Original Article

Risk Factors of Inpatients Mortality of Visceral Leishmaniasis, Khartoum State, Sudan

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Abstract

Background: Visceral leishmaniasis (VL) is one of the common infections in Sudan and can be associated with an increase in morbidity and mortality. The aim of this study was to assess the risk factors associated with mortality and morbidity with VL. **Materials and Methods:** This is a cross-sectional hospital-based study that recruited 150 patients with VL from two centers in Khartoum. Secondary data were extracted from the patient records, and data were analyzed using SPSS version 24.0. **Results:** The study included 2.5% of infants, 39.4% children, and 58% of adults. Male represents 77.3% of the cohort, and total mortality was 16%. Among the death reported 12.5% in infants, 16.7% were children, and 70.8% were in adults. Laboratory parameters significantly associated with mortality in univariate analysis were low white cell count, low platelets, high creatinine, and high liver enzymes. While risk factors such as infant, male, acquired infection from Eastern Sudan or White Nile, weight loss, morbid diseases, and concomitant bacterial infections were also associated with significant mortality in univariate analysis. Importantly, logistic regression analysis revealed significant association with infant ($P = 0.02$), concomitant bacterial infections ($P = 0.003$), comorbid disease ($P = 0.001$), low total blood cell count ($P = 0.018$), low platelets ($P = 0.013$), and high aspartate transaminase/alanine aminotransferase ($P = 0.013$). **Conclusion:** Health education and awareness are needed in terms of prevention and control, especially with high mortality seen in the infant. Treatment of underlying co-morbid diseases and bacterial infections are important to enhance survival. Patients with Leishmania are vulnerable; therefore, regular routine blood tests are an essential part of management to manage complications such as renal, hepatic failure, or severe anemia.

Keywords: Inpatient mortality, risk factors, Sudanese patients, visceral leishmaniasis

Introduction

Leishmaniasis is a serious challenge for health authorities in a big country like Sudan. This can be attributed to the fact that its transmitted by female sand-fly, leading to an intracellular protozoa parasite. Depending on the immune system of the host, the disease may not show any clinical presentation and lead to self-resolving. Unfortunately, leishmaniasis can be associated with cutaneous ulcer localized or disseminated and mutilating mucocutaneous disease. Death can occur as a result of infection of the reticulo-endothelial system and lethal systemic illness.[1] Many factors lead to an increase in infection with leishmaniasis within recent years. For instance, human immunodeficiency virus (HIV) and tuberculosis (TB) are associated with leishmaniasis. The disease affects globally around 12 million people, with 900,000–1.3 million new cases each year. This increase in infection rate was attributed in part to an increase in global travel.[2] Several environmental, social, and economic reasons also lead to an increase in the prevalence of leishmaniasis. For instance, leishmaniasis is the disease of the poor populations who also suffer from malnutrition.

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Environmental factors such as mining, dam building, and large irrigation schemes with road construction in developing countries may all lead to an increase in the number of sand fly and hence leishmaniasis.[3] It worth mentioning that in 1996 in Kabul, the capital of Afghanistan, the resurgence of visceral leishmaniasis (VL) has occurred because of deficiencies in the control of the vector (sand-fly) and lack of access to medical treatment due to the cost and increasing drug resistance to first-line treatment.[4] Because HIV/AID increases susceptibility to infections with leishmaniasis approximately by 100–1000, one challenge for African countries will be how to deal with an increase in the number of individuals who suffer from leishmaniasis and HIV infection.[4] Children are at greater risk than adults in endemic areas. Incomplete therapy of the initial disease is also another important risk factor for recurrence.[1-4]

Sudan has the highest number of reported cases of leishmaniasis in East Africa[5] where the disease is endemic since the early 1900s, in particular in eastern and central regions.[6] Due to lack of or no access to medical facilities in rural areas in Sudan, the diagnosis of VL can be late or when complications were diagnosed.[6] The objective of this study was to investigate the risk factors associated with VL that lead to an increase in morbidity and mortality in hospital patients in Khartoum state, Sudan.

Materials and Methods

Data collection

This a descriptive cross-sectional hospital-based study. The study is conducted in Tropical Medicine teaching Hospital in Omdurman and Jaafar Ibn Auf Pediatric teaching Hospital (both are known centers for the treatment of visceral leishmania), from January 2016 to December 2017. Record of all patients admitted to both hospitals during the study period were included in the study. Secondary Data was extracted from the patient's records and then re-entered into a predesigned data collection form, cleaned and analyzed using SPSS version 24. 24 (SPSS Inc., Chicago, IL, USA).

Statistical analysis

Descriptive statistics in terms of frequency tables with percentages were classified each row by total population column (Survival vs. Death) using cross-tabulation. Furthermore, analysis to determine the associations between the main outcome variable (inpatients' mortality due to VL) was the dependent variable, and the other relevant factors as the independent variable with Chi-square test (for categorical variables) and logistic regression analysis univariate and multivariate were used for analysis odds ratio (OR) with a 95% confidence interval (CI) was calculated and statistical significance was defined as $P < 0.05$.

Ethical clearance and approval

Ethical clearance and approval for conducting this research were obtained from the Khartoum state Ministry of the health research department.

Results

The study included 150 patients, 2.5% (4) were infants, 39.4% (59) were children, and 58% (87) were adults. Male represents 77.3% of the cohort. Areas of acquisition of the disease were Kordofan 34%, East of Sudan 24%, White Nile 14%, South Sudan 8.7%, Dar four 8%, Blue Nile 6%, and Khartoum 4.7%. Among the death reported, 12.5% were among infants, 16.7% of children, and 70.8 were in adults. Importantly, 41.7% of death noted were among those who acquired the disease in Eastern Sudan and 20.8% among those in Kordofan [Table 1].

Table 2 shows the clinical presentations and laboratory investigations of participants and percentages of survival and mortality with VL. The highest percentage of survival and death was seen with a disease duration between 1 and 6 months. Weight loss, edema, bleeding, bleeding, jaundice, and cough were observed in 78.7%, 15.3%, 15.3%, 22.7%, and 7.3%, respectively. Spleen size >8 cm was seen 31.3%, primary infection with VL was encountered in 88%. HIV and TB were reported in 7.3%, 7.3, respectively. Secondary bacterial infections were observed in 41.3%. Laboratory investigations were noted to be also in the abnormal range in the large number of patients. For instance, abnormal hemoglobin, white cell count, platelets, high creatinine, high liver enzymes, and low

Table 1: Showing the age, sex and origin of patients from different parts of Sudan

Variable		Survival (*n*=126) 84%	Death (*n*=24) 16%	Total (*n*=150)100%
Age	Infant	0.8%	(3) 12.5%	(4) 2.6%
	Children	(55) 43.6%	(4) 16.7%	(59)39.4%
	Adult	(70)55.6%	(17)70.8%	(87)58.0%
SEX	Male	100 (79.4%)	16(66.7%)	116(77.3%)
	Female	26(20.6%)	8(33.3%)	34(22.7%)
Area of disease Acquisition	Dar four	(10) 7.9%	(2) 8.3%	(12) 8.0%
	White Nile	(17) 13.5%	(4) 16.7%	(21) 14.0%
	Kordofan	(47)37.3%	(5)20.8%	(52) 34.7%
	South Sudan	(12) 9.5%	(1) 4.2%	(13) 8.7%
	East Sudan	(26) 20.6%	(10) 41.7%	(36) 24.0%
	Khartoum	(7) 5.6%	(0)0.0%	(7) 4.7%
	Blue Nile	(7) 5.6%	(2) 8.3%	(9) 6.0%

Table 2: Clinical presentations and laboratory investigations of participants and percentages of survival and mortality with VL

Variable		Survival(n=126)%	Death (n=24)%	Total (n=150)%
Duration of illness	<1 month	(22) 17.5%	2(8.3%)	(24)16.0%
	1-6m	(96) 76.2%	(20) 83.3%	(116) 77.3%
	6 - 12m	(8) 6.3%	(2) 8.3%	(10) 6.7%
Weight loss	Yes	(101) 80.2%	(17) 70.8%	(118) 78.7%
	No	(25) 19.8%	(7) 29.2%	(32) 21.3%
Oedema	Yes	(17) 13.5%	(6) 25.0%	(23) 15.3%
	No	(109) 86.5%	(18) 75.0%	(127) 84.7%
bleeding	Yes	(14) 11.1%	(9) 37.5%	(23) 15.3%
	No	(112) 88.9%	(15) 62.5%	(127) 84.7%
Jaundice	Yes	(24) 19.0%	(10) 41.7%	(34) 22.7%
	No	(102) 81.0%	(14) 58.3%	(116) 77.3%
Cough	Yes	(9) 7.1%	(2) 8.3%	(11) 7.3%
	NO	(117) 92.9%	(22) 91.7%	(139) 92.7%
Spleen size	No	(24) 19.0%	(6) 25.0%	(30) 20.0%
	≤4CM	(12) 9.5%	(1) 4.2%	(13) 8.7%
	4-8 CM	(49) 38.9%	(11) 45.8%	(60) 40.0%
	≥8cm	(41) 32.5%	(6) 25.0%	(47) 31.3%
Type VL	Primary VL	(111) 88.1%	(21) 87.5%	(132) 88.0%
	Relapse	(15) 11.9%	(3) 12.5%	(18) 12.0%
HIV/VL	Yes	(10) 7.9%	(1) 4.2%	(11) 7.3%
	NO	(116) 92.1%	(23) 95.8%	(139) 92.7%
TB/VL	YES	(9) 7.1%	(2) 8.3%	(11)7.3%
	NO	(117) 92.9%	(22) 91.7%	(139) 92.7%
Comorbid disease	yes	(9) 7.1%	(8) 33.3%	(17) 11.3%
	No	(117) 92.9%	(16) 66.7%	(133) 88.7%
Secondary bacterial infection	yes	(47) 37.3%	(15) 62.5%	(62) 41.3%
	no	(79) 62.7%	(9) 37.5%	(88) 58.7%
HB	Normal	(11) 8.7%	(5) 20.8%	(16) 10.7%
	Abnormal	(115) 91.3%	(19) 79.2%	(134) 89.3%
WBCs	Normal	(28) 22.2%	(3) 12.5%	(31) 20.7%
	Abnormal	(98) 77.8%	(21) 87.5%	(119) 79.3%
Platelets	Normal	(40) 31.7%	(6) 25.0%	(46) 30.7%
	Abnormal	(86) 68.3%	(18) 75.0%	(104) 69.3%
High plasma creatinine	yes	(10) 7.9%	(12) 50.0%	(22) 14.7%
	no	(116) 92.1%	(12) 50.0%	(128) 85.3%
ALT/AST	High	(76) 60.3%	(10) 41.7%	(86) 57.3%
	Normal	(50) 39.7%	(14) 58.3%	(64) 42.7%
Albumin	>3	(73) 57.9%	(10) 41.7%	(83) 55.3%
	<3	(53) 42.1%	(14)58.3%	(67)44.7%

albumin were observed in 89.3%, 79.3%, 69.3%, 14.7, 57.3%, and 44.7%, respectively.

Univariate analysis showed that there was the statistical association with mortality and risk factors such as being infant, male, acquired infection from Eastern Sudan or White Nile, weight loss, morbid diseases, and concomitant bacterial infections. Investigations that significantly associated with mortality in univariate analysis were total white blood cell count (TWBC), low platelets, high creatinine, and high liver enzymes [Table 3]. Importantly, logistic regression analysis, which rely on dependent variable survival versus mortality for univariate and multivariate risk factors, revealed significant statistically association with infants (P = 0.02), concomitant bacterial infections (P = 0.003), comorbid disease (P = 0.001), low WBC (P = 0.018), low platelets (P = 0.013) and high aspartate transaminase/alanine aminotransferase (P = 0.013). However, univariate analysis showed a significant association with risk factors such as males, residency in Eastern Sudan, residency in White Nile, and weight loss. However, other risk factors did not show significant effect [Table 3].

Discussion

VL is the world's second-deadliest parasitic disease after malaria, and one of the most important health problems in Sudan, without treatment, VL is nearly always fatal.[7,8] The present study shows that most of the patients were males (77.3%) with

Table 3: Risk factors associated of inpatient mortality of visceral leishmaniosis, Khartoum state, Sudan, using univariate and multivariate analysis

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age						
Infant	17.857	1.7-179.8	.014	15.934	1.56-163.68	.020
Children	1.165	.4852.802	.732	1.287	.525-3.158	.581
Adult	1.052	.117-9.428	.964	1.103	.121-10.014	.931
Gender						
Male	1.923	0.742-4.983	0.001	1.574	.172-14.367	0.341
Female	.413	0.162-1.051	0.064	.481	.178-1.300	.149
Area of disease acquisition						
Kordafan	.442	.155-1.263	.128	.510	.172-1.508	.223
Darfour	.948	.194-4.627	.948	1.063	.209-5.415	.941
Eastern Sudan	2.747	1.096-6.887	.031	2.291	.869-6.036	.094
White Nile	1.282	.391-4.211	.009	1.136	.338-3.823	.080
Blue Nile	1.545	.301-7.935	.118	1.536	.296-7.962	.610
Khartoum	8.0 E-008	8.033E-008	.000	5.671E-008	5.671E-008	.000
South Sudan	.413	.051-3.335	.017	.408	.050-3.321	.402
Type of VL	1.057	0.281-3.975	.934	.957	0.281-3.975	.948
Clinical presentation						
Duration of illness	2.750	.330-22.921	.350	3.626	.417-31.499	.243
Weight loss	1.664	.622-4.446	.003	1.723	.629-4.722	.290
Odema	.468	.163-1.345	.159	.439	.137-1.402	.165
Bleeding	.208	.077-.564	.002	.146	.048-.442	.001
Jaundice	.329	.131-.831	.019	.297	.114-.777	.013
Cough	.846	.171-4.184	.838	.847	.166-4.310	.841
Spleen size	.585	.170-2.020	.397	.605	.172-2.134	.435
HIV	.504	.062-4.134	.524	.519	.063-4.290	.543
TB	.846	.171-4.184	.838	.846	.171-4.184	.838
Comorbid disease	6.500	2.19-19.260	.001	6.143	2.053-18.379	.001
Concomitant bacterial infections	2.801	1.137-6.903	.025	4.940	1.719-14.193	.003
Hb	.363	.114-1.163	.088	.400	.123-1.297	.127
TWBCs	2.000	.556-7.197	.000	2.153	.590-7.852	.018
Platelets	1.395	.515-3.782	.000	1.420	.520- 3.874	.013
High plasma creatinine	.086	.031-.241	.000	.060	.019-.191	.000
ALT/AST	2.128	.877-5.164	.000	2.641	1.028-6.790	.044
Albumin	1.928	.796-4.673	.146	1.96	.791- 4.809	.147

higher mortality. This inline with the finding of the largest report of a 14-years registry (2002–2015) about cumulative cases and mortality of visceral leishmaniasis done in Eastern Sudan.[7] The high prevalence of VL among males in the study can be attributed to the greater exposure of males than females to the sand fly vector due to differences in occupations.[8-14] The mortality rate (16.0%) observed in the present study is higher than that reported by Nail *et al*., 2013, which was 5.6%,[14] and less than the fatality reported in 1998.[13] Importantly, several studies showed leishmaniasis in children is associated with a higher rate of morbidity and mortality (especially those <1 year).[14-18] Our study showed that the age of the patient is a strong indicator of the poor clinical course of VL as infants shows 17.9 risk of mortality compared to another age group. This can be attributed in part to the immaturity of the immune system in infants and children.[19,20] Furthermore, children exhibit increased interleukin-10 levels and L-arginine secretion, which are factors associated with parasite persistence and greater VL severity. These parameters, coupled with the immaturity of the immune system, could explain the poor prognosis for this age group.[21-27]

Patients who acquire the disease from Eastern Sudan in our study showed 2.74 higher risk of mortality when compared with patients coming from other VL foci. Furthermore, patients from Eastern Sudan in our study were noticed to have the more complicated clinical presentation. For instance, VL was associated with an increased incidence of other comorbid diseases and renal impairment ($P = 0.018–0.002$, respectively). This may explain the higher mortality among patients from Eastern Sudan compared to White Nile patients and patients from other regions. Nail, also noticed that mortality is higher in Eastern Sudan in comparison with other regions of Sudan.[28]

Importantly, it was shown in meta-analysis that thrombocytopenia was the second most important predictor of VL-induced death after bleeding and jaundice, especially when the platelet count is below 50×10^9/l.[17] In this study, low platelet count is associated with 1.39 higher risk of mortality. Although it is not possible to state with certainty the cause of thrombocytopenia in VL patients, splenic sequestration of platelets is possibly the main cause of a low platelet count.[17,29] Thus, detection of bleeding regardless of the cause at the first diagnosis or during treatment is crucial in the identification of severity and reduction of mortality from VL. Ministry of Health of Brazil[30] recommends platelet transfusion for VL patients presented with counts lower than 10×10^9/l. and individuals presenting with hemoglobin levels <7 g/Dl would receive transfusions of packed red cells.

Secondary bacterial infections are known to be an important cause of death among VL-infected individuals.[17] Many studies showed that the presence of coinfections was a strong predictor of adverse evolution.[16,17,20,21,29] This *per se* emphasis the importance of treating and preventing general infections. In this study, we have shown secondary bacterial infection was associated with 2.8 time's higher mortality. Another indicator that secondary bacterial infection was an important risk factor for hospital death from VL, the present study showed that patients with low TWBCs count have a statistically significant higher mortality compared with patients with normal WBCs (OR = 2.0*0* $P = 0.000$). Several studies showed a similar association between TWBCs and high mortality.[16-18,31] Therefore, proper septic screening, use of antibiotics and the constant monitoring of WBCs are mandatory steps throughout treatment.

Even though several studies showed that HIV/TB co-infection were associated with a poor prognosis,[17,18,31-34] the present study showed that HIV/TB co-infection were not associated with increased risk of mortality.[16-18,35,36]

It worth mentioning that renal impairment in the present study was also associated with increased mortality. Daher *et al*. showed an increase in serum creatinine was associated with increased morbidity and mortality.[37] Hence, early identification of these clinical and laboratory characteristics, at the time when patients are first attended, is extremely important for reducing mortality through instituting efficient therapeutic and prophylactic measures.

The study is not without limitations. The cross-sectional design of the study may not allow for the temporal relationship. The study recircuited patients from two centers in Khartoum in limited duration; therefore, the outcome of this study cannot be generalized for all Sudan. Despite these limitations, the study is novel and able to determine factors that associated with increase in mortality and morbidity with VL.

Conclusion

The main demographic features that affect mortality are the age of the patients mainly being infant, and acquisition of VL from Eastern Sudan compared to patients who acquire the disease from other VL foci in Sudan and South Sudan. The main clinical features that result in a higher risk of in-hospital death from VL are secondary bacterial infection and the presence of comorbid disease. HIV/VL and TB/VL co-infection did not increase the risk of in-hospital death from VL among our study participants. The main laboratory investigation that predicts adverse outcome are low platelet count, low WBCs, elevated liver enzymes, and renal impairment.

Research Quality and Ethics Statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting, and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was determined to require the Institutional Review Board/Ethics Committee review and the corresponding protocol/approval issued on 1/2/2019 by the Ministry of Health, state of Khartoum, Sudan. We also certify that we have not plagiarized the contents in this submission and have done a Plagiarism Check.

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Conflicts of interest

There are no conflicts of interest.

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