Predictors of in-hospital mortality among HIV-positive patients presenting with an acute illness to the emergency department

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ORIGINAL RESEARCH

Predictors of in-hospital mortality among HIV-positive patients presenting with an acute illness to the emergency department

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Objectives

Despite better access to antiretroviral therapy (ART) over recent years, HIV remains a major global cause of mortality. The present study aimed to identify predictors of in-hospital mortality among HIV-positive patients presenting to an emergency department (ED).

Methods

In this cross-sectional study, HIV-positive patients presenting to the Charlotte Maxeke Johannesburg Academic Hospital adult ED between 07 July 2017 and 18 October 2018 were prospectively enrolled. Data were compared between participants who survived to hospital discharge and those who died. The data were further subjected to univariate and multivariate logistic regression analyses to determine variables that were associated with in-hospital mortality.

Results

Of a total of 1224 participants, the in-hospital mortality was 13.6% (n = 166). On multivariate analysis, respiratory rate > 20 breaths/min [odds ratio (OR) = 1.90, P = 0.012], creatinine > 120 μmol/L (OR = 1.97, P = 0.006), oxygen saturation < 90% (OR = 2.09, P = 0.011), white cell count < 4.0 × 10^9/L (OR = 2.09, P = 0.008), ART non-adherence or not yet on ART (OR = 2.39, P = 0.012), Glasgow Coma Scale < 15 (OR = 2.53, P = 0.000), albumin < 35 g/L (OR = 2.61, P = 0.002), lactate > 2 mmol/L (OR = 4.83, P = 0.000) and cryptococcal meningitis (OR = 6.78, P = 0.000) were significantly associated with in-hospital mortality.

Conclusions

Routine clinical and laboratory parameters are useful predictors of in-hospital mortality in HIV-positive patients presenting to the ED with an acute illness. These parameters may be of value in guiding clinical decision-making, directing the appropriate use of resources and influencing patient disposition, and may also be useful in developing an outcome prediction tool.

Keywords: acute illness, antiretroviral therapy, CD_4 cell count, emergency department, HIV, HIV survival, HIV viral load, in-hospital mortality, opportunistic infections

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Introduction

Globally, there are approximately 38 million people living with HIV (PLWH) [1]. From 2003 to 2009, HIV was the leading cause of death worldwide, with the annual mortality peaking at just under 1.4 million deaths in 2007 [2]. Better availability and improved access to antiretroviral therapy (ART) over the past 15 years has resulted in a significant reduction in HIV mortality (690 000 deaths in 2019), such that HIV now ranks as the third highest cause of global deaths after cardiovascular disease and cancer [1,2].

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South Africa has approximately one-fifth of the world's HIV cases, with an overall HIV prevalence of 20.4% [3]. In 2017, HIV was reported to be the fifth highest cause of mortality in South Africa [4]. South Africa currently boasts the world's largest HIV programme, the success of which is evident from an increase in life expectancy of 56 years in 2010 to 63 years in 2018 [5]. Although there has been a 47% reduction in new HIV infections and a 40% reduction in HIV-related deaths from 2010 to 2019, the burden of HIV is still substantial, with *c.*200 000 new HIV infections and 72 000 HIV-related deaths reported in South Africa in 2019 [1]. The high mortality associated with HIV has had far-reaching socioeconomic consequences, including a reduction in labour supply, agricultural productivity, human capital and national development as well as an upsurge in widow-and-orphan-headed households [6,7].

Previous studies conducted in both outpatient and inpatient non-emergency department (ED) settings have indicated that various clinical and laboratory parameters such as the presenting diagnosis, requiring admission to the intensive care unit (ICU), a low CD_4 cell count, an elevated HIV viral load (VL), anaemia, renal dysfunction, albuminaemia, hyperlactataemia etc. have been associated with a higher likelihood of mortality in HIV-positive patients [8–13]. However, there is a lack of data emanating from the ED setting. In addition to guiding timely management such as the early initiation of empirical antimicrobial therapy, judicious haemodynamic resuscitation, fast-tracking of special investigations and early ICU admission, the prompt identification of factors associated with poor outcomes at ED presentation may also assist clinicians with the appropriate channelling of resources, particularly in environments where these are limited. Hence, the aim of this study was to determine variables that may be associated with a higher likelihood of in-hospital mortality in HIV-positive patients presenting to the ED with an acute illness. Identifying such variables may also potentially be useful for developing a predictive tool to identify HIV-positive patients with higher risk of mortality.

Methods

This was a cross-sectional study that was conducted at the adult medical ED unit of the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The CMJAH is a 1088-bed tertiary-level academic hospital affiliated to the University of the Witwatersrand. The adult medical ED unit manages all non-trauma patients who are ≥ 16 years of age. On arrival to the ED triage area, patients are briefly assessed and categorized as 'emergent' (red), 'very urgent' (orange), 'urgent' (yellow) or 'routine' (green), based on specific criteria as defined by the South African Triage Scale [14]. As the CMJAH is a tertiary-level facility, in general patients who are categorized as red, orange or yellow are managed at the facility, while stable patients who are categorized as green are referred to an alternate facility. 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.

As per the facility protocol, besides patients who are already HIV-positive (either self-reported or confirmed on laboratory records of patients who previously attended the facility), all other patients attending the ED are offered HIV-rapid diagnostic testing to determine their HIV status. Whole-blood samples of patients consenting to HIV testing are tested with the Abon HIV 1/2/0 Tri-line Rapid test (Abon Biopharm, Hangzhou, China), with reactive samples 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 enzyme-linked immunosorbent assay (ELISA) HIV testing.

Data collection commenced once ethics clearance (University of the Witwatersrand Human Research Ethics Committee, clearance certificate number M160512) and relevant permissions were obtained. Adult patients ≥ 18 years who previously tested positive for HIV as well as those newly diagnosed with HIV after undergoing testing in the ED 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 directly discharged from the ED but excluded patients who were referred to another facility from the triage section. In addition, HIV-negative patients, HIV-status-unknown patients who did not consent to HIV testing and patients not consenting to study participation were excluded.

Prior to the commencement of data collection, informal training pertaining to the methodology and principles of data collection from medical charts was undertaken by the primary investigator. After briefing all doctors employed in the ED regarding the study aim, objectives and design, they were requested to inform the primary investigator of all 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), it was obtained from

the next of kin/legal guardian and later re-obtained from the participant in the event that their mental capacity had improved. Emergency department 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 determine non-adherence to ART [15]. Patients 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 electronically entered 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 obtained directly 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 daily over the entire duration of hospital stay or until data collection was completed. Interrater reliability was assessed by an independent researcher experienced in the methods of data collection and blinded to the study aims and objectives. 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, HIV status, prior ART history including non-adherence, vital signs at presentation, results of relevant laboratory tests that were performed during the current presentation, presenting diagnoses, number of organ systems affected at presentation, disposition from the ED, length of hospital stay and in-hospital mortality. The vital signs data were also used to calculate the quick Sequential Organ Failure Assessment (qSOFA) score and the National Early Warning Score 2 (NEWS-2). The qSOFA score combines three rapid bedside clinical criteria [Glasgow Coma Scale (GCS) < 15, respiratory rate ≥ 22 breaths/min and systolic blood pressure ≤ 100 mmHg) and is aimed at identifying patients who are at higher risk of in-hospital mortality [17]. The NEWS-2 score combines six criteria (respiratory rate, oxygen saturation, temperature, systolic blood pressure, heart rate and level of consciousness) and is aimed at determining severity of illness and prompting critical care interventions in patients being monitored in hospital [18]. The various presenting diagnoses were either microbiologically or histologically confirmed or were deemed to be the most likely diagnosis based on findings of clinical assessment and special investigations and after discussion with the relevant sub-speciality clinician.

Data were exported to Microsoft Excel (Microsoft 365, v.16.0.13029.20232) and thereafter to Stata v.16 (StataCorp Ltd, College Station, TX, USA) for statistical analysis. Besides age, all other continuous variables were categorized based on cut-offs frequently reported in the literature (e.g. CD_4 cell count < 100 cells/μL, albumin < 35 g/L etc.). Linearity was assessed using scatterplots. Frequency and percentage were determined for categorical variables. Depending on the number of participants in each group, either the Pearson χ^2 or Fisher's exact test was used to determine if there were significant differences between the two groups.

The data were further subjected to univariate as well as multivariate analysis to determine factors influencing in-hospital mortality while accounting for possible confounders such as age. On univariate analysis, binary logistic regression was used to determine factors associated with in-hospital mortality. Crude odds ratio (OR) was reported with 95% confidence interval (CI) and *P*-value. For each of the variables assessed in the univariate analysis, all available case information was utilized. In the multivariate model, patients with missing data for the included variables were dropped from the model. All variables with a *P*-value < 0.1 in the univariate analysis were evaluated in the multivariate analysis. Non-significant variables were dropped with stepwise backward regression. To assess for interactions, interaction terms were individually added between variables in the multivariate model. Collinearity was assessed via the variance inflation factor with values > 10 regarded as indicative of multicollinearity. A two-sided $P < 0.05$ was considered significant throughout. Study reporting was in conformance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [19].

Results

During the data collection period, 29 416 patients presented to the adult medical ED triage area, of whom 11 383 were triaged into the ED for further management. The remainder were referred to an alternate facility in accordance with the CMJAH ED triage protocol. Of the 1308 patients who were HIV-positive, 84 were excluded as informed consent could not be obtained. A total of 1224 patients were included in the final study sample. Details of how the final study sample was achieved is described in Fig. 1.

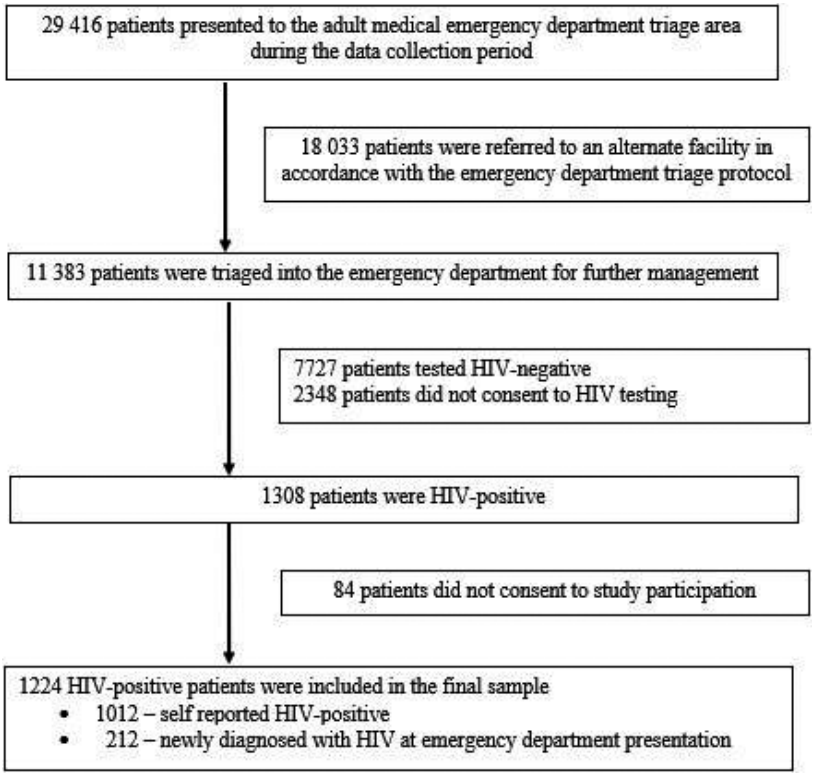

Fig. 1 Description of how the final study sample was achieved.

A total of 166 (13.6%) participants died prior to hospital discharge. Comparisons and OR of in-hospital mortality with regard to demographic details, HIV diagnosis, ART initiation/adherence, vital signs and laboratory parameters are described in Table 1. Although the majority of participants were female (n = 673, 55.0%), the likelihood of in-hospital mortality was 49% higher in males (OR = 1.49, P = 0.017). With regard to the other demographic data collected, there were no statistically significant differences between participants who survived and those who died (P < 0.05). Participants who were newly diagnosed with HIV at ED presentation (OR = 1.98, P < 0.001) and participants who were ART non-adherent (OR = 1.64, P = 0.045) demonstrated a higher likelihood of in-hospital mortality, while participants who had been initiated on ART before presenting to the ED (OR = 1.41, P = 0.002) demonstrated a lower risk of in-hospital mortality. All vital signs listed in Table 1 were associated with a higher likelihood of in-hospital mortality with GCS < 15 (OR = 3.66, P < 0.001) and respiratory rate > 20 breaths/min (OR = 2.17, P < 0.001) displaying the highest likelihoods. All laboratory parameters listed in Table 1 were also associated with a higher likelihood of in-hospital mortality. Notably, the likelihood of in-hospital mortality was more than three times higher among those presenting with a platelet count < 150 × 10^9/L (OR = 3.04, P < 0.001), albumin in the range 25–34 g/dL (OR = 3.06, P < 0.001), HIV viral load > 1000 copies/mL (OR = 3.16, P < 0.001), C-reactive protein (CRP) > 100 mg/L (OR = 3.30, P < 0.001), urea > 10 mmol/L (OR = 3.41, P < 0.001) and creatinine > 200 μmol/L (OR = 3.47, P < 0.001). The likelihood of in-hospital mortality was more than four times higher among participants presenting with an elevated lactate in the range 2.1–5.0 mmol/L (OR = 4.26, P < 0.001) and albumin < 25 g/L (OR = 7.52, P < 0.001), while in-hospital mortality was the highest among those with lactate > 5 mmol/L (OR = 13.19, P < 0.001).

Comparisons and OR of in-hospital mortality with regard to common HIV-related presenting diagnoses, illness severity scores, disposition from the ED and length of hospital admission of study participants are described in Table 2. It is notable that those with meningitis that included tuberculous (OR = 2.87, P = 0.022), cryptococcal (OR = 2.27, P = 0.029) and bacterial (OR = 4.50, P = 0.001) subtypes all displayed significantly higher odds of in-hospital mortality. Additionally, participants

Table 1 Comparison of in-hospital mortality with regard to demographic details, HIV diagnosis, antiretroviral therapy (ART) initiation/adherence, vital signs and laboratory parameters of study participants

	Entire cohort	Survival to discharge	In-hospital mortality	OR (95% CI)	*P*-value
Demographic characteristics					
Age (years) [median (IQR)]	36 (31–44)	36 (31–44)	38 (30–45)	1.01 (0.99–1.02)	0.328
Sex [*n* (%)]					
Female	673 (55.0)	596 (56.3)	77 (46.7)	1.00 (reference)	**0.017**
Male	551 (45.0)	462 (43.7)	89 (53.6)	1.49 (1.07–2.07)	
Race [*n* (%)]					
Black	1174 (95.9)	1017 (95.9)	157 (94.6)	1.00 (reference)	0.349
Other*	50 (4.1)	41 (3.9)	9 (5.4)	1.42 (0.68–2.98)	
Marital status [*n* (%)]					
Single	937 (76.6)	818 (77.3)	119 (71.7)	1.00 (reference)	0.112
Married	287 (23.4)	240 (22.7)	47 (28.3)	1.35 (0.93–1.94)	
Highest level of education [*n* (%)]					
Secondary school	1195 (97.6)	1034 (97.7)	161 (97.0)	1.00 (reference)	0.828
Primary school	16 (1.3)	13 (1.2)	3 (1.8)	1.48 (0.41–5.26)	
Tertiary education	13 (1.1)	11 (1.1)	2 (1.2)	1.17 (0.26–5.32)	
Nationality [*n* (%)]					
South Africa	971 (79.3)	834 (78.8)	137 (82.5)	1.00 (reference)	0.274
Non-South African	253 (20.7)	224 (21.2)	29 (17.5)	0.79 (0.51–1.21)	
HIV diagnosis and ART initiation/adherence					
Newly diagnosed HIV [*n* (%)]	212 (17.3)	167 (15.8)	45 (27.1)	1.98 (1.36–2.90)	**< 0.001**
ART initiated prior to ED presentation [*n* (%)]	761 (62.2)	676 (63.9)	85 (51.2)	0.59 (0.43–0.82)	**0.002**
ART non-adherent [*n* (%)]	245 (32.2)	209 (30.9)	36 (42.3)	1.64 (1.04–2.60)	**0.045**
Vital signs					
Respiratory rate > 20 breaths/min [*n* (%)]	434 (38.8)	349 (36.2)	85 (55.2)	2.17 (1.54–3.06)	**< 0.001**
Oxygen saturation < 90% [*n* (%)]	196 (17.5)	157 (16.3)	39 (25.3)	1.74 (1.16–2.6)	**0.007**
Systolic blood pressure < 90 mmHg [*n* (%)]	116 (10.4)	91 (9.4)	25 (16.2)	1.86 (1.15–3.00)	**0.011**
Heart rate > 110 beats/min [*n* (%)]	565 (50.6)	473 (49.1)	92 (59.7))	1.54 (1.09–2.17)	**0.015**
Glasgow Coma Scale < 15 [*n* (%)]	221 (19.2)	157 (18.8)	64 (68.8)	3.66 (2.55–5.26)	**< 0.001**
Laboratory findings					
CD_4 < 100 cells/μL [*n* (%)]	527 (47.6)	433 (44.8)	94 (67.6)	2.58 (1.77–3.76)	**< 0.001**
HIV viral load > 1000 copies/mL [*n* (%)]	619 (59.0)	537 (58.1)	82 (65.6)	3.16 (2.15–4.65)	**< 0.001**
Haemoglobin [*n* (%)]					
> 10.9 g/dL	550 (48.7)	491 (50.3)	59 (38.3)	1.00 (reference)	
8–10.9 g/dL	366 (32.4)	306 (31.4)	60 (39.0)	1.63 (1.11–2.40)	**0.013**
< 8 g/dL	213 (18.9)	178 (18.3)	35 (22.7)	1.63 (1.04–2.57)	**0.033**
White cell count < 4.0×10^9/L [*n* (%)]	170 (15.1)	137 (14.1)	33 (21.6)	1.68 (1.10–2.57)	**0.017**
Platelet count < 150×10^9/L [*n* (%)]	223 (19.9)	165 (17.0)	58 (38.4)	3.04 (2.11–4.40)	**< 0.001**
Urea > 10 mmol/L [*n* (%)]	277 (25.9)	205 (22.2)	72 (49.3)	3.41 (2.38–4.88)	**< 0.001**
Creatinine [*n* (%)]					
< 120 μmol/L	761 (71.7)	688 (75.2)	73 (50.0)	1.00 (reference)	
120–200 μmol/L	129 (12.2)	102 (11.1)	27 (18.5)	2.49 (1.53–4.06)	**< 0.001**
> 200 μmol/L	171 (16.1)	125 (13.7)	46 (31.5)	3.47 (2.29–5.25)	**< 0.001**
C-reactive protein [*n* (%)]					
≤ 10 mg/L	164 (15.5)	153 (16.7)	11 (7.6)	1.00 (reference)	
11–50 mg/L	193 (18.2)	179 (19.6)	14 (9.7)	1.09 (0.48–2.47)	0.840
51–100 mg/L	186 (17.6)	165 (18.1)	21 (14.5)	1.17 (0.83–3.79)	0.142
> 100 mg/L	516 (48.7)	417 (45.6)	99 (68.3)	3.30 (1.72–6.32)	**< 0.001**
Lactate [*n* (%)]					
< 2.1 mmol/L	648 (58.0)	609 (63.6)	39 (24.4)	1.00 (reference)	
2.1–5.0 mmol/L	387 (34.6)	304(31.7)	83 (51.9)	4.26 (2.84–6.39)	**< 0.001**
> 5.0 mmol/L	83 (7.4)	45 (4.7)	38 (23.8)	13.19 (7.69–22.62)	**< 0.001**
Albumin [*n* (%)]					
> 34 g/L	408 (39.1)	388 (42.8)	20 (14.8)	1.00 (reference)	
25–34 g/L	426 (40.9)	368 (40.6)	58 (42.6)	3.06 (1.80–5.18)	**< 0.001**
< 25 g/L	208 (20.0)	150 (16.6)	58 (42.6)	7.52 (4.37–12.93)	**< 0.001**
Alanine transaminase > 100 mmol/L [*n* (%)]	109 (10.6)	80 (9.0)	29 (20.9)	2.67 (1.67–4.27)	**< 0.001**

Numbers in bold denote statistical significance.
ART, antiretroviral therapy; CI, confidence interval; ED, emergency department; IQR, interquartile range; OR, odds ratio.
*Includes Asian, Caucasian and mixed race.

Table 2 Comparison of in-hospital mortality with regard to common HIV-related presenting diagnoses, illness severity scores, disposition from the emergency department (ED) and length of hospital admission of study participants

	Entire cohort [*n* (%)]	Survival to discharge [*n* (%)]	In-hospital mortality [*n* (%)]	OR (95% CI)	*P*-value
Tuberculosis	244 (19.9)	203 (19.2)	41 (24.7)	1.38 (0.94–2.03)	0.099
Single-organ tuberculosis	174 (14.2)	149 (14.1)	25 (15.1)	1.08 (0.68–1.71)	0.738
Disseminated tuberculosis	70 (5.7)	54 (5.1)	16 (9.6)	1.98 (1.11–3.56)	**0.021**
Pulmonary tuberculosis*	101 (8.3)	84 (7.9)	17 (10.2)	1.32 (0.76–2.29)	0.999
Extrapulmonary tuberculosis	143 (11.7)	119 (11.2)	24 (14.5)	1.33 (0.83–2.14)	0.233
Miliary tuberculosis	38 (3.1)	31 (2.9)	7 (4.2)	1.46 (0.63–3.37)	0.377
Pleural tuberculosis	31 (2.5)	28 (2.6)	3 (1.8)	0.68 (0.20–2.25)	0.52
Abdominal tuberculosis	27 (2.2)	25 (2.4)	2 (1.2)	0.50 (0.12–2.15)	0.354
Tuberculous meningitis	23 (1.9)	16 (1.5)	7 (4.2)	2.87 (1.16–7.08)	**0.022**
Other[†]	29 (2.4)	23 (2.2)	6 (3.6)	1.69 (0.68–4.21)	0.262
Bacterial pneumonia	276 (22.5)	237 (22.4)	39 (23.4)	1.06 (0.72–1.57)	0.754
Pneumocystis jirovecii pneumonia	47 (3.8)	37 (3.5)	10 (6.0)	1.77 (0.86–3.63)	0.119
Cryptococcal meningitis	39 (3.2)	29 (2.7)	10 (6.0)	2.27 (1.09–4.76)	**0.029**
Bacterial meningitis	30 (2.5)	18 (1.7)	12 (7.2)	4.50 (2.13–9.53)	**0.001**
Acute gastroenteritis	56 (4.6)	51 (4.8)	5 (3.0)	0.61 (0.24–1.56)	0.304
Chronic gastroenteritis	30 (2.5)	28 (2.6)	2 (1.2)	0.45 (0.11–1.90)	0.277
No. of organ systems affected					
1	460 (37.6)	430 (40.6)	30 (18.1)	1.00 (reference)	
2	432 (35.2)	384 (36.3)	48 (28.9)	1.79 (1.11–2.89)	**0.016**
≥ 3	332 (27.2)	244 (23.1)	88 (53.0)	5.17 (3.32–8.05)	**< 0.001**
qSOFA score					
Low score (0–1 point)	921 (82.5)	823 (85.5)	98 (63.6)	1.00 (reference)	
High score (2–3 points)	196 (17.5)	140 (14.5)	56 (36.4)	3.35 (2.31–4.88)	**< 0.001**
NEWS-2 score					
Low (0–4 points)	449 (40.2)	415 (43.1)	34 (22.1)	1.00 (reference)	
[‡]Medium (5–6 points)	171 (15.4)	146 (15.2)	25 (16.2)	2.09 (1.21–3.62)	**0.009**
High (≥ 7 points)	496 (44.4)	401 (41.7)	95 (61.7)	2.89 (1.91–4.38)	**< 0.001**
Disposition from the ED					
Ward admission	813 (66.5)	712 (67.3)	101 (60.8)	1.00 (reference)	
ICU admission	205 (16.7)	140 (13.2)	65 (39.2)	3.27 (2.28–4.69)	**< 0.001**
Length of hospital stay					
< 7 days	830 (67.8)	732 (69.2)	98 (59.0)	1.00 (reference)	
≥ 7 days	394 (32.2)	326 (30.8)	68 (41.0)	1.56 (1.11–2.18)	**0.010**

Numbers in bold denote statistical significance.
ART, antiretroviral therapy; CI, confidence interval; ED, emergency department; ICU, intensive care unit; IQR, interquartile range; NEWS-2, National Early Warning Score 2; OR, odds ratio; qSOFA, Sequential Organ Failure Assessment score.
*Only includes participants with isolated pulmonary tuberculosis.
[†]Tuberculous lymphadenitis (n = 10), tuberculous pericarditis (n = 9), tuberculoma (n = 4), urogenital tuberculosis (n = 3), spinal tuberculosis (n = 2), tuberculous osteomyelitis (n = 1).
[‡]Includes patients with an overall low score but achieving three points in any individual parameter.

presenting with pathology affecting more than one organ system displayed an incrementally higher odds of in-hospital mortality. A similar trend was noted with the qSOFA score and the NEWS-2 score. A total of 16.8% (n = 206) of participants were discharged home from the ED. Compared with participants who were admitted to the ward, those who were admitted to the ICU had an approximately three-fold (OR = 3.27, $P < 0.001$) higher likelihood of in-hospital mortality, and compared with participants with a length of hospital stay < 7 days, those with a hospital stay ≥ 7 days had a 56% (OR = 1.56, $P = 0.010$) higher likelihood of in-hospital mortality.

After adjusting for age and HIV VL and after removing participants with missing data, variables with $P < 0.1$ from the univariate analysis were subjected to multivariate logistic regression. A total of 869 (71.0%) participants were included in the final model (Table 3). Only respiratory rate > 20 breaths/min (OR = 1.90, $P = 0.012$), creatinine > 120 μmol/L (OR = 1.97, $P = 0.006$), oxygen saturation < 90% (OR = 2.09, $P = 0.011$), white cell count $< 4.0 \times 10^9$/L (OR = 2.09, $P = 0.008$), ART non-adherence or not yet on ART (OR = 2.39, $P = 0.012$), GCS < 15 (OR = 2.53, $P = 0.000$), albumin < 35 g/L (OR = 2.61, $P = 0.002$), lactate > 2 mmol/L (OR = 4.83, $P = 0.000$) and cryptococcal meningitis (OR = 6.78, $P = 0.000$) were significantly associated with in-hospital mortality.

Discussion

Although many of the variables identified in this study may also be predictors of mortality and severity of illness in patients with other non-HIV-related illnesses [20], the

Table 3 Variables significantly associated with in-hospital mortality after subjecting relevant data to multivariate analysis

	Multivariate analysis	
Parameter	**OR (95% CI)**	***P*-value**
ART non-adherent or not yet on ART*	2.39 (1.21–4.74)	0.012
Glasgow Coma Scale < 15	2.54 (1.51–4.27)	0.000
Respiratory rate > 20 breaths/min	1.90 (1.15–3.13)	0.012
Oxygen saturation < 90%	2.09 (1.18–3.71)	0.011
White cell count < 4.0×10^9/L	2.09 (1.21–3.60)	0.008
Creatinine > 120 μmol/L	1.97 (1.22–3.19)	0.006
Lactate > 2 mmol/L	4.83 (2.91–8.01)	0.000
Albumin < 35 g/L	2.61 (1.41–4.84)	0.002
Cryptococcal meningitis	6.78 (2.52–18.25)	0.000

Model adjusted for age and HIV viral load.
ART, antiretroviral therapy; CI, confidence interval; OR, odds ratio.
*Includes all participants who reported ART non-adherence or were not yet initiated on ART prior to presentation.

combination of variables identified in this study is unique. On univariate analysis of the data, 29 variables were associated with a significantly higher likelihood of in-hospital mortality (male sex, newly diagnosed with HIV, not yet initiated on ART, ART non-adherence, GCS, respiratory rate, systolic blood pressure, oxygen saturation, heart rate, HIV VL, CD_4 cell count, haemoglobin, white cell count, platelet count, urea, creatinine, albumin, lactate, CRP, alanine transaminase, disseminated tuberculosis, tuberculous meningitis, cryptococcal meningitis, bacterial meningitis, number of organ systems affected, qSOFA score, NEWS-2 score, ICU admission and length of hospital admission) and after subjecting the data to multivariate logistic regression, nine variables were found to be associated with a significantly higher likelihood of in-hospital mortality (ART non-adherence or not yet on ART, GCS < 15, respiratory rate > 20 breaths/min, oxygen saturation < 90%, white cell count < 4.0×10^9/L, creatinine > 120 μmol/L, albumin < 34 g/L, lactate > 2 mmol/L and cryptococcal meningitis).

To our knowledge, this is the largest and most comprehensive single-centre study to have determined predictors of in-hospital mortality in consecutive HIV-positive patients in an ED setting. Findings pertaining to other aspects of this study have been published separately [21]. Although multiple studies have reported on the predictive value of various parameters in HIV-positive patients, most of these studies only reported on a few variables and were predominantly conducted in outpatient settings.

In a multicentre study that included data from 12 078 hospitalized HIV-positive patients across 43 hospitals in Portugal over a 3-year period, the risk of hospital mortality was 27% higher in males, with each additional year increase in age being associated with a 1.3% higher risk of in-hospital mortality. Pneumonia and each additional diagnosis were associated with 43% and 2% higher risk of in-hospital mortality, respectively; however, interestingly, tuberculosis was associated with a 22% reduced risk of in-hospital mortality [22]. In a separate study that reviewed data from 2004 to 2013 and included 95 857 HIV-positive patients in Uganda, significant ($P < 0.001$) predictors of overall mortality were male sex (OR = 1.37), age > 45 years or age < 25 years (OR = 1.15), unemployment (OR = 1.28), having no schooling (OR = 1.47) or only primary school education (OR = 1.38), CD_4 cell count < 100 cells/μL (OR = 3.37) and weight < 45 kg (OR = 2.44) [23]. Another study that was conducted in Nepal and included 3799 HIV-positive adult patients who were identified from the national ART register found that baseline predictors of mortality were male gender [adjusted hazard ratio (aHR) = 2.08], clinical stage III (aHR = 1.67) or IV (aHR = 2.21) disease, lower body weight (aHR = 1.04) and CD_4 cell count < 150 cells/μL (aHR = 2.14) [24]. Furthermore, in a systematic review that included 17 studies, all of which were conducted in Ethiopia and comprised 19 321 pooled HIV-positive patients on ART, the following were identified as predictors of mortality: CD_4 < 50 cells/μL at ART initiation (aHR: 1.8–4.5), HIV stage III and IV disease (aHR: 1.4–11.2), poor treatment adherence (aHR: 2.1–27.8), low baseline haemoglobin level (aHR: 1.9–5.5), coinfection with tuberculosis (aHR: 1.3–4.5) and poor functional status (aHR: 2.4–6.9) [25]. Comparatively, in our study, on univariate analysis the likelihood of in-hospital mortality was 1.49 times higher in males and 5.17 times higher in participants presenting with ≥ 3 organ system pathology, and there were no significant differences with regard to age and bacterial pneumonia. Although tuberculosis, in general, was not associated with a higher likelihood of in-hospital mortality, disseminated tuberculosis (OR = 1.98) and tuberculous meningitis (OR = 2.87) were associated with a higher likelihood of in-hospital mortality in this study. Not surprisingly, and in keeping with previous studies [26,27], bacterial meningitis (OR = 4.50) on univariate analysis and cryptococcal meningitis on univariate (OR = 2.27) as well as multivariate (OR = 6.78) analysis were each also associated with a significantly higher likelihood of in-hospital mortality.

With regard to haematological parameters, in this study leucopenia was independently associated with a two-fold higher likelihood of in-hospital mortality, while anaemia (OR = 1.63) and thrombocytopenia (OR = 3.04) were only associated with a higher likelihood of in-hospital mortality on univariate analysis. Anaemia as a predictor of worse outcomes has been described in a number of studies. In a study conducted in Tanzania that enrolled 320 treatment-naïve adults at ART initiation who were

followed up for a median duration of 10.9 months, independent predictors of mortality were haemoglobin < 8 g/dL (aHR = 9.20), haemoglobin 8–9.9 g/dL (aHR = 7.50), haemoglobin 10–11.9 g/dL (AHR = 4.03), thrombocytopenia (aHR = 2.30) and lymphopenia (aHR = 1.72) [28]. Another study demonstrated that every 1 g/dL decrease in haemoglobin was independently associated with a 57% increase in mortality [29]. In a cohort study that included 1350 adults who had been initiated on ART across 27 clinics in South Africa, the aHRs for mortality with haemoglobin < 8 and 8.1–9.9 g/dL were 4.99 and 3.05, respectively [30]. In the Multistate Adult and Adolescent Spectrum of HIV Disease Surveillance Project that retrospectively reviewed the medical charts of 32 867 HIV-positive patients, mortality was significantly higher in patients with anaemia, with a 56% increase in the risk of death in anaemic patients with a baseline CD_4 cell count < 200 cells/μL [31]. In contrast to the studies described, our study differed in that it was conducted in acutely ill HIV-positive patients in the ED.

Similar to the findings of this study, where CRP > 100 mmol/L was associated with a 3.3-fold higher likelihood of in-hospital mortality, other studies have also found CRP to be a predictor of HIV progression and mortality. However, many of these studies did not exclusively include patients presenting with an acute illness. In a multicentre study that comprised 513 HIV-positive men, the degree of CRP elevation was associated with HIV disease progression, which was independent of the CD_4 cell count and HIV VL [32]. In another study, after adjusting for age, body mass index, albumin, CD_4 cell count and HIV VL, CRP was found to be a predictor of mortality, with the increased risk varying from 3.4- to 13.6-fold depending on the degree of CRP elevation [33]. A study conducted in Tanzania reported that a high maternal CRP independently predicted maternal as well as child mortality [34].

In this study, hypalbuminaemia was associated with a significantly higher likelihood of in-hospital mortality, with lower levels (< 25 g/L) being associated with an even higher likelihood of in-hospital mortality. In a study that measured the albumin concentration at ART initiation in 2145 adults, patients with an albumin concentration < 35 g/L had a 4.52-fold higher risk of death after multivariate adjustment [12]. In a multi-institutional study comprising 2056 HIV-infected women at various stages of HIV disease, the aHR for mortality was 3.1 times higher ($P < 0.01$) in patients with albumin < 35 g/L, after adjusting for CD_4 cell count, HIV VL, haematocrit level, age and body mass index [35]. Another study reported that HIV-positive patients with an albumin < 25 g/L had a three-fold higher risk of mortality [36]. Again, these studies investigated the predictive value of albumin in relation to long-term mortality and not in the context of acute in-hospital mortality, as was investigated in this study.

In this study, on both univariate and multivariate analysis, hyperlactataemia was associated with a significantly higher likelihood of in-hospital mortality, with higher levels (>5 mmol/L) associated with an extremely high likelihood of mortality on univariate analysis. While the causes of hyperlactataemia in HIV-positive patients may be manifold [13], previous studies predominantly reported on hyperlactataemia secondary to the use of the older-generation nucleoside reverse transcriptase inhibitor class of ART. In a study that examined this as a cause, the prevalence rates of hyperlactataemia in HIV-positive patients receiving ART and in patients not on ART were 18.7% and 6.7%, respectively [37]. With the introduction of safer ART treatment regimens in the past few years, however, the incidence of ART-induced lactic acidosis has significantly declined [38] In acutely ill patients in general, hyperlactataemia has been shown to predict mortality independently [39]. In one such study, blood lactate levels > 5 mmol/L were associated with an 80% mortality rate [40]. As such, lactate levels may be a useful marker in HIV-positive patients with an acute illness.

While many of the parameters discussed have been shown to be independent predictors of mortality in this or previous studies (as discussed earlier), it is likely that the concurrent presence of more than one of these parameters in a single patient may be associated with higher rates of mortality. Hence, the development of a scoring tool comprising several of these outcome predictive parameters may help clinicians to better classify disease severity and prognostication, as well as guide appropriate clinical management and the use of limited resources.

Limitations

Among the limitations of this study is the fact that it was a single-centre study that focused on in-hospital mortality. Hence, patients were not followed up after hospital discharge, and therefore long-term mortality was not determined. Furthermore, as the study was conducted at a tertiary-level academic hospital and, therefore, patients with less severe presenting illnesses were triaged to a lower level of care facility, our cumulative findings are likely to be overestimated and may not be fully reflective of the actual dynamics of the HIV-positive population residing within the drainage area of the hospital.

Conclusions

Routine clinical and laboratory parameters are useful in predicting in-hospital mortality in HIV-positive patients presenting to the ED with an acute illness. These parameters may be of value in guiding clinical decision-making, directing the appropriate use of resources and influencing patient disposition, and they may also be useful in developing an outcome prediction tool for use in HIV-positive patients in the ED. Interventions such as the prescription of empirical antibiotics, rapid induction of ART and other mechanisms to reduce this mortality need to be evaluated in appropriately conducted clinical trials.

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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 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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