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Ebola Survivors are not at Increased Risk for Gynecologic Surgeries

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ABSTRACT

As the result of multiple signs and symptoms, and complications observed among survivors of the Ebola virus disease (EVD), there is an assumption that survivors might experience perturbations within their clotting parameters. This may eventually lead to increased bleeding time, predisposing them to increased risk for surgical complications. This study aimed to comparatively review specific intra-operative parameters such as uterine fibroids and polyps among a number of EVD survivors and non-survivors undergoing elective gynecologic surgeries at Redemption Hospital, a tertiary specialized referral hospital located within one of the EVD hotspots, in Liberia from January to October 2016. A case-control study was conducted wherein cases were referred from the Partnership for Research on Vaccines and Infectious Diseases in Liberia (PREVAIL), an EVD clinical trial platform, while controls were sampled from the general patient population, at Redemption Hospital. The controls were matched based on age, employment status and parity. All surgeries were performed by single surgeon based on a surgical checklist that included designated intra- and post-operative parameters. Statistical analysis such as counts, percentiles, confidence intervals and relative risks were performed to assess the differences between the cases and controls, respectively. Survivors were between the ages of 42 years and 44 years for controls with an average interval between discharge from the Ebola Treatment Unit (ETU) and surgical intervention of greater than one year. The median duration of surgical procedure was 60 minutes and blood loss of 250 ml in both groups. Besides the relative risks (RR) of receiving antibiotics for more than 3 days of 1.5 (85.7% vs. 57.1%) and hospitalization of more than 7 days of 0.25 (14% vs. 57%) for survivors as compared to controls, most of the indicators were not significantly different. The findings revealed that EVD survivors who present with benign tumors such as uterine fibroids, polyps, or adenomyosis, requiring elective uterine surgery such as myomectomy and/or hysterectomy are generally not at increased risk of surgical complications because most of the indicators (hospitalization, blood loss, antibiotics, etc.) were not significantly different between the two groups. Findings from this study may potentially revise the approaches used by gynecologists and general surgeons during encounters and/or interventions with patient(s) concerning emerging infectious diseases (EIDs).

Keywords: Ebola Virus Disease (EVD); Emerging Infectious Diseases (EIDs); Ebola Survivors; Uterine Surgery; Females; Liberia.

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INTRODUCTION

The Ebola virus disease (EVD) formerly known as the Ebola hemorrhagic disease based on its peculiar bleeding patterns was first discovered in 1976 [1-2]. Initially, outbreaks were confined to the peripheral of East Africa on the margins of the Ebola River, from which the genus Ebolavirus got its name [1-2]. Up until 2014, the history of EVD was marked by a vintage pattern of spread. However, the most recent West African outbreaks showed a divergence due to the distance and the lack of identifiable vectors which could have explained its emergence and spread into Guinea, Liberia and Sierra Leone [1-2].

The West African Ebola outbreaks was considered the largest and deadliest with the capacity to infect large proportion of urban populations unlike previously recorded outbreaks [3]. It is estimated that over 28,000 cases were reported with over 11,000 deaths [3]. The decline in the number of fatality rate (CFR) from 90% to 50% in the West African outbreaks resulted in the creation of the largest pool of survivors registered to-date [3]. Liberia, Guinea and Sierra Leone are underdeveloped countries with fragmented and under-sourced health systems due to decades of political and economic instability [4]. The emergence of the Ebola virus disease further contributed to the total collapse of the health systems.

Ebola survivors deal with series of medical and surgical challenges [5] most of which require specialists and sub-specialists care as an added stressor on these highly fragile and emergent health systems. However, one of the most significant challenges to accessing quality care for survivors is stigma. Also, the lack of scientific literature on the most appropriate management of these pathologies poses a serious challenge. The World Health Organization (WHO) recently revised its guide on the intervals between serum negative tests and the commencement of sexual activity for male survivors; extending it from three (3) to twelve (12) months based on publications of viral persistence in seminal fluid of male survivors [6-9]. These findings preceded a case of confirmed sexual transmission of the Ebola virus in Liberia [7-9]. This event propelled the formation of series of hypothesis which are currently being tested.

The surgical management of conditions which predates the onset of EVD is pertinent to the improvement of the quality and expectancy of life for these survivors. Most presently, there are no guidelines or interventions protocols on the most appropriate care for survivors with elective surgical conditions, an issue that is complicated by the discovery of viral residues in immune privileged sites such as semen, aqueous humor of the eye and the cerebrospinal fluid [6-9]. Therefore, most females continue to suffer the agony of menorrhagia and related symptoms which have compromised their quality of life as survivors.

A number of medical and/or surgical complications have been reported in survivors. These findings have further confounded the conclusion that EVD survivors constitute a high-risk cohort for elective surgical interventions. As a result, most female EVD survivors who might have had pre-existing uterine pathologies such as fibroid and polyps continue to suffer from sequelae such as anemia, abdominal distension, and sexual abstinence due to irregular vaginal bleeding. These conditions significantly affect the quality of life of the survivor and gravely affected their abilities to cope in an already stigmatized environment.

So far, no study has compared the surgical outcomes of EVD survivors undergoing elective uterine surgical procedures and non-survivors matched by age and surgical procedures. This is primarily due to uncertainties regarding the impact of the procedures on the hemodynamic and immunologic components of EVD survivors.

Therefore, the specific aim of this case-control study was to review and further compare the intra- and post-operative parameters (e.g., blood loss, hemoglobin, hospitalization, among a designated quantity of matched EVD survivors and non-survivors (e.g., age, parity, employment status, etc.) undergoing elective gynecological surgical procedures at Redemption Hospital, a tertiary specialized referral hospital located within one of the EVD hotspots in Liberia. As such, this is the first published study, to our knowledge, to compare these gynecological parameters among matched EVD survivors and controls, especially from an EVD affected country.

METHODOLOGY

This is a case-control study with cases selected from referrals by the Partnership for Research on Vaccines and Infectious Diseases in Liberia (PREVAIL), a clinical research partnership between the Ministry of Health (MoH) of the Republic of Liberia (RL) and the National Institutes of Health (NIH) of the United States Department of Health and Human Services (U.S. DHHS), to the gynecological outpatient department at the Redemption Hospital, a tertiary public referral hospital situated within one of the EVD hotspots in Monrovia, the capital city of Liberia. Ebola survivors were primarily received through the clinical referral system established between the Liberian Ministry of Health and PREVAIL. The

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control cases were identified from the pool of gynecological patients seen at the department's outpatient services. Cases and controls were matched according to age, parity, and employment status.

The EVD survivors, referred to Redemption Hospital, were consenting female adults enrolled in a large national study, a Longitudinal Study of Ebola Sequelae in Liberia, that obtained ethical approval from the National Research Ethics Board (NREB) of Liberia [10]. Administrative approval was obtained from Redemption Hospital for matched historical control from the institutional database.

Detailed descriptions of the EVD outbreaks and related epidemiology and mitigation strategies within the sub-region, including the national EVD studies that were conducted in Liberia (e.g., clinical trials on EVD vaccines, clinical research on longitudinal study of EVD sequelae, etc.) have been extensively published elsewhere [10-13].

The main type of intervention was surgical removal of benign uterine growths which could either be myomectomy and/or hysterectomy. The hysterectomy was performed based on the patient's request and reproductive status. All surgical interventions were performed by an experienced gynecologist to minimize intra-operative variations.

Statistical Analysis

The controls were randomized and matched with survivors based on surgical procedures, age, parity and employment status. The median and quartiles were used to summarize continuous variables such as age, estimated blood loss (EBL), days of antibiotics administration, length of hospital admission, duration of surgery, and post-surgical hemoglobin levels.

Counts and percentiles were used to summarize categorical variables such as employment status, parity and the administration of transfusions. Confidence intervals (CI) for differences between EVD survivors and controls for continuous variables were computed using the bootstrap while exact methods were used for categorical variables. All statistical calculations were conducted using the statistical software system R, version 3.2.3. The bootstrap package was used for constructing bootstrap confidence intervals (using studentized intervals).

The relative risk (RR) was also computed for the following surgical parameters: post-surgical hemoglobin less than ten grams per deciliter (10g/dl), antibiotic administration greater than three (3) days and hospital admission greater than seven (7) days. The study excluded females with positive pregnancy tests.

RESULTS

Baseline and Demographic Characteristics

A total of fourteen females underwent elective uterine surgeries during the study period, seven (7) EVD survivors and seven (7) controls. Myomectomies were performed on thirteen (13) patients and hysterectomies on one (1) patient. None of the participants were pregnant and there were no statistically significant differences between survivors and controls.

The median age for survivors to seek surgical intervention were between 42 years and 44 years for controls. The average interval between discharge from the Ebola Treatment Unit (ETU) and surgical intervention was greater than 1 year for all survivors. Most of the survivors were unemployed (71%) while the controls were more likely to be self-employed (43%) or employed (14%) females.

However, the study recorded some differences in terms of the median age at which survivors and controls sought surgical interventions. The median age for survivors was 42 years while those of controls were 44 years. This difference could be explained by the intrinsic urge created as the result of surviving Ebola disease to report any abnormality which might have arisen due to or complicated by being infected. Another variation observed, though not statistically significant, is the high unemployment rate recorded in Ebola survivors. As this study was conducted a year after their discharged from the infectious unit, the issue of stigma and the concept which view Ebola survivors as socially disenfranchised was pivotal in shifting a higher percent of these survivors into unemployment.

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Table 1: Baseline demographic and clinical characteristics of study participants. None of the participants were pregnant and there were no statistically significant differences between survivors and controls.

	Survivors (N=7)	Controls (N=7)	All Participants (N=14)
Age: Median (Quartiles)	42 (36.5, 43)	44 (37, 46)	42.5 (36.3, 45.5)
Parity: Count (Percent)			
Nulligravida	0 (0%)	0 (0%)	0 (0%)
Nulliparous	1 (14%)	1 (14%)	2 (14%)
Primiparous	1 (14%)	2 (29%)	3 (21%)
Multiparous	3 (43%)	1 (14%)	4 (29%)
Grand Multiparous	2 (29%)	3 (43%)	5 (36%)
Employment: Count (Percent)			
Unemployed	5 (71%)	3 (43%)	8 (57%)
Self-employed	2 (29%)	3 (43%)	5 (36%)
Employed	0 (0%)	1 (14%)	1 (7%)

Intra-Operative Outcomes of Participants: Estimated Blood Loss (EBL) and Duration of Surgery

The median duration of the surgical procedures was 60 minutes for both EVD survivors and controls, and the median volume of estimated blood loss (EBL) was 250 ml in both groups. The median post-operative hemoglobin was 10 g/dl in both groups. The Relative Risk (RR) of Ebola survivors receiving post-operative antibiotics for more than 3 days was 1.5 (85.7% vs. 57.1%). However, the RR for hospitalization for more than 7 days was 0.25 for EVD survivors as compared to the controls (14% vs. 57%). None of the differences were statistically significant and the confidence intervals (CI) for the mean differences and RR were very wide due to the small sample size.

These indicators did not significantly differ in terms of statistics for survivors and controls. The two indicators are considered the core of the study, which would inform the decisions of surgeons and the medical community involved with the management of Ebola survivors.

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Table 2: Intra-operative outcomes of participants: data summarized by the median and quartiles. None of the participants needed additional anesthetics or intra-operative blood transfusions. There were no statistically significant differences between survivors and controls. Studentized confidence intervals are presented and were generated using the bootstrap.

	Survivors (N=7)	Controls (N=7)	All Participants (N=14)	95% CI for Difference
Estimated Blood Loss (ml)	250 (250, 325)	250 (250, 325)	250 (250, 362.5)	(-124, 106)
Duration of Surgery (minutes)	60 (47.5, 65)	60 (50, 70)	60 (46.3, 67.5)	(-22, 16)

Intra-operative outcomes of participants: Post-Surgical Outcomes

This study included four clinical parameters to measure post operative recovery of study participants. The post-surgical indicators were Hemoglobin (Hb), length of antibiotic administration, excluding prophylaxis, transfusion of typed and crossed blood, and the length of hospital stay post-surgery. There were no statistically significant need for post-operative blood transfusion between Ebola survivors and controls. However, a survivor was transfused post-operatively with one unit of typed and crossed matched blood.

Table 3: Post-operative outcomes of participants: data summarized by the median and quartiles or counts and percent. No participants experienced wound dehiscence. There were no statistically significant differences between survivors and controls. Studentized confidence intervals are presented and were generated using the bootstrap (unless otherwise noted).

	Survivors (N=7)	Controls (N=7)	All Participants (N=14)	95% CI for Difference
Hemoglobin (g/dl)	10 (10, 11.5)	10 (9.3, 10.25)	10 (10, 10.9)	(-1.8, 2.9)
Length of Antibiotic Administration (days)	4 (4, 4)	4 (3, 4.5)	4(3.3, 4)	(-1.1, 0.9)
Transfusion Administered	1 (14.3%)	0 (0%)	1 (7.1%)	(0, 39)
Length of Post-Operative Stay (days)	7 (7, 7)	12 (6, 13)	7 (7, 11)	(-8.6, 6.1)

DISCUSSION

There are over 10,000 survivors of the EVD and a large number of medical complications have been reported in survivors, including muscle and joint problems, eye problems and mental health issues [3, 5, 8-10]. The Ebola virus persists in some body fluids, including semen [7-10]. Therefore, Ebola survivors need comprehensive medical care. Medical care in this patient population is further complicated by the lack of a scientific literature on the outcomes of various medical therapies and drugs on the perturbed immune and hematological parameters of these patients [3, 5, 10]. This situation is more pronounced in EVD survivors who may have survived with conditions such uterine fibroids, polyps, adenomyosis, and endometriosis which predate the onset of the EVD as there are tremendous unmet medical needs in the regions most impacted by the EVD epidemic.

The literature is silent on the surgical outcomes and appropriateness of the types of elective operative interventions such as myomectomy and hysterectomy among EVD survivors. Consequently, female Ebola survivors continue to encounter obstacles among clinicians as they seek operative interventions [5]. Subsequently, most female survivors choose to suffer in silence instead of experiencing further stigmatization and neglect. Concomitantly, these EVD female survivors are also engulfed in a state of confusion and uncertainty during the process of surgical consents based on the limitations of surgeons and literature to provide information on the expected outcomes of the operative complications [3, 5].

The results and information provided from this study may serve as a reassurance to EVD female survivors with the diagnoses of benign uterine conditions which may require surgery to approach their primary care providers or gynecologists as the risks associated with these procedures are similar to that of non-Ebola survivors because most of the study indicators (hospitalization, blood loss, antibiotics, etc.) were not significantly different between the two groups. Secondly, this study provides relevant information to primary care providers, gynecologists and the general scientific audience regarding the lack of significant differences in the surgical outcomes of elective uterine procedures among EVD survivors and non-survivors; hence these results should help stimulate a change in the attitudes and approaches towards these socially stigmatized EVD female survivors.

Finally, it is the study team's desire that this publication will ignite the flames of interest by scientists and healthcare providers to initiate similar studies using larger sample sizes and/or different surgical interventions.

LIMITATIONS

A significant limitation of the present study is the small sample size which was based on the number and willingness of EVD female survivors to consent to elective uterine procedures. Secondly, this study provided information as it relates only to surgical parameters, measurable within the confines of the hospital. Information on the indications for quality of life (QoL) were also not measured.

ETHICAL APPROVAL

Ethical approval for the PREVAIL EVD study was obtained from the National Research Ethical Board of Liberia (NREB), Approval Code: NREB-002.18.

REFERENCES

[1] World Health Organization. Ebola Hemorrhagic fever in Zaire, 1976 [958 KB, 24 pages]. Report of an International Convention. Bull World Health Organ. 1978; 56(2):271-93.

[2] World Health Organization. Ebola haemorrhagic fever in Sudan, 1976. Report of a WHO/International Study Team. Bull World Health Organ. 1978;56(2):247-70

[3] World Health Organization. Clinical care for survivors of Ebola virus disease interim guidance. WHO/EVD/OHE/PED/Rev.2. April, 2016

[4] International Monetary Fund. World economic outlook database, April 2017.

[5] World Health Organization. WHO meeting on survivors of Ebola virus disease: Clinical care of survivors. Available from: http://apps.who.int/iris/bit-stream/10665/204126/1/9789241509794_eng.pdf.

[6] Deen GF, Broutet N, Xu W, Knust B, Sesay FR, McDonald SLR. Ebola RNA Persistence in semen of Ebola Virus Disease Survivors- Final report. N Engl J Med. 2017; 377: 1428-1437.

[7] Soka MJ, Choi MJ, Baller A, White S, Rogers E, Purpura LJ. Prevention of sexual transmission of Ebola in Liberia through a national semen testing and counseling programme for survivors: an analysis of Ebola virus RNA results and behavioral data. Lancet Glob Health. 2016;4:e736-e743.

[8] Jagadesh S, Seyalie S, Fatoma R, Sesay F, Sahr F, et al. Disability among Ebola Survivors and

GET Journal of Biosecurity and One Health (2022) 1, 34-40.
DOI:10.36108/GJOBOH/2202.10.0140

their close contacts in Sierra Leone: A Retrospective Case Controlled Cohort Study. Clin Infect Dis. 2017 Aug 20 doi: 10.1093/cid/cix705. [Epub ahead of print]

[9] Tiffany A, Vetter P, Miattia J, Dayer JA, Bartsch M et al.Ebola Virus Disease Complications as experienced by Survivors in Sierra Leone. Clin Infect Dis. 2016 ; 62(11): 1360-1366.

[10] PREVAIL II Writing Group; Multi-National PREVAIL II Study Team, Davey RT, Dodd L, Proschan MA, Neaton J, et al.. A Randomized, Controlled Trial of ZMapp for Ebola Virus Infection. N Engl J Med. 2016; 375(15):1448-1456.

[11] Kennedy SB, Neaton JD, Lane HC, Kieh MWS, Massaquoi MBF, Touchette NA, et al. Implementation of an Ebola Virus Disease (EVD) Vaccine Clinical Trial during the Ebola Epidemic in Liberia: Designs, Procedures and Challenges. Clin Trials. 2016 ; 13(1):49-56. DOI: 10.1177/1740774515621037.

[12] Kennedy SB, Bolay F, Kieh M, Grandits G, Badio M, Ballou R, et al. Phase 2 Placebo-Controlled Trial of Two Vaccines to Prevent Ebola in Liberia. N Eng J Med. 2017; 377:1438-47. DoI10.1056/NEJMoa1614067.

[13] Bolay F, Grantis G, Lane HC, Kennedy SB, Johnson M, Fallah MP, et al. . PREVAIL I Cluster Vaccination Study with rVSV∆G-ZEBOV-GP as part of A Public Health Response in Liberia. J Infect Dis. 2019; 219(10): 1635-41