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Co-infection of Lassa Fever with Viral Hepatitis: A Cross-Sectional Analysis of Patients in a Federal Medical Centre in Southwestern Nigeria

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Abstract

Context: Lassa fever (LF) and viral hepatitis diseases are major public health threats in Nigeria, but their co-infection patterns remain unclear despite shared risks and overlapping symptoms. Objective: We studied the seroprevalence of Hepatitis B virus (HBV) and Hepatitis C virus (HCV) in LF patients and analysed demographic, clinical, and outcome disparities.
Materials and Methods: We conducted a hospital-based cross-sectional study involving 215 patients at the Federal Medical Centre, Owo, Ondo State, Nigeria, from August to December 2023. Consecutive patients with suspected LF were confirmed via Altona RealStar Lassa fever virus RT-PCR, while HBV and HCV were detected from serum samples using serological assays. Demographic, clinical, and mortality data were compared between co-infected and mono-infected groups using chi-square tests at a significance level of $p < 0.05$.
Results: Among 215 suspected cases, 37 (17.2%) were confirmed Lassa fever (LF). Confirmed cases primarily involved young adults aged 20–39 years (56.7%, 21/37) and males (67.5%, 25/37; $p = 0.03$). HBV prevalence was 5.4% (2/37, aged 20–39), and HCV prevalence was 2.7% (1/37, aged 40–59). One LF–HBV co-infection (2.7%) occurred in a male aged 20–39 years, with no LF–HCV co-infections or triple infections (LF+HBV+HCV) observed. Mortality was highest in LF cases (16.2%, 6/37), including one HCV-associated death (100%).
Conclusion: HBV and HCV co-infections are uncommon in Lassa fever cases and do not notably affect mortality; however, the disease is highly lethal, particularly in young adult males, highlighting the importance of improved prevention, early diagnosis, and further research.

Keywords: Lassa fever, Hepatitis B virus, Hepatitis C virus, Co-infection, Seroprevalence, Nigeria

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Introduction

Lassa fever (LF) is a severe hemorrhagic fever that has been largely neglected since its discovery[1]. Lassa fever remains endemic in the West African region, including Ghana, Benin, Côte d'Ivoire, Mali, Sierra Leone, Guinea, Liberia, and Nigeria, causing sporadic infections and periodic outbreaks[2]. Lassa

virus is primarily transmitted to humans via synanthropic rodents, such as Mastomys natalensis, M. erythroleucus, Hylomyscus pamfi, Rattus rattus, and Mus musculus[1,2]. Consequently, most human infections result from rodent-to-human transmission, with human-to-human spread occurring less frequently[3,4].

Annually, LF infects 300,000–500,000 people in West Africa[5], with a 15–33% mortality rate in hospitalised cases, rising to 50% during epidemics[6]. Since 2016, Nigeria has experienced rising morbidity and mortality from annual viral hemorrhagic fever outbreaks, primarily caused by LF[7,8]. Reported LF cases increased from 273 in 2016 to 3,728 in 2019, with Edo and Ondo states being the most affected[9]. From 2018 to 2020, LF further expanded geographically across Nigerian states, accompanied by an increasing case density[10]. In early 2023, Nigeria faced a significant LF epidemic, recording 877 confirmed cases and 152 deaths (17% CFR) within the first 15 weeks[11,12]. Climate and land use changes are projected to increase the number of at-risk populations in the coming decades[13]. These epidemiological trends and future projections underscore the urgent need for strengthened surveillance, prevention, and control strategies in endemic regions.

Currently, no approved treatments or vaccines exist for LF, although several candidates are in development.[14,15] Furthermore, no field-ready, approved diagnostic is available, which limits surveillance capacity[16,17]. Thus, LF is classified as a WHO research and development (R&D) Blueprint priority pathogen due to its epidemic potential and the lack of effective countermeasures, prompting accelerated research[18]. Critical gaps in LF's epidemiology, immunology, and pathogenesis, combined with a lack of effective medical solutions, underscore the need for intensified R&D[19]. Strengthening surveillance, prevention, and control requires high-quality biological samples from LF patients and convalescents[20]; however, challenges, including constrained local collection, poor coordination, inadequate service capacity, and demand-supply disconnect, continue to limit specimen availability in Nigeria and beyond[20].

Additionally, five distinct hepatotropic viruses: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV)collectively drive viral hepatitis as a persistent global public health burden[18]. Among these, HBV and HCV account for roughly 90% of hepatitis-related deaths, contributing substantially to the overall disease burden and morbidity[21]. Their transmission and communal spread occur through contact with blood or body fluids, unscreened transfusions, unprotected sex, mother-to-child transmission, and the use of contaminated instruments[22]. If left untreated, both HBV and HCV can progress to chronic hepatitis, cirrhosis, and hepatocellular carcinoma, leading to substantial morbidity and mortality[23]. Together, HBV and HCV affect more than 350 million people worldwide[24], with Sub-Saharan Africa still recognised as a hepatitis hotspot and Nigeria remaining highly endemic[25,26].

Endemic viral hepatitis and hemorrhagic fevers, including LF, persist in Nigeria; however, their co-infection dynamics and burden are understudied[25,26]. To address this gap, this study assessed the seroprevalence and demographic correlates of HBV and HCV among confirmed LF patients in Owo, Ondo State, Nigeria. Findings from this study will inform prevention and control strategies for potential co-occurrences of endemic viral diseases.

Materials and methods

Study Design, Place, Duration, and Population

A hospital-based cross-sectional study was conducted from August to December 2023 at the Federal Medical Centre, Owo (FMC Owo), a designated Lassa fever treatment centre in Ondo State, Southwest Nigeria. A total of 215 consecutive patients (adults and children) presenting with clinically suspected Lassa fever were enrolled, and clinical samples were collected and analysed.

Inclusion and Exclusion Criteria

Each subject was enrolled if he or she was ≥18 years old or, if under 18, had provided informed assent with parental or guardian consent. Exclusion criteria included the inability to consent, health conditions that precluded blood collection, or unreliable follow-up prospects. After informed consent, each participant underwent a clinical examination, during which demographics, medical history, clinical measurements, treatments, and symptoms were collected. LASV1 participants received additional assessments at 4 and 8 weeks to track disease progression. Trained personnel recorded all de-

identified information using unique IDs. Participants who consented but were unable to provide adequate samples were classified as collection failures and were not resampled. All samples were assigned unique codes before transferring to the FMCO molecular laboratory for storage.

Sample Size Determination

The sample size was calculated using the formula proposed by Pourhoseingholi et al.[27]:

N=t^2 p(1-p)/m^2
where N = sample size, p = prevalence rate (0.05), m = margin of error (0.05), and t = level confidence at 95% (1.96).
N=[(1.96)^2×0.05(1-0.05)]\/(0.05)^2= 72.99 ≈ 73

Therefore, based on the reported 5% LF prevalence in Ondo State,[28] The required sample size for this study was 73 cases; however, 215 patients were enrolled.

Lassa Fever: Diagnostic Protocol and Patient Management

The clinical suspects at FMCO facilities underwent a systematic assessment using national guidelines, integrating history, examinations, and laboratory tests[29]. Laboratory confirmation included the Altona RealStar LASV qRT-PCR 2.0 test (Hamburg, Germany: Altona Diagnostics GmbH), the gold standard for LASV RNA detection prior to eligibility screening[30].

LV RNA Inactivation

Samples (70 µL) were added to lysis buffer tubes containing lysis buffer, mixed, and incubated for 10 min. Absolute ethanol (560 µL) was then added, with pipette tips changed between samples to prevent cross-contamination. Tubes were decontaminated before RNA extraction[28].

RNA Extraction

RNA extraction was performed by transferring inactivated samples to labelled spin columns and centrifuging at 8,000 rpm for 1 min. The collection tubes were then replaced, and the columns were washed with 500µL of Wash buffer 1 (8,000 rpm) followed by Wash buffer 2 (14,000 rpm, 3 min, repeated once). The columns were dried by centrifugation at 14,000 rpm for 10 minutes, and the RNA was eluted using 60 µL of elution buffer for 1 minute, followed by an additional 1-minute incubation. The sample was then centrifuged at 8,000 rpm to collect the RNA[28].

PCR Detection of Lassa Fever

The RealStar® Lassa Virus RT-PCR Kit 2.0 (Altona Diagnostics GmbH, Hamburg, Germany) was used according to the manufacturer's instructions. The kit included a GPC gene-specific positive control (0.5µM OWS-1-fwd primer: GCGCACCGG GGATCCTAGGC) and an L gene-specific positive control (0.5µM OWS-1000-rev primer: AGCATGTCACAAAAYTCYTCATCATG). For each reaction, 20 µL of Master G and Master L reagents were pipetted into G- and L-labelled tubes, respectively[31]. This was followed by the addition of 1 µL internal control, 10 µL of extracted RNA, and positive controls to the corresponding G/L tubes. RT-PCR was performed on a Qiagen platform (Hilden, Germany) with reverse transcription at 50°C for 30 minutes followed by 45 amplification cycles—including denaturation at 95°C for 15 min, activation at 95°C for 30 sec, annealing at 55°C, 30 sec), elongation at 72°C for 30 sec, and extension at 30°C for 30 sec—on Eppendorf thermocycler[32].

HBsAg and HCVcag detection using a rapid test kit

HBsAg and HCV core antigen were detected using the SWE-CARE® Rapid diagnostic kit (Nantong Diagnosis Biotechnology Co., Ltd, China). Centrifuged plasma (70–100 µl) was applied to the test device, and results were interpreted after 10–20 minutes as positive (both T and C bands), negative (C band only), or invalid (no C band; repeat test)[33].

Statistical Analysis

Data were analysed using SPSS v23.0, with results expressed as mean ± standard deviation (SD). Associations between variables were assessed using chi-square tests. Statistical significance was defined as $p < 0.05$ (95% confidence level).

Ethical approval

Ethical approval (FMC/OW/380/VOL. CLXXXVII/142) for this research was issued by the Health Research Ethics Committee of Federal Medical Centre, Owo, Nigeria, before the study commencement. Hence, all procedures in this study adhered to the international ethical standards (Declaration of Helsinki, ISO 20387:2019, ICH, WHO GCLP).

Results

Socio-demographic and clinical characteristics

This study enrolled 215 participants (mean age 37.2 ± 20.5 years), including 89 males (44.1%) and 126 females (58.6%) (Table 1). Over one-third of the participants were aged 20–39 years (38.1%), had no formal education (38.6%), or worked as crop farmers (31.2%) (Table 1). Observed symptoms included body aches/headaches (37.3%), fatigue/malaise (24.4%), abdominal pain (19.7%), rashes (16.9%), and nausea/vomiting (1.6%).

Seroprevalence of HBV, HCV among Lassa fever patients

The overall LF prevalence was 17.2% (37/215) (Table 2). Of the 37 LF-positive individuals, 2/37 (5.4%) and 1/37 (2.7%) were positive for Immunoglobulin M (IgM) antibodies against HBV and HCV, respectively (Table 2). The prevalence of LF infection was higher among males (67.5%; 25/37 cases) than among females (44.4%; 12/37 cases), and individuals aged 20–39 years (56.7%, n = 21/37) were the most affected age group (Table 2). Moreover, there are significant associations between the occurrence of Lassa fever, age, and sex ($P < 0.05$)

Table 1: Socio-demographic and clinical characteristics of participants (n=215)

Variable	Description	Frequency	Percentage(%)
Sex	Female	89	41.4
	Male	126	58.6
Age (Years)	0-19	46	21.4
	20-39	82	38.1
	40-59	61	28.4
	60-79	17	7.9
	80-99	9	4.2
Mean age (±SD)	37.2±20.5		
Education	None	83	38.6
	Primary	57	26.5
	Secondary	48	22.3
	College/University	27	12.6
Occupation	Crop Farming	67	31.2
	Employed	29	13.5
	Hunter	24	11.2
	Livestock farming	13	6
	Others	27	12.6
	Student	11	5.1
	Trading	44	20.5
Signs/Symptoms	Headache	58	26.9
	Fatigue/Malaise	35	16.2
	Rashes	54	16.9
	Nausea/Vomiting	5	1.6
	Abdominal pain	63	19.7

Table 2: Seroprevalence of single infection of HBV, HCV among Lassa fever patients and the respective co-infections (n=37)

Variable	Lassa Fever(%)	HBV(%)	HCV(%)	LF + HBV(%)	LF + HCV(%)	LF + HBV + HCV(%)	p-value
Age (Years)							
0-19	5 (13.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
20-39	21(56.7)	2(5.4)	0 (0)	1(2.7)	0 (0)	0 (0)	
40-59	9 (24.3)	0 (0)	1 (2.7)	0 (0)	0 (0)	0 (0)	< 0.001*
60-79	2 (5.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
80-99	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Sex							
Female	12 (32.7)	1(2.7)	0 (0)	0 (0)	0 (0)	0 (0)	
Male	25 (67.6)	1(2.7)	1(2.7)	0 (0)	0 (0)	0 (0)	0.03*
Outcome							
Dead	6(16.2)	0 (0)	1 (2.7)	0 (0)	0 (0)	0 (0)	0.038*
Alive	31(83.8)	2(5.4)	0 (0)	1 (2.7)	0 (0)	0 (0)	

Table 3: Common symptoms of Lassa Fever, Hepatitis B, Hepatitis B and co-infection among the 37 confirmed Lassa fever subjects

Symptoms and signs	Number of subjects (%)			
	Lassa Fever	HBV	HCV	Lassa +HBV
Headache	16 (43.2)	1 (2.7)	1(2.7)	1(2.7)
Fatigue/Malaise	8 (21.6)	0(0)	1(2.7)	0(0)
Rashes	3 (8.1)	0(0)	0(0)	0(0)
Nausea/Vomiting	1 (2.7)	1 (2.7)	0(0)	1(2.7)
Abdominal pain	9 (24.3)	0(0)	1(2.7)	1(2.7)

(Table 2). Only one co-infection (Lassa fever + HBV; 2.7%) was recorded in a male aged 20–39. No cases of Lassa fever + HCV or triple infections (LF+HBV+HCV) were detected (Table 2). About 16.2% LF cases (6/37), and the only HCV case led to death (Table 2).

Among LF patients, headache 16, 43.2%) and abdominal pain 9, 24.3%) were the most prevalent symptoms. HBV and HCV separately showed minimal symptoms (≤2.7% each). The Lassa+HBV co-infection case exhibited headache, nausea/vomiting, and abdominal pain (2.7% per symptom), but no rashes or fatigue, indicating Lassa fever drives acute symptomatology without additive effects from HBV co-infection (Table 3).

Discussion

Viral co-infections pose significant public health challenges in endemic regions, with Lassa Fever-Hepatitis B virus (LF–HBV) or Lassa Fever-Hepatitis C virus (LF–HCV) co-infections being particularly concerning. This study revealed an overall prevalence of 17% of Lassa fever positive individuals, a rate that exceeds the pooled seroprevalence of 8.7% (95% CI: 6.8%–10.8%) for Lassa virus infection in humans across sub-Saharan Africa documented in a 2020 systematic review and

meta-analysis of 49 studies from 1969 to 2020, but aligns closely with the 17.5% case positivity rate observed among 6,791 suspected cases in Nigeria during 2020, as reported in a 2024 epidemiological analysis of national outbreaks from 2020 to 2023[34,35]. The variability in Lassa fever transmission in these studies may be influenced by diagnostic approaches, population sampling, and ecological factors, emphasising the need for enhanced surveillance and rodent control in high-burden regions to mitigate ongoing risks[36]. The data from this study revealed Lassa fever prevalence peaking in the 20-39 age group (56.7%). This finding aligns with a recent report that attributed the highest prevalence of Lassa fever to individuals aged 20–40 years in Nigeria, particularly those working in or around agricultural settings[37]. Contrary to our findings, a study in Liberia found higher LF cases in children under 15, possibly due to demographic variations in surveillance and healthcare access[38,39].

Furthermore, this study revealed a significant LF prevalence in 67.6% males. The male predominance in this study mirrors the Nigerian population's 1.5:1 male-to-female ratio. A study conducted in Sierra Leone found that males accounted for 60% of Lassa fever cases, which was potentially attributed to their involvement in farming and hunting. This consistency highlights the role of occupational exposure as a key risk factor[42]. Conversely, Ochu et al. reported a more equal distribution between the male and female sexes in Benin City, Edo State, Nigeria[43], suggesting that females may have similar exposure risks in some community-based settings. However, the observed variations in age and sex distributions in this study with those of others may reflect differences in study design (hospital-based versus community-based), regional variations in transmission, or healthcare-seeking behaviours[44]. The male predominance in the current study and others underscores the need for targeted interventions in high-risk groups, such as young adult males in endemic areas.

Nevertheless, a prevalence of 5.4% for hepatitis B virus (HBV) was documented in this study, which is higher than the global average of approximately 3.7% among adults[45], though it falls within the intermediate endemicity range (2–8%) as defined by the World Health Organization and is somewhat lower than the regional estimate of 6.1% for the WHO African Region, where HBV remains highly burdensome[45]. Similarly, the 2.7% prevalence of hepatitis C virus (HCV) exceeds the global estimate of approximately 0.8–1.0% for viremic infections,[45,46] but is consistent with recent trends in sub-Saharan Africa, where pooled anti-HCV seroprevalence was reported to be around 2.6–3.0%, according to Kassa et al.[47], though reflecting moderate-to-high endemicity in many settings. However, current data revealed low prevalence of HBV (5.4% in the 20-39 age group) and HCV (2.7% in the 40-59 age group). Global estimates suggest that HBV and HCV prevalence can vary significantly by region[48]. For instance, a systematic review by Spearman et al reported HBV prevalence rates in sub-Saharan Africa range from 5% to 20%[49]. The lower rates in the current study may suggest effective vaccination programs in the region or a lower transmission rate due to behavioural factors[50]. Consistent with this study's data, HCV prevalence has also been reported to be higher in older populations, reflecting chronic infection dynamics[51]. Moreover, males show a higher incidence of Lassa fever and co-infections compared to females. Similar findings have been reported in previous reports. For example, a study by Wada et al. indicated that males are often at a higher risk for various viral infections, likely due to differing exposure risks related to occupational activities[52]. Similarly, Coppola et al. reported that males tend to have higher infection rates of HBV and HCV because of their riskier behaviours or occupational exposures[53].

It is worth noting that only one LF–HBV co-infection (2.7%) and no LF–HCV co-infections were observed, which is lower than the 7.8% HBV co-detection rate reported in a larger Nigerian metagenomic study of LASV-positive febrile patients[54] and the national HBV prevalence of 9.5%[55]. All hepatitis markers and the single co-infection were confined to the 20–39-year age group, consistent with the known predominance of both Lassa fever and HBV transmission in sexually active young adults in Nigeria[56]. In contrast to a Ghanaian study of suspected viral haemorrhagic fever, in which HBV alone accounted for 39% of cases[57]. Furthermore, the LF cohort showed no increase in mortality from viral hepatitis co-infection, indicating that HBV and HCV are uncommon and non-aggravating comorbidities in acute Lassa fever in this study. These findings support the integration of rapid HBV and HCV screening in Lassa fever treatment centres to identify the approximately 5% of patients with chronic infection

who would benefit from linkage to care.

This study recorded an unexpectedly high survival rate (83.8% alive with Lassa fever) compared to the mortality rate (16.2% dead). This aligns with findings from Kamara et al[58], which indicated that with proper medical interventions, the mortality rate for Lassa Fever can be significantly reduced. The survival rates in endemic regions tend to improve with timely diagnosis and treatment, highlighting advancements in medical care[58]. Additionally, the incidence of headache (7.4%) and abdominal pain (4.2%) among Lassa fever patients aligns with the general understanding of Lassa fever symptomatology, as described in several studies[12,49]. Initial symptoms of Lassa fever often include nonspecific signs, such as fever, weakness, myalgia, followed by headache, sore throat, and abdominal pain. In more severe cases, these can lead to haemorrhages and multi-organ impairment.

Unlike our LF symptoms data, we recorded a very low number of symptoms (≤0.5%) for HBV or HCV mono-infections. This aligns with the known asymptomatic nature of hepatitis infections, particularly in early stages[7]. A Lassa fever and HBV co-infection case showed symptoms identical to those of Lassa fever alone, supporting the literature indicating that Lassa fever dominates clinical presentation in co-infections[50].

Conclusion

This study revealed predominantly high incidences of LF in young adults, with higher cases in males compared to females; highly limited HCV cases, mainly in older adults; limited cases of LF–HBV co-infection, which primarily affected young males; and no cases of LF–HCV or LF–HBV–HCF co-infections. The recorded mortalities were mainly traced to LF infection, with some cases caused by HCV. Overall, our findings underscore the need for ongoing research to better comprehend the factors contributing to the prevalence of viral infections in males and young adults, as well as the dynamics of co-infections, to inform the development of more effective prevention and treatment strategies.

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Conflict of Interests

The authors declare that they have no conflict of interest.

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