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Development of a Malawi Intensive care Mortality risk Evaluation (MIME) model, a prospective cohort study

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Abstract

Introduction: Intensive care medicine can contribute to population health in low-income countries by reducing premature mortality related to surgery, trauma, obstetrical and other medical emergencies. Quality improvement is guided by risk stratification models, which are developed primarily within high-income settings. Models validated for use in low-income countries are needed.

Methods: This prospective cohort study consisted of 261 patients admitted to the intensive care unit (ICU) of K***** Central Hospital in Malawi, from September 2016 to March 2018. The primary outcome was in-hospital mortality. We performed univariable analyses on putative predictors and included those with a significance of 0.15 in the Malawi Intensive care Mortality risk Evaluation model (MIME). Model discrimination was evaluated using the area under the curve.

Results: Males made up 37.9% of the study sample and the mean age was 34.4 years. A majority (73.9%) were admitted to the ICU after a recent surgical procedure, and 59% came directly from the operating theater. In-hospital mortality was 60.5%. The MIME based on age, sex, admitting

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service, systolic pressure, altered mental status, and fever during the ICU course had a fairly good discrimination, with an AUC of 0.70 (95% CI 0.63–0.76).

Conclusions: The MIME has modest ability to predict in-hospital mortality in a Malawian ICU. Multicenter research is needed to validate the MIME and assess its clinical utility.

Keywords

global surgery; low-income; critical care; risk model

Introduction

The delivery of high-quality intensive care medicine may decrease mortality from trauma, infectious disease, obstetric conditions, and surgical complications[1–3]. Morbidity and mortality from these conditions are disproportionately high in low- and middle-income countries (LMICs), where intensive care unit (ICU) expertise and bed availability is lowest[4]. In order to effectively assess the provision and quality of intensive care medicine in LMICs, appropriate risk stratification models are needed. These models may allow for better interpretation of the severity of illness and corresponding mortality rates in regions where critical care services are still developing, facilitate risk-adjusted comparisons of critical care populations in disparate settings, and inform resource allocation in LMICs[5].

The majority of ICU risk stratification models developed to date have been based upon cohorts in high-income settings, which limits their generalizability to LMIC populations, where population demographics, environmental exposures, and critical care capabilities and practices are different [6–12]. Many ICU risk models are also not feasible for LMICs because they require too many assessments and/or laboratory measurements. The objective of this study was to utilize routinely collected data to develop an ICU mortality prediction model for use in Malawi and other LMICs.

Methods

This was prospective, observational cohort study of all patients admitted to the ICU of K***** Central Hospital (KCH) in Lilongwe, Malawi. Data collection occurred from September 2016 to March 2018 based on the funding period. Based on our previous work at this and nearby study sites[13, 14], we anticipated that this timeline would be adequate to achieve a sample size of approximately 250 patients, consistent with other similar studies in the field [15, 16]. The study protocol was developed *a priori* and approved by the National Health Sciences Research Council of Malawi and the Institutional Review Boards of both American universities with which the study was affiliated, and the requirement for written informed consent was waived by all. The study was registered at researchregistry.com under protocol 4330. Malawi is a country in southern Africa with a population of 18 million people, a life expectancy of 63.8 years, and a Human Development Index rank of 170 out of 187 countries[17]. It is the sixth poorest country in sub-Saharan Africa[18]. KCH is a central referral hospital in the central region of Malawi with a catchment area of approximately 5 million.

The data were collected prospectively by clerks specifically trained in ICU data abstraction. The clerks started data collection for each patient at the time of ICU admission by medical chart review and followed the patients to hospital discharge or death. Data collected included date of hospital admission, location before ICU admission (e.g. Emergency Room, Operating Theater, Ward), admitting service (e.g. Surgery, Obstetrics and Gynecology, Medicine, Pediatrics), vital signs and laboratory measurements at the time of ICU admission treatments utilized in ICU (e.g. mechanical ventilation, blood transfusion), location to which patients were discharged, and the hospital discharge date.

Vital signs collected included an assessment of mental status using the AVPU scale (Alert, Verbally-responsive, Painful-stimulus responsive, and Unresponsive), which was simpler and more acceptable to local clinicians than the Glasgow Coma Scale Because AVPU was frequently confounded by postoperative residual anesthesia, during data analysis we simplified it into an assessment of altered mental status (any value other than Alert). In addition to standard vital sign measurements, we also assessed for the clinical suspicion of infection at ICU admission and for the presence of fever (>38.4°C) at any time during the ICU course. Questions about data points were addressed by an author who is full-time ICU clinical officer at KCH (CK). All records were initially kept on paper and then maintained in a de-identified computer database.

Exclusion criteria for patients included age ≤15 years old, readmission to ICU (e.g. only the index admission was included), and ICU admission for a reported head injury; supplemental analyses included patients (1) with missing HIV serostatus managed via list-wise deletion, forced into the model, or imputed as negative and positive as per other studies in the literature[19], and (2) with a reported head injury to assess the validity of the predictive model in the larger cohort. The primary outcome was in-hospital mortality.

We first described the cohort, looking for differences between survivors and non-survivors. We performed a univariable analysis on all independent predictors for in-hospital mortality and included those that reached a significance level of ≤0.15 and had a low proportion of missing values (<10%) in the final model, the Malawi Intensive care Mortality risk Evaluation (MIME). A simplified Malawi Intensive care Mortality Evaluation (simple MIME) was explored and developed using a backward elimination procedure with a criterion of $p < 0.10$ from the full model, to provide an alternative that would be especially simple to implement in low-resourced environments. Model discrimination was evaluated using the area under the receiver operating characteristic curve (AUROC, or c-statistic) with 95% confidence intervals (CI). The area under the curve (AUC) summarizes how well a model is able to accurately delineate hospital survival after ICU admission. Model fit was assessed using Hosmer-Lemeshow Goodness-of-Fit, Akaike information criterion (AIC), and R-squared. Internal validation of model accuracy was performed using 10-fold cross validation. Statistical analyses were conducted using SAS Version 9.4 (SAS Institute, Inc., Cary, NC). The results are reported in line with the STROCSS criteria.[20]

Results

Between September 2016 and March 2018, 431 patients were admitted to the study ICU. After excluding readmissions (n=7), patients ≤15 years of age (n=84), and those with a head injury (n=88), 276 patients were eligible for analysis. Exclusion criteria were not mutually exclusive. Fifteen patients were missing outcome data and were also excluded, for a total cohort of 261 patients. Males accounted for 37.9% of the cohort, and the mean age was 34.4 ±15.1 years (range 16–84 years). A majority of the patients (73.9%) were admitted to the ICU after a recent surgical procedure, and 58.6% came directly from the operating theater while 24.5% were admitted from one of the hospital's four High-Dependency Units. Overall in-hospital mortality in the cohort was 60.5%. (Table 1)

The full Malawi Intensive care Mortality risk Evaluation (MIME) model includes the following variables: age, sex, ICU admitting service, systolic blood pressure at ICU admission, altered mental status at ICU admission, and the presence of a fever during the ICU course. All variables included in the final model had <10% in missing responses. (Appendix, Table A1) The model demonstrated good discrimination, with an AUC of 0.70 (95% CI 0.63–0.76), an average sensitivity of 83.9% (±10.6) in the 10-fold cross-validation. (Tables 2 and 3, Figures 1 and 2)

We examined an alternative model, the simplified Malawi Intensive care Mortality Evaluation (sMIME), which included ICU admitting service, altered mental status at ICU admission, and the presence of fever during the ICU course. (Table 2) This model included fewer variables and demonstrated similar discrimination as the full model with an AUC of 0.68 (95% CI 0.62–0.75). When internally validated, the sMIME model also performed with the same level of sensitivity as the full model. (Tables 2 and 3, Figure 3)

Sensitivity analyses of the multivariable models were explored with the missing HIV serostatus cases managed via list wise deletion, when forced in the model, or imputed as negative and as positive. With the missing HIV serostatus cases imputed as negative or as positive, the model also included the HIV status. The model AUC for the MIME in both these analyses was 0.71 (95% CI 0.64–0.77). By excluding missing HIV status cases but forcing HIV status into the predictive model, the model AUC was 0.72 (95% CI 0.65–0.79). (Appendix Tables A2–3)

Supplemental analyses that included patients with a severe head injury at ICU admission yielded similar results. In these analyses, which included 325 patients, the MIME included the same variables as the primary analysis and demonstrated modest discrimination with an AUC of 0.69 (95% CI 0.63–0.75) and an average of 81% (±9.4) sensitivity in the 10-fold internal validation assessment. With the inclusion of patients with head injuries, the simplified MIME incorporated systolic blood pressure at ICU admission and demonstrated a model AUC of 0.68 (05% CI 0.62–0.74). (Supplement Tables S1–6, Supplement Figures S1–S3)

Discussion

The Malawi Intensive care Mortality Evaluation model (MIME) demonstrated modest ability to predict in-hospital mortality in a population of Malawian ICU patients. Its component variables were easily collected during the clinical care of an ICU patient in a low-resource setting without the need for invasive monitors or laboratory measurements. This score may be considered as a useful retrospective tool to evaluate expected versus observed in-hospital mortality for patients with critical illness in low-income settings but should be externally validated within other sub-Saharan African populations before broad application in future studies. We anticipate its utility to be derived in comparative retrospective studies of critical care services worldwide.

The World Health Organization recommends that any facility providing surgery should have critical care services[21]. This is still a challenge in many LMICs[4], including Malawi where ICU bed availability is only 1 bed per 1 million population[22]. The overall in-hospital mortality for ICU patients at this study site is high (60.5%). Although this is a relatively new area of research, the available prospective literature confirms high in-hospital mortality for ICU patients throughout the Eastern and Central African region, ranging from 46.6% to 50%[15, 16, 23]. An assessment of patients' critical illness severity is imperative to contextualize this mortality rate. The MIME serves this purpose, and has discrimination within range of other newly developed models for sub-Saharan Africa[15, 16]. The development of all of these models suffers from small sample sizes, but it is nonetheless a first step towards framing critical care services in this region.

The past decade of research in global public health has demonstrated the importance of addressing non-communicable diseases [24, 25] and surgery[26] to improve population health in LMICs. Public health interventions are most successful when they are multimodal, incorporating both disease-specific interventions (e.g. medications) and systems-level improvements (e.g. protocols and infrastructural improvements). For example, the rollout of medications for human immunodeficiency virus (HIV) in Rwanda between 1996 and 2013 was supplemented by changes in the healthcare system (namely, decentralization of testing centers and changes in user fee structures), which led to improved overall success in slowing the HIV epidemic[27]. Improving access to safe surgical care should take these lessons into account; quality critical care services are essential to this mission. Scoring models feasible for use in low-resourced settings will contribute to better understanding of critically ill patients in this region and form one piece of this effort to improve access for safe surgery.

Critical care services must be tailored to the local disease epidemiology, practice patterns, and resources. Though there is scarce ICU research within LMICs to date, available data demonstrate that ICU patients in LMICs are younger and more likely to be admitted to ICU following trauma or surgery compared to cohorts in high-income settings[13, 14, 28–31]. Our findings are consistent with these observations. However, the effects of endemic tropical diseases (e.g. HIV, malaria) on critical illness are not yet well-defined. These conditions, including malaria, typhoid [32], schistosomiasis[33], and HIV[34] are common in hospitalized patients in sub-Saharan Africa. These infections affect endothelial and immune function[35, 36], which may have implications for the development, and severity of sepsis or

other multiorgan dysfunction states. This may be a missing link in developing risk stratification models with better discrimination. We attempted to address this question in part by including sensitivity analyses on the HIV serostatus of our patients, but future research may aim to evaluate a broader spectrum of endemic tropical diseases.

There are several limitations to this study. First, the challenges of conducting prospective clinical research in a low-resource setting must be emphasized and underlies some of the missing values in our dataset. Our supplemental analyses were designed to remain consistent with other reports in the literature, but also to address this limitation. Second, we did not include laboratory or clinical values frequently measured in high-income settings. While we recognize that certain laboratories (e.g. white blood cell count, lactate) and clinical assessments such as the Systemic Inflammatory Response Syndrome (SIRS) have been used for critical illness risk stratification [37–40], these are not regularly available in the study ICU. Therefore, this was done as part of our commitment to working within the confines of the Malawi healthcare system, and to increase the generalizability of this work to other LMICs. Finally, since we developed the MIME and simple-MIME model from this dataset, the model AUC needs to be externally validated.

Conclusions

Risk stratification models are necessary to inform critical care systems worldwide. Models created within and for LMICs are critical to improving the quality of global surgery and treatments for non-communicable diseases. The MIME model provides moderate discrimination for ICU in-hospital mortality in Malawi. It may be considered as a measure of in-hospital mortality risk for patients with critical illness in low-resource settings and may facilitate comparisons with high-income regions. Further application will rely on external validation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix

Table A1.

Proportion of Missing Responses in Potential Variables for Malawi Intensive care Mortality risk Evaluation (MIME) Model

Potential Variables in New Model	No. of Missing (%)
Age	0 (0)
Male Sex	0 (0)
ICU Admitting Service	0 (0)
Post-Operative Status	1 (0.4)
Fever (>38.4C) During ICU Course	2 (0.8)
Measured at ICU Admission:	

Tachypnea (Heart Rate ≥100 bpm)	4 (1.5)
Systolic Blood Pressure	5 (1.9)
Altered Mental Status	6 (2.3)
Presence of Breathing Tube	0 (0)
Suspected Infection	1 (0.4)
Plasma Hemoglobin	30 (11.5)
HIV Status	48 (18.4)
Malaria Status	75 (28.7)

Table A2.

Summary of hospital mortality and univariable analysis of independent predictors of hospital mortality, with HIV status excluded when missing versus imputation as positive or negative when missing

Variables	Hospital Mortality						Hospital Mortality Yes vs No	P-value
	Total		No		Yes			
	N	Mean ± SD, Median (IQR) or No. of patients (%)	N	Mean ± SD, Median (IQR) or No. of patients (%)	N	Mean ± SD, Median (IQR) or No. of patients (%)	Crude OR (95% CI)	
HIV Status – exclude missing	213	32 (15)	86	8 (9.3)	127	24 (18.9)	2.28 (0.97, 5.33)	0.06
HIV Status – missing as negative	261	32 (12.3)	103	8 (7.8)	158	24 (15.2)	2.13 (0.92, 4.94)	0.08
HIV Status – missing as positive	261	80 (30.7)	103	25 (24.3)	158	55 (34.8)	1.67 (0.96, 2.91)	0.07

CI: confidence interval; HIV: human immunodeficiency virus; IQR: interquartile range; No.: number; SD: standard deviation; OR: odds ratio

Table A3.

Sensitivity Analysis Tables for HIV in Primary Analysis of Model Performance (excluding head injury patients)

	MIME Model				sMIME Model			
	N	Adj. OR (95% CI)	Covariates in model	Model AUC (95% CI)	N	Adj. OR (95% CI)	Covariates in model	Model AUC (95% CI)
HIV – missing as positive	252	1.72 (0.94, 3.18)	Age, sex, service, systolic blood pressure, fever, altered mental status	0.71 (0.64, 0.77)	254	1.94 (1.07, 3.54)	Age, fever, and altered mental status	0.68 (0.61, 0.74)
HIV – missing as negative	252	2.19 (0.89, 5.38)	Age, sex, service, systolic blood pressure, fever, altered mental status	0.71 (0.64, 0.77)	254	2.21 (0.91, 5.35)	Service, fever, and altered mental status	0.69 (0.63, 0.76)

HIV – exclude missing, force into model	208	2.39 (0.96, 5.96)	Age, sex, service, systolic blood pressure, fever, altered mental status	0.72 (0.65, 0.79)	209	2.67 (1.09, 6.52)	Sex, fever, and altered mental status	0.68 (0.61, 0.75)

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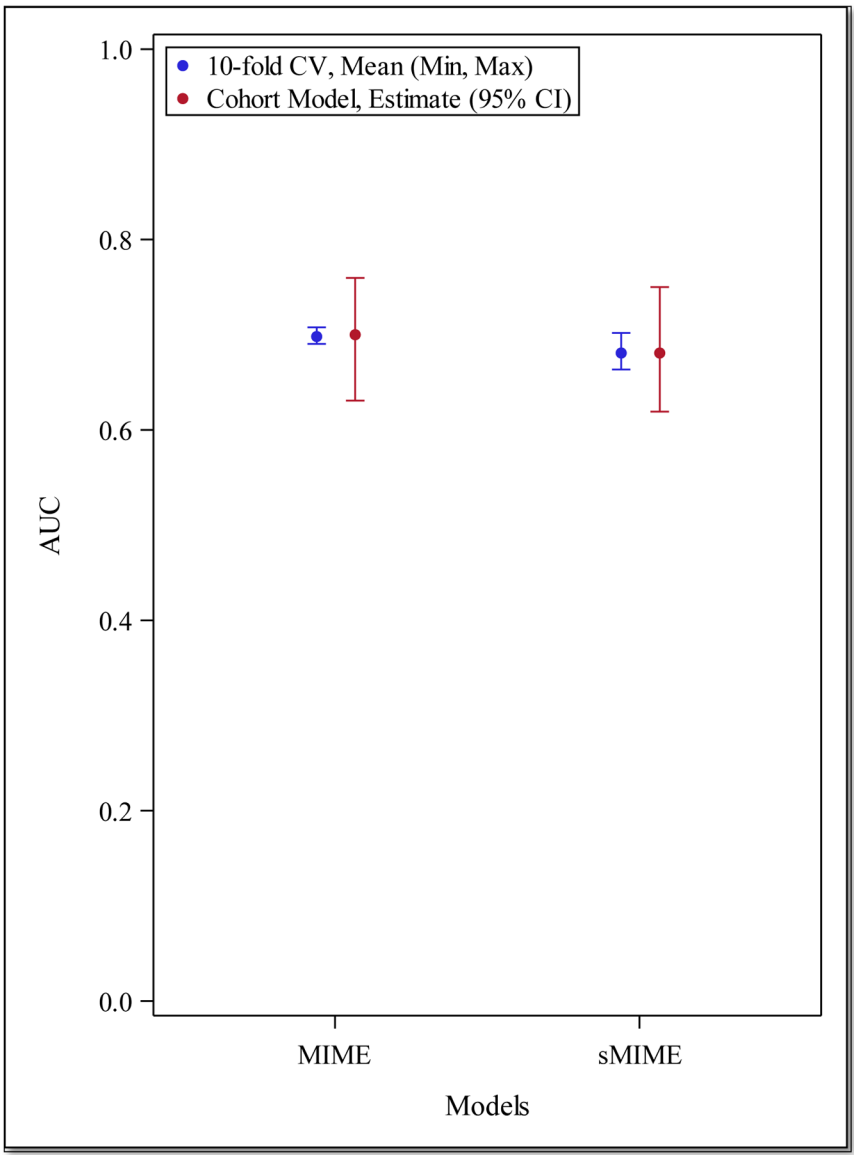

Figure 1.

Area Under the Receiver Operating Curve (AUC) with 95% Confidence Intervals (CI) for Malawi Intensive care Mortality risk Evaluation (MIME) Model and simplified MIME (sMIME), and AUC for 10-fold cross validation (CV) results

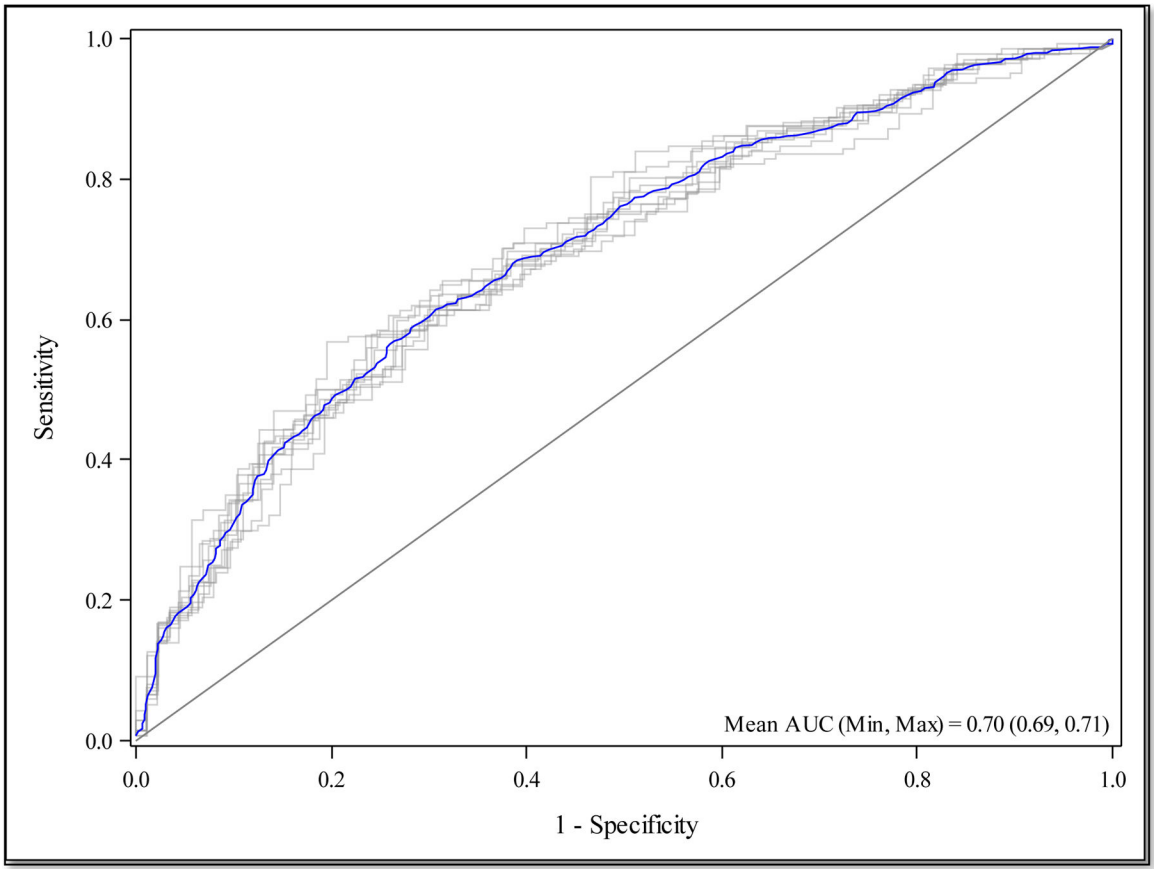

Figure 2.

10-fold cross-validated Receiver Operating Curve for Malawi Intensive care Mortality risk Evaluation (MIME) Model

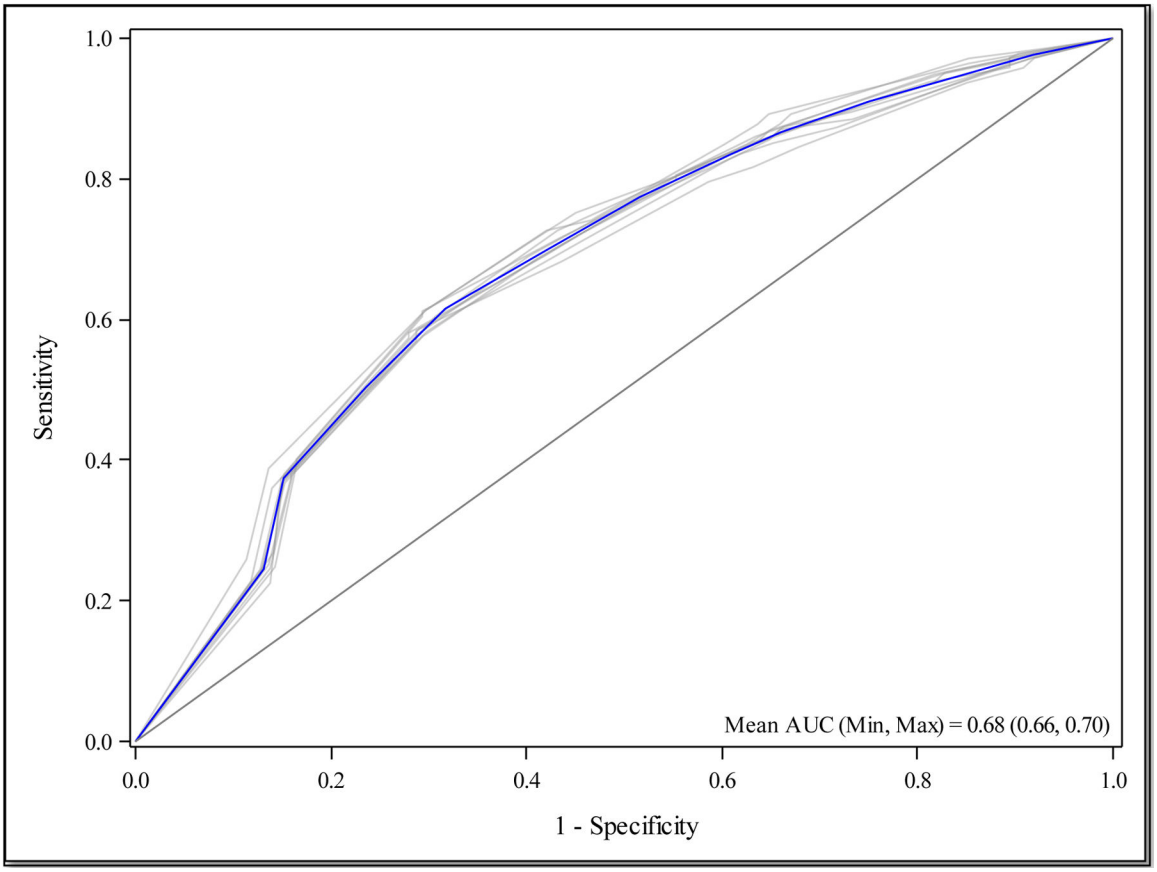

Figure 3.

10-fold cross-validated Receiver Operating Curve for simplified Malawi Intensive care Mortality risk Evaluation (sMIME) Model

Table 1

Univariable analysis of independent predictors for hospital mortality among ICU patients at a central referral hospital in Malawi.

Variables	Hospital Mortality						Crude OR (95% CI)	*P*-value
	Total		Survived		Died			
	N	Mean ± SD, Median (IQR) or No. of patients (%)	N	Mean ± SD, Median (IQR) or No. of patients (%)	N	Mean ± SD, Median (IQR) or No. of patients (%)		
Age, years	261	34.4 ± 15.1	103	32.6 ± 14.3	158	35.6 ± 15.6	1.01 (1.00, 1.03)	0.12
Male Sex	261	99 (37.9)	103	32 (31.1)	158	67 (42.4)	1.63 (0.97, 2.76)	0.07
ICU Admitting Service								0.004
General Surgery	261	112 (42.9)	103	33 (32)	158	79 (50)	Reference	
Obstetrics & Gynecology	261	78 (29.9)	103	42 (40.8)	158	36 (22.8)	0.36 (0.20, 0.65)	
Medicine	261	71 (27.2)	103	28 (27.2)	158	43 (27.2)	0.64 (0.34, 1.20)	
Admitted to ICU Postoperatively	260	192 (73.9)	103	76 (73.8)	157	116 (73.9)	1.01 (0.57, 1.77)	0.99
Fever (> 38.4C) during ICU Course	259	117 (45.2)	102	34 (33.3)	157	83 (52.9)	2.24 (1.34, 3.76)	0.002
Measured at ICU Admission:								
Tachycardia (HR ≥ 100 bpm)	257	198 (77)	102	79 (77.5)	155	119 (76.8)	0.96 (0.53, 1.75)	0.90
Systolic Blood Pressure, mmHg	256	115.4 ± 31	102	119.9 ± 30.9	154	112.4 ± 30.8	0.99 (0.98, 1.00)	0.06
Altered Mental Status	255	212 (83.1)	100	75 (75)	155	137 (88.4)	2.54 (1.30, 4.95)	0.006
Presence of Endotracheal Tube	261	151 (57.9)	103	58 (56.3)	158	93 (58.9)	1.11 (0.67, 1.83)	0.68
Provision of Tracheostomy	259	12 (4.6)	102	3 (2.9)	157	9 (5.7)	2.01 (0.53, 7.60)	0.31
Suspected Infection	260	155 (59.6)	103	59 (57.3)	157	96 (61.2)	1.17 (0.71, 1.95)	0.53
Hemoglobin, g/dL	231	9.7 (7.3, 11.5)	95	9.6 (7, 11.6)	136	10 (7.5, 11.4)	1.04 (0.95, 1.13)	0.39
HIV Status	213	32 (15)	86	8 (9.3)	127	24 (18.9)	2.28 (0.97, 5.33)	0.06
Malaria Status	186	21 (11.3)	74	6 (8.1)	112	15 (13.4)	1.75 (0.65, 4.75)	0.27

HIV: Human immunodeficiency virus; HR: Heart Rate; ICU: Intensive Care Unit; IQR: interquartile range; No., N: Number; OR: odds ratio; SD: standard deviation.

Table 2

Multivariable analysis of hospital mortality, for Malawi Intensive care Mortality risk Evaluation (MIME) Model and simplified MIME.

Models	Hospital Mortality Yes vs No	*P*-value
MIME (N = 252)	Adjusted OR (95% CI)	
Age	1.01 (0.99, 1.04)	0.21
Male Sex	1.14 (0.57, 2.27)	0.71
ICU Admitting Service		0.20
General Surgery	Reference	
Obstetrics & Gynecology	0.55 (0.26, 1.19)	
Medicine	1.01 (0.50, 2.08)	
Fever (> 38.4C) During ICU Course	2.27 (1.30, 3.96)	0.004
Systolic Blood Pressure at ICU Admission	0.99 (0.98, 1.00)	0.11
Altered Mental Status at ICU Admission	2.13 (1.03, 4.38)	0.04
sMIME (N = 254)	Adjusted OR (95% CI)	
ICU Admitting Service		0.01
General Surgery	Reference	
Obstetrics & Gynecology	0.39 (0.21, 0.73)	
Medicine	0.76 (0.39, 1.47)	
Fever During ICU Course	2.08 (1.21, 3.58)	0.008
Altered Mental Status at ICU Admission	2.07 (1.02, 4.20)	0.04

HIV: Human immunodeficiency virus; HR: Heart Rate; ICU: Intensive Care Unit; IQR: interquartile range; No.: Number; OR: odds ratio; SD: standard deviation.

Table 3

Model discrimination, fit, and internal validation for final scoring methods.

	MIME	sMIME
Model Discrimination and Fit		
AUC (0–1, higher indicates better prediction)	0.70 (0.63, 0.76)	0.68 (0.62, 0.75)
AIC (lower indicates better model fit)	325.59	325.54
Hosmer-Lemeshow chi-square statistic	4.22	5.89
Hosmer-Lemeshow p-value (lower indicates more evidence of a lack in model fit)	0.84	0.44
R^2 (0–1, higher indicates better prediction)	0.14	0.12
Performance on 10-fold cross-validated testing cohort		
Accuracy, %, Mean (SD)	62.8 (7.9)	66.3 (8.7)
Sensitivity, %, Mean (SD)	83.9 (10.6)	84.0 (10.1)
Specificity, %, Mean (SD)	31.8 (12.7)	39.7 (12.8)

AIC: Akaike information criterion; AUC: Area Under the Receiver Operating Curve; SD: standard deviation.