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Severity score for predicting in-facility Ebola treatment outcome

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ABSTRACT

Purpose: Sierra Leone recorded the highest incidence rate for the 2013–2016 West African Ebola outbreak. In this investigation, we used the medical records of Ebola patients with different socio-demographic and clinical features to determine the factors that are associated with Ebola treatment outcome during the 2013–2016 West African Ebola outbreak in Sierra Leone and constructed a predictive in-facility mortality score.

Methods: We used the anonymized medical records of 1077 laboratory-confirmed pediatric and adult patients with EVD who received treatment at the 34 Military Hospital and the Police Training School Ebola Treatment Centers in Sierra Leone between the period of June 2014 and April 2015. We later determined the in-facility case fatality rates for Ebola, the odds of dying during Ebola treatment, and later constructed a predictive in-facility mortality score for these patients based on their clinical and socio-demographic characteristics.

Results: We constructed a model that partitioned the study population into three mortality risk groups of equal patient numbers, based on risk scoring: low (score ≤ -5), medium (score -4 to 1), and high-risk group (score ≥ 2). The CFR of patients with EVD belonging to the low- (≤ -5), medium (-4 to 1), and high- (≥ 2) risk groups were 0.56%, 9.75%, and 67.41%, respectively.

Conclusions: We succeeded in designing an in-facility mortality risk score that reflects EVD clinical severity and can assist in the clinical prioritization of patients with EVD.

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Introduction

Ebola virus disease (EVD) is a severe infection by a member of the filovirus family which causes various symptoms such as fever, hemorrhage, myalgia, and diarrhea [1,2]. The West African EVD outbreak in 2013–2016 affected more than 28,000 individuals and resulted in over 11,000 deaths [3]. Before the 2013–2016 EVD outbreak, there were just over 2300 EVD cases and just over 1500 EVD-related deaths documented globally [4]. Sierra Leone was among the hardest-hit countries, and the country recorded more than 10,000 EVD cases and over 4000 EVD-related deaths during the 2013–2016 EVD outbreak [5]. Several EVD treatment outcome studies [6,7–10] have demonstrated variability (37%–74%) in EVD case fatality rates (CFRs). Such variability has prompted calls for further investigation to understand the reasons for these differences in CFRs and hence offer differentiated EVD treatment and management options. Symptoms of EVD are similar to many tropical infections and hamper, therefore, specificity in predictive algorithms. Even though EVD disease onset is nonspecific, it is often characterized by symptoms such as fever, myalgia, chills, vomiting, and diarrhea. These symptoms evolve within an incubation period of 2–21 days from the time of infection; mostly within 4–10 days [1,2]. A maculopapular rash, erythema, and desquamation are often visible by the fifth–seventh day of EVD infection and can serve as a valuable differential diagnostic feature for the infection [11]. Patients with EVD may also present with other symptoms including

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nausea, stomach ache, headache, profound weakness, coma, dyspnea, rhinorrhea, and generalized symptoms relating to cardiovascular system failure which can result in shock [2,11,12]. The phase of severe EVD is also characterized by hemorrhagic complications and multiple organ failure [1,2]. The paucity of published age-specific symptom data for admitted pediatric EVD cases make the use in this subgroup of algorithms that are based on studies in adults a challenge. Mupere et al reported data for 20 of 168 laboratory-confirmed EVD admitted cases less than 18 years of age but failed to disaggregate their clinical observations by age [13]. The World Health Organisation (WHO) Ebola Response Team in West Africa, however, reported symptom history of EVD cases on arrival as well as the age-specific outcomes for EVD cases in Guinea, Liberia, and Sierra Leone during the 2013–2016 EVD outbreak [3]. Nonetheless, there appears to be general similarities in the clinical symptoms for both pediatric and adult EVD cases. Several studies have listed fever, disorientation, hiccups, hemorrhage, vomiting, diarrhea, anorexia, weakness, breathlessness, dysphagia, confusion, and bleeding in both pediatric and adult EVD cases [1–3,11,12]. Shah et al reported weakness, loss of appetite, fever, and distress in 63% of pediatric EVD cases [14], whereas Qin et al specifically reported weakness, fever, and distress in 50% of their all-age cohort inpatient EVD cases [15] during the 2013–2016 West Africa EVD outbreak. McElroy et al reported slightly different prevalence rates for hemorrhage for pediatric (40.5%) and adult (32.7%) Sudan-strain EVD cases during the Uganda outbreak in 2000–2001 [16]. Some characteristics and clinical symptoms of patient with EVD have been associated with high CFRs. Age [7–9,17]; higher viremia [18,19] at admission; longer symptom duration before admission [7–9,17–20]; and clinical symptoms such as confusion, diarrhea, and conjunctivitis [7–9,17], and biochemical evidence of kidney injury [8] have also been associated with high CFRs. Currently, there is no officially approved medication or vaccine for Ebola, but standard management care, including the use of antibiotics, antimalarials, resuscitation by application of fluids and symptomatic treatments have proven to be effective [20]. Several WHO-approved experimental therapies and vaccines such as ZMapp [21], brincidofovir [22], TKM 130803 [23], favipiravir [24], monoclonal antibody MAb114 [25], and convalescent plasma of patients [26] with EVD are now used during EVD outbreaks on trial or compassionate grounds. The age of a patient with EVD and the level of medical interventions received during treatment influence EVD treatment outcomes and hence the CFR. The CFR for EVD tends to be high in children and in adults of advanced age. The CFR for the first 6 months of the 2013–2016 West Africa EVD outbreak for patients in Guinea, Sierra Leone, and Liberia who were less than 15 years, 15–44 years, and those 45 years and above were 73.4%, 66.1%, and 80.4%, respectively [20], even though these figures changed as the outbreak progressed. In addition, findings from the 2013–2016 EVD outbreak in West Africa and those from the 1995 and 2001 outbreaks in Kikwit, Democratic Republic of Congo and in Gulu, Uganda, respectively, indicate that older adults have higher CFRs for EVD than children, adolescents, and young adults [27]. Most literature relating to Ebola clinical manifestations and treatment outcome is generated from outbreaks in which limited data were collected from small sample sizes. Of 780 admissions at the Médecins Sans Frontières Ebola case management center in Kailahun, Sierra Leone during the 2013–2016 West African EVD outbreak, only 525 (67%) polymerase chain reaction (PCR)–confirmed EVD cases had a documented treatment outcome [28]. In another Sierra Leonean study, treatment mortality for 249 patients with EVD was associated with a high-viral load (adjusted relative risk 2.6; 95% CI 1.8 ± 3.6) and vomiting at first presentation (adjusted relative risk 1.4; 95% CI 1.0 ± 2.0) [29].

One major challenge in managing EVD cases is the paucity of prognostic tools that can stratify EVD in-facility mortality risk. Such prognostic tool should be able to identify patients with EVD who are in need of intensive treatment as well as providing the basis for clinical decision-making. One EVD staging model which was based on a WHO protocol and adapted from the clinical presentation of Lassa fever [30] comprises 3 symptomatic stages: 1) early infection stage, 2) gastrointestinal stage, and 3) late complicated stage which is associated with hemorrhagic and organ failure features. This EVD symptomatic staging model although it broadly correlates with EVD treatment outcome [8] yet, still requires improvement. The WHO staging model, for example, does not account for the sociodemographic characteristics of patients with EVD such as age which is an important CFR predictor for people infected with Ebola [20,27]. In addition, its use of the various clinical characteristics of patients with EVD makes it broad and hence, a challenge for differential diagnosis with other tropical infections with similar clinical features. Previous studies have used single symptom such as confusion [15,20], diarrhea [9,20,31], asthenia [20], haemorrhagic signs [8,20], dizziness [9], and fatigue [15] to construct a univariate predictive score for EVD. However, because EVD is a disease with a nonspecific symptomology there is a need for a prognostic tool built on multivariate rather than a univariate logistic model analysis that can accurately predict EVD treatment mortality.

In this mixed cohort study, we used the clinical and sociodemographical characteristics of 1077 positive EVD patients to construct a statistically weighted scoring system which is predictive of EVD treatment mortality.

Methods

Study design

This retrospective study analyzed post hoc the anonymized medical records of 1077 PCR-confirmed patients with EVD who received treatment at the 34 Military Hospital and Police Training School Ebola Treatment Centers (ETCs) in Sierra Leone in the period of June 2014 to April 2015. The analyzed medical records contained the sociodemographic, clinical, laboratory, and treatment outcome data of the patients with EVD that have been collected at the time of their admission. The medical records, which were first collected on hard copies of the case report form by data clerks attached to the 34 Military Hospital and Police Training School ETCs, were later transferred to a Microsoft Excel [32] form for pooled analyses.

Ethics review

The Sierra Leone Ethics and Scientific Review Committee (Opinion Date March 29, 2017) and the Institutional Review Board at the Ludwig-Maximilians-Universität in Munich, Germany (Opinion No. LMU 17–582) provided ethical clearance and approved this study. The Sierra Leone Ethics and Scientific Review Committee waivered the requirement to obtain informed consent from the study subjects since we were analyzing facility-specific aggregated medical records.

Data collection and processing

The patients with EVD whose medical history were analyzed in this study either self-reported or were brought to the triage center of the 34 Military Hospital and the Police Training School in Freetown by the National Ebola Response Committee surveillance system as suspected EVD cases. These suspected patients with EVD were initially screened on their appearance at the triage center and their medical history recorded on the case report form before they were transferred to the isolation unit (EVD holding center) for temporary admission while they waited for their laboratory test

result. An EVD suspected case was defined as a person with an acute onset of fever >38°C with any of the following additional symptoms: severe headache, muscle pain, vomiting, diarrhea, abdominal pain, or unexplained hemorrhage and had a direct contact with a suspected/confirmed EVD case or has unexplained multisystem illness that is not explained by a confirmed course of malaria. Only suspected EVD cases who tested positive for Ebola virus infection by quantitative reverse transcriptase PCR assay had their medical records analyzed in this study. This study considered an EVD treatment outcome to be successful when a patient with EVD was released alive after treatment and is tested negative for Ebola virus with reverse transcriptase PCR. Patients with EVD who died during treatment within the facility were considered as treatment failures.

Study setting

Most government referral hospitals, district health hospitals, and foreign-owned health care facilities in Sierra Leone served either as an ETC or as an Ebola Holding Center during the 2013–2016 outbreak. Military personnel employed by the 34 Military Hospital worked at both the 34 Military Hospital and the Police Training School ETCs, both of which provided data for this study. At the time this study was conducted, the Police Training School ETCs had 120 bed spaces, whereas the 34 Military Hospital had 30 bed spaces for the admission of confirmed patients with EVD and 20 bed spaces serving as holding center for suspected EVD cases who awaited their laboratory results. At the time of the 2013–2016 EVD outbreak, the 34 Military Hospital was headed by a Brigadier Surgeon General and assisted by military medical doctors and paramedics.

Statistical analysis

R software package version 3.3.1 [33] was used for all data analysis in this study. A *P*-value < .05 was used as our statistical significance cutoff point for all two-sided statistical tests. We used frequencies, proportions, means, and standard deviations (for continuous variables); medians and the interquartile range (for categorical variables) to represent sociodemographic characteristics and clinical symptoms of patient with EVD. We compared the proportions of the various sociodemographic characteristics and clinical symptoms of patient with EVD using chi-square tests. To quantify the prognostic utility of sociodemographic characteristics and clinical symptoms of patient with EVD in predicting EVD in-facility mortality, we used a multivariable logistic regression model with a binary treatment outcome (death yes/no) as dependent variable followed by a stepwise backward selection algorithm based on the Akaike Information Criterion (AIC) to select the final predictive model. We multiplied the regression coefficient of each predictor in the AIC-based final stepwise backward predictive model by two into the nearest integer [34] to obtain a weighted prognostic score for treatment mortality of patient with EVD. We internally validated our predictive mortality model with the R package broom using the bootstrap method with 1000 repetitions and resampling without replacement [26,27]. We first obtained the area under the curve original ($AUC_{Original}$) for our multivariable logistic regression model and later determined the area under the curve for the bootstrap-corrected ($AUC_{corrected}$) model. To determine the performance of our model to predict EVD treatment outcome, we calculated the area under the curve optimism ($AUC_{optimism}$) by subtracting the $AUC_{original}$ from the $AUC_{corrected}$. Our large data set makes it more appropriate to use the bootstrap method for the internal validation of our predictive model because the bootstrap method has unavoidable limitations when used for the internal validation of small data sets with a large numbers of predictors [35]. We then derived our in-facility mortality risk groups (low-, medium-, and high-risk groups) by attributing a third of the patients with EVD each into low-, medium-, and high-risk groups, respectively, based on their range of risk scores.

Results

Study participants' background characteristics

The majority of the EVD cases is this study were men (614/1077; 57.0%), belonged to the age group 25 years–35 years (301/1077;

Table 1
Treatment outcome and sociodemographic factors of patients with EVD

EVD patients characteristics	N (%)	Cured (%)	Dead (%)	Case fatality rate (%)	*P*-value*
Total	1077 (100)	798 (74.1)	279 (25.9)	25.9	
Sex					
Female	463 (43.0)	375 (47.0)	88 (31.5)	19.0	<.0001
Male	614 (57.0)	423 (53.0)	191 (68.5)	31.1	
Age groups					
0– < 5 years	37 (3.4)	23 (2.9)	14 (5.0)	37.8	<.0001
5– < 15 years	102 (9.5)	85 (10.7)	17 (6.1)	16.7	
15– < 25 years	217 (20.2)	179 (22.4)	38 (13.5)	17.5	
25– < 35 years	301 (28.0)	236 (29.6)	65 (23.3)	21.6	
35– < 45 years	287 (26.7)	197 (24.7)	90 (32.3)	31.4	
45 years and above	133 (12.4)	78 (9.8)	55 (19.7)	41.4	
Education					
No education	43 (4.0)	29 (3.6)	14 (5.0)	32.6	.129
Elementary education	133 (13.4)	109 (13.7)	35 (12.5)	24.3	
Secondary education	775 (72.0)	584 (73.2)	191 (68.5)	24.7	
Tertiary education	115 (10.7)	76 (9.5)	39 (14.0)	33.9	
Occupation					
Child	52 (4.8)	34 (4.3)	18 (6.5)	34.6	.0002
Pupil	174 (16.2)	147 (18.4)	27 (9.7)	15.5	
Student	51 (4.7)	41 (5.1)	10 (3.6)	19.6	
Nurse	39 (3.6)	29 (3.6)	10 (3.6)	25.6	
Banker	109 (10.1)	84 (10.5)	25 (9.0)	22.9	
Housewife	167 (15.5)	134 (16.8)	33 (11.8)	19.8	
Craftsman	382 (35.5)	253 (31.7)	129 (46.2)	33.8	
Unemployed	103 (9.6)	76 (9.5)	27 (9.7)	26.2	

* *P*-values were obtained by applying chi-square tests comparing the case fatality rates and sociodemographic characteristics of patients with EVD.

Table 2
Clinical characteristics and treatment outcome of patients with EVD

EVD patients' characteristics	N (%)	Cured (%)	Dead (%)	Case fatality rate (%)	*P*-value*
Total	1077 (100)	798 (74.1)	279 (25.9)	25.9	
Abdominal pain	776 (72.1)	550 (68.9)	226 (81.0)	29.1	.0002
Anorexia	1064 (98.8)	790 (99.0)	274 (98.2)	25.8	.471
Bleeding	111 (10.3)	45 (5.6)	66 (23.7)	59.5	<.0001
Chest pain	912 (84.7)	679 (85.1)	233 (83.5)	25.6	.595
Cough	490 (45.5)	330 (41.4)	160 (57.3)	32.7	<.0001
Diarrhea	769 (71.4)	506 (63.4)	263 (94.3)	34.2	<.0001
Dysphagia	309 (28.7)	100 (12.5)	209 (74.9)	67.6	<.0001
Dyspnea	166 (15.4)	38 (4.8)	128 (45.9)	77.1	<.0001
Fatigue	664 (61.7)	404 (50.6)	260 (93.2)	39.2	<.0001
Fever	844 (78.4)	642 (80.5)	202 (72.4)	23.9	.006
Headache	1047 (97.2)	772 (96.7)	275 (98.6)	26.3	.167
Muscle pain	1041 (96.7)	775 (97.1)	266 (95.3)	25.6	.219
Sign of conjunctivitis	193 (17.9)	61 (7.6)	132 (47.3)	68.4	<.0001
Skin rash	28 (2.6)	0 (0)	28 (10.0)	100	<.0001
Stage one EVD infection	319 (29.6)	310 (38.8)	9 (3.2)	2.8	<.0001
Stage two EVD infection	582 (54.0)	470 (58.9)	112 (40.1)	19.2	
Stage three EVD infection	176 (16.3)	18 (2.3)	158 (56.6)	89.8	
Vomiting	537 (49.9)	300 (37.6)	237 (84.9)	44.1	<.0001

* *P*-values were obtained by applying χ^2 test by comparing the case fatality rates and clinical characteristics of patients with EVD.

27.9%), were craftsmen (382/1077; 35.5%), and secondary school graduates (775/1077; 72.0%). The median age of the EVD cases was 31 years (interquartile range = 22–38 years). The minimum age of the patients with EVD was 2.5 months, and the maximum age was 83 years (Table 1).

Clinical symptoms

The majority of the patients with EVD reported at the time of admission to be suffering from fatigue (664/1,077, 61.7%), diarrhea (769/1077; 71.4%), abdominal pain (776/1077; 72.1%), fever (844/

Table 3
Association of sociodemographic characteristics and clinical symptoms of patient with EVD and in-facility CFR

EVD patient characteristics	Crude OR	95% CI	*P*-value	Adjusted OR for predictive model	95% CI	*P*-value*
Sex male reference = female	1.92	1.45–2.58	<.0001	1.61	0.99–2.63	.056
Age groups of patients with EVD reference = 0–5 y						
5 to <15 y	0.33	0.14–0.77	.01	0.15	0.03–0.70	.017
15 to <25 y	0.35	0.17–0.75	.006	0.08	0.01–0.49	.006
25 to <35 y	0.45	0.22–0.95	.03	0.09	0.02–0.56	.009
35 to <45 y	0.75	0.37–1.56	.43	0.16	0.02–1.02	.053
45 y and above	1.16	0.55–2.50	.70	0.21	0.03–1.44	.113
Educational levels of patients with EVD reference = No education						
Elementary education	0.67	0.32–1.43	.28	0.82	0.11–5.85	.841
Secondary education	0.67	0.36–1.35	.25	0.54	0.07–4.36	.564
Tertiary education	1.06	0.51–2.29	.87	1.63	0.19–14.80	.660
Occupation status of patients with EVD reference = Child						
Pupil	0.35	0.29–0.93	.003	0.72	0.09–5.57	.758
Student	0.46	0.17–0.71	.09	1.34	0.12–14.20	.808
Nurse	0.65	0.18–1.11	.36	1.77	0.14–22.05	.661
Banker	0.56	0.25–1.61	.12	0.50	0.05–5.35	.575
House wife	0.47	0.24–0.93	.03	1.09	0.11–10.97	.940
Craftsmen	0.96	0.53–1.80	.90	1.29	0.14–11.80	.825
Unemployed	0.67	0.33–1.39	.28	4.08	0.42–40.15	.233
Clinical symptoms of patients with EVD						
Fever	0.64	0.47–0.88	.005	1.55	0.93–2.61	.093
Headache	2.32	0.89–7.90	.12			
Chest pain	0.89	0.62–1.30	.53			
Abdominal pain	1.92	1.39–2.71	<.0001			
Cough	1.91	1.45–2.516	<.0001			
Vomiting	9.37	6.62–13.56	<.0001	4.79	2.78–8.49	<.0001
Diarrhea	9.49	5.79–16.66	<.0001	4.38	2.14–9.67	.0001
Fatigue	13.35	8.43–22.39	<.0001	2.90	1.52–5.78	.002
Dysphagia	20.84	14.88–29.53	<.0001	6.34	3.96–10.28	<.0001
Bleeding	5.19	3.46–7.84	<.0001	2.37	1.31–4.32	.005
Red eyes	10.85	7.67–15.50	<.0001	3.42	2.00–5.89	<.0001
Dyspnea	16.95	11.45–25.63	<.0001	4.18	2.41–7.38	<.0001
Anorexia	0.56	0.18–1.85	.31			
Muscular pain	0.61	0.31–1.25	.16	0.09	0.03–0.25	<.0001

* *P*-values were obtained after predictive backward stepwise logistic regression of our final multivariable model.

Table 4
Ebola mortality score based on predictive sociodemographic characteristics and clinical symptoms

EVD patients' predictive characteristics	Coefficients	Weights*
Sex Reference = Female		
Male	0.47	1
Age group in years Reference = 0 to less than 5 y		
5 to <15 y	−1.93	- 4
15 to <25 y	−2.47	- 5
25 to <35 y	−2.39	- 5
35 to <45 y	−1.84	- 4
45 y and above	−1.55	- 3
Education Reference = No education		
Elementary education	−0.20	0
Secondary education	−0.61	−1
Tertiary education	0.49	1
Occupation Reference = Child		
Pupil	−0.33	−1
Student	0.29	1
Nurse	0.57	1
Banker	−0.68	−1
House wife	0.09	0
Craftsmen	0.25	1
Unemployed	1.41	3
EVD patient clinical symptom		
Fever	0.44	1
Vomiting	1.57	3
Diarrhea	1.48	3
Fatigue	1.06	2
Dysphagia	1.85	4
Bleeding	0.86	2
Sign of conjunctivitis	1.23	2
Dyspnea	1.43	3
Muscular pain	−2.40	−5

* Weights were obtained by multiplying the coefficients of the sociodemographic characteristics and clinical symptoms of patients with EVD in the final logistic model by two and rounding the product to the nearest integer.

1077; 78.4%), chest pain (912/1077; 84.7%), muscle pain (1041/1077; 96.7%), headache (1047/1077; 97.2%), and anorexia (1064/1077; 98.8%). There were more WHO stage one EVD infection (319/1077; 29.6%) or stage two EVD infection (582/1077; 54.0%) patients than stage three EVD infection (176/1077; 16.3%) patients.

Case fatality rates

We recorded an overall CFR of 25.9% (279/1077) among the patients with EVD. There was a statistically significant ($P < .05$) association between gender, age groups, and occupational levels and their respective CFRs. Men had higher CFR (31.1%) than women (CFR = 19.0%, $P < .0001$). Patients with EVD belonging to the age groups 0 to less than 5 years (CFR = 37.8%), 25 years to less than 35 years (CFR = 21.6%), 35 years to less than 45 years (CFR = 31.4%), and 45 years and above (CFR = 41.4%) recorded statistically significantly ($P < .0001$) higher CFRs than patients with EVD in the age groups 15 years and less than 25 years (CFR = 17.5%) and 5 years and less than 15 years (CFR = 16.7%). Patients with EVD with no education (CFR = 32.6%) or tertiary education (CFR = 33.9%) recorded statistically insignificantly ($P = .13$) higher CFRs than those with elementary school (CFR = 24.3%) or secondary school (CFR = 24.7%) levels of education. Children (CFR = 34.6%) and craftsmen (CFR = 33.8%) recorded statistically significantly (p = 0.0002) higher CFRs than patients with EVD who were pupils (CFR = 15.5%), students (CFR = 19.6%), nurses (CFR = 25.6%), bankers (CFR = 22.9%), housewives (CFR = 19.8%), and those patients with EVD who were unemployed (CFR = 26.2%). Patients with EVD who reported skin rash (CFR = 100%, $P < .0001$), or had stage three EVD infection (CFR = 89.8%, p < 0.0001), dyspnea (CFR = 77.1%, $P < .0001$), sign of conjunctivitis (CFR = 68.4%, $P < .0001$), dysphagia (CFR = 67.6%, $P < .0001$) or bleeding (CFR = 59.5%, $P < .0001$) reported high and statistically significant associations between these clinical features and their respective CFRs compared with those who did not report them. However, patients with EVD who reported fever (CFR = 23.9%, $P = .006$), abdominal pain (CFR = 29.1%, $P < .0002$), vomiting (CFR = 44.1%, $P < .0001$), fatigue (CFR = 39.2%, $P < .0001$), cough (CFR = 32.7%, $P < .0001$), or diarrhea (CFR = 34.2%, $P < .0001$) reported low but statistically significant positive association between these clinical features and their respective CFRs (Table 2).

Prognostic potential and scoring model

To predict the risk of dying during EVD treatment, we performed a backward stepwise logistic model on our final multivariable model based on the AIC. Only the EVD patients' characteristics sex; age group; education and occupation levels; and the clinical symptoms fever, muscle pain, diarrhea, vomiting, fatigue, bleeding, dysphagia, sign of conjunctivitis, and dyspnea were in the end of the backward selection process included in our final predictive model (Table 3).

To assess the risk of in-facility mortality, we used the methodology of Hartley et al [34] to construct a mortality risk score for the sociodemographic characteristics and clinical symptoms of patients with EVD that were included in our final predictive model by multiplying the coefficients by two and rounding the product to the nearest whole integer (Table 4).

We later obtained three in-facility mortality risk groups (low-, medium-, and high-risk groups) by consecutively attributing a third of the patients with EVD based on their range of risk scores; two vertical separator lines demarcated the entire risk score graph into these groups for ease of identification purposes (Table 5).

Calculating an exemplary EVD patient in-facility mortality risk score

As an example, using Table 4 and Figure 1, a male patient with EVD (+1), who belonged to the age group 5–15 years (−4) and was in elementary school (0), unemployed (+3), and reported fever (+1), vomiting (+3), fatigue (+2), dysphagia (+4), bleeding (+2), muscular pain (−5), diarrhea (+3), and had sign of conjunctivitis (+2) at the time of admission would have had an in-facility mortality risk score of 12; placing such patient with EVD in the high-risk category in this study. Patients with an in-facility risk score of 12 had in 100% of cases with fatal outcome. For example, of all the patients with EVD with an in-facility risk score of five, 63.2% ($n = 24/38$) had a fatal outcome.

The sensitivity and specificity of our predictive model-derived in-facility mortality risk scoring system based on the AUC shows

Table 5
Ebola in-facility mortality scorecard divided into low, medium, and high risk groups

Risk category	Low risk	Medium risk	High risk
Proportion of all patients with EVD	359	359	359
Risk group–specific CFR	0.56% (2/359)	9.75% (35/359)	67.41% (242/359)
In-facility mortality risk score	−5 and below	−4 to 1	2 and above

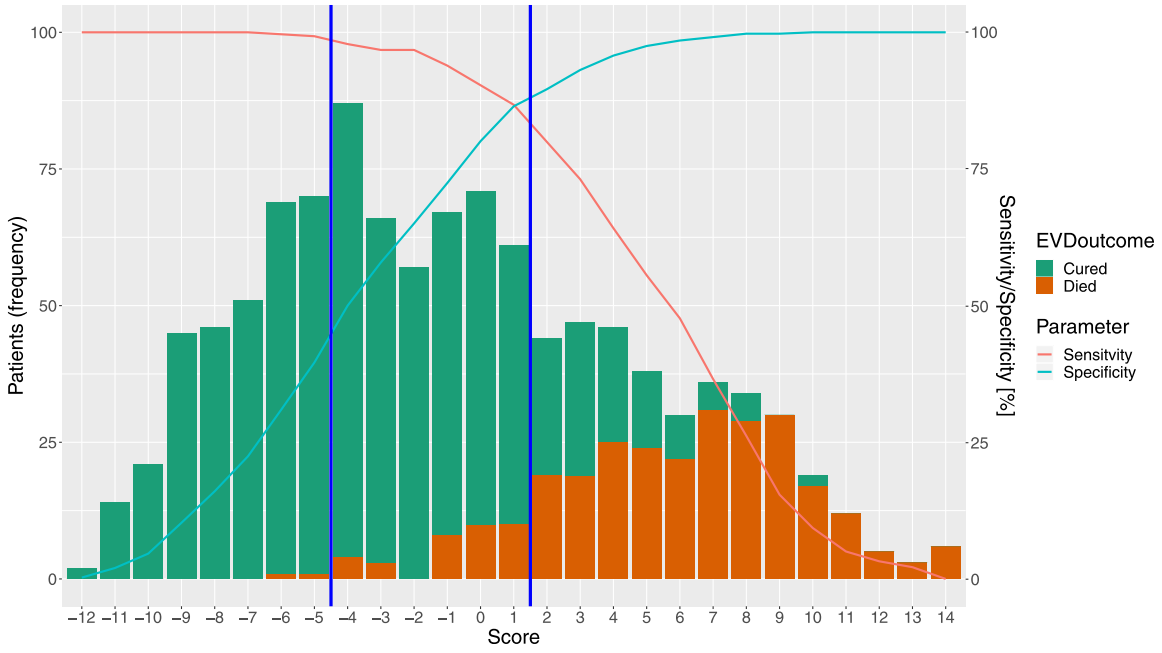

Fig. 1. EVD in-facility mortality and survival frequencies per risk score. The frequency of treatment outcome of patients with EVD with survival (green) and death (orange) based on the constellation of their sociodemographic and clinical characteristics were displayed as vertical bars on the risk score graph. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

that the following sociodemographic characteristics and clinical symptoms of patient with EVD; age group of 15 to <25 years; patient with EVD who reported diarrhea, vomiting, fatigue, bleeding, signs of conjunctivitis, muscular pain, dyspnea, and dysphagia; and can discriminate EVD cases who were cured or died during treatment with an AUC_{boot} of 93.3%. Our multivariate (original) model produced an $AUC_{original}$ of 93.4%. Our mean optimism is 0.05% [($AUC_{original}$−AUC_{boot}) × 0.5], whereas our optimism corrected AUC ($AUC_{correctedoptimism}$) for our predictive model was 93.35% ($AUC_{original}$−mean optimism). We later analyzed the prevalence rates of the clinical characteristics of the patients with EVD present in our predictive model alongside their respective in-facility mortality rates. The characteristics of being a male patient with EVD; patient with EVD with secondary education; and reporting muscle pain, fever, diarrhea, fatigue, and vomiting were each present in at least 50% of all patients and at the same time were each present in at least 60% of the fatal cases. Dysphagia that was not in our final predictive model and had <50% prevalence rate among EVD patients, however, recorded a prevalence rate of 74.9% in the in-facility fatal cases. All other sociodemographic characteristics and clinical symptoms of the patients with EVD that were not included in our predictive model had prevalence rates of <50% and were each associated with <50% in the in-facility fatal cases (Table 2).

Discussion

The main contribution of our study is to present an internally validated multivariable prognostic model for EVD treatment that was constructed from 1976 to 2016 the largest single Ebola treatment outcome data set containing the clinical and sociodemographic characteristics of patients with EVD to date. A patient with EVD exhibits a heterogeneous range of features from oligosymptomatic presentations to multiple organ failure. This characteristic could be associated with the pathophysiology of the Ebola virus when it affects different types of human organ tissues [16,36,37]. Diseases with a wide range of nonspecific clinical symptoms that are associated with different treatment outcomes present a challenge for case definition and detection because they are difficulty to differentiate from other endemic infectious diseases. Similarly, the establishment of the prognosis for a given patient based on signs of presentation poses a comparable challenge. Our statistically significant odds for dying and the respectively associated characteristics (age group 15 to < 25 years of age, presence of dysphagia, dyspnea, diarrhea, and vomiting) of patient with EVD in our predictive model were similar to those reported by Hartley et al in a study to predict Ebola infection among a cohort of Sierra Leonean patients [35]. Dyspnea and diarrhea which were highly weighted in our model were also reported as strong predictors of mortality in the multivariate prognostic score in the Hartley et al study, although with different AUC values: 91.0% (patient with EVD mortality rate at triage) and 97.5% (patient with EVD mortality rate after admission) [34].

One finding from our study is that patients with EVD who belonged to the age group 15 to < 25 years of age and those who reported dysphagia, dyspnea, diarrhea, or vomiting during the time of admission may have benefitted from clinically prioritization. As reported elsewhere, early and well-monitored administration of intravenous fluids can play a crucial role for patient outcomes [38]. Generally, the survival of such patients in resource-limited countries especially in Africa, where EVD outbreaks are taking place, is poor. The high CFR associated with EVD is thus within certain limits related to the supportive care patients receive in resource-limited rural settings which often reflects the difficulties in accessing basic medical care in a health care structure that is often overwhelmed during outbreak in this setting [17,20]. As a consequence there is a need for focused clinical attention, which due to limited resources requires risk stratification as a basis. This risk stratification can take the form of strict triage admission procedure during the early period of EVD outbreak when suspect cases mostly outnumber bed spaces in the specialized care facilities. Thus, our EVD risk scoring system and our rapidly calculable in-facility mortality scorecard will provide a more rigorous assessment of prognosis of patient with EVD by the clinician in resource-limited settings.

During an evolving EVD outbreak, our in-facility mortality risk scoring system will have a significant advantage over the WHO Ebola staging system [30] which includes stage one—that is characterized by nonspecific fever, headache, myalgia and can last for few days and has lower odds for dying than stages two and three [39]. The different levels of CFRs in the different EVD stages render the provision of uniform attention and therapies across all stages both inefficient and inappropriate [34]. Such blanket clinical attention by clinicians for all admitted patients with EVD may divert the much needed medical attention and logistics for assessing and treating of patients who have high risk scores in our predictive model but may have been overlooked in the WHO Ebola staging system. Our EVD in-facility mortality risk scoring system produced by a large number of permutations of the significant predictors of patient with EVD in-facility mortality and hence, serves as a good basis for clinical prioritization and patient admission.

In conclusion, our EVD in-facility mortality risk score provides a simplistic scoring system for patients with EVD of all ages with the aim of establishing a prognosis of the EVD infection. Our score can use also as a triage tool for differentiating levels of EVD case management on admission.

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