Prevalence of American Tegumentary Leishmaniasis in Brazil
– A systematic review and meta-analysis

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Highlights:
(1) The prevalence of LTA in the systematic review and meta-analysis was 40% in Brazil.
(2) In the South and Southeast regions, a prevalence of up to 48% was found.
(3) Studies carried out in Pernambuco and Amazonas show a prevalence of 68% in males.

ABSTRACT

American tegumentary leishmaniasis (ATL) is a zoonotic disease that affects the skin and mucous membranes, and that is caused by different species of protozoa of the genus *Leishmania.* This disease has different clinical forms: cutaneous, disseminated cutaneous, diffuse and mucocutaneous leishmaniasis. The objective of this systematic review is to investigate the prevalence and distribution of ATL in Brazil. Studies that analised patients with ATL diagnosed by at least one of the parasitological gold standard methods, PCR, or by serological methods were included. Thirteen studies from PubMed, Regional Portal of the Virtual Health Library (BVS), Brazilian Society of Dermatology, Virtual Health Library (IBECS), Literature in the Health Sciences in Latin America and the Caribbean (Lilacs), Medical Literature Analysis and Retrieval System Online (Medline), Elsevier Embase, Cochrane Library, The National Institute for Health and Care Excellence (Nice), and Cumulative Index to Nursing and Allied Health Literature (CINAHL) were included. We found a combined prevalence in the general population of 40.0% (95% CI: 17.0–63.0%; weight 100%). When the prevalence was analyzed by state, we found a prevalence of 97.0% in Rio de Janeiro. The South and Southeast regions showed the highest percentage, with 48.0% followed by the Central-West region with 24.0%. The Montenegro's intradermal reaction and cultures were the most used test to diagnose. This study revealed a high prevalence of ATL in several studies conducted in Brazil, a value that was influenced by the most studied regions such South and Southeast.

Keywords: leishmania; leishmaniasis, cutaneous; leishmaniasis mucocutaneous; diagnosis; distribution.

PREVALÊNCIA DA LEISHMANIOSE TEGUMENTAR AMERICANA NO BRASIL – UMA REVISÃO SISTEMÁTICA E METANÁLISE

RESUMO

A leishmaniose tegumentar americana (LTA) é uma zoonose que acomete pele e mucosas, sendo causada por diferentes espécies de protozoários do gênero Leishmania. Esta doença apresenta diferentes formas clínicas: leishmaniose cutânea, cutânea disseminada, difusa e mucocutânea. O objetivo desta revisão sistemática é investigar a prevalência e a distribuição da LTA no Brasil. Foram incluídos estudos que analisaram pacientes com LTA diagnosticados por, pelo menos, um dos métodos parasitológicos padrão-ouro, PCR, ou por métodos sorológicos. Treze estudos do PubMed, Portal Regional da Biblioteca Virtual em Saúde (BVS), Sociedade Brasileira de Dermatologia, Biblioteca Virtual em Saúde (IBECS), Literatura em Ciências da Saúde da América Latina e Caribe (Lilacs), Sistema de Análise e Recuperação de Literatura Médica On-line foram incluídos. Encontramos uma prevalência combinada na população geral de 40,0% (IC 95%: 17,0-63,0%; peso 100%). Quando a prevalência foi analisada por Estado, encontramos uma prevalência de 97,0% no Rio de Janeiro. As Regiões Sul e Sudeste apresentaram os maiores percentuais, com 48,0%, seguidas da Região Centro-Oeste, com 24,0%. A reação intradérmica de Montenegro e as culturas foram os testes mais utilizados para o diagnóstico. Este estudo revelou alta prevalência de LTA em diversos estudos realizados no Brasil, valor que foi influenciado pelas Regiões mais estudadas como Sul e Sudeste.

Palavras-chave: leishmania; leishmaniose cutânea; leishmaniose mucocutânea; diagnostico; distribuição.

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INTRODUCTION

American tegumentary leishmaniasis (ATL) is a zoonotic disease that affects the skin and mucous membranes, and that is caused by different species of protozoa of the genus *Leishmania*[1,2]. This disease has different clinical presentations, with the most common ones being cutaneous leishmaniasis (CL), disseminated cutaneous leishmaniasis (DCL), diffuse leishmaniasis (DL), and mucosal/mucocutaneous leishmaniasis (ML)[3].

Although in some ways a neglected disease, ATL is considered a significant disease due to its high detection coefficient and capacity to produce deformities. Moreover, the disease mainly affects individuals of low socioeconomic status, and the number of cases in endemic areas has increased significantly in recent years[4–7].

Data from the Pan American Health Organization (PAHO) show that in the Americas, during the period from 2001 to 2017, a total of 940,396 new cases of CL and ML were reported by 17 of the 18 endemic countries, with an annual average of 55,317 cases. Brazil accounted for 72.6% of these cases[8]. Moreover, the World Health Organization estimates that Brazil is one of the ten countries responsible for approximately 87% of CL cases in the world (in 2015)[9]. In this sense, some studies confirm a high incidence in the states of Amazonas and Pará, with no sign of a declining trend[9,10]. In the state of Mato Grosso, a total of 52,637 cases were reported through the Information System of Notifiable Diseases (SINAN), between 2001 and 2017. This means that 12.75% of the cases reported in the country in this period was in this state[11].

The epidemiology of ATL has traditionally been defined as a zoonosis transmitted to humans when they come into contact with vectors in forests; however, this concept has been changing with the results of new research indicating that the disease is increasingly appearing in peri-urban and urban areas[12]. A series of cases analyzed between 2010 and 2014 reported that no differences were found between urban and rural areas in terms of the percentage distribution of new ATL cases in Amazonas[9].

In Brazil, ATL is a compulsory notifiable disease and classified as a vector-transmitted zoonosis. It has a wide territorial distribution with defined endemic zones in several states –especially in the Northern region – with intense transmission[13].

Regarding the demographic profile of patients affected by ATL, data registered in the Leishmaniases Regional Information System (*Sistema de Informação Regional de Leishmanioses nas Américas* – SisLeish), in 2017, inform that 68.7% (34,305) of the cases were male patients, and the most affected age group was between 20 and 50 years old[8]. Regarding the occupational profile, this disease is mainly associated with activities such as mining or gold prospecting, agriculture, deforestation for cattle production, and environmental transformations related to increased rural migration[14,15].

The ATL diagnosis is based on epidemiological data, clinical characteristics, and laboratory test results. These include a parasitological test, the Montenegro's intradermal reaction, serological tests such as an enzyme-linked immunosorbent assay (Elisa) and indirect immunofluorescence (IFI), in addition to molecular tests such as a polymerase chain reaction (PCR)[3]. A parasitological diagnosis is based on evidence of the parasite by microscopy and/or culture[16]. Although direct parasite detection is the gold standard for ATL diagnosis, it has low sensitivity. The association with molecular biology, especially in reference treatment centers, offers greater diagnostic accuracy and good sensitivity and specificity of results[17].

Although the current literature presents some data on the prevalence of ATL in certain regions, no analysis gathering information on prevalence according to geographic area, municipality, sex,

clinical form, and tests used in Brazil has been published to date. The objective of this pioneering systematic review is to investigate the prevalence and distribution of ATL in Brazil.

METHODS

The protocol for this systematic review was published in the International Prospective Register of Systematic Reviews (Prospero 2018: XXX) prior to its implementation and based on the Cochrane Handbook for Systematic Reviews of Interventions[18].

Review question

What is the prevalence and geographical distribution of American tegumentary leishmaniasis in endemic regions in Brazil?

Inclusion and exclusion criteria

This review considered studies that included patients with ATL diagnosed by at least one of the parasitological gold standard methods (Montenegro's intradermal reaction, microscopy, and/or culture), by PCR, or by serological methods (Elisa or IFI). Studies that analyzed cases confirmed as ATL using only one of the methods mentioned were excluded, but not for diagnostic purposes, but to assess the effectiveness of treatments or other types of intervention.

Search strategy

An initial search limited to Medline was performed using MeSH index terms and related keywords. This search was followed by an analysis of words throughout the text that were also cited in the titles, abstracts, and index terms used to describe the studies. A second search using all the identified keywords and index terms was performed in all included databases. In the third search, the reference lists of all theses and dissertations with clearly detailed precision values were evaluated.

Considering that ATL is a disease that affects the American continent, and that the aim of the present study is to investigate the prevalence of this disease in Brazil, the search was limited to the English, Spanish, and Portuguese languages. The search for primary literature was not limited to a specific start date and was concluded in May 2022.

Studies were searched in the following databases: Virtual Health Library Regional Portal, Brazilian Society of Dermatology, Spanish Bibliographic Index of the Health Sciences, Latin American and Caribbean Health Sciences Literature (Lilacs), United States National Library of Medicine bibliographic database, Elsevier database, Cochrane Library, National Institute for Health and Clinical Excellence (Nice), and Cumulative Index to Nursing and Allied Health Literature.

The MeSH index terms searched were "cutaneous leishmaniasis," "mucocutaneous leishmaniasis," "diagnosis," "*Leishmania,*" and "Brazil." The terms were combined using the Boolean operators "AND" and/or "OR" to compose the search patterns.

Evaluation of methodological quality

The articles selected for data retrieval were analyzed by two independent reviewers to evaluate the methodological validity of each article before their inclusion in this review. We evaluated the quality of the included publications based on the criteria of the Grading of Recommendations Assessment, Development and Evaluation (Grade) method. Studies received one point if they did not present limitations in their design or execution (risk of bias), inconsistency of results, indirectness of

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evidence, imprecision, or publication bias. A score of four to five points was considered high quality, a three-point score was considered moderate quality, and two to zero points was considered low quality.

Data extraction

The data were entered into Review Manager (RevMan 5.3) for analysis. A data extraction table was designed to assess the quality of demographic data, study site, number of cases, number of positives, and diagnostic tests.

Data synthesis

A meta-analysis random-effects model was applied to analyze the pooled prevalence, with a 95% confidence interval (CI), of leishmaniases in different states of Brazil. Heterogeneity among studies was analyzed using the Higgins test (I^2), which describes the percentage of total variation across studies that is due to heterogeneity, rather than chance. The meta-analysis was performed using Stata software, version 12 (StataCorp LLC, Texas, USA).

RESULTS

Our search resulted in 801 manuscripts related to laboratory diagnosis of ATL by the combined application of descriptors in the databases described above. After applying the eligibility criteria (duplicate texts, articles related to other topics, text excluded based on review or methodological quality criteria), 13 studies were selected for analysis (Table 1)[19,31]. Some studies evaluated the percentage of patients positive for ATL before any intervention. The results of the search strategy are shown in a PRISMA flowchart (Figure 1).

The 13 included studies had high methodological quality, with a GRADE score of five. Publication bias was not assessed because currently available methods are not considered useful in studies on proportions.

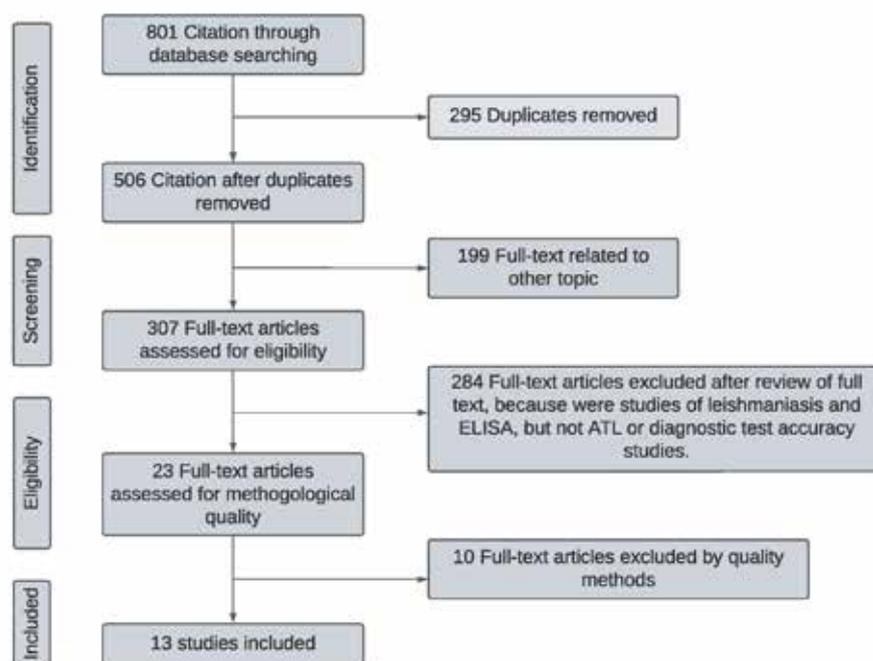Figure 1 – A flowchart of the steps performed in the systematic review

Table 1 – A summary of the included studies

AUTHOR	YEAR	STATE	MUNICIPALITY	TOTAL	SAMPLES		POSI-TIVE	POS-ITIVE (%)	POSITIVE SAMPLES		CLINICAL FORMS
					F	M			F +	M +	
Almeida et al.[19]	2021	RR	Boa Vista, Mucajai, Caroebe and Pacaraima	262	–	–	76	49.27	14	62	–
Melo et al.[20]	2020	PE, AM	Igarassu and Cabo de Santo Agostinho	213	66	147	195	91.5	–	–	CUTANEOUS
Ribeiro et al.[21]	2017	RJ	Rio de Janeiro	445	163	282	432	94.9	155	277	–
Brito et al.[22]	2008	PE, AM	Moreno	481	256	225	144	29.9	–	–	–
Guerra et al.[23]	2007	AM	Manaus	451	–	–	17	3.76	6	11	–
Dorval et al.[24]	2006	MS	Bela Vista	14	–	–	9	64.2	–	9	–
Nunes et al.[25]	2006	MG	Varzelândia	1170	577	593	282	24.1	–	–	–
Andrade et al.[26]	2005	PE	Paudalho	352	–	352	89	25.2	–	89	–
Follador et al.[27]	1999	BA	Santo Amaro	555	–	–	29	5.22	–	–	CUTANEOUS, MUCOCUTANEUS AND DISSEMINATED
Silveira et al.[28]	1999	PR	Maringá	1418	–	–	955	67.3	297	658	CUTANEOUS
Silveira et al.[29]	1996	PR	Jussara and Terra Boa	684	–	–	136	19.8	–	–	–
Nunes et al.[30]	1995	MS	Corguinho	150	–	–	32	21.3	–	–	–
Pignatti et al.[31]	1995	SP	Itupeva	144	17	17	34	23.6	17	17	–

F = Female; F+ = Positive Female; M = Male; M+ = Positive Male. Am = Amazonas; BA = Bahia; MG = Minas Gerais; MS = Mato Grosso do Sul, PE = Pernambuco; PR = Paraná; RR = Roraima; RJ = Rio de Janeiro; SP = São Paulo.

Leishmaniasis in Brazil

We analyzed studies published between 1995 and 2021 that investigated the prevalence of ATL in different municipalities of the states of Amazonas, Roraima, Pernambuco, Bahia, Minas Gerais, Rio de Janeiro, São Paulo, Paraná, and Mato Grosso do Sul. Table 1 shows the list of municipalities studied in each state. These studies evaluated samples in the municipalities and disease prevalence was analyzed by serological and molecular methods and Montenegro's intradermal reaction.

The prevalence percentages of ATL varied from 3.76% to 94.9% in the selected studies, with the states of Rio de Janeiro and Pernambuco showing the highest values. A total of 6,339 patients were analyzed in the 13 studies, and 2,430 (38.3%) of those showed a positive result by any of the methods employed for laboratory diagnosis (parasitological, PCR, or serological). Only seven studies segregated 1,612 positive patients according to sex, of which 1,123 (69.7%) were male patients and 489 (30.3%)

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were female patients. Regarding the labor profile, we observed that the most affected population were agricultural and military workers.

ATL prevalence in Brazil

The meta-analysis was performed using a random effects model. We found a combined estimated prevalence in the general population of 40.0% (95% CI: 17.0-63.0%; weight 100%). When the prevalence was analyzed by state, we found a prevalence of 97.0% in Rio de Janeiro; followed by 49% in Roraima; 48% in Paraná; 25% in Pernambuco; 24% in Mato Grosso do Sul, Minas Gerais, and São Paulo; 5% in Bahia; and 4% in Amazonas. Finally, two studies analyzed samples of patients from the states of Amazonas and Pernambuco, which represented 26.8% of the samples included in this meta-analysis, in which we found a combined prevalence of 64%. Figure 2 shows the combined prevalence with complete 95% CI values for each state.

Regarding sex, the 1,123 male patients represent 68.0% (95% CI: 66.0-70.0%; weight 71%), while the 489 female patients represent 32.0% (95% CI: 30.0-34.0%; weight 29%).

Regarding the clinical form diagnosed, only three studies described this information. Three studies reported on CL, and one study reported on DCL and ML (Table 1).

We analyzed the combined prevalence according to regions and observed that the South and Southeast regions showed the highest percentage, with 48.0% and CIs of (95% CI: 46.0-50.0%; weight 15.51%) and (95% CI: -9.0-105%; weight 23.22%), respectively. The midwest region followed with 24.0% (95% CI: 18.0-30.0%; weight 14.80%), after which came the Northeast region with 8.0% (95% CI: 6.0–10.0%; weight 15.50%) and finally the North region with 7.0% (95% CI: 6.0-9.0%; weight 15.48%) (Figure 3).

Figure 2 – Forest plot for a random-effect meta-analysis of LTA prevalence infection in the Brazilian population by state
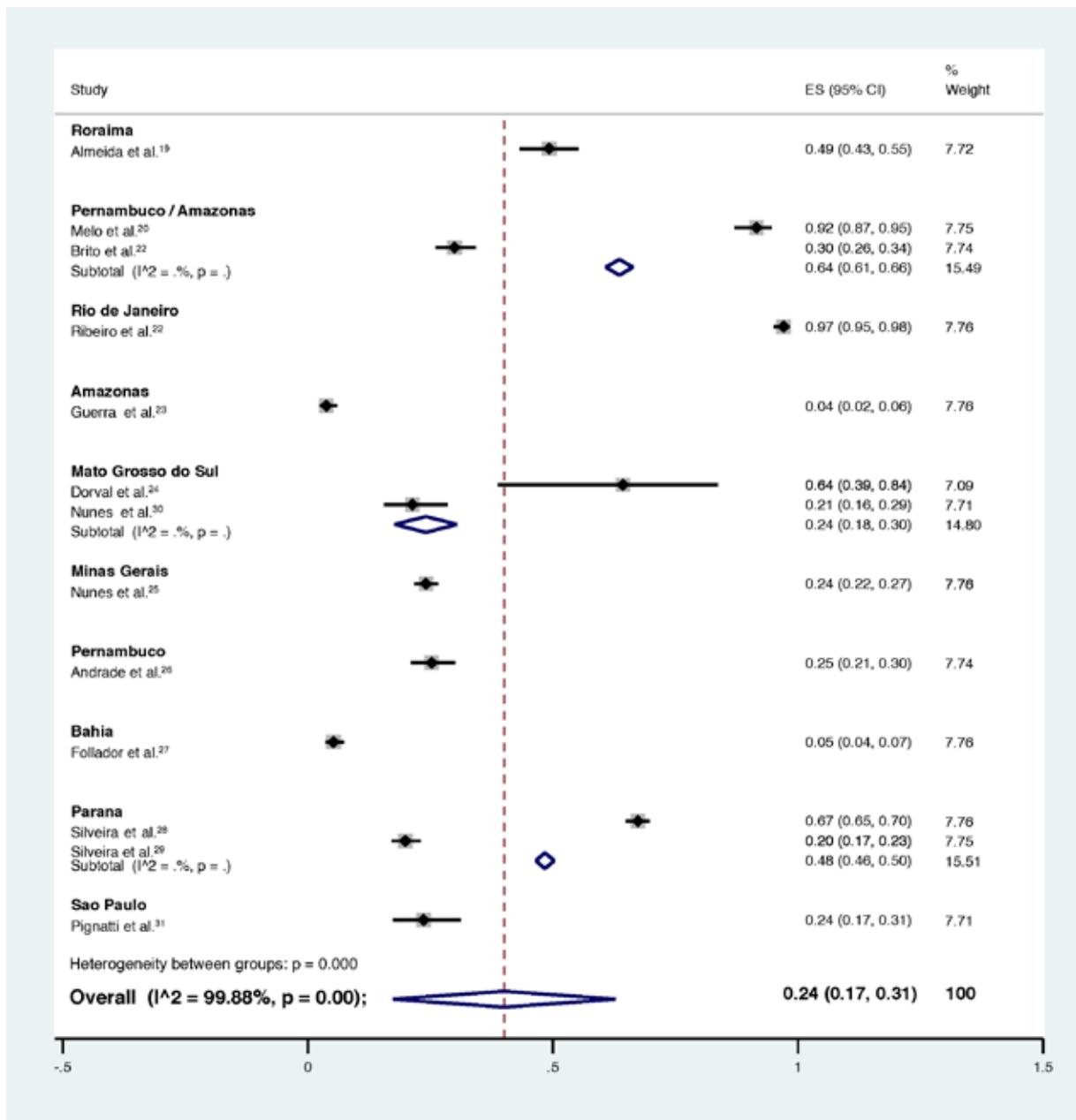
Two studies analyzed samples from Pernambuco and Amazonas, states belonging to the Northeast and North regions, resulting in a combined prevalence of 64.0% (95% CI: 61.0–66.0%; weight 15.49%).

Figure 3 – Forest plot for a random-effect meta-analysis of LTA prevalence infection in the Brazilian population by regions
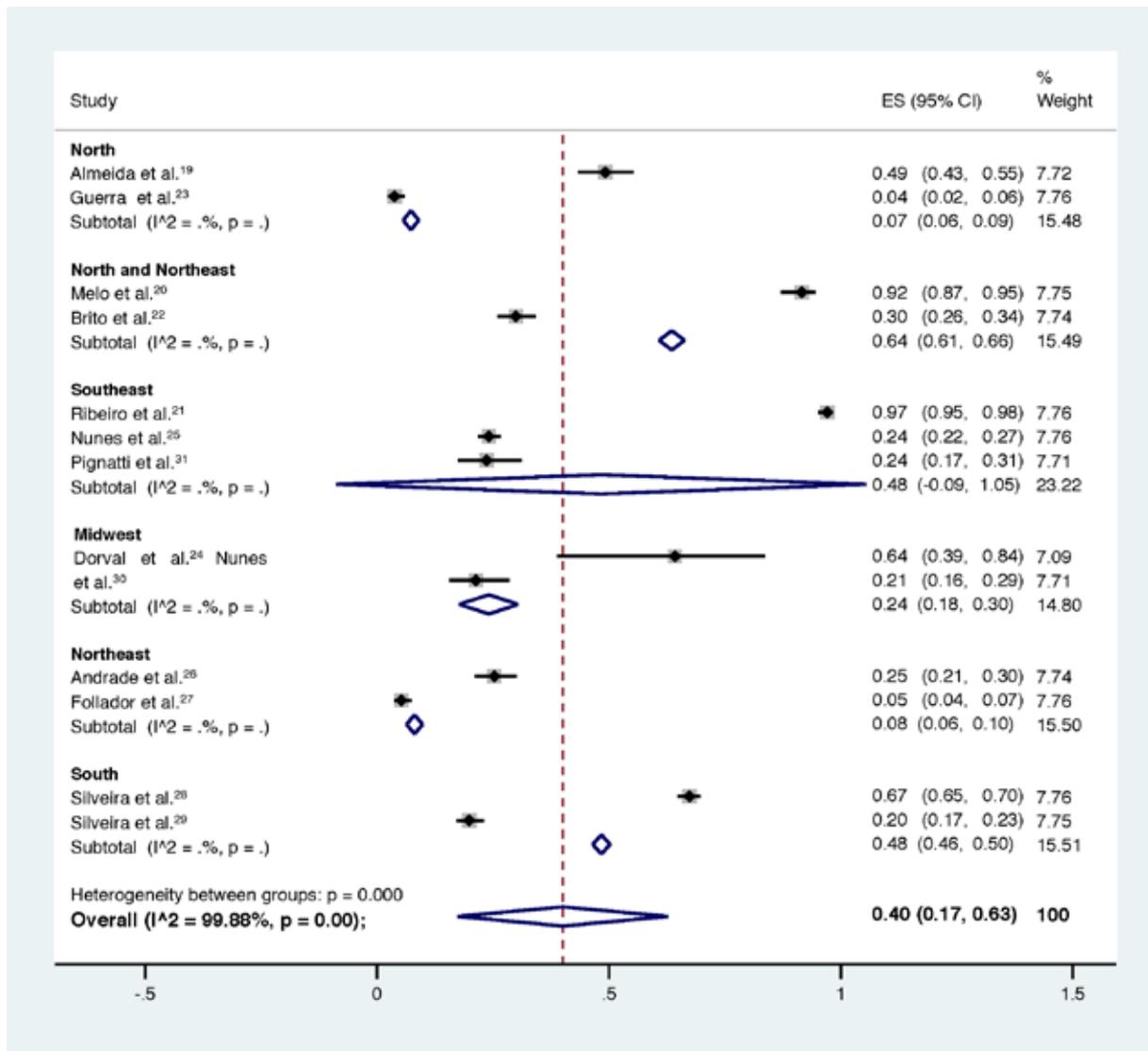
Diagnostic tests used

Two parasitological methods (Montenegro's intradermal reaction and culture), PCR and two serological methods (Elisa and IFI) were used for the ATL diagnosis in the patients analyzed in the included studies, totaling 4,272 tests performed. In this sense, the Montenegro's intradermal reaction gave a positive result in 1,822 (41.7%) patients, while cultures were used to diagnose 795 (18.2%) patients. PCR was used for the diagnosis of 165 (3.8%) patients, and regarding serological methods, 536 (12.3%) patients were positive for Elisa and 1,054 (24%) for IFI (Table 2).

Table 2 – Distribution of specified samples according to the type of diagnostic test used

	YEAR	STATE	MUNICIPALITY	TOTAL	MIR	PCR	CULTURE	IFI	ELISA
Almeida et al.[19]	2021	RR	Boa Vista, Mucajai, Caroebe and Pacaraima	262	–	–	–	–	–
Melo et al.[20]	2020	PE	Igarassu and Cabo de Santo Agostinho	213	–	–	–	–	–
Ribeiro et al.[21]	2017	RJ	Rio de Janeiro	445	347	129	342	284	350
Brito et al.[22]	2008	PE	Moreno	481	144	–	–	32	–
Guerra et al.[23]	2006	AM	Manaus	451	–	–	–	–	–
Dorval et al.[24]	2006	MS	Bela Vista	14	–	–	–	–	–
Nunes et al.[25]	2006	MG	Varzelândia	1170	282	–	–	127	170
Andrade et al.[26]	2005	PE	Paudalho	352	89	–	–	–	–
Follador et al.[27]	1999	BH	Santo Amaro	555	26	–	–	–	16
Silveira et al.[28]	1999	PR	Maringá	1418	820	–	453	611	–
Silveira et al.[29]	1996	PR	Jussara and Terra Boa	684	80	36	–	–	–
Nunes et al.[30]	1995	MS	Corguinho	150	–	–	–	–	–
Pignatti et al.[31]	1995	SP	Itupeva	144	34	–	–	–	–

IRM = Montenegro's intradermal reaction; PCR = Polimerase Chain Reaction; IFI = Indirect Immunofluorescence; ELISA = Enzyme-Linked ImmunoSorbent Assay.

DISCUSSION

The combined prevalence of ATL in this systematic review and meta-analysis was 40% in the 13 articles included in the meta-analysis. When we analyze the demographic profile of the patients included in this meta-analysis, we observe that the proportion of male patients was higher (68%), and CL was the main clinical form, although ML and DCL were also reported. This pattern was also observed in other similar studies carried out in the state of Amazonas and in several municipalities in Mato Grosso[9,15]. However, we could not find the most affected age in the studies analyzed, as they did not segregate the patients by age. Nevertheless, we emphasize that ATL represents a public health problem that can lead to physical, economic, and moral harm in the productive male population in Brazil, as this is the group at risk according to the PAHO report[8].

When we analyzed the prevalence by regions, we observed that the South and Southeast regions (48%) had the highest percentages among the five regions of Brazil. However, two studies that analyzed samples from Amazonas and Pernambuco, (North and Northeast) showed a higher prevalence (64%) overall. According to the 2021 epidemiological bulletin of neglected tropical diseases of the Brazilian Ministry of Health, ATL is distributed throughout the Brazilian territory, with the highest percentage of cases recorded in the North region (42.8%) with the Northeast region in second place, although the percentage for this region is not reported in this review. These data were prepared from

the stratification of cases between 2000 and 2019. Thus, we can infer that the combined prevalence between both studies that used samples from the states of Pernambuco and Amazonas (64%) would be closer to reality when compared to the prevalence when the samples from these regions are analyzed separately. The South and Southeast regions presented the highest prevalence in this study, probably due to these regions having more academic and research centers developing and publishing more data on ATL than the other regions in the country.

Regarding the tests used, the included studies did not use the smear technique, a simple and inexpensive procedure that is part of the gold standard for the diagnosis of this disease. We also observed that new serological techniques have been increasingly used to help in the laboratory diagnosis of this disease. Among the indirect tests that evaluate the immune response, the Elisa method was the most widely used for the serological diagnosis of leishmaniasis. The sensitivity of this method may vary according to the technique and the antigens used. Therefore, when this method is used, the number of positives and negatives may vary, depending on the antigen[32]. It should be noted that few studies used PCR as a diagnostic procedure. However, the implementation of this technique as a routine diagnostic method for patients with suspected ATL would result in a great contribution in the fight against this disease[33].

The present study has some limitations. First, some authors did not segregate the results of positive samples by sex, which decreased the number of samples available to assess the prevalence of this variable. Second, the samples were not segregated according to age, an important detail, considering that this disease affects mainly male individuals of working age. Third, our results are affected by the combined prevalence in the South and Southeast regions, since these regions present higher scientific production in the country.

CONCLUSION

This study revealed a high prevalence (40%) of ATL in several studies conducted in Brazil, a value that was influenced by the most studied regions (South and Southeast), where a prevalence of up to 48% was found. However, studies developed in Pernambuco and Amazonas (simultaneously) show an important percentage, with male patients being the most affected group with 68%. ELISA was the most used laboratory method for ATL diagnosis. Finally, we recommend the implementation of effective control measures that help prevent the transmission of this disease, especially in regions and municipalities with high transmission intensity.

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