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MAJOR ARTICLE

Virus Load Kinetics in Lassa Fever Patients Treated With Ribavirin: A Retrospective Cohort Study From Southern Nigeria

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Background. The standard of care for Lassa fever is the use of ribavirin with supportive therapy. There is little information on the course of viremia and its relationship with clinical outcomes in patients treated with ribavirin.

Methods. We conducted a retrospective analysis of virologic and clinical parameters of 152 reverse transcription polymerase chain reaction–confirmed Lassa fever cases admitted and treated with ribavirin therapy. We describe the Lassa virus RNA kinetics in blood in relation to the clinical course of the patients.

Results. The overall mortality was 9%. The median duration (interquartile range [IQR]) of illness before admission was 8 (5–12) days. Median (IQR) Ct values on admission (t_0) were lower among patients who died (21 [20–27]) than in those who survived (34 [30–37]; $P < .01$). The receiver operating characteristics curve of the association between outcome and Ct value at t_0 had a high classification performance, with an AUC of 0.92 (95% CI, 0.86–0.98). The median time to viral clearance (IQR) was 10 (5–15) days. The viral load decreased steadily with the duration of treatment, and all survivors achieved viral clearance within 25 days of hospitalization.

Conclusions. Our study demonstrates that the Ct value on admission has prognostic value and Lassa fever patients treated with ribavirin typically clear the virus within 3–4 weeks of hospitalization. This kinetics has implications for the design of clinical case management and future clinical trial protocols.

Keywords. clinical outcomes; clinical trial; Ct value; Lassa virus; ribavirin treatment; viral load; viremia.

Lassa fever (LF) is a zoonotic disease caused by the Lassa virus (LASV), an enveloped RNA virus, belonging to the family of Arenaviridae. It is an acute febrile illness that is endemic in some West African countries, including Nigeria, where several outbreaks and sporadic cases have been reported with an estimated incidence of 300 000 infections and >5000 deaths per year [1–3]. Because of the public health impact of the disease in the underdeveloped affected populations in endemic countries and the lack of effective medical countermeasures, the World Health Organization (WHO) has included LF in its blueprint of priority diseases for research and development [4].

The clinical course of LF is highly variable, making it a challenge to distinguish Lassa fever from other common febrile illnesses such as malaria, typhoid fever, and influenza, which are also common in endemic areas [5]. An estimated 80% of people infected with the Lassa virus have subclinical or no obvious symptoms, while 20% present with a wide spectrum of systemic manifestations requiring hospitalization [5, 6].

The case fatality rate (CFR) among hospitalized patients is between 9% and 31% depending on the clinical stage of the disease at presentation and level of care at the treatment facility [5, 7, 8]. During nosocomial outbreaks, CFRs as high as 36% to 65% have been reported [9–11].

Received 15 April 2024; editorial decision 24 September 2024; accepted 29 September 2024; published online 15 October 2024

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https://doi.org/10.1093/ofid/ofae575

To date, there is no vaccine for LF, and there is currently no licensed therapeutic agent for its treatment. The off-label use of ribavirin, an antiviral agent, in combination with supportive measures is currently the standard of treatment [7, 12–14]. Ribavirin, a nucleoside analog of guanosine with broad-spectrum direct antiviral activity, is also used in the treatment of hepatitis C (HCV) [15], severe respiratory syncytial virus (RSV) infections [16], Crimean-Congo hemorrhagic fever (CCHF) [17], and other viral hemorrhagic fevers. The rationale for its current use in the treatment of LF is largely based on the results of the clinical study by McCormick et al. in Sierra Leone, which was published in 1986 [12]. Although in 2017 the WHO included ribavirin in the model list of essential medicines for the treatment of certain hemorrhagic fevers, including LF [18], the evidence for its efficacy has been questioned in recent reevaluations, which found serious methodological deficits in the McCormick trial, ranging from participant selection, groupings, randomization, and protocol adherence [19, 20].

The ribavirin regimen as described by McCormick and colleagues consisted of intravenous administration of a loading dose of 2 g, followed by 1 g 6 hourly for 4 days and 0.5 g 8 hourly for another 6 days [12]. However, based on our clinical experience and considerations of personnel safety, we have at Irrua Specialist Teaching Hospital (ISTH) developed a separate ribavirin regimen. Unlike the McCormick regimen, which is administered 3–4 times daily, the Irrua regimen for adults is administered once daily with a higher starting dose and subsequent lower doses as follows: a 100-mg/kg loading dose on day 1 (up to a maximum of 7 g), followed by 25 mg/kg once daily on days 2–5 and 12.5 mg/kg once daily on days 6–10 [7, 13, 14]. There are many advantages to the use of this regimen. The major ones include a reduction in physician/nurse–patient contact time and visits, and thus reduced potential for occupational exposure to infection, cost savings in the amount of personal protective equipment used, reduction in the total dose of ribavirin, and reduced risk of dose-related adverse effects of ribavirin such as anemia [14]. As ISTH is a national referral hospital for the diagnosis and treatment of Lassa fever, we have used this regimen in the management of hundreds of confirmed cases of LF with satisfactory results [3, 7, 21, 22], and it has been adopted for use across LF treatment centers in Nigeria as a component of the national treatment guidelines [13, 14]. The Irrua regimen for children is, however, similar to McCormik et al. and takes the child's body weight into consideration: a loading dose of 33 mg/kg followed by 16 mg/kg 6 hourly for 4 days and 8 mg/kg 8 hourly from days 5 to 10 [13, 23].

In addition to the administration of ribavirin, our patients also receive a range of supportive treatment, including intravenous fluids, antibiotics, analgesics, antimalaria, hematinics, blood transfusion, hemodialysis, and oxygen therapy, as warranted by the clinical presentation [2, 7, 13, 21]. During treatment, we monitor the viral load using quantitative Lassa virus reverse transcriptase polymerase chase reaction (LASV RT-PCR) tests at 5-day intervals until discharge or death. We discharge our patients following completion of the standard 10-day course of ribavirin, resolution of fever and other major symptoms, and a negative post-treatment LASV RT-PCR test. For those who remain positive after 10 days of treatment, we continue them on intravenous therapy or discharge them home on oral ribavirin depending on their clinical condition. In either case, we schedule them for a repeat RT-PCR test every 5 days until a negative result is returned.

Study Rationale

To date, there is very little information available on the course of viremia during treatment with ribavirin, and it is important to address the dearth against the backdrop of continued reliance on ribavirin for the treatment of LF in endemic areas [2, 7, 21–23], despite concerns that have been raised regarding its efficacy [19, 20].

Apart from the preceding, several observational studies that reported a reduction in CFR in patients treated with ribavirin [21, 24, 25] have been criticized. In particular, the use of biochemical indicators such as levels of creatinine and aspartate aminotransferase (AST) to assess disease severity and monitor treatment response are of concern as they are not specific [26, 27] and may not directly reflect the treatment response, being more related to the presence of disease complications. Our aim in this study was to address these concerns using LASV kinetics and the clinical course of patients on the Irrua ribavirin regimen. Our findings could inform the development of treatment protocols and the design of clinical trials.

METHODS

We collected data from the medical and laboratory records of all 152 LASV RT-PCR-confirmed cases admitted during the 2018 LF outbreak between January and March. All patients were managed according to standard of care including the Irrua ribavirin regimen as described above [13, 14, 21, 23].

Data sets collected included sociodemographic characteristics and clinical and virologic parameters at presentation and during the period of treatment. Clinical parameters included duration of illness before admission, signs and symptoms, treatments given, duration of admission, complications, and outcome. Virologic parameters included the RT-PCR cycle threshold (Ct) at admission (first tested sample [t_0]) and serially during treatment at 5-day time points until discharge or death (t_5, t_{10}, t_{15}, t_{20}, and t_{25}). LASV-RT-PCR tests and viral load quantification were done using the RealStar Lassa virus RT-PCR Kit 2.0 (Altona Diagnostics GmbH, Hamburg, Germany).

Statistical Analysis

We summarized continuous variables using the median and interquartile range (IQR) and categorical values using frequency and percentage. We used Ct value as a measure of viral load; a low Ct value indicates a high viral load, and a high Ct value indicates a low viral load [28]. Based on the calculated baseline median Ct value (IQR) of 34 (29–37) among our patients, we categorized the participants into 2 groups of low Ct values (range, 18–34) and high Ct values (range, 34–45). We also classified the participants into early presenters (<6 days) and late presenters (≥6 days) based on the duration of illness before hospitalization [12].

The analysis of demographic and admission data has a cross-sectional nature; thus we calculated the prevalence ratios (PRs) and 95% CIs to show associations between 2 binary variables. The distribution of continuous variables among 2 groups was compared using the Wilcoxon rank-sum test. Pearson's correlation coefficient (r) was calculated to show associations between 2 continuous variables. We determined the association between patients' initial Ct values and disease outcomes by computing the area under receiver operating characteristic curve (AUROC).

Time to event (viral clearance) was calculated using the Kaplan-Meier estimator. All analyses were done with R (version 4.3.1) using the packages *epiR* to estimates PRs, *confintr* to calculate *r*, *pROC* to calculate AUROC, and *survival* to calculate the Kaplan-Meier estimators.

RESULTS

We tested a total of 1515 suspected cases of LF between January and March 2018 by real-time RT-PCR. Of those, 152 (10%) were LF-positive and admitted for treatment. The demographic and clinical characteristics of the patients with confirmed LF are as summarized in Table 1. The majority were male (61%) and between 20 and 49 years of age (70%). Constitutional (100%), cardiovascular (82%), and gastrointestinal (63%) symptoms, in that order, were the most common sets of symptoms at presentation. The median duration (IQR) of illness before admission was 8 (5–12) days, and the median (IQR) Ct value at baseline (t_0) was 34 (29–37) (Table 1).

All patients were given intravenous ribavirin and intravenous fluids. The proportions of patients managed with other modalities of supportive care are shown in Figure 1 and differed between the patients, in keeping with their clinical states and laboratory test results.

The overall mortality was 13/152 (9%), but CFR was higher among those >40 years of age (7/42, 17%, compared with 6/110, 5%, in those aged <40 years; PR, 2.1; 95% CI, 1.2–3.8). Table 2 shows that there was no difference ($P = .37$) between the baseline median Ct values of those patients who presented before and after day 6 of the onset of illness. Also, the clinical outcome did not depend on time of presentation ($P = .72$).

Figure 2*A* shows that the median Ct values at t_0 (IQR) were lower among patients who died (21 [20–27]) than in those who survived (34 [30–37]; $P < .01$). The ROC curve of the association between outcomes and Ct values at t_0 had a high classification performance, with an AUC of 0.92 (95% CI, 0.86–0.98) (Figure 2*B*). Viral clearance time correlated with the Ct value at t_0 (Ct_0). Patients with a negative PCR test at day 5 had the highest Ct_0 values (median [IQR], 36 [34–38]), and there was a steady decline of median Ct_0 values toward later clearance times (day 10: median [IQR], 34 [32–37]; day 15: median [IQR], 31 [27–34]; day ≥20: median [IQR], 26 [26–31]; $r = -0.55$; 95% CI, −0.64 to −0.41) (Figure 2*C*).

The trend of Ct values with duration of treatment is further illustrated in Figure 3. Seventy-nine (57%) patients were still PCR positive on day 5, 44 (32%) on day 10, 16 (12%) on day

Table 1. Demographic and Clinical Characteristics of LF Patients (n = 152)

Characteristic		Summary
Gender	Male, No. (%)	93 (61)
	Female, No. (%)	59 (39)
Median age (IQR), y		30 (22–43)
Age distribution, No. (%)		
	<10 y	5 (3)
	10–19 y	21 (14)
	20–29 y	43 (28)
	30–39 y	38 (25)
	40–49 y	25 (16)
	50–59 y	14 (9)
	60–69 y	4 (3)
	≥70 y	2 (1)
Median duration of illness before admission (IQR), d		8 (5–12)
Median Ct value (IQR)		34 (29–37)
Clinical symptoms complex present at presentation		
	Constitutional[a]	152 (100)
	Gastrointestinal[b]	96 (63)
	Respiratory[c]	38 (25)
	Cardiovascular[d]	125 (82)
	Hemorrhage[e]	34 (22)
	Renal[f]	11 (7)
	Central nervous[g]	16 (11)

Abbreviations: Ct, cycle threshold; IQR, interquartile range; LF, Lassa fever.

[a]Fever ≥38°C, headache, weakness, myalgia, arthralgia, low appetite, weight loss.

[b]Abdominal pain, vomiting, diarrhea, sore throat.

[c]Cough, shortness of breath.

[d]Signs of cardiogenic shock (heart rate >100 bpm, systolic <90 mmHg, diastolic <60 mmHg).

[e]Macroscopic hematuria, melena, vaginal bleeding, hematemesis, bleeding from venous puncture site, hematochezia, epistaxis, hemoptysis.

[f]Reduction in urinary out, increase in serum creatinine.

[g]Altered level of consciousness, signs of encephalopathy—seizure, meningeal syndrome, tinnitus, impaired hearing loss.

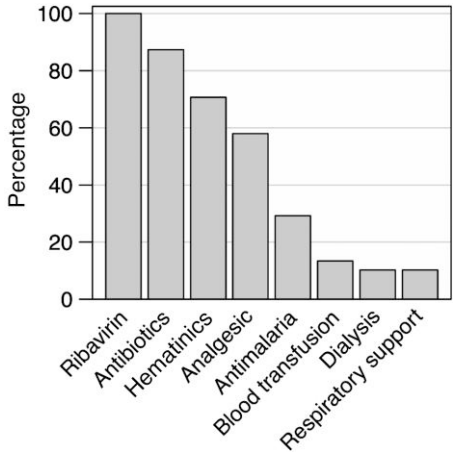

Figure 1. Proportion of patients with Lassa fever with different supportive treatment modalities (n = 152).

15, 3 (2%) at day 20, and all patients were negative on day 25 (Figure 3*A*). The median time to viral clearance (IQR) was 10 (5–15) days. All fatalities occurred before the third sampling time point, and the majority, 9/13 (69%), died before the fifth day after admission. Median Ct values increased stepwise in survivors (IQR) from 34 (29–37) at day 0 to 35 (33–38) at day 5, 36 (35–38) at day 10, and 39 (37–40) at day 15 (Figure 3*B*).

Ct values at t_0 varied with disease symptoms, indicating an association of symptoms with viral load, as shown in Figure 4 in which the dotted line depicts the median Ct value for all study participants. Patients with hemorrhage, renal, and gastrointestinal symptoms had Ct values below the group median. Hemorrhage was the only symptom that was associated with case fatality (PR, 3.0; 95% CI, 1.1–8.3).

DISCUSSION

This study provides insight into Lassa virus RNA kinetics and its relationship with clinical outcomes in LF patients treated with ribavirin. The baseline demographics and clinical features of the study cohort are largely in keeping with the observations in previous studies [5, 7, 11, 12].

The overall CFR of 9% in this study is also within the range previously reported from among hospitalized patients in endemic areas [5, 8–10, 12]. It is, however, considerably lower than the 31% reported over a decade ago from ISTH by Asogun et al. [7]. We think the difference might be due to continuing improvements in case management standards in our hospital [3]. We observed also that fatality was higher among the older age groups. This is consistent with our previous findings at ISTH, which demonstrated a 1.5-fold increased mortality risk for every 10-year rise in age [21]. The reason why elderly people are at higher risk of dying may be related to a reduced immune status or immune dysfunction [28, 29].

Table 2. Baseline Viral Load and Outcomes vs Duration of Illness Among Patients With LF

		Duration of Illness		
Variable	Status	No. (%) <6 Days	No. (%) ≥6 Days	*P*
Baseline Ct values	High (34–45)	16 (43.2)	57 (51.8)	.367
	Low (18–33.9)	21 (51.8)	53 (48.2)	…
Outcome	Survived	36 (90.0)	102 (91.9)	.715
	Died	4 (10.0)	9 (8.1)	…

Abbreviation: LF, Lassa fever.

Our results showed a steady increase in Ct values with time, which indicates a steady decline in viral load as Ct values are inversely related to the viral load in a sample [30]. Our results also showed that patients with higher viral loads had longer virus clearance times and duration on admission. In addition, we also found that baseline viral load was higher among patients who died than survivors, in line with previous reports [14, 21, 31]. The association between viral load and poor clinical outcomes is further supported by our findings of higher viral loads in patients with presenting symptom groupings that are known to be clinical indicators of poor outcomes in our previous studies [3, 7, 21]. The association of high viral load with complications and poor clinical outcomes could mean that early reduction of the viral load in severely ill patients through additional treatment measures, including exchange blood transfusion, partial exchange transfusion with convalescent plasma, and transfusion with monoclonal antibodies, may reduce the risk of developing complications and improve the clinical outcome of severe disease. There is a need for operational studies and clinical trials to confirm this.

We found in this study that by day 10, which is the standard duration of treatment with ribavirin [12–14], over two-thirds (71%) of the patients who survived had cleared their viremia and about two-thirds of the fatalities (69%) had already occurred. These observations are in tandem with our other observations in this study, namely that virus clearance time is related to the viral load on admission, that the viral load was higher in those who died than survivors, and that the presence of biomarkers of adverse outcomes on presentation [3, 14, 21] is related to the viral load, although we found no correlation between duration of illness and viral load on presentation among our patients. Taken together with the lack of an association between CFR and duration of illness before admission among our patients, we are of the view that although some of our findings may not support the claims of the effectiveness of ribavirin as an antiviral agent in the treatment of LF [12], they do not exclude the potential for other survival-enhancing mechanisms of ribavirin in patients with LF such as immune

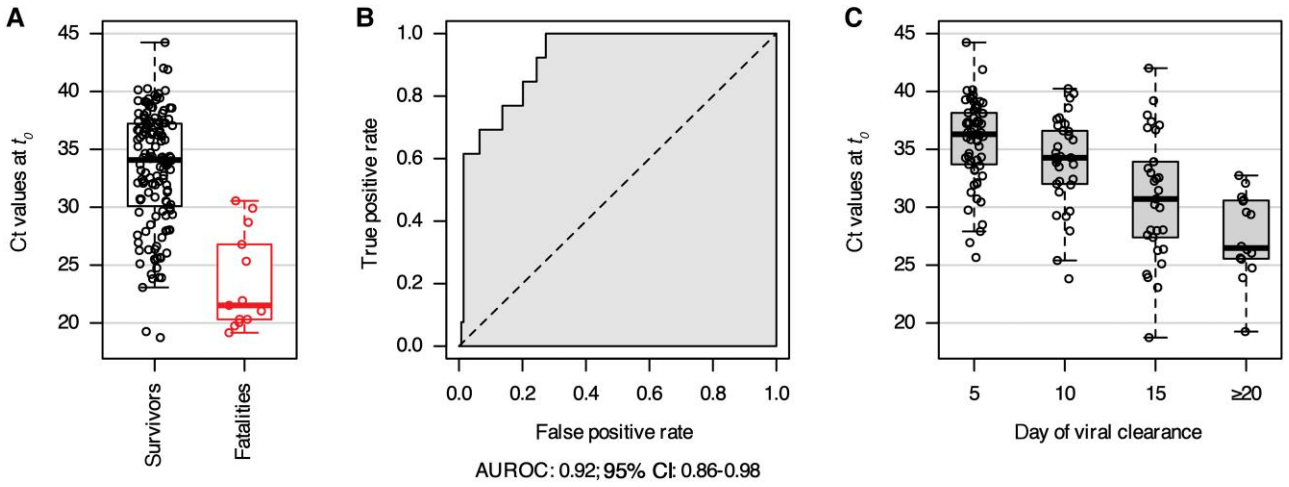

Figure 2. *A*, Ct values at t_0 in survivors vs fatalities. *B*, AUROC of Ct values at t_0 vs outcome. *C*, t_0 Ct values over the day of viral clearance. Abbreviations: AUROC, area under the receiver operating characteristic curve; Ct, cycle threshold.

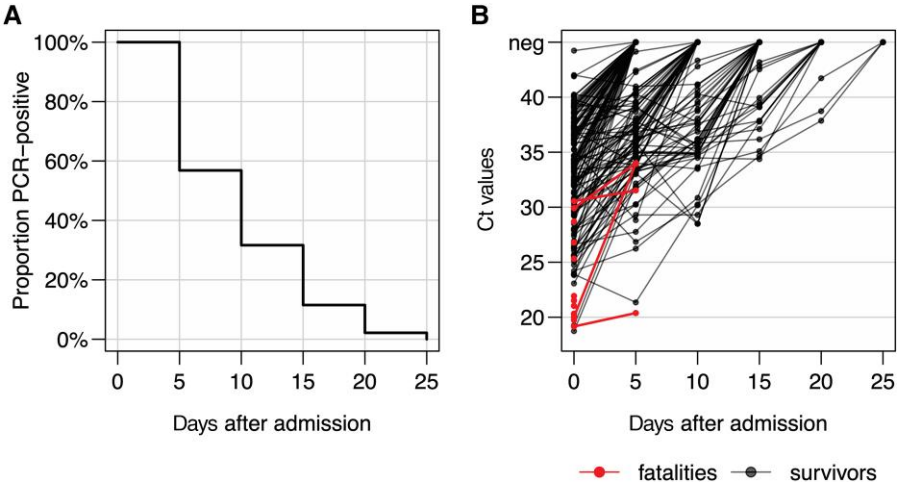

Figure 3. *A*, Probability of Lassa virus RNA detection. *B*, Progression of Ct values during hospitalization.

modulation [32–34]. Furthermore, it might also be that the effectiveness of ribavirin on viral load through inhibition of viral replication [35–38] in those patients who died was swamped by the high viral load ab initio before the commencement of treatment, a mechanism akin to the inoculum effect in some respiratory viral infections, in which a higher initial dose can lead to a higher disease severity and mortality [39, 40], or that they were already prone to dying from the severity of the complications that antedated admission. This brings to light the importance of early diagnosis and treatment, including enhanced or critical care in the management of Lassa fever, which unfortunately has remained underdeveloped in most endemic areas [3].

As noted above, our findings do not support previous reports of a poor outcome in patients with delayed presentation (>6 days of fever) [12], although this should not detract from the importance of early presentation and commencement of treatment. It might be that immunological and genetic factors are at play that predispose some patients to severe infections and others to milder forms, as in Ebola [41, 42] and coronavirus disease 2019 [43]. Prompt immune response has been recognized as a critical factor in host survival, and severe and fatal diseases are often characterized by impaired or delayed immune responses [31, 32]. Clearly, further studies are required to substantiate this, and rather urgently, in view of the potential implications for vaccine development and the quest for improved outcomes of LF.

The mechanism of action of ribavirin remains unclear. Available data suggest that ribavirin mediates its action through 2 major pathways, inhibition of viral replication [33, 36–38] and modulation of cellular immune functions, by

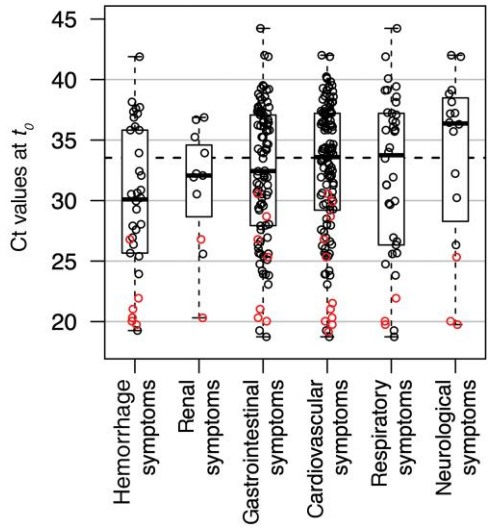

Figure 4. Variation of median Ct_0 values with disease symptom grouping in patients with Lassa fever. Black circles indicate survivors, and red fatalities.

reducing cell damage and inflammatory response [34, 44]. In our study, all the patients achieved viral clearance within 25 days of treatment. However, due to the lack of a control group not treated with ribavirin, we may not conclude from our data whether the drug facilitates or delays virus RNA clearance. Nevertheless, our findings have implications for the clinical case management of LF and future clinical trials. Trials for new therapeutic interventions for LF will likely be conducted with a comparator arm including ribavirin treatment as standard of care. Thus, our data will inform the design of drug trials for LF, specifically with respect to the required observation period to measure virological response and to estimate the pharmacodynamic properties of new interventions relative to standard of care.

Previously, biochemical markers such as the levels of serum creatinine (Cr) and aspartate aminotransferase (AST) have been used to monitor treatment response in LF [26, 27]. These markers are not specific to LF but are also elevated in other conditions of severe or chronic renal and liver diseases, unrelated to LF [26, 27, 45]. Also, acutely ill LF patients with renal and liver pathologies as comorbidities could have high levels of these markers that are disproportionate to the level of viremia. Thus, viral load is a more specific indicator of severity and response to therapy in LF disease compared with the biochemical markers.

Our study has some limitations. First, because the study lacked controls, we were unable to determine whether the viral load kinetics among our patients was due to treatment with ribavirin or a natural history of Lassa fever. A randomized controlled trial on the efficacy of ribavirin [46] could help resolve this question. Second, our sample size was not large enough to enable an in-depth subgroup analysis of clinical features and mortality, thus limiting the generalizability of our findings. Third is the lack of concurrent studies of immunologic response in our patients, for which reason we could only speculate on the putative mechanism of action of ribavirin and its possible relationship to the clinical course of our patients. Fourth, we measured virus kinetics based on virus RNA levels, as reflected by Ct values. Thus, RNA in noninfectious Lassa virus particles or Lassa virus RNA released into the bloodstream due to cell damage may have contributed to the PCR signals. The kinetics might be different when measuring infectious virus particles, and this might be relevant for therapeutic interventions aiming to reduce the ratio between infectious and noninfectious virus particles, for example, through lethal mutagenesis. We also suggest that this should be addressed in further studies.

Acknowledgments

We thank Chinonye Afebuero and the staff of the medical records department for their support in retrieving patients' medical records and the staff of the laboratory data unit for data retrieval. We acknowledge the support of Dr. Chikwe Ihenkhwazu, formerly of the Nigerian Centre for Disease Control. The Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany sourced the grant to support this study.

Author contributions. O.E., A.G., S.G., and O.S. conceptualized and designed the study; O.F., T.E., A.D., and O.P. conducted the review of the literature and methodology; A.N., A.P., E.C., I.K., I.C., E.C., R.M.O., A.D., E.O., O.J., and E.R. carried out the review of patients' case notes and medical records and extracted clinical data in the different clinical departments; O.I., A.J., A.D., O.M., O.W., E.A., and M.E. reviewed laboratory worksheets to extract laboratory data; O.K., E.P., J.M., J.H., M.P., A.T., S.D., and L.O. verified and matched clinical and laboratory data and carried out the descriptive analysis. R.K. carried out the statistical analysis and interpreted the data; E.O., A.G., S.G., and R.K. drafted the manuscript. All authors revised the manuscript critically for important content and approval for submission.

Financial support. S.G. has received funding from DFG (GU 883/4-2), BMG (GHPP AfroLabNet, ZMVI1-2517-GHP-704), and EDCTP (Pandora ID-Net, RIA2016E-1609). L.O. received funding from the Leibniz Association (J59/2018).

Potential conflicts of interest. The authors: no reported conflicts of interest.

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