Early clinical sequelae of Ebola virus disease in Sierra Leone: a cross-sectional study

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SUMMARY

Background Limited data are available on the prevalence and predictors of clinical sequelae in survivors of Ebola virus disease (EVD). The EVD Survivor Clinic in Port Loko, Sierra Leone, has provided clinical care for 603 of 661 survivors living in the district. We did a cross-sectional study to describe the prevalence, nature, and predictors of three key EVD sequelae (ocular, auditory, and articular) in this cohort of EVD survivors.

Methods We reviewed available clinical and laboratory records of consecutive patients assessed in the clinic between March 7 and April 24, 2015. We used univariate and multiple logistic regression to examine clinical and laboratory features of acute EVD with the following outcomes in convalescence: new ocular symptoms, uveitis, auditory symptoms and arthralgias.

Findings Among 277 survivors (59% female), median age was 29 years (IQR 20–36) and median time from discharge from an EVD treatment facility to first survivor clinic visit was 121 days (82–151). Clinical sequelae were common, including arthralgias (n=210, 76%), new ocular symptoms (n=167, 60%), uveitis (n=50, 18%), and auditory symptoms (n=67, 24%). Higher Ebola viral load at acute EVD presentation (as shown by lower cycle thresholds on real-time RT-PCR testing) was independently associated with uveitis (adjusted odds ratio [aOR] 3.33, 95% CI 1.87–5.91, for every five-point decrease in cycle threshold) and with new ocular symptoms or ocular diagnoses (aOR 3.04, 95% CI 1.87–4.94).

Interpretation Clinical sequelae during early EVD convalescence are common and sometimes sight threatening. These findings underscore the need for early clinical follow-up of EVD survivors and urgent provision of ocular care as part of health systems strengthening in EVD-affected West African countries.

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INTRODUCTION

The Ebola virus disease (EVD) outbreak in west Africa is the largest in history. As of November, 2015, over 28,500 EVD cases have been reported with an estimated 15,000 survivors. Community-led survivor networks have alerted health-care providers to a variety of convalescent symptoms, including vision and hearing loss and arthralgia.

Understanding of the nature, timing, and prevalence of EVD sequelae remains limited. Disabling sequelae, including ocular, auditory, and arthritic symptoms, have been described in small studies from previous outbreaks. In the current outbreak, one qualitative study of 100 survivors in Sierra Leone reported blurred or partial loss of vision in convalescence but did not quantify these sequelae. Surveys of 105 survivors in Guinea and of 81 survivors in Sierra Leone noted frequent musculoskeletal pain and visual problems, neither study included a clinical examination of survey participants. No studies from the west African outbreak have examined possible relations between features of acute EVD and the frequency or severity of clinical sequelae. Therefore, we did a cross-sectional study to describe the prevalence, nature, and predictors of three key EVD sequelae (ocular, auditory, and articular) in a large cohort of survivors of EVD in Port Loko district, Sierra Leone.

METHODS

Study Setting

By Nov 12, 2015, 1485 EVD cases were reported from the rural district of Port Loko (population 572,369), with 661 survivors according to the Sierra Leone Association for Ebola Survivors registry. Before Nov 30, 2014, some patients were referred for care in Ebola treatment units...
(ETUs) outside the district, since ETU scale-up was still underway in Port Loko. After Nov 29, 2014, 90% of patients with EVD in Port Loko received care at one of three ETUs (Maforki, Mathaska, and Lunsar) in the district. The Port Loko EVD Survivor Care Clinic was established on March 7, 2015, at the Baptist Eye Hospital Lunsar as a clinical partnership between Partners in Health (PIH), the PIH-supported EVD Survivor Network, GOAL Global, International Medical Corps, and Christian Blind Mission under the oversight of the Sierra Leone Ministry of Health and Sanitation (MoHS) District Health Management Team, with technical support from WHO.

Patient population

Survivors of EVD were identified via the MoHS-WHO registry of patients residing in Port Loko District, regardless of where originally treated. All were laboratory confirmed to have EVD through real-time RT-PCR testing on serum and discharged from ETUs after clinical improvement and a negative convalescent real-time RT-PCR. The registry was cross checked against the Sierra Leone Association for Ebola Survivors registry to generate a complete list (appendix). The EVD Survivor Network led community sensitisation regarding the establishment of the clinic. Survivors were systematically contacted by mobile phone by the clinic coordinator according to village of residence. Bus pick-ups were scheduled for each village and patients were assessed in the clinic irrespective of symptoms. We started with villages with resident survivors discharged in the remote past, until all villages were covered. As of Nov 12, 2015, the clinic had assessed 603 survivors of EVD residing in Port Loko at least once.

Data Collection
We extracted demographic and clinical data from patient charts (appendix) on the first 277 consecutive survivors of EVD assessed in the survivor clinic between March 7, 2015, and April 24, 2015. Eight patients were self-referred with ocular symptoms, but all would nevertheless have been identified through the village selections over the study period. Each patient received a clinical assessment and an eye examination, including visual acuity and slit-lamp examination. Patients with ocular symptoms, decreased visual acuity, or abnormalities on slit-lamp examination also received dilated fundoscopic assessment. Clinical data were entered into an electronic database and linked to two other datasets using the EVD laboratory number, and cross-checked with a unique patient identifier, sex, date of acute EVD testing, and patient residence or age. The additional datasets included: EVD surveillance data, which provided symptoms on presentation; and real-time RT-PCR and cycle threshold (an inversely correlated marker of viral load) results on the subset of patients who were diagnosed or cared for in a Port Loko ETU. The real-time RT-PCR assay used for testing changed after Feb 1, 2015 (appendix). After linkage, anonymised data were used for analyses. The study was approved by the Sierra Leone MoHS and Ethics and Scientific Review Committee.

Data Analysis
We used descriptive statistics to report features of acute EVD and clinical symptoms at the first convalescent visit. We used $\chi^2$ or Fisher’s exact test for categorical data and the $t$ test or Wilcoxon rank-sum test for continuous data to assess the relation between demographics (age, sex), cycle threshold at EVD diagnosis, duration of acute illness (days from symptom onset to the first negative real-time RT-PCR during acute EVD), self-reported symptoms of acute
EVD, and the absence or presence of each of four key sequelae present at the first convalescent visit: uveitis diagnosed on slit-lamp and dilated fundoscopic examination; new ocular symptom or diagnosis (including uveitis or conjunctivitis); new auditory symptoms (tinnitus, subjective hearing loss, aural fullness); and new arthralgias or diagnosis of arthritis. Symptoms were considered new if onset was either while in the ETU or after discharge. We explored all self-reported symptoms of acute EVD in the univariate analyses, excluding individual responses listed as missing or could not recall.

We used multiple logistic regression to delineate predictors of EVD sequelae. To preserve model parsimony, independent variables were chosen a priori to show severity of acute EVD (duration of acute illness and cycle threshold value at diagnosis\(^ {17} \)) and acute clinical features based on previously established links to post-infectious immunological sequelae (presence of red eyes [for ocular outcomes only], presence of diarrhoea\(^ {18} \)). The model was adjusted for age and sex.

We did a sensitivity analysis to determine if time period of cycle threshold value measurement (before or after real-time RT-PCR assay changed on Feb 1, 2015) affected the final models as an interaction effect. Analyses were done using SAS software, version 9.3 (SAS Institute).

**Role of Funding Source**

The research was funded in part by the Canadian Institutes of Health Research. The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The study leads (JGM, MJV) and corresponding author (SM) had full access to all the data in the study and had final responsibility for the decision to submit for publication.
RESULTS

Demographic and clinical features during acute EVD in the 277 survivors included in the study are presented in table 1. Just over half (n=163, 59%) were female, and the median age was 29 years (IQR 20–36). Median time from ETU discharge to first clinic visit was 121 days (IQR 82–151).

Symptoms and diagnoses at first convalescent clinic visit are presented in table 2. 210 (76%) patients reported arthralgias (joint pain or ache without swelling or evidence of an effusion on examination), predominantly of an oligoarthralgia pattern (one to four joints), with most (n=180, 86%) reporting bilateral joint involvement. One patient also had tenosynovitis.

Patients reported tinnitus (n=56, 20%), aural fullness (n=23, 8%), and subjective hearing loss (n=17, 6%), and 167 patients (60%) reported at least one ocular symptom. The self-reported median time from ETU discharge to onset of symptoms varied according to symptom: articular (1 week [IQR 0–4·3]; n=156), auditory (2 weeks [0–8·6]; n=51), and ocular (2 weeks [0–8·6]; n=119) symptoms. Symptoms began while in the ETU in 52 (25%) of 210 patients with auditory symptoms, 18 (27%) of 67 patients with articular symptoms, and 33 (20%) of 167 patients with ocular symptoms.

Based on slit-lamp and dilated fundoscopic examination, 50 (18%) patients were diagnosed with uveitis involving 68 eyes (46% anterior, 26% posterior, 3% intermediate uveitis, and 25% panuveitis). Uveitis was predominantly unilateral (64% of cases). Five (10%) patients with uveitis also had early cataracts, and their median age was 29 years (IQR 18–40) years compared
with 45 years (38–52·5) in the 16 patients with cataracts but without uveitis, although we did not have statistical power to assess for differences. Patients with uveitis developed ocular symptoms a median of 3 weeks (IQR 0·4–8·6; range 0–17·2) after ETU discharge. Each ocular symptom, compared with its absence, was associated with uveitis (appendix). The presence of blurry vision, light sensitivity, or itchy eye was 88·0% sensitive and 50·7% specific for underlying uveitis. Conjunctivitis was present in 31 (11%) of 277 patients.

Table 3 shows the univariate analyses of differences in demographic, clinical, and laboratory features during acute EVD and sequelae reported at the first convalescent visit. Other than arthralgia, which was more common in older persons, sequelae occurred with similar frequencies in both sexes and across age groups. On additional exploratory analysis, ocular symptoms during acute EVD were associated with subsequent ocular symptoms, but not specifically with uveitis. Acute symptoms such as gingival bleeding, red eyes, and blurry vision were more commonly reported among those with subsequent auditory or articular sequelae. A history of fever during acute EVD was associated with uveitis and with ocular symptoms in convalescence. Lower cycle threshold values at acute EVD presentation were significantly associated with uveitis in convalescence (median 22·4 [IQR 19·5–26·1] for those with uveitis versus 26·8 [23·5–29·0] for those without, p<0·0001) but not with arthralgias or auditory symptoms.

Data on cycle threshold value and duration of acute EVD were available for a subset of 190 patients who were either diagnosed or treated in ETUs in Port Loko. The demographic and clinical features of patients with and without laboratory data are shown in the appendix. Patients with missing laboratory data were not significantly different in age, sex, or symptoms
Table 4 shows the independent predictors of clinical sequelae on multivariable analyses. After adjusting for age, sex, and duration of acute illness, a lower cycle threshold value at acute presentation was independently associated with uveitis (adjusted odds ratio [aOR] 3.33, 95% CI 1.87–5.91, for every five-point decrease in cycle threshold) and with new onset ocular symptoms or diagnoses overall (aOR 3.04, 95% CI 1.87–4.94). Neither diarrhoea nor red eyes during acute EVD were associated with uveitis. Nor was diarrhoea during acute EVD associated with arthralgias or auditory sequelae. The association between cycle threshold value and EVD sequelae was not significantly affected by time period (before or after Feb 1, 2015).

**DISCUSSION**
We found that 50 (18%) patients who survived acute EVD developed uveitis, with ocular symptoms developing as early as during the ETU stay or as late as 17 weeks after discharge. Ebola viral load at the time of EVD diagnosis, which has also been associated with increased mortality in past studies, was the key independent predictor of ocular symptoms and specifically uveitis.17,19,20

Our findings generate important hypotheses regarding the pathogenesis of EVD sequelae. Ebola virus is rapidly cleared from most body fluids after resolution of acute disease,21–23 but might persist in immunologically privileged sanctuary sites.10,21 For example, viable Ebola virus was isolated from the aqueous humour at high concentrations (cycle threshold of 18·7) in a patient who developed severe sight-threatening uveitis 9 weeks after surviving acute EVD with high...
viraemia. The findings from this case and our findings from Sierra Leone support the hypothesis that virus persistence and replication in ocular chambers might play a part in the pathogenesis of uveitis in survivors of EVD. Furthermore, the fact that the patient was critically ill during his acute infection is consistent with the hypothesis that severe disease, which generally correlates with level of viraemia, might lead to virus persistence and long-term complications. The same survivor had prolonged persistence of virus in the semen (Crozier I, unpublished) and shedding of virus in semen has been reported up to 9 months after acute illness in survivors in Sierra Leone. Determination of the early predictors of persistence in semen and its relation to ocular complications would be of interest as a potentially less invasive marker of intraocular persistence.

Persistent immune activation, rather than direct viral cytopathic effect, has been postulated to lead to some post-EVD sequelae, although the processes are not necessarily mutually exclusive; immune activation might be driven by persistent virus replication or delayed antigen clearance in immune-privileged tissues. In our study, there was no association between the level of viraemia at acute EVD presentation and convalescent arthralgias or auditory symptoms, a finding which suggests a potentially different mechanism of non-ocular disease post-EVD. However, we cannot exclude the possibility that the lack of apparent association relates to how outcomes were measured (eg, in this study lack of audiometry) or defined (any joint involvement rather than specific distribution of joints), or to potential differences in levels of viraemia required to penetrate into various sites. IgG antibody titres were significantly higher in 29 survivors of EVD with arthralgias than in those without after the 1995 outbreak in Kikwit,
Democratic Republic of Congo, a finding consistent with persistent immune activation as the pathogenic mechanism. Unfortunately, we were not able to do antibody testing on our patients to assess relations between antibody titre and sequelae.

The prevalence of arthralgias in our series is similar to that noted in a survey of survivors of EVD in Guinea (87%) a median of 103 days into convalescence, but was higher than that reported in survivors of EVD at 21 months after the aforementioned Kikwit outbreak (48%) and up to 29 months after the 2007 Bundibugyo outbreak (25%), perhaps suggesting attenuation over time.

Systematic clinical care for survivors of EVD was absent during the early part of the current outbreak due to the overwhelming need to care for those with acute disease. Furthermore, in Sierra Leone, there are just two ophthalmologists and eight mid-level ophthalmological care-providers in the National Eye Health Program.

Systematic and universal access to ocular care for survivors of EVD is further restricted by lack of equipment (especially slit-lamps) and ocular medications, and by mobility of clinicians and patients. Addressing these barriers holds the potential to provide early diagnoses and treatment to survivors of EVD while strengthening eye care service delivery during health system reconstruction in west Africa. Our findings also signal the need for operational research into the feasibility and safety of syndromic treatment, including the use of topical steroids and cycloplegic agents, for survivors of EVD with clinical presentations consistent with uveitis, especially when slit-lamp examination is not possible.
A recent survey of 105 survivors of EVD in Guinea reported no ocular symptoms or hearing loss.\textsuperscript{14} The discrepancy with our results might be explained by the fact that the Guinea study only reported vision loss (noted in seven \([3\%]\) of our study participants) and that patients were not asked about tinnitus or aural fullness.\textsuperscript{14} In a survey of 81 survivors of EVD in Kenema, Sierra Leone, up to at least 4 months after resolution of acute disease, 42\% reported visual problems.\textsuperscript{15} The variability in prevalence of sequelae reinforces the need for systematic and harmonised clinical assessments (including physical and ocular examination) and data collection and analyses across west Africa.

Although various case reports and surveys have been published,\textsuperscript{14,15,24,27,28} the data reported here comprise the largest systematic study of survivors of EVD from the 2014–15 outbreak. Furthermore, unlike studies from previous clinical cohorts, the clinical data are drawn from a more representative sample of survivors, with all but eight (3\%) of the participants (who self-presented with ocular complaints) drawn from systematic inclusion of villages and assessed irrespective of symptoms. Furthermore, protocol-defined clinical charting and documentation provided structured data. Because all patients underwent a slit-lamp examination and, when indicated, a dilated fundoscopic examination, the prevalence of uveitis noted is a reliable estimate, with minimal selection and measurement bias. However, since our data are derived from baseline clinic visits done at a range of periods after the onset of disease, the frequencies of the symptoms recorded might not reflect those that would be noted if clinic visits were scheduled at uniform times after recovery from acute EVD.
There are important limitations to this study. First, its cross-sectional nature prohibits measurement of the true incidence of EVD sequelae. Second, we did not have a comparison group of patients not infected with Ebola virus, and thus cannot infer the relative risk of the sequelae against background rates from other aetiologies of arthralgias, auditory, or ocular symptoms endemic to west Africa. Third, the clinic was not equipped for audiometry to objectively assess hearing. Fourth, symptoms during acute EVD were drawn from surveillance data (collected at the time of acute infection) and via symptom recall during convalescence, which might have resulted in recall bias. The proportion of patients with fever and diarrhoea during acute EVD noted in our study is similar to the proportion reporting fever (84–89%) and diarrhoea (51–62%) in other smaller clinical cohorts of acute EVD.\textsuperscript{29–31} However, red eyes and severe symptoms such as bleeding (including gingival bleeding) were more common compared with data collected at the time of acute EVD diagnosis in other studies.\textsuperscript{29–31} The higher frequency of certain symptoms might also reflect new symptoms developing during acute illness but that were not present at the time of diagnosis. Fifth, the denominator of EVD survivors in the district might vary with inter-district migration, or willingness of survivors to disclose their current district of residence to the survivor network. Finally, laboratory data were missing for a subset of patients, although the primary outcomes (specifically uveitis) and other patient characteristics were similar to those for whom laboratory data were available.

Further research is needed to understand the pathogenesis of various EVD sequelae and to optimise treatment. The largest EVD outbreak in history has logically led to the largest number of survivors of EVD in history. These findings emphasise the importance of ongoing clinical follow-up and care of all patients, starting at discharge from an ETU, and underscore the urgent
need for the greater provision of ocular care as part of the strengthening of health systems in
west Africa.

RESEARCH IN CONTEXT

Evidence before this study

A MEDLINE search on the prevalence of post-Ebola virus disease (EVD) clinical sequelae using
search terms “Ebola” and “survivor OR sequelae OR convalescen*” yielded 227 unique citations
published by Nov 12, 2015. There were no language restrictions. Excluding case reports,
commentaries, and expert reviews, nine studies (case series, cohorts, and cross-sectional surveys)
provided clinical information post-Ebola sequelae, including three from the current west Africa
outbreak. Only six studies quantify the prevalence of clinical sequelae, of which four explored
early clinical sequelae in 240 survivors of Ebola within 3–4 months of convalescence. To date,
measurement of clinical sequelae was based on a clinical examination in only 57 patients (from
two studies of previous outbreaks), and only four patients in these studies received a complete
ophthalmological examination (visual acuity, slit-lamp, dilated fundoscopy). The largest (n=105)
published study of early EVD clinical sequelae was based on self-reported symptoms without a
clinical examination, with restricted questions on ocular and auditory symptoms that were self-
reported in none of the 105 survivors of EVD. None of the studies examined the predictors of
developing early or late EVD clinical sequelae.

Added value of this study

This study’s systematic clinical examination of EVD sequelae includes the largest representative
sample of west African survivors of EVD from the 2014–15 outbreak. Unlike studies from
previous clinical cohorts, the clinical and laboratory data were drawn from a more representative
sample, with detailed and protocol-defined clinical charting and clinical examination, and
provide information on the timing of sequelae. All patients underwent a slit-lamp examination,
and as indicated, a dilated fundoscopic examination, such that the prevalence of uveitis is a
reliable estimate with minimal selection and measurement bias. This study is also the first to
examine the clinical and laboratory predictors of EVD clinical sequelae in convalescence.

Implications of the available evidence
These findings signal an immediate need to systematically provide early clinical follow-up for all
survivors of EVD with particular attention paid to the potential for ocular complications. Further
research is needed to understand the pathologies underlying the various EVD sequelae.

CONTRIBUTORS
JGM, MJV, SMi, JCC, LM, SMa, and AR conceived of and designed the study. AKC, JGM,
DGB, and SMi did the literature search. JGM, JCC, SMi, LM, SMa, DEP, KD, SC, JS, SY,
RAF, AKC, and MJV developed the data collection tools. JGM, YM, APK, JCC, DEP, KD, SC,
APS, SMi, LM, TB, AR, and VP collected the data. RP, SMi, AKC, and RAF did the data
analysis. All authors contributed equally to the data interpretation. JGM, SMi, and AKC wrote
the first version of the manuscript. All authors contributed equally to the critical review and
editing of the manuscript.

DECLARATION OF INTERESTS
TO’D, AKC, and SMi report personal fees as clinical consultants from WHO during the conduct
of the study. VP, AR, and VW report personal fees from International Medical Corps, financed
through donor funding from USAID/OFDA and Children’s Investment Fund Foundation, during
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<table>
<thead>
<tr>
<th>Sex</th>
<th>Number of survivors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>163 (59%)</td>
</tr>
<tr>
<td>Male</td>
<td>114 (41%)</td>
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</table>

<table>
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<tr>
<th>Age group</th>
<th>Number of survivors (%)</th>
</tr>
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<tbody>
<tr>
<td>&lt;5 years</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>5-20 years</td>
<td>64 (23%)</td>
</tr>
<tr>
<td>21-40 years</td>
<td>158 (57%)</td>
</tr>
<tr>
<td>&gt;40 years</td>
<td>49 (18%)</td>
</tr>
</tbody>
</table>

**Self-reported acute EVD clinical features**

1. **Fever**: 255 (92%)
2. **Diarrhoea**: 211 (77%)
3. **Eye redness**: 207 (75%)

EVD = Ebola virus disease

1. At any time during acute EVD illness (before and within Ebola facility, including the Ebola treatment unit), self-reported; fever included history of fever within the 2 days before or temperature >38·0°C at the time of EVD case-investigation by the surveillance team or Ebola facility admission.
2. Missing data in 1 patient (cannot recall and not answered in the surveillance data)
3. Missing data on 2 patients (cannot recall and not answered from the surveillance data)
### Table 2. Ebola virus disease sequelae at first convalescent clinic visit in 277 survivors.

<table>
<thead>
<tr>
<th>Symptom / Syndrome</th>
<th>Number of Survivors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgias (symptom onset during ETU or after discharge)</td>
<td>210 (76%)</td>
</tr>
<tr>
<td>Any auditory symptoms (tinnitus, aural fullness, hearing loss) that started during ETU or after discharge</td>
<td>67 (24%)</td>
</tr>
<tr>
<td><strong>Ocular symptoms</strong> (onset during ETU or after discharge)</td>
<td>167 (60%)</td>
</tr>
<tr>
<td>Blurry vision</td>
<td>104 (38%)</td>
</tr>
<tr>
<td>Light sensitivity</td>
<td>86 (31%)</td>
</tr>
<tr>
<td>Itchy eye</td>
<td>86 (31%)</td>
</tr>
<tr>
<td>Tearing</td>
<td>79 (29%)</td>
</tr>
<tr>
<td>Pain</td>
<td>72 (26%)</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>68 (25%)</td>
</tr>
<tr>
<td>Floaters</td>
<td>46 (17%)</td>
</tr>
<tr>
<td>Redness</td>
<td>46 (17%)</td>
</tr>
<tr>
<td>Flashes of light</td>
<td>43 (16%)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>39 (14%)</td>
</tr>
<tr>
<td>Burning sensation</td>
<td>29 (11%)</td>
</tr>
<tr>
<td>Loss of vision</td>
<td>7 (3%)</td>
</tr>
<tr>
<td><strong>Uveitis diagnosed on slit-lamp and dilated fundoscopic examination</strong></td>
<td>50 (18%)</td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>31 (46%)</td>
</tr>
<tr>
<td>Posterior uveitis</td>
<td>18 (26%)</td>
</tr>
<tr>
<td>Intermediate uveitis</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Panuveitis</td>
<td>17 (25%)</td>
</tr>
</tbody>
</table>

ETU = Ebola treatment unit. *A patient could have >1 type of uveitis if both eyes were involved.
Table 3. Features of acute Ebola virus disease illness associated with convalescent symptoms and diagnoses at first survivor clinic visit.

<table>
<thead>
<tr>
<th></th>
<th>Uveitis</th>
<th>Ocular symptom or ocular diagnoses</th>
<th>Auditory symptoms</th>
<th>Arthralgias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (N=50)</td>
<td>No (N=227)</td>
<td>p</td>
<td>Yes (N=167)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>35 (70%)</td>
<td>128 (56%)</td>
<td>0.08</td>
<td>105 (63%)</td>
</tr>
<tr>
<td>Male</td>
<td>15 (30%)</td>
<td>99 (44%)</td>
<td></td>
<td>62 (37%)</td>
</tr>
<tr>
<td>Age-group (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>0 (0%)</td>
<td>6 (3%)</td>
<td>0.34</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>5-20</td>
<td>10 (20%)</td>
<td>54 (24%)</td>
<td></td>
<td>33 (20%)</td>
</tr>
<tr>
<td>21-40</td>
<td>34 (68%)</td>
<td>124 (55%)</td>
<td></td>
<td>98 (59%)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>6 (12%)</td>
<td>43 (19%)</td>
<td></td>
<td>33 (20%)</td>
</tr>
<tr>
<td>Acute EVD clinical features*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>50 (100%)</td>
<td>205 (90%)</td>
<td>0.02</td>
<td>161 (96%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>49 (98%)</td>
<td>221 (98%)</td>
<td>1.00</td>
<td>163 (98%)</td>
</tr>
<tr>
<td>Headache</td>
<td>48 (96%)</td>
<td>206 (91%)</td>
<td>0.38</td>
<td>187 (94%)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>47 (94%)</td>
<td>195 (86%)</td>
<td>0.13</td>
<td>149 (89%)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>40 (80%)</td>
<td>173 (77%)</td>
<td>0.60</td>
<td>134 (80%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>34 (68%)</td>
<td>158 (70%)</td>
<td>0.79</td>
<td>114 (68%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>41 (82%)</td>
<td>170 (75%)</td>
<td>0.31</td>
<td>130 (78%)</td>
</tr>
<tr>
<td>Blood in the stool</td>
<td>14 (28%)</td>
<td>61 (27%)</td>
<td>0.89</td>
<td>42 (25%)</td>
</tr>
</tbody>
</table>
Data are n (%) or median (IQR) unless otherwise stated. EVD = Ebola virus disease.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>n (%)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgias or arthralgias</td>
<td>47 (94%)</td>
<td>203 (90%)</td>
<td>0.44&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sore throat</td>
<td>14 (28%)</td>
<td>92 (41%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hiccups</td>
<td>18 (26%)</td>
<td>86 (36%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Red eyes</td>
<td>37 (74%)</td>
<td>170 (76%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Blurry vision</td>
<td>27 (54%)</td>
<td>136 (60%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Bleeding gums</td>
<td>11 (22%)</td>
<td>68 (30%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>2 (4%)</td>
<td>10 (4%)</td>
<td>1.00&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cycle threshold values at EVD diagnosis (N=190)</td>
<td>22.4 (19.5-26.1)</td>
<td>26.8 (23.5-29.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of acute EVD (N=190)</td>
<td>14 (9-19)</td>
<td>12 (9-17)</td>
<td>0.18&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup>Symptoms began during ETU stay or after discharge; diagnoses includes uveitis or conjunctivitis

<sup>2</sup>Symptoms began during ETU stay or after discharge

<sup>3</sup>Fisher’s exact test

<sup>4</sup>At anytime during acute EVD illness (before and within Ebola facility, including ETU), self-reported. Fever included history of fever within the 2 days prior to Ebola facility admission or temperature >38.0°C at the time of EVD case-investigation by the surveillance team. Acute EVD symptom data were missing in 32 of 4,155 responses (0.1%).

<sup>5</sup>All patients with uveitis had a history of fever during acute EVD

<sup>6</sup>A subset of patients had data on cycle-threshold and duration of acute EVD

<sup>7</sup>Wilcoxon rank-sum 2-sided test was used because the distribution of the data were skewed
Table 4. Features of acute Ebola virus disease associated with sequelae: multivariable analyses

<table>
<thead>
<tr>
<th></th>
<th>Uveitis</th>
<th>Any ocular symptom of diagnoses</th>
<th>Any auditory symptom</th>
<th>Arthralgias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Female (vs. male)</td>
<td>1.73 (0.73-4.09)</td>
<td>0.21</td>
<td>1.57 (0.81-3.07)</td>
<td>0.18</td>
</tr>
<tr>
<td>Age in years&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1.08 (0.92-1.26)</td>
<td>0.34</td>
<td>1.21 (1.07-1.37)</td>
<td>0.002</td>
</tr>
<tr>
<td>Self-reported acute EVD clinical features&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0.75 (0.28-1.99)</td>
<td>0.56</td>
<td>0.91 (0.41-1.99)</td>
<td>0.81</td>
</tr>
<tr>
<td>Red eyes</td>
<td>0.74 (0.30-1.79)</td>
<td>0.50</td>
<td>1.52 (0.73-3.17)</td>
<td>0.26</td>
</tr>
<tr>
<td>Cycle threshold values at EVD diagnosis (N=190)&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>3.33 (1.87-5.91)</td>
<td>&lt;0.0001</td>
<td>3.04 (1.87-4.94)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of acute EVD (N=190)&lt;sup&gt;5,7&lt;/sup&gt;</td>
<td>1.11 (0.84-1.46)</td>
<td>0.48</td>
<td>1.01 (0.80-1.27)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

EVD (Ebola virus disease). OR (odds ratio).

<sup>1</sup>Symptoms began during ETU stay or after discharge; diagnoses include uveitis or conjunctivitis.

<sup>2</sup>Symptoms began during ETU stay or after discharge.

<sup>3</sup>For every 5-year increase in age

<sup>4</sup>At anytime during acute EVD illness (before and within Ebola facility, including ETU), self-reported. Fever included history of fever within the 2 days prior to Ebola facility admission or temperature >38.0°C at the time of EVD case-investigation by the surveillance team.

<sup>5</sup>Restricted to subset of the population with cycle threshold values and data on duration of acute EVD.

<sup>6</sup>For every 5-point decrease in the cycle threshold value.

<sup>7</sup>For every increase in 5 days (from symptom onset to first negative EVD RT-PCR during acute EVD infection).
REFERENCES


