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Treatment outcome and survival analysis of Ebola patients receiving treatment in Sierra Leone

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Abstract

Background

Ebola Virus Disease (EVD) was first discovered in 1976 in Zaire along Ebola River affecting more than 250 people and had a mortality rate of 53%. Currently, there are five (Zaire ebolavirus, Reston ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus and Bundibugyo ebolavirus) strains of Ebola Virus. The Zaire ebolavirus has the highest (88%) mortality rate; Reston ebolavirus was discovered in Reston, Virginia, USA in 1989 in imported monkeys from Mindanao, Tai Forest ebolavirus was accidently discovered in 1994 in Tai Forest, Cote d'Ivoire. In 2005, the first direct evidence implicating bats as reservoir host for Ebola Virus emerged. EVD has various symptoms including fever, hemorrhage, myalgia, and diarrhea. There were more than 8,000 confirmed EVD cases and more than 4,000 EVD-related deaths were reported in Sierra Leone during the 2013 - 2016 West Africa EVD outbreak.

Method

We anonymized and later separately analysed the medical records of laboratory-confirmed pediatric, adult EVD patients, and a mixed cohort of EVD cases who received treatment at the 34 Military Hospital and the Police Training School ETCs in Sierra Leone; we also analysed the anonymized medical records of mixed cohort of laboratory-confirmed EVD cases who received treatment at the Kenema Government Hospital ETC (KGHETC).

Results

Majority of the 139 paediatric EVD cases in our study reported anorexia (99.1%), chest pain (98.6%), muscle pain (97.8%), headache (95.0%), fever (82.7%), diarrhoea (71.3%), fatigue (67.0%), had Stage 2 EVD infection (64.0%) upon admission at the 34 Military Hospital ETC. The associations between the Case Fatality Rate (CFR), sex, age groups and occupational levels for our adult EVD cases admitted at the 34 Military Hospital were all statistically significant. Our predictive EVD patients mortality risk score for our mixed cohort of 1077 EVD patients admitted at the 34 Military Hospital shows that, those EVD patients who had an in-facility risk score of 12 had in 100% of cases a fatal outcome. The CFR for the 205 EVD patients treated at KGHETC was lower for those EVD patients who came from outside Kenema District compared to those who were admitted directly from within Kenema.

Conclusion

Based on the findings of our studies we recommend an adaptation of current EVD case definitions. We were able to identify a range of characteristics of EVD patients that were associated with adverse treatment outcomes. However, as both setting and virus strains may be different in future situations, the adoption of our model in future outbreak situations has to be taken with caution.

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Abbreviations

CFR: Case Fatality Rate is the proportion of people who die from a specified disease among all individuals diagnosed with the disease over certain period

ETC: Ebola Treatment Center is a facility were people infected with Ebola were treated

EVD: Ebola Virus Disease

LMU: Ludwig-Maximilians-Universität in Munich

PCR: Polymerase Chain Reaction

WHO: World Health Organisation

ZMapp: An experimental biopharmaceutical drug that is comprised of three chimeric monoclonal antibodies that was under development for the treatment of Ebola Virus disease.

1. Introduction

1.1 Global History of Ebola Virus Disease

Ebola Virus Disease (EVD) belongs to the filovirus family [1, 2]. The disease first was discovered in 1976 along the Ebola River in Zaire in Sudan and Zaire [3]. The first EVD outbreak recorded over 250 people and had a mortality rate of 53% [4]. There are currently five (Zaire ebolavirus, Reston ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus and Bundibugyo ebolavirus) strains of Ebola Virus; Zaire ebolavirus has the highest (88%) mortality rate [5]. Reston ebolavirus was discovered in 1989 in monkeys that were imported from Mindanao, Philippines into Reston, Virginia, USA. [6]Tai Forest ebolavirus was accidently discovered in 1994 in Tai Forest, Cote d'Ivoire [7].The first direct evidence implicating bats as reservoir host for Ebola Virus emerged [8]was obtained in 2005; indicating the effective replication of the virus and subsequent survival by bats of the infection [9].

1.1.1 Ebola Virus Disease in Sierra Leone

An outbreak of EVD in West Africa in March 2014forced The World Health Organization (WHO) to declare it a “public health emergency of international concern”[10, 11]. The West African EVD outbreak in 2013 – 2016 was caused by a different pathogen from those that were responsible for previous outbreaks in the Democratic Republic of Congo and Gabon [12]. There were more than 8,000 probable and confirmed EVD cases and more than 4,000 EVD-related deaths recorded in Sierra Leone during the 2013 - 2016 West Africa EVD outbreak [13].The first case of the 2013 - 2016 West Africa EVD outbreak emerged in Meliandou, Guinea in late December 2013 [14] and was the first active filovirus infection to be detected in the West Africa Lassa fever zone since 1994; the first was the outbreak of the Taï Forest Ebolavirus [7].

2. Rationale and Objectives

2.1 EVD symptoms, case fatality rates and treatment

One key objective of this study was to identify the clinical symptoms of EVD. EVD has non-specific clinical symptoms that are similar to many tropical infections. The disease presents itself with various symptoms and the mode of acquisition of Ebola Virus is important in determining its incubation period[10-15].Barry and colleagues reported asthenia (80%), fever (72%), vomiting (60%), diarrhea (34%), myalgia (23%), headache, general body ache, rash and haemorrhagic diathesis[10]; while Qin et al reported weakness, fever and distress in half of all inpatients EVD cases[16] treated during the 2013 - 2016 West Africa EVD outbreak. Erythema and desquamation which are often visible by the 5^{th} - 7^{th} day of EVD infection, as well as macropapular rashes can serve as a valuable differential diagnostic feature for the infection.[17, 18] Schieffelin et al had previously discovered evidence of liver damage in both deceased and surviving EVD patients in Sierra Leone [19]; another Sierra Leone study reported confusion and conjunctivitis.[20]One Uganda study reported that majority of the 56 laboratory-confirmed EVD cases had non-bloody diarrhoea (81%), severe headache (81%), and asthenia (77%). [21]

There were different types of Case Fatality Rates (CFR) that were reported for the 2013 - 2016 EVD outbreak [21-29]. Haaskjold Y et al reported 35% as the CFR for EVD cases treated in Sierra Leone during the 2013 – 2016 EVD outbreak [29] while the CFR reported by the WHO 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.[30]Different types of characteristics and clinical symptoms of EVD patients have been associated with different CFRs during EVD outbreak[19, 24-37].Mupere et al reported data for 20 out of 168 laboratory-confirmed EVD admitted cases below 18 years of age but failed to disaggregate their clinical observations by age. [38]

Most studies on EVD clinical manifestations and treatment outcomes are challenged by their sample sizes. Majority (67%) of the2013 - 2016 West African EVD outbreak admissions at the Médecins Sans Frontières Ebola case management centre in Kailahun, Sierra Leone were older people[39] while another Sierra Leone study associate high viral load (Adjusted Relative Risk 2.6; 95%CI 1.8 ± 3.6) and vomiting at admission (Adjusted Relative Risk 1.4; 95%CI 1.0 ± 2.0) with treatment mortality. [40]

Antibiotics, anti-malarials, resuscitation by application of fluids as well as symptomatic treatments have proven to be effective in Ebola management care.[11,39]The WHO had also approved brincidofovir[43], ZMapp[44], TKM 130803[45], favipiravir [46], monoclonal antibody MAb114 [47], and convalescent plasma of EVD patients[48]for the treatment of EVD on compassionate grounds.

2.1.2 EVD mortality risk scoring model

One EVD staging model based on the WHO protocol and adapted from the clinical presentation of Lassa fever[49] requires improvement since it does not account for the sociodemographic characteristics including the age of EVD patients which is an important CFR predictor for people infected with Ebola [10, 50] while other studies have used single symptom such as confusion [16, 33], diarrhoea [10, 16, 33], asthenia [33], haemorrhagic signs [9, 10], dizziness [19] and fatigue [15] to construct a univariate predictive score for EVD.

In these studies we determined the factors associated with EVD treatment mortality for various subpopulations and treatment centers as well as construct an EVD in-facility mortality risk score. We also determined the factors that are associated with length of stay during EVD treatment and treatment outcomes.

3. Methods

3.1 Study Design

We separately analysed the anonymized medical records of laboratory-confirmed of 139 pediatric (0 – 15 years), 938 adult EVD patients (15 years of age and above), 1077 mixed cohort of EVD cases who received treatment at the 34 Military Hospital and the Police Training School ETCs in Sierra Leone from June 2014 to April 2015.

We also analysed the anonymized medical records containing the clinical symptoms and sociodemographic characteristics of 205 mixed cohort of laboratory-confirmed EVD cases who received treatment at the Kenema Government Hospital ETC (KGHETC) in Sierra Leone from 13th September 2014 to 26th November 2014. 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 assay using EVD specific primers and probes.

3.1.1 Study Setting

Medical data for this study was obtained from the 34 Military Hospital, Police Training School and Kenema Government Hospital (KGH) ETCs. The KGH serve as the national referral center for Lassa fever [51]. Prior to the 2013 – 2016 EVD outbreak the KGH had 472 staff and volunteers and was equipped with a surgical, adult medicine, pediatric, and maternity wards [52].However, KGH expanded its operation and number during the 2013 - 2016 EVD as the number of EVD cases increased. [53]Those EVD patients whose medical records we analysed either self-reported at the various ETCs or were brought to these ETCs by National Ebola Response Center personnel as suspected EVD case and then screened by data entry clerks.

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 a disease unexplained multisystem illness that is not explained by a confirmed course of malaria [(49)].

All 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. All confirmed EVD patients treated at the 34 Medical Hospital 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 the Stage Three (organ dysfunction phase) EVD patients who are characterised by organ dysfunction. The WHO-approved treatment protocols [(49)] that was used at the various ETCs in Sierra Leone during the 2013 - 2016 was mostly supportive care aimed at maintaining electrolyte balance included routinely providing oral rehydration salts and other supplements. The treatment protocol also included acetaminophen or ibuprofen (for muscle pain and headache), ranitidine or omeprazole (for abdominal pain) ciprofloxacin or cefixime (for bacterial infection), and naphthoquine phosphate tablets (for malaria).

3.1.2 Statistical Analysis

The R software package version3.3.1[(54)]was used for all statistical analysis while p-values of< 0.05 were considered significant for all two-sided statistical tests. Chi square tests and Fisher's exact test were used when the sample sizes were more than 5 or less than 5 respectively for categorical variables comparison. 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.

To quantify the prognostic capacity of EVD patients' sociodemographic characteristics and clinical symptoms in predicting EVD in-facility mortality we used stepwise backward selection algorithm based on the Akaike Information Criterion to select the final predictive model. We also multiplied the regression coefficient of each predictor in stepwise backward predictive model by two into the nearest integer [55] to obtain a weighted prognostic score for EVD patient treatment mortality and later used bootstrap method with 1,000 repetitions and re-sampling without replacement [56] to internally validate our model.

We then constructed our in-facility mortality risk groups (low, medium and high risk groups) by attributing a third of the EVD patients each into low, medium and high risk groups respectively based on their range of risk scores.

4. Results

4.1 Publication One

Epidemiological characteristics, clinical manifestations, and treatment outcome of 139 paediatric Ebola patients treated at a Sierra Leone Ebola Treatment Center

We used the epidemiological characteristics and clinical symptoms of 139 laboratory-confirmed paediatric EVD patients who were admitted at the 34 Military Hospital Ebola Treatment Center (ETC) in Sierra Leone during the study period of June 2014 to April 2015 to determine those factors that are associated with their treatment outcomes. Anorexia (99.1%), chest pain (98.6%), muscle pain (97.8%), headache (95.0%), fever (82.7%), diarrhoea (71.3%), fatigue (67.0%), Stage 2 EVD infection (64.0%) and abdominal pain (59.7%) were present among the majority of the pediatric EVD cases at the time of admission in this study (See Table 1 publication 7.1). We reported a statistical significant association for paediatric EVD patients with Stage 2 and 3 EVD infections, skin rash, vomiting, bleeding, fatigue, diarrhoea, difficulty in swallowing, difficulty in breathing and conjunctivitis compared to those without these characteristics. Paediatric EVD patients who reported skin rash at the time of admission had high CFR (100%, $p = 0.05$) compared to those paediatric EVD patients who did not report skin rash (CFR = 21.2%).

We also reported an overall CFR of 22% (n= 31/139) for all pediatric EVD cases in this study. Paediatric EVD patients who reported Stage 3 EVD infection (CFR = 81.3%, $p < 0.05$), difficulty in breathing (CFR = 76.9%, $p< 0.05$), bleeding (CFR = 70.0%, $p < 0.05$), difficulty in swallowing (CFR = 56.5%, $p < 0.05$), conjunctivitis (CFR = 50.0%, $p < 0.05$), vomiting (CFR = 40.4%, $p < 0.05$), fatigue (CFR = 30.1%, $p < 0.05$), diarrhoea (CFR = 28.3%, $p< 0.05$), abdominal pain (CFR = 26.5%, $p = 0.21$) and anorexia (CFR = 22.5%, $p = 1$) at the time of admission had higher CFRs compared to those who did not report those conditions at the time of admission.

4.1.1 Publication Two

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

Our large dataset of 938 adult EVD patients was used to describe both the clinical and socio-demographic determinants for EVD case treatment outcomes and to construct an in-facility CFR predictive model using the clinical and sociodemographic characteristics of these patients. Majority of the 938 adult EVD patients were males (59.0%, n = 553/938) and had secondary school education (79.3%, n = 744/938). Majority also belonged to the age groups 25 years to 35 (32.1%, n = 301/938), and 35 years to 45 (30.6%, n = 287/938). The overall CFR recorded for this cohort of adult EVD patients in this study was 26.4%. There were statistically significant associations between CFR, sex ($p = 0.0005$), age groups ($p = < 0.00001$) and occupational levels ($p = 0.0008$). Our model matrix was able to successfully predict all those EVD patients who survived by identifying 79.4% (197/248) of those that died during treatment. Majority of the EVD patients reported 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) at the time of admission. We reported different CFRs for the different clinical symptoms in this study.

There was an increased odds of dying for EVD patients who were 65 years and above (Adjusted Odd Ratio = 12.50, 95% CI = 2.32–80.74, p = 0.005) compared to EVD patients in the other age groups (See Table 3 publication 7.2). Our Area Under the Curve Original was 0.935, while our optimism-corrected Area Under the Curve for the age group 65 years and above, as well as for those EVD patients who reported vomiting, diarrhoea, fever, cough, fatigue, dysphagia, conjunctival injection, and dyspnea at the time of admission was 0.932 (See Figure 1 publication 7.2). The mean optimism (Area Under the Curve Original - optimism-corrected Area Under the Curve from × 0.5) was 0.0002. The sensitivity, specificity, positive predictive and negative predictive values for our model are 79.4% (197/248), 100% (690/690), 100% (197/197) and 93.1% (690/741) respectively (see Table 2 publication 7.2). Our model matrix was able to successfully predict all those EVD patients who survived by identifying 79.4% (197/248) of those that died during treatment (See Table 4 publication 7.2).

4.1.2 Publication Three

Severity Score for Predicting In-facility Ebola Treatment Outcome

In this study we described the clinical symptoms and socio-demographical characteristics and later constructed a statistically weighted scoring system to predict EVD treatment mortality for a mixed cohort of 1,077 positive EVD patients who went for Ebola treatment at The 34 Military Hospital from June 2014 to April 2015. We used the following weighted EVD patients' sociodemographic characteristics (age group, education, sex, occupation levels) and clinical symptoms (muscle pain, vomiting, diarrhoea, fever, fatigue, bleeding, sign of conjunctivitis, dysphagia and dyspnea) that were produced from the Akaike Information Criterion and obtained from our final multivariable logistic model to predict the risk of dying during EVD treatment in this study.

We constructed a three in-facility mortality risk groups (low, medium and high risk groups) by consecutively attributing one-third of the EVD patients' range of risk scores and later demarcated the entire risk score graph into low, medium and high risk groups for ease of identification purposes by inserting two vertical separator lines. For example we observed that an in-facility risk score of 12 for EVD patients was discovered to have a 100% of cases with fatal outcome.

4.1.3 Publication Four

Factors associated with length of stay and treatment outcome at an Ebola treatment center in Sierra Leone during the West African Ebola Outbreak 2013 – 2016

In this retrospective study, we investigated the effects of treatment delay, length of symptomatic period, EVD patients' sex, age, occupation level, regions of residence, EVD patients' symptom, and length of stay had on the treatment outcome of 205 laboratory-confirmed EVD patients at the KGHETC.

We recorded an overall CFR of 48.3 % (n = 99/205) in this study; male EVD patients recorded an insignificantly higher CFR (52.1 %, n = 50/96, p = 0.379) compared to female EVD patients (CFR = 45.0 %, n = 49/109). There was an insignificantly higher CFR for EVD patients belonging to the age group 0 year to 4 years (CFR = 72.7 %, n = 8/11, p = 0.682) compared to EVD patients in the other age groups. The odds of dying during treatment for low skilled worker EVD patients and EVD patients who were children and pupils in junior school over the odds of dying for high skilled worker EVD patient were 1.52 (95 % CI = 0.32 – 8.07, p = 0.61) and 0.73 (95 % CI = 0.11 – 4.86, p = 0.74) respectively.

5. Discussion

We succeeded in identifying the sociodemographic and clinical characteristics that are associated with the in-facility CFR for paediatric, adults, and mixed cohort of EVD caseswho were admitted at both the 34 Military Hospital and Kenema Government Hospital ETCs in our studies. We attributed the high CFR for the 139 paediatric EVD patients admitted at the 34 Military Hospital for the age group 0 – < 5 years compared to the other subpopulations in our paediatric cohort to the lack of health education in that subset of our EVD patients[57, 58]. Our overall CFR for the 938 adult EVD cases was lower than that computed by Wong et al (CFR= 74.2%, 95% CI: 72.6% - 75.5%) [59], and the WHO (CFR = 28%, n = 3956/14124) [60] for the same subset of EVD patients during the same outbreak in Sierra Leone.

We attributed this low overall CFR to the type of treatment regimen and professional health care that was provided in well-managed and equipped military healthcare facilities. Our preferred model for our adult EVD cohort is similar to those reported by Hartley and colleagues in a similar study involving Sierra Leonean EVD patients.[55] Our high overall CFR for the 205 KGHETC patients compared to the WHO-computed CFR[60] for Sierra Leone for the same outbreak was surprising. We attributed this high overall CFR for those EVD patients admitted at the KGHETC to poor EVD case management strategies, insufficient and inappropriate logistics as well as from the poor clinical training during the EVD outbreak period [61-62]. KGH provided staff for KGHETC during the EVD outbreak and is considered to have one of the best facilities in West Africa for EVD case management due to their years of experience in handling Lassa fever cases.[61]

The significantly higher CFR among EVD patients who resided in Kenema District and sought treatment at the KGHETC compared to those from other districts who sought the same treatment at the same place could be attributed to the following; admission of mostly severed EVD patients from within Kenema District who delayed in seeking early EVD treatment, survival bias brought about as a result of the admission of less severe non-Kenema District based EVD cases since the more severed ones may have been so weak to not even venture to travel for admission to KGHETC, or that they died before they could reach the KGHETC [20, 64], high viral load, incomplete case ascertainment, thoroughness of reporting EVD clinical outcome and the epidemiological case definitions that were been used [68], the decentralized treatment of a subpopulation of non-Kenema District EVD patients in holding centers[20] en route to KGHETC, thereby providing them additional advantage compared to those EVD patients who resided within Kenema District. Additionally, the lack of or poor adherence to both the EVD health messages passed on during the outbreak caused by the false sense of security due to the misinformation that previous exposure to Lassa fever either in the community or in the clinical setting makes one immune to EVD; as well as to that of the EVD infection prevention and control practices [63] may have also been responsible for the high CFR among Kenema District based EVD patients.

Theocharopoulus et al had previously reported that the low EVD viral load of patients from outside the district where the EVD patients was referred from compared to those EVD patients admitted from within the district may be due to their longer admission time, as well as in-transit admission prior to their referral to the distance ETC [20], while other studies have reported high viral load as a significant predictor of EVD mortality [20, 40].

There is a challenge to develop case definitions for diseases that have wide range of non-specific clinical symptoms that are associated with different treatment outcome due to their similarity with other endemic diseases.

Our statistically significant odds of dying for EVD patient characteristics with the following characteristics; age group 15 to < 25 years of age, dysphagia, dyspnea, diarrhoea, and vomiting reported in our predictive model were similar to those reported by Hartley and colleagues for a similar study in Sierra Leone that predicted EVD infection among Sierra Leonean patients.[55] We are thus recommending that EVD patients that contained those specific sociodemographic characteristics and clinical symptoms that have been identified in our predictive model should be targeted for early and well-monitored intravenous fluids administration.[66] High CFRs that reflected the challenges in accessing basic medical care due to the exhaustion of the healthcare structure during EVD outbreak [10, 33] have been reported for resource-constrained communities. We are also recommending a focused clinical attention that require risk stratification and may include strict triage admission procedure during the early period of EVD outbreak to mitigate the effect of limited basic medical care in these resource constrained communities during EVD outbreaks. Our in-facility mortality risk scoring system which has a significant advantage over the Ebola staging system of the WHO [67] can be used during the early onset of an EVD outbreak. Some advantages of our in-facility mortality risk scoring system over that of the WHO Ebola staging system is that it incorporates Stage one EVD symptoms, and can rapidly calculate EVD in-facility mortality score which can be used to provide a more rigorous clinical assessment of an EVD patient's prognosis.

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6. Publications

6.1 Publication A: Kangbai JB, Heumann C, Hoelscher M, Sahr F, Froeschl G. *BMC Infect Dis* (2019) Epidemiological characteristics, clinical manifestations, and treatment outcome of 139 paediatric Ebola patients treated at a Sierra Leone Ebola Treatment Center. 19:81 ttps://doi.org/10.1186/s12879-019-3727-7

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BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Epidemiological characteristics, clinical manifestations, and treatment outcome of 139 paediatric Ebola patients treated at a Sierra Leone Ebola treatment center

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Abstract

Background: The West Africa Ebola Virus Disease (EVD) outbreak in 2014–2016 was declared by the World Health Organization (WHO) a public health emergency of international concern. Most of the previous studies done in Sierra Leone relating to the clinical and epidemiological features of EVD during the 2014–2016 West African outbreak focused on adult EVD patients. There have been conflicting reports about the effects of EVD on children during previous outbreaks.

Methods: This is an observational retrospective analysis of medical data of all laboratory confirmed paediatric EVD patients below 15 years of age who were admitted at the 34 Military Hospital Ebola Treatment Center (ETC) in Wilberforce, Sierra Leone between June 2014 to April 2015. We analyzed the sociodemographic and clinical characteristics of paediatric EVD cases contained in case report forms that were collected by Ebola surveillance officers and clinicians at the 34 Military Hospital ETC. Both univariate and multivariate logistic regression models were used to determine the sociodemographic and clinical characteristics of paediatric EVD patients that were associated with EVD facility-based mortality.

Results: The majority of the paediatric EVD cases in this study were female (56.1%), pupils (51.1%), and 43.2% belonged to the age group between 10 years and below 15 years. The median age of the paediatric EVD cases was 9 years (interquartile range = 4 to 11 years). Adjusting for other covariates in the model, male paediatric EVD patient (AOR = 13.4, 95% CI = [2.07–156-18], $p < 0.05$), EVD patient with abdominal pain (AOR = 11.0, 95% CI = [1.30–161.81], $p < 0.05$), vomiting (AOR = 35.7, 95% CI = [3.43–833.73], $p < 0.05$), signs of conjunctivitis (AOR = 17.4, 95% CI = [1.53–342.21], $p < 0.05$) and difficulty in breathing (AOR = 23.3, 95% CI = [1.92–713.01], $p < 0.05$) at the time of admission had increased odds of dying during EVD treatment.

Conclusions: We recommend the adoption of case definitions currently in vigour to cater for specific characteristics of paediatric patients. Subgroups that can be identified by applying the model developed in this study may require special attention and intensified care.

Keywords: Ebola, Ebola treatment center, Paediatric, Treatment outcome, Sierra Leone

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There is no approved EVD treatment or vaccine against EVD [6, 30] but supportive care and management by intravenous fluids intake proved to be crucial for EVD patient survival during the 2014–2016 outbreak [6, 30]. However currently there are series of experimental therapies and vaccines including brincidofovir [31], ZMapp [18], TKM 130803 [32], Favipiravir [33], the monoclonal antibody MAb114 [34], and convalescent plasma of EVD patients [35] that has been approved by the WHO for use during outbreaks on compassionate ground.

In this study we describe the epidemiological characteristics, clinical manifestations and treatment outcome of 139 laboratory-confirmed paediatric EVD patients below 15 years of age who were admitted at the 34 Military Hospital Ebola Treatment Center (ETC) in Wilberforce, Sierra Leone between June 2014 to April 2015. We also determine the factors that are associated with EVD treatment outcomes of these EVD confirmed paediatric EVD cases using a large dataset. Early studies that investigated paediatric EVD cases were faced with many limitations including small sizes, incomplete patient information, selection and lead time biases. The main strength of this study is our large sample size of paediatric EVD cases belonging to the age group 0 – below 5 years coupled with the fact that our data came from an operational and hence reflect the ground reality.

Methods

Study design

Our study is an observational retrospective study that included all laboratory confirmed EVD patients below 15 years of age who were admitted at the 34 Military Hospital ETC situated in Wilberforce section of Freetown in Sierra Leone between June 2014 to April 2015.

These confirmed paediatric EVD patients were brought to the 34 Military Hospital triage center that was located at the Accident and Emergency Department by their parents or relatives because they were referred by EVD surveillance health workers of the National Ebola Response Surveillance Team, self-referred after coming in contact with a suspected or confirmed Ebola case, or because they presented with key Ebola signs and symptoms such as fever, headache, joint pain, diarrhoea, vomiting, or and bleeding [1, 2, 5, 9, 10, 12]. All EVD paediatric patients were first screened by trained clinicians against the WHO definition for a suspected EVD case [28] prior to EVD laboratory confirmation testing. Ebola is classified in three clinical stages: Stage one EVD which is also known as the dry or early phase is characterised by the absence of vomiting, diarrhoea, or organ dysfunction; Stage two which is also referred to as the wet phase is characterised by vomiting and diarrhoea; and Stage three or the organ dysfunction phase of which human organ failure is the most prominent feature.

For all paediatric EVD cases laboratory confirmation tests were done using real-time quantitative reverse transcriptase polymerase-chain-reaction (qRT-PCR) method at the National Public Health Laboratory at Lakkah in Freetown, Sierra Leone.

EVD treatment protocol

All laboratory-confirmed EVD cases in this study were routinely provided oral rehydration salts with dose dependent on the severity of the dehydration of the paediatric EVD patient; intravenous lactated Ringer's solution and other supplements to correct for electrolyte imbalance; acetaminophen or ibuprofen for muscle pain and headache, anti-infective ciprofloxacin or cefixime, and the antimalaria drug naphthoquine phosphate tablets. The antacid drugs ranitidine or omeprazole were given to patients experiencing upper abdominal pain. EVD treatments in this study were performed in accordance with the World Health Organisation (WHO) protocol of urgent interim guidance for EVD case management for viral haemorrhagic fever [30]. The treatment method in the other ETCs that were operating in Sierra Leone during the 2014–2016 EVD outbreak was mostly supportive and mostly included maintaining electrolyte balance in EVD patients.

Sierra Leone health infrastructure

Sierra Leone is located in West Africa. There is one government referral hospital in each of the 5 provinces or national areas. The rural areas of Sierra Leone are also served by several district health hospitals (DHHs), community health centers (CHCs) and community health posts (CHPs). All government referral hospitals and some DHHs served as either an ETC or an Ebola Holding Center (EHC) during the 2014–2016 Ebola outbreak. During the EVD outbreak 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 is a 150-bed hospital located in the capital city Freetown. The hospital which is headed by a Brigadier Surgeon General is operated by medical doctors and paramedics that are attached to the 34th Military Battalion of the Sierra Leone Armed Forces (SLAF).

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) approved this study. The Sierra Leone Ethics and Scientific Review Committee provided ethical clearance for conducting this study and waived the requirement to obtain informed consent on the grounds that this is an observational retrospective study on patients in charge in a medical facility under circumstances that did not allow at that time for individualized

informed consent, and that data is resented in an aggregate manner focusing on outcome in one entire facility.

Data collection and processing

At the 34 Military Hospital ETC trained clinicians and Ebola surveillance officers compiled on hard copies of CRF the medical history containing demographic, laboratory and clinical information of all suspected paediatric EVD patients who presented themselves with key signs and symptoms associated with EVD. We later transferred the medical data of all laboratory confirmed paediatric EVD patients from the CRF to a Microsoft Excel (Microsoft, Redmond, Washington, USA) [36] form for both descriptive and analytical statistics processing. The medical data of confirmed paediatric EVD patients included both clinical (whether patient had fever, headache, joint pain, anorexia, muscle pain, chest pain, abdominal pain, cough, diarrhoea, vomiting, fatigue, bleeding, skin rash, difficulty in swallowing or breathing, conjunctivitis and being in a confused state at the time of admission) and demographic data (age group, sex, education level). This study analysed the anonymized medical data of 139 paediatric EVD patients. The data were anonymized by Ebola surveillance data entry clerks and clinicians attached at the 34 Military Hospital in Freetown, Sierra Leone. The anonymized data were later stored in secured computer files at the 34 Military Hospital in Freetown, Sierra Leone.

Statistical analysis

R software package version 3.3.1 [37] was used for all data analyses; the source codes are available upon request. A p-value < 0.05 was considered as statistical significance for all two-sided statistical tests. We present as frequencies, proportions, means (standard deviations) and medians (interquartile ranges) the outputs of descriptive analysis and used Fisher's Exact test to compare proportion of various variables. Both univariate and multivariate logistic regression model were used to determine the clinical and non-clinical characteristics of paediatric EVD patients that were associated with EVD in-facility mortality. To understand the association between education and in-facility mortality (CFR) we grouped the paediatric EVD patients into two; no-education and education groups. The education group is comprised of paediatric EVD cases with either primary or secondary education while the paediatric EVD patients in the no-education group have no education experience. We later used the Receiver Operating Characteristic Curve (ROC) to determine our logistic model's ability to predict whether a paediatric EVD patient will be cured given certain clinical and sociodemographic characteristics of a patient. We then calculated the Area Under the Curve (AUC) value obtained from the ROC curve to determine the accuracy of the model to predict paediatric EVD patient treatment outcome.

Results

Descriptive characteristics of cases

Between June 2014 to April 2015, 1076 confirmed EVD cases, of which 139 (12.9%) were paediatric cases below 15 years of age, were admitted at the 34 Military Hospital ETC for EVD treatment. January 2015 recorded the highest number of confirmed EVD cases to be admitted at the 34 Military Hospital ETC, with 326 patients in total admitted, of which 52 (16.0%) were paediatric cases.

Demographic factors

The majority of the paediatric EVD cases were female (78/139, 56.1%), pupils (71/139, 51.1%), and (60/139, 43.2%) belonged to the age group between 10 years and below 15 years (Table 1). The median age of the paediatric EVD cases was 9 years (interquartile range = 4 to 11 years).

Case fatality rate

The overall CFR among the admitted 139 confirmed paediatric EVD patients was 22.3% (31/139). One hundred and eight out of 139 (77.7%) paediatric EVD patients were discharged alive from the 34 Military Hospital ETC after treatment. There was a statistically significant association between gender, age groups and education levels and the CFR for paediatric EVD cases. Male paediatric patients had higher (34.4%) CFR than female (CFR = 12.8%, $p < 0.05$). There was a negative correlation between paediatric EVD patient age and CFR. The CFR for paediatric EVD patients below 5 years of age was higher (CFR = 37.8%, $p < 0.05$) than those of patients between 5 years to less than 10 years of age (CFR = 26.2%); and 10 years to less than 15 years of age (CFR = 10.0%).

The CFR for paediatric EVD patients with no education was higher (CFR = 37.8%, $p < 0.05$) compared to those at primary level education (CFR = 23.9%). All paediatric EVD patients with secondary level education who were treated in this study were released alive after treatment.

Clinical symptoms

The majority of the paediatric EVD cases at the time of admission had anorexia (99.1%), chest pain (98.6%), muscle pain (97.8%), headache (95.0%), fever (82.7%), diarrhoea (71.3%), fatigue (67.0%), Stage 2 EVD infection (64.0%) and abdominal pain (59.7%) when they reported at 34 Military Hospital ETC for admission (Table 2). There was a statistically significant association between EVD paediatric patients with diarrhoea, vomiting, fatigue, skin rash, bleeding, difficulty in swallowing, conjunctivitis, difficulty in breathing, Stage 2 and 3 EVD infections compared to those without these characteristics. All paediatric EVD patients with skin rash at the time of admission died during treatment (CFR = 100%, $p = 0.05$) compared to 21.2% of paediatric EVD patients without skin rash at the time of admission who died during treatment. Paediatric

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Table 1 Sociodemographic factors, treatment outcome and case fatality rates of paediatric EVD patients treated at the 34 Military Hospital in Sierra Leone during the 2014–2016 EVD outbreak

EVD patients' sociodemographic Characteristics	N (%)	Survived N (%)	Died N (%)	Case fatality rate (%)	*p*-value*
Total	139 (100)	108 (77.7)	31 (22.3)	22.3	
Female	78 (56.1)	68 (63.0)	10 (32.3)	12.8	< 0.05
Male	61 (43.9)	40 (37.0)	21 (67.7)	34.4	
0 to < 5 years	37 (26.6)	23 (21.3)	14 (45.2)	37.8	< 0.05
5 to < 10 years	42 (30.2)	31 (28.7)	11 (35.5)	26.2	
10 to < 15 years	60 (43.2)	54 (50.0)	6 (19.4)	10.0	
No education	37 (26.6)	23 (21.3)	14 (45.2)	37.8	< 0.05
Primary education	71 (51.1)	54 (50.0)	17 (54.8)	23.9	
Secondary education	31 (22.3)	31 (28.7)	0 (0.0)	0	

*p-value was obtained by applying chi square test by comparing the case fatality rates and sociodemographic characteristics of paediatric EVD patients

EVD patients with Stage 3 EVD infection (CFR = 81.3%, $p < 0.05$), difficulty in breathing (CFR = 76.9%, $p < 0.05$), bleeding (CFR = 70.0%, $p < 0.05$), difficulty in swallowing (CFR = 56.5%, $p < 0.05$), conjunctivitis (CFR = 50.0%, $p < 0.05$), vomiting (CFR = 40.4%, $p < 0.05$), fatigue (CFR = 30.1%, $p < 0.05$), diarrhoea (CFR = 28.3%, $p < 0.05$), abdominal pain (CFR = 26.5%, $p = 0.21$) and anorexia (CFR = 22.5%, $p = 1$) at the time of admission have higher CFR compared to paediatric patients who did not report vomiting, fatigue, bleeding, difficulty in swallowing, difficulty in breathing, conjunctivitis, anorexia, abdominal pain, Stage 3 EVD infection or diarrhoea at the time of admission.

Paediatric EVD patients who reported fever (CFR = 21.7%, $p = 0.79$), headache (CFR = 22.0%, $p = 0.65$), muscle pain (CFR = 19.3%, $p = 0.13$) and chest pain (CFR = 19.3%, $p = 0.08$) at the time of admission have reduced CFR as compared to paediatric patients who did not report fever, headache, muscle pain or chest pain at the time of admission.

Table 2 Clinical symptoms, treatment outcome and case fatality rates of paediatric EVD patients treated at the 34 Military Hospital in Sierra Leone during the 2014–2016 EVD outbreak

EVD patients clinical symptoms	N (%)	Survived N (%)	Died N (%)	Case fatality rate (%)	*p*-value*
Total	139 (100)	108 (77.7)	31 (22.3)	22.3	
Fever	115 (82.7)	90 (82.3)	25 (80.7)	21.7	0.79
Headache	132 (95.0)	103 (95.4)	29 (93.6)	22.0	0.65
Anorexia	138 (99.3)	107 (99.1)	31 (100.0)	22.5	1.00
Muscle pain	136 (97.8)	107 (99.1)	29 (93.6)	21.3	0.13
Chest pain	119 (98.6)	96 (88.9)	23 (74.2)	19.3	0.08
Abdominal pain	83 (59.7)	61 (56.5)	22 (71.0)	26.5	0.21
Cough	67 (48.0)	54 (50.0)	13 (41.9)	19.4	0.54
Diarrhoea	99 (71.3)	71 (65.7)	28 (90.3)	28.3	< 0.05
Vomiting	57 (41.0)	34 (31.5)	23 (74.2)	40.4	< 0.05
Fatigue	93 (67.0)	65 (60.2)	28 (90.3)	30.1	< 0.05
Skin rash	2 (1.4)	0 (0.0)	2 (6.5)	100.0	0.05
Bleeding	10 (7.2)	3 (2.8)	7 (22.6)	70.0	< 0.05
Difficulty swallowing	23 (16.6)	10 (9.3)	13 (41.9)	56.5	< 0.05
Conjunctivitis	20 (14.4)	10 (9.3)	10 (32.3)	50.0	< 0.05
Difficulty breathing	13 (9.4)	3 (2.8)	10 (32.3)	76.9	< 0.05
Stage one EVD infection	34 (24.5)	34 (31.5)	0 (0.0)	0.0	< 0.05
Stage two infection	89 (64.0)	71 (65.7)	18 (58.1)	20.2	
Stage three EVD infection	16 (11.5)	3 (2.8)	13 (41.9)	81.3	

*p-value was obtained by applying chi square test by comparing the case fatality rates and clinical characteristics of paediatric EVD patients

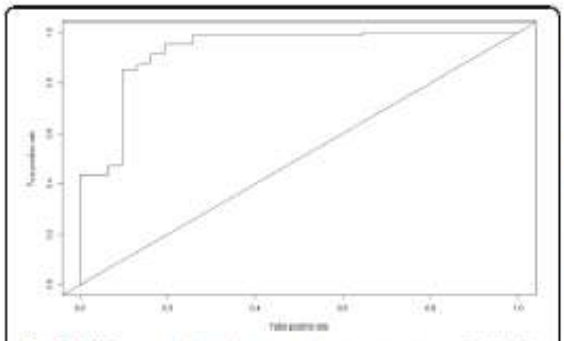

Fig. 1 ROC Curve on determinants and treatment outcome. The ROC curve shows that the model after stepwise logistic regression selection has a high capacity to discriminate paediatric EVD patient treatment outcome using their clinical and demographic characteristics

previous study, EVD has a shorter incubation period among paediatric cases below 10 years of age [39]. Our overall CFR (22.3%) was substantially lower compared to the CFR for the 13 previous Zaire EVD outbreaks combined (81.0%) [40] as well as for the average CFR (71.0%) computed by the WHO for mixed age groups for the 2014–2016 West African EVD outbreak [5]. However, it has to be kept in mind that our study is reporting facility based CFRs. Some studies associated the high case fatalities in previous Zaire EVD outbreaks with clinical determinants such as multiple foci of hemorrhage [28, 29].

Our higher CFR for paediatric EVD patients with no education compared to those with primary and secondary levels education may not be unconnected to the role played by health workers and school authorities in raising awareness and sensitizing school children about the transmission methods and effects of Ebola during the 2014–2016 outbreak. Both primary and secondary schools pupils benefited from daily health education programs dealing with the signs and symptoms, transmission methods, preventive and control measures of Ebola. Early identification of EVD signs and symptoms backed by early treatment increases one's odds of surviving EVD treatment. EVD patients that report early for treatment experience less severe presentation at the time of diagnosis compared to those who report late. T.E.C. Jones-Konneh et al. reported that the expert knowledge and skills of health practitioners made the difference in controlling and reducing the impact of the Ebola epidemic in Sierra Leone [41]. Another Sierra Leone study by Stehling-Ariza T and colleagues attributed the quicker identification of suspected Ebola cases as well as the interruption of Ebola transmission to active case surveillance and health education during the outbreak period [42].

The majority of the paediatric EVD cases in our study reported fever, headache, anorexia, muscle pain, chest pain, abdominal pain, diarrhoea, fatigue and Stage 2 EVD infection at the time for admission at 34 Military Hospital ETC. Elhadji Ibrahim Bah et al. [30], Olupot-Olupot [31], and Theocharopoulos et al. [32] had similar findings for mixed age groups but excluding Stages of EVD infection for patients investigated during 2014–2016 West African outbreak. Elhadji Ibrahim et al. described 37 laboratory-confirmed mixed cohort EVD patients with median age of 38 years, majority (65.0%) of whom were men, fever (84.0%), fatigue (65.0%), and diarrhea (62.0%) with a CFR of 43.0% [30]. In his review Olupot-Olupot noted that typical paediatric EVD symptoms for cases less than 12 years of age include mostly fever, weakness, loss of appetite, profuse diarrhea, vomiting and bleeding; in older children headache, backache, chest pain and abdominal pain are playing a more prominent role [31]. Theocharopoulos G et al. studied 249 confirmed mixed-cohort of EVD cases with a 45.0% CFR of which malaise (90.0%), fever (83.0%), diarrhoea (63.0%), headache (73.0%) and vomiting (60.0%) were the most common symptoms. Considering the fact that EVD is a disease with non-specific symptoms, these can pose as a dilemma in EVD outbreak foci because paediatric EVD clinical features are similar to those of other common childhood infections. In order to mitigate a potentially high risk of nosocomial infections in non-EVD cases that present themselves with symptoms compliant with EVD case definitions in vigor, criteria that are discriminative in terms of both probability of true positive cases and of level of adverse outcome would serve as a valuable individualized risk assessment. Some of our findings on the clinical symptoms of paediatric Ebola cases are different from those for adult EVD cases. Barry et al. recorded a high (60.0%) proportion of adult EVD cases with vomiting compared to ours (41.0%); as well as a statistically significant increase in the odds of dying for adult EVD cases who presented with bleeding at the time of admission ($p = 0.001$) [43]. Our study reported that the odds of dying from bleeding for paediatric EVD cases were not statistically significant ($p > 0.05$). Ohuabunwo et al. reported a high (30.0%) proportion of adult EVD cases with bleeding [44]; ours was 7.2%. Barry et al. also reported lower proportions for diarrhoea (34.0%) and muscle pain (23.0%) for adult Ebola cases [43] compared to ours for paediatric EVD cases (diarrhoea = 71.3%, muscle pain = 97.8%). The proportion of adult EVD cases presenting with anorexia reported by Ohuabunwo et al. was also lower (55.0%) [44] than ours (99.3%). We recorded a higher (98.6%) proportion of paediatric EVD cases who presented with chest pain than those reported by Dallatomasina S et al. (44.0%) for adult EVD cases [2]. We also reported a 100% CFR ($p = 0.05$) for paediatric EVD patients who presented with skin rash (maculopapular rash) at the time of admission but this feature was not prominent among adult EVD cases during the 2014–2016 West African EVD outbreak [45].

One limitation of our study is the lack of follow up to determine the outcome of paediatric EVD cases that

were released alive which may have revealed late mortality. Additionally, considering that our medical records did not capture the viral load of EVD patients at the time of their admission and the date of EVD onset as determined by the appearance of EVD signs and symptoms, we were thus unable to determine the effect of treatment delay and viral load on EVD treatment outcome. The findings of our facility-based EVD patient treatment outcomes have to be seen in the context of a specialized treatment facility that was located in the heart of a country's capital, therefore the potential external validity of our findings has to be taken with caution.

Our logistic model has an ROC with a high AUC of 0.94 to discriminate between paediatric EVD patients who were cured from those who died during treatment by using the characteristics sex of the patient, reported abdominal pain, vomiting, difficulty in breathing or showing signs of conjunctivitis at the time of admission. An individual's high risk of dying as implied by our model would as a consequence justify prompt and intensified treatment, which may be a scarce resource during peak periods of an ongoing outbreak.

Conclusions

Our study identified both epidemiological and clinical features that were associated with EVD infection, CFRs as well as those that are significant predictors for paediatric EVD treatment outcome. We reported that slightly more females were infected with EVD compared to males and that EVD cases below 5 years of age, as well as those cases that reported difficulty in breathing, difficulty in swallowing, signs of conjunctivitis and those with Stage 3 EVD infection at the time of admission recorded higher CFRs compared to the other paediatric EVD cases without these criteria. Additionally, we observed that male paediatric EVD patients, paediatric EVD patient who reported abdominal pain, difficulty in breathing, vomiting and showed signs of conjunctivitis at the time of admission tended to have increased odds of dying during EVD treatment. Our model suggests an adapted set of criteria for case definitions that would allow a differentiated approach to clinical management that can be assumed to be beneficial to a subgroup of paediatric patients at high risk of dying in the course of treatment. We are also suggesting the formulation of a separate paediatric EVD case definition to handle the dissimilarities in CFRs and clinical symptoms between childhood EVD cases and adult EVD cases and to facilitate discrimination from other childhood diseases that have similar clinical symptoms like those of paediatric EVD.

Abbreviations

AOR: Adjusted odds ratio; AUC: Area under the curve; CFR: Case fatality rate; CI: Confident interval; ETC: Ebola treatment center; EVD: Ebola virus disease; OR: Odds ratio; qRT-PCR: quantitative reverse transcriptase polymerase-chain-reaction; ROC: Receiver operating characteristic curve; WHO: World health organization

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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 but are available from the corresponding author on reasonable request and only after respective permission is granted by the Ministry of Health of Sierra Leone.

Authors' contributions

JK, MH 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. All authors read and approved the final manuscript.

Authors' information

Not applicable.

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-Maximilians-Universität München, Germany (Opinion No. LMU 17–582) approved this study. The Sierra Leone Ethics and Scientific Review Committee provided ethical clearance for conducting this study and waivered the requirement to obtain informed consent from the patients whose medical records were analysed in this study on the grounds that this is an observational retrospective study that did not allow at that time for individualized informed consent to be obtained. The Surgeon General of the 34 Military Hospital in Freetown, Sierra Leone also provided official clearance to access the medical records of these patients.

Consent for publication

Not Applicable.

Competing interests

The authors declared they have no competing interest.

Publisher's Note

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RESEARCH ARTICLE Open Access

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

Jia Bainga Kangbai[1,2*], Christian Heumann[3], Michael Hoelscher[1,4], Foday Sahr[5,6] and Guenter Froeschl[1,4]

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; with more than 28,000 probable and confirmed EVD cases and 11,000 deaths. 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 who 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%). We reported a low overall in-facility case fatality rate of 26.4%. The associations between case fatality rates and EVD patients who reported fever, abdominal pain, cough, diarrhoea, vomiting, fatigue, haemorrhage, dysphagia, conjunctival injection, dyspnea, and skin rash at the time of admission were all statistically significant ($p < 0.05$). Our preferred model with the age group 65 years and above alongside the following clinical symptoms; diarrhoea, vomiting, fatigue, dysphagia, conjunctival injection, dyspnea and cough produced a receiver operating characteristic (ROC) curve with an AUC (area under the curve) value of 0.93.

Conclusions: We constructed a simple model that can be optimally used alongside other rapid EVD diagnostic tools to identify EVD in-facility treatment mortality predictors based on the sociodemographic characteristics and clinical symptoms of adult EVD patients. We also reported low EVD cases among patients with secondary and tertiary education. These subpopulations of our patients who are generally informed about the signs and symptoms of EVD, alongside our treatment regimen may have been responsible for our comparatively lower case fatality rate.

Keywords: Ebola, Ebola treatment center, Treatment outcome, Case fatality rate, Sierra Leone

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Background

More than 28,000 probable and confirmed Ebola Virus Disease (EVD) cases and 11,000 EVD-related deaths [1] were documented in the 2013–2016 West Africa outbreak; the highest prevalence and mortality since the discovery of the Ebola Virus Disease (EVD) in Zaire in 1976 [2]. The pathogen responsible for the West African EVD outbreak was different from those of previous outbreaks in the Democratic Republic of Congo and Gabon [3]. Sierra Leone recorded its first EVD case in May 2014 and had the highest burden of the disease (14,121 EVD cases, 3955 EVD-related deaths) during the outbreak [4]. The gender rather than the sex of a person plays an important role in the transmission and vulnerability to EVD infection. Sierra Leone's first EVD case was a woman [5]. Several factors including the mode of acquisition of Ebola Virus determines the incubation period for EVD; direct Ebola Virus acquisition may lead to shorter incubation period [6, 7]. Several clinical symptoms of EVD have being identified; Barry et al. reported asthenia (80%), fever (72%), vomiting (60%), diarrhea (34%),myalgia (23%) as common clinical signs of EVD infection alongside headache, general body ache, rash and haemorrhagic diathesis [8]. Different types of Case Fatality Rates (CFR) for the 2013–2016 EVD outbreak have been reported. The CFR reported by Haaskjold Y et al. for a mixed cohort of EVD cases treated in Moyamba district in Sierra Leone during the 2013–2016 EVD outbreak was 40% [9]. The CFR of confirmed EVD 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 [10]. The WHO Ebola Response Team reported similar CFR (70.8%) among EVD patients who reported specific haemorrhagic symptoms and "unexplained bleeding" [11] during the 2013–2016 EVD. 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 [12]. Another Sierra Leone study in 2014 recorded a low number of EVD patients with confusion and conjunctivitis [13]. Several factors have been associated for the different CFRs during EVD outbreak. Generally, predictors of higher CFR are age [12–14], diarrhoea, conjunctivitis [12–15] and high Ebola Virus viremia [12, 13, 16]. The CFR values were also varied according to the patient's occupational status. Dallatomasina S, et al. recorded a higher (68%) CFR among health workers compared to other occupation (52%, $p = 0.05$) [17].

Previous studies relating to EVD infection were usually limited by their small sample sizes. Majority of the 56 laboratory-confirmed EVD cases in one Ugandan study had non-bloody diarrhoea (81%), severe headache (81%), and asthenia (77%) [18]. The CFR for 62 positive EVD patients treated at Moyamba Ebola Treatment Center in Sierra Leone during the 2013–2016 EVD outbreak was 68.9% [19].

In this investigation, we report on the factors associated with the treatment outcomes (CFR) of 938 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 dataset to describe the clinical and sociodemographic determinants for EVD case treatment outcomes and to construct a model that can best predict EVD in-facility CFR using the clinical and sociodemographic characteristics of these patients.

Methods

Study design

We analysed the anonymized medical records of 938 laboratory-confirmed EVD patients who are 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. The period of June 2014 to April 2015 was the peak of the Ebola outbreak in Sierra Leone. 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. All laboratory confirmatory tests on suspected EVD patients were done at the National Public Health Laboratory based at Lakkah in Freetown. The medical records of these EVD patients included their clinical symptoms and 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 converted them to digital form. We later used Microsoft Excel [20] for both descriptive and model-based data analysis.

Study area

During the 2013–2016 Ebola outbreak, some government referral hospitals and district health centers, as well as private hospitals and clinics managed by foreign organisations inside Sierra Leone served as either an ETC or an Ebola Holding Centers (EHC). The 34 Military Hospital which provided data for this study, operated two geographically different ETCs three kilometers apart; The 34 Military Hospital and The Police Training School. The 34 Military Hospital ETC started EVD treatment in June 2014 but as the outbreak progresses and the facility became over burden with EVD cases, they extended their operation by opening The Police Training School center in August 2014; the two ETCs closed operation in April 2015. Both centers served the Western Area and Western Urban populations and were managed

value that exceeds 5 or 10 indicates a problematic amount of collinearity [24].

We then constructed an Area Under the Curve (AUC) from the Receiver Operating Characteristic Curve (ROC curve) in order to determine the discriminating capacity of our adjusted mortality model to discriminate between EVD patient who will be released alive as compared to those who die during treatment given certain clinical and sociodemographic characteristics. To internally validate our predictive mortality model, we used the R package broom and bootstrap method with 1000 repetitions and re-sampling without replacement. We initially obtained the Area Under the Curve Original ($AUC_{Original}$) for our multivariable logistic regression model as well as the Area Under the Curve for the bootstrap-corrected ($AUC_{corrected}$) model. We then determined the performance of our predictive model by calculating the Area Under the Curve Optimism ($AUC_{optimism}$) by subtracting the $AUC_{original}$ from the $AUC_{corrected}$.

Results

Ebola patient characteristics

We used bivariate analysis to determine the significance of the association between EVD patients with a sociodemographic characteristics and the CFR. Out of the 938 EVD patients whose medical records were analysed, majority were males (59.0%, $n = 553/938$) and had secondary school education (79.3%, $n = 744/938$). The majority of the EVD patients belonged to age groups 25 years to 35 (32.1%, $n = 301/938$), and 35 years to 45 (30.6%, $n = 287/938$) (Fig. 1). The median age of our cohort group was 33 years (interquartile range = 25–40 years).

The majority of the EVD patients were of the age groups 25 years to 35, and 35 years to 45.

Bivariate analysis was also used to determine the proportion of EVD patients with a clinical symptom as well as to determine the significance of the association between the clinical symptom and the CFR. 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. The overall CFR recorded in this study was 26.4%. We recorded different CFRs for the different clinical symptoms reported by EVD patients. Skin rash (CFR = 100.0%, $n = 26/26$, $p = < 0.001$), dyspnea (CFR = 77.1%, $n = 118/153$, $p = < 0.001$), conjunctival injection (CFR = 70.5%,, $n = 122/173$, $p = < 0.001$), dysphagia (CFR = 68.5%,, $n = 196/286$, $p = < 0.001$), and haemorrhage (CFR = 58.4%, $n = 59/101$, $p = < 0.001$) recorded high CFRs with significant association. Vomiting (CFR = 44.6%,, $n = 214/480$, $p = 0.01$), fatigue (CFR = 40.6%, $n = 232/571$, $p = < 0.001$), diarrhoea (CFR = 35.1%, $n = 235/670$, $p = < 0.001$), cough (CFR = 34.8%, $n = 147/423$, $p = < 0.001$), abdominal pain (CFR = 29.4%, $n = 204/693$, $p = < 0.001$), and fever (CFR = 24.3%, $n = 177/729$ $p = 0.006$) recorded low CFRs with significant association. The associations between anorexia (CFR = 26.2%, $n = 243/926$, $p = 0.39$), muscle pain (CFR = 26.2%, $n = 237/905$, $p = 0.48$) and chest pain (CFR = 26.5%, $n = 210/793$, $p = 1.00$) and CFR were not significant (Fig. 2a).

The clinical symptoms that are less frequent have high CFRs compared to those clinical symptoms that are common.

There were more (52.6%) Stage Two EVD patients compared to either Stage One or Stage Three EVD patients. Patients with Stage Three EVD infection (CFR = 90.6%, $n = 145/160$, $p = < 0.001$) recorded higher CFR compared to patients with Stage Two EVD infection (CFR = 19.1%, $n = 94/493$ $p = < 0.001$) or Stage One EVD infection (CFR = 3.2%, n = 9/285, $p = < 0.001$) (Fig. 2b).

EVD patients with Stage Three EVD infection have higher CRF compared to EVD patients with either Stage One or Stage Three EVD infections.

The associations between CFR, sex ($p = 0.0005$), age groups ($p = < 0.00001$) and occupational levels ($p = 0.0008$) was statistically significant. The CFR for male EVD patients (30.7%, $n = 170/553$) was higher than female EVD patients (20.3%, $n = 78/385$) (Fig. 3).

Generally, the majority of the EVD patients were men and they also recorded higher CFR compared to women.

There was a positive correlation between age groups and CFRs; the CFR for the age groups 15 years to 25, 25 years to 35, 35 years to 45, 45 years to 55, 55 years to 65, and 65 years and above, were 17.5% ($n = 38/217$), 21.6% ($n = 65/301$), 31.4% ($n = 90/287$), 34.9% ($n = 29/83$), 43.2% ($n = 16/37$) and 76.9% ($n = 10/13$) respectively. Craftsmen (33.9%, $n = 129/381$) and nurses (28.6%, n = 10/35) recorded the highest CFRs amongst EVD patients with occupational record. The association between CFR and the education levels was not statistically significant ($p = 0.13$). For any increase in the education level there was a corresponding increase in the CFR; elementary (CFR = 22.8%, $n = 18/79$), secondary (CFR = 25.7%, $n = 191/744$) and tertiary (CFR = 33.9%, $n = 39/115$).

Factors associated with in-facility EVD treatment mortality

We used multivariate logistic regression analysis to determine those EVD patients sociodemographic characteristics and clinical symptoms that are associated with in-facility EVD treatment mortality. Our stepwise multivariate logistic regression analysis following VIF check for multicollinearity shows that the Adjusted Odd Ratio (AOR) for EVD patients who were 65 years and above (AOR = 12.50, 95% CI = 2.32–80.74, $p = 0.005$) had increased odds of dying during treatment compared to EVD patients in the other age groups. Also, EVD

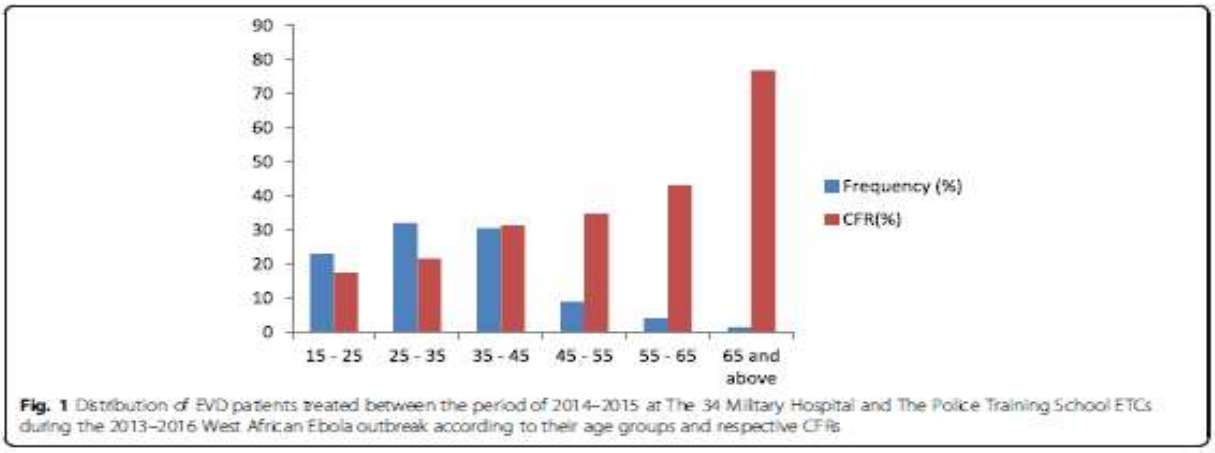

Fig. 1 Distribution of EVD patients treated between the period of 2014–2015 at The 34 Military Hospital and The Police Training School ETCs during the 2013–2016 West African Ebola outbreak according to their age groups and respective CFRs

patients who reported cough (AOR = 1.79, 95% CI = 1.12–2.86, $p = 0.02$), diarrhoea (AOR = 4.01, 95% CI = 1.85–9.40, $p = 0.0008$), vomiting (AOR = 3.21, 95% CI = 1.88–5.58, p = < 0.00001), fatigue (AOR = 2.64, 95% CI = 1.38–5.29, p = < 0.00001), dysphagia (AOR = 7.16, 95% CI = 4.40–11.80, p = < 0.00001), dyspnea (AOR = 3.63, 95% CI = 2.07–6.46, p = < 0.00001), and conjunctival injection (AOR = 3.45, 95% CI = 2.02–5.94, p = < 0.00001) during admission time had increased odds of dying during treatment compared to those who did not report these symptoms during admission time. However, the association for EVD patients who reported fever upon admission (AOR = 1.46, 95% CI = 0.87–7.98, $p = 0.16$) had increased odds of dying yet not statistically significant (Table 1).

To internally validate our multivariate logistic model, we calculated the mean optimism of our model by subtracting the AUC value of our optimism-corrected ROC curve from the AUC value of our multivariate (original) ROC curve and multiplied it by 0.5. The Akaike Information Criterion (AIC) value of the ROC curve for our multivariate (original) model produced an $AUC_{original}$ of 0.935 (Fig. 4) while our optimism-corrected AUC ($AUC_{corrected\text{-}optimism}$) for our final (adjusted) model which included the age group 65 years and above, and EVD patients who reported fever, cough, vomiting, diarrhoea, fatigue, dysphagia, conjunctival injection, and dyspnea at the time of admission model was 0.932. Our mean optimism $[(AUC_{original} - AUC_{corrected\,optimism}) \times 0.5]$ is 0.0002.

Using the clinical and demographic characteristics of our EVD patients and the ROC curve, our final model has the capacity to discriminate their treatment outcomes.

Using an arbitrary threshold of 0.945 to prioritize an optimal positive predictive value for fatal outcome, our model successfully identified 79.4% (Sensitivity = 197/248) of those EVD patients who actually died during treatment (Table 2). Our 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

We analyzed the aggregated medical information of adult EVD cases who registered for treatment at our study sites in order to determine the CFRs for the various subsets of these patients. We believe that the clinical characteristics and treatment outcomes of adult EVD cases are likely to be different and non-linear along age groups if adults and children are combined as well as for the various subsets of adult EVD cases. Different values of CFRs for different locations and settings [10–13, 25] which can be attributed to the subpopulations investigated and pre-selection biases, [10, 25] were reported during the 2013–2016 EVD outbreak. We reported a low CFR (26.4%) for EVD cases treated at The 34 Military Hospital and The Police Training School ETC in Sierra Leone compared to the CFR computed by Wong et al. and the WHO for the same outbreak in Sierra Leone were 74.2% (95% CI: 72.6–75.5%) [24] and 28% (3956/14124) [26] respectively. We may attribute the reasons for our low CFR to the type of professional health care that was provided in a well-staffed and equipped military facility in a capital city setting, and to the treatment regimen used in our ETCs compared to those implemented in other ETCs in the country.

Specifically, unlike other ETCs that only administered ORS, nutritional supplements, antiemetic, fever and pain relieving drugs to their EVD patients during the EVD outbreak in Sierra Leone [27], the medical personnel at The 34 Military Hospital and The Police Training School ETCs administered ORS, IVT, and other medications at different rates to their EVD patients throughout the outbreak period. Intravenous parenteral drug administration

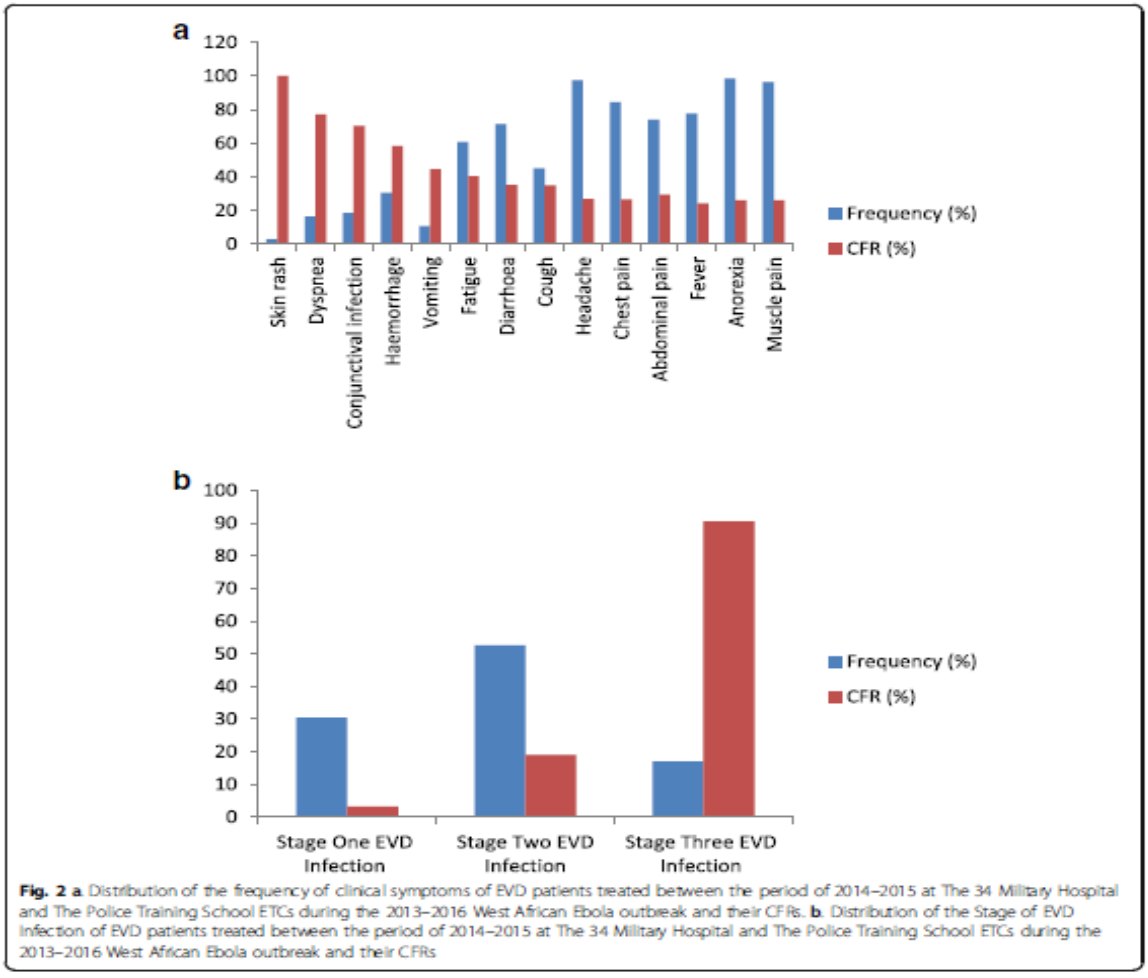

Fig. 2 **a** Distribution of the frequency of clinical symptoms of EVD patients treated between the period of 2014–2015 at The 34 Military Hospital and The Police Training School ETCs during the 2013–2016 West African Ebola outbreak and their CFRs. **b** Distribution of the Stage of EVD Infection of EVD patients treated between the period of 2014–2015 at The 34 Military Hospital and The Police Training School ETCs during the 2013–2016 West African Ebola outbreak and their CFRs

provides an easy and rapid drug administration leading to immediate drug action. It also enable drugs to be administered either continuously or intermittently thereby resulting into rapid changes in the cardiocirculatory system [28], increase in blood and plasma volumes [28–30] and makes the monitoring of the delivered fluids, electrolytes and nutrients easier. Generally, for EVD patients at the various stages of infection, the loss of bodily fluid, electrolytes and nutrients are the major clinical effects of the disease. Replacing lost bodily fluids effectively and rapidly via IV drug administration is a life saver for EVD patients [30].

One unique feature of the treatment regimen offered to EVD patients in our study is the IV 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; malaria peaks during the period in which this study was conducted. The high malaria transmission during the study period 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 [31–37] hence treating patients for EVD and malaria simultaneously will invariably improve their prognosis.

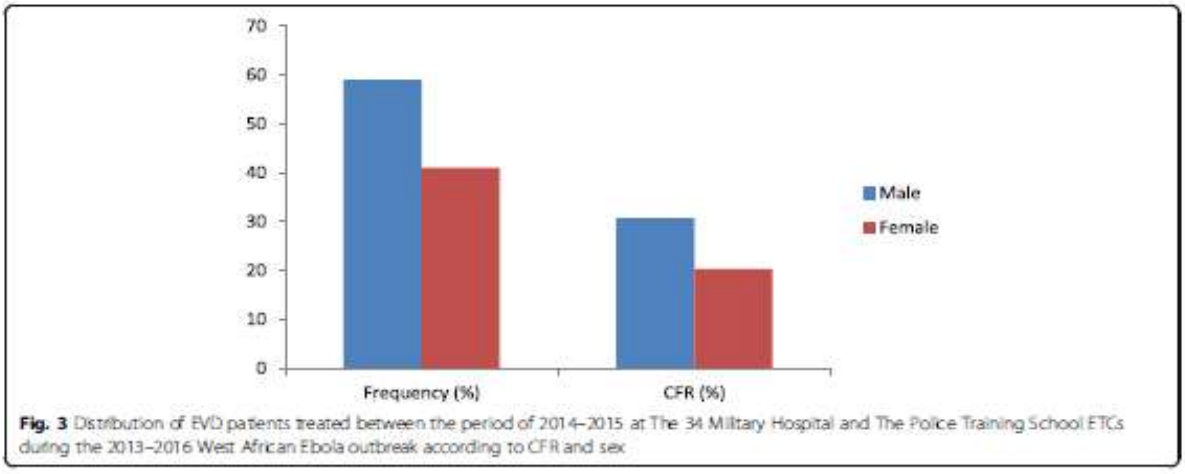

Fig. 3 Distribution of EVD patients treated between the period of 2014–2015 at The 34 Military Hospital and The Police Training School ETCs during the 2013–2016 West African Ebola outbreak according to CFR and sex

Other reasons for these CFR variations may include incomplete EVD case ascertainment, thoroughness of reporting EVD clinical outcome, and the epidemiological case definitions used [25]. Our failure to account for the delay in seeking EVD treatment outcome following onset of signs and symptoms however implies our cases may not have been true representative of the national characteristics of reported EVD cases. Generally, studies that are less representative produce CFR estimates that vary with the national estimate and are often considerably lower [8, 19].

Table 1 The Adjusted Multivariate Analysis of In-facility Case Fatality Rates of EVD patients treated between the period of 2014–2015 at The 34 Military Hospital and The Police Training School ETCs during the 2013–2016 West African Ebola outbreak

Patient symptoms	Adjusted OR	95% CI	*P* value
Sex – Male Reference = Female	1.50	0.95–2.26	0.09
Reference age group = 15 to < 25 years			
25 to < 35 years	1.09	0.58–2.38	0.80
35 to < 45 years	1.84	0.98–3.49	0.06
45 to < 55 years	1.64	0.70–3.90	0.26
55 to < 65 years	2.81	0.91–8.27	0.07
65 years and above	12.50	2.32–80.74	0.005
Fever	1.46	0.87–7.98	0.16
Cough	1.79	1.12–2.86	0.02
Vomiting	3.21	1.88–5.58	< 0.00001
Diarrhoea	4.01	1.85–9.40	0.0008
Fatigue	2.64	1.39–5.29	< 0.00001
Dysphagia	7.16	4.40–11.80	< 0.00001
Conjunctival injection	3.45	2.02–5.94	< 0.00001
Dyspnea	3.63	2.07–6.46	< 0.00001

[a] Adjusted OR is Adjusted odds ratio

Our high CFR and AOR associated with nurses, craftsmen and unemployed patients which may be attributed to EVD over exposure. Healthcare workers have been specifically linked with high EVD incidence and CFR [17, 38–40] due to occupational exposure and the non-specific clinical symptomology of EVD [41, 42]. This nonspecific clinical symptomology of EVD makes it difficult for healthcare workers to differentiate it from other tropical febrile infections during the early phase [42] of an outbreak resulting to delay in seeking EVD treatment and hence leading to its high CFR and AOR. The high CFR and AOR for both craftsmen (auto mechanics, electricians, farmers, truck pushers, mine workers, hunter, builder and carpenter) and unemployed EVD patients can be attributed to their unstable risky living conditions and high mobility which can potentially lead to over-exposure. Public health education is important in understanding EVD's signs and symptoms [43, 44], evolution and mode of transmission which 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 [45]. Additionally, we may also want to associate our low CFR to the large number of EVD patients with secondary and tertiary levels of education. Although we observed a positive association between education levels, age groups and CFRs which may be associated with the increasing number of old EVD cases as one progresses from one education level or age group to the other, we believe that the large number of EVD patients with both levels of education in our study could have been the major factor for this low CFR. Educational attainment influence treatment mortality through other dimensions including access to treatment and seeking treatment early. Our low in-facility CFR may in fact refer to a pre-

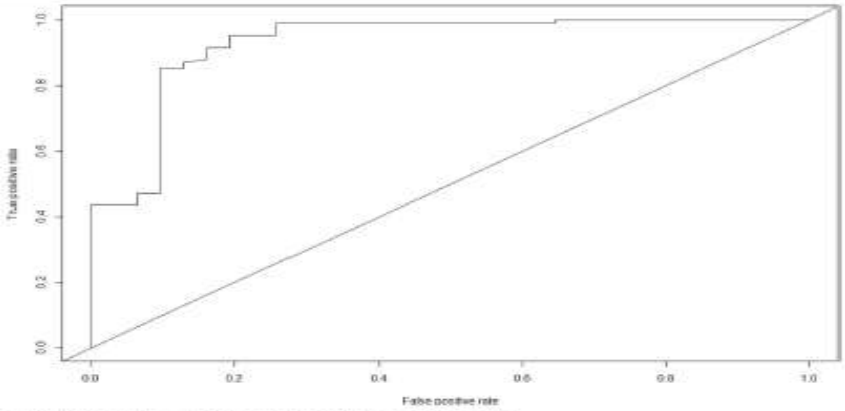

Fig. 4 ROC Curve on EVD Treatment Survival Determinants and Treatment Outcome

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 thus be used to assess and evaluate the efficacy of our EVD treatment methods as well as to compare it with others in different parts in Sierra Leone. However, the fact that our CFR is based on in-facility data presents a challenge, since external validity towards settings outside an ETC is limited.

Our study report clinical symptoms similar to those reported in other EVD studies [8, 9, 19] but which are also common to other tropical infections including malaria, yellow fever, dengue, cholera or Lassa fever. We recorded a higher prevalence and CFR for EVD cases with gastrointestinal symptoms (diarrhoea and vomiting). Gastrointestinal symptoms often lead to electrolyte abnormalities including hypokalemia, hypoglycemia, and hypocalcaemia that were common clinical presentations during the 2013–2016 West Africa EVD outbreak [9, 14, 19, 46]. We observed that EVD patients with diarrhoea had increased odds of dying during EVD treatment than those without it. Our high CFR for diarrhoea and vomiting may 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 [47]. Schieffelin JS et al. had previously reported the presence of acidosis and elevated blood urea nitrogen and creatinne as predictors for EVD diagnosis and fatality [12]. Our statistically significantly higher CFR values and odds ratios for both diarrhoea and vomiting indicates 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 [43], Mupere et al. [48], and Theocharopoulos et al. [49] Bah et al. reported a 43.0% CFR in their study in which majority of the study participants had fever (84.0%), fatigue (65.0%), and diarrhoea (62.0%) [43]. Mupere et al. reported more than 50% of EVD cases presented with either fever, headache, weakness, anorexia, diarrhea, or vomiting at the time of admission [48]. The most common symptoms for 249 EVD cases with a CFR of 45.0% reported by Theocharopoulos G and colleagues were malaise (90.0%), fever (83.0%), diarrhoea (63.0%), headache (73.0%) and vomiting (60.0%) [49].

Table 2 Matrix of actual and predicted treatment of outcome for EVD patients

EVD Patients predicted status	EVD treatment survivors	EVD treatment fatalities	Total
Predicted EVD survivors	690	51	741
Predicted EVD fatalities	0	197	197
Total	690	248	938

One challenge in the early detection of EVD cases in resource poor settings is the similarity of its clinical symptoms to that of other tropical infections. This similarity makes the use of a single EVD symptom checklist inadequate in outbreak foci; and hence calls for EVD case definition criteria with higher discriminatory capacity during early outbreak period. Such an EVD outbreak case definition tool is needed especially in settings with both logistical challenges and high risk of nosocomial EVD transmission and during the early EVD outbreak phase; to differentiate non-EVD patients from confirmed, suspected or probable EVD cases. Any tool that can make use of the clinical symptoms and sociodemographic characteristics contained in our final model to identify those confirmed EVD patients with high risk of dying during the early phase of an EVD outbreak will reduce the CFR as well as ensures the diversion of much needed logistics to other areas of EVD case management, control and prevention. EVD outbreaks in Low- and Middle-Income Countries usually occur in remote communities with poor road network and limited or no laboratory facilities. Blood samples from confirmed, suspected or probable EVD cases usually had to be transported long distances to bigger towns for laboratory tests; all of which increase the delay in seeking EVD treatment and CFR. Mupere E et al. had earlier proposed an EVD case definition to include the categorization of risk into EVD suspected, probable or contact cases [48]. Such EVD risk categorization if applied to EVD case definition lacks the descriptive specificity for a clinically useful case definition and hence cannot be incorporated for widespread use during EVD outbreak. Our high AUC (0.935) which quantitatively discriminate between EVD patients who were treated and released alive from those who died during treatment has both clinical and prognostic relevance which allows the best possible identification of patients 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 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 the safety of patients with respect to avoiding nosocomial EVD infections within healthcare facilities is a dominant concern.

Because this is a retrospective study in which we only analysed data that have been previously collected, we were not able to determine the effect viral load had on the treatment outcome of an EVD patient; our medical record did not capture such variable. This limitation only permitted us to determine the onset of EVD by the clinical signs and symptoms of the EVD patient and not by the presence of Ebola Virus viral load. Another limitation is the unavailability of data on presented but unconfirmed patients. The comparison to this group would have allowed for a differentiated analysis of clinical presentation between confirmed and unconfirmed patients. 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 lack of 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. Another challenge within the clinical context of our study was the difficulty in providing adequate clinical care for all patients within our treatment facilities as well as how to keep track and ensure that they receive the therapies they were supposed to receive. We also believe that in spite of these limitations our low CFR may have also been due to the fact that our patients were admitted to a military hospital which was supported with better resources that may not have been present in other ETCs operating in the country during the outbreak.

Additionally, our study may not be generalized to the entire Sierra Leone population at the time because the Western Area where this study was conducted benefited from a lot of community engagement and educational campaigns which may have affected the access and transfer of EVD patients to our study sites. These community engagement and educational campaigns may have also led to the less prevalence of EVD-related stigma compared to other areas in the country.

Conclusion

We constructed a simple CFR risk classification system that can identify EVD in-facility treatment mortality predictors based on the sociodemographic characteristics and clinical symptoms of the EVD patient. We also reported low EVD cases among patients with secondary and tertiary education. These subpopulations of our patients who are generally informed about the signs and symptoms of EVD, alongside our treatment regimen may have been responsible for our comparatively lower case fatality rate.

Abbreviations

AIC: Akaike Information Criterion; AOR: Adjusted Odd Ratio; AUC: Area Under the Curve; CFR: Case Fatality Rates; EHC: Ebola Holding Center; ETC: Ebola Treatment Center; EVD: Ebola Virus Disease; IVT: Intravenous Therapy; LMU: Ludwig-Maximilian's Universidad; NERC: National Ebola Response Center; ORS: Oral Rehydration Salts; ROC: Receiver Operating Characteristic Curve; RT-PCR: Reverse Transcriptase Polymerase Chain Reaction; SLAF: Sierra Leone Armed Forces; WHO: World Health Organisation; VIF: Variance Inflation Factor

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Authors' contributions
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. All authors have read and approved the manuscript, and ensure that this is the case.

Authors' information
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Availability of data and materials
The data that support the findings of this study are available from The 34 Military Hospital in Sierra Leone but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Sierra Leone Ethics and Scientific Review Committee, and The 34 Military Hospital in Sierra Leone which was managing the ETCs at The 34 Military Hospital and The Police Training School.

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) provided ethical clearance and approved this study. 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. All data used in this study were anonymized before they were used. Administrative clearances were obtained from the Sierra Leone Ethics and Scientific Review Committee and The 34 Military Hospital in Sierra Leone which was managing the ETCs at The 34 Military Hospital and The Police Training School prior to the use of the said datasets.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Original article

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.

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

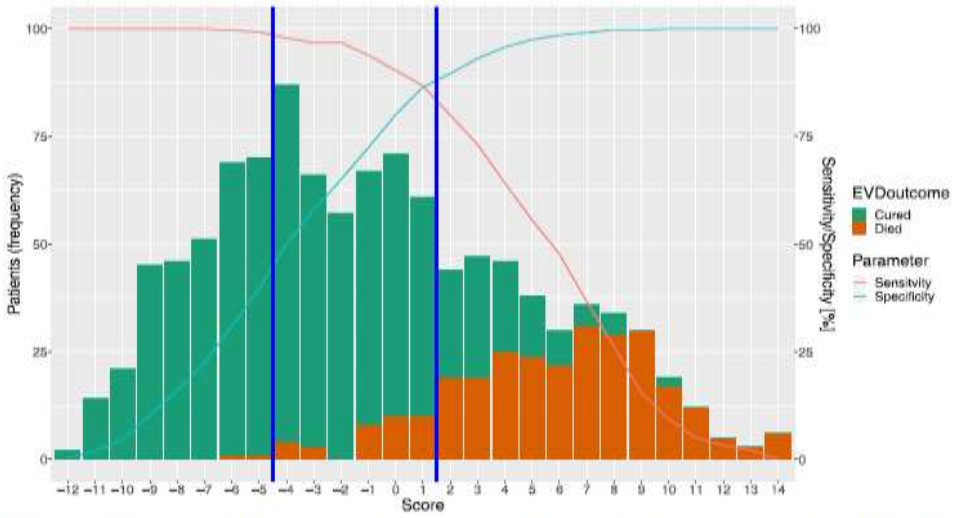

Fig. 1. EVD in-facility mortality and survival frequencies per risk score. The frequency of treatment outcome of patients with EVD with survival (green) and death (orange) based on the constellation of their sociodemographic and clinical characteristics were displayed as vertical bars on the risk score 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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6.1.3 Publication D. Kangbai JB, Heumann C, Hoelscher M, Sahr F, Froeschl G. BMC *Arch Public Health.* (2021) Factors associated with length of stay and treatment outcome at an Ebola treatment center in Sierra Leone during the West African Ebola Outbreak 2013-2016 (Currently under peer review)

Abstract

Background: The World Health Organization (WHO) declared the West Africa Ebola epidemic as a Public Health Emergency of International Concern in August 2014. During the outbreak period, there were calls for the affected countries to construct Ebola treatment centres and reliable diagnostic laboratories closer to areas of transmission in order to improve the quality care of Ebola Virus Disease (EVD) patients. Delay in seeking treatment has been reported to have led to poor treatment outcome of EVD patients. Sierra Leone recorded more than 8,000 probable and confirmed cases and more than 4,000 EVD -related deaths nation-wide.

Methods: In this retrospective study, we investigated the effects of treatment delay, length of symptomatic period, EVD patients' sex, age, occupation, region of residence, and clinical characteristics on the treatment outcome of 205 laboratory-confirmed EVD patients at the Kenema Government Hospital Ebola Treatment Center (KGHETC) during the 2013 - 2016 EVD outbreak. Specifically also, we determined the factors that were associated with the length of stay for EVD treatment for patients who were released alive.

Results: Of the 205 patients, 99 (48.3 %) had a fatal outcome. For EVD patients that survived, we recorded a significant association between the Length of Stay (LOS) and for each kilometer travelled to seek treatment (-0.06, 95 % CI = - 0.14 – 0.02, p = 0.004) at the KGHETC. However, the association between EVD patients that were low skilled workers (- 5.91, 95 % CI = - 24.60 – 12.79, p = 0.73), EVD patients who were children and pupils in junior school (- 0.86, 95 % CI = - 12.86 – 11.14, p = 0.73), health seeking delay for EVD patients who resided in Kenema District where the KGHETC was located

(- 0.49, 95 % CI = - 0.12 – 1.09, p = 0.24), sex (- 1.77, 95 % CI = - 8.75 – 5.21, p = 0.50), age (0.21, 95 % CI = - 0.36 – 0.77, p = 0.57), referral status (1.21, 95 % CI = -

17.67 – 20.09, p = 0.89) and the LOS in surviving patients were not statistically significant.

Conclusion: The high LOS for either treatment outcome for EVD patients that resided in the district in which the EVD treatment facility was located compared to those patients from other districts implies that health authorities should consider intensive health education with high priority given to seeking early EVD treatment, and the construction of strategic ETCs as important components in their response strategy.

7. Conclusion

In our studies we recommended the adoption of case definitions, special attention and intensified care for the specific characteristics identified amongst our EVD study. We are of the opinion such subgroups that were identified in the various models in our studies require special attention. Also, the age of adult EVD patients, adult EVD patient with symptoms of vomiting, diarrhoea, fatigue, dysphagia, conjunctival injection, dyspnea or muscle pain, have high odds of dying during treatment and hence will require prompt and intensive clinical attention upon admission. The high proportion of EVD patients with higher educational levels may have played an important role for the low CFR among our adult EVD patient cohort. This finding once more emphasizes the need for intensive health education, information sharing and communication during the early period of an EVD outbreak. Specifically, one conclusion drawn from our analysis of the medical records of the KGHETC patients was that in any future Ebola outbreak where community EVD transmission is well underway, health authorities should consider constructing strategic ETCs as an important component of their response strategy.

8.1.2 Statement of pre-release and Contribution

This study and the subsequent publications (dissertation) that emerged were done during the period of October 2016 to January 2020 at both the Center for International Health in Munich, Germany and The 34 Military Hospital in Freetown, Sierra Leone. The following studies; *Epidemiological characteristics, clinical manifestations, and treatment outcome of 139 paediatric Ebola patients treated at a Sierra Leone Ebola Treatment Center*, *Sociodemographic and clinical determinants of in-facility case fatality rate for 938 adult Ebola patients treated at Sierra Leone Ebola Treatment Center*, and *Severity Score for Predicting In-facility Ebola Treatment Outcome;* have been published in BMC Infectious Diseases and Annals of Epidemiology respectively. The fourth study titled *Factors associated with length of stay and treatment outcome at an Ebola treatment center in Sierra Leone during the West African Ebola Outbreak 2013 – 2016* is currently undergoing peer reviewing with BMC Archives in Public Health.

In all of these studies, I was responsible for gathering, compiling and collating the medical data that were used in the analytical sections in these studies. I was also responsible for securing the ethical and Institution Review Board approvals for these studies from the Sierra Leone Ethics and Scientific Review Committee in Sierra Leone and the Ludwig-Maximilians-Universität in Munich, Germany respectively. Under the supervision of my LMU supervisors I also conceived, organised and designed the various studies mentioned above alongside their respective objectives and analysis plans. Also, under the supervision of my LMU supervisors I did the analysis of the data that were reported in the various result sections in the published articles relating to this research and the diagrams (figures and tables) as well as drafted all the manuscripts. I was also responsible for registering and submitting all the manuscripts from these studies to the various journals for publication and served as the corresponding author for each manuscript that was submitted to each journal. As corresponding author I was also responsible for responding to each journal's editor and peer reviewers' comments and queries with respect to the various manuscripts submitted on behalf of these work.

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Finally, I will like to extend my sincere thanks to the health workers, military personnel attached to the 34 Military Hospital and the Kenema Government Hospital for collecting and collating the medical data that were analyzed in this study, as well as all those who suffered in diverse ways during the Ebola outbreak in Sierra Leone from 2013 to 2016.

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LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

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