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MAJOR ARTICLE

Characteristics and Outcomes of Pediatric Patients With Ebola Virus Disease Admitted to Treatment Units in Liberia and Sierra Leone: A Retrospective Cohort Study

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Background. The clinical and virologic characteristics of Ebola virus disease (EVD) in children have not been thoroughly documented.

Methods. Consecutive children aged <18 years with real-time polymerase chain reaction (RT-PCR)–confirmed EVD were enrolled retrospectively in 5 Ebola treatment units in Liberia and Sierra Leone in 2014/2015. Data collection and medical management were based on standardized International Medical Corps protocols. We performed descriptive statistics, multivariate logistic regression, and Kaplan-Meier survival analyses.

Results. Of 122 children enrolled, the median age was 7 years and one-third were aged <5 years. The female-to-male ratio was 1.3. The most common clinical features at triage and during hospitalization were fever, weakness, anorexia, and diarrhea, although 21% of patients were initially afebrile and 6 patients remained afebrile. Bleeding was rare at presentation (5%) and manifested subsequently in fewer than 50%. The overall case fatality rate was 57%. Factors associated with death in bivariate analyses were age <5 years, bleeding at any time during hospitalization, and high viral load. After adjustment with logistic regression modeling, the odds of death were 14.8-fold higher if patients were aged <5 years, 5-fold higher if the patient had any evidence of bleeding, and 5.2-fold higher if EVD RT-PCR cycle threshold value was ≤20. *Plasmodium* parasitemia had no impact on EVD outcomes.

Conclusions. Age <5 years, bleeding, and high viral loads were poor prognostic indicators of children with EVD. Research to understand mechanisms of these risk factors and the impact of dehydration and electrolyte imbalance will improve health outcomes.

Keywords. Ebola, child, malaria, mortality, PCR.

The Ebola virus disease (EVD) outbreak in West Africa from 2014 to 2016 was the largest and deadliest in history, with 28 616 EVD cases and 11 310 deaths, including a significant number of children [1]. Prior to this epidemic, there was a paucity of data describing children with EVD. However, the recent outbreak presented unique opportunities to characterize pediatric EVD patients systematically in order to understand the natural history of disease and to identify clinical and virologic prognostic indicators and predictors of mortality [2].

Consistent with sparse information from previous smaller epidemics, the limited pediatric data from the recent outbreak show that the youngest children had the highest case fatality ratios, which approximated those of adults aged >45 years [3]. The data also show that the overall incidence of EVD among children was significantly lower than that among adults, possibly because of traditional burial practices [4–9]. Detailed descriptions of the natural history of EVD largely have been limited to adult, ex-patriot healthcare workers returning for treatment in the United States and Europe [10–14]. These cases highlight the favorable prognoses of adult patients treated in advanced intensive care units with meticulous fluid resuscitation, electrolyte replacement, and certain experimental therapies. Not surprisingly, prognosis is significantly worse in regions with poor healthcare resources where sophisticated supportive care is unavailable. Therefore, more detailed studies of highly vulnerable populations, such as children, are critical to maximize efficient use of limited resources.

Caring for proven or suspected Ebola virus–infected children presents unique challenges in resource-limited countries. Socioeconomic and cultural factors frequently contribute to worse outcomes, especially when this devastating disease has led to infected children being orphaned. Many children may have been treated in Ebola treatment units (ETUs) without dedicated caregivers, given the risks associated with having an uninfected family member in the ETU. In addition, EVD may affect children's immunologic responses and endothelial function

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differently compared with adults, which could adversely affect their survival [15, 16].

Although there are some studies of Ebola virus–infected adults from low-resource settings [17–21], there remain significant gaps in our knowledge about the determinants and evolution of adverse outcomes in children with EVD [15, 16, 22, 23]. Our aim in this study was to characterize systematically a large cohort of retrospectively enrolled children with EVD during the West African epidemic in 2014 to 2015 in order to identify clinical and virologic risk factors for mortality. Knowledge of potentially modifiable risk factors may be useful to guide effective social and medical interventions in future EVD outbreaks.

METHODS

Study Setting

This retrospective, cohort study includes patient data collected at 5 ETUs operated by International Medical Corps (IMC) in Liberia and Sierra Leone from 15 September 2014 to 15 September 2015 as part of its comprehensive response to the West African EVD epidemic.

All patients who presented to the study ETUs with symptoms concerning for EVD were triaged to ensure that they met the suspect case definition, which was created based on World Health Organization (WHO) [24] and Ministry of Health guidelines from each country (Supplementary Appendix 1). After triage, patients who met the suspect case definition were admitted to the ETU suspect ward and had a blood sample drawn within 24 hours for EVD and malaria diagnostic testing. Patients with an initial negative EVD test remained as inpatients for repeated testing after 2 days. Patients with a second negative EVD result were discharged or transferred to another healthcare facility. Patients with positive EVD test results were moved to the ETU confirmed ward.

Inclusion Criteria

All patients aged <18 years who were admitted at any of IMC's 5 ETUs with a positive EVD test and outcome data were included for analysis.

Clinical Procedures

All patients were treated according to standard treatment protocols based on guidelines developed by the WHO [24], Médecins Sans Frontières [25], and local ministries of health, as permitted by local resources. Empiric treatment included antimalarial medications, broad-spectrum antibiotics, and nutritional supplementation, as well as focused supportive treatment (Appendix 1). Patients were cared for by trained medical staff who recorded clinical data on paper forms. These data were digitized at each ETU and unified into a database, as described previously [26].

Laboratory Data

Laboratory data, including EVD real-time polymerase chain reaction (RT-PCR) and malaria testing, were linked to clinical data for analyses. RT-PCR testing was performed by the US Naval Medical Research Center for ETUs in Liberia, by Public Health England laboratories for Lunsar and Makeni ETUs in Sierra Leone, and by the Nigerian laboratory for the Kambia ETU in Sierra Leone. Cycle threshold (Ct) values, which are based on RT-PCR of the same Ebola virus (EBOV) Zaire locus, are presented in this study as surrogates of viral load. A Ct >40 was considered negative in all cases, though RNA extraction procedures differed slightly between laboratories. Malaria testing (conducted in Sierra Leone only) was performed at each laboratory site using the commercially available BinaxNow rapid diagnostic test, which identifies 4 *Plasmodium* species: *falciparum*, *malariae*, *vivax*, and *ovale*.

Data Collection

Throughout hospitalization, patients were cared for by trained local or international nurses, physician assistants, or physicians, who rounded at least daily and recorded vital signs, clinical data, and laboratory results on paper forms. Patient temperatures were measured with infrared or oral thermometers. For children who were unable to communicate history and who had no accompanying guardians, only objective signs were recorded. These data were transferred to separate electronic databases at each ETU and later combined. A random sampling audit concluded that >99% of the data in IMC's unified database was accurate [26].

Data Analyses

The variables of interest included demographic and clinical characteristics, malaria status, initial EVD RT-PCR Ct values, and mortality. Length of stay was calculated as the number of days from date of admission to date of discharge. Age was categorized into the following groups: <2 years, 2–4 years, 5–9 years, 10–14 years, and 15–17 years. For descriptive statistics, median values with interquartile ranges (IQRs) were calculated for nonnormally distributed continuous data, and proportions were calculated for categorical data. Bivariate analyses were performed to determine the associations between mortality, the primary outcome of interest, and independent covariates using the Mann-Whitney U test for continuous variables and χ^2 or Fisher exact test for categorical variables where appropriate. Covariates that had a P value <0.1 from bivariate analyses were entered in a backward stepwise logistic regression model to determine which variables independently predicted mortality. Goodness of fit was determined using the Hosmer and Lemeshow test. We used Kaplan-Meier curves and the log-rank test to compare survival among children by age group, hemorrhagic features, and viral loads estimated by Ct values. A 2-tailed $P < .05$ was considered to be statistically significant. Statistical analyses were performed with SPSS Statistics, version 22.0.

Ethics Approval

The Sierra Leone Ethics and Scientific Review Committee, the University of Liberia–Pacific Institute for Research & Evaluation Institutional Review Board, and the Lifespan (Rhode Island

Hospital) Institutional Review Board provided ethics approval for this study and exemption from informed consent.

RESULTS

Among the 547 pediatric cases admitted to IMC ETUs in Liberia and Sierra Leone during the study period, 123 had PCR-confirmed EVD. One patient, whose outcome was unknown, was transferred to another facility, leaving 122 patients available for analysis. Included in this number were 7 patients who were previously admitted briefly with suspected EVD but whose diagnosis was confirmed during second admissions.

Incidence in females (56%) and males (44%) was similar. Median age was 7 years (IQR, 3–13). Children were divided into 5 age categories: younger than 2 years (15%), 2–4 years (21%), 5–9 years (25%), 10–14 years (26%), and 15–17 years (13%). The median length of stay was 9 days (IQR, 6–15; range, 1–31). Almost all children (94%) had a history of contact with documented cases of EVD.

At triage, more than 50% of children had fever, anorexia, and weakness (Table 1). The most commonly observed signs and symptoms during hospitalization were weakness, fever, diarrhea, and anorexia (Table 1). Hemorrhagic features were present in 5% at triage and 45% any time during admission.

Malaria testing was available at the Sierra Leone sites only; 68 of 84 (81%) children were tested, of whom 27 (40%) were positive for *Plasmodium* parasitemia. The differences in incidence by age group were significant ($P = .024$), with the most cases reported among children aged <5 years (56%) compared with 5–9 years (50%), 10–14 years (25%), and 15–17 years (9%). There was no difference in rates of *Plasmodium* parasitemia in children with or without fever (38% vs 43%, respectively; $P = 1.0$).

The overall case fatality rate (CFR) was 57%. As shown in Table 2, median length of stay was significantly longer for those who survived compared with those who died (16 vs 6 days; $P < .001$). The median age of patients who died was significantly younger than of patients who survived (4 vs 11 years; $P < .001$). Stratified by age, the CFR was highest (89%) for children aged <5 years compared with other age groups (5–9 years, 43%; 10–14 years, 41%; 15–17 years, 25%; $P < .001$; Figure 1). In addition to age, other significant predictors of mortality included evidence of bleeding at any time during hospitalization (58% in children who died vs 27% in survivors; $P = .003$; Figure 2) and median initial PCR Ct values (19.2 in children who died vs 25.0 in survivors; $P < .001$). Overall, a PCR Ct cutoff value of 20 predicted mortality across age groups better than a cutoff value of 25, except for children aged <2 years (Figure 3, Supplementary Figure 1). A diagnosis of *Plasmodium* parasitemia did not influence mortality in aggregate ($P = .76$) or by age stratified analyses (data not shown). No other characteristics differed between the groups.

Approximately one-fifth of children (26/121) presented without fever. Of these children, 73% developed fever but 6 remained afebrile throughout their hospitalization. The difference in death rates among afebrile hospitalized children stratified by age (<5 years, 2; 5–9 years, 2; 10–14 years, 2) was not significant ($P = .6$). Fifty percent of the afebrile children died, but no distinguishing clinical features or RT-PCR Ct values predicted these deaths.

Significant variables from the bivariate analyses (Table 2) were entered in backward stepwise logistic regression models.

Table 1. Clinical Characteristics of Ebola Virus Disease Patients Observed at Triage and During Hospitalization at Ebola Treatment Units in Liberia and Sierra Leone

Symptom/Sign	Number at Triage (%)						Number of Inpatients (%)					
Age, y	All Ages	<5	5–9	10–14	15–17	*P* Value	All Ages	<5	5–9	10–14	15–17	*P* Value
Fever [a]	95/121 (79)	35/43 (81)	23/30 (77)	25/32 (78)	12/16 (75)	.94	99/108 (92)	36/39 (92)	22/25 (88)	26/29 (90)	14/15 (93)	.92
Anorexia	26/38 (68)	5/9 (56)	7/11 (64)	11/13 (85)	3/5 (60)	.47	90/112 (80)	27/40 (68)	24/27 (89)	27/30 (90)	12/15 (80)	.07
Weakness	77/121 (64)	21/43 (49)	15/30 (50)	27/32 (84)	14/16 (88)	.001	103/112 (92)	34/40 (85)	25/27 (93)	29/30 (97)	15/15 (100)	.18
Headache	53/121 (44)	11/43 (26)	11/30 (37)	20/32 (63)	11/16 (69)	.002	72/112 (64)	15/40 (38)	19/27 (70)	24/30 (80)	14/15 (93)	<.001
Diarrhea	45/106 (43)	12/34 (35)	14/27 (52)	11/29 (38)	8/16 (50)	.51	89/112 (80)	31/40 (78)	22/27 (82)	25/30 (83)	11/15 (73)	.85
Bone or muscle pain	44/121 (36)	11/43 (26)	6/30 (20)	14/32 (44)	13/16 (81)	<.001	53/112 (47)	9/40 (23)	14/27 (52)	18/30 (60)	12/15 (80)	<.001
Vomiting	34/121 (28)	5/43 (12)	11/30 (37)	10/32 (31)	8/16 (50)	.01	75/112 (67)	21/40 (53)	19/27 (70)	26/30 (87)	9/15 (60)	.02
Abdominal pain	30/121 (25)	2/43 (5)	7/30 (23)	11/32 (34)	10/16 (63)	<.001	64/112 (57)	12/40 (30)	16/27 (59)	25/30 (83)	11/15 (73)	<.001
Swallowing problems	19/121 (16)	1/43 (2)	7/30 (23)	5/32 (16)	6/16 (38)	.005	33/111 (30)	6/40 (15)	8/27 (30)	12/29 (41)	7/15 (47)	.04
Breathlessness	16/121 (13)	3/43 (7)	3/30 (10)	3/32 (9)	7/16 (44)	.002	31/112 (28)	14/40 (35)	2/27 (7)	8/30 (27)	7/15 (47)	.03
Bleeding	6/121 (5)	2/43 (5)	0/30 (0)	2/32 (6)	2/16 (13)	.30	50/112 (45)	18/40 (45)	13/27 (48)	14/30 (47)	5/15 (33)	.80
Nonhemorrhagic rash	ND	ND	ND	ND	ND	ND	22/112 (20)	7/40 (18)	4/27 (15)	5/30 (17)	6/15 (40)	.20

Abbreviation: ND, no data available.

[a] Self-reported at triage; measured during hospitalization at least daily (range 1–6 times per person per day).

Table 2. Comparison of Demographic and Clinical Characteristics in Children Who Survived Vs Those Who Died

Characteristics	Survived [a]	Died [a]	*P* Value
Number	53 (43%)	69 (57%)	-
Sex			
Female	28/68 (41%)	40/68 (59%)	
Male	25/54 (46%)	29/54 (54%)	.7
Age, y [b]	11 (7–14)	4 (1.7–9.5)	<.001
<5	5/44 (11%)	39/44 (89%)	
5–9	17/30 (57%)	13/30 (43%)	
10–14	19/32 (59%)	13/32 (41%)	
>14	12/16 (75%)	4/16 (25%)	<.001
Fever at triage	42/53 (79%)	53/68 (78%)	1
Vomiting at triage	20/53 (38%)	14/68 (21%)	.06
Diarrhea at triage	23/51 (45%)	22/55 (40%)	.74
Bleeding at triage	1/53 (2%)	5/68 (7%)	.34
Vomiting anytime during hospitalization	35/48 (73%)	40/64 (63)	.34
Diarrhea anytime during hospitalization	38/48 (79%)	51/64 (80%)	1
Bleeding anytime during hospitalization	13/48 (27%)	37/64 (58%)	.002
Maximum temperature during hospitalization, °C [b]	39.3 (38.5–40.4)	39.8 (39.1–40.5)	.12
Duration of fever during hospitalization, days	3.5 (2–7)	3 (1–5)	.11
Plasmodium parasitemia (Sierra Leone only)	17/40 (43%)	10/28 (36%)	.76
Ebola virus disease real-time polymerase chain reaction (cycle threshold) [b]	25 (21.3–27.5)	19.2 (16.9–23.7)	<.001
Length of stay, days [b,c]	16 (12–20)	6 (4–8.5)	<.001

[a] Number (%) unless otherwise stated.

[b] Median value (interquartile range).

[c] Differences remained significant when stratified by age (<5, 5–9, 10–14, 15–17 years; $P < .02$ for each comparison of outcomes).

In the first model that excluded PCR tests (n = 112; goodness of fit, 0.68), the odds of mortality were 20.1-fold higher for patients aged <5 years compared with older children (95% confidence interval [CI], 5.9–69.0) and 5.9-fold higher if there was evidence of bleeding at any time during hospitalization (95% CI, 2.2–15.6). When EVD RT-PCR Ct values were added to the model (n = 86; goodness of fit, 0.53), the odds of mortality were 14.8-fold higher for patients aged <5 years compared with older children (95% CI, 3.5–62.1), 5.2-fold higher if the RT-PCR Ct value was ≤20 (95% CI, 1.5–18.3), and 5.0-fold higher if there was evidence of bleeding at any time during hospitalization (95% CI, 1.6–15.8).

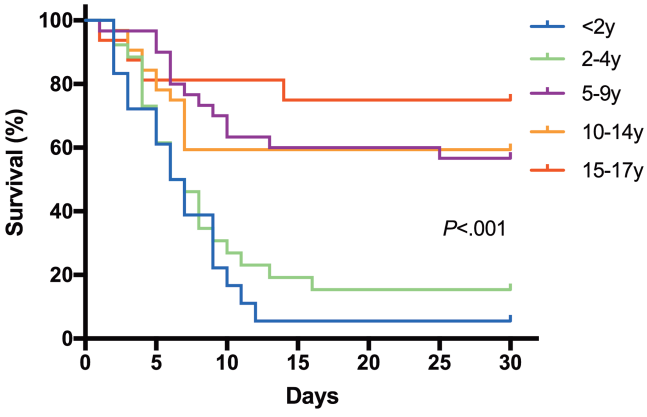

Figure 1. Kaplan-Meier curve for overall survival among 122 Ebola virus disease patients stratified by age. Children aged <5 years had significantly greater mortality than older children (log rank test, $P < .001$).

DISCUSSION

This is one of the largest cohort studies of children and adolescents with EVD published to date. The odds of death were 20-fold higher in EVD patients aged <5 years compared with older children. This finding is consistent with other data reported from the West African EVD epidemic [4, 21, 27, 28]. Days of hospitalization before death for half of those aged <2 years ranged from 6 to 12 days. This range is comparable to that reported by Shah et al [21, 28]. Hemorrhagic features developed in fewer than half of pediatric patients; when present, they were associated with a 5-fold higher odds of mortality. This observation is in line with other reports that bleeding was not a prominent finding among all EVD patients during this epidemic [19, 21, 22, 29]. It is also noteworthy that 1 in 5 children presented without fever and, of these, 27% never developed fever, which is similar to findings from one study [28] but not another [30]. Our findings support the mounting evidence that fever is not a sensitive screening tool for EVD [17, 28]. In fact, the low frequency of hemorrhagic features and the conspicuous absence of fever at presentation in up to 20% of patients during the West African epidemic questions the utility of referring to EVD as a disease characterized primarily as "viral hemorrhagic fever," which may mislead clinicians [31].

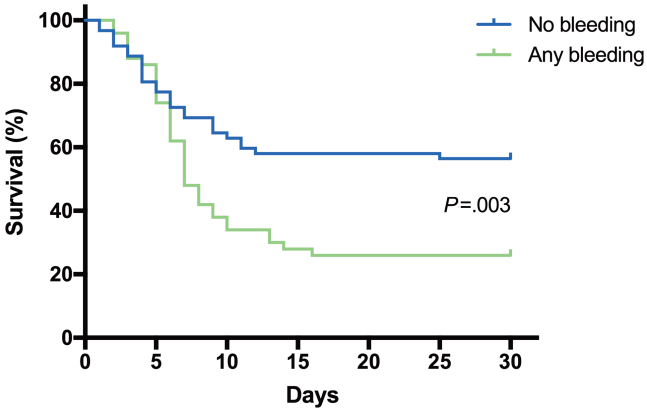

Figure 2. Kaplan-Meier curve for overall survival among 112 Ebola virus disease patients stratified by bleeding status. Children with evidence of bleeding at any time during their hospitalization had significantly greater mortality (log rank test, $P = .003$).

We confirmed that a high viral load estimated by a low RT-PCR Ct value (<20) at the time of presentation reliably predicted mortality in infected children who had 5-fold higher odds of mortality [28]. We also confirmed that mortality was highest in children aged <2 years [28]. The fact that PCR Ct values did not differ between survivors and fatal cases in those aged <2 years (unlike the older age groups) suggests that factors other than viral load, such as immunological or physiological dysregulation, contributed to death in the youngest age group [5]. Therefore, semiquantitative molecular diagnostic testing at the time of initial evaluation is a simple and effective method for screening for EVD as well as for prognosticating outcomes (especially in children aged >2 years) if Ct values are below a predefined threshold and should be used routinely.

A diagnosis of *Plasmodium* parasitemia did not impact the risk of mortality or presence of fever in a subpopulation of children who had testing performed, which differs from a recent report in which a diagnosis of malaria reduced the risk of EVD mortality [32].

Prominent features of EVD in children included constitutional and gastrointestinal signs and symptoms. Considering that children's body surface area to volume ratio is higher than that of adults and some children are malnourished, children are particularly susceptible to life-threatening dehydration and nutritional decompensation. Chertow et al made the observation that large volumes of diarrhea caused by EVD were "not unlike that of cholera" [31]. Treatment protocols for future EVD outbreaks could potentially improve outcomes by instituting early and aggressive rehydration strategies. This along with serum electrolyte balance and nutrition could be the most important treatments to reduce mortality in those aged <5 years in a low-resource setting. Furthermore, prompt, accurate diagnosis and isolation precautions are critically important to reduce transmission both in the community and in healthcare facilities.

It is likely that death of children from EVD results from 3 main causes. The first and historically most often associated reason is multiorgan failure secondary to coagulopathy associated with a cytokine storm and immune dysregulation [33]. The odds of mortality in our cohort were significantly higher in children with the "classic" presentation of viral hemorrhagic fever. Bleeding,

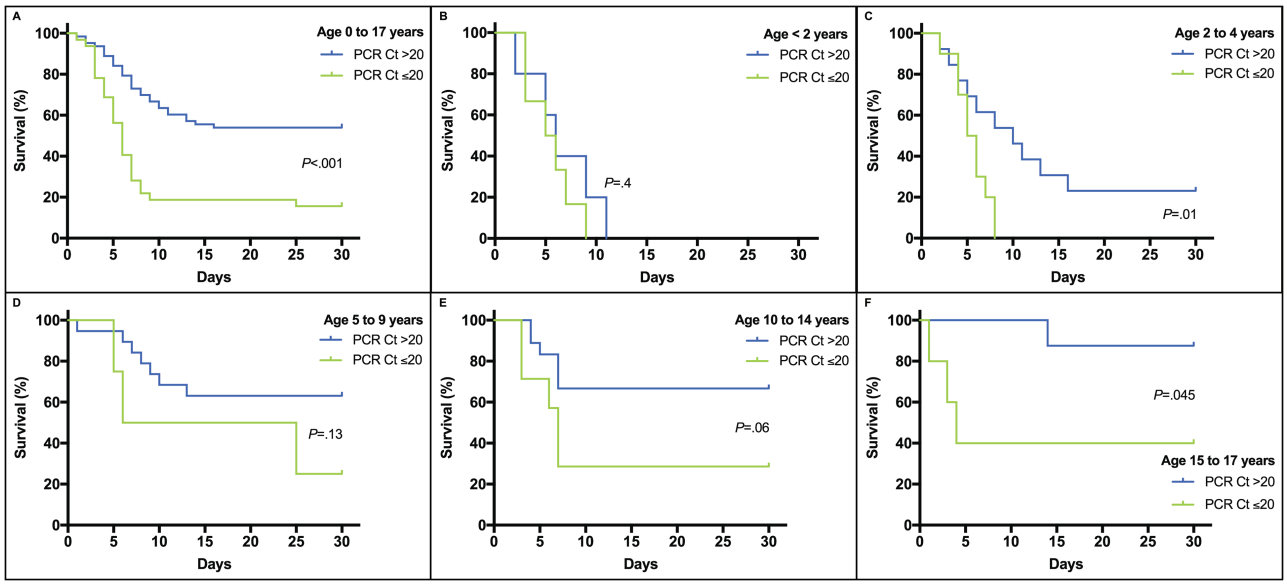

Figure 3. Kaplan-Meier curve for overall survival among 95 Ebola virus disease (EVD) patients based on initial EVD real-time polymerase chain reaction (RT-PCR) cycle threshold (Ct) cutoff of 20, stratified by age. Overall, mortality of children with initial RT-PCR Ct values ≤20 was significantly greater than for those with higher values (log rank test, $P < .001$). The youngest and oldest groups of children accounted for most of the difference in outcome. Abbreviations: Ct, cycle threshold; PCR, polymerase chain reaction.

however, was not a feature in most of our patients. The second reason for death is cumulative dehydration. The large volumes of diarrhea often accompanied by vomiting and exacerbated by weakness and inability to drink fluids quickly depletes the younger children. In the low-resource settings of West Africa, the scarcity of healthcare providers to administer oral fluids frequently or appropriate continuous intravenous (IV) fluids probably resulted in numerous deaths that could have been prevented with more resources. The third reason for death is cardiac arrest from electrolyte disturbances. In patients treated in high-resource settings, abnormal serum levels of potassium and magnesium were observed, along with cardiac arrhythmias; similar electrolyte findings were noted in children in West Africa [34–36]. The abnormal electrolyte levels may result from profuse diarrhea, prerenal kidney dysfunction from dehydration, or direct acute kidney injury (AKI) from EVD. Beyond the direct effects of the virus on the kidney, EVD has been associated with rhabdomyolysis, which can cause AKI and subsequent electrolyte abnormalities [20].

This study had limitations in common with others conducted during the West African EVD epidemic. Environmental conditions made it challenging for clinicians to collect patient data, given that they were working in full EVD personal protective equipment in extreme heat, which limited the time with each patient. Patients' temperatures were measured with an infrared digital thermometer gun or oral thermometer, which may be less accurate than the gold standard rectal thermometer. Frequently, clinicians were unable to collect dependable medical histories because of patients' severity of illness, absence of accompanying guardians, varying skills of clinicians, or language and cultural barriers. Because accurate nutritional assessments were not performed, the additional impact of malnutrition was not taken into account. Without clinicians' ability to confirm the length of illness prior to arrival at ETUs, we were limited in determining the total duration of illness and in assessing accurately patients' clinical courses. A few of the patients included in this analysis received an experimental antiviral treatment as part of a separate trial, which may have impacted their outcomes. In addition, it is quite likely many patients either died or recovered from EVD without seeking medical attention, thereby potentially introducing ascertainment bias.

Two important interventions that were not accounted for in the analyses could have impacted mortality rates. First was whether or not patients received IV fluids, which typically was inconsistent among ETUs because of varying practices relating to the use of IV catheters. The second intervention that was not taken into consideration was whether young children had constant bedside caregivers, either family members or healthcare workers, who administered and encouraged oral rehydration and nutrition and provided critical emotional support. Practices varied among ETUs because some parents were incapacitated or did not want to assume the risk of nosocomial infection and caregivers were not always continuously available.

In conclusion, we found that 3 clinical and virologic factors, after adjustment, were significant poor prognostic factors for children with EVD: aged <5 years, bleeding at any time during hospitalization, and high viral loads as estimated by RT-PCR Ct values. There is an urgent need to investigate the mechanisms of disease to understand how these risk factors as well as malnutrition, dehydration, and electrolyte imbalance contribute to severe outcomes. The goal is to identify simple, scalable, and relatively inexpensive measures that can improve health outcomes substantially in children in resource-limited settings. These fundamental interventions will effectively complement vaccines and antiviral agents that are currently undergoing human trials.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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