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TREATMENT OUTCOME AND DETERMINANTS AMONG PATIENTS WITH VISCERAL LEISHMANIASIS IN ARBA MINCH GENERAL HOSPITAL LEISHMANIASIS RESEARCH AND TREATMENT CENTER, GAMO GOFA ZONE, SNNPR, ETHIOPIA

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Abstract: - Introduction: *Visceral Leishmania represents a challenging diagnosis and treatment because the clinical picture of Visceral Leishmaniasis, so that the treatment outcome is compromised with many factors, thus study try to asses real picture of treatment outcome with determinants.*
Objective: *To assess treatment outcome and determinant factors among patient with visceral Leishmaniasis in Arba Minch General Hospital Leishmania Research and Treatment Center.*
Methods: *Institution-based, Cross-sectional, retrospective study was conducted among Leishmaniasis patients in Arba Minch general hospital. Patient charts that have been treated from January 2011-December 2015 were reviewed. A total of 348 charts were selected by Simple Random Sampling technique and included in the study. The data were entered and cleaned using Epi-info version 7.0 and analysis was carried out using SPSS-20 statistical packages. Multi-variate logistic regression analysis was carried out to identify the independent predictors of treatment outcome.*
Result: *A total of 348 patient's charts were included in the study. The prevalence of poor outcome was found to be 8.6%. The presence of bleeding/Epsitaxis[AOR=5;95% CI:1.3,19.3], tuberculosis[AOR=3.7;95%CI:1.83,6.3], septic syndrome[AOR=4.3;95% CI: 6.1,32], and adverse drug side effect[AOR=4.5;95%CI:2.73,13.6] were the independent predictors of treatment outcome.*
Conclusion and recommendation: *The prevalence of poor treatment outcome among patients with VL in the study area is high. Concomitant infection; bleeding/Epsitaxis, tuberculosis, septic syndrome and adverse side effect were independently associated with poor treatment outcome. The clinical management of VL in co-infected patients is a major challenge that requires new treatment approaches to improve its outcome.*
Keywords: *Level and Factors Associated With Dietary Diversity among Children Aged 6-23 Months in Aroressa Woreda, Sidama Zone, Snnpr, Ethiopia*

Introduction:

Leishmaniasis are a group of diseases prevalent in areas of the tropics, subtropics and southern Europe caused by more than 21 species of the protozoan genus Leishmania parasites and over 30 vectors maintain transmission (1, 2).The disease considering at risk of 350 million people and 2 million new cases occur yearly in over 98 endemic countries, of which 1–1.5 million are cutaneuse leishmania and 500,000 are Visceral Leishemania and most of them in the poorer regions of the globe (3, 4).

VL is the most severe form of leishmaniasis, almost always fatal if untreated [5]. An estimated 200,000 to 400,000 new cases and over 50 000 deaths annually occur worldwide each year, and from this, greater than 90% of VL human cases occur in six countries, namely Bangladesh, Brazil, Ethiopia, India, South Sudan, and Sudan [4,6]. Eastern Africa has the second highest number of VL cases, after the Indian Subcontinent. The disease is endemic in Eritrea, Ethiopia, Kenya, Somalia, Sudan, South Sudan, and Uganda (7, 8).

In Ethiopia, the first case of VL was documented in 1942 in the lower Omo plains, the southwestern part of the country (9). The disease has spread to become endemic in many parts of the country. The disease is prevalent mostly in lowland, arid areas, and the parasite involved is mainly Leishmania donovani, with an estimated annual incidence of more than 4,000 cases (10). Most important endemic foci include the Humera and Metema plains in the northwest, the Omo plains, the Aba Roba focus, and the Weyto River Valley in the southwest (11).

The socioeconomic impact of the leishmaniasis is not fully recognized though it is obvious they are poverty-related. The diseases are generally associated with malnutrition, displacement, poor housing, illiteracy, gender discrimination, weakness of the immune system, and lack of resources; they are also linked to environmental changes, such as deforestation, building of dams, new irrigation schemes and urbanization, and the accompanying migration of non-immune people to endemic areas (12)

Leishmaniasis is a treatable and curable disease. Early diagnosis and effective treatment prevent disability and death. The treatment of leishmaniasis depends mainly on its form and the parasite species involved. A limited number of drugs are available for the treatment of leishmaniasis and these face challenges including development of drug resistance, limited efficacy for different strains and species, and cost (12).

Drug toxicity and efficacy are the main factors to consider when choosing treatment, since relapse/recurrence is independent of drug choice. Relapses become increasingly unresponsive to anti-leishmanial drugs (10).

The risk of VL relapse/recurrence is related to at least two predictors, the number of previous VL episodes and the co commentate infection like HIV and tuberculosis (TB) adds a 2-fold increased the risk. This is likely to reflect the fact that such patients have had major co-infection other than VL. Therefore, vulnerable patients are patients with previous VL episodes, and patients with co morbidity (co-infection)(14).

VL can be a risk factor for malnutrition and can lead to low body mass index (BMI) (15). HIV, intestinal parasitic infections, anemia, poor protein, energy, iron, vitamin A, and zinc nutritional status increase the risk of VL manifestation and play a role in the expression of clinically overt VL disease in the endemic areas (16).

Malnourished children, who often suffer simultaneously from associated diseases such as tuberculosis, respiratory and/or intestinal infections are particularly vulnerable (6, 17). A cross sectional study conducted in Northwest Ethiopia indicated a significant association between severe malnutrition, intestinal parasitic infection, and VL (15).

In Ethiopia co infected patients are at higher risk of increased drug toxicity and poor treatment response like relapse and death(3,18).Worse outcomes and the treatment challenges faced by co infected patients as compared to immuno-competent patients are well documented (19).

Statement of the problem

The epidemiology of leishmaniasis is diverse and complex. Visceral leishmaniasis is being highly endemic in India, Brazil and East Africa. More than 90% of new cases are reported from six countries: Bangladesh, Brazil, Ethiopia, India, South Sudan and Sudan. The number of new cases worldwide each year is currently estimated to 300 000. (20) Visceral leishmaniasis causes an estimated over 50 000 deaths annually, placing leishmaniasis ninth in a global analysis of infectious diseases.(21)

The South-East Asia Region is the only Region with

a target for elimination of VL (kala-azar) as a public health problem (that is, < 1 case per 10 000 population per year at district or sub-district level) (22).

Leishmaniasis in East Africa remains a major public health problem, with no signs of reduction in case trends. The situation is complicated by remoteness, and difficult to access, recurrent epidemics, a weak health system, lack of appropriate tools, malnutrition, concomitant infections including co-infection with HIV and Leishmania, and insecurity in some of those areas and the difficulties of transporting diagnostic tests and medicines for case management (7).

Poverty increases the risk for VL. Poor housing and poor sanitary conditions may increase sand fly breeding and resting sites, as well as their access to humans. The flies are mainly attracted to crowded housing, as these provide a good source of blood-meals. Sleeping outside or on the ground may increase the risk of infection. This is especially more evident in nomadic populations and in men who work in agricultural or pastoral settings due to increased time spent outdoors and thus higher exposure to the sand fly. Part of a community that lives and/or has frequent contact with acacia trees and termite hills are at increased risk, since acacia trees and termite hills are common breeding and resting sites for certain species of sand flies (6, 23).

Ideally, treatment for visceral leishmaniasis should cure the patient, reduce the risk for relapse and for post kal azar dermal leishmania (PKDL) and reduce transmission of resistant parasites. Poor prognostic factors in antimony-treated visceral leishmaniasis patients are age > 45 years (in Africa), malnutrition (hypoalbuminaemia, edema), renal and hepatic co morbidity, concomitant infections, such as pneumonia, tuberculosis or HIV infection, or other immunosuppressive condition(3).

VL in Ethiopia is mainly endemic in five out of nine regions, with 2000–4500cases reported each year. The regions of Amhara and Tigray account for more than 85% of the cases. The disease has spread to new localities (Benishangul-Gumuz and Gambella). There are currently 17 treatment sites in five regions (6 in Tigray, 5 in Amhara, 1 in Southern Nations, Nationalities, and Peoples' Region, 3 in Oromia and 2 in Somali)(24).

The north-western VL focus in Ethiopia has the highest known VL/HIV co-infection rate in the world. Approximately 20-30% of VL patients are estimated to have HIV.(25,26) Co-infection, especially when combined with malnutrition, contributes to an increased fatality rate.(27)

In the southwest foci the Omo plains, Aba Roba plains and Weyto River Valley in Southern Nations and Nationalities People's Region (SNNPR) are areas of lowland with low rainfall. The majority of people in these foci are nomadic or semi-nomadic pastoralists. In such case Most of the population has been exposed to the disease and acquired some immunity, as indicated by a positivity rate of up to 64% using the leishmania skin test in some tribes (28).

Arba Minch General Hospital is one of the leishmania research and treatment centers of Leishmaniasis in SNNPR, Ethiopia which established to overcome the burden of the problem. Even though those few researches which had been undertaken in Ethiopia showed the magnitude, the predisposing factors and its complication in very few areas of the country, little has been explored about the effectiveness of anti leishmania drugs, but to my knowledge status of treatment outcome and determinants of VL in SNNPR in general and in Gamogoffa zone in particular was not conducted. Thus, this study is the sole study will be conducted in Gammo Goffa zone, Arba Minch General Hospital VL treatment and research center with the aim of identifying the status of treatment outcome and determinant factors among VL patients at Arba Minch General Hospital and will come up with up to date information.

Rationale of the study

Visceral leishmania is still one of the world's most neglected diseases, affecting largely the poorest of the poor, mainly in developing countries that are transmitted between humans and other mammalian hosts by phlebotomine sand flies. Studs conducted so far deal among visceral leishmania case that had HIV confection and their associated factors on treatment outcome. However treatment outcome may also be affected with different factors among HIV negative leishmania cases in other way. HIV may also be a predisposing factor on treatment outcome. Therefore, it is important to assess the reason of treatment outcome and factors related to treatment regimen to control and prevent the disease (10, 28).

Besides the limited studies undertaken on treatment outcome and associated factors in Ethiopia, there is no research based evidence in my study area of interest so far. Therefore, this study aims at assessing the treatment outcome and associated

factors of VL among patients in Arba Minch General Hospital leishmania Research and Treatment Centre. The study may significantly help in planning and implementing the future strategies for control of the disease. Moreover, this study may provide pathways and information for other researchers who want to conduct further study on the issue; consequently findings will help as a baseline data for future study.

Literature review:

There are an estimated annual incidence in half million new cases per year of visceral leishmaniasis (VL) globally. Although 90% of the new cases occur in just five countries (India, Bangladesh, Brazil, Nepal and Sudan), the unique problems posed by the disease in each setting affect the choice of treatment. In South Asia and East Africa, humans with VL, or post *kala-azar* dermal leishmaniasis, are the main reservoir for ongoing transmission of infection. Therefore, partially treated patients from these areas can develop VL parasites resistant to treatment, which in turn may be transmitted to new patients causing 'primary drug resistance' as has happened in India.(29)

In other foci, such as the Mediterranean, Middle East and Brazil, where the domestic dog is the principle reservoir of infection, parasite drug resistance is not such a concern. However, the infection principally occurs in children or immune compromised adults in these areas, which also affects treatment choices. (30)

Often, in East Africa, treatment is given under difficult field conditions with little possibility of monitoring or follow-up to malnourished and under-the-threat-of-war population (4,5,31).In a retrospective study conducted in Saptari District, Nepal from available data of last five years (2007-2012), Epidemiologically, VL cases seem to be in declining trend during last five years.(32)

Ethiopia is one of the six countries in which more than 90% of global Visceral Leishmaniasis (VL) cases occur and one of the ten countries with the highest estimated case counts, which together account for 70 to 75% of global estimated VL incidence VL are growing health problems in Ethiopia, with endemic areas that are continually spreading. Geographically, VL is found in Tigray, Amhara, Oromia, Afar, Somali and SNNPR [33].

Review of the burden of neglected tropical diseases in Ethiopia in the year 2012 indicated that every year, an estimated 3700–7400 cases occur in Ethiopia. The disease occurs in the lowlands of the northwest, central, south and southwestern parts of the country. In the north, the vector is associated with Acacia-Balanites forest, in the south with termite hills. In Ethiopia, VL affects mainly children and young adults (the mean age of affected in northern Ethiopia is 23) in endemic areas the mean age is much lower. In northwest Ethiopia, where migrant laborers are at risk of exposure to VL, annual incidence ranges from 5 to 8 cases per 1000(33).

A study conducted in Trend Analysis of Visceral Leishmaniasis at Addis Zemen Health Center North west Ethiopia in the year 2014 indicated that the overall prevalence of VL was found to be39.1%. The treatment outcome is better in VL patients who are treated in an early stage. Untreated VL patients act as a source of infection and therefore contribute to disease transmission in anthroponotic VL areas. (34)

Case series studied conducted in Somalia show information on good treatment outcome was available for (95.4%).An overall case-fatality rate of 3.9%. Clinical recovery rate was 93.2%. A total of (2.9%) patients were defaulted (35).

In addition, high treatment failure to SSG has been identified in some endemic areas with an incidence of up to 60% in some regions of Bihar, India [36]. However, no resistance to SSG has been documented in Africa. SSG has also been shown to be less effective and more toxic in HIV-infected patients. (37)

The study done related with risk factor of hospital death in Uganda Several risk factors were identified: age <6 and >15 years (in particular >45 years), female sex in patients with spleen sizes <14 cm, spleen size >14 cm in males, concomitant tuberculosis or liver disease, and occurrence of adverse events during treatment (39).

HIV /VL co-infection is the most contributors factors for treatment outcome of VL among leishmania patients were reviewed in different literatures.The study done in northwest Ethiopia confirms that patients with HIV /VL co-infection had poorer response rates to anti-leishmanial treatment and increased mortality three times higher in HIV positive than HIV-negative patients.(37,40).

Concomitant infections were routinely suspected in patients with poor clinical progress, for instance no subsiding or recurrent fever, during VL treatment. Concomitant TB infection was seen in 27.2% of

HIV-positive but only 6% of HIV-negative patients with VL (41)

The other study on bacterial infections in patients with visceral leishmaniasis show as bacterial infections in patients with VL can be as common as 60%, with respiratory and skin infections being the commonest (42).

A Retrospective Study of Risk Factors and Trends done in Southern Sudan shows higher odds of poor outcome (relapse) were associated with splenomegaly (on admission for, and discharge from, treatment for primary VL) and with SSG/PM treatment of primary VL. Including age, sex, year and treatment centre, admission spleen size grade >3 was associated with >4-fold higher odds of poor outcome (relapse) compared with size 0. In A similarly-adjusted model, 17-day SSG/PM was associated with >2-fold higher odds of relapse compared with 30-day SSG mono therapy. Young age (< 5 years) was not associated with risk of relapse. However, among children >5 years old, infancy (age <1 year) compared with age 1–4 years was associated with higher risk of relapse. (43)

A study conducted in Northern-west Ethiopia on university of Gonder revealed parasitic load has significantly associated with treatment outcome. Patients treated with SSG and by the end of treatment only 43.9% of patients were cured. The parasitological treatment failure and the case fatality rate were 31.6% and 14.0% respectively. High baseline parasite load (graded more than 4+) was significantly associated with treatment failure. (44)

HIV co-infection with VL leishmaniasis has significant association with treatment outcome a study conducted in northern Ethiopia showed that HIV Co-infected patients had a poorer outcome of treatment i.e. either death or treatment failure as compared to HIV negative leshmania patients. Same evidence was revealed on a study conducted in Brazil rural area that HIV co- infection was the risk factor for poor treatment outcome that is, VL and HIV co-infected patients had a higher mortality and treatment failure than immuno-competent patients. (5, 25, 45, 46)

Although sepsis has high prevalence and affects the outcome of patients with VL, studies done in Brazil showed sepsis was a main factor that affected the treatment outcome of patients with VL. (47)

In addition the peer review studies conducted in Addis Ababa implicate bacterial infections and sepsis among VL patients has been reported ranging from 15% to 84%. This review revels that sepsis was one of the associated factors with poor treatment outcome (death) in patients with VL. Patients with VL and sepsis have six times more risk to die than with VL but not sepsis. (48)

Nutritional status and Tb are also other risk factors for treatment outcome; in a study conducted in Tigray region indicated that Individuals with a body mass index (BMI) of less than 16 were four times more likely to die than those with a BMI of 16 or more. In similar study conducted in Gondar university Hospital and Addis Ababa university showed that nutritional status and Tuberculosis were some of the predicting variables in that individuals with body mass index (BMI) of 15 and below were identified as independent variable predicting death.(5,24,45)

A cross sectional study done in Northwest Ethiopia shows that intestinal parasitic infection was found to be significantly associated with severe malnutrition among VL patients. In this study 47.6% of VL patients were infected with one or more intestinal parasites. (49)

Considering clinical cure as the absence of hepatosplenomegaly On physical examination, the disappearance of fever and the normalization of all hematologic parameters, the analysis showed that 69% and 91% immunocompetent patients were cured at 2 and 6 months after treatment, respectively. (46)

Hepatomegaly was found in 47.1% of cases and history of bleeding in 53.8% of cases. Epistaxis accounted for 76.4 of the bleeding. Lymphadenopathy was found in 22% of the VL patients in this study. (45)

HIV infection and several other risk factors have been related to death, such as the presence of very low counts of neutrophils and platelets, dyspnea, jaundice, mucosal bleeding and bacterial infections (50-52). Death can be due to VL itself or direct drug toxicity. Moreover, both parasite and host determinants can influence the treatment failure rate (53).

VL is one of the neglected diseases in the world, affecting the poorest segment of rural populations. Studies have shown that In East Africa, the annual number of cases of VL in is estimated at 30,000 and related deaths at 4000.Especially in Sudan, Ethiopia and Kenya, VL is associated with high mortality and morbidity, exacerbated by poor nutritional status and the remote location. Incidence of VL is increasing

due to different risk factors like the higher incidence of immunosuppressive conditions such as HIV/AIDS, bacterial infection and sepses, poor nutritional states and other concomitant infection.

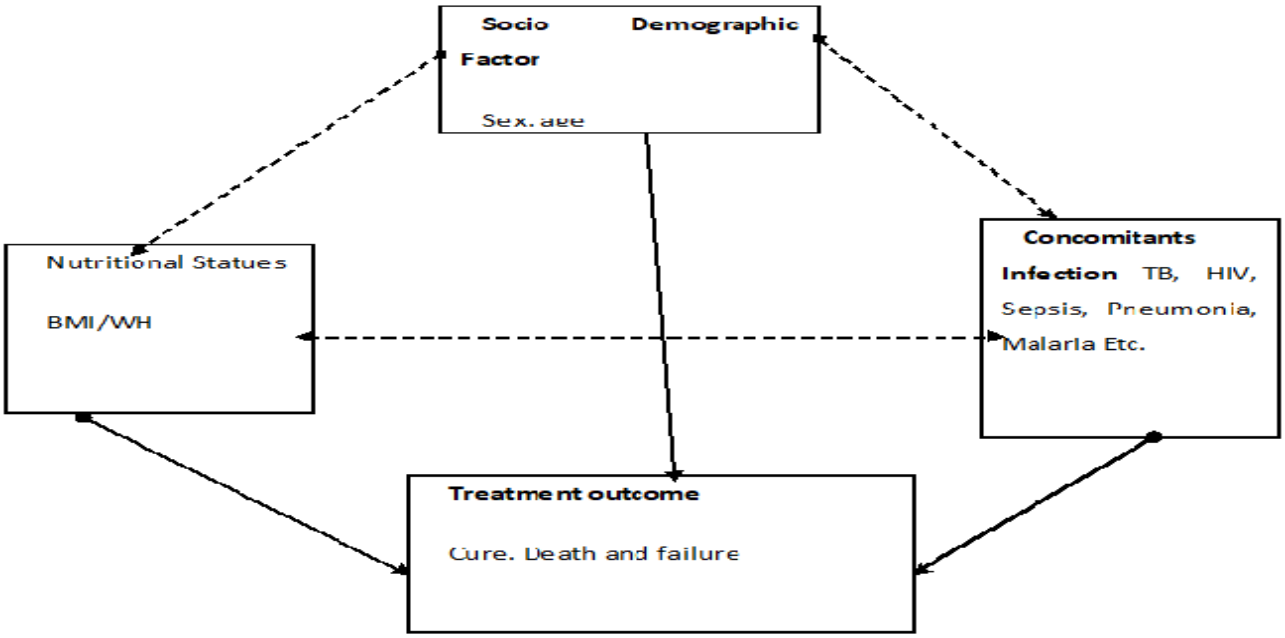
Research question

In regarding to the problem that needs to be researched on, researcher developed two major research questions that need to be answer at the end of time.

1. What factors determine the treatment outcome of VL among patients in AGH?

2. Is the treatment outcome of VL is good or poor among patient at AGH?

Conceptual frame work



Objectives:

General objectives

1. To assess treatment outcome and it's determinant among patients with visceral leishmaniasis(VL) who had been treated in Arba Minch General Hospital leishmania research and treatment centre.

2. 3.2 Specific objective
3. To identify the treatment outcome of visceral leishmaniasis treated at Arba Mimch general hospital, 2016.
4. To determine factors associated with the treatment outcome of visceral Leishmaniasis treated at Arba Minch General hospital, 2016.

Methods and Materials:

Study area and period

This study was conducted at Arba Minch general hospital which was established in 1961 E.C and located in Arba Minch town, the capital city of GamoGofa zone, southern Ethiopia.

Arba Minch hospital has a total of 410 workers. Among these 251 are health professionals, and 159 are administrative staffs. This hospital acting like a referral hospital and provides preventive, curative and rehabilitative care for people from GamoGofa Zone and other nearby zones. Though according to the information given from officials of the hospital, it serves more than two million people and annual patient flow is about 100,000. The hospital has 270 beds including Leishmaia Research and Treatment Center (LRTC). Major services given in the hospital are Dental treatment, Emergency services, ophthalmic service; chronic illness follow up care services for diabetic and other chronic illness, laboratory services, outpatient department service, pharmacy, Radiology, Ward activities and Leishmaia Research and Treatment Center (LRTC). Africa's first clinical research facility dedicated to

visceral leishmaniasis (VL), was opened in February 2006 by Drugs for Neglected Diseases initiative (DND*i*) in Arba Minch, Ethiopia. The building has 24 beds, separate examination and treatment rooms, a laboratory, offices for medical personnel, a rest area for patients and families, cooking facilities, and a water storage tank. In addition to leishmaia research, the center provides free treatment and care to all patients with leishmaniasis. Patients present to the center either spontaneously or are referred from other health institutions in the catchment area.

Study design

Institution-based, Cross-Sectional retrospective study was conducted by reviewing a five-year patient chart/record at Arba Minch General Hospital Leishmania research and treatment center.

4.3. Source population

All visceral leishmaniasis patients who had been treated at Arba Minch General Hospital Leishimania Research and Treatment Center.

Study population

Randomly selected Visceral Leishmaniasis patients who had been treated between January 2011 to December 2015 at AGH Leishmaniasis Research and Treatment Center.

Inclusion criteria

All Patients who were confirmed to be Visceral leishmaniasis patients, started treatment and declared completed treatment regimen or died within the course of treatment

Exclusion criteria

Patient's charts with incomplete clinical and laboratory (diagnostic workup) information were excluded.

Sample size and sampling procedure

Single population proportion formula was used to determine the sample size with prevalence of good treatment outcome of VL patients, 84.6% from a study in Gondar (40).

$$n = \frac{(Z_{\alpha/2})^2 (p) (1-P)}{d^2}$$

$$n = \frac{(1.96)^2 (0.846) (1-0.846)}{(0.05)^2} \qquad n = 200$$

Where, n = is desired sample size

$Z_{\alpha/2}$= is reliability coefficient which is 1.96 with 0.05 level of significance (α=5%)

P= is taken 84.6 percent for possible maximum estimation

d = margin of error (5%),

The investigator used EPi-info software to calculate the sample by using different factors which were associated with treatment outcome from different studies. From selected variables the patient with vomiting during treatment time is the maximum sample of this study. Therefore, the total calculated sample size for this study is 348 (Table 1). Simple random sampling technique was used to select 348 cases from the total 552 cases from the registration book.

Table 1: Factors associated with poor treatment outcome in patients with VL used from different previous study to calculate sample size (47,49,50).

Variables		%	OR	% CI	power	Sample size
Malnutrition	**Yes**	**45.9**	**2**	**95**	**90**	**306**
	No	**27.5**				
Vomiting	**Yes**	**28.6**	**2.5**	**95**	**90**	**348**
	No	**13.9**				
Dhiarria	**yes**	**25.2**	**3**	**95**	**90**	**306**
	No	**10.4**				

Study variable

Dependent variable: Treatment outcome (cure, death and treatment failure)

Independent variables: Socio-demographic characteristics (Age and Sex), Basic Clinical information (duration of illness, general condition of the patient) and condition at admission(Lymphadenopathy, Vomiting, Spleen size (cm), hematocrit (g/dl), Bleeding/Epestaxies),

parasite greed, fever, diarrhea, loss of appétit Presence of concomitant infection (Tuberculosis, Malaria, Sepsis, Pneumonia, HIV/ADIS), Nutritional status, and type of treatment and drug **failure**

Good treatment outcome (Initial Cure**)- is defined as a negative Test of Cure(ToC) at the end of the standard treatment [13].**

Initial cure: Eradication of parasites and/or improvement in clinical signs and symptoms (defervescence, weight gain, spleen size decrease) at the end of treatment.

Poor treatment outcome- Death or treatment failure

Treatment failure: A positive Test of Cure (ToC) at the end of the standard treatment indicates treatment failure

A total white cell count and **Platelet count** of <4500 ⁄ ll and of <150 000 ⁄ ll were used to define leucopenia and thrombocytopenia, respectively.

Concomitant infections: Are identified using a clinical algorithm supported with laboratory examinations of clinical specimens whenever possible.

Data collection procedure and collection instrument

After patients past exposure data extracted from previous medical records and electronic sources from LRTC, the patient folder was drawn by clinical Nurses from Arba Minch General hospital. The record reviews was done by two BSc nurses from Arba Minch General hospital and facilitated by the principal investigator. Data was extracted by using structured tool that was taken from previous studies and English version of tool was used to collect data, since it secondary data.

Data processing and analysis

The data was entered and cleaned using Epi-info version 7.0 and analysis was carried out using SPSS-20 statistical packages. Frequency, mean, and standard deviation were used to describe data and table and diagram were used to present important finding. Bivariable and multi- variable logistic regression analysis were employed to assess the association between independent and dependent variables. Odds ratio (OR) with 95% confidence interval was computed to show degree and presence association between independent and side effect.

Operational definitions

Treatment outcome- **Cure, Death, or treatment** dependentariable. Bivariate logistic regression was performed and variable with p<0.25 was transferred to multivariable logistic regression analysis. Step wise back ward Likelihood ratio method of model building was used. Goodness of test (model fitness) was checked by using Hosmer and Lemeshow test and the model was good (p-value >0.05). The association between predictor and outcome was checked and summarized by using Crude Odd ratio, Adjusted Odds ratio and 95% Confidence interval.

Data quality management

A carefully designed tool was prepared in English. Training was given to the data collectors about research objectives, sampling procedures, data collection mechanism and tool to collect data. Information on clinical evaluations and laboratory result form was cross checked with collected data in daily basis to check for completeness, accuracy, clarity, and consistency by the principal investigator on daily basis. Any error or ambiguity and incompleteness were corrected accordingly. The data was intensively cleaned up before its analysis

5. Ethical considerations

This study was conducted after obtaining ethical approval from Arba Minch University ethical review offices, since this is secondary data; it is difficult to assure informed and written consent from the patients, so that permission was secured from AMG Leshimania Treatment center. But confidentiality, and anonymity was kept and stored in password blocked PC.

6. Result:

General characteristics of study subjects

A total of 552 (443 males: 109 females) VL patients were admitted and treated at Arba Minch General Hospital from January 2011 to December 2015. Of whom, 348 fulfilled the inclusion criteria were included in the study. The mean age of participants was 15.5$\pm$ 9 SD. Two hundred and ninety two (83.9%) were males. Majority of the patients were children aged <16 years (55.7%), with a male: female ratio of 5:1.Majority, 151(43.4%) of patients were from Konso. Mean duration of illness before first consultation was 11.5 weeks (Table 2).

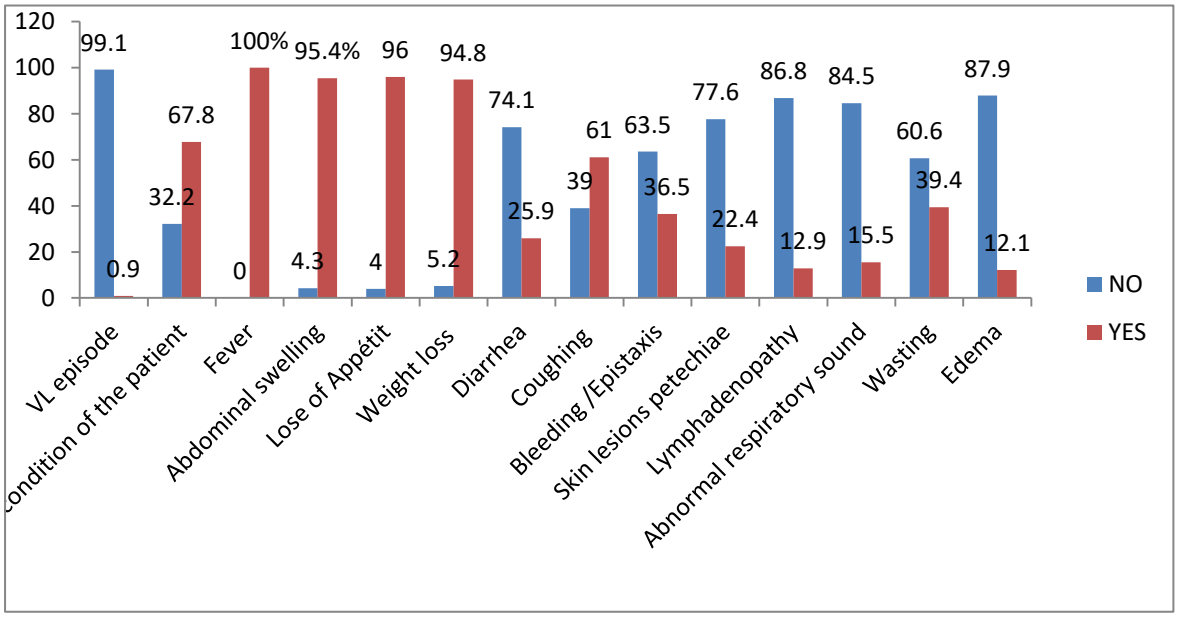
Table 2: General characteristics of VL patients who were treated at Arba Minch General Hospital, Gamo Gofa Zone, from January 2011-december 2015(N=348)

Variables	Characteristics	Frequency	Percent
Sex of respondent	Male	292	83.9
	Female	56	16.1
Travel to kalazar endemic area	No	272	78.2
	Yes	76	21.8
Place of resident	Konso	151	43.4
	Liben	104	29.9
	Gordola	23	6.6
	Hammer	36	10.3
	Derashe	20	5.7
	Other	14	4.1
Age of the respondent	0-5	36	10.3
	6-15	158	45.4
	≥16	154	44.3
Duration of illness	0-5 weeks	75	21.6
	6-10 weeks	93	26.7
	>10 weeks	180	51.7

Baseline Clinical characteristics and laboratory finding of study subjects

Mean length of fever is 3.73 days followed by 28.85 day of hospital stay. The core clinical features of VL commonly observed were: fever, splenomegaly, weight loss/ wasting, and clinical anemia. Cough, bleeding/epistaxis, and vomiting were frequently reported accompanying symptoms. Diarrhea, Skin Lesions, and lymph node enlargement were infrequent. Almost all of VL patients, 345(99.1%) with primary episodes. Fever was reported by all of the VL patients. Abdominal swelling, loss of appetite, weight loss, and cough was reported by 333(95.4%), 334(95.7), 330(94.8%), and 210(60.3%) VL patients respectively. (Figure 2).

Figure 2: Beseline clinical characteristics of VL patients who treated at Arba Minch general hospital, Gamo Gofa zone frome January 2011-Deceber2015(N=348)



For most of patients, 313(89.9%) VL diagnosis was confirmed by both serological through rk39 and parasitological exam of spleen aspirate. Spleenic aspiration was the commonest procedure employed in 304(87%)(Table 3).

Table 3: Baseline laboratory finding of VL patients who were treated at Arba Minch general hospital, GamoGofa zone, from January 2011-december 2015(N=348)

Variables		No	%
VL Diagnosis	serological	32	9.2
	parasitological	3	.9
	Both	313	89.9
Rapid Diagnostic Test Procedure(rk39)	Negative	4	1.1
	positive	337	96.8
	Not Done	7	2.0
Direct Agglutination Test Procedure(DAT)	positive	6	1.7
	Not done	342	98.3
parasitological diagnoses	Negative	2	.6
	Positive	317	91.1
	Not done	29	8.3
Aspiration Site	Spleen	304	87.4
	Bone Marrow	15	4.3
	Not Done	29	8.3
HIV Diagnosis	Negative	337	96.8

	Positive	11	3.2

Table 4 shows the key clinical and laboratory parameters in relation with treatment response. The mean spleen size on hospital admission is 11cm. While Spleen size at hospital discharge decreased more significantly in cured patients compared with, Spleen size at hospital admission there was a more pronounced increase in hematocrit at discharge and a greater increment in WBC and platelet count. And in similar way parasite grade at hospital admission and test of cure or hospital discharge sows dramatic change after VL treatment (Table 4).

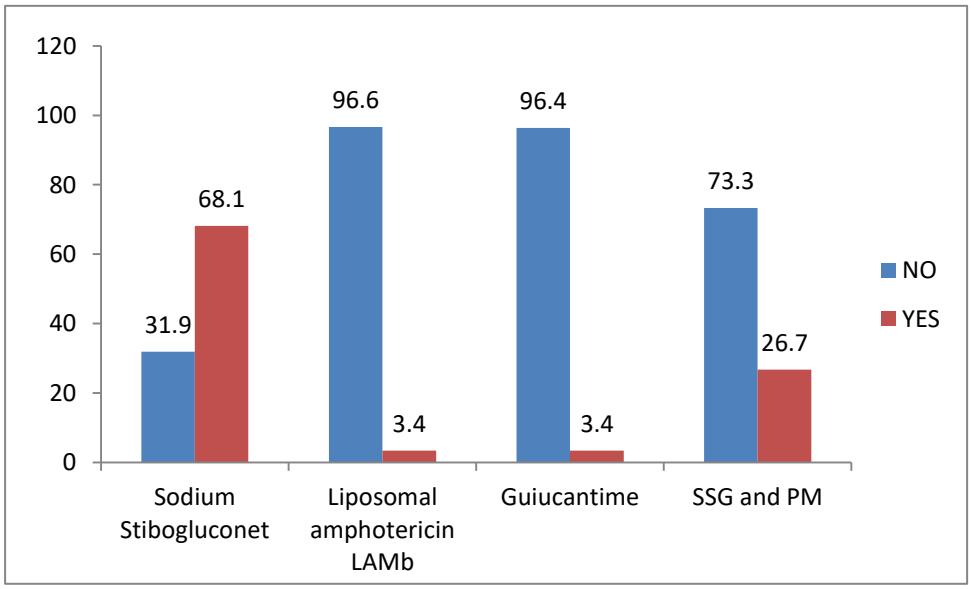
Table 4: Clinical and Laboratory parameters in relation with before and after treatment response of VL patients who were treated at Arba Minch general hospital, GamoGofa zone, from January 2011-december 2015(N=348)

Variables		No	%
Spleen size admission	<11cm	181	52
	≥11cm	165	47.4
Spleen size discharge	<11cm	313	92.6
	≥11cm	25	7.4
Parasite grad at admission	Negative	17	4.9
	positive	331	95.1
Parasite grad at discharge or Test of cure	Negative	318	91.4
	positive	30	8.6
Hemathocrit at admission	≤15 severe anemia	20	5.8
	>16 or ≤25moderate	187	54.0
	>26 or ≤30 mild	97	28.0
	>30 normal	42	12.1
Hematocrit discharge	≤15 severe anemia	7	2.1
	>15or≤25moderate	36	10.9
	>25 or ≤30 mild	104	31.4
	>30 normal	184	55.6
Platelet count at admission	<150 000/ll	276	79.8
	≥150 000/ll	70	20.2
Platelet count at discharge	<150 000/ll	55	16.8
	≥150 000/ll	273	83.2
white blood cell at admission	<4500/ll	320	93.6
	≥4500/ll	22	6.4
White blood cell at discharge	<4500/ll	211	65.5
	≥4500/ll	111	34.5
BMI=(154)	<16	62	40.3
	17-18.49	18	11.7
	≥18.5	73	48.0
W/H=(194)	>90	42	21.7
	80-90	81	41.6
	70-80	37	19.2
	<70	34	17.5

Type of treatment given for study subjects

With respect to type of treatment categories, 237(68.1%) of the VL patient has been treated by sodium stibogluconet followed by sodium stibogluconet (SSG) and paromomycin (PM) combination 93(26.7%) (Figure 3). There was difference in treatment outcome between the different treatments used (80% for sodium stibogluconet and 13.3% for sodium stibogluconet and paromomycin combination with poor outcome.

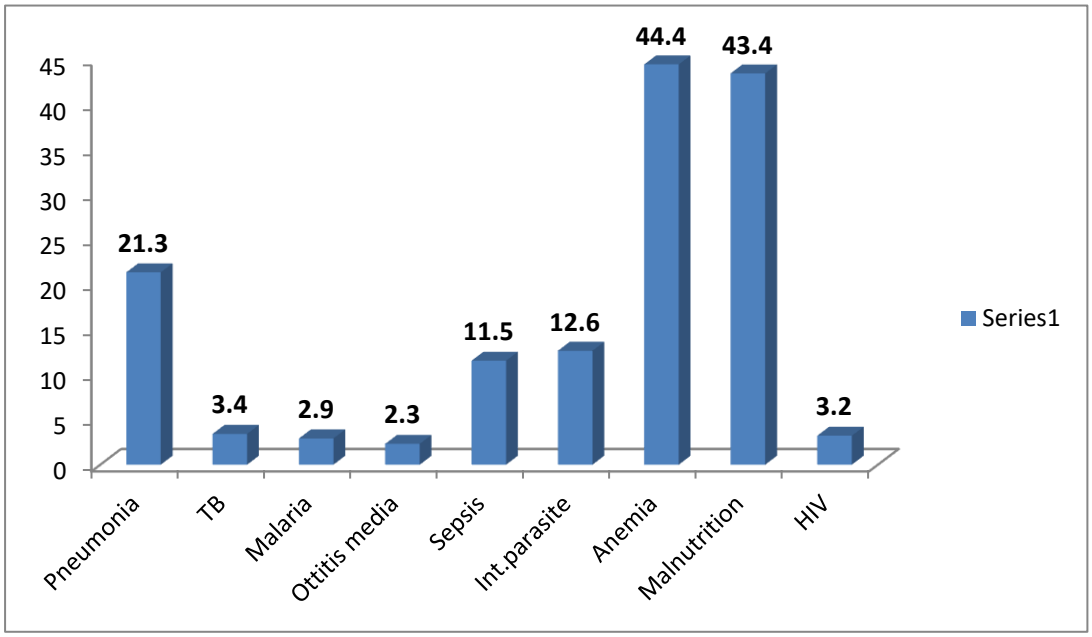
Figure 3: Type of treatment given for VL patients who were treated at Arba Minch General hospital, GamoGofa zone, from January 2011-december 2015(N=348)



Concomitant infections

From the total of VL patient nearly half, 168(48.3%) had reported the presence of more than one concomitant infection in their stay. The most frequent concomitant manifestations are anemia (44.4%) and malnutrition(43%) (fig 4).

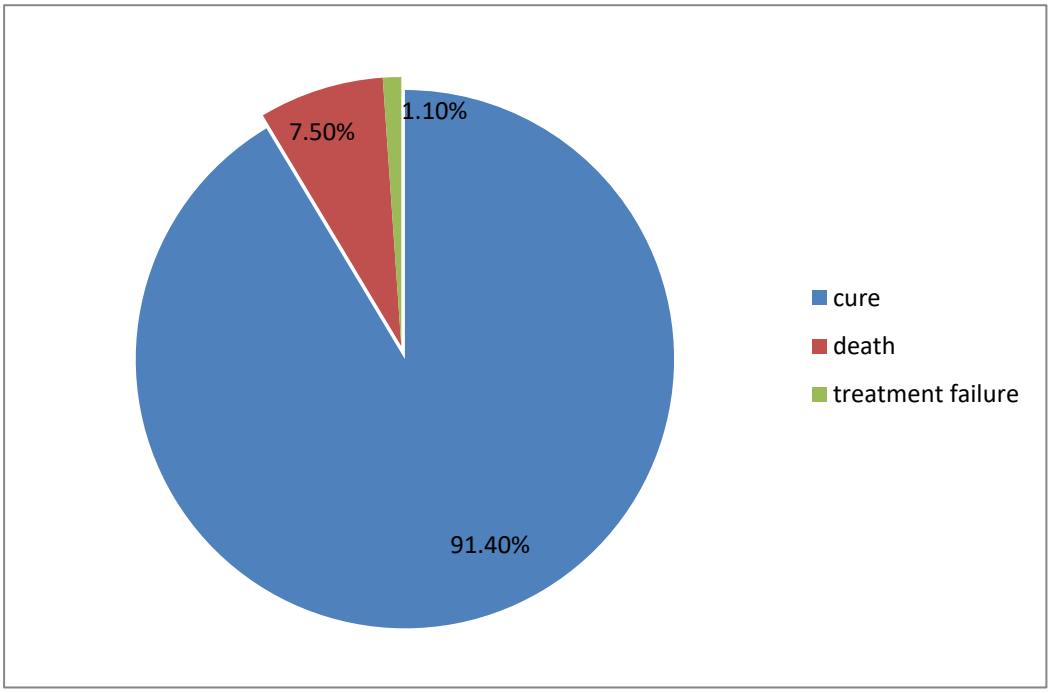
Figure 4: Common Concomitant manifestations Reported By VL Patients At Arba Minch General Hospital Gamogofa Zone, From January 2011-December 2015(N=348)



Treatment outcomes of study subjects

Information on treatment outcome was available for all 348 VL patients. They have a documented treatment outcome (i.e. cured, died, and treatment failed). A total of clinical recovery rate was 318(91.4%) and 26 (7.5%) deaths and 4(1.1%) of patients was treatment failed recorded from January 2011 to December 2015. An overall poor treatment outcome was 8.6 %(95%CI)(Fig 5)

Figure 5: Treatment outcomes of patient Reported By VL Patients at Arba Minch General Hospital among Gamogofa Zone, From January 2011-December 2015(N=348)



Bivariate logistic regression analysis

To select potential candidate variables for the multi variable logistic regression analysis, crude association was estimated. Based on preset p-value criteria of ≤0.25, the following covariates were selected as a potential candidate for the adjusted binary logistic regression analysis (Table 5).

Table 5: Bivariate logistic regression analysis for VL treatment outcome among 348 cases at Arba Minch General Hospital, January 2011-December 2015(N=348).

Variables		Poor outcome		COR	95%CI	p-value
		Yes N(%)	No N(%)			
General c.ion	Wake	13(5.5)	223(94.5)	1		
	Not wake	17(15.2)	95(84.8)	3.070	1.4 - 6.6	.004
HIV Statues	Negative	28(8.3)	309(91.7)	1		
	Positive	2(18.2)	9(81.8)	2.5	0.5-11.9	0.27
Diarrhea	No	17(6.6)	241(93.4)	1		
	Yes	13(14.4)	77(85.6)	2.4	1.1-5.2	0.25
Coughing	No	5(3.6)	133(96.4)	1		
	Yes	25(11.9)	185(88.1)	3.6	1.34-.9.6	.011
Bleeding /Epistaxis	NO	9(4.1)	212(95.9)	1		
	Yes	21(16.5)	106(83.5)	4.7	2.1-10.5	.000
Abnormal R/ Sound	No	23(7.8)	271(92.2)	1		
	Yes	7(13)	47(87)	1.8	0.71-4.3	.221
Wasting	No	9(4.3)	202(95.7)	1		
	Yes	21(15.3)	116(84.7)	4.06	1.8-9.2	.001
Edema	No	22(7.2)	284(92.8)	1		
	Yes	8(19)	34(81)	3.04	1.3-7.4	.014
Sodium Stibogluconte	No	6(5.4)	105(94.6)	1		
	Yes	24(10.1)	213(89.9)	1.97	.78-4.9	.15
SSG and PM	No	26(10.2)	229(89.8)	1		
	Yes	4(4.3)	89(95.7)	2.53	.86-7.45	.093
Pneumonia	No	9(3.3)	265(96.7)	1		
	Yes	21(28.4)	53(71.6)	11.67	5.1-26.9	.000
Pulmon /TB	No	22(6.6)	310(93.4)	1		
	Yes	8(50)	8(50)	28.54	8-102	.000
Malaria	No	25(7.4)	313(92.6)	1		
	Yes	5(50)	5(50)	12.5	3.4-46.2	.000
Sepsis	No	14(4.5)	204(95.5)	1		
	Yes	16(40)	24(60)	14	6.1-32	.000
Intestinal parasite	No	8(2.8)	281(97.2)	1		
	Yes	22(37.3)	37(62.7)	37	15-92.6	.000
Anemia	No	8(3.2)	240(96.8)	1		
	Yes	22(22)	78(78)	8.5	3.6-19.8	.000
Treatment side effect	No	15(4.6)	308(95.4)	1		
	Yes	15(60)	10(40)	62.6	20-195	.000
Spleen size discharge	<11 cm	16(5.1)	297(94.9)	1		
	≥11 cm	4(16)	21(84)	2.206	.09-1.77	.22

Multivariable logistic regression analysis

Among 18 variables fulfilled the inclusion criteria to be a potential candidate in bivarate logistic regression analysis, four variables were found to be significantly associated with poor treatment outcome of VL, and were included in the final model after adjusting for confounders. After stabilizing the effect of pulmonary TB, Sepsis, adverse side effect of drug, and Bleeding/Epistaxies had statistically significant association with poor outcome of VL treatment. When we compare the odds of poor outcome of VL treatment among VL patients with Epistaxies and without Epistaxies, patients with Epistaxies had more than 5 times poor outcome than their counter parts (OR= 5.02, 95%CI: 1.31-19.3) (Table 6). Similarly, pulmonary TB, Sepsis, and apparent drug side effect were the independent predictors of poor outcome of VL treatment (Table 6).

Table 6: Factors associated with poor treatment outcome in patients with VL at Arba Minch General Hospital, January 2011-December 2015, (N=348)

Variables	Poor outcome		COR(95%CI)	AOR (95% CI)
	Yes	No		
Bleeding/epstaxisis				
No	9(4.1)	212(95.9%)	1.00	1.00
Yes	21(16.5%)	106(83.5%)	*4.7(2.07,10.5)	*5.02 (1.31,19.3)
Pulmonary TB				
No	22(6.5%)	314(93.5%)	1.00	1.00
Yes	8(66.7%)	4(33.3%)	*28.54(7.97, 102)	*3.7(1.83,6.26)
Sepsis				
No	14(15.5%)	294(84.5%)	1.00	1.00
Yes	16(40%)	24(60%)	*14(6.1,32.08)	*4.3(6.1,32.08)
Apparent drug side effect				
No	15(4.6)	313(95.4)	1.00	1.00
Yes	15(75%)	5(25%)	*62.6(20,195)	*4.5(2.73,13.6)

Discussion:

VL has long been recognized as remains a major public health problem, with no signs of reduction in case trends. Co infection is a serious concern. WHO 2015 showed that poor treatment outcome of VL patients treated in 12 treatment centers in Ethiopia, Kenya, Sudan and Uganda illustrate with an average of 4.9% at the end of treatment(2,6). The different study conducted in Ethiopia confirms that patients with VL co infection had poorer response rates to antileishmanial treatment and increased mortality (29).The current study revealed that the overall level of poor treatment outcome at Arba Minch general hospital among VL patients enrolled at leshmaniasis treatment center from January 2011-December 2015

was 8.6%. This finding is consistent with a study conducted among VL patients who were treated in Huddur center, Bakool region, Somalia that 6.8% of patients had poor treatment outcome. (35).

However this finding is inconsistent with a study conducted in Gondar University, college of medicine and health science, northwest Ethiopia, that the good treatment outcome achieved in patients with VL was 84.6% and poor treatment outcome was found to be 15.4%(40). The possible reason for this difference could be; in the case of Gondar University, majority of patient with VL were cases with HIV- co infection so that the HIV co infection might have delayed the positive outcome of treatment .

Several risk factors for poor treatment outcome were identified in this study: Tuberculosis Bleeding/epstaxisis, Sepsis, and occurrence of adverse drug effect during treatment have statistically significant association with treatment outcome.

The odds of VL patients co-infected with sepsis syndrome were about four times higher to have poor out come as compared to their counterparts. This finding is consistent with a study conducted in North West Ethiopia that Sepsis was one of the associated factors with poor treatment outcome (death) in patients with VL patients. Patients with VL and sepsis had higher risk to die than with VL but not sepsis (40).

Moreover, the finding is similar with other studies (40, 42, and 47) that Sepsis is the primary cause of death that contributes 34% to 75% of the total deaths in patients with VL. Bacterial sepsis still remains the primary cause of death from infection in spite of advanced modern medicine, including vaccines, antibiotics and acute care.

The risk of having poor outcome in patients with in VL patient with Tuberculosis co-infection was about 3.7 times higher than VL patients with no co-infection with TB. This finding is in line with the studies conducted in Uganda and Gondar University, college of medicine and health science, northwest Ethiopia (39, 40). The presence of tuberculosis among patients with VL was independently predicted death or treatment failure.

Similarly, bleeding/Epistaxies and apparent drug side effects were the independent predictors of poor outcome of VL treatment. In the current study bleeding/Epistaxies was directly and significantly associated with poor treatment outcome and the finding was similar with study finding in Gondar University, college of medicine and health science, northwest Ethiopia and Brazil (44,45).

There was four times higher poor treatment outcome in apparent drug side effect than without drug side effect in the study. This could be because almost all patients in the group had severe concomitant infections with advanced level of immunosuppression, which might have caused poor outcome independently of VL. This finding is comparable with a study finding conducted in Uganda (39).

In general, most studies demonstrate that conducted in Northern Ethiopia, India and Brazil; HIV co-infected VL patients had a poorer outcome of treatment i.e. either death or treatment failure as compared to HIV negative Leishmania patients. However, in the current study, HIV co-infection failed to show association with treatment outcome. This difference might be due to the very low prevalence of HIV co-infected VL patients in Arba Minch general hospital Leishmania research and treatment center.

Strength and limitation of the study

Strength of the study: Due to using secondary data, all extracted information's were recorded in the past at the time when patient came to the health facility, so the collected data was not depended on patients memory and it minimized recall bias.

Limitations of the study: Since the study was conducted by using prerecorded data, there might be lack of accuracy. Information on exposure level may be insufficient and may not be adequate.

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Conclusion:

The level of poor treatment outcome among patients with VL in the study area is high. Some factors;

bleeding/Epsitaxis, tuberculosis, septic syndrome and adverse side effect of drugs were independent predictors of poor treatment outcome. The clinical management of VL in co-infected patients is a major challenge that requires new treatment approaches to improve its outcome.

Recommendation:

Sepsis and Tuberculosis were found to be the most common concomitant infections with VL patients and significant factor that ended up in poor treatment outcome. Awareness creation and community mobilization with regard to early screening of VL patients for sepsis and careful clinical evaluation for focal infections and prompt initiation of empiric antibiotic treatment is warranted. Moreover, the drug side effect is the major problem that contributes for poor treatment outcome; emphasis should be given with regard to treatment protocol.

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