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Predictors of In-hospital Mortality In Patients With RT-PCR Confirmed Lassa Fever Infection Treated At A National Treatment Center, South West Nigeria

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ABSTRACT

***Background**: Lassa fever (LF) infection is one of the viral hemorrhagic fever diseases found mainly in Sub-Saharan West Africa, including Nigeria. The case fatality rate is 60% among patients with Lassa fever complicated by AKI in one center study in Nigeria.*

Clinical and laboratory parameter has been documented as predictors of mortality among confirmed Lassa fever infected patients. Therefore, we decided to conduct similar study in our hospital to determine predictors of in-hospital mortality among Lassa fever infected patients.

***Aim**: This study was designed to determine the in-hospital clinical and laboratory predictors of outcome among RT-PCR (Real Time- Polymerase Chain Reaction) diagnosed Lassa fever patients.*

***Methodology**: This was a descriptive retrospective study involving the assessment of records of confirmed LF infected patients that were managed at the center from December 2019 to December 2020. 147 medical case record files of patients were retrieved for this study.*

***Results**: We found in our hospital setting, altered sensorium (p=0.001), seizures (p=0.001), bleeding diathesis (p=0.001), oliguria (p=0.001), elevated urea (p=0.001), elevated creatinine (p=0.001), hypoalbuminaemia (P=0.001), elevated SGOT (P=0.008) as significant predictors on in-hospital mortality.*

***Conclusion**: This study has helped us to identify the clinical parameters such as bleeding, central nervous system affectation, oliguria, tachycardia, tachypnea, hypoxaemia and laboratory parameters such as, elevated urea, elevated creatinine, hypoalbuminaemia as predictors of in-hospital mortality in RT-PCR confirmed Lassa fever patients. We believe early recognition of derangements of these parameters and with prompt intervention shall help to improve standards of care and outcome.*

Keywords
Lassa fever, In-hospital mortality, RT-PCR, Outcome, Federal Medical Center Owo.

Introduction
Lassa fever (LF) infection is one of the acute viral hemorrhagic fever diseases found mainly in Sub–Saharan West–Africa, including Nigeria [1]. Lassa mammarenavirus (LASV) is an arenavirus that causes LF infection in humans and other primates. LASV is an emerging virus and a selected agent, requiring Biosafety Level 4-equivalent containment. The multimammate rat– *Mastomys natalensis,*[1], was found to be the main reservoir (primary host) of this zoonotic virus in Sub–Saharan West–Africa, able to shed LASV in its urine and feces without exhibiting visible symptoms of infestation [1,2]. It is estimated that about 100,000 to 300,000 LF infections occur annually, with approximately 5,000 deaths [1-3].

The clinical spectrum of Lassa fever disease ranges from asymptomatic to fulminant multisystemic disease with a case fatality rate (CFR) of 24% from a retrospective review at Irrua Specialist Teaching Hospital in Edo State, Nigeria [4]. The incubation period is six to twenty-one days; however, the virus is shed in the urine of infected individuals for three to nine weeks and in semen for up to three months [5].

AKI a known predictor of outcome, complicating Lassa fever infection has a case fatality rate as high as 60% in one center study in Nigeria [6].

A previous study done has documented the presence of hypoalbuminaemia, reversal of albumin globulin ratio and acute kidney injury as factors associated with morbidity among hospitalized Lassa fever patients [7,8].

Complications of Lassa fever such as, acute kidney injury and central nervous manifestations were associated with poor outcome in a study done in South, South Nigeria [9].

This study is aimed at determining factors that may predict the outcome of Lassa fever infected patients treated in our hospital with the aim of strengthening monitoring, evaluation of our patients and to recommend treatment guidelines to improve standard of care for patients with Lassa fever disease.

Methodology
The study was conducted in the Infection Control Center of Federal Medical Center, Owo, Ondo State Nigeria a dedicated treatment center for Lassa Fever Virus Infection. This Hospital is located in the South West region of Nigeria.

It was a retrospective observational study that was aimed to determine the factors that may be associated with mortality among confirmed cases of Lassa Fever Virus Infection.

We retrieved and reviewed 147 case files of confirmed Lassa Virus infection from the hospital records department from December 2019 to December 2020.

Using our questionnaire, we documented patient's demographic, Social, Clinical and Laboratory data.

Inclusion Criteria
Case file of confirmed LF infected patients that were managed at the Infection Control Unit of the hospital.

Ethical Consideration and Informed Consent
Ethical clearance/approval was obtained from the Institutional Health Research Ethical Committee before commencing this study. Participants' confidentiality was respected and maintained by ensuring that no unauthorized person had access to the information on the data information sheets, that no information can be traced to the subjects as coding system was used for the data information sheets instead of writing the patients' names on them and no unauthorized use of information was made.

Data Analysis
The statistical package software for social sciences (SPSS^{R}) version 21.0 was used for data entry, validation and analysis. Frequencies and proportions were generated and presented using tables and figures where necessary. Bivariate analysis was carried out using Pearson correlation test, Chi-square test and Fisher exact test for comparison of proportions for categorical variables and independent student t-test for comparison of means for continuous variables where necessary. The level of statistical significance was defined by $p < 0.05$.

Equipment
Quantitative PCR machine, Model Rotor-Gene Q, S/N RO516117, Qiagen Hilden,Germany, manufactured in Malaysia was used to diagnose positive cases of Lassa fever.

Biochemistry analyzer Piccolo, type: TS-100C, S/N: 01014316120781, made in Latvia, Biosan SIA. Extraction centrifuge, Eppendorf AG, S/N 5418FL724392, Designed and engineered in Germany, assembled in USA. This was used to analyze biochemical parameters.

Automated Haematology analyzer pocH-100i, S/N G5669, Sysmex corporation,03/2018 made in Japan. This was used to analyze haematological parameters.

Results
There were 147 case file of Lassa fever infected patients retrieved for this study out of which, 79 (53.7%) were males, 68 (46.3%) were females. Majority of them were within the age group of 18 – 44 years (61.2%), the mean age of the patients was 38.47 ± 16.48 years. The overall case fatality was 32%. The males were worst hit (55%). Laboratory parameter influencing outcome with associated case fatality rate with statistical significance set at $P<0.05$ includes;

urea (p=0.001), elevated Creatinine (p=0.001), hypoalbuminaemia (P=0.001), elevated serum glutamic oxaloacetic transaminase (SGOT) (P=0.008). The mean random blood sugar (RBS), neutrophil and lymphocytes were found to be statistically significantly lower for those who survived; this could mean lower inflammatory response among this category of patients and should open the doors for future study.

Table 1: Social demographic parameters of patients managed for Lassa fever.

Variables	Frequency	Percentage
Gender		
Male	79	53.7
Female	68	46.3
Total	147	100
Age		
<18 years	5	3.4
18-44years	90	61.2
45-64years	41	27.9
=>65years	11	7.5
Occupation		
Artisan	14	9.5
Civil Servant	3	2.0
Clergy	4	2.7
Farming	6	4.1
Health attendant	1	.7
Housewife	1	.7
Lab Worker	1	.7
Nurse	3	2.0
Retired	4	2.7
Student	16	10.9
Trading	11	7.5
Total	147	100
Marital status		
Single	23	32.9
Married	46	65.7
Widowed	1	1.4
Total	70	100.0
Ethnicity		
Yoruba	64	84.2
Igbo	10	13.2
Hausa	2	2.6
Total	76	100.0

Table 2 below shows the mean biochemical parameters of confirmed Lassa fever patients that were managed at the treatment center.

Table 2: Mean biochemical parameters of confirmed Lassa fever cases.

Variable	Frequency	Mean ± SD
NA	144	135.7500 ± 8.68042
K	139	4.1281 ± .95409
Cl	142	103.352 ± 6.53327
HCO	142	21.470 ± 5.55194
Urea	146	14.3151 ± 15.60302
Creatinine	143	360.0979 ± 415.97451
Albumin	100	26.6900 ± 6.84562
SGOT	91	135.1758 ± 208.46511
SGPT	86	279.5116 ± 403.76853

Table 3: Laboratory Outcome Defining Variables.

Variable	Survived (Mean ± *S.D*)	Died (Mean ± *S.D*)	P-Value
Sodium	134.81 ± 8.43	137.84 ± 9.09	0.047
Potassium	3.92 ± 0.76	4.65 ± 1.18	**0.020**
Chloride	103.43 ± 5.42	103.14 ± 8.59	**0.037**
Bicarbonate	23.68 ± 4.01	16.83 ± 5.64	**0.001**
Urea	7.43 ± 10.14	28.40 ± 15.45	**0.001**
Creatinine	180.75 ± 273.80	456.41 ± 407.45	**0.020**
Albumin	29.21 ± 6.06	20.70 ± 4.57	**0.001**
SGOT	89.63 ± 114.24	116.04 ± 128.54	**0.008**
RBS	5.22 ± 2.56	7.41 ± 6.18	**0.009**
PCV	29 ± 8	30 ± 9	0.279
Neutrophil	5004.4 ± 4493.34	9414 ± 7579.90	**0.001**
Lymphocytes	2105.18 ± 1229.80	4418.98 ± 4101.21	**0.001**
Platelet	217011 ± 10424.5	135309.5 ± 99196.16	**0.001**

Further analysis as seen in table 4 below, shows that a total of 47(32.4%) confirmed cases died during the period of this study, the outcome of the last patients could not be verified, majority of the patients survived 98(67.6%).

The major clinical predictors of mortality were; bleeding diathesis, altered sensorium, oliguria, and seizures, see table 5 below.

Table 4: Outcome indices among confirmed Lassa fever cases (survived/died).

Variable	Frequency	Percentage
Died	47	32.4
Survived	98	67.6
Total	145	100.0

Table 5: Clinical outcome defining variables.

Variables	Died	Survived	p-value
Fever			
Yes	47	95	
No	0	3	0.306
Cough			
Yes	16	29	
No	31	68	0.375
Altered sensorium			
Yes	22	11	
No	23	87	**0.0001**
Bleeding diathesis			
Yes	35	29	
No	11	66	**0.0001**
Diarrhea			
Yes	29	45	
No	18	52	0.061
Vomiting			
Yes	29	70	
No	18	28	0.162
Oliguria			
Yes	31	12	
No	16	84	**0.0001**
Seizures			
Yes	**11**	**4**	
No	**35**	**93**	**0.0001**

Abdominal pain			
Yes	**31**	**55**	
No	**16**	**43**	0.172
Headache			
Yes	**25**	**62**	
No	**22**	**36**	0.164
Sore throat			
Yes	**9**	**16**	
No	**37**	**81**	0.408

Table 6: Mean clinical outcome defining parameters.

Variables (Mean ± SD)	Survived	Died	P=value
Temperature	37.71 ± 1.01	38.56 ± 1.03	0.0001
Respiratory rate	23.55 ± 4.31	31.82 ± 10.52	0.0001
Pulse rate	89.31 ± 16.60	101.47 ± 17.17	0.0001
Oxygen saturation	97.80 ± 1.92	82.32 ± 19.43	0.0001

Discussion

As stated in the introduction above, the aim of this study is to determine the clinical and laboratory predictors of in-hospital mortality among confirmed Lassa fever cases.

Although some studies have reported outcome defining criteria among confirmed Lassa fever patients [9], this study did not only corroborate those studies but clearly outlined the outcome defining variables such as survival or death and the clinical and laboratory parameters that are predictors of outcomes. This study has shown a case fatality of 32.4% compared to 60%, which is lower than what was reported in a similar study [6]. The reason could be because treatment in our center is free and patient had adequate access to supportive treatment such as antibiotics, intravenous fluids, blood transfusion and haemodialysis. The observed clinical predictors of in-hospital mortality include, bleeding diathesis (p=0.001) presenting as haemoglobinuria, craniofacial bleeds, bleeding from intravenous sites, miscarriages. Contributors to bleeding diathesis may be due to superimposed sepsis, bone marrow suppression and platelet dysfunction [10]. Another, clinical predictor of outcome was encephalopathy which is a central nervous system manifestation, which manifest as altered sensorium (p=0.0001), confusion (p=0.0001), seizures (p=0.001). Majority of patients who presented with encephalopathy had worst outcome when compared with patients who did not. We also found that patient who presented with oliguria (p=0.0001) a sign of AKI had worst outcome which is death compared with those who did not.

The study has also shown the mean temperature, respiratory rate, pulse rate and low oxygen saturation using pulse oximeter as significant predictors of in-hospital outcome of confirmed Lassa fever infected patients. Laboratory evidences of elevated urea, elevated Creatinine, hypoalbuminaemia and elevated SGOT, neutrophilia and lymphocytosis are predictors of worst outcome in confirmed patients with Lassa fever when compared to patients who do not have any of the above. A recent study showed that plasminogen activator inhibitor-1, soluble thrombomodulin and soluble tumour necrosis factor receptor superfamily member 1A have high prediction accuracy to outcome (death, survived) [11].

Conclusion

This study has demonstrated in our hospital setting, clinical parameters such as bleeding, central nervous system affectation, oliguria and laboratory parameters such as; elevated urea, elevated creatinine, hypoalbuminaemia as predictors of intra-hospital mortality in RT-PCR confirmed Lassa fever patients and therefore, should be evaluated for promptly to improve the standard of care and outcomes.

Recommendations

We recommend prompt Dialysis intervention and ICU care for patients with oliguria, azotemia and electrolyte derangement and seizures. Prompt transfusion with platelet concentrate or fresh whole blood transfusion should be given to those presenting with bleeding diathesis. Continuous oxygen administration should be available for those with low SpO2. Mechanical Ventilation may be necessary for those with rapidly deteriorating blood oxygen saturation.

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