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Post-treatment Clinical Outcomes of Cutaneous Leishmaniosis in the Bam Area, South Eastern Iran: Analysis of over 9,000 Cases

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SUMMARY

Background: Knowledge about risk or protective factors for post-treatment outcomes in Cutaneous Lishmaniosis are rare, especially in endemic areas such as Iran. The present study aimed to evaluate the association between the outcome of infection, clinical manifestation, and treatment with adverse post-treatment outcomes in Cutaneous Lishmaniosis patients.
Methods: This was a cross sectional study based on recently collected data of 9077 Cutaneous Lishmaniosis patients (4585 female and 4492 male) from March 2003 to March 2011 in the Bam area, Iran. Multivariable multinomial logistic regression was applied to assess the effect of outcome of infection, clinical manifestation and treatment on relapse, treatment after interruption, treatment failure and clinical resistance.
Results: Head lesions were strongest risk factor for relapse (Odds Ratio, OR=4.21; CI 95%: 3.56-4.98), treatment after interruption (2.00; 1.70-2.35), treatment failure (6.61; 5.17-8.45) and clinical resistance (2.62; 2.00-3.44). Family occurrence (yes vs. no), intra lesion therapy method, treatment duration (>3 v. ≤ 3 week) and source of detection by Surveillance (active vs. passive), were the most protective factors for relapse (OR=0.58; CI 95%: 0.46-0.74), treatment after interruption (0.36; 0.31-0.42) treatment failure (0.24; 0.20-0.29) and clinical resistance (0.24; 0.09-0.67).
Conclusion: Head lesions and treatment variables (e.g. therapy method and duration) could predict the occurrence of adverse post-term outcomes of Cutaneous Lishmaniosis. Further longitudinal studies have to clarify cause and effect relationships.

1. Introduction

Cutaneous leishmaniasis (CL) is the most common form of the leishmaniosis.[1] It is estimated that the majority of CL cases is restricted to some tropical and sub-tropical countries, including Iran.[2] Zoonotic Cutaneous Leishmanias (ZCL) and Anthroponotic Cutaneous Leishmaniasis (ACL) are occurring in different parts of Iran, ZCL in central,[3] north, north-east,[4] ad south-west,[5] while ACL is endemic in large cities including Tehran, Shiraz, Mashhad, Kerman and small cities like Bam.[6] The Kerman province, especially the city of Bam, was one of the known old focal points of ACL in Iran.[7] There is clear evidence that *leishmania tropica* species is the causative parasite of ACL in urban areas that is transmitted by the bite of the infected sand-fly (*Phelebotomus sergenti*). After the 2003 earthquake in the Bam area, the prevalence of CL significantly increased.[8] CL usually produces ulcers on the exposed parts of the body, such as the face, arms and legs. These lesions may persist for a long time (6-15 months).[9]

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Many different therapeutic interventions, including topical, systemic and nonpharmacological treatments, have been introduced, such as paromomycin ointments, thermotherapy, intralesional pentavalent antimonials and cryotherapy; systemic treatment consists of pentavalent antimonial salts at a daily dose of 20/mg/kg Sb^{5+} of pentavalent antimony.[10] In Iran, specific treatment for cutaneous leishmaniosis is meglumine antimoniate compound.[11]

Due to a large number of lesions and permanent scars, prolonged duration of treatment (several months) is required in some cases.[12] Unfortunately, there are unwanted side effect according to type of treatment, e.g. pain at the injection site in the case of interlesional or cardiac and pancreatic toxicity, toxicity-related mortality in systemic administration, which may be the reason for non-adherence and non-compliance.[9] Subsequently, studies have shown that as a result, clinical resistance,[13] failure[14] and consequently disease relapse can occur.[15,16] Not only does the occurrence of relapse and/or treatment failure depend on the quality of the treatment program, but also the clinical manifestation of CL may be important.

It should be emphasized that in CL the epidemiologic relationship between the vector and the human reservoir host still remain a major challenge. Therefore effective control is not a realistic goal.[1] Nevertheless, reducing the burden of disease by focusing on the outcomes of infection, clinical manifestation and treatment can be achieved. However, there is very little evidence regarding the characteristics of CL patients, particularly in Iran. Hence, the objectives of the present study were to describe the post event pattern in CL and to identify determinant risk factors of adverse outcomes following treatment in south eastern Iran.

2. Materials and Methods

This cross sectional study using pre-existing data from epidemiologic surveillance systems was conducted from March 2003 to March 2011 in the Kerman province including Bam and Normashir. 9,077 individuals infected by CL caused by *L.tropica* were included in the study. Definitive cases were confirmed microscopically by smear or culture from cutaneous lesions.[11]

To achieve the study objective, these variables were included: demographic variables (age, sex and nationality) and outcome of infection, clinical manifestation and treatment including source of detection of cases (passive or active surveillance), previous scar, family occurrence, scar covering, comorbidity, therapy duration, therapy method (intramuscular, local and cryotherapy), body region involved, scar duration and number of healed lesions. We classified the participants into five case types: a) patients presenting with active lesion(s) and receiving CL treatment for the first time classified as *new case*, b) patients who have been declared cured of CL in the past by a physician, after one full course of systemic or local treatment, and returned because of the reactivation of apparently cured lesion(s) classified as *Relapse*, c) patients who interrupt systemic and local treatment for 10 and 7 days or more, and return to the health service with active lesion, classified as *treatment after interruption*, d) patients who had active lesion after 4 to 6 months despite complete systemic or local treatment, classified as *treatment failure*, e) patients with relapse or treatment failure who had active lesion 6 weeks after completing at least 2 rounds of systemic treatment, classified as *clinical resistance*.[17]

Distribution of continuous and ordinal variables were assessed by Histogram plot and Kolmogorov-Smirnov test. According to normality of data, the Kruskal Wallis H test was used to compare outcome of infection, clinical manifestation, and treatment among case types. In addition, the Chi-squared test was used to assess the association between categorical variables. Multivariable multinomial logistic regression (adjusted by age, sex and nationality) by new cases as a baseline comparison group was used to model case types as a nominal dependent variable and infection, clinical manifestation and treatment as independent variable. Odds ratios (OR) with 95% confidence intervals (CI 95%) were calculated. To avoid over-parameterization, we excluded some variables because of low sample sizes: e.g. back and abdomen categories. If there are more parameters to estimate than observations in the dataset, then the model is over-parameterized and there is not enough information to yield valid parameter estimates.

A multivariable multinomial logistic regression model including all explanatory variables was constructed to calculate the probability of each adverse post-term treatment outcomes to assess the discriminant power of all explanatory variables assessed by the Receiver Operating Characteristic curve (ROC curve). In a ROC curve, the true positive rate (Sensitivity) is plotted as a function of the false positive rate (100-Specificity) for different cut-off points of a parameter. Area under the Curve (AUC) measures discrimination, i.e, the ability of the test to correctly diagnosis each post-treatment outcomes. Statistical analyses were conducted using Stata software, version 11 (Stata Corp, College Station, TX, USA). The level of statistical significance for all tests was $p \leq 0.05$.

3. Results

Median (IQR) age was 21[28] years (range 1 to 110). The cases detected by passive surveillance in female and male subjects was 94.8 and 95%, respectively. The proportion (%) of new, relapse, treatment after interruption, treatment after failure and chronic cases in CL patients was 72, 9, 10, 5 and 4, respectively. Age-sex distribution of the outcomes showed that the proportion of adverse post-treatment outcomes for male was higher than for female subjects, except for clinical resistance. Most new reported cases and relapses were aged under 10 years and between 20 and 40 years, as shown in Figures 1 and 2. A cross tabulation outcome of infection, clinical manifestation and treatment of CL patients by case type in detail is presented in Table 1.

Table 2 presents the adjusted prevalence odds ratios (POR) for all study variables by adverse outcomes after treatment. Multivariable multinomial logistic regression after adjusting age, sex and nationality showed that the occurrence of scar on head (face, ear and neck) had the strongest effect size on relapse, treatment after interruption, treatment failure and clinical resistance cases (OR= 4.21, 2, 6.61 and 2.62 respectively, $p \leq 0.001$). In the case of compared intramuscular (IM) injection, as result of intra leshional

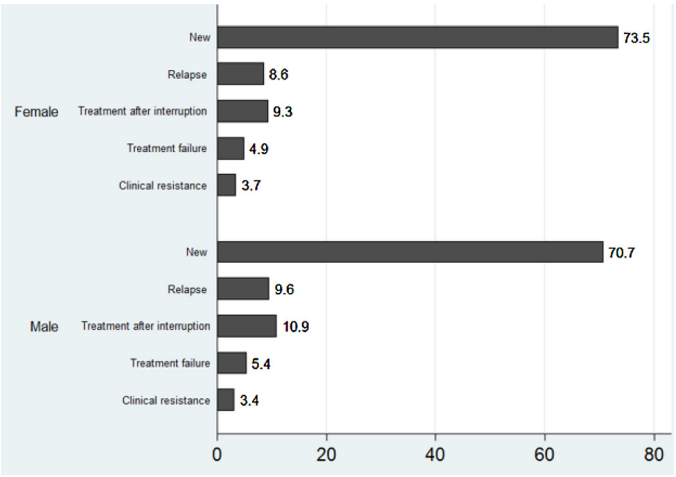

Figure 1. The proportion of cutaneous leishmaniosis patients by gender (2003-2011).

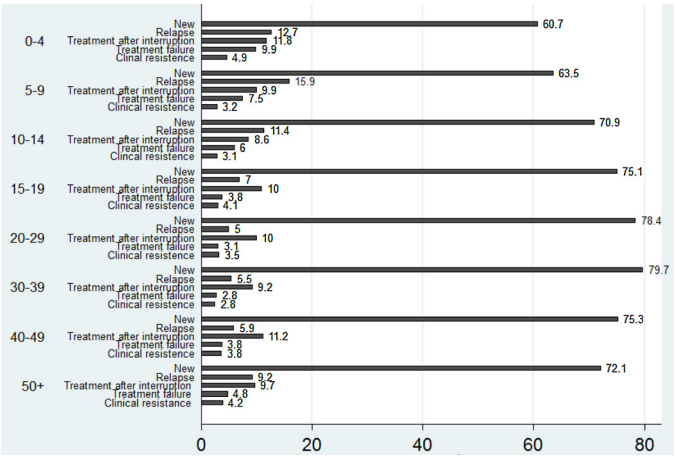

Figure 2. The proportion of cutaneous leishmaniosis patients by age group (2003-2011).

therapy, the odds occurrence adverse outcomes after treatment are decreased (OR=0.76, 0.36, 0.24 and 0.42 respectively. $p \leq 0.01$)

The ROC analysis for discrimination power of all explanatory variables showed that the area under the curve (AUC) for treatment failure (0.72) was larger than other post-treatment outcomes (Figure 3).

4. Discussion

It is obvious that the proportion of adverse post- treatment outcomes in CL patients is notable. That means, approximately one-third of the treatments lead to relapse, treatment after interruption, treatment failure and clinical resistance. Our results also show that risk of adverse post-treatment outcomes are associated with each of the assessed explanatory variables (Outcome of infection, clinical manifestation and treatment), although strength of associations was quite different. Head lesions were more modest to strongly significant associated with all outcomes, also therapy duration of more than 3 weeks showed a significant relationship to all dependant variables.

In the present study the most lesions were localized on the upper extremities in both sexes. Adverse post treatment outcomes were observed in all age groups. 5 to 9 year olds had the highest relapse rate, while 30 to 39 years olds showed the lowest proportions. Gurel et al. found that the highest rate of new cases occurred in 5 to 9 year group and they pointed out, that as a result of acquired immunity by increasing age, the occurrence of CL infection declines.[15] However our results show that most of the new cases have been reported in 20 to 40 year old participants. Some of these cases could be attributed to the migration of non-immune workforce and laborers into the Bam area after the earthquake of 2003. Also, our results indicate disease development and adverse post-treatment outcomes are a common phenomenon

Table 1
Outcome of infection, clinical manifestation and treatment of Cutaneous Leishmaniasis patients by case type (n=9077)

Variables	Case type					
	New (n=6548)	Relapse n(827)	Treatment after interruption n(922)	Treatment failure n(474)	Clinical resistance n(306)	*p*-value
Age	22 (26)	12 (26)	20 (29)	12 (25)	20 (32)	<0.001
Sex						
Female	3370 (51.5)	395 (47.8)	430 (46.6)	228 (48.1)	162 (52.9)	
Male	3178 (48.5)	432 (52.2)	492 (53.4)	246 (51.9)	144 (47.1)	0.016
Nationality						
Non-Iranian	149 (2.3)	9 (1.1)	14 (1.5)	18 (3.8)	6 (2)	
Iranian	6399 (97.7)	818 (98.9)	908 (98.5)	456 (96.2)	300 (98)	0.012
Surveillance						
Passive	6218 (95)	754 (91.2)	872 (94.6)	466 (98.3)	302 (98.7)	
Active	330 (5)	73 (8.8)	50 (5.4)	8 (1.7)	4 (1.3)	<0.001
Previous scar						
No	6261 (95.6)	718 (86.8)	865 (93.8)	446 (94.1)	292 (95.4)	
Yes	287 (4.4)	109 (13.2)	57 (6.2)	28 (5.9)	14 (4.6)	<0.001
Family occurrence						
No	5544 (84.7)	743 (89.8)	771 (83.6)	423 (89.2)	269 (87.9)	
Yes	1004 (15.3)	84 (10.2)	151 (16.4)	51 (10.8)	37 (12.1)	<0.001
Comorbidity						
No	6030 (92.1)	766 (92.6)	841 (91.2)	445 (93.9)	283 (92.5)	
Yes	518 (7.9)	61 (7.4)	81 (8.8)	29 (6.1)	23 (7.5)	0.49
Therapy duration						
≤3	1414 (21.6)	211 (25.5)	390 (42.3)	249 (52.5)	118 (38.6)	
>3	5134 (78.4)	616 (74.5)	532 (57.7)	225 (47.5)	188 (61.4)	<0.001
Therapy method						
Intramuscular (glucantime 20 mg/kg per day for 14 days)	1410 (21.5)	212 (25.6)	388 (42.1)	247 (52.1)	117 (38.2)	
Intra lesional (glucantime; 20 mg/kg per day for 10 to 20 days)	4942 (75.5)	578 (69.9)	494 (53.6)	216 (45.6)	179 (58.5)	<0.001
Cryotherapy with liquid nitrogen, once per week for 6 weeks)	196 (3)	37 (4.5)	40 (4.3)	11 (2.3)	10 (3.3)	
Body region involved						
Hand	3108 (47.5)	234 (28.3)	351 (38.1)	90 (19)	99 (32.4)	
Leg	761 (11.6)	43 (5.2)	84 (9.1)	19 (4)	24 (7.8)	
Head (face, ear & neck)	1493 (22.8)	474 (57.3)	338 (36.7)	286 (60.3)	125 (40.8)	<0.001
Back	54 (0.8)	3 (0.4)	5 (0.5)	1 (0.2)	0	
Abdomen	30 (0.5)	1 (0.1)	6 (0.7)	1 (0.2)	0	
Multi region involved	1102 (16.8)	72 (8.7)	138 (15)	77 (16.2)	58 (19)	
Duration of scar incidence	8 (12)	8 (12)	32 (28)	28 (28)	20 (28)	<0.001
Number of lesion	1 (1)	2 (2)	1(1)	1(1)	1(1)	<0.001

§ Categorical variables shown as n (%) with *p*-value according to $\chi 2$, Continuous variables shown as (Median, IQR) ‡ with *p*-value according to Kruskal Wallis H test
* *p*.value ≤0.05

Table 2
Odds ratios (ORs) and 95% confidence intervals (CIs) of explanatory variable among case types

Variables	Relapse	Case type, OR* (95% CI), new case as reference		
		Treatment after interruption	Treatment failure	Clinical resistance
Source of detection (Surveillance) (active vs. passive)	1.83 (1.40-2.38) †	1.08 (0.8-1.47)	0.32 (0.15-0.65) ‡	0.24 (0.09-0.67) ‡
Previous scar (yes vs. no)	3.37 (2.66-4.27) †	1.44 (1.08-1.94) §	1.40 (0.93-2.09)	1.04 (0.6-1.81)
Family occurrence (yes vs. no)	0.58 (0.46-0.74) †	1.08 (0.89-1.30)	0.59 (0.44-0.80) ‡	0.74 (0.52-1.05)
Scar covering (yes vs. no)	0.97 (0.41-2.29)	1.13 (0.53-2.39)	0.87 (0.27-2.80)	0.84 (0.20-3.47)
Comorbidity (yes vs. no)	1.28 (0.96-1.71)	1.25 (0.97-1.62)	1.12 (0.74-1.67)	0.98 (0.62-1.56)
Therapy duration (>3 vs. ≤3) week	0.80 (0.67-0.94) ‡	0.37 (0.32-0.43) †	0.24 (0.20-0.29) †	0.42 (0.33-0.54) †
Therapy method				
Intramuscular (glucantime 20 mg/kg per day for 14 days)	Reference	Reference	Reference	Reference
Intra lesional (glucantime; 20 mg/kg per day for 10 to 20 days)	0.78 (0.64-0.91) ‡	0.36 (0.31-0.42) †	0.24 (0.20-0.29) †	0.42 (0.33-0.54) †
Cryotherapy with liquid nitrogen, once per week for 6 weeks)	1.41 (0.96-2.08)	0.78 (0.54-1.12)	0.35 (0.18-0.66) ‡	0.59 (0.30-1.15)
Body region involved				
Hand	Reference	Reference	Reference	Reference
Leg	0.75 (0.53-1.04)	0.97 (0.76-1.25)	0.86 (0.52-1.42)	0.99 (0.62-1.55)
Head (face, ear & neck)	4.21 (3.56-4.98) †	2 (1.70-2.35) †	6.61 (5.17-8.45) †	2.62 (2-3.44) †
Multi region involved	0.86 (0.66-1.14)	1.10 (0.90-1.36)	2.41 (1.76-3.29) †	1.65 (1.18-2.30) ‡
Duration of scar incidence (week)	1.02 (1.01-1.03)	1.05 (1.04-1.06)	1.05 (1.03-1.06)	1.04 (1.01-1.07)
Number of lesion	1.32 (1.27-1.37) †	1.10 (1.05-1.15) †	1.22 (1.16-1.29) †	1.18 (1.11-1.26) †

* Adjusted by age, sex and nationality.
† *p*-value ≤0.001; ‡ *p*-value ≤0.01; § *p*-value ≤0.05.

in higher ages. Some of the studies that describe the epidemiological context of CL in Iran have shown that most patients have multiple lesions– mostly frequently in the upper extremities. The peak infection rate is after the age of 20.[3,4] Our findings support these results, although in our study nearly 62% of patients had only one lesion.

Furthermore, our results show that the occurrence of lesions on the head (face, ear and neck) had the highest effect on adverse post-treatment outcome. This might be due to the high frequency of lesions on the face.

A study reported that after the 2003 earthquake in the Bam area, lesions on the face were more frequent than before the natural disaster.[8] A recent study found that a negative skin test was a significant prognostic determinant for post treatment relapse. It has been identified that there was no significant relationship between the relapses and socio demographic (income or schooling) or clinical characteristics, such as number of lesions or comorbidity,[18] whereas the present study shows that with per unit increase in the lesion number, the odds of relapse, treatment after interruption, treatment failure, and clinical resistance is increased

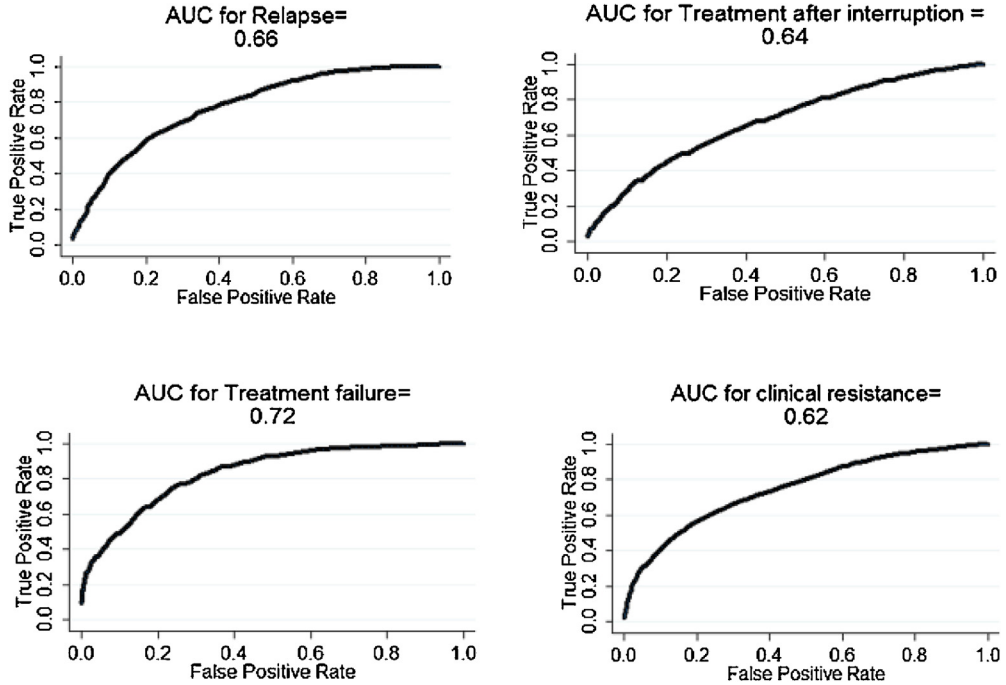

Figure 3. Area under the curve (AUC) for assessing discriminant power of explanatory variables (infection outcome, clinical manifestation and treatment) to diagnosis of adverse post-treatment outcomes.

by 0.32, 0.10, 0.22, and 0.18, respectively; after adjustment for confounding factors.

Our results showed that the complete duration of treatment was a significant protective factor for all adverse post-treatment outcomes. Intra-lesional treatment seem to be effective in CL caused by *L.tropica* in Iranian patients, compared to cryotherapy. A study in another endemic area, i.e. Turkey, indicated that intra lesional treatment was not effective and 90% of cases were cured by cryotherapy.[19] One could hypothesize that geographic area in which infection was acquired is a determinant factor in treatment effectiveness. Additionally, results from two Iranian studies showed that the combination therapy (intra-lesional meglumine antimoniate and cryotherapy) is highly effective for CL, caused by *L.major* and *L.tropica.*[20,21] A study of resistant parasites contributing to treatment failure for ACL caused by *L.tropica* found that an increasing proportion of patients with ACL are failing meglumine antimoniate therapy other SbV-containing drug Pentostam.[22,23] In ROC analyses combination of all the outcome of infection, clinical manifestation and treatment had different power (low to moderate) to discriminate patients with and without each adverse post-treatment outcomes. This means, discrimination or diagnostic power, as reflected in the areas under the ROC curves, was generally higher for treatment failure compared to other outcomes.

The present study could be important because of the scarcity of research on clinical outcomes after treatment of CL in Iran. Our study has some limitations that should be considered. Some relevant determinants were not considered, such as time lag between the appearance of a CL lesion and the first diagnosis, and size of lesions. Other important factors were demographic and socioeconomic variables such as occupation, because after the 2003 earthquake the huge workforces and laborers had rushed into the Bam area. Unfortunately, data regarding the seasonal and epidemiologic pattern of CL was not available. Because of migration movement into the Bam area of Iranian and non Iranians it is difficult to define a plausible population and generalize the results to other endemic regions.

To the best of our knowledge, there is a lack of published data on the association between outcome of infection, clinical manifestation, treatment and adverse post-treatment outcomes in CL. After the disastrous earthquake in the Bam area in 2003 the number of adverse post-treatment outcomes increased. Reasons for this are likely to be multifactorial. The results of this study imply that the risk of outcome, e.g. relapse, depends on the body region involved. Therefore, the occurrence of lesions on the head (face, ear and neck) had the strongest effects. Completing treatment duration could be an important protective factor to preclude adverse outcomes. Finally, further longitudinal studies are required to establish time order of predictor factors on adverse post-treatment outcome.

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