Age and Ebola viral load correlate with mortality and survival time in 288 Ebola virus disease patients

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SUMMARY

Background: A Chinese medical team managed Ebola virus disease (EVD) patients in Sierra Leone from October 2014 to March 2015 and attended to 693 suspected patients, of whom 288 had confirmed disease.
Methods: A retrospective study was conducted of the 288 patients with confirmed disease. Clinical symptoms, manifestations, and serum viral load were analyzed and compared among the different groups for mortality and survival time.
Results: Among the 288 confirmed EVD patients (149 male and 139 female, median age 28 years, and median log viral load 6.68), 98 died, 36 recovered, and 154 were lost to follow-up. Common symptoms were fever (77.78%), fatigue (64.93%), abdominal pain (64.58%), headache (62.85%), and diarrhea (61.81%). Compared to patients aged < 18 years, those who were older than 40 years had a higher probability of death (odds ratio 2.855, $p = 0.044$). Patients with a viral load of $>10^6$ copies/ml had a higher case fatality rate than those with $<10^6$ copies/ml (odds ratio 3.095, $p = 0.004$). Cox regression showed that age, viral load, and the presence of diarrhea correlated with mortality.
Conclusion: Patients with a high viral load, of older age, and with diarrhea had a higher mortality and shorter survival time.

1. Introduction

The first outbreak of Ebola virus was described in 1976 near the Ebola River in Zaire. The Ebola virus infected 318 cases and caused 280 deaths.[1] Fever and bleeding were the major symptoms observed at that time; therefore, the Ebola virus disease (EVD) was initially termed Ebola hemorrhagic fever. To date, there have been 33 sporadic outbreaks worldwide, including 23 human-to-human transmission epidemics, three laboratory-induced outbreaks, and seven animal-to-human transmission outbreaks.[2] The Ebola virus is spread easily by close personal contact and by the use of contaminated needles and syringes in hospitals and clinics.[2,3] The current epidemic began in Guinea in December 2013[4] and spread rapidly to surrounding countries in West Africa (Sierra Leone and Liberia). On August 8, 2014, the World Health Organization (WHO) declared the epidemic to be a public health emergency of international concern (PHEIC).[5] By March 25, 2015, 24 907 probable and 10 326 confirmed cases had been reported in West Africa. Sierra Leone was the most affected country, with 11 841 confirmed cases and 3747 deaths.[6]

At the time of the Ebola outbreak, the public health system of Sierra Leone had nearly collapsed because of a 10-year civil war. In 2014, the United Nations Development Program declared the Human Development Index in Sierra Leone to be 0.374, ranking it 183rd in the world, and gave life expectancy as around 45.6 years.[7] During the outbreak, Ebola infection spread rapidly in Sierra Leone, particularly in the capital, Freetown. By March 25, 2015, there were 3382 confirmed cases of EVD in Freetown, comprising 39.65% of cases in the whole country.[8] In response to the EVD outbreak, the Sierra Leone government established an emergency response system via the Ministry of Health and Sanitation (MoHS) and the National Ebola Response Centre (NERC). The latter is responsible for the coordination and management of medical treatment for EVD patients among 29 Ebola treatment centers (ETCs), Ebola holding centers (EHCs), and Community Care Centers (CCCs); these have been run by medical teams from the USA, UK, France, Australia, South Korea, China, and Cuba.[9] The Sierra Leone – China Friendship Hospital (Jui Government Hospital), built by the Chinese government, is a well-equipped hospital in Freetown, Sierra Leone. A Chinese medical team comprising 123 medical staff started working in this hospital on September 15, 2014.

From October 1, 2014 to December 30, 2014, the Jui Government Hospital was an EHC, and from December 31, 2014 to March 20, 2015, it was an ETC. Six hundred and ninety-three probable cases and 288 confirmed patients with EVD were admitted to the Jui Government Hospital. The demographic characteristics, signs and symptoms, and clinical outcomes of these patients are reported here. Factors that influenced the prognosis of these 288 EVD patients were analyzed. However, the outcome is known for only 134 patients. Among those with a known outcome, the case fatality rate was 73% and mortality was associated with diarrhea, fatigue, and difficulty in swallowing. These data validate previous studies and contribute to the growing literature on the treatment of EVD patients in the outbreak setting.

2. Methods

2.1. Study patients

A patient who presented with fever, nausea, vomiting, diarrhea, and bleeding was defined as a 'person under investigation' (PUI). The healthcare facilities that they visited had to report the case to the NERC. Patients or their relatives could also call 117 (free medical aid hotline in Sierra Leone). NERC would send an ambulance to bring the patient to an EHC or alternatively let the patient 'walk in' to an EHC.

In the triage area of the Jui Government Hospital, healthcare workers (mostly nurses) collected the medical history of the PUI and made their initial diagnosis. In accordance with the standard routines, suspected EVD patients and probable EVD patients were hospitalized and a blood sample collected. The blood sample was sent to the mobile biological safety protection level 3 laboratory (BSL-3) of the Chinese Center for Disease Control and Prevention (China CDC). During observation, patients with severe dehydration were given a venous infusion, and those with fever were given antimalarial and antibiotic therapy. All medical practices were performed in accordance with the WHO guidelines,[10,11] and all healthcare workers (including cleaners and security) were trained and strictly examined on the processes for putting on and removing personal protective equipment (PPE), treating contaminated waste safely, and the management of percutaneous or mucocutaneous exposure. Patients with disease confirmed by reverse-transcription PCR (RT-PCR) were transferred to ETCs coordinated by the NERC. Patients with a negative result by RT-PCR (tested on blood samples collected three or more days after the

onset of symptoms) were defined as non-EVD patients and discharged.

On December 31, 2014, the Jui Government Hospital was formally made an ETC by authorization of the MoHS. Thereafter, confirmed patients were transferred to the 'confirmed ward' (also in Jui, but isolated from the 'suspect ward') and received comprehensive treatment. If the retest RT-PCR result was negative and the patient's condition had improved according to the discharge standard, they were discharged.

2.2. Data collection

After admission, suspected and confirmed patients underwent a physical examination, their medical history details were collected (including demographics, epidemiology, symptoms, signs, and past history), and their general condition was evaluated; an 'Ebola case investigation form' or a 'Viral hemorrhagic fever case investigation form' (NERC) was completed. After daily ward rounds, doctors would fill in the EVD 'patient observation sheet'. All of these sheets were transmitted from the contaminated area to the hygienic areas by closed circuit television (CCTV) or using a Wi-Fi camera. The data were imported into an Excel database by two staff, separately, to ensure accuracy.

The information technician contacted the patients transferred to others ETCs or their relatives by telephone during follow-up, or would ask for information from other ETCs. Usually, the information comprised only the outcome (died or recovered) and the date of the outcome.

2.3. Viral load test

After the registration of information, blood samples were inactivated in a water bath at 60 °C for 1 h in the BSL-3 area. A MagMAXTM-96 Viral RNA Isolation Kit (Applied Biosystems, Foster City, CA, USA) was used to extract nucleic acid using a MagMAX express 96 nucleic acid extraction instrument. After surface disinfection, 50 μl of the sample was sent to the BSL-2 area for the RT-PCR test. A standard curve was used to convert the value of cycle times to the number of genome copies.

2.4. Supportive treatment for EVD patients

High fever and diarrhea usually lead to severe dehydration and are the major reasons why EVD patients die. Thus, maintaining the water and electrolyte balance in these patients is important. The degree of dehydration in EVD patients is often evaluated on the basis of state of consciousness, pulse, temperature, peripheral blood capillary filling, skin elasticity, and daily urine output. In general, all of the EVD patients received oral rehydration salts. Simultaneously, some of the patients with severe dehydration received intravenous fluids if their condition permitted, which mainly included sodium lactate Ringer's solution and glucose Ringer's solution (GNS).

In addition, to prevent severe pathogen infection and reduce mortality, antibiotics (cefixime or ciprofloxacin) and antimalarial treatment (compound naphthoquine phosphate tablets) were administered empirically for the EVD patients with a high fever before the related testing data were available. Simultaneously, patients with pain and fever were usually treated with paracetamol. Patients with excess gastric acid and vomiting were given omeprazole and metoclopramide.

2.5. Ethics review

As a retrospective non-comparative case series study, the ethics committee of the People's Liberation Army 302 Hospital, which is