Multi - Bacillary Leprosy Under Chinese Leprosy Elimination Program

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Research article

Keywords: Multibacillary leprosy, Factors, Retrospective observational study

Posted Date: December 14th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-122947/v1>

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Multi-bacillary leprosy under Chinese leprosy elimination program

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Word count : 1849

Abbreviations

MB: Multi-bacillary leprosy; LEPMIS: the leprosy management information system;

PB: pauci-bacillary leprosy; **OR:** odds ratio; **CI:** Concentration Index; **PCPs:** Primary Care Physicians

Abstract (words: 211)

Background: Objectives: To analyze the sociodemographic and clinical factors associated with multi-bacillary (MB) leprosy in elimination planning areas in Northwest China. **Design:** Retrospective observational study. **Setting:** Three specialized hospitals were included. **Participants:** The medical records of leprosy in Shaanxi Province from 2004 to 2020 were collected from the leprosy management information system (LEPMIS). **Primary and secondary outcome measures:** The basic situation of leprosy treatment and follow-up were investigated. **Results:** 305 new cases of leprosy were included in the study. 272 cases (89.18%) were MB leprosy,

and 33 (10.82%) were pauci-bacillary (PB) leprosy. Male patients were more likely to have neurological injury ($P<0.001$; OR:0.35; 95%CI:0.194-0.630). Patients over 60 years old were more likely to have leprosy deformity ($P<0.001$; OR:0.113; 95%CI:0.027-0.478) and nerve injury ($P=0.035$; OR:0.333; 95%CI:0.115-0.965). Patients with marriage histories were more likely to have leprosy deformities ($P=0.018$; OR:0.842; 95%CI: 0.718-0.987). Patients with passive detection had a lower probability of leprosy reaction ($P=0.011$; OR:4.268; 95%CI:1.276-14.272); Patients with nerve damage, positive skin smear test or level I or level II disability were more likely to be classified as MB leprosy. **Conclusions:** MB leprosy is related to social and demographic factors (with or without marriage history, age at diagnosis, discovery mode) and clinical factors (such as the number of skin lesions and nerve lesions).

Key words: Multibacillary leprosy; Factors; Retrospective observational study

Summary box:

What is already known about this subject:

1. Leprosy is widespread throughout the world and seriously endangers human health
2. The condition of patients with MB leprosy is more complex, the treatment course is longer and the prognosis is poorer, which seriously affect the life quality of the patients
3. The incidence of polybacterial leprosy was different in different conditions.

What are the new findings:

1. Patients over 60 years old were more likely to have leprosy deformity and nerve

injury.

2. Patients with marriage histories were more likely to have leprosy deformities.

3. Patients with passive detection had a lower probability of leprosy reaction.

4. Patients with nerve damage, positive skin smear test or level I or level II disability were more likely to be classified as MB leprosy.

How might it impact on clinical practice in the foreseeable future?

1. This study is the first time to analyze the differences in the classification of leprosy patients in western China and the related influencing factors, aiming to provide theoretical support for proposing better prevention and treatment measures.

2. 305 cases of leprosy patients in western China for 17 years were included, with reliability and validity guaranteed. Medical records are clear and complete, and the research value is high.

3. We can improve the ability of clinical diagnosis and treatment of MB leprosy by intervening the related risk factors, and provide valuable demographic data for the clinical study of leprosy.

Introduction

Leprosy, caused by mycobacterium tuberculosis, is a chronic infectious disease¹ and mainly induces injuries of skin and peripheral nerves.² If not treated in time, leprosy can cause permanent damage to peripheral nerves and may lead to amputation and deformity.³ The diagnosis of leprosy is based on a series of clinical manifestations. According to different therapeutic purposes, cases are divided into two types: Paucibacillary (PB) leprosy and Multibacillary (MB) leprosy. MB leprosy is an

aggressive progression of the disease, which is mainly caused by unresponsiveness of cellular immunity of leprosy bacilli,⁴ and is characterized by high infectivity and functional disability rate.⁵ Leprosy disability severely affects the quality of life of leprosy patients, and the social discrimination caused by it may induce psychological problems. The World Health Organization (WHO) aimed to achieve the goal of global eradication of leprosy.⁶ However, despite effective prevention and control measures were extensively implemented, the number of new cases worldwide has remained almost unchanged in the past ten years, with about 250,000 new diagnosed cases each year.⁷ The way to the destination, is not easy and smooth, and the potential deformity⁸ caused by leprosy aggravates related social, health and economic loads.⁹ Although leprosy is generally in a low epidemic state in northwest China,¹⁰ but the proportion of MB types¹¹ and the rate of disability¹² are still at a high level.¹³

Methods

1. Criteria of diagnosis

The diagnoses of new and recurrent leprosy were based on Leprosy Prevention Manual for Primary Care Physicians (PCPs) and Leprosy Diagnosis Standard WS291-2008. Cases were classified according to the Leprosy Classification Standard, WHO, 1987. Disability classification was bases on the Disability Classification Standard for Leprosy, WHO, 1988.

2 Data sources

All new and recurrent leprosy cases were collected from the Leprosy Prevention and Control Management Information System in China (LEPMIS). Population data came

from the Shaanxi Statistical Yearbook.

3 This study was an observational and retrospective study, involving 368 cases collected in the LEMPIS from 2004 to 2015. The variables included gender, nationality, occupation, education level, marital status, residence history, age, method of detection, skin lesions, bacteria detection, nerve damage, and disability classification. Cases with incomplete information (n=63) were excluded. This retrospective cross-sectional study was reviewed and approved by the institutional ethics committee.

4 Statistical analysis

EXCEL 2010 were used to establish a new and recurrent leprosy case report database. Appropriate statistical methods including *U* test, χ^2 test, Fisher exact test, and multivariate logistic regression were used to carry out statistical analysis in SPSS 19.0 software. Quantitative variables were expressed in descriptive statistics, and qualitative variables were expressed in rates and 95% confidence intervals (CI). For statistical purposes, we have divided the analysis variables into different categories. We conducted Kolmogorov-Smirnov test and Levene test respectively to evaluate the normality and variance homogeneity of quantitative variables. χ^2 test was used to analyze the influence of various factors, and the results were expressed by dominance ratio (socio-demographic factors and clinical factors). The significance level was $P<0.05$. Logistic regression analysis was used to adjust the confounding variables to determine the independent risk factors of leprosy MB. In order to determine which independent risks are related to the operational classification of leprosy, we used the

forward stepwise logistic regression method. This method used a model designed for two-class qualitative variables to analyze the significance of each independent variable, and a logistic regression model was obtained to classify the subjects into PB type and MB type. The percentage of correct identification was 89.2%. The results showed that the correct rate of this method is higher than the random correct rate (50%). The global test of the model has statistical significance ($P < 0.001$). The Hosmer-Lemeshow goodness-of-fit test showed that there is no statistical significance ($P = 0.713$) between the expected frequency obtained from the prediction probability and the observed frequency, which means the model fitted well.

Results

1. Basic situation of leprosy cases

It was shown in the system that there were 368 leprosy cases in Shaanxi province between 2004 and 2020, of which 69.5% were male cases. 98.7% patients were Han ethnics. Most of the new leprosy cases were farmers (91.1%). 6 cases (2.0%) received education more than 9 years, 198 cases (64.9%) received education between 1 year and 9 years, 101 cases (33.3%) received education less than 1 year. 216 cases (70.8%) had marriage history, and 97.4% of the cases resided permanently in the locality. The average age of diagnosed with leprosy was 45.79 ± 13.6 years. 16.1% cases were diagnosed older than 60 years. 32.8% cases were infected from within the family, 12.5% cases were infected from outside of the family, and 54.8% cases had no definite sources of infection. The detected cases were mostly MB (272 cases, 89.2%). Compared with female patients, males were more prone to nerve injury ($P < 0.001$;

OR:0.35; 95%CI:0.194-0.630). Patients diagnosed older than 60 years were relatively prone to disability ($P<0.001$; OR:0.113; 95%CI:0.027-0.478) and nerve injury ($P=0.035$; OR:0.333; 95%CI:0.115-0.965). Patients with marriage histories were more prone to leprosy disability ($P=0.018$; OR:0.842; 95%CI:0.718-0.987). The incidence of leprosy reaction was lower in the patients detected passively than those detected actively ($P=0.011$; OR:4.268; 95%CI:1.276-14.272).

2. MB leprosy and socio-demographic factors

The χ^2 test results showed that there were statistically significant differences in sex, education level, marital status, residence history, age at diagnosis, mode of diagnosis, and leprosy classification of patients ($P<0.05$), as shown in Table 1. Univariate analysis showed that there were statistically significant relationships between sex ($p=0.043$), education level ($p=0.006$), marital status ($p<0.001$), residence history ($p=0.014$), age at diagnosis ($p=0.019$), mode of diagnosis ($p=0.001$) and MB leprosy. The adjusted logistic regression analysis showed that marriage history ($P=0.006$; OR=3.592; 95%CI:1.444-8.934), the age at diagnosis older than or equal to 60 years ($P<0.05$; OR=1.034; 95%CI=1.001-1.068), and active detection ($P=0.002$; OR=3.640; 95%CI=1.590-8.333) were significantly correlated with multi-bacterial leprosy.

Table 1 Relationship between sociodemographic factors and leprosy types

	MB leprosy N=272	PB leprosy N=33	P value	OR	95%CI
Sex					
Male	184 (67.65)	28 (84.85)	0.043	0.373	(0.139-1.000)
Female	88 (32.35)	5 (15.15)			
Ethnics					
Han	268 (98.53)	33 (100.00)	0.483	0.89	(0.856-0.926)
Others	4 (1.47)	0 (0.00)			
Profession					
Farmer	24 (8.82)	3 (9.09)	0.959	0.968	(0.275-3.407)
Others	248 (91.18)	30 (90.91)			
Education level, y					
More than 9	6 (2.21)	0 (0.00)	0.002	3.145	(1.504-6.573)
Between 1 and 9	184 (67.65)	14 (42.42)			
Less than 1	82 (30.15)	19 (57.58)			
Marital status					
Unmarried	69 (25.37)	20 (60.61)	<0.001	0.221	(0.104-0.468)
Married	203 (74.63)	13 (39.39)			
Living history					
Local	267 (98.16)	30 (90.91)	0.014	5.34	(1.215-23.465)
Nonlocal	5 (1.84)	3 (9.09)			
Age, y					
Older than 60	40 (14.71)	9 (27.27)	0.063	0.460	(0.199-1.061)
Between 20 and 60	224 (82.35)	23 (69.70)			
Younger than 20	8 (2.94)	1 (3.03)			
Mode of diagnosis					
Active detection	53 (19.49)	15 (45.45)	0.001	0.290	(0.137-0.614)
Passive detection	219 (80.51)	18 (54.55)			

3. Analysis of MB leprosy and its clinical factors

Of the cases of MB leprosy (89.2%), 21.32% cases had less than 5 skin lesions, 85.66% cases had no obvious leprosy reaction, 34.93% cases had no positive bacteria detection, 19.49% had no nerve damage, and 22.43% cases had no deformity, as show in Table 2. Analysis showed that patients with less than 1 skin lesion were less likely to be classified as MB leprosy than those with more than 5 lesions. Patients with nerve damage, positive skin smear results, or grade I or II disability were more likely to be classified as MB leprosy. The adjusted logistic regression analysis showed that clinical variables related to MB leprosy included >5 lesions ($P<0.01$; $OR=7.880$; $95\%CI=2.506-24.775$), and ≥ 2 nerve lesions ($P<0.05$; $OR=3.516$;

169 95%CI=1.076-11.491).

Table 2 Relationship between clinical factors and types of leprosy

	MB leprosy (n=272)	PB leprosy (n=33)	P value	OR	95% CI
Skin lesion			<0.001	0.170	(0.052-0.554)
None	8 (2.94)	5 (15.15)			
1 lesion	6 (2.21)	7 (21.21)			
2-5 lesions	44 (16.18)	15 (45.45)			
>5 lesions	214 (78.68)	6 (18.18)			
Leprosy reaction			0.3	0.597	(0.174-2.053)
No reaction	233 (85.66)	30 (90.91)			
I reaction	15 (5.51)	3 (9.09)			
II reaction	20 (7.35)	0 (0.00)			
Mixed reaction	4 (1.47)	0 (0.00)			
Skin smear result			<0.001	13.508	(4.612-39.566)
Positive	177 (65.07)	4 (12.12)			
Negative	95 (34.93)	29 (87.88)			
Nerve damage			0.003	1.355	(0.500-3.678)
None	53 (19.49)	5 (15.15)			
1 nerve	31 (11.40)	11 (33.33)			
≥2 nerves	188 (69.12)	17 (51.52)			
Disability			0.007	0.578	(0.266-1.259)
None	61 (22.43)	11 (33.33)			
Grade I	93 (34.19)	3 (9.09)			
Grade II	103 (37.87)	19 (57.58)			
Not clear	15 (5.51)	0 (0.00)			

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172 Discussion

173 These results of our study showed high endemic characteristics of leprosy in this
 174 investigated area, suggesting that the delay on leprosy diagnosis still existed in
 175 northwest China,¹⁴ which led to more serious consequences and disabilities of
 176 leprosy.¹⁵

177 Female leprosy patients were prone to have poor prognosis. MB leprosy had greater
 178 impact on males than PB leprosy, even after adjusting the model. This result was
 179 consistent with previous results conducted in other parts of our country.¹⁶ Leprosy
 180 showed a low prevalence trend at this stage, and male patients still accounted for a

relatively high proportion of the new diagnosed cases in each year, which may be related to different genetic susceptibility in different genders.¹⁷ Meanwhile, females got more skin consultations than males, and males may be more easily exposed to leprosy bacilli related to behavioral and cultural factors,¹⁸ which may partly explain the dominant position of male cases. In addition, there may be some correlation between androgen and MB leprosy, especially in adolescent males,¹⁹ and the immune response stimulated by a large amount of androgen secreted had poor disease control effect.²⁰ The susceptibility of the elderly to MB leprosy may be related to the prolonged incubation period of leprosy bacilli, resulting to delayed response.²¹ In addition, the aging of immune system in the elderly²² was an aggravating factor for infection control.²³ A previous related study showed that the higher incidence of leprosy changed from PB to MB, from the young to the elderly (especially people over 60 years old), and from women to men.²⁴ Even after the adjustment of the model, less years of education were related to MB leprosy. People with higher education are more inclined to seek medical services to avoid delaying diagnosis and treatment.²⁵ Data showed that people with marriage history are the advantage group of MB leprosy, which may indicate that close contact in the home was related to exposure to leprosy bacilli, but we cannot rule out the importance of social contact in disease transmission.²⁶ A related study abroad concluded that the spread of leprosy is not limited to the indoor environment, and outdoor infection also affects the spread of the disease.²⁷ Passive detection was a protective factor for MB leprosy, so it is necessary to increase the publicity and education of leprosy prevention and control knowledge

in low-prevalence areas, and to improve the awareness rate of the masses and self-care awareness.^{28, 29} More than 5 lesions were associated with MB leprosy, which indicated that high concentration of leprosy bacilli infection can lead to more tissue destruction, more skin damage and worse deformation. Related studies abroad have analyzed the innate immune factors related to skin lesions of leprosy patients. For example, in cases of MB infection, the activation of complement protein will aggravate the inflammatory process and lead to peripheral nerve injury, resulting in significantly higher incidence of skin lesions in MB patients than in PB patients.³⁰

Disability degree is an indicator of the ability to diagnose and monitor leprosy of health service departments, and patients classified as Class I or Class II disability were related to delayed diagnosis or monitoring failure.³¹

It was shown that MB cases have a higher probability of grade I or II disability after model adjustment. By adding Class I disability (96 cases, 31.48%) to Class II disability (122 cases, 40.0%), the number of patients with disabilities increased to 218 (71.48%), which represented a high percentage of the overall disability. In addition, the incidence rate of Class II disability in our sample is far higher than the global average of 6% reported by the World Health Organization in 2016,³² which indicated that there is a delay in diagnosis or misdiagnosis in these patients.

This study was based on second-hand data obtained from the LEPMIS, so it has some limitations, such as inconsistent information, prevalence bias and the defect of cross-sectional design. Future studies need to consider longitudinal studies or geographical distribution to clarify factors related to leprosy. MB patients were the

main infectious source of leprosy, so early detection and treatment can effectively block the transmission of leprosy in the infectious source control link, which is of great significance to reduce the probability of leprosy patients with disability. This study elaborated the epidemic characteristics and regional characteristics of MB leprosy in northwest China, which may be helpful to effectively prevent and control leprosy.

Statements

Acknowledgements

We would like to thank all participants in the study on leprosy. In particular we would like to express our thanks to National Health Commission of the People's Republic of China and Health Commission of Shaanxi Province.

Contributorship statement

Ge Li and Hong Zhang co-wrote the article. Ping Chen has contributed to the collection and acquisition of the article data. Yaofei Wang gave guidance on research methods and case review. Xiaodong Yang was involved in data collection and statistical analysis. Qingping Zhang, the corresponding author, reviewed the data and results of this article.

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Funding

There is no funding to report for this submission. The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

No competing interests exist in this study, all authors have approved the manuscript for submission on your journal, the content of the manuscript has not been published or submitted elsewhere, and the retrospective study was reviewed and approved by the institutional ethics committee. All authors declare no known conflict of interest.

Data sharing statement

Data are available in a public, open access repository.

Patient and public involvement statement

Our research did not involve patients. LEPMIS is a legal and open information platform for leprosy prevention and research personnel in China with a view to strengthen Global Health and Global Health Research. The case information does not involve the patient's personal information, but is collective and provides the basis for the country's strategic prevention and control of leprosy. No patient involved under the sub-heading Patient and public involvement.

Patient consent for publication Not required.

Ethics approval Not required. Our research did not involve patients. LEPMIS is a legal and open information platform for leprosy prevention and research personnel in China with a view to strengthen Global Health and Global Health Research. The case information does not involve the patient's personal information, but is collective and provides the basis for the country's strategic prevention and control of leprosy. No patient involved under the sub-heading Patient and public involvement.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The authors confirm that the data supporting the findings of this article are available within the article.

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References

- 1 Limeira OM, Gomes CM., Morais OO, *et al.* Active search for leprosy cases in Midwestern Brazil: a serological evaluation of asymptomatic household contacts before and after prophylaxis with bacillus Calmette-Guerin. *Rev Inst Med Trop Sao Paulo* 2013;55:173-177.
- 2 Queiros MI, Ramos AJ, Alencar CH, *et al.* Clinical and epidemiological profile of leprosy patients attended at Ceara, 2007-2011. *An Bras Dermatol* 2016;91:311-317.
- 3 Camuset G, Lafarge S, Borgherini G, *et al.* Leprosy on Reunion Island, 2005-2013: Situation and Perspectives. *PLoS Negl Trop Dis* 2016;10:e4612.
- 4 Moschioni C, Antunes C M, Grossi M A, *et al.* Risk factors for physical disability at diagnosis of 19,283 new cases of leprosy. *Rev Soc Bras Med Trop* 2010;43:19-22.
- 5 Sales A M, Ponce D L A, Duppre N C, *et al.* Leprosy among patient contacts: a multilevel study of risk factors. *PLoS Negl Trop Dis* 2011;5:e1013.

- 297 6 Sehgal V N, Sardana K, Dogra S. The imperatives of leprosy treatment in the pre- and
298 post-global leprosy elimination era: appraisal of changing the scenario to current status. J
299 Dermatolog Treat 2008;19:82-91.
- 300 7 Rodrigues L C, Lockwood D N. Leprosy now: epidemiology, progress, challenges, and research
301 gaps. The Lancet Infectious Diseases 2011;11:464-470.
- 302 8 Martins R J, Carloni M E, Moimaz S A, *et al.* Sociodemographic and epidemiological profile of
303 leprosy patients in an endemic region in Brazil. Rev Soc Bras Med Trop 2016;49:777-780.
- 304 9 Global leprosy update, 2016: accelerating reduction of disease burden. Wkly Epidemiol Rec
305 2017;92:501-519.
- 306 10 Siyu Long, Meiwen Yu, Liangbin Yan, *et al.* Epidemiological characteristics of leprosy in
307 China in 2011 and 2015. Chin J Derm 2017;50:400-403.
- 308 11 Global leprosy update, 2014: need for early case detection. Wkly Epidemiol Rec
309 2015;90:461-474.
- 310 12 Global leprosy update, 2013; reducing disease burden. Wkly Epidemiol Rec 2014;89:389-400.
- 311 13 Global leprosy update, 2016: accelerating reduction of disease burden. Wkly Epidemiol Rec
312 2017;92:501-519.
- 313 14 Yaofei Wang, Ningxia An, Huimin Wang, *et al.* Discussion on the causes of delayed diagnosis
314 of leprosy in Chenggu County, Shaanxi Province. Chin J Derm Venereol 2008;01:42-43.
- 315 15 Monteiro L D, Martins-Melo F R, Brito A L, *et al.* Physical disabilities at diagnosis of leprosy
316 in a hyperendemic area of Brazil: trends and associated factors. Lepr Rev 2015;86:240-250.
- 317 16 Yuanguai Li, Tiejue Wu. Analysis of 9 new cases of leprosy in Zunyi in 2013. Chin J Derm
318 Venereol 2016;32:496.
- 319 17 Shuxia Chang, Xiaohua Wang, Daocheng Zheng. Research Progress of leprosy susceptibility
320 Genes. J Diagn Ther Dermat-Venereol 2018;25:253-256.
- 321 18 Silva M E, de Souza C D, Costa E S S, *et al.* Epidemiological aspects of leprosy in
322 Juazeiro-BA, from 2002 to 2012. An Bras Dermatol 2015;90:799-805.
- 323 19 Guerra-Silveira F, Abad-Franch F. Sex bias in infectious disease epidemiology: patterns and
324 processes. PLoS One 2013;8:e62390.
- 325 20 Modlin R L. The innate immune response in leprosy. Curr Opin Immunol 2010;22:48-54.
- 326 21 Nobre M L, Illarramendi X, Dupnik K M, *et al.* Multibacillary leprosy by population groups in
327 Brazil: Lessons from an observational study. PLoS Negl Trop Dis 2017;11:e5364.
- 328 22 Chou J P, Effros R B. T cell replicative senescence in human aging. Curr Pharm Des
329 2013;19:1680-1698.
- 330 23 Hepper H J, Sieber C, Walger P, *et al.* Infections in the elderly. Crit Care Clin
331 2013;29:757-774.
- 332 24 Nobre M L, Illarramendi X, Dupnik K M, *et al.* Multibacillary leprosy by population groups in
333 Brazil: Lessons from an observational study. PLoS Negl Trop Dis 2017;11:e5364.
- 334 25 Teasdale K, De Wildt G, Das P K, *et al.* The patient perspective of the diagnostic process for
335 leprosy in Brazil. An exploratory study. Lepr Rev 2015;86:21-36.
- 336 26 Klusener S, Dribe M, Scalone F. Spatial and Social Distance at the Onset of the Fertility
337 Transition: Sweden, 1880-1900. Demography 2019;56:169-199.
- 338 27 Santos S D, Penna G O, Costa M C, *et al.* Leprosy in children and adolescents under 15 years
339 old in an urban centre in Brazil. Mem Inst Oswaldo Cruz 2016;111:359-364.
- 340 28 Fayang Kang, Lihua Ruan, Yongchao Jia, *et al.* Analysis of risk factors of abnormal deformity

341 in newly discovered leprosy patients in Guangyuan City from 1999 to 2008. J Prev Med Inf
342 2010;26:610-612.

343 29 Yongkui Hu, Zhiguang Zhou. Comparison of methods of leprosy detection. Occup
344 Health;2007;20:1837-1838.

345 30 Bahia E I N, Iyer A M, Ramaglia V, *et al.* In Situ complement activation and T-cell immunity in
346 leprosy spectrum: An immunohistological study on leprosy lesional skin. PLoS One
347 2017;12:e177815.

348 31 Global leprosy update, 2016: accelerating reduction of disease burden. Wkly Epidemiol Rec
349 2017;92:501-519.

350 32 Assis B P N, Lyon S, Grossi M A D F, *et al.* Risk factors for physical disability upon release
351 from multidrug therapy in new cases of leprosy at a referral center in Brazil. Revista do Instituto
352 de Medicina Tropical de São Paulo 2019;61:e13..