Original Article

Factors Affecting Outcome in Reverse Transcriptase-Polymerase Chain Reaction-Positive Lassa Fever Patients with Acute Kidney Injury: A Retrospective Analysis

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Abstract

Abstract: Lassa fever (LF) is a viral haemorrhagic fever (VHF) endemic in the West African sub-region. It causes regular outbreaks with a significant case fatality rate (CFR). An estimated 100,000–300,000 people are infected with Lassa fever virus (LASV) every year in West Africa. Acute kidney injury (AKI) is a recognized complication of LF and may contribute significantly to the high CFR. We retrospectively studied 187 reverse transcriptase-polymerase chain reaction (RT-PCR)-positive LF patients admitted and managed at the infectious diseases centre of Abubakar Tafawa Balewa University Teaching (ATBUTH), Bauchi, to shed more light on the effect of AKI on the outcome. **Materials and Methods:** The case files of 187 RT-PCR-positive LF patients admitted between January 2018 and December 2020 at the infectious disease centre of ATBUTH were retrieved. We performed parametric and nonparametric statistical analyses including logistic regression to determine factors associated with poor outcomes. **Results:** During the study period, 187 RT-PCR-positive LF patients were admitted and treated in our centre; 130 (69.5%) were males and 27 (30.5%) were females. The mean age of presentation was 37.3 ± 15.5 years, and nearly all the patients presented with fevers of varying duration. There were 53 deaths with a CFR of 28.3%. More than 2/3 of the deaths were among the age group of 18–47 years. AKI was observed in 12.8% of the patients whose mean age was 37.17 ± 13.13 years. AKI was significantly associated with poor outcomes. Raised systolic blood pressure (odds ratio [OR] = 1.042, 95% confidence interval [CI] 1.008–1.076, $P = 0.014$) and serum creatinine (OR = 0.952, 95% CI 0.904–1.002, $P = 0.000$) were found as significant risk factors for developing AKI. **Conclusion:** Lassa fever is a multisystemic illness. Kidney involvement occur early and can lead to acute kidney injury with its attendant complications. Our study highlighted the significance of AKI as a contributor to poor outcome among patients with Lassa Fever infection.

Keywords: Acute kidney injury, Bauchi, Lassa fever, North-East Nigeria, outcome, reverse transcriptase-polymerase chain reaction test

Introduction

Since its first reported in Nigeria in 1969,[1] Lassa fever (LF) has continued to cause outbreaks in Nigeria[2] and other West African countries, particularly in Sierra Leone,[3] Togo,[4] Republic of Benin,[5] and Liberia[6] with significant case fatality rate (CFR).[7] It has also been reported in Europe[8] and the United States[9] where it is mainly exported from West Africa. LF is caused by the Lassa virus (LASV) which is an arenavirus with a primary reservoir as the multimammate rat – *Mastomys natalensis*. The virus is transmitted through the blood, urine, or feces of infected rats or the body fluids of infected individuals.

The clinical features of LF range from asymptomatic to fulminant multisystemic disease. Initial symptoms of LF are similar to other febrile illnesses and include body weakness, malaise, fever, nausea, vomiting, diarrhoea, chest and muscle pains, and hearing loss, this makes its diagnosis difficult in the early phase of the infection with consequent delay in instituting appropriate management. Acute kidney injury (AKI) is often a component of multisystem syndrome that includes involvement and dysfunction of the central nervous system, pulmonary, cardiovascular, haematopoetic system, gastrointestinal system, and liver.[10]

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Most of the studies done in Nigeria are from the Southern part of the country; however, LF is equally endemic in the Northern region most importantly the Northeast where it was first described. Therefore, this study is aimed at determining factors associated with the development of AKI and its relation to poor outcomes in confirmed cases of LF treated at the infectious diseases centre of Abubakar Tafawa Balewa University Teaching (ATBUTH), Bauchi, Northeast Nigeria.

Materials and Methods

This is a retrospective study of all adult patients confirmed to have LF by reverse transcriptase-polymerase chain reaction (RT-PCR) test at the infectious diseases centre of ATBUTH, Bauchi, Northeast Nigeria between January 2018 and December 2020. The center consists of a dedicated treatment facility, comprising an isolation ward, laboratory, training centre, and dialysis unit. The facility receives a referral from all North-Eastern states, and neighboring Plateau and Jigawa States of Nigeria. All patients with suspected LF were confirmed by the use of the RealStar Lassa Virus RT-PCR kit 2.0 (altona Diagnostics, Hamburg, Germany). All confirmed patients were admitted to the centre and received intravenous ribavirin according to Nigeria Centre of Disease Control (NCDC) guidelines.[11] In addition, intravenous fluids, broad-spectrum antibiotics, antimalarial drugs, and other supportive care were instituted as indicated.

All the records of patients who had been treated at the facility between January 2018 and December 2020 were included. Clinical records were used to extract information on age, sex, occupation, duration of symptoms, vital signs, laboratory investigations such as serum creatinine (SCr) and potassium, haemoglobin, comorbidities, and outcome. Confirmed LF patients were defined based on the NCDC guidelines as patients with fever, vomiting, diarrhoea, sore throat, myalgia, abnormal bleeding, hearing loss, confusion, seizure, restlessness, and/or facial/neck swelling with a positive RT-PCR test.[11] Normal SCr is defined as 53 μmol/L to 106 μmol/L (0.6 mg/dl–1.2 mg/dl), whereas normal serum potassium is defined as 3.5 mmol/L to 5.5 mmol/L. AKI is defined as any of the following: an increase in SCr by ≥0.3 mg/dl (≥26.5 μmol/L) within 24 h or an increase in SCr to ≥1.5 times the baseline which is known or presumed to have occurred within the prior 7 days.[12]

Data were entered into Statistical Package for the Social Sciences version 23 (IBM Corp., Armonk, NY, USA). Mean was used to summarize continuous variables. Chi-square was used to test associations between selected categorical variables, whereas an independent sample *t*-test was used to examine the relationship between continuous variables. Paired sample *t*-test was used to determine the association between paired results (SCr and potassium). Multiple logistic regression analysis was used to determine risk factors for mortality among patients who developed AKI. The level of significance was set at $P \leq 0.05$. Tables and charts were drawn as appropriate to present the data.

Results

During the period under review, 187 RT-PCR-confirmed cases of LF were admitted of which 130 (69.5%) were males and 57 (20.5%) were females with a male-to-female ratio of 2:1. Farmers constituted about 63 (33.7%) patients, whereas civil servants constituted 17 (9.1%) patients. There were 31 (16.5%) students out of which 24 (12.4%) were males and 7 (12.2%) were females, the remaining 50 (87.8%) females were housewives. Among the patients, 165 (88.2%) were from Bauchi state, whereas 22 (11.8%) were from neighboring Plateau, Kaduna, Adamawa, and Yobe States. Within Bauchi State, Bauchi, Dass, Toro, and Tafawa Balewa local government areas (all in Southern Bauchi) had the highest number of cases. Table 1 shows the demographic characteristics of the patients.

The mean age of the patients was 37.3 ± 15.5 years, and there was no statistically significant difference between the mean ages of males and females in this study. About 103 (69.2%) males are below 47 years of age. Table 2 shows the frequency of occurrence of various signs and symptoms of LF in the patients. All the patients presented with fever, and the mean

Table 1: The demographic characteristic of the study cohort

Variables	*n* (%)
Gender	
Male	130 (69.5)
Females	57 (20.5)
Total	187 (100.0)
Age	
18-27	57 (32.5)
28-37	59 (31.6)
38-47	31 (16.6)
46-57	13 (7.0)
≥58	27 (14.4)
Total	187 (100.0)
Occupation	
Civil servants	17 (9.1)
Farmers	63 (33.7)
Trading	28 (15.0)
Students	24 (12.8)
Unskilled	5 (2.7)
Housewives	50 (26.5)
Total	187 (100.0)

Table 2: Frequency of occurrence of symptoms

Variables	*n* (%)
Fever	186 (99.5)
Vomiting	98 (52.4)
Diarrhea	31 (16.6)
Cough	162 (86.6)
Body weakness	35 (18.7)
Bleeding	49 (26.2)
Jaundice	13 (7)

duration of the fever was 6.15 ± 3.5 days with a median of 5 days. Bleeding from the orifices and jaundice were seen in 49 (26.2%) and 13 (7%) patients, respectively. The mean systolic and diastolic blood pressures were 117 ± 18.82 mmHg and 72.62 ± 12.85 mmHg. There was no statistically significant difference between the blood pressure among the sexes (P = 0.913 for males and P = 0.86 for females).

About 50 (27.3%) patients presented in shock with low blood pressure (SBP <70 mmHg) and tachycardia (heart rate >120 beats/min). The mean heart rate in the patients was 95.2 ± 27.23 beats/min with a statistically significant higher heart rate in the females (91.8 ± 21.89 vs. 103.23 ± 35.59, P = 0.008). The mean serum potassium and creatinine on admission were 4.5 ± 0.9 mmol/L and 150.12 ± 68.6 µmol/L, respectively. On admission, 19 (10.2%) patients presented with hypokalemia out of which 15 (78.9%) had profuse diarrhoea. Hyperkalemia was seen in 27 (14.4%) patients. Furthermore, 126 (67.4%) patients presented with high SCr. Table 3 shows the mean SCr and potassium on admission and on the 5th day of admission.

There were 53 deaths among the patients during the study period with a CFR of 28.3%. Among this number, 17 died before the 5th day of admission with a 5-day CFR of 9.1%. All the remaining 134 (71.7%) survived and were discharged. As shown in Figure 1, the age groups of 18–47 years contributed more than 60% of the death among the patients. AKI was seen in 24 (12.8%) patients with a mean age of 37.17 ± 13.13 years. More than 80% of the AKI patients were below 47 years of age. Figure 2 shows the number of patients in various stages of AKI.

AKI is significantly associated with death (P = 0.009). There is no significant association between AKI and gender, age group, or duration of fever. In univariate analysis, farmers (odds ratio [OR] = 0.063, 95% confidence interval [CI] 0.004–0.99, P = 0.049), high systolic blood pressure (OR = 1.042, 95% CI 1.005–1.07, P = 0.017), high diastolic blood pressure (OR = 0.947 95% CI 0.899–0.99 P = 0.046), and SCr (OR = 1.01 85% CI 1.005–1.014 P = 0.000) were found to be significant predictors of death. However, on multivariate analysis, only high systolic blood pressure (OR = 1.042 95% CI 1.008–1.076 P = 0.014) and SCr (OR = 0.952, 95% CI 0.904–1.002 P = 0.000) were found to predict mortality among the study patients.

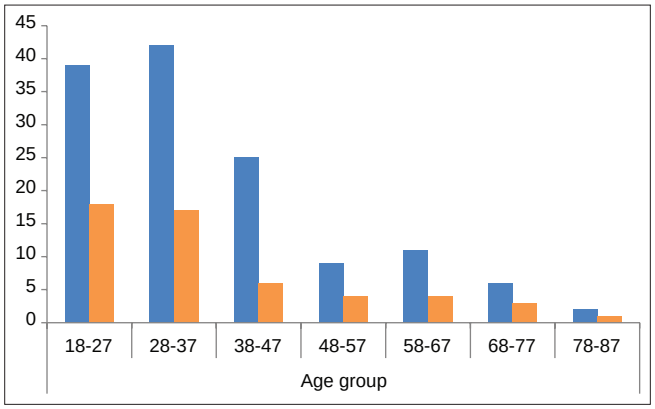

Figure 1: Showing outcome of male and female patients stratified according to age group

Discussion

To our understanding, this is the most recent comprehensive report of LF epidemiology from the Northeast region, the region where it was first described in 1969. Although several publications were published on the outcome and predictors of mortality in LF patients, mostly from Southwest and South-South Nigeria, there are little or no contributions from the northeast. Our study showed a male preponderance of 69.5% which is higher than previously reported.[13-15] This could be due to the fact that males are more commonly associated with activities that expose them to contact with rodents (such as farming and bush burning). Furthermore, the purdah system in the Muslim community restricts females (housewives) from unnecessary movement without the approval of their husbands, this could be denying them some access to health-care services.

LF is a disease of all ages, however, in our study which includes only adults; the mean age of the patients was 37.3 ± 15.5 years. This is in agreement with Olatunde *et al*. who retrospectively reviewed 147 confirmed LF in Owo Southwest Nigeria and reported a mean age of 38.4 ± 16.4 years.[15] This is further corroborated by another study in which the median age of presentation was 34 years. Moreover, in a prospective cohort study of 534 confirmed LF patients about 54% of the patients were in the age group of 18–44 years. In our study, 69% of the patients were below 47 years. Overall, this suggests that although LF can affect all ages it is more common in the young and middle ages where the effects of the disease are mostly felt.

Table 3: The mean serum potassium and creatinine on days 1 and 5

Variables	Day 1	Day 5	*P*
Serum potassium	4.5±0.91	4.7±2.8	0.362
Serum creatinine	150.12±68.6	190.12±114.7	0.000

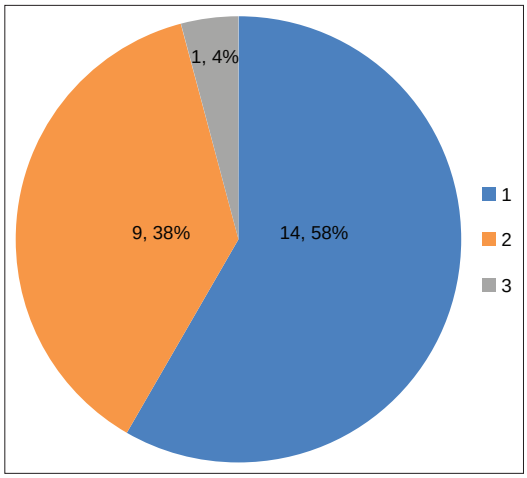

Figure 2: Showing number of patients in different stages of AKI. 1= Stage 1 AKI, 2=Stage 2 AKI, 3=Stage 3 AKI

Our study also showed a high proportion of the patients coming from the Southern part of Bauchi State. This geographic disparity may not be unconnected with the climatic condition, whereas the North and Central Bauchi are in the grassland area, whereas the Southern part has more dense vegetation which could harbor the breeding ground of the vector of the disease. In addition, the Southern part of the state is largely inhabited by the Sayawa and Jarawa ethnic groups who consumed bush meat (mostly small rodents including rats, squirrels, and mice) allowing direct contact with the vector. The practice of bush burning may also be a factor in the high number of patients seen from the Southern part of the state.

The clinical features of LF range from asymptomatic to fulminant multisystemic disease. In our study fever, cough, vomiting, bleeding, body weakness, diarrhea, and jaundice were the major clinical features in order of occurrence. This is similar to a retrospective observational study of 291 patients with confirmed LF in Irrua Specialist Teaching Hospital in which Okokhere *et al*. observed the occurrence of vomiting, body weakness, headache, cough, diarrhea, and bleeding as the common symptoms.[13] Merson *et al*. also reported fever, headache, cough, vomiting, and abdominal pain as the dominant presenting symptoms after systematically reviewing all clinical reports and researches on LF published before 2021.[14]

All patients received a loading dose of intravenous ribavirin at 100 mg/kg in two divided doses (2/3 of the dose stat and 1/3 of the dose 8 h later), followed by 25 mg/kg daily for 7 days and 12.5 mg/kg for the next 3 days (Irrua Regimen). Intravenous fluids mostly normal saline were administered to 145 patients, whereas 25 patients had inotropic support. Furthermore, 19 patients had a full dose of antimalarial and 119 patients had broad-spectrum antibiotics. Blood transfusion was administered to 32 patients who had low packed cell volume (PCV). Seventeen patients died within the first 5 days of admission comprising 12 patients who presented in hypovolemic shock and five patients who developed severe bleeding while on admission.

Overall, 53 patients died with a CFR of 28.3% (53 of 187) of which 16 were females. This is similar to the 30% reported from a systematic review of 147 publications comprising more than 8000 patients of whom more than 90% were from Nigeria or Sierra Leone.[14] Similarly, Olatunde *et al*.[15] reported a CFR of 32.4% in a retrospective analysis of 147 case files of confirmed LF patients treated at the infection control center of Federal Medical Centre, Owo (one of the national centers for LF research and control centre in Nigeria). However, it was lower than the 69% reported by Shaffer *et al*. from Sierra Leone.[16] The higher CFR from that study could be due to several factors. The study was conducted immediately after the country's civil unrest with consequent decay in health-care delivery services and late presentation to hospitals due to fear by the people.

Although AKI has been described in other VHF,[17-19] little is known about the incidence of AKI in LF. In our study, 12.8% of the patients developed AKI during admission, and this is consistent with the finding of 9.4% among 416 patients seen within 22 months in a tertiary medical center in Southwest Nigeria.[20] It is, however, lower than 28% reported from another center in South-South Nigeria.[14] The marked disparity between the two studies may be related to the definition of AKI used in the latter, in which SCr was used at a reference value of <2 mg/dl (177 μmol/L), this could lead to an overestimation of the prevalence.

Several studies have documented the adverse effect of AKI among patients with LF.[13,14,20,21] This is also true in this study in which AKI was found to be significantly associated with worse outcomes. Advancing age, serum urea, and creatinine were each associated with mortality after adjusting for confounders. From these studies, it has become obvious that deranged kidney function presenting as either raised serum urea, creatinine, or decreased urine output are major factors affecting outcomes in patients with LF. This observation signifies that in patients the LF, maintenance of euvolemia is the single most important intervention to prevent the development of AKI and subsequent poor outcome.

This study also found that elevated systolic blood pressure is associated with the development of AKI in LF patients. This suggests that hypertensive nephrosclerosis may be a factor contributing to or aggravating the deranged kidney function seen in LF patients. Hence, the assessment of other comorbid conditions should be an integral part of the management of these patients to prevent worse outcomes. Although there was no significant statistical association between the time of presentation to the health-care facility and outcome, prompt administering of ribavirin in all confirmed LF patients will certainly help in reducing viremia, and subsequent effects of the virus on other organs such as the kidney.

Conclusion

LF is a neglected tropical disease that is associated with significant CFR. Being a multisystemic illness, adequate attention should be given to the maintenance of euvolemia and treatment of other comorbidities to curb the higher prevalence of AKI among patients. It is also important that adequate attention be given to the early institution of the antiviral drug – ribavirin. These factors will help in reducing the number of patients that may develop AKI and who may require haemodialysis.

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Conflicts of interest

There are no conflicts of interest.

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