High subsequent mortality of Ebola virus disease survivors in Guinea: a nationwide retrospective cohort study.

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Abstract

Background

The 2013-2016 West African Ebola outbreak left a record number of Ebola survivors, and this has been added to in subsequent outbreaks. A range of post-Ebola sequelae in survivors have been reported, but little is known about subsequent mortality of those discharged from Ebola Treatment Units (ETU).

Methods

The Guinean national survivors' monitoring program (SA-Ceint) contacted all survivors and recorded deaths from December 2015. Survivors were followed up until September 2016, a mean of 21 months after ETU discharge. Deaths were investigated using verbal autopsy. We calculated the age-standardised mortality ratio compared to the Guinean population, and assessed risk factors for mortality using survival analysis and Cox regression.

Findings

Information was retrieved on 1130/1270 Guinean Ebola virus disease survivors (follow-up rate 89%). Survivors had an over five-fold increased risk of dying, compared to the Guinean population (age-standardised mortality ratio 5.2, 95% CI 4.0-6.8), a mean of one year of follow-up after ETU discharge, with no increase in risk for the subsequent 9 months. Mortality rates were increased in all age groups and were similar for males and females. Of the 59 deaths, cause of death was tentatively attributed to renal failure for 37, usually based only on reported anuria. Cause of death was unknown for 7. Longer hospitalisation in the ETU was associated with an increased risk of late death.

Interpretation

The subsequent mortality rate in individuals who survived the acute phase of Ebola Virus Disease and were discharged from ETU was high. The finding that survivors that experienced longer hospitalisation had an increased risk of death, may be of help in the set-up of current and future survivors' programs and the prioritisation of funds in resource-constrained settings. The suggestion of renal failure as a potential contributor to the late deaths needs further investigation.

Funding

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Keywords: Ebola, Survivor, Resurgence, Surveillance, Guinea, Kidney, Mortality, late death

Research in context

Evidence before this study

Little evidence exists on the subsequent mortality rate in people surviving Ebola. Up to April, 4th, 2019, we used the following search string for a PubMed search: (Ebola OR ebolavirus) AND (survivor) AND (death OR mortality). The search yielded 68 citations. Of those, some reported post-Ebola sequelae and Ebola virus persistence in survivors' body fluids; only one study looked at late deaths among Ebola survivors, and reported 4 deaths out of 151 survivors who were followed-up for a mean time of 10 months.

Added value of this study

This is the largest study, and the first nationwide cohort study to report subsequent mortality of people who survived Ebola virus disease (EVD). We report high mortality among Ebola survivors in Guinea, with an age-standardised mortality rate over five times that of the general population in the first year. Mortality was higher in survivors who spent longer in an Ebola treatment unit, , possibly highlighting a higher-risk group within the cohort of Ebola survivors. Renal failure was tentatively suggested as a contributor to more than half the deaths.

Implications of all available evidence

The increased mortality among survivors is alarming: future studies aimed at establishing whether renal failure may be a long-term effect of EVD are warranted. This study confirms the high vulnerability of Ebola survivors, particularly those with more prolonged acute disease, and suggests an underestimation of the overall EVD case fatality rate.

Background

The Ebola virus disease (EVD) epidemic in West Africa caused ~28,616 cases and ~11,310 deaths. As a result, West Africa has the biggest cohort of EVD survivors (hereafter survivors) in history – over 17,000 individuals. [1]

Ebola sequelae were reported by cohort studies of survivors of the 1995 Kikwit EVD outbreak, and included arthralgia, myalgia, abdominal pain, fatigue, anorexia and late ocular complications. [2–4] Studies from subsequent outbreaks, including the 2013-2016 outbreak in West Africa, have confirmed that many EVD survivors suffer from a broad range of sequelae, which also include hearing loss and neurological signs.[5–10] A large cohort study from Liberia has reported that symptoms such as urinary frequency, headache, memory loss, fatigue, joint pain and muscle pain were more frequent among survivors than controls (ie antibody-negative close contacts).[11] Long viral persistence in semen and other bodily fluids of survivors can occasionally cause EVD recrudescence in the individual, and EVD re-emergence in the community by infecting other people. [11–15]

Despite the extensive literature on Ebola sequelae, little information is available on deaths occurring after discharge from Ebola Treatment Units (ETU) in cohorts of EVD survivors. A study in Sierra Leone followed up 151 survivors at a mean time of 10 months after discharge from an ETU and reported the death of four of them, all within 6 weeks of discharge.[16]

Initially, survivors in Guinea were followed up mainly within research-focused cohort studies and no exhaustive national cohort was established.[9,17–20] The World Health Organization (WHO) advised that an intensive integrated program was necessary to address the medical and psychosocial needs of survivors as well as the risk of virus reintroduction, ideally to be integrated into existing routine health services and facilities.[21] Therefore, the national coordination for the fight against EVD (Coordination National pour la Lutte contre le virus Ebola, CNLEB), WHO Country office, and its partners, developed and implemented a community monitoring program for EVD survivors, called SA-Ceint (from

98 'Surveillance Active en ceinture'; ie cordon sanitaire), to follow survivors closely with the aim of
99 avoiding Ebola virus reintroduction into the community.

100 Using these national level data, we estimate the standardised mortality ratio of EVD survivors in Guinea,
101 describe the potential contributors to the deaths identified during death investigations, and report on the
102 risk factors associated with death after ETU discharge.

103

104 **Methods**

105 *Study design and participants*

106 The names and contacts of all eligible survivors were identified from the EVD database managed by the
107 Ministry of Health (MoH) and partners. All survivors were eligible to participate in the SA-Ceint
108 program if they were able to show the certificate of medical clearance that they were given at discharge
109 from the ETU. From December, 2015, the teams of the survivors' monitoring program attempted to
110 contact all EVD survivors, and classified them as: i) willing to participate, ii) lost to follow-up, and iii)
111 reportedly dead. For those who were reported to have died, a field team was in charge of the death
112 investigation. The closest member of the family completed a verbal autopsy. Verbal autopsy interviews
113 collect a description of illness and events and a checklist of symptoms. WHO medical epidemiologists
114 in charge of the death investigation suggested the main contributor to death based on the verbal autopsy
115 and medical files shared by the family member, when available. Each cause of death was reviewed and
116 validated by a panel of experts from WHO and the MoH. The survivors who responded were actively
117 followed up from January 1st until September 30th, 2016, which corresponded to at least one year after
118 discharge from the ETU for over 99% of survivors. All participants received a monthly allowance,
119 including free cell phone with monthly credit, as well as other forms of support (such as rice and flour)
120 as part of the survivor package.

121 *Statistical analysis*

For all statistical analyses, we used the official MoH Ebola virus database that was curated in collaboration with WHO and other partners. This database was used for notification purposes during the outbreak and reviewed on a weekly basis; it contained complete epidemiological information available to the MoH and information on laboratory confirmation (yes/no) for all suspected, probable and confirmed cases of EVD in Guinea.

The outcome of this analysis, late death, was defined as death from any cause after ETU discharge. Independent variables (age group, sex, number of days of hospitalisation, date of ETU discharge and area of residence) were recorded as at ETU discharge. Categorical variables were reported using numbers and percentages and compared by the Pearson's chi-squared test. Date of ETU discharge was divided in four categories based on the median and interquartile range dates. Duration of hospitalisation was divided in number of days above or below the median. Missing observations for this variable were included in the Cox regression models as unknown. Survival of the participants by each independent variable was compared using the log-rank test.

For the survival analysis, the observation period was calculated from the date of ETU discharge, available for all survivors, to the date of death or the date of the end of the SA-Ceint program (September 30th, 2016). All deaths of survivors with unknown date of death occurred by December, 31st, 2015. Therefore, we used the midpoint between ETU discharge and December 31st, 2015 as an estimate of the date of death.

The standardised mortality ratio (SMR) was calculated using indirect standardization. Since the risk of death associated with Ebola is likely to decrease over time, we calculated SMR for two different periods: from ETU discharge until December 31st, 2015 (the date by which all deaths with unknown dates had occurred), corresponding to a mean of 12.6 months of follow-up (range 2 days-23.8 months), and from January 1st to September 30th, 2016, a mean of 8.9 months of follow-up (range 1.1-9.0 months) The age-specific mortality rates in the Guinean population from the third General Population and Housing Census (RGPH3), National Institute for Statistics (2014),[22] and the number of survivors by age group in the

study population were used to calculate the age-specific expected deaths. These were then compared to the age-specific observed deaths to derive the SMR.

A multivariable proportional hazards (Cox) regression model was constructed to identify factors associated with late death. Variables giving $p<0.2$ in the log-rank test were included in the first model, and variables with likelihood ratio test p-value<0.1 were kept in the final model. The proportionality assumption was checked using the Schoenfeld and scaled Schoenfeld residuals' test and no violation of the final model's proportionality was found. The goodness of fit of the final model was evaluated by the Cox-Snell residuals. All tests were two sided with 95% confidence interval (CI), and analyses were performed using STATA (version14, StataCorp, LP, TX, USA) software.

Analyses were repeated calculating the person-years at risk for those whose date of death was unknown in two ways: i) as if they all died the day after ETU discharge (shortest possible delay of a late death), ii) as if they all died on December 31st, 2015 (earliest date by which all deaths with unknown date of death were confirmed). A complete case analysis was also carried out including only those with known dates of death, and known duration of hospitalization.

Ethics approval and consent to participate

This study is an analysis of data collected from the SA-Ceint program, which was implemented following the guidelines from the WHO Ebola response phase 3 strategic document. The SA-Ceint program was integrated in the workflow of other research projects, *i.e.* Postebogui, the JIKI trial, EBOSEX, and Ebola ça suffit vaccination trial, that were all approved by the National Committee for Ethics in Research and Health (CNERS) before their start. All the participants signed a written informed consent at the beginning of this study.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. 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

Characteristics of study participants

We aimed to enroll all survivors of the 2013-2016 EVD outbreak in Guinea (N=1270). Of these, 140 were lost to follow-up (follow-up rate 89%, Figure). Fifty-five individuals were reported to have died between ETU discharge and when they were first sought for this study, and 4 more died during follow-up. The characteristics of the survivors, including those lost to follow-up, and those who subsequently died, are shown in Table 1. The baseline characteristics of those who were lost to follow-up were similar to those who were followed up except for area of residence and month of ETU discharge (Table 1). Among those for whom follow-up information was available, half (610) were female and the median age at ETU discharge was 28 years (range 1 month - 90 years). Twenty-one per cent were from Conakry (240/1130). The median number of days hospitalised was 12 (IQR 9-15), and was missing for 6% of survivors (73/1130), because date of admission was missing.

Because of the retrospective nature of the cohort study, for 43/59 deaths we only knew that death occurred between the date of ETU discharge and December 31st, 2015. Among the 16 survivors for whom we were able to retrieve the exact date of death, five died within a month following ETU discharge (at 2, 6, 10, 14 and 30 days), three died within the first 3 months after ETU discharge (at 53, 57 and 87 days), four died 3-12 months after ETU discharge (at 5, 6, 6 and 10 months), and four more than a year after ETU discharge (at 16, 17, 19 and 21 months).

Age-specific mortality rates and age-standardised mortality ratio

The mean follow-up time for the 1130 survivors was 21.2 months. The shortest follow-up among those who did not die was 5.4 months, and the longest 32.7 months. Total follow-up time was 1987.4 person-years. The mortality rate varied by age, being higher in those over 55 (Table 2). To account for background mortality the observed deaths were compared to the number of deaths expected according to the Guinea 2014 census.[22] There were more observed deaths than expected deaths at all ages; the ratio between observed and expected deaths varied by age, but with no consistent pattern (Table 3). It was highest at age 5-14 and lowest in the under 5s. For the period until December 2015, EVD survivors had over five times greater risk of death than the Guinean population (SMR 5.2, 95% CI 4.2-7.2, Table 3). For the period between January 1st and September 30th, 2016, the SMR was 0.6 (95% CI 0.2-1.4). Those with unknown dates of death contributed 23.0 person years at risk in the main analysis. Taking extreme values (assuming all deaths were early or all were late), the SMR for the first period hardly changed (SMR estimates = 5.4 and 5.1, respectively).

Risk factors for late death among survivors

The post-ETU mortality rate was similar in males and females and in those seen at different stages of the epidemic. It was lower in Conakry than elsewhere, and was higher in those with longer stays in the ETU (Table 1). We used a Cox regression model to identify potential risk factors for death after ETU discharge. Age, area of residence and duration of stay in the ETU were independently associated with mortality (Table 4). Survivors who were hospitalised for ≥12 days during their episode of Ebola virus infection had over twice the risk of late death compared to those hospitalised less than 12 days (adjusted HR 2.62, 95% CI 1.43-4.79). Taking extreme values for the dates of death of those with unknown dates, and the complete case analysis gave similar results (Supplementary Table).

Investigations of cause of late death of Ebola virus disease survivors

We could gather limited information on possible cause of death for 52/59 reported deaths. Unfortunately, due to data management challenges encountered in Guinea, we were unable to link this information to each study participant and the medical files reviewed for each death are no longer available. In over half of the late deaths (37/59), a role of renal failure was evoked by a team of medical epidemiologists who reviewed the available medical files and the verbal autopsy completed by a family member. Of those deaths, three were reported by the Centre of haemodialysis of the main hospital in Conakry, where the survivors were hospitalised when they died. Most of the rest of the purported renal failure verbal autopsy diagnoses were based on anuria declared by the family or on creatinine levels. Other conditions that were judged to have a main role in the late deaths were malaria (5) pulmonary tuberculosis (3) high blood pressure (3), septicemia (1), brain tumor (1), accident (1) and suicide (1).

Discussion

Though much is known about sequelae caused by EVD, little was known before this study about the risk of death among the Ebola virus disease survivors. Here, we report an unexpectedly high mortality among EVD survivors in Guinea. Among the risk factors we were able to investigate, we found a higher risk among survivors who had longer stays in the ETU and in older adults.

Bower et al. reported four late deaths among 151 survivors from Sierra Leone with a mean follow-up of 10 months (2.6%).[16] This is consistent with our overall risk of death (5.2% with a mean follow-up of 21 months). Mortality rates were not constant over time. All 4 deaths in Sierra Leone occurred within the first 6 weeks. In our study the date of death was only known for 16: half died within the first 3 months, and 11 within 10 months. Almost all the deaths (55/59) had occurred by 31st December 2015, a mean of 12.6 months after ETU discharge, giving a mean mortality risk of 4.9% by this time. It is possible that the true mortality rate was higher, as mortality is likely to have been higher among those lost to follow-up.

For the first year of follow-up, the mortality rate we measured was over five times that expected in the Guinean population, having adjusted for age. For the subsequent 9 months, the SMR among survivors

was not significantly higher than in the general population. This is in line with observations from a cohort study that recruited Liberian survivors on average a year after ETU discharge, and found no increased risk of death compared to controls.[11] The data we used for the comparison of mortality rates were representative of the Guinean population and came from the report on mortality of the latest available census (2014). This census was undertaken by the Guinean National Institute for Statistics under the technical assistance of experts of the United Nations Population Fund, and published in 2017.[22] A limitation of the census was that the number of deaths were not based on death records but extrapolated from the questionnaire given to the census study participants.

Although poorer sections of the population, who would have higher background mortality rates, may have been more affected by Ebola, and so over-represented, this is unlikely to explain such a large increase in early mortality and is not supported by the mortality rates in 2016 . The lower risk of death among survivors residing in Conakry may be due to easier access to health care in the city, compared to non-urban areas. Limitations include that for most deaths date of death was missing, and that verbal autopsy and clinical data used to determine possible cause of death are no longer available. However, the distribution of deaths over time, and the possibility that renal failure contributed to over 60% of the deaths may suggest that the majority were linked to Ebola sequelae.

While evidence of the role of renal failure is weak for most patients, it is biologically plausible. EBOV is often detected in urine samples during the acute phase of the disease because it can infect the kidney, [23] and EVD patients may develop acute kidney injury. [24,25] Acute kidney injury may lead to longer term renal failure and increased mortality rates even after initial apparent recovery.[26,27]

This analysis used the data collected by the SA-Ceint program, so variables to investigate were limited to those collected for the program. No information about sequelae or exposure to drugs was available, so we could not further assess whether treatment was associated with adverse outcome, as tentatively observed by Etard *et al*. [9] The SA-Ceint program had an almost 90% follow-up rate among the survivors, which is a remarkable achievement. Of note, Guinea has many fewer survivors than Sierra Leone (over

10,000) and Liberia (almost 6,000), possibly explaining why the implementation of a nationwide follow-up program with such a high follow-up rate may have been possible.

However, Guinean health authorities encountered challenges in coordinating such a rapidly implemented program within a health system that was ravaged by the epidemic. An example is that although the main contributor to death for EVD survivors was investigated and available for most deaths, we do not know on which data it was based, and the information to link it to the MoH database could not be retrieved.

This study reveals that post-Ebola sequelae include an increased mortality rate. This demonstrates that survivors' monitoring programs should be strengthened and should not exclusively focus on body fluid testing. Moreover, this study gives preliminary evidence that survivors hospitalised for longer periods may be particularly at risk and should be targeted, and, perhaps, that renal function should be monitored. Guidelines on how to implement such programs, to be followed by Ministries of Health of affected countries, are being constantly updated by a pool of Ebola experts coordinated by WHO.

Future research should focus on the long-term effect of Ebola virus infection, including on the potential role of kidney function; illness duration and viral persistence in body fluids should be considered as potential risk factors in future epidemiological studies.

In conclusion, we have shown a five-fold higher age-adjusted mortality rate among EVD survivors during the first year of follow-up, compared to the Guinean population. This study should be replicated in Sierra Leone and Liberia, and steps taken to understand, and, if possible, prevent these late deaths.

Author contributions

B.D., M.H.D., A.M., I.S.F., K.Y.N., N.M., A.B.D., M.K.K., A.B., M.O.B., R.P., J.R.G., L.S. and M.K. designed and performed the study. S.M., B.B. and S.C. managed the data. A.O.B and M.S.B provided documentation for cases hospitalised in the Nephrology department. M.K. and S.S. performed the appraisal of the program. L.S. and J.R.G. performed the statistical analyses. M.K., P.F., S.V.G., J.R.G. and L.S. wrote the manuscript. All authors reviewed the final draft. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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