Sociodemographic and clinical determinants of in-facility case fatality rate for 938 Ebola patients treated in Sierra Leone

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Abstract

Background The 2013 – 2016 West Africa Ebola Virus Disease (EVD) outbreak recorded the highest incidence and mortality since the discovery of the virus in Zaire in 1976. Studies relating to previous outbreaks usually involved small sample sizes. In this study we are set to identify those sociodemographic and clinical features that predict in-facility mortality among EVD patients using a large sample size. Methods We analysed the anonymized medical records of 938 laboratory-confirmed EVD patients 15 years old and above that received treatment at the 34 Military Hospital and the Police Training School EVD Treatment Centers in Sierra Leone in the period June 2014 to April 2015. We used both univariable and multivariable logistic regression to determine the predictors for in-facility mortality of these patients based on their sociodemographic and clinical characteristics. Results The median age of the EVD cases was 33 years (interquartile range = 25 to 40 years). The majority of the EVD cases were male (59.0%) and had secondary level education (79.3%). A low overall in-facility case fatality rate of 26.4% was shown. The associations between case fatality rates and EVD patients who reported fever, abdominal pain, cough, diarrhoea, vomiting, fatigue, haemorrhage, dysphagia, conjunctival injection, dyspnoea, and skin rash at the time of admission were statistically significant ($p < 0.05$). Our preferred model with age group of EVD patients and the presence of the symptoms diarrhoea, vomiting, fatigue, dysphagia, conjunctival injection, dyspnoea and muscle pain produced a receiver operating characteristic (ROC) curve with an AUC (area under the curve) value of 0.94. Conclusions The age of EVD patients, as well those patients who reported vomiting, diarrhoea, fatigue, dysphagia, conjunctival injection, dyspnoea and muscle pain have increased odds of dying during treatment and hence will require prompt and intensive treatment at the time of admission. We argue that the high proportion of individuals with higher educational levels may have been a critical determinant for the low case fatality rate.

Introduction

The West Africa Ebola Virus Disease (EVD) outbreak in 2013 – 2016 recorded the highest prevalence and mortality since the discovery of the virus in Zaire in 1976.[1] A full genomic sequencing and phylogenetic analysis showed that the causative agent of the West African EVD outbreak was different from the strain responsible for previous EVD outbreaks in the Democratic Republic of Congo and Gabon.[2] More than 28,000 probable and confirmed EVD cases and 11,000 deaths were documented during the 2013 – 2016 EVD outbreak.[3] Sierra Leone recorded its first EVD case in May 2014 and also registered the highest incidence rate during the outbreak.[4] Differences in gendered EVD exposure level rather than sex differences are responsible for EVD transmission and vulnerability differences between men and women. The first EVD cases diagnosed in Sierra Leone occurred in women.[5] The incubation period for EVD depends on the mode of acquisition. Typically the EVD incubation period ranges from 2 – 21 days but may be shortened when transmission occurs directly e.g. by contaminated injection needles.[6,7] Different studies have identified several clinical symptoms for EVD. Barry et al reported asthenia (80%), fever (72%), vomiting (60%), diarrhea (34%),myalgia (23%) as frequent clinical signs of EVD infection alongside headache, general body ache, rash and haemorrhagic diathesis in either external or internal bleeding.[8] The overall Case Fatality Rate (CFR) for all cases of the West African EVD outbreak was 40% (11,314/28,634)[9] while the overall mean CFR based on WHO estimated confirmed cases with clinical outcomes for Guinea, Liberia and Sierra Leone for the same outbreak was 62.9% (95% CI 61.9–64.0%).[10] The CFR for confirmed cases with clinical outcomes for Sierra Leone, Guinea and Liberia were 68.9% (62.1% - 74.5%), 65.7% (61.4% - 69.5%), and 61.4% (55.9% - 67.3%) respectively.[11] The CFR for EVD cases with a prevalence of < 1% to 5.7% and 18.0% for specific haemorrhagic symptoms and “unexplained bleeding respectively during the 2013 – 2016 outbreak was 70.8%.[12]

Several organs and systems are generally affected during EVD infection. Schieffelin et al, discovered evidence of liver damage in both deceased and surviving EVD patients in Sierra Leone.[13] Another Sierra Leonean study in 2014 recorded low frequency for confusion and conjunctivitis among a mixed cohort of EVD patients.[14] The magnitude of CFR is associated with several factors. Generally, in a mixed cohort of EVD patients comprising of different sociodemographic groups, predictors of higher CFR were age [13-15], clinical presentation with confusion, diarrhoea, and conjunctivitis [13-16] and higher viremia following diagnosis. [13,14, 17] Additionally, CFR has been reported to vary according to the patient's occupational status. Dallatomasina S, et al recorded a higher (68%) CFR among health workers compared to other occupations (52%, p = 0.05). [18]

Previous studies relating to EVD infection usually involved small sample size. In one Ugandan study involving 56 laboratory confirmed EVD cases investigated by Roddy P et al, majority of the cases had non-bloody diarrhoea (81%), severe headache (81%), and asthenia (77%).[19] Qin E et al reported that the CFR for 62 positive EVD patients was 68.9% while the CFR for 31 positive EVD patients treated at the Moyamba Ebola Treatment Center in Sierra Leone was 58%.[20] In this investigation, we report on the clinical and sociodemographic characteristics as well as the treatment outcomes (CFR) of all laboratory - confirmed EVD cases that were treated by military personnel attached to the 34 Military Hospital and the Police Training School ETCs during the 2013 - 2016 outbreak in Sierra Leone. Our aim is to use our large dataset of 938 EVD patients to describe clinical and socio-demographic determinants for case outcomes and to construct a model that can best predict EVD in-facility CFR using the clinical and sociodemographic characteristics of these patients.

Materials And Methods

Study Design

In this retrospective cohort study we analysed the anonymized medical records of laboratory-confirmed EVD patients 15 years of age and above who received treatment at the 34 Military Hospital and the Police Training School ETCs in Sierra Leone from June 2014 to April 2015. A laboratory-confirmed EVD patient is defined as an ill person whose full blood, serum, or plasma specimen has been tested positive by quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay using EVD specific primers and probes. The medical records of the EVD patients that were analysed included the clinical symptoms as well as their sociodemographic characteristics. Data clerks attached to the 34 Military Hospital and the Police Training School first collected these data on hard copies of Case Report Form (CRF) at the time of admission of these EVD patients and later transferred them to a Microsoft Excel [21] form for both descriptive and model-based analyses.

Study Setting

During the 2013 - 2016 Ebola outbreak, most government referral hospitals and some district health hospitals in Sierra Leone served as either an ETC or an Ebola Holding Center (EHC). Additionally, several hospitals and health care facilities that were run by foreign organizations also operated ETCs. The 34 Military Hospital which provided data for this study, operated two ETCs; 34 Military Hospital and the Police Training School. Both ETCs were served by medical personnel attached to the 34th Military Battalion of the Sierra Leone Armed Forces (SLAF). The 34 Military Hospital is headed by a Brigadier Surgeon General and is assisted by medical doctors and paramedics.

Ethics Review

This study was approved by 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). The Sierra Leone Ethics and Scientific Review Committee granted us ethical clearance and waivered the requirement to obtain individual informed consent from EVD patients on confidentiality purpose since we were analyzing facility-specific aggregated medical records.

Data Collection and Processing

EVD patients in this study had reported at the 34 Military Hospital and the Police Training School ETCs in Freetown either independently or through the National Ebola Response Committee (NERC) surveillance system. The suspected EVD patients were first screened at the 34 Military Hospital Accident and Emergency Department that was converted into a triage center to handle all suspected EVD cases during the outbreak. Similar screening for signs and symptoms of EVD was also done for suspected EVD patients at the Police Training School triage. At the triage center data entry clerks compiled the medical records of all suspected EVD cases. An EVD suspected case is defined as a person with acute onset of fever >38˚C with any of the following additional symptoms: severe headache, muscle pain, vomiting, diarrhoea, abdominal pain, or unexplained haemorrhage; and had a direct contact with a suspected/confirmed EVD case or has unexplained multisystem illness that is not malaria.[22]The suspected EVD patients were later transferred to an isolation unit (EVD holding center) for temporary admission while they were awaiting their EVD laboratory test result. Confirmed EVD patients were categorized into: Stage One (early phase) EVD patients that were febrile and presented with no vomiting, diarrhoea, or organ dysfunction at the time of admission; Stage Two (wet phase) EVD patients presented with vomiting or diarrhoea; and Stage Three (organ dysfunction phase) EVD patients are characterised by organ dysfunction. This study considered an EVD treatment outcome to be successful when an EVD patient was released alive after treatment. EVD patients who died during treatment within the facility are considered as treatment failure. Our medical records did neither account for Ebola viral load which is reflected by the cycle threshold on RT-PCR, nor for the delay in seeking treatment which is determine by the date of EVD symptom onset and the first day of seeking treatment.

Treatment Protocol

All EVD cases in this study were routinely provided oral rehydration salts (ORS) and other supplements to correct for electrolyte imbalance. The dose of ORS depended on the degree of dehydration of the EVD patient. Also, acetaminophen or ibuprofen (for muscle pain and headache), the anti-infective ciprofloxacin or cefixime, and the anti-malaria drug naphthoquine phosphate tablets were also given. Additionally, ranitidine or omeprazole were given to those patients experiencing upper abdominal pain. These treatment protocols practiced by clinicians at the two ETCs remained the same throughout the period under investigation and were performed in accordance with the World Health Organisation (WHO) protocol of urgent interim guidance for EVD case management for viral haemorrhagic fever. [22] The treatment protocols in the other Sierra Leone ETCs operating during the 2013 - 2016 EVD outbreak practiced mostly supportive care aimed at maintaining electrolyte balance by providing ORS to EVD patients.

Statistical Analysis

All data analysis in this study were done using R software package version3.3.1.[23] In this study, p-values < 0.05 were considered significant for all two-sided statistical tests. The outputs of our descriptive analysis were presented as frequencies, proportions, means and standard deviations (for continuous variables if they are normally distributed); medians and interquartile ranges (for continuous variables that are not normally distributed). Chi square tests were used to compare proportions of categorical variables. We used both univariable and multivariable logistic regression analysis to identify the clinical and non-clinical characteristics of EVD patients that were associated with EVD in-

facility mortality. An Area Under the Curve (AUC) obtained from the Receiver Operating Characteristic curve (ROC curve) was used to determine the discriminating capacity of our model's ability to discriminate between EVD patient who will be released alive from those who die during treatment given certain clinical and sociodemographic characteristics.

Results

Ebola patient characteristics

Overall we analysed the medical records of 938 EVD cases. Majority of the patients were male (59.0%, n = 553/938) and had secondary school education (79.3%, n = 744/938). The median age of our cohort group was 33 years (interquartile range = 25 - 40 years). Fever (77.7%, n = 729/938), headache (97.6%, n = 915/938), anorexia (98.7%, n = 926/938), muscle pain (96.5%, n = 905/938) chest pain (84.5%, n = 793/938), abdominal pain (73.9%, n = 693/938), diarrhoea (71.4%, n = 670/938), and fatigue (60.9%, n = 571/938) were the most reported symptoms at admission. A majority (52.6%, n = 493/938) of the cases were Stage Two EVD infection. The overall CFR recorded in this study was 26.4%. The differences in CFRs by sex, age group and occupational level for our cohort were statistically significant ($p < 0.05$). The CFR for male (30.7%, n = 170/553) was higher than female (20.3%, n = 78/385). EVD patients belonging to the age group 15 years to < 20 recorded the lowest CFR (10.7%, n = 8/75) while those of the age groups 60 years to < 65 years (66.7%, n = 12/18) and 65 years and above (76.9%, n = 10/13) recorded the highest. Craftsmen (33.9%, n = 129/381), and nurses (28.6%, n = 10/35) recorded the highest CFRs amongst the occupational group in this study. There was an increase in CFRs by an increase in education level; elementary (CFR = 22.8%, n = 18/79), secondary (CFR = 25.7%, n = 191/744) and tertiary (CFR = 33.9%, n = 39/115) although this association was not statistically significant ($p = 0.13$) (Table 1).

Table 1. Sociodemographic characteristics and case fatality rates of EVD patients treated at 34 Military Hospital and Police Training School ETCs during the 2013-2016 Ebola outbreak

Skin rash (CFR = 100.0% , n = 26/26, $p < 0.05$), Stage Three EVD infection (CFR = 90.6%, n = 145/160, $p < 0.05$), dyspnea (CFR = 77.1%, n = 118/153, $p < 0.05$), conjunctival injection (CFR = 70.5%, n = 122/173, $p < 0.05$), dysphagia (CFR = 68.5%, n = 196/286, $p < 0.05$), and haemorrhage (CFR = 58.4%, n = 59/101, $p < 0.05$) recorded higher CFRs when compared to other symptoms in this study. Vomiting (CFR = 44.6%, n = 214/480, $p < 0.05$), fatigue (CFR = 40.6%,n = 232/571, $p < 0.05$), diarrhoea (CFR = 35.1%,n = 235/670, $p < 0.05$), cough (CFR = 34.8%, n = 147/423, $p < 0.05$), abdominal pain (CFR = 29.4%,n = 204/693, $p = 0.001$), and fever (CFR = 24.3%, n = 177/729, $p < 0.05$) recorded statistically significantly lower CFRs (Table 2).

Table 2. Clinical symptoms and case fatality rates of EVD patients treated at 34 Military Hospital and Police Training School ETCs during the 2013-2016 Ebola outbreak

EVD In-facility Case Fatality Rates

From our stepwise multivariate logistic regression analysis, EVD patients 25 years to < 30 years (AOR = 4.24, 95% CI =1.06 – 18.30, $p < 0.05$), 35 years to < 40 years (AOR = 4.26, 95% CI = 0.10 – 19.24, $p < 0.05$), 40 years to < 45 years (AOR = 4.98, 95% CI =1.12 – 24.09, $p < 0.05$), 50 years to < 55 years (AOR = 14.92, 95% CI = 2.37 – 100.28, $p < 0.05$), 60 years to < 65 years (AOR = 75.51, 95% CI = 1.07 – 582.61, $p < 0.05$), and 65 years and above (AOR = 29.51, 95% CI = 2.95 – 340.35, $p < 0.05$), diarrhoea (AOR = 6.93, 95% CI = 2.76 – 19.59, $p < 0.05$), vomiting (AOR = 4.83, 95% CI = 2.57 – 9.43, $p < 0.05$), fatigue (AOR = 3.95, 95% CI = 1.79 – 9.30, $p < 0.05$), dysphagia (AOR = 10.08, 95% CI = 5.77 – 18.05, $p < 0.05$), dyspnea (AOR = 3.44, 95% CI = 1.82 – 6.61, $p < 0.05$), haemorrhage (AOR = 1.45, 95% CI = 0.29 – 7.15, p <

0.05) and conjunctival injection (AOR = 4.05, 95% CI = 2.19 – 7.65, p < 0.05) at the time of admission had increased odds of dying compared to patients in other age groups or those that did not report these symptoms at the time of admission. EVD patients who reported muscle pain (AOR = 0.08, 95% CI = 0.02 – 0.43, p < 0.05) have reduced odds of dying compared to those who did not report this symptom at the time of admission (Table 3).

Table 3. Multivariate Analysis of In-facility Case Fatality Rates

Table 3 shows the output of a univariate and a multivariate analysis of EVD patients' sociodemographic and clinical variables associated with treatment outcomes. The crude OR was obtained by a logistic regression model with only one variable as predictor. The adjusted OR was obtained from a multivariate logistic regression model, starting with all available sociodemographic and clinical predictors, after a stepwise backward elimination using the Akaike Information Criterion (AIC).

The AUC value of the ROC curve for our preferred model which included the age group of EVD patients and the presence of the symptoms diarrhoea, vomiting, fatigue, dysphagia, conjunctival injection, dyspnea and muscle pain at the time of admission was 0.94 (Figure 1).

Figure 1. ROC Curve on EVD Treatment Survival Determinants and Treatment Outcome

The ROC curve shows that the logistic model after stepwise logistic regression selection has a high capacity to discriminate EVD patient's treatment outcome using patients' clinical and demographic characteristics.

When prioritizing an optimal positive predictive value for fatal outcome, a threshold of 0.945 was arbitrarily set. Here, our model was able to successfully identify in terms of test sensitivity 197/ 248 (79.4%) those EVD patients who actually died during treatment (Table 4).

Table 4. Matrix of actual and predicted treatment of outcome for EVD patients

From the matrix, the test sensitivity, specificity, positive predictive value and negative predictive value of our model are 79.4% (197/248), 100 % (690/690), 100% (197/197) and 93.1% (690/741) respectively.

Discussion

A wider range of CFRs were reported during the 2013 - 2016 EVD outbreak in different locations and settings.[10-14] The heterogeneities in the CFR has been associated with the subpopulation investigated as well as various pre-selection biases.[10,11] We reported a favorable CFR (26.4%) among confirmed EVD cases treated at two ETCs in Freetown, Sierra Leone as compared to the WHO overall mean CFR (62.9%) for Guinea, Liberia and Sierra Leone[12] and the estimated CFR of 74.2% (95% CI: 72.6%–75.5%) for Sierra Leone computed by Wong et al [24] for the same category of EVD cases during the same outbreak. The WHO computed CFR of 28% (3956/14124) [25] for Sierra Leone was also slightly higher than ours. The reasons for these CFR variations is unclear but could not be unconnected to the existence of well-established health education programs in certain communities which enable suspected EVD patients to seek early medical treatment, the type of professional health care and treatment regimen in our ETCs at the time compared to those implemented in other ETCs in the country. Unlike other ETCs across the country such as those ran by Medecins Sans Frontier that only administered to their EVD patients oral medications like oral rehydrating salts (ORS), nutritional supplements, fever and pain relieving drugs, as well as drugs to reduce vomiting and diarrhoea[26]; the medical staff at the 34 Military Hospital and the Police Training School ETCs intravenously administered the following treatment at different rates to their EVD patients throughout the entire period of the epidemic in the country:

dextrose 500 mL + normal saline 500 mL, every 8 hours daily, metroclopramide 10 mg three times daily for 3 days, ceftriaxone 1 g, once daily for 3 days, metronidazole 500 mg/100-mL 3 times daily for 2 days, and ciprofloxacin 200 mg/100-mL twice daily for 2 days. Parenteral drug administration - especially intravenous (IV) drug administration provides immediate onset of drug action. It also offers an easy method to rapidly administer solution and other bodily nutrients into either continuously or intermittently. Additionally, administering drugs via IV yields rapid changes in the cardiocirculatory system [27], as well as lead to an appreciable increase in blood and plasma volumes [27-29]which makes the monitoring of the delivered fluids, electrolytes and nutrients – especially in patients with gastrointestinal tract impairment much easier. For patients at the various stages of EVD infection, the loose of bodily fluid, electrolytes and nutrients are the major clinical effect of the disease. Replacing lost bodily fluids effectively and rapidly via IV administration is thus a life saver for EVD patients. Also, the IV administration of drugs offers added advantage when specifically applied to Stage Three EVD patients who are characterised with organs and systems dysfunctions - which makes the oral administration of medication ineffective. Using IV drug administration on Stage Three EVD patients will ensure the rapid and effective delivery of the much needed body fluids and electrolytes to this subset of patients. One unique feature of the treatment regimen offered to EVD patients in our study is the intravenous administration of the antimalarial drug; artesunate 120-mg once daily for 3 days irrespective of their malaria status. Sierra Leone is a malaria endemic country with malaria incidence peaking during the period in which this study was conducted; the occurrence of such malaria transmission period at the period during which this study was conducted raised the suspicion of occult malaria infection and hence warranted the administration of such drug. Many studies have reported different treatment outcomes for EVD patients co-infected with malaria.[30-36] Treating patients for EVD and malaria simultaneously will invariably improve the prognosis of these patients and hence lower the CFR. In addition to the specific case management offered to our EVD patients, medical staffs also provided analgesic such as paracetamol tablets 500 mg (twice daily for 2 days) to relieve their pain as well as the vitamin supplement; immunoboost capsules to boost their appetite. Many patients in our cohort reported muscle pain (n = 905, 96.5%), chest pain (n = 793, 84.5%) abdominal pain (n = 693, 73.9%) and anorexia (n = 926, 98.7%) at the time of admission which makes the administration of such analgesic and vitamin supplement drugs necessary.

This CFR difference may also have been due to incomplete case ascertainment, thoroughness of reporting EVD clinical outcome and the epidemiological case definitions used.[10] For example during the peak of the West African EVD outbreak, clinical outcome was reported for nearly all confirmed cases in Guinea, but for only few for such cases in Liberia and Sierra Leone due to the overstretching of healthcare facilities.[10] Our CFR differs from those naïve CFRs which were simply obtained by dividing the number of deaths by the point prevalence. Naïve CFR fails to account for the significant proportion of reported EVD cases that died; delays in EVD onset and its final outcome, and only recognizes the clinical outcome computed for a fraction of the EVD cases.[10,11] Our low CFR which stemmed from the analysis of the cumulative EVD incidence cases and the total number of those cases that died during treatment in our ETCs however also failed to account for the delay from the onset of EVD signs and symptoms to the time of seeking treatment; hence our cases may not have been truly representative of the overall national characteristics of reported EVD cases in Sierra Leone. Generally, studies that are less representative produce CFR estimates that vary with the national estimate and are often considerably lower. [8, 20] We agree that our low CFR may be associated with the large number of Stage One (n = 285, 30.5%) and Stage Two (n = 493. 52.6%) EVD patients in our cohort compared to Stage Three EVD patients (n = 160, 17.1%). Both Stage One (CFR = 3.2%) and Stage Two (CFR = 37.9%) EVD patients have low risk of dying compared to Stage Three EVD patients (CFR = 90.6%). However, one major finding in our study that's worth discussing is the high CFR and AOR associated with nurses (CFR = 28.6%, AOR = 1.41, 95% CI = 0.21 – 8.39), craftsmen (CFR = 33.9%, AOR = 1.13, 95% CI = 3.10 – 4.10), and patients in the unemployed category (CFR = 26.2%, AOR = 1.44, 95% CI= 1.00 – 14.65) compared to EVD patients of other occupation status. These high CFR and AOR can be attributed to both the EVD over - exposure and the lack of knowledge about the transmission dynamics of the

infection during the early period of the epidemic. Nurses like other healthcare workers have been specifically linked with high EVD incidence and CFR [18, 37-39] as a result of occupational exposure. Also, the nonspecific clinical symptomology of EVD makes it's differentiation from other tropical febrile infections during the early phase of the outbreak a challenge to many clinicians and health care workers[40] resulting to delay in seeking EVD treatment and hence leading to high CFR and AOR. The high CFR and AOR for both craftsmen and unemployed EVD patients can be attributed to their unstable risky living conditions which over-exposed them to people with high risk for EVD infection. This over - exposure to EVD when coupled with the lack of EVD health education and transmission dynamics can results to high CFRs and AORs. Public health education has been very useful in understanding the signs and symptoms of EVD, its evolution and mode of transmission [41, 42] since it enables people to seek early treatment. Levy B et al have previously linked the severity (CFR) of an EVD outbreak to the level of prior knowledge and health education of the general population. [43]

That notwithstanding, one major strength of our study is that in-facility investigations like ours are essential when investigating the determinants of CFR since they often have well-defined inclusion criteria. On the other hand, we have to admit that an in-facility CFR in fact does refer to a pre-selected subgroup of patients, and a-priori excludes an important group of EVD-cases that either does not make it to an ETC, or that are not admitted due to limited sensitivity in the employed case definitions. Our study can be used to assess and evaluate the efficacy of the treatment methods used in our treatment facilities as well as to compare them with others in different parts in Sierra Leone. However, the fact that our CFR is based on in-facility data this presents a challenge, since external validity towards settings outside an ETC is limited.

Haemorrhagic manifestation generally was not a prominent feature during the West Africa EVD outbreak.[13] Our haemorrhagic prevalence of 10.8% (n = 101/938) was higher than that of the WHO Ebola team in West Africa (< 1% to 5.7%)[12] but lower than those of Barry M, et al (26%)[8], Qin et al (13.1%)[20], Haaskjold Y, et al (35%)[9] and Bah et al (51.0%)[44] for the 2013 – 2016 outbreak. Bah et al had also reported subconjunctivital bleeding/conjunctivitis for the 2013 – 2016 EVD outbreak [44] which is associated with death in EVD infected children[45]; a predictive EVD sign [46], that is detectable in 45% - 60% of the patients[47] but was not considered a risk factor for death during the 2014 EVD outbreak in the Democratic Republic of Congo.[48] Our haemorrhagic prevalence indicates that the symptom was a not un-common clinical symptom among EVD patients in the West African outbreak, hence patients presenting with haemorrhage should be prioritized at all levels of EVD patient treatment and management. We recorded a higher prevalence and CFR for EVD cases with gastrointestinal symptoms (diarrhoea and vomiting). The CFR for diarrhoea and vomiting were 35.1% (n = 235/670, $p < 0.05$) and 44.6% (n = 214/480, $p < 0.05$) respectively. Correspondingly, EVD patients with diarrhoea (AOR =6.93, 95% CI = [2.76 – 19.59], $p < 0.05$) and vomiting (AOR = 4.83, 95% CI = [2.57 – 9.43], $p < 0.05$) have increased odds of dying during EVD treatment than those without these symptoms. Gastrointestinal symptoms were common clinical presentations during the 2013 - 2016 West Africa EVD outbreak. [9,15,20,49] Although metabolic tests were not done on our EVD patients both at the time of admission or during hospitalization, the high CFR for both diarrhoea and vomiting in this study can be associated with their roles on several metabolic abnormalities including metabolic acidosis and alkalosis. Diarrhoea and vomiting can cause hypovolemic shock and metabolic hyperchloraemic acidosis through dehydration.[50] Schieffelin JS et al had previously reported the presence of acidosis and elevated blood urea nitrogen and creatinine as predictors for EVD diagnosis and fatality.[13]Our statistically significantly higher CFR values and odds ratios for both diarrhoea and vomiting thus indicate that these clinical features should be recognized during EVD screening, patient management and transmission control mechanism during early EVD outbreaks. The majority of the EVD cases in our study had fever, headache, anorexia, muscle pain, chest pain, abdominal pain, diarrhoea, and fatigue which are consistent with

studies by Bah et al[44], Mupere et al [51], and Theocharopoulos et al[52]. Bah et al reported a 43.0% overall CFR in their study in which majority of the study participants had fever (84.0%), fatigue (65.0%), and diarrhoea (62.0%).[44] Mupere et al reported that more than 50% of EVD cases presented with either fever, headache, weakness, anorexia, diarrhea, or vomiting at the time of admission.[51]Theocharopoulos G, et al studied 249 confirmed EVD cases and reported a 44.0% overall CFR of which malaise (90.0%), fever (83.0%), diarrhoea (63.0%), headache (73.0%) and vomiting (60.0%) were the common symptoms.[52] The majority of these EVD clinical symptoms are similar to that of other tropical infections such as malaria, yellow fever, dengue, cholera or Lassa fever. This similarity in clinical symptomology makes the use of a single symptom checklist inadequate in EVD outbreak foci. This dilemma leads to calls for EVD case definition criteria with higher discriminatory capacity during early outbreak periods. An EVD outbreak case definition tool with high discriminatory capacity is needed during the early phase of EVD outbreak in order to differentiate non-EVD patients from confirmed, suspected or probable EVD cases especially within healthcare setting where the risk of nosocomial EVD transmission is high. Additionally, such tool will be able to identify those cases with high risk of dying during the early phase of an EVD outbreak based on the clinical symptoms and sociodemographic characteristics contained in our model thereby ensuring the diversion of much needed logistics. Mupere E et al had earlier proposed an EVD case definition to include the categorization of risk for EVD as suspected, probable or contacts cases.[51] Such EVD risk categorization if included in the case definition for EVD lacks the descriptive specificity for a clinically useful case definition and hence cannot be incorporated for widespread use during EVD outbreak. Our high AUC (0.94) as quantification of discriminatory capability to discriminate between EVD patients who were treated and released alive from those who died during treatment has both clinical and prognostic relevance because it allows a best possible identification of patients that are in need of the usually scarce resource of intensified attendance. Given the limited availability of EVD treatment logistics during EVD outbreaks in resource-constrained settings, the allocation of resources (medical attention, materials, bed space) to individuals identified as high-risk patients at the time of admission through the use of algorithms as stipulated by our model could have predicted with 100% and 93.1% accuracy these patients as dying or surviving in the past outbreak respectively. Our model will be equally useful where patient safety with avoidance of nosocomial EVD infections within facilities becomes a dominant concern.

One important limitation of our study is that our medical records did not capture the Ebola viral load of our patients at the time of their admission as well as the date of EVD onset as determined by the appearance of EVD signs and symptoms. Because of this limitation we were unable to determine the effect treatment delay and viral load would have had on EVD treatment outcome. Hence our findings have to be seen in the context of the treatment facilities that were located in Sierra Leone which therefore requires its potential external validity to be taken with caution. Another limitation is the non-availability of data on presented but non-confirmed patients. The comparison to this group would have allowed for a differentiated analysis of clinical presentation between confirmed and non-confirmed patients. In any case, in the triage settings as they were found in the 2013 - 2016 outbreak in West Africa, data on CFR for non-confirmed patients is largely missing due to generally lacking further management capacities for these patients at the height of the epidemic: they were mostly dismissed and left on their own. Additionally, we did not follow up EVD patients who were released alive following treatment in order to determine the factors that may be associated with late post-release mortality. An important finding from these follow up visits would have been to conduct a comparison between confirmed EVD and non-EVD patients alongside their calculable attributable risks. The non-inclusion of non-EVD patients in our data base who may have suffered from substantial morbidity and mortality collaterally to EVD should thus receive considerably attention in future settings.

Conclusion

Our study successfully showed that, the age of EVD patients, as well those patients who reported vomiting, diarrhoea, fatigue, dysphagia, conjunctival injection, dyspnea and muscle pain have increased odds of dying during treatment and hence will require prompt and intensive treatment at the time of admission. We also argued that the high proportion of individuals with higher educational levels may have been a critical determinant for the low case fatality rate in our study.

Declarations

Ethics approval and consent to participate

The Sierra Leone Ethics and Scientific Review Committee (Opinion date 29 March 2017) and the Institutional Review Board at the Ludwig-Maximillian's Universidad Munched, Germany (Opinion No. LMU 17-582) approved this study. The Sierra Leone Ethics and Scientific Review Committee provided ethical clearance for conducting this study.

Consent for publication

Not Applicable

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to patient confidentiality and the sensitive nature of this study. This is an aggregate dataset that is being protected by the Sierra Leone Ethics and Scientific Review Committee in order to protect the identity of the patients whose medical data were analyzed.

Competing interests

None

Funding

No part of this study received funding or compensation whatsoever during its conception, execution or for publication.

Authors' contribution

JK and GF conceived and designed this study as well as organized the conduct of this research in the research field. JK, CH and GF performed the statistical analysis. JK and GF drafted the manuscript. GF, CH, FS and MH critically reviewed and revised the manuscript. FS oversaw the collection and collating of the research data. JK obtained ethical clearance.

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Authors' information

Not applicable.

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Tables

Table 1. Sociodemographic characteristics and case fatality rates of EVD patients treated at 34 Military Hospital and Police Training School ETCs during the 2013-2016 Ebola outbreak

EVD patients' sociodemographic Characteristics	N (%)	Survived N (%)	Died N (%)	Case fatality rate (%)	p-values*
Total	938 (100)	690 (73.6)	248 (26.4)	26.4	
Female	385 (41.0)	307 (44.5)	78 (31.4)	20.3	< 0.05
Male	553 (59.0)	383 (55.5)	170 (68.5)	30.7	
15 to < 20 years	75 (8.0)	67 (9.7)	8 (3.2)	10.7	< 0.05
20 to < 25 years	142 (15.1)	112 (16.2)	30 (12.1)	21.1	
25 to < 30 years	119 (12.7)	82 (11.9)	37 (14.9)	31.1	
30 to < 35 years	182 (19.4)	154 (22.3)	28 (11.3)	15.4	
35 to < 40 years	162 (17.3)	113 (16.4)	49 (19.8)	30.2	
40 to < 45 years	125 (13.3)	84 (12.2)	41 (16.5)	32.8	
45 to < 50 years	52 (5.6)	38 (5.5)	14 (5.7)	26.9	
50 to < 55 years	31 (3.3)	16 (2.3)	15 (6.0)	49.4	
55 to < 60 years	19 (2.0)	21 (2.2)	4 (1.6)	21.1	
60 to < 65 years	18 (1.9)	6 (0.9)	12 (4.8)	66.7	
65 and above	13 (1.4)	3 (0.4)	10 (4.0)	76.9	
Elementary Education	79 (8.4)	61 (8.8)	18 (7.3)	22.8	0.13
Secondary Education	744 (79.3)	553 (80.1)	191 (77.0)	25.7	
Tertiary Education	115 (12.3)	76 (11.0)	39 (15.7)	33.9	
Uncategorized Employment	96 (10.2)	82 (11.9)	14 (5.7)	14.6	< 0.05
Student	50 (5.3)	40 (5.8)	10 (4.0)	20.0	
Nurse	35 (3.7)	25 (3.6)	10 (4.0)	28.6	
Banker	109 (11.6)	84 (12.2)	25 (10.1)	22.9	
Housewife	164 (17.5)	131 (19.0)	33 (13.3)	20.1	
Craftsman	381 (40.6)	252 (36.5)	129 (52.0)	33.9	
Unemployed	103 (11.0)	76 (11.0)	27(10.9)	26.2	

***** p - value was obtained by applying chi square test

Table 2. Clinical symptoms and case fatality rates of EVD patients treated at 34 Military Hospital and Police Training School ETCs during the 2013-2016 Ebola outbreak

EVD patients clinical symptoms	Total with available data N (%)	Survived N (%)	Died N (%)	Case fatality rate (%)	p-value*
Total	938 (100)	690 (73.6)	248 (26.4)	26.4	
Fever	729 (77.8)	552 (80.0)	177 (71.4)	24.3	< 0.05
Headache	915 (97.6)	669 (97.0)	246 (99.2)	26.9	0.09
Anorexia	926 (98.7)	683(99.0)	243(98.0)	26.2	0.39
Muscle pain	905 (96.5)	668 (96.8)	237(95.6)	26.2	0.48
Chest pain	793 (84.5)	583(84.5)	210 (84.7)	26.5	1.00
Abdominal pain	693 (73.9)	489 (70.9)	204 (82.3)	29.4	< 0.05
Cough	423(45.1)	276(40.0)	147 (59.3)	34.8	< 0.05
Diarrhoea	670 (71.4)	435 (63.0)	235 (94.8)	35.1	< 0.05
Vomiting	480 (51.2)	266 (38.6)	214 (86.3)	44.6	< 0.05
Fatigue	571 (60.9)	339 (49.1)	232 (93.6)	40.6	< 0.05
Skin rash	26 (2.8)	0 (0.0)	26 (10.5)	100.0	< 0.05
Haemorrhage	101(10.8)	42 (6.1)	59 (23.8)	58.4	< 0.05
Difficulty swallowing	286 (30.5)	90 (13.0)	196 (79.0)	68.5	< 0.05
Conjunctival injection	173 (18.4)	51 (7.4)	122 (49.2)	70.5	< 0.05

Difficulty breathing	153 (16.3)	35 (5.1)	118 (47.6)	77.1	< 0.05
Stage One EVD infection	285 (30.4)	276 (40.0)	9 (3.6)	3.2	< 0.05
Stage Two infection	493 (52.6)	399 (57.8)	94 (37.9)	19.1	
Stage Three EVD infection	160 (17.1)	15 (2.2)	145 (58.5)	90.6	

* p - value was obtained by applying chi square

Table 3. Multivariate Analysis of In-facility Case Fatality Rates

Patient symptoms	Crude OR	95% CI	Adjusted OR	95% CI
Sex–Male	1.75	1.29 -2.38	1.28	0.73 - 2.26
20 to < 25 years	2.24	1.01 - 5.51	3.26	0.93 - 12.39
25 to < 30 years	3.78	1.72 - 9.23	4.24	1.06 - 18.30
30 to < 35 years	1.52	0.69 - 3.74	2.04	0.47 - 9.47
35 to < 40 years	3.63	1.70 - 8.70	4.26	0.10 - 19.24
40 to < 45 years	4.09	1.88 - 9.93	4.98	1.12 - 24.09
45 to < 50 years	3.09	1.21 - 8.36	1.96	0.38 - 10.68
50 to < 55 years	7.85	2.92 - 22.70	14.92	2.37 -100.28
55 to < 60 years	2.23	0.54 - 8.13	1.05	0.11 – 9.63
60 to < 65 years	16.75	5.16 - 61.26	75.51	1.07 – 582.61
65 and above	27.92	6.99-146.27	29.51	2.95 - 340.35
Secondary education	1.17	0.69 - 2.08	0.83	0.22 – 3.29
Tertiary education	1.74	0.92 - 3.39	2.43	0.72 - 8.53
Student	1.46	0.59 - 3.57	0.94	0.21 - 4.00
Nurse	2.34	0.91 - 5.91	1.41	0.21 - 8.39
Banker	1.74	0.86 - 3.67	0.55	0.11 - 2.62
Housewife	1.48	0.76 - 3.00	0.80	0.19 - 3.29
Craftsmen	3.00	1.69 - 5.70	1.13	0.31 - 4.10
Unemployed	2.08	1.03 - 4.36	3.81	1.00 - 14.65
Fever	0.62	0.45 - 0.87	1.44	0.26 - 7.98
Headache	3.86	1.12 - 24.25	0.66	0.12 - 5.50
Chest pain	1.01	0.68 - 1.53	1.61	0.36 - 7.18

Abdominal pain	1.91	1.33 - 2.77	0.71	0.14 - 3.58
Cough	2.18	1.62 - 2.94	1.56	0.27 - 9.12
Vomiting	10.03	6.86 -15.08	4.83	2.57 - 9.43
Diarrhoea	10.60	6.17 - 19.85	6.93	2.76 - 19.59
Fatigue	15.01	9.13 - 26.44	3.95	1.79 - 9.30
Dysphagia	25.12	17.36 -36.97	10.08	5.77 - 18.05
Haemorrhage	4.82	3.15 - 7.42	1.45	0.29 - 7.15
Conjunctival injection	12.13	8.36 - 17.84	4.05	2.19 - 7.65
Dyspnoea	16.99	11.26 -26.21	3.44	1.82 - 6.61
Muscle pain	0.71	0.35 - 1.54	0.08	0.02 - 0.43
Anorexia	0.50	0.16 - 1.70	0.51	0.06 - 4.44

Table 3 shows the output of a univariate and a multivariate analysis of EVD patients' sociodemographic and clinical variables associated with treatment outcomes. The crude OR was obtained by a logistic regression model with only one variable as predictor. The adjusted OR was obtained from a multivariate logistic regression model, starting with all available sociodemographic and clinical predictors, after a stepwise backward elimination using the Akaike Information Criterion (AIC).

Table 4. Matrix of actual and predicted treatment of outcome for EVD patients

Predicted EVD treatment outcome	EVD treatment survivors	EVD treatment fatalities	Total
Predicted EVD survivors	690	51	741
Predicted EVD fatalities	0	197	197
Total	690	248	938

From the matrix our model was successful in predicting all those EVD patients who survived where as it only identified 79.4% (197/248) of those that died during treatment. The test sensitivity, specificity,

positive predictive value and negative predictive value of our model are 79.4% (197/248), 100% (690/690), 100% (197/197) and 93.1% (690/741) respectively.

Figures

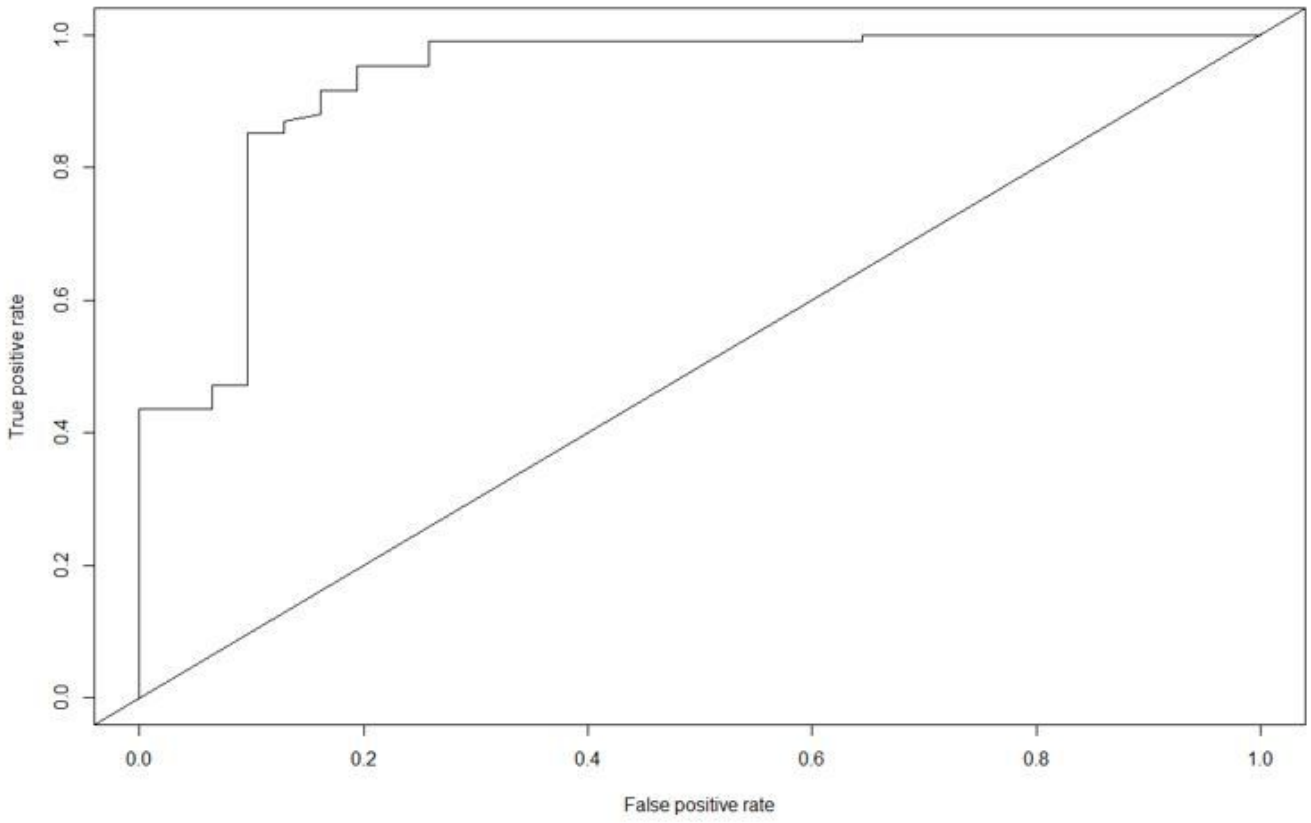

Figure 1

ROC Curve on EVD Treatment Survival Determinants and Treatment Outcome The ROC curve shows that the logistic model after stepwise logistic regression selection has a high capacity to discriminate EVD patient's treatment outcome using patients' clinical and demographic characteristics.