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Understanding Long-term Evolution and Predictors of Sequelae of Ebola Virus Disease Survivors in Guinea: A 48-Month Prospective, Longitudinal Cohort Study (PostEboGui)

Mamadou Saliou Kalifa Diallo,[1,2] Abdoulaye Toure,[2,3] Mamadou Saliou Sow,[4] Cécé Kpamou,[2] Alpha Kabinet Keita,[1,2] Bernard Taverne,[1] Martine Peeters,[1] Philippe Msellati,[1] Thierno Alimou Barry,[2] Jean-Francois Etard,[1] René Ecochard,[5,6,7,8] Eric Delaporte[1]; for the PostEboGui Study Group*

[1]IRD/INSERM/Montpellier University, Montpellier, France; [2]Centre de Recherche et de Formation en Infectiologie de Guinée, Université Gamal Abdel Nasser de Conakry, Conakry, Guinea; [3]Institut National de Santé Publique, Conakry, Guinea; [4]Donka National Hospital, Conakry, Guinea; [5]Hospices Civils de Lyon, Service de Biostatistique, Lyon, France; [6]CNRS UMR 5558 Laboratoire de Biométrie et Biologie Évolutive, Équipe Biostatistique-Santé, Villeurbanne, France; [7]Université de Lyon, Lyon, France; and [8]Université Lyon 1, Villeurbanne, France.

Background. Longitudinal analyses are needed to better understand long-term Ebola virus disease (EVD) sequelae. We aimed to estimate the prevalence, incidence, and duration of sequelae and to identify risk factors associated with symptom occurrence among EVD survivors in Guinea.

Methods. We followed 802 EVD survivors over 48 months and recorded clinical symptoms with their start/end dates. Prevalence, incidence, and duration of sequelae were calculated. Risk factors associated with symptom occurrence were assessed using an extended Cox model for recurrent events.

Results. Overall, the prevalence and incidence of all symptoms decreased significantly over time, but sequelae remained present 48 months after Ebola treatment center discharge with a prevalence of 30.68% (95% confidence interval [CI] 21.40–39.96) for abdominal, 30.55% (95% CI 20.68–40.41) for neurologic, 5.80% (95% CI 1.96–9.65) for musculoskeletal, and 4.24% (95% CI 2.26–6.23) for ocular sequelae. Half of all patients (50.70%; 95% CI 47.26–54.14) complained of general symptoms 2 years' postdischarge and 25.35% (95% CI 23.63–27.07) 4 years' post-discharge. Hemorrhage (hazard ratio [HR], 2.70; $P = .007$), neurologic (HR 2.63; $P = .021$), and general symptoms (HR 0.34; $P = .003$) in the EVD acute phase were significantly associated with the further occurrence of ocular sequelae, whereas hemorrhage (HR 1.91; $P = .046$) and abdominal (HR 2.21; $P = .033$) symptoms were significantly associated with musculoskeletal sequelae.

Conclusions. Our findings provide new insight into the long-term clinical complications of EVD and their significant association with symptoms in the acute phase, thus reinforcing the importance of regular, long-term follow-up for EVD survivors.

Keywords. Ebola survivors; sequelae; prevalence; Cox models; recurrent events.

INTRODUCTION

Ebola virus disease (EVD) is a severe and often fatal illness that was first identified in 1976 in the Democratic Republic of the Congo. Until 2013, the World Health Organization had reported 24 outbreaks involving 2387 cases with 1590 deaths, mainly in central Africa [1]. The 2013–2016 outbreak in West Africa was the largest and most complex outbreak of Ebola virus (EBOV) since its discovery with over 28 000 cases, 11 000 deaths, and an estimated 17 000 survivors, notably in Guinea, Liberia, and Sierra Leone [2].

EVD survivors face health problems even after the clearance of EBOV from their blood. Several studies have reported short- and long-term sequelae experienced by survivors [3–19] including auditory problems, psychological sequelae, extreme fatigue, and abdominal pain, as well as neurologic, musculoskeletal, and ocular symptoms. The evolution of these sequelae over time still needs to be investigated and is a topic of ongoing studies. An observational study of EVD survivors in Liberia showed that most sequelae decreased during the first year, except for uveitis [15]. However, in another study in the same country, the frequency of these sequelae was shown to remain largely unchanged during the 4 years after the onset of acute infection [20]. Apart from the latter study, all remaining reports have covered a follow-up period of no more than 2 years postdischarge from the Ebola treatment center (ETC).

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*PostEboGui Study Group members are listed in the Acknowledgment section

Correspondence: E. Delaporte, IRD UMI233-INSERM U1175, Montpellier University, Délégation Régionale Occitanie, 911 avenue Agropolis, BP 64501, Montpellier Montpellier, France (eric.delaporte@ird.fr).

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In addition, previous studies of EVD survivors have been either cross-sectional or longitudinal, but with only a cross-sectional analysis at each study visit, thus ignoring the evolution of sequelae between visits. Observed sequelae were very intermittent, while only a continuous evaluation has the capacity to capture this aspect accurately.

To our knowledge, no study has investigated the duration of symptomatic episodes in survivors. For this purpose, a longitudinal, rather than a cross-sectional analysis, is necessary to improve our understanding of the long-term sequelae of EVD and to provide useful data to inform and guide the planning and delivery of health services to patients who have recovered from the acute phase of the disease. Indeed, previous longitudinal studies have analyzed the presence or absence of symptoms at the time of the visit, which obviously limits the type of data and analysis available. To address these gaps, we conducted a 48-month, prospective, longitudinal, multidisciplinary cohort study in Guinea to assess the long-term clinical, psychological, sociological, and viral outcomes potentially manifest in EVD survivors [11]. Here we report our findings concerning the prevalence, incidence, and duration of sequelae 18 to 48 months after discharge from the ETC. We also identified risk factors associated with the occurrence of symptoms in this patient population.

METHODS

Study Design and Patients

We conducted a prospective, multicenter, open cohort study (known as the PostEboGui study) between 23 March, 2015, and 11 July, 2016, among 802 EVD survivors to evaluate the long-term clinical, psychosocial, biological, psychological, sociological, and viral consequences of EVD in Guinea. A minimum of 6 months' follow-up was required for inclusion in the final analysis. Patients were aged at least 1 year and recruited at 4 sites (Donka National Hospital, Conakry, Forecariah Prefectoral Hospital, Forecariah, Macenta Prefectoral Hospital, Macenta, N'Zérékoré Regional Hospital, N'Zérékoré). Median delay between ETC discharge and study enrolment was 350 days (interquartile range [IQR], 223–491) [11].

Procedures

Patients were assessed at inclusion and at 1 and 3 months thereafter, and then every 6 months up to 48 months, but unscheduled visits were possible. At each visit, EVD survivors had a consultation with a trained clinician including documentation of medical history, physical examination, and laboratory evaluation (details of study tools are provided in the Supplementary Appendix of reference [11]. Participants were asked if they had any sequelae at the time of examination or since the last study visit; start and end dates were recorded for each sequelae [11].

Data Management

We divided the patient's visit history into segments composed of 2 consecutive visit dates to correctly assess the duration of the presence of each symptom. Each time segment therefore had a start and end date. Four situations were observed: a) the symptom was present all along the time segment; b) the symptom was absent all the time; c) the symptom occurred during the time segment; and d) the symptom stopped during the time segment. The latter 2 situations were considered as interval-censored data. We reconstructed the duration of symptoms day-by-day to obtain the number of days each symptom was present or absent for each patient.

Statistical Analysis

A detailed description of the demographic characteristics of study participants at baseline has been reported elsewhere [11]. In addition, other substudies from PostEbogui about ocular complication, depressive symptoms, characteristics of the musculoskeletal symptoms, and Ebola viral ribonucleic acid in semen have been already published [17, 21–23]. For this analysis, we focused on the long-term clinical follow-up of patients after discharge from the ETC (ie, from 18 to 48 months). Qualitative variables were assessed by proportions and 95% confidence intervals (CI). Quantitative variables were described by mean and standard deviation if normally distributed, and by median and IQR if not normally distributed. We used χ^2 tests to compare the proportions. A comparison of continuous variables was tested with either Student's *t*-test if normally distributed or the Mann-Whitney rank-sum test if not normally distributed.

Prevalence (percentage) was defined as the proportion of EVD survivors with sequelae at a specified time. The incidence rate during a period of time was the ratio of the number of EVD survivors who newly developed a symptom during this period divided by the total duration of follow-up of the patients during this time interval. For interval-censored data, we estimated the missing dates following the Turnbull method for interval-censored events using multiple imputation and created 5 imputed datasets, as suggested elsewhere [24]. We calculated the estimates of interest (prevalence, incidence, duration in days) for each imputed dataset. The 5 estimates were then averaged. The 95% CI of these estimates incorporating both the within and between imputation variability were calculated using Rubin's rules based on asymptotic theory [25].

The occurrence of symptoms in EVD survivors were analyzed using an extension of the Cox model adapted for recurrent events using the counting process formulation of Andersen and Gill [26]. Recurrent events refer to events of interest experienced repeatedly by a given individual. The goal pursued here was to understand the factors associated with the repeated occurrence of events over time. Risk factors considered were the symptoms of the acute phase of EVD as described previously [11] (ie general symptoms, hemorrhage, abdominal symptoms,

myalgia, and neurologic disorders). All models were adjusted for age and sex. To take account of the nonlinear effect of age, we introduced age squared into the model. The proportional risk assumption has been verified and validated by the method described elsewhere [27]. Hypothesis tests were 2-sided and the significance threshold was set at $\alpha = 0.05$. All data cleaning, management, and analysis were performed using R, version 3.6.0 (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among the 802 patients, 722 (>90%) had 6 months or more of follow-up and were included in the current analysis; 320 (44%) patients were male, and 585 (81%) were over 18 years (median age, 28.7 years; IQR, 19.6–39.7). Median patient follow-up was 35.7 months (IQR, 31.3–41.6). Median number of study visits was 12 (range, 1–48; IQR, 10–16). A total of 710 of 722 patients (98%) reported at least 1 clinical event during follow-up.

Prevalence

Overall, all symptoms reported were recurrent, but their prevalence decreased continuously and significantly between 18 and 48 months postdischarge from the ETC (Figure 1; Table 1). At 2 years' post-discharge from the ETC, more than half of all EVD survivors had general symptoms (50.70% [95% CI, 47.08–54.31]; Table 1) with a prevalence of 33.16% (95% CI, 31.16–35.17) at 3 years' postdischarge, followed by a significant decrease to 25.35% (95% CI, 23.42–27.27) at year 4 postdischarge. A similar trend was observed for neurological disorders where the prevalence decreased significantly from 46.30% (95% CI, 42.19–50.41) at year 2 to 34.25% (95% CI, 31.53–36.97) at year 3, and 27.68% (24.20; 31.17) at year 4 postdischarge. A slight decrease of 26.77% (95% CI, 22.52–31.03) to 17.08% (95% CI, 15.22–18.93) was observed for abdominal sequelae between years 2 and 4 postdischarge. The prevalence of ocular sequelae was low and decreased from 9.17% (95% CI, 6.98–11.37) in year 2 to 6.07% (95% CI, 5.04–7.11) in year 4 post-discharge. Detailed data on the prevalence of individual symptoms stratified by age and sex are available in the Supplementary Table 1.

Incidence

Tables 2 and 3 show the incidence (cases/10 000 person-years) of clinical events stratified by sex and age among Ebola survivors over time. The incidence of abdominal symptoms, neurologic disorders, musculoskeletal problems, and general

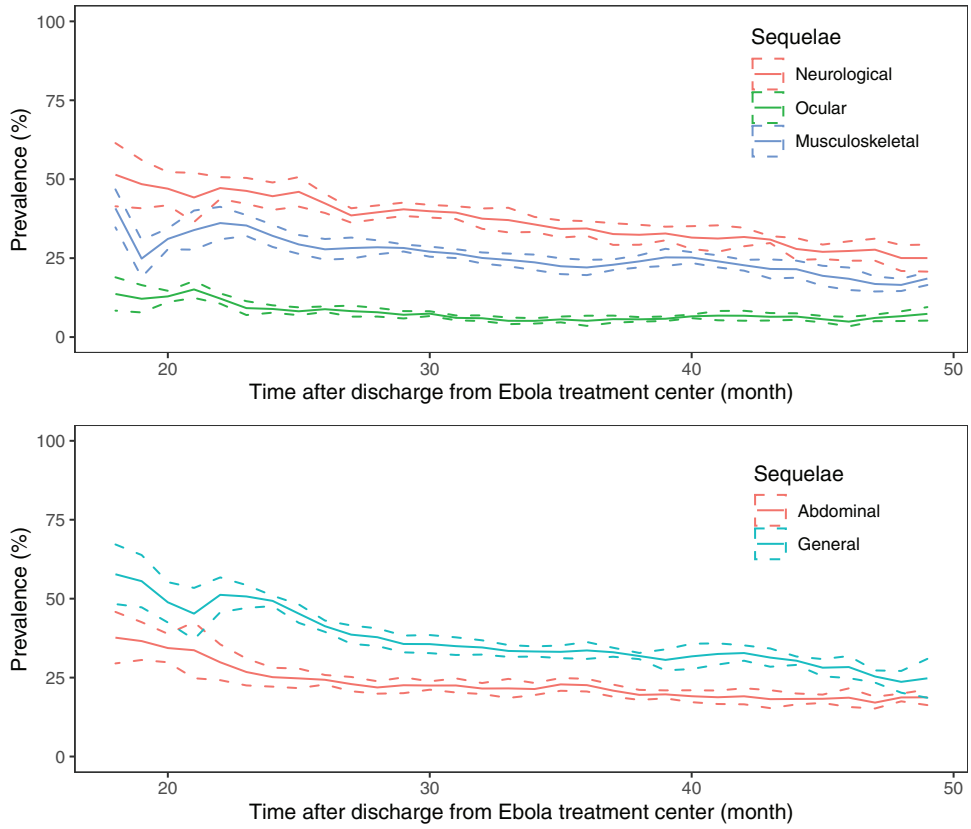

Figure 1. Prevalence and 95% confidence interval of clinical events among Ebola virus disease survivors over time (post-discharge from the Ebola Treatment Center) in the PostEboGui cohort. Abdominal = abdominal or pelvic pain, gastritis; Neurological = headache, dizziness, and other (neurosensitive disorders, neuromotor disorders, behavioral problems); Ocular = conjunctivitis, iridocyclitis, cataract, glaucoma, vision problems, ocular pain; Musculoskeletal = neck pain, back pain, joint pain, myalgia; General = fever, fatigue, anorexia.

Table 1. Prevalence and 95% Confidence Interval (CI) of Clinical Events Among Ebola Virus Disease Survivors Over Time (Postdischarge from Ebola Treatment Center) in PostEboGui Cohort

	24 months after ETC discharge				36 months after ETC discharge				48 months after ETC discharge			
Clinical Sequelae (%)	All (95% CI)	Adults (95% CI)	Children (95% CI)	*P* value	All (95% CI)	Adults (95%CI)	Children (95% CI)	*P* value	All (95% CI)	Adults (95% CI)	Children (95% CI)	*P* value
Abdominal[a]	26.77 (22.64–30.91)	23.24 (17.80–28.68)	40.77 (33.08–48.45)	.000	22.85 (20.91–24.79)	21.45 (19.90–23.01)	30.20 (25.12–35.28)	.000	17.08 (15.38–18.78)	14.67 (11.90–17.44)	30.68 (21.40–39.96)	.000
Neurological[b]	46.30 (42.34–50.27)	44.47 (40.51–48.42)	53.88 (43.91–63.84)	.000	34.25 (31.61–36.90)	34.31 (31.05–37.57)	33.94 (27.82–40.07)	.721	27.68 (24.31–31.05)	27.15 (22.95–31.34)	30.55 (20.68–40.41)	.016
Ocular[c]	9.17 (7.07–11.27)	8.60 (6.55–10.65)	11.42 (8.41–14.42)	.003	5.59 (4.73–6.45)	6.07 (4.99–7.14)	3.08 (1.84–4.32)	.000	6.07 (5.15–7.00)	6.41 (5.17–7.65)	4.24 (2.26–6.23)	.005
Musculoskeletal[d]	35.34 (32.20–38.47)	37.64 (34.33–40.95)	25.70 (19.26–32.15)	.000	22.44 (20.01–24.88)	24.06 (21.82–26.31)	13.96 (9.16–18.76)	.000	16.82 (14.55–19.08)	18.91 (16.35–21.47)	5.80 (1.96–9.65)	.000
General[e]	50.70 (47.26–54.14)	50.37 (47.11–53.64)	51.98 (43.37–60.60)	.326	33.16 (31.26–35.07)	33.75 (31.05–36.46)	30.04 (27.17–32.91)	.000	25.35 (23.63–27.07)	25.01 (22.03–27.98)	27.15 (19.19–35.11)	.137

Abbreviation: ETC, Ebola Treatment Center.

[a]Abdominal = abdominal or pelvic pain, gastritis.

[b]Neurological = headache, dizziness and other (neurosensitive disorders, neuromotor disorders, behavioral problems).

[c]Ocular = conjunctivitis, iridocyclitis, cataract, glaucoma, vision problems, ocular pain.

[d]Musculoskeletal = neck pain, back pain, joint pain, myalgia.

[e]General = fever, fatigue, anorexia.

Table 2. Incidence (Cases/10 000 Person-Years) and 95% Confidence Interval (CI) of Clinical Events by Sex Among Ebola Virus Disease Survivors Over Time (Since Ebola Treatment Center Discharge) in PostEboGui Cohort

	24–36 months after ETC discharge				36–48 months after ETC discharge			
Clinical events	All (95% CI)	Male (95% CI)	Female (95% CI)	*P* value	All (95% CI)	Male (95% CI)	Female (95% CI)	*P* value
Abdominal[a]	46.44 (42.70–50.18)	36.31 (31.34–41.28)	54.46 (49.04–59.88)	.0000	37.39 (33.90–40.88)	31.11 (26.28–35.95)	42.21 (37.27–47.14)	.0023
Neurological[b]	100.71 (94.53–106.89)	87.77 (79.17–96.37)	111.27 (102.52–120.03)	.0002	68.47 (63.35–73.60)	55.97 (49.00–62.94)	78.39 (71.05–85.73)	.0000
Ocular[c]	7.63 (6.26–9.00)	6.59 (4.62–8.56)	8.38 (6.50–10.27)	.2399	8.45 (6.91–9.99)	8.21 (5.86–10.56)	8.62 (6.59–10.66)	.8691
Musculoskeletal[d]	47.14 (43.29–50.98)	49.05 (42.97–55.13)	45.78 (40.82–50.73)	.4134	39.22 (35.56–42.88)	42.67 (36.69–48.64)	36.84 (32.23–41.46)	.1370
General[e]	93.15 (87.36–98.95)	95.26 (86.14–104.38)	91.68 (84.18–99.18)	.5709	73.95 (68.58–79.33)	76.30 (67.74–84.86)	72.35 (65.44–79.25)	.5014

Abbreviation: ETC, Ebola Treatment Center.

[a]Abdominal = abdominal or pelvic pain, gastritis.

[b]Neurological = headache, dizziness and other (neurosensitive disorders, neuromotor disorders, behavioral problems).

[c]Ocular = conjunctivitis, iridocyclitis, cataract, glaucoma, vision problems, ocular pain.

[d]Musculoskeletal = neck pain, back pain, joint pain, myalgia.

[e]General = fever, fatigue, anorexia.

Table 3. Incidence (Cases/10 000 Person-Years) and 95% Confidence Interval (95% CI) of Clinical Events by Age Among 2013–2016 Ebola Virus Survivors Over Time (Since Ebola Treatment Center Discharge) in PostEboGui Cohort

Clinical events	24–36 months after ETC discharge				36–48 months after ETC discharge			
	All (95% CI)	Adults (95% CI)	Children (95% CI)	*P* value	All (95% CI)	Adults (95% CI)	Children (95% CI)	*P* value
Abdominal[a]	46.44 (42.70–50.18)	42.24 (38.39–46.09)	71.53 (59.28–83.78)	.0000	37.39 (33.90–40.88)	34.60 (30.96–38.24)	53.52 (42.64–64.39)	.0002
Neurological[b]	100.71 (94.53–106.89)	104.38 (97.46–111.29)	83.09 (69.56–96.61)	.0130	68.47 (63.35–73.60)	69.80 (64.15–75.44)	61.49 (49.32–73.67)	.2655
Ocular[c]	7.63 (6.26–9.00)	8.27 (6.70–9.84)	4.53 (1.96–7.09)	.0589	8.45 (6.91–9.99)	9.03 (7.29–10.76)	5.45 (2.36–8.53)	.1213
Musculoskeletal[d]	47.14 (43.29–50.98)	51.80 (47.34–56.26)	26.53 (19.82–33.24)	.0000	39.22 (35.56–42.88)	44.45 (40.15–48.75)	15.35 (9.95–20.76)	.0000
General[e]	93.15 (87.36–98.95)	94.63 (88.22–101.03)	85.92 (72.40–99.45)	.2862	73.95 (68.58–79.33)	75.05 (69.14–80.95)	68.20 (55.27–81.12)	.3857

Abbreviation: ETC, Ebola Treatment Center.

[a]Abdominal = abdominal or pelvic pain, gastritis.

[b]Neurological = headache, dizziness and other (neurosensitive disorders, neuromotor disorders, behavioral problems).

[c]Ocular = conjunctivitis, iridocyclitis, cataract, glaucoma, vision problems, ocular pain.

[d]Musculoskeletal = neck pain, back pain, joint pain, myalgia.

[e]General = fever, fatigue, anorexia.

symptoms decreased significantly during follow-up (Table 2), whereas the incidence of ocular sequelae remained stable. Women were significantly more likely to report new abdominal sequelae and neurologic disorders than men. The incidence of other targeted sequelae did not differ significantly between men and women. Children were significantly less likely to report new musculoskeletal problems and significantly more likely to report abdominal symptoms than adults (Table 3). The incidence of other targeted sequelae did not differ significantly between children and adults. Detailed data on the prevalence of individual symptoms stratified by age and sex are available in the Supplementary Table 2).

Duration of Symptomatic Episodes

Tables 4 and 5 show the mean and median days duration of symptomatic episodes stratified by age and sex. Between years 2 and 4 postdischarge from the ETC, the median duration was 204 days (IQR, 99–312) for neurologic disorders, 190 days (IQR, 81–314) for general sequelae, and 121 days (IQR, 37–218) for abdominal sequelae (Table 4). The highest mean duration was 213 days (95% CI, 201–224) for neurologic sequelae. For musculoskeletal problems, the mean duration of symptomatic episodes was significantly higher in adults (193; 95% CI, 179–206) than in children (148; 95% CI, 115–180). Mean duration of other sequelae did not differ significantly between adults and children. Mean duration of abdominal symptomatic episodes and neurologic disorders was significantly higher among women. There were no significant differences in the duration of other sequelae between men and women.

Risk Factors Associated With Occurrence of Symptoms in EVD Survivors

Results of the Cox model are presented in Table 6. Overall, age had a positive and significant, but nonlinear (rapid then slow increase with age) effect on general sequelae and ocular and musculoskeletal sequelae. The immediate risk of developing post-ETC sequelae did not differ significantly between men and women. The risk of neurologic sequelae occurrence did not differ according to age, sex, and other sequelae of the acute phase considered in our analysis. Occurrence of ocular sequelae was significantly higher in survivors who had symptoms of hemorrhage (hazard ratio [HR], 2.70; $P = .007$) or neurologic disorders (HR, 2.63; $P = .021$) during the acute phase of EVD (Table 6). Of note, the risk of ocular sequelae was approximately 3-fold lower in survivors who had general symptoms (HR, 0.34; $P = .0007$) during the acute phase of EVD. Symptoms of hemorrhage (HR, 1.91; $P = .046$) and abdominal pain (HR, 2.21; $P = .033$) during the EVD acute phase were positively and significantly associated with an occurrence of musculoskeletal sequelae during follow-up. The occurrence of abdominal sequelae was approximately 3-fold lower (HR, 0.32; $P = .038$) in survivors who had general symptoms during the acute phase of EVD. Risk factors associated with the occurrence of general sequelae were myalgia

Table 4. Median and Mean Duration (Days) and 95% Confidence Interval (CI) of Clinical Events by Age Among 2013–2016 Ebola Virus Disease Survivors Over Time (Since Ebola Treatment Center Discharge) in PostEboGui Cohort

	Mean				Median			
Clinical events	All (95% CI)	Adults (95% CI)	Children (95% CI)	*P* value	All (IQR)	Adults (IQR)	Children (IQR)	*P* value
Abdominal[a]	145.21 (134.44–155.98)	142.01 (130.13–153.89)	163.59 (140.04–187.15)	.112	120.60 (37.10–217.90)	116 (37.00–211.00)	154 (61.00–248.00)	.56
Neurological[b]	212.87 (201.29–224.45)	216.65 (203.79–229.52)	190.57 (163.30–217.84)	.092	203.90 (98.50–312.05)	206 (109.50–308.00)	159.5 (71.75–302.00)	.045
Ocular[c]	114.31 (98.88–129.74)	114.76 (97.94–131.57)	89.66 (56.96–122.35)	.265	79.80 (30.50–157.15)	72 (31.00–150.00)	73 (30.00–102.00)	.11
Musculoskeletal[d]	184.71 (172.12–197.30)	192.69 (179.16–206.22)	147.62 (115.23–180.01)	.018	167.80 (64.35–280.35)	174 (80.00–285.00)	127 (27.00–243.00)	.001
General[e]	205.87 (193.95–217.85)	211.41 (197.99–224.83)	188.27 (159.39–217.16)	.157	190.00 (81.10–314.20)	186 (87.00–337.75)	169 (59.50–281.50)	.064

Abbreviation: IQR, interquartile range.

[a]Abdominal = abdominal or pelvic pain, gastritis.

[b]Neurological = headache, dizziness and other (neurosensitive disorders, neuromotor disorders, behavioral problems).

[c]Ocular = conjunctivitis, iridocyclitis, cataract, glaucoma, vision problems, ocular pain.

[d]Musculoskeletal = neck pain, back pain, joint pain, myalgia.

[e]General = fever, fatigue, anorexia.

Table 5. Duration in Days and 95% Confidence Interval (CI) of Clinical Events by Sex among 2013–2016 Ebola Virus Disease Survivors Over Time (Since Ebola Treatment Center Discharge) in the PostEboGui Cohort

	Mean				Median			
Clinical events	All	Male	Female	*P* value	All	Male	Female	*P* value
Abdominal[a]	145.21 (134.44–155.98)	130.17 (113.00–147.34)	155.43 (141.72–169.14)	.004	120.60 (37.10–217.90)	97.5 (21.8–201.55)	131.2 (58.85–228.85)	.35
Neurological[b]	212.87 (201.29–224.45)	192.79 (175.32–210.27)	226.68 (211.42–241.94)	.004	203.90 (98.50–312.05)	179.4 (77.5–287.55)	220.0 (115.20–327.40)	.027
Ocular[c]	114.31 (98.88–129.74)	109.71 (84.37–135.04)	117.91 (98.79–137.03)	.934	79.80 (30.50–157.15)	65.6 (22.90–150.65)	89.0 (33.70–169.30)	.09
Musculoskeletal[d]	184.71 (172.12–197.30)	182.40 (163.17–201.62)	186.55 (169.88–203.22)	.572	167.80 (64.35–280.35)	162.5 (60.15–272.35)	171.1 (67.95–284.95)	.007
General[e]	205.87 (193.95–217.85)	203.64 (184.38–222.89)	207.55 (192.31–222.83)	.855	190.00 (81.10–314.20)	178.1 (67.15–319.10)	197.4 (92.75–310.00)	.060

[a]Abdominal = Abdominal or pelvic pain, gastritis.

[b]Neurological = headache, dizziness and other (neurosensitive disorders, neuromotor disorders, behavioral problems).

[c]Ocular = conjunctivitis, iridocyclitis, cataract, glaucoma, vision problems, ocular pain.

[d]Musculoskeletal = neck pain, back pain, joint pain, myalgia.

[e]General = fever, fatigue, anorexia.

Table 6. Final Hazard Ratio Estimates and 95% Confidence Intervals (CI) Based on Multivariate Cox Models for Recurrent Events Estimating Risk Factors Associated With Repeated Occurrence of Ebola Virus Disease Sequelae After Ebola Treatment Center Discharge

Symptoms of the acute phase	Abdominal[a] sequelae		Neurological[b] sequelae		Ocular[c] sequelae		Musculoskeletal[d] sequelae		General[e] sequelae	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex (male)	1.24 (0.58–2.61)	.581	1.28 (0.51–3.21)	.600	1.09 (0.60–1.97)	.781	0.62 (0.32–1.20)	.156	0.71 (0.25–1.95)	.503
Age (Linear Trend)	1.06 (0.89–1.25)	.515	1.61 (0.68–3.81)	.280	1.12 (1.01–1.27)	.045	1.15 (1.05–1.26)	.002	1.27 (1.00–1.62)	.048
Age^2 (Quadratic Trend)	0.99 (0.99–1.01)	.602	0.71 (0.46–1.11)	.140	0.99 (0.99–1.00)	.117	0.99 (0.99–1.00)	.013	0.99 (0.99–1.00)	.099
General	0.32 (0.11–0.94)	.038	1.12 (0.35–3.62)	.840	0.34 (0.18–0.64)	.003	0.60 (0.32–1.12)	.110	0.56 (0.21–1.50)	.250
Hemorrhage	0.81 (0.32–2.02)	.650	0.55 (0.19–1.59)	.270	2.70 (1.31–5.60)	.007	1.91 (1.02–4.06)	.045	0.91 (0.27–3.06)	.888
Abdominal[a]	1.70 (0.67–4.28)	.260	2.00 (0.64–6.27)	.240	1.27 (0.62–2.62)	.509	2.21 (1.06–4.58)	.033	1.84 (0.52–6.53)	.343
Myalgia	1.92 (0.80–4.61)	.144	0.83 (0.32–2.13)	.700	0.96 (0.46–1.97)	.902	0.68 (0.32–1.40)	.294	5.04 (1.52–16.75)	.008
Neurological[b]	2.28 (0.75–6.91)	.143	1.39 (0.39–4.99)	.610	2.63 (1.15–6.01)	.021	1.07 (0.47–2.43)	.871	0.34 (0.10–0.98)	.049

Recurrent events refer to events of interest experienced repeatedly by a given individual.

Abbreviation: HR, hazard ratio.

[a]Abdominal = abdominal or pelvic pain, gastritis.

[b]Neurological = headache, dizziness and other (neurosensitive disorders, neuromotor disorders, behavioral problems).

[c]Ocular = conjunctivitis, iridocyclitis, cataract, glaucoma, vision problems, ocular pain.

[d]Musculoskeletal = neck pain, back pain, joint pain, myalgia.

[e]General = fever, fatigue, anorexia.

(HR, 5.04; $P = .008$) and neurologic disorders (HR, 0.34; $P = .049$) during the acute phase of the disease.

DISCUSSION

In this prospective, longitudinal cohort study, we observed that the prevalence of all EVD sequelae decreased between 18 and 48 months after discharge from the ETC, similar to other reports [11, 13, 15], although these findings are in contrast to a recent study describing a highly prevalent and stable prevalence of post-EVD sequelae [20]. However, all these studies only performed a cross-sectional analysis of follow-up visits, without knowledge of events occurring between follow-up visits. Thus, the disadvantages of these studies include not only the impossibility of knowing the duration of the symptomatic episodes, but also the fact that the prevalence can be considerably modified depending on whether a sequela is reported on the day of the visit.

We revealed an association between age and the incidence of some sequelae as already shown [11] in that children were less likely to report new musculoskeletal problems and more likely to report abdominal sequelae than adults.

Our analysis shows that while some symptomatic episodes are relatively brief in survivors despite their recurrence, others are long-lasting. Indeed, over a period of 2 years (ie between 2 and 4 years postdischarge from the ETC), survivors had accrued on average 7.1 months of neurologic disorders, 6.8 months of general symptoms, and 6.2 months of musculoskeletal problems. It is known that these persisting clinical complications after the acute phase of infection result in negative health outcomes [14, 28, 29] and can have a major impact on the productivity of survivors, as well as their quality of life.

We also investigated detailed associations between the symptoms of the acute phase of EVD and post-ETC sequelae with a Cox model adapted to recurrent events. Only 1 previous cross-sectional study of 277 survivors in Sierra Leone analyzed risk factors related to 3 post-EVD clinical sequelae (ocular, auditory, and articular) [10]. The sole symptoms considered were diarrhea and red eyes and were found to be not significant.

Our analysis revealed a positive and significant association between age and the occurrence of ocular, general signs, and musculoskeletal sequelae. These results are in line with the findings of previous studies [13, 20]. The positive coefficient for age and the negative one for age squared indicate a monotonic increasing function of sequelae by age until a turning point is reached (at approximately 44 years of age) and from which point the function starts to decrease. We showed that the occurrence of post-ETC ocular sequelae was significantly associated with the age of survivors, but also with hemorrhage and general and neurologic symptoms during the acute phase of EVD. Similarly, we observed that the occurrence of post-ETC musculoskeletal sequelae was significantly associated with the age of survivors, but also with hemorrhage and abdominal symptoms during the acute phase. In addition, survivors who had myalgia during the acute phase were 5 times more likely to have general sequelae. We observed no association between age, EVD symptoms at the acute phase, and post-EVD neurologic sequelae.

These interesting results show that there are significant associations between acute phase symptoms and post-EVD sequelae. This provides a considerable advance in current knowledge to help healthcare workers to build strategies to optimize the care and follow-up of EVD survivors, taking into account their history at the ETC and risk factors associated with

the occurrence of sequelae. In addition, our results could help to develop a package of care adapted to survivors. Some EVD survivors require long-term follow-up, with appropriate management taking into account the patient's history during the acute phase as EVD is not only an acute viral infection and its sequelae continue to evolve over the long term. Continuous, regular and targeted care would not only improve the quality of life of survivors, but also reduce the economic burden of this long-term pathology for both the individual and the healthcare system.

Our study has some limitations. The main limitation is the absence of a control group without a history of EVD that would have allowed us to make comparisons with survivors. Although this makes it difficult to attribute the sequelae reported by survivors to EVD, the results obtained are similar to previous studies using a control group [15, 19] and confirm our conclusions. Another limitation is the lack of sufficient cycle threshold data at the acute phase of EVD to study the link with symptom persistence. Our study does not cover all EVD survivors in Guinea. However, given that the PostEboGui cohort includes two-thirds of Guinean survivors with coverage in urban and rural areas recruited from 4 different locations, we consider that it is sufficiently representative of the national survivor population. Finally, the retrospective and declarative nature of some symptoms may have resulted in a likely recall bias. However, the questionnaire was the same at each visit and the questions systematically asked covered all functional signs. In addition, follow-up visits were made in the event of a recurrent symptom in a patient, thus providing almost accurate information on the date of symptom onset.

In conclusion, the prevalence of post-EVD sequelae among survivors decreases over time, but still persists 48 months after discharge from the ETC. There was a significant association between age, EVD symptoms in the acute phase, and post-ETC sequelae, apart from neurologic sequelae. The impact of the persistence of these sequelae on the quality of life of survivors and their possible immune response to Ebola virus deserves further investigation.

Supplementary Data

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

Notes

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PostEboGui Study Group: Ahidjo Ayouba (IRD/INSERM/Montpellier University, Montpellier, France), Sylvain Baize (Pasteur Institute/Unit of Biology of Emerging Viral Infections, Lyon, France), Kaba Bangoura (Donka National Hospital, Conakry, Guinea), Alimou Barry (Centre de Recherche et de Formation en Infectiologie de Guinée, Université Gamal Abdel Nasser de Conakry, Conakry, Guinea), Moumié Barry (Donka National Hospital, Conakry, Guinea), Mamoudou Cissé (Forecariah Prefectoral Hospital, Forecariah, Guinea), Mohammed Cissé (Donka National Hospital, Conakry, Guinea), Eric Delaporte (IRD/INSERM/Montpellier University, Montpellier, France), Jean-François Delfraissy (Reacting, INSERM, Paris, France), Christelle Delmas (Reacting, INSERM, Paris, France), Alice Desclaux (IRD/INSERM/Montpellier University, Montpellier, France), Saliou Bella Diallo (Donka National Hospital, Conakry, Guinea), Mamadou Safiatou Diallo (Donka National Hospital, Conakry, Guinea), Mariama Sadjo Diallo (Donka National Hospital, Conakry, Guinea), Jean-François Étard (IRD/INSERM/Montpellier University, Montpellier, France), Cécile Etienne (Reacting, INSERM, Paris, France), Ousmane Faye (Donka National Hospital, Conakry, Guinea), Ibrahima Fofana (Macenta Prefectoral Hospital, Macenta, Guinea), Bruno Granouillac (IRD/INSERM/Montpellier University, Montpellier, France), Suzanne Izard (IRD/INSERM/Montpellier University, Montpellier, France), Djenaba Kassé (Donka National Hospital, Conakry, Guinea), Alpha Kabinet Keita (IRD/INSERM/Montpellier University, Montpellier, France; Centre de Recherche et de Formation en Infectiologie de Guinée, Université Gamal Abdel Nasser de Conakry, Conakry, Guinea), Sakoba Keita (Ministry of Health, Conakry, Guinea), Lamine Koivogui (Institut National de la Santé Publique, Conakry, Guinea), Cécé Kpamou (Centre de Recherche et de Formation en Infectiologie de Guinée, Université Gamal Abdel Nasser de Conakry, Conakry, Guinea), Christine Lacarabaratz (INSERM,Paris,France), Sandrine Leroy (IRD/INSERM/Montpellier University, Montpellier, France), Claire Levy Marchal (INSERM, Paris, France), Yves Levy (INSERM, Paris, France), N'Fally Magassouba (Laboratory of Virology, Projet de Recherche sur les Fièvres Hémorragiques en Guinée, Conakry University, Conakry, Guinea), Laura March (IRD/INSERM/Montpellier University, Montpellier, France), Vincent Mendiboure (ALIMA, Conakry, Guinea), Philippe Msellati (IRD/INSERM/Montpellier University, Montpellier, France), Harissatou Niane (Donka National Hospital, Conakry, Guinea),Martine Peeters (IRD/INSERM/Montpellier University, Montpellier, France), Yves-Marie Pers (Montpellier University, Montpellier, France), Hervé Raoul (Laboratoire P4 INSERM-Jean Mérieux, US003 INSERM, Lyon, France), Sidi Lamine Sacko (Macenta Prefectoral Hospital, Macenta, Guinea), Ibrahima Savané (Macenta Prefectoral Hospital, Macenta, Guinea), Mamadou Saliou Sow (Donka National Hospital, Conakry, Guinea), Bernard Taverne (IRD/INSERM/Montpellier University, Montpellier, France), Abdoulaye Touré (Institut National de Santé Publique, Conakry, Guinea; Centre de Recherche et de Formation en Infectiologie de Guinée, Université Gamal Abdel Nasser de Conakry, Conakry, Guinea), Fodé Amara Traoré (Donka National Hospital, Conakry, Guinea), Falaye Traoré (Institut National de la Santé Publique, Conakry, Guinea), Yamoussa Youla (N'Zérékoré Regional Hospital, N'Zérékoré, Guinea), Yazdan Yazdanpanah (Reacting, INSERM, Paris, France).

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