Association of clinical signs and symptoms of Ebola viral disease with case fatality: a systematic review and meta-analysis

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Background: Ebola virus disease (EVD) is a public health emergency of international concern. There is limited laboratory and clinical data available on patients with EVD. This is a meta-analysis to assess the utility of clinical signs, symptoms, and laboratory data in predicting mortality in EVD.

Aim: To assess the utility of clinical signs, symptoms, and laboratory data in predicting mortality in EVD.

Method: Study selection criterion: EVD articles with more than 35 EVD cases that described the clinical features were included. Data collection and extraction: Articles were searched in Medline, PubMed, Ovid journals, and CDC and WHO official websites. Statistical methods: Pooled proportions were calculated using DerSimonian Laird method (random effects model).

Results: Initial search identified 634 reference articles, of which 67 were selected and reviewed. Data were extracted from 10 articles (N = 5,792) of EVD which met the inclusion criteria. Bleeding events (64.5% vs. 25.1%), abdominal pain (58.3% vs. 37.5%), vomiting (60.8% vs. 31.7%), diarrhea (69.9% vs. 37.8%), cough (31.6% vs. 22.3%), sore throat (47.7% vs. 19.8%), and conjunctivitis (39.3% vs. 20.3%) were more often present in pooled proportion of fatal cases as compared to EVD survivors.

Conclusions: Clinical features of EVD that may be associated with higher mortality include bleeding events, vomiting, diarrhea, abdominal pain, cough, sore throat, and conjunctivitis. These patients should be identified promptly, and appropriate management should be instituted immediately.

Keywords: Ebola viral disease; clinical signs; clinical symptoms; mortality; meta-analysis; systematic review

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ebola virus. Of these, the Z. ebola species is the most notorious for causing sporadic EVD outbreaks in the sub-Saharan African region (5, 6). The recent EVD epidemic in West Africa has been the largest and most severe to date with a conservatively estimated case fatality rate of 71% (range 46–72%) (1, 7).

Patients with EVD typically develop signs and symptoms within 9–11 days of exposure to the Ebola virus (7). The initial prodrome is most often characterized by fever, chills, myalgia, and malaise. Gastrointestinal symptoms such as watery diarrhea, nausea, vomiting, or abdominal pain typically follow. Other symptoms and signs including chest pain, dyspnea, headache, confusion, conjunctival injection, and bleeding may occur (1, 7). The virus enters the host through breaks of the skin or mucosal surfaces; invades the monocytes, macrophages, and dendritic cells; replicates; and then disseminates via lymphatic and hematogenous routes. The characteristic hemorrhagic nature of EVD is believed to occur due to the release of cytokines that cause vascular instability, endothelial leakage, and coagulation abnormalities. The end result of the disease process mimics septic shock with impaired host immune response, hypotension, and multi-organ failure (6).

Given that the non-specific viral prodromal presentation and the limited clinical and laboratory resources in Ebola virus endemic regions (8, 9), the identification of prognostic features in EVD is a significant challenge. Although such prediction of risk factors for fatality has been attempted with individual outbreaks, there has not been a comprehensive assessment of factors across multiple outbreaks. Here, we present the findings of a meta-analysis done to assess the utility of clinical signs, symptoms, and laboratory markers in predicting EVD case mortality. The major focus of our study is to help in effective triage of EVD patients based on the clinical features and laboratory values. Such strategies could potentially improve the management and prognosis of Ebola-infected patients.

Methods

Study selection criteria

Studies and reports describing clinical EVD from 1976 to November 2014, with a minimum of 35 patient cases, were included. The number 35 was chosen to improve the reliability of results. Only studies that described patients’ clinical signs and symptoms along with case fatality were included.

Data collection and extraction

Articles were searched in Medline, PubMed, Ovid journals, EMABSE, Cumulative Index for Nursing and Allied Health Literature, ACP journal club, DARE, International Pharmaceutical Abstracts, old Medline, Medline non-indexed citations, Ovid Healthstar, Cochrane Central Register of Controlled Trials (CENTRAL), and CDC and WHO official websites. The search was performed for the years 1976 to November 2014. Abstracts were manually searched in the major infectious disease journals for the past 3 years. Study authors for the abstracts included in this analysis were contacted when the required data for the outcome measures could not be determined from the publications. The search terms used were Ebola, Ebola hemorrhagic fever, clinical illness, clinical signs, clinical symptoms, case fatality, mortality, and blood chemistry measurements. Four authors (HM, VM, SD, and RB) independently searched and extracted the data into an abstraction form. Any differences were resolved by mutual agreement. The agreement between reviewers for the collected data was quantified using the Cohen’s k (10).

Quality of studies

Clinical trials designed with control and treatment arms can be assessed for quality of the study. A number of criteria could be used to assess the quality of a study (e.g., randomization, selection bias of the arms in the study, concealment of allocation, and blinding of outcome) (11, 12). There is no consensus on how to assess studies designed without a control arm. Hence, these criteria do not apply to studies without a control arm (12). All the articles included in this meta-analysis were observational studies. There were no randomized controlled trials where interventions were compared.

Statistical methods

Proportion meta-analysis was performed on pooled data. Freeman–Tukey variant of arcsine square root transformed proportion was used to transform individual study proportion into a quantity. Random effects model was performed using DerSimonian Laird weights (13, 14). Pooled results and individual study results were displayed using forest plots. The weight of each study was indicated by the width of point estimates on forest plots. P-value of more than 0.10 rejects the null hypothesis that the studies are heterogeneous. Cochran’s Q-test was used to test the heterogeneity among studies (15). Harbord Egger and Begg Mazumdar bias indicators (16, 17) were used to estimate selection and publication bias. Publication bias was also evaluated by the construction of funnel plots (18, 19).

Results

Initial search identified 634 articles from which 67 were selected for review. Data were extracted from 10 articles or studies (N = 5,792) of Ebola viral disease (2–4, 8, 9, 20–24), which met the inclusion criteria. Figure 1 shows the flow chart with study selection criteria. Four of 10 articles are WHO Ebola reports collected from WHO and CDC official websites. The 10 studies included in this
meta-analysis are published as full text articles. All the pooled proportions given are the estimates calculated by the random effects model. Random effects model was preferred due to the heterogeneity of the results. Table 1 shows the basic study characteristics.

In the pooled proportion of EVD patients, bleeding events occurred in 42.5% (95% CI = 26.9–58.9), fevers were present in 92.9% (95% CI = 87.3–96.9), headaches in 73.4% (95% CI = 52.9–89.7), and diarrhea in 73.3% (95% CI = 66.4–79.7). Table 2 shows the overall association of clinical symptoms and signs with EVD. Table 3 compares the association of clinical signs and symptoms of EVD in patients with fatal outcomes versus survivors. Bleeding events (64.5% vs. 25.1%), abdominal pain (58.3% vs. 37.5%), vomiting (60.8% vs. 31.7%), diarrhea (69.9% vs. 37.8%), cough (31.6% vs. 22.3%), sore throat (47.7% vs. 19.8%), and conjunctivitis (39.3% vs. 20.3%) were more often present in the pooled proportion of fatal cases compared to the pooled proportion of EVD survivors. Meaningful association of fevers, fatigue, headache, dyspnea, arthralgia, myalgia, elevated aspartate transaminase (AST), alanine transaminase (ALT), blood urea nitrogen (BUN), and creatinine with case fatality could not be made either due to similar prevalence of these symptoms in both groups or due to the limited sporadic data available. Table 4 shows the heterogeneity data and risk of bias associated with individual symptoms in pooled patient population. Figures 2 and 3 are Forest plots for bleeding events and fever respectively. Figure 4 is a Funnel plot to assess publication bias.

Discussion

Fever, fatigue, and headache were the commonly described symptoms in most outbreaks of EVD (25, 26). A maculopapular rash that appeared between days 5 and 7 of the disease was also common. The current outbreak though has predominantly gastrointestinal symptoms that include abdominal pain, nausea, vomiting, and diarrhea (5). Patients who succumb to the illness usually die of shock and multi-organ failure as evident on the hematological and chemistry labs (5). Hematological changes include lymphopenia and neutropenia at the onset of the disease. As the disease progresses, some patients develop thrombocytopenia and increased prothrombin and partial thromboplastin time suggesting consumptive coagulopathy (5). In patients who survive, clinical improvement is seen with the development of antibodies, and it has been observed that sometimes antibody response may be absent in lethal cases suggesting the possible role of antibody response as a prognostic factor (27, 28).

The WHO response team found that, in the recent West African epidemic, a higher rate of fatal outcomes was associated with the clinical features of diarrhea, conjunctivitis, difficulty breathing or swallowing, confusion or disorientation, coma, hemorrhagic symptoms (unexplained bleeding, bleeding gums, bloody nose, bleeding at the

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Table 1. General characteristics of studies in this meta-analysis

| Study/source          | Outbreak – the study was conducted on this particular outbreak | Ebola subtype virus | Cases (confirmed + probable) | Deaths | Case fatality (%) |
|-----------------------|---------------------------------------------------------------|---------------------|------------------------------|--------|------------------|
| WHO Ebola Response Team (2) | West Africa 2014                                               | Zaire              | 4,010                        | 2,839  | 71               |
| Schieffelin et al. (8)   | Sierra Leone 2014                                              | Zaire              | 106                          | 78     | 74               |
| Rollin et al. (9)        | Uganda 2000                                                    | Sudan              | 123                          | 55     | 45               |
| Bah et al. (20)          | Guinea 2014                                                    | Zaire              | 37                           | 16     | 43               |
| WHO Weekly record June (21) | Gabon and Congo 2001                                           | Ebola              | 122                          | 96     | 78               |
| Okware et al. (22)       | Uganda 2000                                                    | Sudan              | 425                          | 224    | 53               |
| Georges et al. (23)      | Gabon 1994                                                     | Ebola              | 52                           | 31     | 60               |
| Khan et al. (24)         | Congo 1995                                                     | Ebola              | 315                          | 250    | 81               |
| WHO report (3)           | Sudan 1976                                                     | Sudan              | 284                          | 151    | 53               |
| WHO report (4)           | Zaire (Congo) 1976                                             | Ebola              | 318                          | 280    | 88               |

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Table 2. Overall association of clinical symptoms and signs with EVD

| Symptom/sign         | % of pooled proportion of patients with this symptom/sign |
|----------------------|--------------------------------------------------------|
| Fever                | 92.9 (95% CI = 87.3–96.9)                              |
| Headache             | 73.4 (95% CI = 52.9–89.7)                              |
| Diarrhea             | 73.3 (95% CI = 66.4–79.7)                              |
| Fatigue              | 68.6 (95% CI = 58.6–77.8)                              |
| Myalgia/arthralgia    | 65.7 (95% CI = 37.9–88.7)                              |
| Vomiting             | 61.3 (95% CI = 53.9–68.4)                              |
| Abdominal pain       | 44.1 (95% CI = 29.3–59.4)                              |
| Bleeding eventsa     | 42.5 (95% CI = 26.9–58.9)                              |
| Sore throat          | 40.3 (95% CI = 18.6–64.2)                              |
| Conjunctivitis       | 38.8 (95% CI = 19.9–60.1)                              |
| Cough                | 33.3 (95% CI = 24.4–42.8)                              |

aBleeding events include melena, bright red bleed per rectum, epistaxis, hemoptysis, hematemesis, petechiae, conjunctival hemorrhage, gingival hemorrhage, unexplained bleeding, bleeding per vagina, hematuria, and bleeding under skin.

Table 3. Association of clinical signs and symptoms of EVD patients with fatal outcome versus survivors

| Symptom/sign         | % of pooled proportion of dead patients with this symptom/sign | % of pooled proportion of EVD survivors with this symptom/sign |
|----------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Diarrhea             | 69.9 (95% CI = 60.7–78.4)                                     | 37.8 (95% CI = 13.8–65.6)                                     |
| Bleeding events      | 64.5 (95% CI = 14.8–99.0)                                     | 25.1 (95% CI = 5.3–53.4)                                     |
| Vomiting             | 60.8 (95% CI = 49.9–71.2)                                     | 31.7 (95% CI = 3.8–70.8)                                     |
| Abdominal pain       | 58.3 (95% CI = 30.8–83.3)                                     | 37.5 (95% CI = 20.7–55.9)                                     |
| Sore throat          | 47.7 (95% CI = 11.6–85.3)                                     | 19.8 (95% CI = 11.4–29.7)                                     |
| Conjunctivitis       | 39.3 (95% CI = 16.1–65.4)                                     | 20.3 (95% CI = 10.2–32.7)                                     |
| Cough                | 31.6 (95% CI = 26.1–37.4)                                     | 22.3 (95% CI = 20.4–25.1)                                     |

There are some limitations to our study primarily due to the drawbacks of the individual studies in reporting the complete clinical and laboratory data. There has been some non-uniformity in the data collection because of inherent difficulties in collecting information from deceased persons (24), and the challenges of clinical follow-up, limited laboratory services, and infection control precautions during the epidemic (20). Although there are more than 10,000 documented EVD patients, detailed clinical data are available in only about 50–60% of the total patient population and thus may not be representing the entire patient population. There were many suspected Ebola deaths during the epidemics, and patients may have died before confirmation, skewing the case fatality rates. Also, case fatality is affected by a number of other factors including age and coexisting conditions, as well as biological characteristics of various strains of the virus (2, 3). Signs and symptoms at presentation are derived from outbreaks in Africa where presentation can be close to five or more days on average after the day of symptom onset. The situation may be different elsewhere (e.g., in a Western facility), where individuals may present for care earlier. The pooled data in this analysis are from different viruses (Z. ebola and S. ebola), and because these viruses...
have different case fatality rates, a sign or symptom in an individual with one virus may not necessarily translate to the same implications in an individual infected with the other virus.

Studies with statistically significant positive results tend to be published and cited. Additionally, smaller studies may show larger treatment effects compared with larger studies. This publication and selection bias may affect the summary estimates. The bias can be estimated using Egger bias indicators and the construction of funnel plots whose shape can be affected by bias. In the present meta-analysis and systematic review, bias calculations using both Egger (16) and Begg Mazumdar (17) bias indicators showed no statistically significant bias. Furthermore, analysis using funnel plots showed no significant publication bias among the studies included in the present analysis.

There is a dire need to develop more reliable therapies for EVD. Should more reliable therapies become globally available for patients with active EVD, and if said therapies were in relatively short supply and needed to be rationed in an outbreak, then perhaps the signs and symptoms noted here could be used as a basis for determining who gets said therapy in addition to aggressive supportive care versus who does not.

Table 4. Heterogeneity data and risk of bias associated with individual symptoms in pooled patient population

| Symptom/sign         | I² (inconsistency) | Harbord bias |
|----------------------|--------------------|--------------|
| Fever                | 99.2% (95% CI = 99 - 99.4) | 2.33 (92.5% CI = -0.85 -5.51), P = 0.17 |
| Headache             | 99.1% (95% CI = 99 - 99.2) | 6.46 (92.5% CI = -1.69 -14.6), P = 0.14 |
| Diarrhea             | 92.4% (95% CI = 87.9 - 94.7) | 2.02 (92.5% CI = -1.66 -5.69), P = 0.28 |
| Fatigue              | 99% (95% CI = 99 - 99.1) | -2.37 (92.5% CI = -7.91 -3.17), P = 0.37 |
| Myalgia/arthralgia   | 99.5% (95% CI = 99.4 - 99.5) | 9.99 (92.5% CI = -3.05 -23.03), P = 0.14 |
| Vomiting             | 92.1% (95% CI = 87.3 - 94.5) | -2.40 (92.5% CI = -6.29 -1.49), P = 0.23 |
| Abdominal pain       | 97.6% (95% CI = 96.7 - 98.2) | 1.59 (92.5% CI = -11.04 -14.23), P = 0.76 |
| Bleeding events      | 98.8% (95% CI = 98.5 - 99) | 10.50 (92.5% CI =2.36 -18.63), P = 0.03 |
| Sore throat          | 99% (95% CI = 98.8 - 99.2) | 9.43 (92.5% CI = -8.01 -26.87), P = 0.24 |
| Conjunctivitis       | 98.2% (95% CI = 97.4 - 98.6) | 8.09 (92.5% CI = -7.89 -24.07), P = 0.22 |
| Cough                | 93.2% (95% CI = 86.1 - 95.9) | 2.06 (92.5% CI = -10.18 -14.29), P = 0.62 |

Fig. 2. Forest plot: pooled proportion (random effects) of EBV patients with bleeding events.
Conclusions
In EVD, the presenting clinical features of vomiting, diarrhea, bleeding events, abdominal pain, cough, sore throat, and conjunctivitis may be associated with the increased risk of mortality. EVD with such features should promptly be identified, and rigorous management options should be pursued emergently. Although prior studies have shown that increased AST, BUN, and creatinine have

Fig. 3. Forest plot: pooled proportion (random effects) of EBV patients with fever.

Fig. 4. Funnel plot: bias assessment for EBV patients with bleeding events.
been associated with high mortality (2, 3), we could not synthesize meaningful outcomes in this regard due to the limited available data.

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**Conflict of interest and funding**

None of the authors have a conflict of interest.

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