sensitivity (86.4%) and low negative likelihood ratio (0.2), the “presence of at least one IMAI emergency sign” is a potentially useful bedside tool. This variable could assist clinicians to rule out high likelihood of in-hospital death.

In contrast to the IMAI emergency signs, all the IMAI severity criteria evaluated (IMAI severe sepsis or septic shock, IMAI severe respiratory distress, and IMAI severe pneumonia) showed a limited ability to discriminate patients at increased risk of death. The limited performance of the IMAI severity criteria could be explained by a number of factors. Among the febrile patients included in our study, 160 (38.1%) were HIV-infected. Of these, 109 (68.1%) presented with advanced immune depression (CD4 count < 200 cells/ μL) and 60 (37.5%) were diagnosed with anemia (Hb < 9 g/dL).

TABLE 6

Evaluation of the association between severity scores and in-hospital mortality among febrile inpatients, Kilimanjaro Christian Medical Center and Mawenzi Regional Referral Hospital, 2007–2008. Logistic regression analysis

	HIV-infected and uninfected population (N = 419)		HIV-infected population (N = 160)	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Peripheral oxygen saturation < 90%	3.8 (1.7–8.3)	2.8 (1.0–7.8)	3.1 (1.2–7.9)	5.4 (1.5–19.5)
GCS < 15	11.4 (5.1–25.3)	3.6 (1.0–13.6)	8.0 (2.6–24.9)	12.7 (2.9–54.7)
Hb < 9 g/dL	4.3 (2.2–8.1)	3.3 (1.4–7.5)	2.8 (1.3–6.3)	6.7 (2.1–21.1)
Neurologic syndrome	6.0 (2.7–13.3)	11.3 (4.2–30.6)	5.1 (1.6–15.8)	10.8 (2.5–46.7)
Systemic syndrome	0.3 (0.1–0.7)	0.6 (0.2–1.3)	0.6 (0.3–1.69)	0.7 (0.2–2.4)
Neck stiffness	5.2 (2.1–13.2)	6.5 (2.2–19.1)	7.2 (2.1–24.7)	7.4 (1.8–30.8)
Unconsciousness	7.8 (3.8–15.9)	11.2 (3.1–40.1)	13.6 (4.3–43.4)	19.7 (4.6–85.4)
Convulsions	4.2 (1.7–10.5)	3.9 (1.0–15.0)	4.6 (1.2–17.1)	2.5 (0.4–16.4)
Respiratory distress	2.2 (1.2–4.2)	3.6 (1.5–8.5)	1.5 (0.7–3.4)	3.5 (1.0–12.5)
HIV infection	4.8 (2.4–9.8)	4.7 (1.9–11.7)	—	—
CD4 ⁺ count < 200 cells/ μ L	—	—	6.9 (1.6–30.5)	9.7 (1.4–68.7)
IMAI severe sepsis and septic shock	1.7 (0.5–5.1)	1.9 (0.5–7.1)	1.7 (0.5–6.0)	1.6 (0.3–8.8)
IMAI SRD without shock	3.2 (1.4–7.5)	2.7 (0.9–7.8)	2.1 (0.8–5.6)	3.6 (0.7–19.3)
IMAI severe pneumonia	1.7 (0.3–8.2)	0.7 (0.1–6.1)	0.7 (0.1–6.0)	0.1 (0.0–1.4)
qSOFA $\geq$ 2	2.3 (1.2–4.5)	0.7 (0.3–1.8)	1.7 (0.7–3.7)	0.8 (0.2–2.4)
MEWS $\geq$ 5	1.9 (0.9–4.2)	0.6 (0.2–1.9)	0.9 (0.4–2.3)	0.8 (0.2–3.6)

CI = confidence interval; HIV = human immunodeficiency virus; IMAI = Integrated Management of Adolescent and Adult Illness; MEWS = Modified Early Warning Score; OR = odds ratio; qSOFA = quick Sequential Organ Failure Assessment; SRD = severe respiratory distress. Statistically significant values are in bold.

Based on the results of the logistic regression analysis, we could hypothesize that the patients' baseline comorbidities were closely associated with in-hospital mortality. As a consequence, it would be important to assess in the future the performance of the IMAI severity criteria in a study population with a lower prevalence of HIV infection. The slightly better performance of IMAI severe respiratory distress without shock compared with other severity indicators should be acknowledged. Because 218 (52.0%) of 419 participants included in our analysis had evidence of respiratory infections, the IMAI severe respiratory distress without shock criterion might be expected to perform better than the IMAI severe sepsis and septic shock criterion and other scores in identifying patients at increased risk of fatal outcome. Nevertheless, its clinical utility is limited by its low discriminatory power for predicting mortality (AUROC 0.58). This syndrome criterion showed a low discriminatory power even when applied to the subset of patients mainly presenting with respiratory symptoms and signs.

The qSOFA score showed a low discriminatory power in our setting. The suboptimal performance of the qSOFA score is unsurprising. A previous study by Churpek et al.³¹ showed qSOFA to be less sensitive than other severity scores in predicting in-hospital mortality among patients suspected to have an infection. The low sensitivity reported for the qSOFA score is concerning because it may lead to failure to recognize the signs of potentially lethal infection until the derangement of vital signs is significantly more likely to be deadly. At this regard, we suggest a cautious interpretation of the results of the study performed in Gabon by Huson et al.¹¹: in that setting, the AUROC estimated for qSOFA was superior to the AUROC estimated for qSOFA in our study (0.83 versus 0.60). This difference could be due to the fact that the Gabon study may have enrolled a more severe patient population: inclusion in the Gabon study required the fulfillment of at least two Systemic Inflammatory Response Syndrome (SIRS) criteria, whereas inclusion in our study was based only on the presence of fever.

Modified Early Warning Score showed a poor diagnostic accuracy when applied to our population. The

variation of the cutoff values used to calculate this score did not improve its discriminatory ability in identifying patients likely to have a poor outcome. Furthermore, the persistent association of HIV infection and low hemoglobin with in-hospital mortality in the logistic regression models emphasizes the contribution of preexisting clinical conditions to the clinical outcome of febrile patients in our setting.

Our study also highlighted a strong association between altered level of consciousness and in-hospital mortality. Irrespective of the pathophysiologic mechanism causing impairment of consciousness (e.g., central nervous system infection versus sepsis-related end-organ dysfunction), its presence warrants prompt interventions to avert fatal outcomes.

This study has several limitations. First, this is a secondary analysis of prospective data collected in the period 2007–2008 in northern Tanzania, which may not reflect the epidemiological and clinical characteristics of febrile patients currently hospitalized in this area. Second, more than one-third of the febrile patients admitted at KCMC and MRRH and more than two-thirds of the patients who died during their hospital stay were HIV infected: the impaired and dysregulated immune response associated with HIV infection could have influenced the development of severity symptoms and signs and could have affected the performance of the early warning scores evaluated in this study. Moreover, our analysis is not exhaustive: because of the secondary nature of our study design, we were not able to investigate the performance of scores that include metrics not collected during the original parent study. In this regard, it is worth noting that we were not able to assess the presence of the IMAI emergency sign "weakness/inability to stand" because this information was not collected in the original study. As a consequence, we may have underestimated the diagnostic accuracy of the criteria "presence of at least one IMAI emergency sign," "presence of at least two IMAI emergency sign," and "presence of at least three IMAI emergency signs." Finally, caution should be used in generalizing our results to epidemiologically different settings.

In conclusion, the “presence of at least one IMAI emergency sign” showed good diagnostic accuracy and high sensitivity for predicting in-hospital mortality among febrile inpatients, whereas the qSOFA score had poor discriminatory power in our patient population. Further studies are needed to derive and refine early warning scores that have good clinical performance in settings throughout sub-Saharan Africa, including where HIV infection is uncommon.

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