Characteristics and survival of patients with Ebola virus infection, malaria, or both in Sierra Leone: a retrospective cohort study

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Summary

Background The 2014–15 Ebola virus disease (EVD) epidemic strained health systems in west Africa already overburdened with other diseases, including malaria. Because EVD and malaria can be difficult to distinguish clinically, and rapid testing was not available in many Ebola Treatment Units (ETUs), guidelines recommended empirical malaria treatment. Little is known, however, about the prevalence and characteristics of patients entering an ETU who were infected with malaria parasites, either alone or concurrently with Ebola virus.

Methods Data for sociodemographics, disease characteristics, and mortality were analysed for patients with suspected EVD admitted to three ETUs in Sierra Leone using a retrospective cohort design. Testing for Ebola virus was done by real-time PCR and for malaria by a rapid diagnostic test. Characteristics of patients were compared and survival analyses were done to evaluate the effect of infection status on mortality.

Findings Between Dec 1, 2014, and Oct 15, 2015, 1524 cases were treated at the three ETUs for suspected EVD, of whom 1368 (90%) had diagnostic data for malaria and EVD. Median age of patients was 29 years (IQR 20–44) and 715 (52%) were men. 1114 patients were EVD negative, of whom 365 (33%) tested positive for malaria. Of 254 EVD positive patients, 53 (21%) also tested positive for malaria. Mortality risk was highest in patients diagnosed with both EVD and malaria (35 [66%] of 53 died) and patients diagnosed with EVD alone (105 [52%] of 201 died). Compared with patients presenting to ETUs without malaria or EVD, mortality was increased in the malaria positive and EVD positive group (adjusted hazard ratio 9·36, 95% CI 6·18–14·18, p<0·0001), and the malaria negative and EVD positive group (5·97, 4·44–8·02, p<0·0001), but reduced in the malaria positive and EVD negative group (0·37, 0·20–1·23, p=0·0010).

Interpretation Malaria parasite co-infection was common in patients presenting to ETUs and conferred an increased mortality risk in patients infected with Ebola virus, supporting empirical malaria treatment in ETUs. The high mortality among patients without EVD or malaria suggests expanded testing and treatment might improve care in future EVD epidemics.

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Introduction

The 2014–15 epidemic of Ebola virus disease (EVD) in parts of west Africa was the largest ever recorded, with nearly 12 000 deaths.[1] The affected countries are also highly endemic for malaria, cases of which might have increased as a secondary effect of the EVD epidemic.[2,3] Even before 2014, malaria overburdened a strained health system in Sierra Leone, accounting for nearly 30% of hospital admissions and half of outpatient visits.[3]

Despite the prevalence of malaria in countries at risk for EVD outbreaks, little data exist pertaining to Ebola virus and malaria parasite co-infection. One case report[4] describes a health-care worker co-infected with Ebola virus and *Plasmodium falciparum* with multiorgan failure, and a retrospective study[5] of patients in Liberia showed a prevalence of co-infection of 15%. The antimalarial amodiaquine might have activity against Ebola virus.[6] However, research is conflicting regarding the effect of malaria parasite co-infection on mortality. A laboratory-based study[7] from Liberia reported that co-infection was associated with reduced mortality among patients with EVD admitted at a single Ebola Treatment Unit (ETU). Another study in Guinea, by Kerber and colleagues,[8] found a high case fatality rate in patients co-infected with Ebola virus and malaria parasites. To our knowledge, no multisite studies have been published evaluating clinical characteristics and mortality in patients with variable malaria parasite and Ebola virus infection states.

During the EVD epidemic, WHO guidelines recommended that all patients admitted to ETUs be empirically treated with artesunate combination therapy.[9] However, the evidence supporting empirical malaria treatment during an EVD outbreak is limited. We investigated this issue to inform protocols for triage and management during future EVD epidemics in malaria-endemic settings.

Methods

Study design and participants

We did a retrospective cohort study using data collected from Sierra Leone during the 2014–15 EVD response to define the proportion of patients admitted to ETUs who

Research in context

Evidence before this study

Little evidence exists regarding the characteristics and outcomes of patients co-infected with Ebola virus disease (EVD) and malaria. In a 2016 literature review, Waxman and colleagues searched PubMed and Google Scholar using combinations of the terms "malaria", "Ebola", Ebola virus disease", "Ebola treatment units", and "Sierra Leone." One study found that *Plasmodium falciparum* parasitaemia conferred a decreased mortality in patients infected with Ebola virus in Liberia. Another study supported the use of malaria diagnostic testing during EVD epidemics. A number of studies reported the significance of malaria mortality in Sierra Leone and the effect of the EVD epidemic on malaria treatment.

Added value of this study

To our knowledge, our study is the first to assess survival outcomes and baseline characteristics of patients by different combinations of EVD and malaria infection. Mortality was higher in patients co-infected with malaria and Ebola virus compared with patients with EVD alone. Our results contradict a previous study showing that *Plasmodium falciparum* co-infection with EVD conferred a mortality benefit. We also found an unexpectedly high mortality in patients who were admitted to the Ebola treatment unit and tested negative for both EVD and malaria. This suggests that diagnostic testing should be expanded beyond EVD and malaria in future epidemics. Finally, we report differences in demographics and baseline symptoms for each infection state. These results should inform decision making in future EVD epidemics.

Implications of all the available evidence

This study is the second to look at the outcomes of patients with EVD and malaria co-infection. These divergent results of the effect of malaria on mortality in co-infected patients warrant further analysis with a larger number of patients from the EVD epidemic in west Africa. Our study contributes to a growing body of evidence supporting WHO recommendations for empirical treatment of malaria during EVD epidemics. The expanding literature on EVD and malaria co-infection warrants investigation into the immunological basis for the interactions between these two clinically overlapping diseases.

were infected with malaria parasites, either alone or in combination with Ebola virus, and to compare case characteristics and survival outcomes between groups with varying infection states. We included all patients admitted to the three ETUs operated by International Medical Corps in Sierra Leone, in Lunsar, Makeni, and Kambia, in cooperation with local public health ministries from Dec 1, 2014, to Oct 15, 2015.

All patients presenting to the study ETUs were triaged to ensure that they met the case definition for suspected EVD, which was based on WHO[9] and Médecins Sans Frontières (MSF) guidelines,[10] in consultation with local health authorities (appendix p 5). After triage, patients meeting the case definition for suspected EVD were admitted to the ETU suspect ward and had a blood sample drawn for Ebola virus and malaria diagnostic testing. Patients with an initially negative EVD test remained as inpatients for repeated testing after 2 days. Patients with a second negative EVD result were discharged if clinically well or transferred to another health facility if available. Patients with positive EVD test results were moved to the ETU confirmed ward.

See Online for appendix

Procedures

All patients were treated in accordance with standard treatment protocols based on guidelines developed by WHO[9] and MSF.[10] Empirical treatment included antimalarial medications, broad-spectrum antibiotics, and nutritional supplementation, as well as focused supportive treatment (appendix p 7). Patients who were not able to take oral medications or had evidence of severe disease were treated with parenteral artemether or artesunate, while all other patients were given oral artemether–lumefantrine (ACT; appendix p 33). Patients were cared for by trained medical staff who recorded clinical data, presenting symptoms, and exposure history on paper forms at triage by interviewing the patient or their family.[11] These data were digitised at each ETU, audited for data quality, and unified by International Medical Corps staff into a single database, as described previously.[11] Laboratory data included Ebola virus real-time (rt) PCR and malaria parasite testing. A cycle threshold (CT) of less than 40 was considered positive for Ebola virus testing.[11] Testing for malaria parasites was done using the commercially available BinaxNow (Alere, Waltham, MA, USA) rapid diagnostic test, which identifies four plasmodium species: *P falciparum*, *Plasmodium malariae*, *Plasmodium vivax*, and *Plasmodium ovale*.

Statistical analysis

Cases admitted to the ETUs with diagnostic data for both EVD and malaria were included in the analyses. Categorical variables are shown as n (%) and continuous parameters as mean (SD) or median (IQR). Cases were analysed in aggregate and stratified by infection status as malaria negative and EVD negative, malaria positive and EVD negative, malaria negative and EVD positive, or malaria positive and EVD positive. Pairwise deletion was used to handle missing data for all comparisons, and missing data were not included in the denominator for any given descriptive statistic. Differences in characteristics between infection subgroups were assessed using independent sample *t* tests or Mann-Whitney tests

for continuous variables and χ^2 or Fisher's exact tests for categorical covariates.

We calculated prevalence and incidence per 100 person-days with associated 95% CI. Mortality outcomes at 28 days were assessed using Kaplan-Meier analyses with significant differences assessed using log-rank tests. Cox proportional hazards models were done to evaluate survival outcomes yielding hazards ratios (HR) and adjusted hazards ratios (aHR). Multivariate models were adjusted a priori for patient age and the malaria negative and EVD negative subgroup was used as the baseline comparator in the overall cohort. We directly compared the infection statuses with subanalyses using the same methods.

We calculated survival time based on the difference in date of ETU admission and date of transfer or death up to 28 days of care. Transferred patients were censored at time of departure from the ETU. Cases alive and in care at 28 days were censored at that time. In view of the statistical requirements of proportional hazards models and the high probability that patients would return for care if needed after treatment, survival time for cases discharged alive before 28 days was set to 28 days.[12] We did a sensitivity analysis to assess the effect of the assumed survival time (appendix). To evaluate the representativeness of cases meeting inclusion criteria compared with the overall cohort treated at the ETUs, we compared baseline and outcome characteristics between those with and without serological testing data. We analysed data using Stata version 13.0.

Role of the funding source

All resources were provided by International Medical Corps. All data were collected by International Medical Corps staff at International Medical Corps operated ETUs, although analyses were performed by independent academics. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

1524 patients were admitted to one of three study ETUs for suspected EVD between Dec 1, 2014, and Oct 15, 2015 (figure 1, table 1). Among admitted patients, 1368 (90%) had diagnostic test results available for both malaria and EVD infection. Patients without available diagnostic data were younger on average than those with complete data, more likely to be treated at the Makeni ETU, and had higher mortality (appendix). 1114 (81%) of patients with available diagnostic data tested negative for EVD, of whom 365 (33%) tested positive for malaria. Conversely, 254 (19%) of patients tested positive for EVD, of whom 53 (21%) also tested positive for malaria (figure 1).

We stratified characteristics by infection status (table 2, appendix p 1). The median age of co-infected patients was lower than that of the other subgroups. Seven of ten presenting symptoms were significantly different between infection status subgroups: fever, headaches, abdominal pain, emesis, diarrhoea, arthralgia or myalgia, and dyspnoea. Abdominal pain was significantly more common among cases without EVD than in patients with EVD (585 [53%] of 1114 *vs* 94 [37%] of 254, p<0·0001).

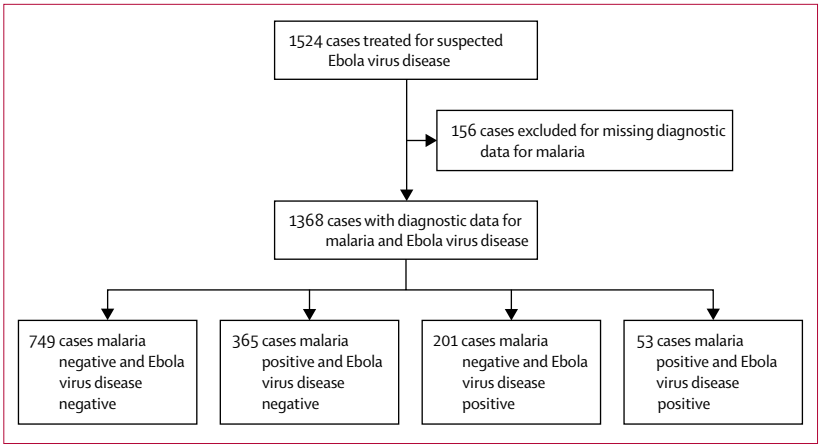

Figure 1: **Study profile**

	Patients
Sex	
Male	715/1361 (53%)
Female	646/1361 (47%)
Age, years	29 (20–44)
Presenting symptoms	
History of fever	1013/1368 (74%)
Headaches	786/1368 (58%)
Abdominal pain	679/1368 (50%)
Anorexia	894/1368 (65%)
Emesis	534/1368 (39%)
Diarrhoea	474/1252 (38%)
Arthralgia or myalgia	834/1368 (61%)
Fatigue	928/1368 (68%)
Dyspnoea	385/1368 (28%)
Abnormal haemorrhage	113/1368 (8%)
Exposure history	
Contact with a patient with EVD	339/1218 (28%)
Any illness in family	249/1198 (21%)
Visited someone ill	224/1181 (19%)
Contact with person who died	251/1205 (21%)
Care and outcomes	
Clinic site	
Lunsar	439/1368 (32%)
Kambia	157/1368 (12%)
Makeni	772/1368 (56%)
Days of treatment	3 (3–4)
Mortality	230 (17%)

Data are n (%) or median (IQR). EVD=Ebola virus disease.

Table 1: **Cohort characteristics**

	Malaria negative, EVD negative (n=749)	Malaria positive, EVD negative (n=365)	Malaria negative, EVD positive (n=201)	Malaria positive, EVD positive (n=53)	p value*
Sex					<0·0001
Male	435/745 (58%)	192/363 (53%)	69/200 (35%)	19/53 (36%)	
Female	310/745 (42%)	171/363 (47%)	131/200 (66%)	34/53 (64%)	
Age, years	32 (24–45)	23 (8–35)	30 (20–45)	13 (4–27)	<0·0001
Presenting symptoms					
History of fever	553/749 (74%)	293/365 (80%)	128/201 (64%)	39/53 (74%)	<0·0001
Headaches	445/749 (60%)	213/365 (58%)	106/201 (53%)	22/53 (42%)	0·0340
Abdominal pain	395/749 (53%)	190/365 (52%)	83/201 (41%)	11/53 (21%)	<0·0001
Anorexia	501/749 (67%)	233/365 (64%)	129/201 (64%)	31/53 (59%)	0·4980
Emesis	272/749 (36%)	175/365 (48%)	74/201 (37%)	13/53 (25%)	<0·0001
Diarrhoea	233/680 (34%)	124/346 (36%)	99/179 (55%)	18/47 (38%)	<0·0001
Arthralgia or myalgia	490/749 (65%)	207/365 (57%)	116/201 (58%)	21/53 (40%)	<0·0001
Fatigue	530/749 (71%)	232/365 (64%)	134/201 (67%)	32/53 (60%)	0·0580
Dyspnoea	240/749 (32%)	92/365 (25%)	41/201 (20%)	12/53 (23%)	0·0030
Abnormal haemorrhage	71/749 (10%)	29/365 (8%)	9/201(5%)	4/53 (8%)	0·1480
Exposure history					
Contact with patient with EVD	111/663 (17%)	50/337 (15%)	135/169 (80%)	43/49 (88%)	<0·0001
Any illness in family	77/662 (12%)	36/338 (11%)	99/153 (65%)	37/53 (82%)	<0·0001
Visited someone ill	65/658 (10%)	34/335 (10%)	91/146 (62%)	34/42 (81%)	<0·0001
Contact with person who died	72/657 (11%)	29/335 (9%)	118/165 (71%)	33/48 (69%)	<0·0001
Care and outcomes					
Clinic site					<0·0001
Lunsar	218/749 (29%)	88/365 (24%)	111/201 (55%)	22/53 (42%)	
Kambia	85/749 (11%)	50/365(14%)	20/201 (10%)	2/53 (4%)	
Makeni	446/749 (60%)	227/365 (62%)	70/201 (35%)	29/53 (55%)	
Days of treatment	3 (2–3)	3 (3–3)	7 (4–12·5)	6 (3–12)	<0·0001
Mortality	77 (10%)	13 (4%)	105 (52%)	35 (66%)	<0·0001

Data are n (%) or median (IQR). Missing data were excluded from each analysis, so the denominator is different between variables. Statistical testing was done using either Mann-Whitney for continuous variables or χ^2 for categorical variables. Fisher's test was used for proportional comparisons in which there were less than five observations per variable. EVD=Ebola virus disease. *p values reflect comparisons between all four groups.

Table 2: **Characteristics of cases stratified by infection status**

Mortality was highest in co-infected patients (66%), followed by patients infected with Ebola virus alone (52%; table 2). Patients testing negative for both malaria parasites and Ebola virus had a higher mortality than malaria positive and EVD negative patients (10% *vs* 4%; table 2).

Survival outcomes by subgroup are depicted in figure 2. 134 (58%) of 230 deaths occurred within 3 days and 208 (90%) of all deaths occurred within 7 days of ETU admission. Table 3 shows 28-day mortality, which was highest for co-infected patients (8·2 per 100 person-days, 95% CI 5·9–11·4). Compared with the malaria negative and EVD negative group, mortality risk was increased in the malaria positive and EVD positive group, and the malaria negative and EVD positive group, but reduced in the malaria positive and EVD negative group (table 3).

Sensitivity analyses using Cox and logistic regression models showed the same trends in mortality risks and likelihoods across subgroups by infection status as were found in the model using assumed survival times (appendix p 2). In the focused subgroup analysis of patients diagnosed with EVD, mortality was higher in patients with malaria than in those without malaria (aHR 1·69, 95% CI 1·14–2·52, p=0·0091). Similarly, in a post-hoc subgroup analysis of patients diagnosed with malaria, patients with EVD had higher mortality than did patients without EVD (26·2, 13·8–50·0, p<0·0001; appendix p 2).

Discussion

In this study, a large proportion of patients admitted to ETUs in Sierra Leone were infected with malaria parasites. Of the varying infection states, patients co-infected with malaria parasites and Ebola virus had the highest mortality. The high prevalence of malaria among patients admitted to ETUs in Sierra Leone, coupled with the increased mortality risk conferred by malaria parasite infection in patients diagnosed with EVD, lends support to existing WHO recommendations for empirical malarial treatment of patients admitted to ETUs.[9]

Our data also improve understanding of differences in demographic, epidemiological, and presenting clinical characteristics among patients with Ebola virus or malaria parasite infection, or both. Previous research[13,14] from Liberia has highlighted the difficulty in clinically differentiating EVD from other infectious processes. Although the WHO case definition of EVD is sufficiently sensitive to capture likely cases, it has low specificity, resulting in large resource allocations for patients admitted to an ETU without EVD. Lack of access to rapid diagnostic tests for malaria parasites and Ebola virus makes this clinical decision even more challenging. The stakes are extremely high: admitting an EVD negative patient who has malaria into an ETU exposes that patient to the possibility of nosocomial Ebola virus infection. Similarly, incorrectly diagnosing an EVD positive patient with another disease like malaria and placing them in a non-ETU setting could propagate EVD in the community. Our findings show the difficulty in differentiating acute illnesses in settings with epidemic illnesses superimposed on endemic diseases, and highlight the need for rapid dianostic testing in these settings.[15]

Presenting symptoms differed between infection statuses. Patients with malaria alone were more likely to have fever, headache, abdominal pain, and emesis than those with EVD alone, whereas those with EVD alone were more likely to have diarrhoea than those with malaria alone. Patients with EVD were more likely to have a history of exposure to someone who had been ill or died than patients with malaria. Additionally, a larger proportion of people with EVD were female and the average age of patients with malaria was lower. Although it might be impossible to develop a perfect clinical screening tool, improved understanding of the unique demographic, clinical, and epidemiological characteristics of patients with EVD might lead to an improved case definition and more effective triage during future epidemics.

The subgroup of patients admitted for suspected EVD who tested negative for both EVD and malaria had higher mortality than did those diagnosed with malaria alone. These patients represented the largest proportion of admitted cases, indicating that many patients with clinical findings consistent with EVD probably had alternative disease processes; the absence of diagnostic capabilities or appropriate treatment protocols could have contributed to the relative increased mortality in this subgroup. Other endemic communicable diseases common in Sierra Leone, such as typhoid, meningitis, bacterial pneumonia, tuberculosis, and HIV[16] probably also accounted for the high mortality in this group. Research to investigate whether the empirical antibiotics being used in ETUs are necessary and sufficient to treat alternative disease process should be undertaken. Our results also support consideration for expanded diagnostic testing to evaluate for a broader set of communicable and non-communicable diseases in future EVD epidemics. However, in the absence of expanded diagnostic testing, the continued use of broad-spectrum antibiotics can be justified.

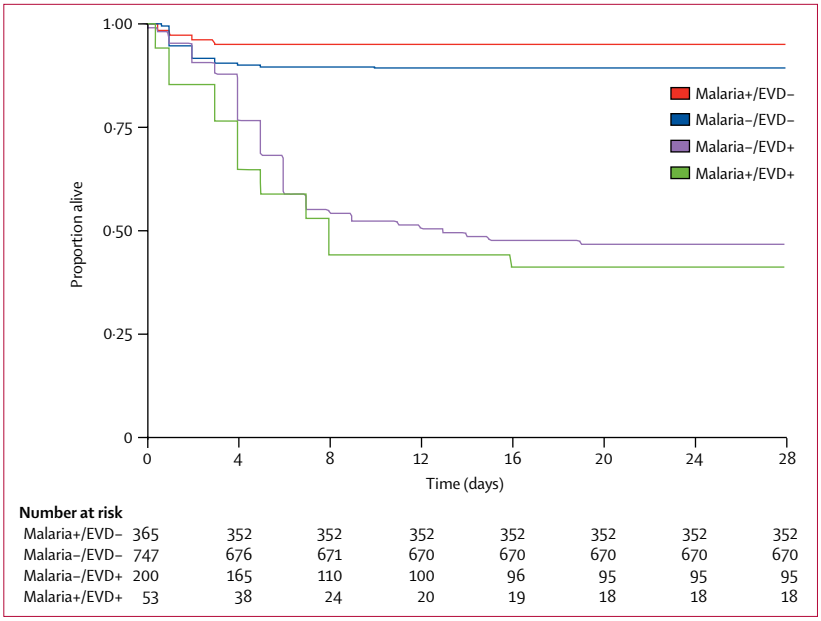

***Figure 2*: Kaplan-Meier plot of survival outcomes**
EVD=Ebola virus disease.

Our study found that among patients with EVD, mortality was higher in patients with malaria than in those without. This finding contrasts with those from Rosenke and colleagues,[7] who found a 20% increase in survival among co-infected patients. Our study population and analytical methods differed, which might explain the discrepancy in these findings. Rosenke and colleagues' investigation was a laboratory-based study at a single Liberian ETU, and determined the clinical outcome for patients included by cross-referencing laboratory samples with a list of deceased patients. Their analysis assumes that all patients not on the deceased list survived to discharge and that all patients who died had laboratory testing carried out before death, introducing bias into their results by excluding sicker patients who might have either died before testing or who might not have been identified before dying.[17] In our study, we documented outcomes for all patients admitted to the ETUs, as well as available EVD and malaria testing for 90% of patients, and we reported differences in baseline characteristics and outcomes between those patients with and without testing. The study by Rosenke and colleagues used overall survival as their primary outcome rather than more robust survival time analyses and excluded children younger than 5 years in some of their models, which was the population we found to be at highest risk for co-infection and at the highest risk for mortality.[13] A potential strength of Rosenke and colleagues' study was the use of rtPCR testing for malaria parasites, as opposed to the less sensitive rapid diagnostic tests used in our study that could have resulted in some false negative tests for malaria.[18,19] Such misclassification

	Incidence per 100 person-days	Univariate model		Multivariate model	
		Hazard ratio (95% CI)	p value	Adjusted hazard ratio* (95% CI)	p value
Malaria negative, EVD negative	3·5 (2·8–4·4)	..	..	..	..
Malaria positive, EVD negative	1·2 (0·7–2·1)	0·3 (0·2–0·6)	<0·0001	0·4 (0·2–0·7)	0·0010
Malaria negative, EVD positive	6·0 (4·9–7·2)	5·8 (4·3–7·8)	<0·0001	6·0 (4·4–8·0)	<0·0001
Malaria positive, EVD positive	8·2 (5·9–11·4)	8·1 (5·4–11·5)	<0·0001	9·4 (6·2–14·2)	<0·0001

Cases censored at time of death or at 28 days if discharged alive from treatment centre. EVD=Ebola virus disease. *Multivariate model adjusted for patient age.

***Table 3*: Mortality outcomes by infection status**

would bias our results towards the null, however, and the statistically significant finding of increased mortality risks with co-infection would be an underestimation of the true association, further strengthening our findings.[20] Additionally, rtPCR testing is highly sensitive and might have picked up background parasitaemia in patients without clinical findings. These conflicting results highlight the need for further research on Ebola virus and malaria parasite co-infection to improve understanding of this complex pathology.

Despite use of standardised guidelines at all three ETUs studied, differences in treatment provision might have affected patient outcomes in our study because we did not assess the specific treatments provided to individual patients. Although a rigorous process to ensure data quality was used, missing data is a potential limitation of this study. Although analyses showed some differences in characteristics and outcomes between patients with and without laboratory data, only a small proportion of patients had missing data, and the included sample is probably representative of the overall study population.

Our study did not ascertain if patients used ACT before admission for presumed malaria, which is common in Sierra Leone. If pretreatment with ACT did occur it might have resulted in false negative rapid diagnostic testing results, which could have reduced the number of patients analysed in the co-infected group. If this was the case, a lack of previous ACT treatment in the co-infected group might have increased the relative mortality. This possibility would not affect the validity of our findings, which reflect actual practice, or their implications, because self-reported previous ACT use would probably not direct treatment in an outbreak setting.

Another limitation to our study was patient follow-up. Because data were collected retrospectively, definitive follow-up information about patients who were discharged alive was not available. The variables used in the survival analyses were based on the assumption that patients discharged alive would return to the ETUs to seek care if needed, and if they did not, that they survived through 28 days. In view of the absence of alternative facilities in the areas of the study sites, this assumption seemed reasonable. Although this assumption does threaten the internal validity of the results, the sensitivity analyses, which used censoring at time of discharge and logistic regression models, did not differ significantly from the primary analyses. Finally, we did not control for viral load or its surrogate marker of CT values, which have previously been found to be independent predictors of mortality in patients with EVD.

Our study shows a high prevalence of malaria parasite infection in patients cared for in ETUs, a factor that should be considered when developing response guidelines for future EVD outbreaks and supports the use of empirical antimalarial treatments for patients admitted to ETUs when rapid diagnostic testing is not available or feasible. The high mortality seen in patients who tested negative for both Ebola virus and malaria parasites might justify expanded diagnostic testing and empirical treatment regimens during subsequent epidemics. Patients with EVD and malaria had significantly higher mortality than patients with EVD alone, and further research on co-infected states is needed to improve pathophysiological understanding and inform future care provision.

Contributors

MW was responsible for inception of the study idea, study design, and preparation of manuscript. ARA did statistical analysis and prepared the tables and figures. SR prepared the manuscript and did statistical analysis. ACL contributed to study design, managed the dataset, and provided editorial support.

Declaration of interests

We declare no competing interests. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of International Medical Corps or any governmental bodies.

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