Development and internal validation of the HIV In-hospital Mortality Prediction (HIV-IMP) risk score

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Abstract

Background: Despite advances in availability and access to antiretroviral therapy (ART), HIV still ranks as a major cause of global mortality. Hence, the aim of this study was to develop and internally validate a risk score capable of accurately predicting in-hospital mortality in HIV-positive patients requiring hospital admission.

Methods: Consecutive HIV-positive patients presenting to the Charlotte Maxeke Johannesburg Academic Hospital adult emergency department between 7 July 2017 and 18 October 2018 were prospectively enrolled. Multivariate logistic regression was used to determine parameters for inclusion in the final risk score. Discrimination and calibration were assessed by means of the area under the receiver operating curve (AUROC) and the Hosmer–Lemeshow goodness-of-fit test, respectively. Internal validation was conducted using the regular bootstrap technique.

Results: The overall in-hospital mortality rate was 13.6% (n = 166). Eight predictors were included in the final risk score: ART non-adherence or not yet on ART, Glasgow Coma Scale < 15, respiratory rate > 20 breaths/min, oxygen saturation < 90%, white cell count $< 4 \times 10^9$/L, creatinine > 120 µmol/L, lactate > 2 mmol/L and albumin < 35 g/L. After internal validation, the risk score maintained good discrimination [AUROC 0.83, 95% confidence interval (CI): 0.78–0.88] and calibration (Hosmer–Lemeshow $\chi^2 = 2.26$, $p = 0.895$).

Conclusion: The HIV In-hospital Mortality Prediction (HIV-IMP) risk score has overall good discrimination and calibration and is relatively easy to use. Further studies should be aimed at externally validating the score in varying clinical settings.

Keywords : AUROC, calibration, discrimination, HIV, in-hospital mortality, internal validation, outcome prediction score

INTRODUCTION

The widespread availability of safer regimens of antiretroviral therapy (ART) over recent years has resulted in a substantial reduction in HIV-related morbidity and mortality [1]. Despite this, the global burden of HIV remains high, with HIV currently ranking as the third highest cause of global mortality after cardiovascular disease and cancer [2]. In 2019, there were approximately 1.7 million new cases of HIV with 690 000 HIV-related deaths [3].

Even in regions with high rates of ART coverage, HIV-related hospital admissions and deaths remain disproportionately high [4]. In addition, the cost of hospitalization due to an acute HIV-related illness is a major contributor to the overall financial burden of the disease [5, 6]. Hence, identifying factors that are associated with unfavourable outcomes in HIV-positive patients requiring hospitalization may be useful in guiding clinical decision-making, directing the allocation of scarce resources and influencing patient disposition.

Outcome prediction scores or models are clinical tools that are designed to assist healthcare professionals with reasonably predicting patient outcomes [7]. Many such models have previously been developed and validated in various disciplines of clinical medicine [8-10]. Although previous prediction tools have been developed for use in people living with HIV (PLWH), these predominantly focused on predicting the virological response to ART and other specifics relating to HIV presentation [11-13]. However, there are currently no models that are able to predict mortality in HIV-positive patients requiring hospital admission. Hence, the aim of this study was to develop and internally validate a risk score that will be capable of accurately predicting in-hospital mortality in HIV-positive patients requiring hospital admission.

METHODS

Study setting

The study was conducted at the adult medical emergency department (ED) unit of the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The CMJAH is a 1088-bed tertiary-level academic hospital that is affiliated to the University of the Witwatersrand. The adult medical ED unit manages all non-trauma patients who are ≥ 16 years old. Upon presentation to the triage section of the ED, patients are briefly assessed and thereafter categorized into one of four triage categories – 'emergent' (red), 'very urgent' (orange), 'urgent' (yellow) or 'routine' (green) – based on specific criteria as defined by the SA Triage Scale [14]. As CMJAH is a tertiary-level facility, in general patients who are categorized as red, orange or yellow are managed at the facility, while more stable patients who are categorized as green are referred to an alternate facility for further care. Additionally, clinically stable patients not residing within the drainage area of the facility are also referred to an alternate facility closer to the patient's residence.

HIV testing protocol at the study site

As per the facility protocol, excepting patients who are known to be HIV-positive (either self-reported or based on past laboratory records), all other patients attending the ED are

first counselled and thereafter encouraged to undergo in-unit rapid HIV testing to determine their HIV status. Whole blood samples of patients consenting to HIV testing are subjected to diagnostic testing with the Abon HIV 1/2/0 Tri-line Rapid test (Abon Biopharm, Hangzhou, RR China). Reactive samples are thereafter subjected to a second confirmatory rapid test (First Response HIV 1–2.0 card; PMC Medical India Pvt, Ltd, Daman, India). In those in whom the first test is positive, but the confirmatory test is negative, a sample of whole blood is collected and sent to the laboratory for HIV enzyme-linked immunosorbent assay testing.

Inclusion criteria, exclusion criteria and primary outcome measure

Adult patients ≥ 18 years who previously tested positive for HIV as well as those who were newly diagnosed with HIV after ED presentation were prospectively enrolled into the study between 7 July 2017 and 18 October 2018. This included HIV-positive patients who required admission as well as patients who were discharged from the ED but excluded patients who were referred to another facility from the triage area. In addition, HIV-negative patients, HIV-status-unknown patients not consenting to HIV testing as well as patients not consenting to study participation were excluded. The primary outcome measure of the study was in-hospital mortality, which we defined as death occurring at any time during hospital admission.

Data collection

Data collection commenced once ethics clearance (University of the Witwatersrand Human Research Ethics Committee- clearance certificate number M160512) and the relevant permissions were obtained. Prior to the commencement of data collection, informal training pertaining to the methods and principles of data collection from medical charts was undertaken by the primary investigator. After briefing all doctors employed at the ED about the study aim, objectives and design, doctors were requested to inform the primary investigator of any HIV-positive patients being managed in the ED. Written informed consent for study participation was obtained from potential participants by either the primary investigator or the doctor on shift. In the event that participants were unable to grant consent (e.g. decreased level of consciousness), consent was obtained from the next of kin/legal guardian and later re-obtained from the participant in the event that there was an improvement in mental capacity. The ED registers were also reviewed daily in an effort to identify potential participants who may have been missed by the ED doctors.

The four-question AIDS Clinical Trials Group Adherence Questionnaire (ACTG-AQ) was utilized to identify participants who were non-adherent to ART [15]. Those who responded ‘yes’ to any of the questions were regarded as being ART-non-adherent. The questionnaire was administered to all participants who had been prescribed ART at any time in the past.

Data were extracted from the patient's hospital file by the primary investigator and thereafter captured into an anonymized and standardized data collection form that was created in the RedCap system [16]. Additional information relevant to the study but not found in the patient's hospital records was directly obtained from the participant, the participant’s laboratory records, or the participant’s next of kin/legal guardian where

applicable. Only where the next of kin/legal guardian indicated that they were aware of the participant's HIV status were they questioned regarding relevant HIV history, such as treatment adherence. Data from hospital records were collected over the entire duration of hospital stay or until data collection was completed. Inter-rater reliability was assessed by an independent researcher experienced in the methods of data collection but blinded to the study's aim and objectives. To assess this, data extracted from a random sample of 43 medical charts were compared with data extracted by the primary investigator.

Data relevant to this study included demographic details (age, sex and marital status), whether participants were newly or previously diagnosed with HIV, ART non-adherence, whether ART was initiated prior to ED attendance, vital signs at ED arrival [Glasgow Coma Scale (GCS) score, respiratory rate, systolic blood pressure, oxygen saturation and heart rate] and laboratory findings at presentation [CD4 cell count, HIV viral load (VL), haemoglobin, white cell count, platelet count, urea, creatinine, albumin, lactate, C-reactive protein (CRP) and alanine transaminase]. The data were thereafter exported to Microsoft Excel (Microsoft 365, v.16.0.13029.20232) and subsequently to Stata v.16 (StataCorp Ltd, College Station, TX, USA) for statistical analysis. Although data pertaining to vital signs and laboratory parameters were collected as continuous variables, these were reported as categorical variables based on cut-offs that are commonly regarded as clinically significant (e.g. CD4 cell count < 100 cells/μL; albumin < 35 g/L etc.). Study reporting was in conformance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [17].

Risk score development

Selection of predictor variables

In developing the HIV In-hospital Mortality Prediction (HIV-IMP) score, we initially determined which factors were associated with a higher likelihood of in-hospital mortality. Hence, we first subjected relevant data to univariate and thereafter multivariate logistic regression analysis. In the univariate analysis, for each variable assessed by means of binary logistic regression, all available case information was utilized. Variables from the univariate analysis with a p-value < 0.1 were thereafter subjected to multivariate analysis. Patients with missing data pertaining to variables that were included in the multivariate analysis were dropped from the model. Thereafter, through the process of stepwise backward regression, non-significant variables were dropped until the final risk score was achieved. Variables from the multivariate logistic regression analysis with a two-sided p-value < 0.05 (independent predictors of in-hospital mortality) were selected for inclusion in the predictive risk score. Crude odds ratio (OR) with 95% confidence interval (CI) were reported for parameters included in the univariate and multivariate analyses.

Each of the independent predictors were thereafter assessed to create a scoring system. The weighting score allocated to each of the independent variables was based on the regression coefficient (β) for that variable, where variables with $\beta < 1$ were assigned a score of 1 point and variables with β in the range 1–2 were assigned a score of 2 points. Weighting scores were assigned to each study participant for each of the included variables. For variables that were outside the defined cut-off range (e.g. oxygen saturation ≥ 90%, albumin

≥ 35 g/L, etc.), a weighting score of zero was allocated. The final risk score for each participant was calculated by summing up the weighting scores achieved for each of the included variables. Hence, the minimum achievable risk score was 0 and the maximum was 10 points.

Evaluating the performance of the developed risk score

Various approaches were implemented to evaluate the performance of the risk score. First, to determine whether higher risk scores were associated with higher rates of in-hospital mortality, we calculated and tabulated the actual rate of in-hospital mortality for the entire range of risk scores (0–10) achieved by the study population on whom the risk score was developed. Second, we plotted the relationship between the approximate predicted probability of in-hospital mortality and the risk score. Thereafter, we evaluated discrimination and calibration of the risk score on the entire study sample prior to subjecting it to internal validation.

Discrimination refers to the ability of a risk score or model to distinguish between patients with the outcome (in-hospital mortality) from those without the outcome and can be quantified with measures such as sensitivity and specificity. We assessed discrimination using the area under the receiver operating characteristic curve (AUROC) (also known as the *C* statistic), which plots the sensitivity (true positive rate) against 1 – specificity (false-positive rate) for consecutive cut-offs for the probability of an outcome. While an AUROC of 0.5 implies that the model is worthless (true-positive rate = false-positive rate), an AUROC > 0.8 implies good accuracy and an AUROC > 0.9 implies very good accuracy of a model [18, 19].

Calibration refers to the agreement between observed outcomes and expected outcomes (predictions) [20]. For example, if we predict a 20% risk of in-hospital mortality in HIV-positive patients admitted from the ED, the observed frequency of in-hospital mortality should be approximately 20 out of 100 patients. We assessed calibration using the Hosmer–Lemeshow goodness-of-fit test for logistic regression. The frequency of observed and expected outcomes were divided into 10 deciles of predictive index, with each corresponding to a defined probability of in-hospital mortality. Therefore, in the context of this study, the test was used to determine whether differences between observed and expected probabilities of in-hospital mortality were non-significant, thereby indicating acceptable model fit. Hence, a lower χ^2 statistic with a higher (non-significant) *p*-value is indicative of a better-fitting model and good calibration [21]. A limitation of the Hosmer–Lemeshow test is that it does not give an indication of the magnitude of the difference or whether there is variation among patients with high versus low risk of the outcome [20].

Internal validation refers to the performance of the developed risk score in patients from a similar population to that from which the sample originated. The regular bootstrap technique with correction for optimism in risk score performance (optimism-corrected bootstrapping) was used to internally validate the risk score that was developed. Bootstrapping is the process of random sampling with replacement from an original dataset for use in obtaining statistical inference [22-24]. Optimism is a form of bias that may occur when fixing a model to the same data that were used for testing. The difference between

the apparent performance, which estimates the performance in the bootstrap sample, and the test performance, which estimates the performance in the original sample, is an estimate of the optimism in the apparent performance [22]. In this study, the predictive risk score, which was developed from the entire original sample, was applied to each of 200 bootstrap samples that were randomly drawn with replacement from the original study sample with each bootstrap sample comprising approximately 70% (≈ 670) of the original study sample. Discrimination (AUROC) and calibration (Hosmer–Lemeshow χ^2 statistic and *p*-value) were determined for each bootstrap sample, whereafter optimism and the optimism-corrected average AUROC and χ^2 statistic with *p*-value for the entire risk score were determined and reported.

RESULTS

Of the 29 416 patients that presented to the triage area of the adult medical ED over the period of data collection, 11 383 were triaged into the ED for further management while the remainder were referred to an appropriate facility, in accordance with the CMJAH ED triage protocol. A total of 1308 patients were HIV-positive, of whom 84 were excluded from the study as informed consent could not be obtained; hence, the final study sample comprised 1224 patients. The in-hospital mortality rate was 13.6% (*n* = 166). Clinical characteristics of study patients with univariate logistic regression analysis to determine factors that were associated with a higher likelihood of in-hospital are described in Table 1.

TABLE 1. Clinical characteristics of study patients with univariate logistic regression to determine factors associated with a higher likelihood of in-hospital mortality

	SURVIVAL TO DISCHARGE [*N* (%)]	**IN-HOSPITAL MORTALITY** [*N* (%)]	**OR (95% CI)**	***P*-VALUE**
AGE (YEARS) [MEDIAN (IQR)]	36 (31–44)	38 (30–45)	1.01 (0.99–1.02)	0.328
MALE SEX	462 (43.7)	89 (53.6)	1.49 (1.07–2.07)	**0.017**
MARRIED	240 (22.7)	47 (28.3)	1.35 (0.93–1.94)	0.112
NEWLY DIAGNOSED HIV	167 (15.8)	45 (27.1)	1.98 (1.36–2.90)	**<0.001**
ART NON-ADHERENCE OR NOT YET ON ART	592 (56.0)	116 (69.9)	1.83 (1.28–2.60)	**0.001**
RESPIRATORY RATE > 20 BREATHS/MIN	349 (36.2)	85 (55.2)	2.17 (1.54–3.06)	**<0.001**
OXYGEN SATURATION < 90%	157 (16.3)	39 (25.3)	1.74 (1.16–2.6)	**0.007**
SYSTOLIC BLOOD PRESSURE < 90 MMHG	91 (9.4)	25 (16.2)	1.86 (1.15–3.00)	**0.011**
HEART RATE > 110 BEATS/MIN	473 (49.1)	92 (59.7)	1.54 (1.09–2.17)	**0.015**
GLASGOW COMA SCALE < 15	157 (18.8)	64 (68.8)	3.66 (2.55–5.26)	**<0.001**
CD4 < 100 CELLS/ML	433 (44.8)	94 (67.6)	2.58 (1.77–3.76)	**<0.001**

HIV VIRAL LOAD > 1000 COPIES/ML	537 (58.1)	82 (65.6)	3.16 (2.15–4.65)	**<0.001**
HEMOGLOBIN < 11 G/DL	484 (49.7)	95 (61.7)	1.63 (1.15–2.31)	**0.006**
WHITE CELL COUNT < 4 × 10^9/L	137 (14.1)	33 (21.6)	1.68 (1.10–2.57)	**0.017**
PLATELET COUNT < 150 × 10^9/L	165 (17.0)	58 (38.4)	3.04 (2.11–4.40)	**<0.001**
UREA > 10 MMOL/L	205 (22.2)	72 (49.3)	3.41 (2.38–4.88)	**<0.001**
CREATININE > 120 MMOL/L	225 (24.8)	73 (50.0)	3.06 (2.14–4.37)	**<0.001**
C-REACTIVE PROTEIN > 100 MG/L	417 (45.6)	99 (68.3)	3.30 (1.72–6.32)	**<0.001**
LACTATE > 2 MMOL/L	349 (36.4)	121 (75.6)	5.41 (3.69–7.95)	**<0.001**
ALBUMIN < 35 G/L	518 (57.2)	116 (85.2)	4.34 (2.66–7.11)	**<0.001**
ALANINE TRANSAMINASE > 100 MMOL/L	80 (9.0)	29 (20.9)	2.67 (1.67–4.27)	**<0.001**

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; OR, odds ratio.

The bold signify that the respective *p*-values are statistically significant.

HIV-IMP risk score development

Nineteen of the 21 variables that were analysed by means of univariate regression analysis were associated with a significantly higher likelihood of in-hospital mortality (Table 1). Lactate > 2 mmol/L (OR = 5.41, 95% CI: 3.69–7.95, $p < 0.001$), albumin < 35 g/L (OR = 4.34, 95% CI: 2.66–7.11, $p < 0.001$) and GCS < 15 (OR = 3.66, 95% CI: 2.55–5.26, $p < 0.001$) displayed the highest ORs.

After adjusting for age and HIV VL, variables from the univariate regression analysis with a *p*-value < 0.1 were thereafter subjected to multivariate regression analysis. The final risk score comprised 958 (78.3%) study participants with complete data for the included variables. Table 2 describes the eight variables that were associated with a significantly higher likelihood of in-hospital mortality after multivariate regression analysis and were hence selected for inclusion in the predictive risk score along with their respective regression coefficient (β), OR, 95% CI, *p*-value and allocated weighting toward the risk score. The process as to how weighting scores for each variable and the final risk score was determined is described in the 'Methods' section.

TABLE 2. Variables associated with a significantly higher likelihood of in-hospital mortality on multivariate analysis, along with the associated regression coefficient (*β*), odds ratio (OR), 95% confidence interval (CI), *p*-value, and allocated weighting score

PARAMETER	*B*	OR (95% CI)	*P*-VALUE	WEIGHTING SCORE
ART NON-ADHERENT OR NOT YET ON ART	0.75	2.12 (1.30–3.43)	0.002	1
GLASGOW COMA SCALE < 15	1.17	3.23 (1.99–5.24)	<0.001	2
RESPIRATORY RATE > 20 BREATHS/MIN	0.46	1.59 (1.01–2.51)	0.045	1
OXYGEN SATURATION < 90%	0.78	2.19 (1.28–3.74)	0.004	1
WHITE CELL COUNT < 4 × 10^9/L	0.65	1.92 (1.14–3.24)	0.014	1
CREATININE > 120 MMOL/L	0.70	2.02 (1.29–3.15)	0.002	1
LACTATE > 2 MMOL/L	1.62	5.05 (3.15–8.11)	<0.001	2
ALBUMIN < 35 G/L	0.86	2.37 (1.36–4.14)	0.002	1

Abbreviation: ART, antiretroviral therapy.

Actual rates of in-hospital mortality

Actual rates of in-hospital mortality for the entire range of risk scores achieved by the cohort of 958 study participants on whom the predictive risk score was developed are given in Table 3. It is notable that every unit increase in risk score was associated with a higher rate of in-hospital mortality.

TABLE 3. Actual rates of in-hospital mortality for the entire range of risk scores achieved by the cohort of study participants on whom the risk score was derived

TOTAL SCORE	SURVIVAL TO DISCHARGE (*N* = 806)	IN-HOSPITAL MORTALITY (*N* = 152)	IN-HOSPITAL MORTALITY RATE (%)
0	80	0	0
1	111	2	1.8
2	142	8	5.4
3	154	9	5.5
4	139	27	16.3
5	106	36	25.3
6	48	30	38.4
7	16	18	52.9
8	9	17	65.4
9	1	4	80.0
10	0	1	100

Probability of in-hospital mortality

The relationship between the risk score achieved among study participants and their approximate predicted probability of in-hospital mortality is plotted in Figure 1. Notably, the distribution points suggests a positive relationship between the two: that is, the higher the risk score, the higher the predicted probability of in-hospital mortality. For example, if a patient has a risk score of 7, the probability (95% CI) of in-hospital mortality is 46.67% (42.82–50.51%) and if a patient has a risk score of 8, the probability (95% CI) of in-hospital mortality is 64.12% (62.36–65.89%).

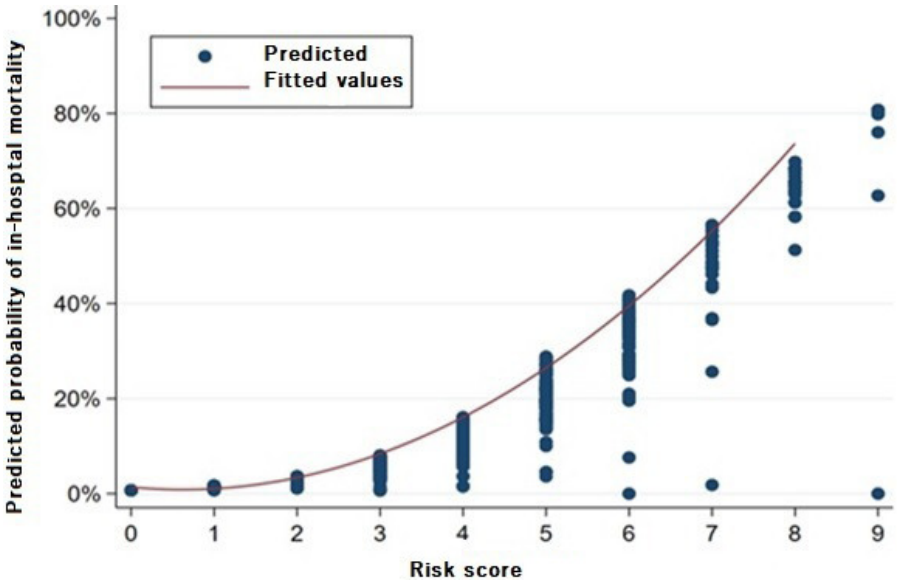

FIGURE 1. Relationship between the HIV In-hospital Mortality Prediction (HIV-IMP) risk score and the predicted probability of in-hospital mortality. Risk score and associated probability of in-hospital mortality (95% confidence interval): risk score = 0: 0.72 (0.72–0.74); risk score = 1: 1.45 (1.41–1.49); risk score = 2: 2.91 (2.81–3.01); risk score = 3: 5.70 (5.49–5.92); risk score = 4: 11.67 (11.26–12.08); risk score = 5: 20.41 (19.63–21.18); risk score = 6: 32.79 (31.16–34.42); risk score = 7: 46.67 (42.82–50.51); risk score = 8: 64.12 (62.36–65.89); risk score ≥ 9: 67.33 (42.00–96.68)

Assessing discrimination and calibration of the HIV-IMP risk score

After applying the predictive risk score to the study cohort, the estimated AUROC (Figure 2) was 0.83 (95% CI 0.78–0.86), indicating good discriminative ability of the risk score.

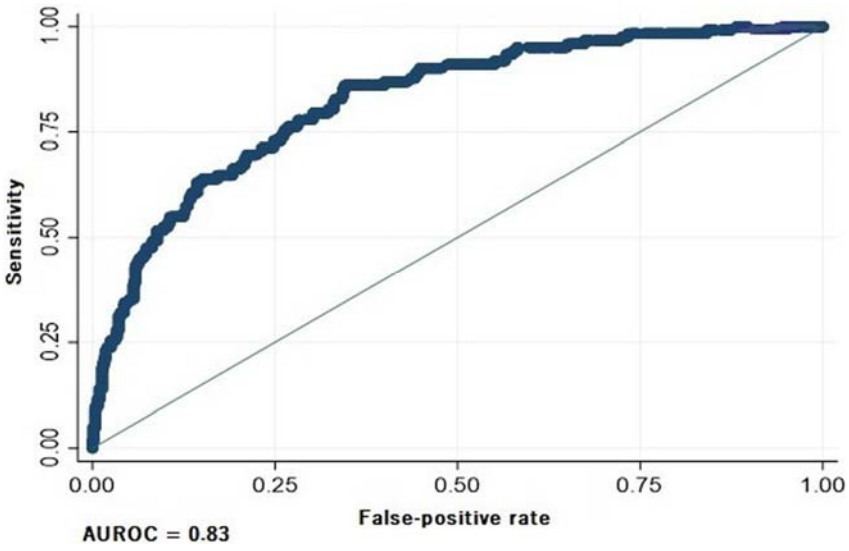

FIGURE 2. Receiver operating characteristic curve of the HIV In-hospital Mortality Prediction (HIV-IMP) risk score viewed at wm]

The Hosmer–Lemeshow goodness-of-fit test describing the probability of in-hospital mortality in each decile of predictive index and their associated frequency of outcomes are given in Table 4. Notably, the expected and observed numbers of participants with in-hospital mortality in each decile of the predictive index were similar, with only a slight over- or under-fit in deciles 1–9 and a perfect fit of the risk score in decile 10. The χ^2 estimate was 4.05 (p = 0.853) indicating acceptable calibration of the HIV-IMP risk score.

TABLE 4. Hosmer–Lemeshow goodness-of-fit test describing the probability of in-hospital mortality for each decile of predictive index and their associated frequency of outcomes

DECILE OF PREDICTIVE INDEX	PROBABILITY OF IN-HOSPITAL MORTALITY	OBSERVED IN-HOSPITAL MORTALITY (*N*)	EXPECTED IN-HOSPITAL MORTALITY (*N*)	OBSERVED SURVIVAL (*N*)	EXPECTED SURVIVAL (*N*)	TOTAL OBSERVED (*N*)
1	0.012	0	0.7	96	95.3	96
2	0.017	2	1.4	94	94.6	96
3	0.032	3	2.2	93	93.8	96
4	0.047	5	3.5	91	92.5	96
5	0.068	4	5.4	91	89.6	95
6	0.105	7	8.0	89	88.0	96
7	0.150	14	12.0	82	84.0	96
8	0.215	13	16.7	83	79.3	96
9	0.348	27	25.1	69	70.9	96
10	0.807	47	47.0	48	48.0	95

Note

χ^2 = 4.05, p = 0.853.

Internal validation of the HIV-IMP risk score

Internal validation of the developed risk score was assessed by estimating the AUROC for each of 200 bootstrap samples [each sample comprised approximately 70% (≈ 670) of the study sample]. The pooled average optimism for the AUROC was 0.006 (95% CI: −0.04–0.05) while the optimism-corrected average AUROC was 0.832, with a tight distribution between samples (95% CI: 0.78–0.88), indicating that the discriminative ability of the risk score did not change appreciably between bootstrap samples. After applying the Hosmer–Lemeshow goodness-of-fit test to each of the 200 bootstrap samples, the average estimated χ^2 was 2.26 (p = 0.895), indicating good overall calibration of the risk score.

DISCUSSION

Despite 30 years having passed since the HIV epidemic began, and with HIV still ranking as one of the leading causes of global mortality [2], the HIV-IMP score is the first outcome prediction score to have been developed and internally validated for use in HIV-positive patients requiring hospital admission. Findings relating to other aspects of this study, including a discussion pertaining to the predictors of in-hospital mortality reported in this article, have been published elsewhere [25-28].

The risk score is relatively simple to use and comprises only eight predictor variables, four of which are non-laboratory-based (ART non-adherent or not yet on ART, GCS < 15, respiratory

rate > 20 breaths/min and oxygen saturation < 90%) that can easily be acquired within minutes of the patient's arrival to the ED, while the remaining four variables can be considered routine laboratory investigations (white cell count < 4×10^9/L, creatinine > 120 µmol/L, lactate > 2 mmol/L and albumin < 35 g/L) where results may be available within a few minutes of drawing the blood sample in facilities that have access to in-unit point-of-care (POC) testing. It is hoped that the HIV-IMP risk score will positively contribute to the timely and appropriate management of acutely ill HIV-positive patients requiring hospital admission.

With regard to evaluation of the performance of the risk score, various methods have been described to estimate internal validity of predictive logistic regression models. In a study that compared three different methods of internal validation, the authors concluded that performance of both the split-sample and cross-validation methods were suboptimal compared with the bootstrap method [22]. Hence, in this study we utilized the regular bootstrap method to internally validate our risk score. After subjecting the risk score to bootstrapping, it retained good discrimination (AUROC = 0.83, 95% CI: 0.78–0.88) and calibration (Hosmer–Lemeshow $\chi^2 = 2.26$, $p = 0.895$). However, prior to implementation in clinical practice, the risk score must be subjected to external validation in other population groups and varying clinical settings.

Currently existing predictive models pertaining to mortality outcomes in acutely ill, hospitalized patients were predominantly conducted in the acute care setting. The most well known of these is the Acute Physiology and Chronic Health Evaluation II (APACHE II) score that was developed by Knaus *et al*. [8] in 1985 and aimed to predict in-hospital mortality in intensive care unit (ICU) patients. The model includes 14 variables that relate to age, underlying organ dysfunction, temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, pH, sodium, potassium, creatinine, haematocrit, white cell count and GCS [8]. In 1996, Vincent *et al*. [9] developed the Sepsis-related Organ Failure Assessment (SOFA) score that also aimed at predicting in-hospital mortality in ICU patients. The model included six variables relating to oxygenation, GCS, blood pressure, bilirubin, platelet count and creatinine. The quick SOFA (qSOFA) score was developed in 2016 by Seymour *et al*. [29] and aimed to predict in-hospital mortality as well as ICU length of stay in patients presenting to the ED with sepsis. The model comprises three variables that include blood pressure, respiratory rate and GCS. Comparatively, the HIV-IMP risk score was developed in HIV-positive patients presenting to the ED with an acute illness with the aim of predicting in-hospital mortality and comprises eight variables, five of which are also included in the models described earlier and which predominantly relate to the acuity of presenting illness (GCS, respiratory rate, oxygen saturation, white cell count and creatinine). Of the three remaining variables, lactate also relates to the acuity of presenting illness while ART non-adherence or not yet on ART and albumin predominantly relate to HIV disease control and chronicity. In a study that investigated outcomes in HIV-positive patients admitted to a tertiary-level hospital ICU, the APACHE II score was shown to overestimate mortality by approximately two-fold [30].

Similar to this study, previous studies conducted in the HIV population also reported poor ART treatment adherence [31], leukopenia [32], renal dysfunction [33] and hypoalbuminaemia [34, 35] as independent predictors of mortality. These and other studies

also reported other variables such as male sex [36, 37], age [36], low CD4 cell count [31, 36, 37], anaemia [31, 32], thrombocytopenia [32] and low CRP [38] as independent predictors of mortality. In this study, these additional factors were significantly associated with in-hospital mortality on univariate regression analysis but not multivariate regression analysis. Furthermore, most of these studies were conducted at outpatient settings and did not specifically investigate in-hospital mortality. With regard to other independent predictors of in-hospital mortality that we had identified, tachypnoea, [39] hypoxia [40] and hyperlactataemia [41] have been reported as predictors of mortality in the general population but not specifically in the HIV-positive population.

A limitation of this study is that it was a single-centre study and as patient outcomes may have been influenced by resource availability, clinical management protocols and clinician expertise at the study site, our findings may differ from that of other facilities. Hence, there is a need to externally validate the risk score prior to clinical use. Another limitation is that we did not account for terminally ill patients who may have been discharged for home-based palliative care, some of whom may have died at home shortly thereafter. Also, when determining the cut-offs for variables such as respiratory rate > 20 breaths/min and GCS < 15, we did not account for younger patients who may present with relatively normal vital signs prior to sudden decompensation. A possible limitation to the implementation of the developed risk score in low- and middle-income settings is that some of the laboratory-based variables may not be readily available.

CONCLUSIONS

The HIV-IMP risk score for predicting in-hospital mortality in HIV-positive patients requiring hospital admission has overall good discrimination and calibration and is relatively easy to use. The risk score may be useful in guiding clinical decision-making, directing the allocation of scarce resources and influencing patient disposition. Further studies should be aimed at externally validating the risk score in varying clinical settings.

ACKNOWLEDGEMENTS

The authors would like to thank the staff at the Charlotte Maxeke Johannesburg Academic Hospital for their assistance with identifying potential study participants.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

AEL was the primary author and was responsible for the study design, data collection, data analysis, interpretation of results, manuscript write-up, revision and approval of the final manuscript. FP, WDFV, FM, MM and GAR assisted with the study design, interpretation of the results, revision of the manuscript and approval of the final manuscript. OAA assisted with statistical analysis, interpretation of the results and approval of the final manuscript.

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