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Clinical features and risk factors for adverse outcome in Ebola virus disease in Moyamba District, Sierra Leone

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ABSTRACT

BACKGROUND

The current outbreak of Ebola virus disease (EVD) in West Africa has attacked 24000 people, killed more than 10000 and disrupted social life.

METHODS

We studied retrospectively the clinical presentation and risk factors for fatal outcome in EVD among all patients admitted to the Ebola Treatment Center in Moyamba District, Sierra Leone.

RESULTS

Among a total of 88 admitted patients, eighty-two were tested by PCR and 31 (38%) were positive for Ebola virus. Ninety percent reported previous contact with EVD patients and 35% had participated in burials of EVD suspect deceased. No health-workers were admitted. The most common symptoms on admission were weakness (97%), diarrhea (68%), fever (62%), loss of appetite (62%), vomiting (58%), pain in muscles (62%) and joints (55%), headache (55%), abdominal pain (45%) and conjunctivitis (42%). On admission, bleeding was present in one-third (11/31), while more than half (17/31) bled during the hospital stay. Fifty-eight percent (18/31) died, most within 4-11 days of onset. Significant predictors for fatal outcome were shorter time from onset to admission ($P=0.02$), high initial viral load ($P<0.001$), bleeding ($P=0.004$), and severe pain ($P=0.001$). The only two patients with hiccups died.

CONCLUSIONS

Bleeding was more common in our cohort than reported elsewhere during this epidemic, and predicted poor prognosis. Severe pain was common, particularly in fatal cases, and calls for improved and safe palliation, for instance with transdermal opiates. The lack of fever in one third of EBV cases may have implications for screening procedures and case definitions.

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Abstract: 246 (max 250)
Main text: 2668
(background 393, methods 412, results 785 (260+190+138+181), discussion 1094)

BACKGROUND

Since its discovery in 1976 [1], Ebola virus has caused a number of small outbreaks with very high case-fatality rate (CFR), mostly in rural areas in central and eastern Africa [2]. The major West African outbreak of Ebola virus disease (EVD) starting in Guinea in December 2013 [3, 4], subsequently spreading to Sierra Leone and Liberia [5] is the largest known to date with over 24000 reported cases and over 10000 deaths [6]. Weak health systems, international indifference, deep-rooted traditional burial customs, high population mobility and early urban spread contributed to the unprecedented spread of the epidemic [5, 7, 8]. The high death toll among health-care workers further undermined existing health systems [9]. Apart from Medecins Sans Frontieres (MSF) and a few other organizations, the international community responded slowly [8, 10]. The UN resolution on August 8 2014 that led to creation of UNMEER (UN Mission for Ebola Emergency Response) on September 19th was a turning point. As leading public health agencies predicted that the epidemic could spiral out of control with a worst-case scenario estimate of 1.4 million cases [11], an increasing number of international stakeholders got involved, including direct contributions from several countries' national authorities. Eventually, the epidemic peaked in September-October in Liberia and in December 2104 in Sierra Leone and Guinea, followed by a decline in the number of new cases [6, 8].

As the Ebola virus is maintained in a natural reservoir, probably involving bats [4], new outbreaks should be expected in the future and preparedness of health system is key to respond adequately [12]. Differences in clinical presentation and varying CFR are among the unresolved concern. In the 13 previously described outbreak of Zaire EVD the average CFR was 81% (1123/1390) [13]. In the West African outbreak, figures from the WHO Situation Reports [14] probably underestimates the CFR(41%, 10689/25791). The CFR among health-care workers has been 58% (503/864) [14] and a large WHO-led study across the region found an average CFR of 70.8% [15]. No experimental antiviral treatments have proved efficacious, although a trial in Guinea has suggested beneficial effect of favipiravir in patients with low viremia [16]. However, comprehensive supportive treatment has resulted in CFR as low as 23.4% (71/304) [17-20].

This article describes clinical features, survival and risk factors for death among patients admitted to the Ebola treatment center (ETC) in Moyamba District, Sierra Leone.

Methods

Study design

We performed a retrospective, descriptive study of clinical data from all patients admitted at the ETC in Moyamba District, Sierra Leone. With a rural population dispersed across 14 chiefdoms, Moyamba District is located on the Atlantic coast southeast of the Freetown, the capital of Sierra Leone, the country hardest hit by the current Ebola epidemic. The Moyamba ETC, one of 23 in the country, was established by the United Kingdom's Department for International Development (DFID), administrated by the non-governmental organization Medicos del Mundo (MdM), and manned by Sierra Leonean and Norwegian health-care workers [21]. We collected available data for all patients admitted to the ETC from the opening of the ETC on 19th December 2014 until its closure by 31st March 2015, including demographic data, potential exposure situations, symptoms, findings, treatment given

and outcome. We retrospectively defined severe pain as pain clinically assessed to be so severe as to lead the clinician to prescribe opiates. Data were compiled from multiple sources; including triage forms, patient records and laboratory registries and plotted anonymously in EpiData 2.0 (The EpiData Association, Odense, Denmark).

The Sierra Leonean Ethics and Scientific Review Committee and the Western Norwegian Regional Committee for Medical and Health Research Ethics approved the study.

Diagnostic methods

Diagnostic services were provided by the U.S. CDC laboratory using the Ebola virus (Zaire) nucleoprotein Real Time Reverse Transcription Polymerase Chain Reaction (Real Time RT-PCR) in Bo before 12th January 2015, and thereafter on-site by the US DoD MEDaC Laboratory. The two Real Time RT-PCR assays used by the MEDaC Laboratory were the Ebola Zaire Emergency Use Authorization Diagnostic (EZ1 EUA) and the Ebola Zaire surveillance assay as provided by the Department of Defense (DoD) Critical Reagent Program (CRP) with pre-Emergency Use Authorization submission to the Food and Drug Administration (FDA). Genetic material from whole blood was extracted using an automatic extraction robot (Qiagen, Hilden, Germany). Subsequently, the real-time RT-PCR is performed using the AB 7500 Fast Dx Real-Time PCR Instrument (Applied Biosystems Carlsbad, CA, USA). This analysis gives quantitative results expressed as cycle threshold (CT) values.

Statistical analysis

We used Fisher's exact test for univariate analysis of proportions. The magnitude and statistical significance of risk factors was expressed in terms of odds ratio (OR), 95% confidence interval (95%CI), and p-values with a two-tailed $p<0.05$ considered threshold for statistical significance. For comparison of continuous variables, we used two-sample Wilcoxon rank-sum (Mann-Whitney) test. Statistical analysis was performed in STATA 13 (Stata corporation, College Station, Texas).

Results

Patients

Among a total of 88 patients admitted to the Moyamba ETC, eighty-two (93%) were tested by Ebola-PCR. A total of 31 (39%) individuals tested positive for Ebola virus. Ninety percent (n=28) reported prior contact with confirmed or suspected EVD cases, most frequently household members (64%, 18/28). Eleven (35%) had participated in burials of EVD suspect deceased persons. There were no health-care workers among the confirmed cases. Most of the confirmed EVD cases (87%, n=27) and all of the fatal cases (100%) came from the Ribbi chiefdom. Fifteen (48%) of the patients were males (Table 1). The median age of the confirmed EVD cases was 30 years, (range 3 months – 85 years), with the majority (58%, n=18) being adults aged 21-45 years. The CFR was 58% (18/31). The CFR was significantly higher among males (80%, 12/15) than females (38%, 6/16, p=0.03). There was no significant correlation between age and adverse outcome (p=0.4).

Incubation time

The time of exposure could only be established for 10/18 fatal and 10/13 non-fatal cases. The median incubation time was 8 days (range 1-17), with no significant difference between fatal and non-fatal cases (Table 1). However the median time from onset of symptoms to admission was significantly shorter in fatal cases than in survivors (p=0.02). The median time from symptom onset to death was 6 days (range

2-18) with the majority of fatal cases (16/18, 89%) dying 4 to 11 days after onset. Ebola-survivors were discharged at a medium time of 19.5 days (range 12-45) after onset of symptoms, when asymptomatic and negative on Ebola-PCR.

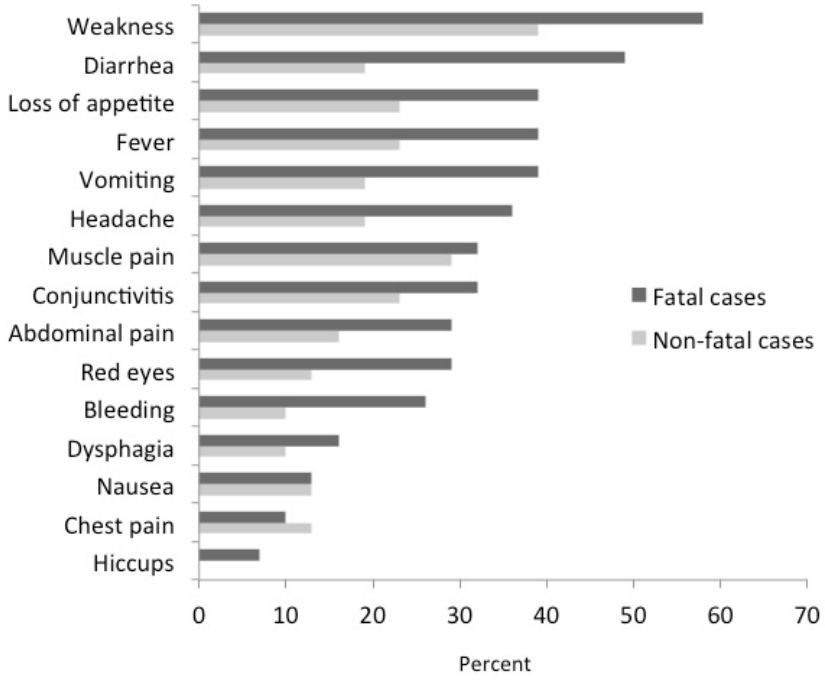

Figure 1. Prevalence of symptoms among fatal and non-fatal cases of Ebola virus disease admitted to the treatment center in Moyamba

Clinical features

On admission, the most frequent symptoms were weakness (97%), diarrhea (68%), fever (62%), loss of appetite (62%), vomiting (58%), pain in muscles (62%) and joints (55%), headache (55%), abdominal pain (45%) and conjunctivitis (42%) (Figure 1). Diarrhea was present in the majority of fatal cases (15/18, 83%), but this was not significantly higher than in non-fatal cases (46%, 6/13, OR 5.8 95%CI 0.94-36, p=0.052).

Bleeding manifestations was present in 35% (11/31) of patients on admission and 55% (17/31) at any time during their hospital stay. Fatal cases had significantly higher frequency of bleeding during hospital stay than the non-fatal cases (78% versus 31%, OR 12, 95%CI 1.5-92, p=0.004) (Figure 2c). Bloody stools was the most frequent hemorrhagic manifestation, present in 72% (13/18) of fatal cases and none of the survivors ($p < 0.001$, OR not applicable). Bleeding from the mouth (p=0.045) and from puncture sites (p=0.03) were also associated with fatal outcome. Diarrhea was very common, but not associated with fatal outcome unless present in combination with bleeding manifestations. The odds ratio for death among patients with diarrhea but no bleeding manifestation was 0.2 (0.028-1.1), p=0.052 (Figure 2d).

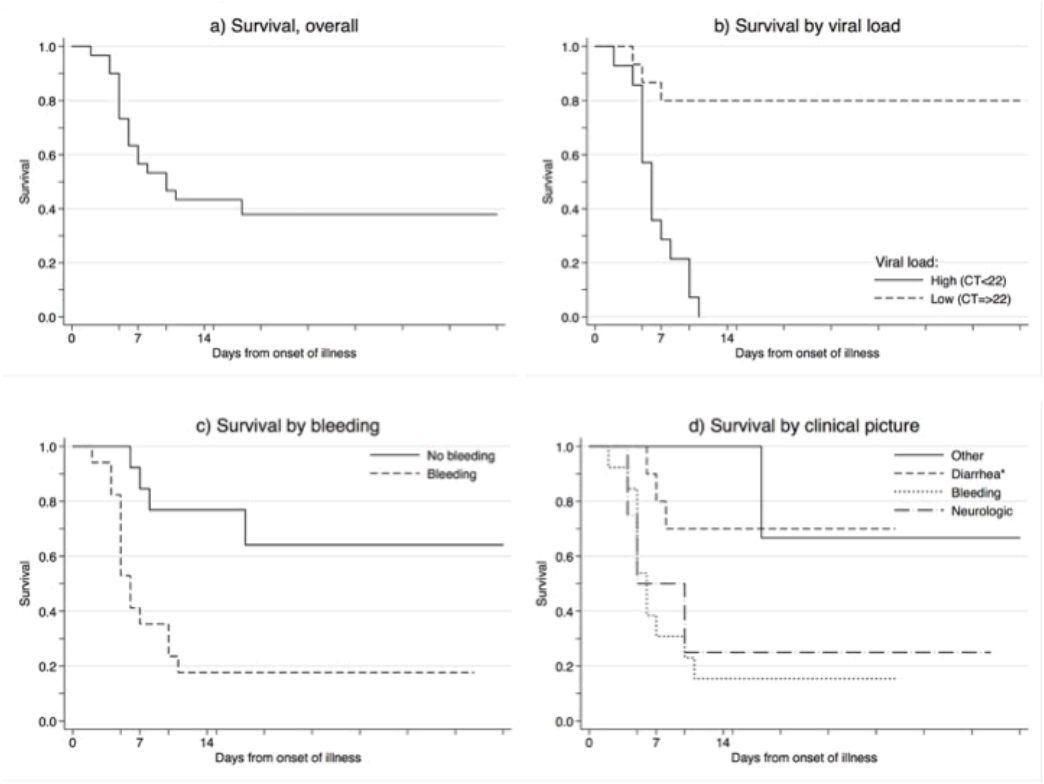

Figure 2. Survival curves for cases of Ebola virus disease admitted to the Ebola treatment center in Moyamba District, Sierra Leone: a) Overall survival of patients; b) survival of patients with initial PCR showing high and low viremia with cycle threshold (CT) values of <22 and ≥22, respectively; c) survival in patients with and without bleeding manifestations during admission; d) survival in patients by dominating clinical picture including bleeding, neurologic presentation and *diarrhea without bleeding manifestation.

Pain was a dominant clinical feature in many patients and was often severe. While all (18/18) of the fatal cases reported pain, this was not significantly more than in non-fatal cases (85%, 11/13). Headache (61%), as well as pain in muscles (56%), joints (56%) and the abdomen (50%) was commonly reported among the fatal cases. Opiate-demanding pain was significantly higher among fatal than non-fatal cases (89%, 16/18 vs 23%, 3/18, OR 27 95%CI 1.9-384, p<0.001). The mean daily morphine doses given were 5.9mg (range 2.3-15.0mg) for fatal cases and 4.4 mg (range 2.5-7.5mg) for non-fatal cases.

Major neurologic symptoms were infrequent, but most patients with presumed neurologic signs on, or early after admission, died, including one 3 years old child with generalized seizures, one 50 years old man with ataxic gait and two patients had hiccups (Figure 2d).

Table 1. Demographic characteristics, clinical features and risk factors for fatal outcome in confirmed Ebola patients admitted to the Ebola treatment center in Moyamba District, Sierra Leone

	All patients (total = 31) n (%)	**Patients who died** (total = 18) n (%)	**Patients who recovered** (total = 13) n (%)	**OR (95%CI)**	**P**
Demographic characteristics					
Males sex	15 (48)	12 (67)	3 (33)	6.7 (1.1-41)	0.03
Age group					
<15 years	6 (19)	4 (22)	2 (15)	1.6 (0.23-11)	1
15-44 years	19 (61)	11 (61)	8 (62)	0.98 (0.22-4.4)	1
≥45 years	6 (19)	3 (17)	3 (23)	0.67 (0.11-4.1)	0.7
Health care workers	0 (0)	0 (0)	0 (0)		
Time (median, range)†					
Incubation time	8 (1-17)	7 (1-10)	8.5 (5-17)		0.1
From onset to admission	3 (0-23)	2 (0-17)	4.5 (1-23)		0.02
From onset to death/discharge	10 (2-45)	6 (2-18)	19.5 (12-45)		<0.001
Symptoms and signs					
Weakness	30 (97)	18 (100)	12 (92)	*(*)	0.4
Diarrhea	21 (68)	15 (83)	6 (46)	5.8 (0.94-36)	0.052
Fever	19 (62)	12 (67)	7 (54)	1.7 (0.38-7.7)	0.7
Loss of appetite	19 (62)	12 (67)	7 (54)	1.7 (0.38-7.7)	0.7
Vomiting	18 (58)	12 (67)	6 (46)	2.3 (0.52-11)	0.3
Conjunctivitis	13 (42)	9 (50)	4 (31)	2.3 (0.48-11)	0.5
Nausea	8 (26)	4 (22)	4 (31)	0.64 (0.12-3.4)	0.7
Dysphagia	8 (26)	5 (28)	3 (23)	1.3 (0.25-6.9)	1
Hiccups	2 (7)	2 (11)	0 (0)	*(*)	0.5
Pain					
Pain overall	29 (94)	18 (100)	11 (85)	*(*)	0.2
- Muscle pain	19 (62)	10 (56)	9 (69)	0.56 (0.12-2.6)	0.5
- Joint pain	17 (55)	10 (56)	7 (54)	1.1 (0.25-4.6)	1
- Headache	17 (55)	11 (61)	6 (46)	1.8 (0.42-8.1)	0.5
- Abdominal pain	14 (45)	9 (50)	5 (38)	1.6 (0.36-7.1)	0.7
- Chest pain	7 (23)	3 (17)	4 (31)	0.45 (0.08-2.6)	0.4
Pain needing opiates	19 (61)	16 (89)	3 (23)	27 (1.9-384)	<0.001
Bleeding on admission					
Bleeding	11 (35)	8 (44)	3 (23)	2.7 (0.51-14)	0.3
- stools	5 (16)	5 (28)	0 (0)	* (*)	0.06
- mouth	2 (6)	1 (6)	1 (8)	0.71 (0.04-13)	1
- eyes	1 (3)	0 (0)	1 (8)	0 (*)	0.4
- genitals	3 (10)	1 (6)	2 (15)	0.32 (0.02-4.3)	0.6
-puncture sites	1 (3)	1 (6)	0 (0)	*(*)	1
Bleeding in hospital					
Bleeding	17 (55)	14 (78)	3 (23)	12 (1.5-92)	0.004
- stools	13 (42)	13(72)	0 (0)	* (*)	0.001
- mouth	9 (29)	8 (44)	1 (8)	9.6 (0.08-115)	0.045
- eyes	4 (13)	3 (17)	1 (8)	2.4 (0.21-28)	0.6
- genitals	6 (19)	4 (22)	2 (15)	1.6 (0.23-11)	1
-puncture sites	7 (23)	7 (39)	0 (0)	* (*)	0.03
PCR results†					
Median CT values (range)	22 (15-36.5)	20.5 (15-23)	26.5 (22-36.5)		<0.001

OR: odds ratio, 95%CI: 95% confidence interval, P: P-values by Fisher exact test, except for time variables and PCR values where Mann Whitney U test was used.

*= OR and/or 95%CI not applicable

† Incubation time was not known for 8 fatal and 3 non-fatal cases, time from onset to admission and time from onset to discharge was unknown for 1 non-fatal case. Quantitative PCR value was unknown for 1 fatal case.

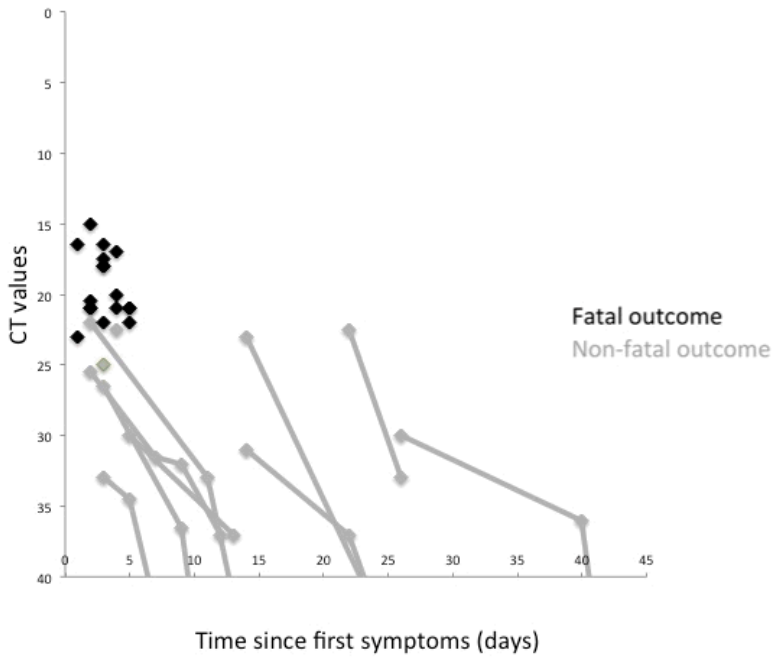

Figure 3. Ebola viral load expressed as PCR cycle threshold (CT) values in fatal and non-fatal cases of Ebola virus disease admitted to the Ebola treatment center in Moyamba District, Sierra Leone

Laboratory findings

Ebola PCR was performed a median of 3 and 3.5 days after symptom onset in fatal and non-fatal cases, respectively (p=0.4). The results of quantitative Ebola PCR shows the level of viremia quantified according to cycle threshold (CT) values, with lower CT values equaling higher viremia (Figure 2b and Figure 3). The viremia on the first PCR after admission was significantly higher in fatal cases than in non-fatal cases (CT values 20.5 (range 15-23) vs 26.5 (range 22-36.5) p<0.001) (Table 1). All patients with CT values <22 (high viremia) died, while all patients with CT values >23 (low viremia) survived.

Treatment given

Oral rehydration solution (ORS) was administered freely and patients were encouraged to drink abundantly. Intravenous fluids were given to 26 (84%) of the cases with confirmed EVD. In total, 29 (94%) patients received antimalarial treatment. Antibiotics was used empirically and administrated to 26 (84%) of the confirmed cases. Among the fatal cases, fourteen (78%) and eight (44%) received intravenous ceftriaxone and metronidazole, respectively. There was no statistically significant difference in medications given to fatal and non-fatal cases.

Table 2. Treatment given to confirmed cases of Ebola virus disease admitted to the Ebola treatment center in Moyamba District, Sierra Leone

Treatment	All patients (Total = 31) n (%)	Patients who died (Total = 18) n (%)	Patients who recovered (Total = 13) n (%)	OR (95%CI)	p
Intravenous fluids	26 (84)	17 (94)	9 (69)	7.6 (0.61-94)	0.1
Antimalarials	29 (94)	17 (94)	12 (92)	1.4 (0.077-26)	1
Ceftriaxone	23 (74)	14 (78)	9 (69)	1.6 (0.30-8.1)	0.7
Metronidazol	13 (42)	8 (44)	5 (38)	1.3 (0.29-5.6)	
Albendazol	5 (16)	1 (6)	4 (31)	0.1 (0.011-1.6)	0.1
Zinc	29 (94)	17 (94)	12 (92)	1.4 (0.077-26)	1

OR: odds ratio, 95%CI: 95% confidence interval, P: P-values by Fisher exact test.

Discussion

The majority of the patients were most likely infected through contact with persons with suspected or confirmed EVD. None of the confirmed cases were health-care workers, which differ from reports from treatment facilities in the current and in past epidemics [22-24].

The overall CFR of confirmed EVD was 58% at the ETC in Moyamba, which is slightly lower than that of 70.8% reported across Sierra Leone, Liberia and Guinea [15] and similar to that of health-care workers in the region [14]. Other ETCs, however, notably the ETC in Hastings, Sierra Leone, have documented CFR as low as 23.4% in patients given comprehensive supportive treatment [17]. While there was no significant difference in incubation time between fatal and non-fatal groups, the fatal cases presented with a picture of rapidly proceeding illness. The median time from onset to admission was shorter in fatal cases than in survivors. The majority of those who died did so from day 4 to 11 after onset of symptoms. This coincides with observations from other centers in Western-Africa during the outbreak [20, 23]. Extremes of age, young and old, have been suggested to be an independent risk factor regardless of any coexisting conditions [23, 25]. We did not find any association between older age and fatal outcome in our material.

Weakness was the most frequently reported symptom, reported by almost everybody on admission. The lack of fever in one third of the patients may have implications for screening procedures and case-definitions. In the early phase of the epidemic, cases were missed because of lack of fever. Large-scale screening with thermometers at various check-points, such as airports, road-blocks, shops and health care services, may not be a very sensitive tool to pick up cases.

Diarrhea and bleeding was significantly associated with fatal outcome. Interestingly, diarrhea without bleeding manifestations, was not a significant risk factor for death, while bloody diarrhea was a very poor prognostic sign. Bloody diarrhea has been attributed to severe enterocolitis caused by the Ebola virus, possibly in combination with coagulation disturbances or bacterial superinfection [24]. Bleeding manifestations in general was seen more frequently in our cohort than reported from other treatment facilities in Sierra Leone [20, 22], but was less frequent than in the 1976 outbreak [1]. Chest pain was frequent, and may suggest upper gastrointestinal tract involvement, particularly in combination with dysphagia. However, previous studies have also suggested that pericarditis and myocarditis may cause chest pain in EVD [24]. While rhabdomyolysis has been postulated as a contributing factor to progressive renal failure and adverse outcome in EVD [20], muscle pain was common in our study, but not a risk factor for death. Abdominal pain in EVD is probably of multifactorial, although underlying pancreatitis has been

proposed as a cause [26]. While a frequent finding, abdominal pain was not a risk factor for death in this study.

While almost all EVD patients reported pain, severe pain necessitating opiate treatment was significantly more frequent in fatal cases. Clinicians in charge speculated whether fatal outcome after severe pain in the chest and abdomen could be due to viral aortitis and aneurysm development, although no investigations could be done to substantiate this theory.

Attention should be given to palliation of the severe pain in EVD. However, the short hands-on time with patients because of personal protection procedures limits the possibility to give adequate pain relief with parenteral opiates. Transdermal administration of opiates (such as fentanyl-containing adhesive plasters) was not available in the study period, but would be an attractive way to provide safe pain relief to EVD patients.

High viremia on admission was a very strong predictor for fatal outcome with 100% fatality among patients with CT values <22, while low viremia was a good prognostic sign with 100% survival among patients with CT values >23. This supports findings from other studies [20, 23, 24], and should be kept in mind when interpreting trials of experimental treatments for EVD [16].

All patients admitted were treated according to the protocols developed by WHO and Sierra Leonean authorities, but the study design and sample size is not adequate to assess associations between treatment and outcome. While systematic, comprehensive supportive therapy, including antimalarial, antibacterial and antihelmintic treatment, has been suggested to improve the prognosis of EVD [17], other factors such as education level, cultural and socioeconomically factors and health-seeking behavior may contribute. According to local health care workers, the populations of some of Moyamba's chiefdoms trust more in traditional healers than in government health services, and there have been difficulties reaching out to these communities with information regarding EVD and the importance of seeking health care early. This situation may result in a selection bias of late presentation to the ETC and more severe patients being hospitalized. Due to lack of laboratory resources, it was not possible to perform targeted clinical testing based on clinical suspicion at the ETC in Moyamba. This, combined with limited time for clinical observations, as health care workers for safety reasons could only spend limited time inside the patient wards, may have lead to challenges in defining the correct indication for supportive medical interventions.

The study was limited by small sample size, although the study population included all patients admitted to the Moyamba ETC. Furthermore, the retrospective design may have resulted in missing data. Many of the patients were in a critical state upon admission, making clinical assessment and history taking suboptimal. The limited hands-on time with patients due to infection control considerations probably resulted in intermittent and incomplete clinical observations. The presence of highly skilled international health-care workers at the ETC, including almost continuous presence of medical doctors, was an asset. However, the mixture of personnel from multiple countries and their cultural and linguistic differences could represent a challenge for communication and lead to a potential a bias in patient investigations.

In summary, our findings concur with those reported elsewhere, although bleeding manifestations appeared to be more common than reported from other ETCs during the current outbreak. Significant predictors for fatal outcome were shorter time from onset to admission, male sex, bleeding manifestations, severe pain and high viral load on initial lab test. We observed that severe pain was common, particularly among moribund cases, and this calls for attention to adequate safe pain relief, for instance with transdermal administration of opiates. The lack of fever in as much as a third of EVD cases may have implications for temperature screening practices and case definitions. We hope that sharing clinical experiences regarding

this, hitherto rare disease, will help prepare health-systems to give more effective patient care in future outbreaks.

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Appendix

The authors are as follows:
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