INPLASY

The diagnostic accuracy of laboratory tests for human leishmaniasis: a systematic review and meta-analysis

INPLASY2023110066

doi: 10.37766/inplasy2023.11.0066

Received: 16 November 2023

Published: 16 November 2023

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ADMINISTRATIVE INFORMATION

Support - This research was funded by Universidad Católica de Santa María (grants 27574-R-2020, and 28048-R-2021).

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2023110066

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 November 2023 and was last updated on 16 November 2023.

INTRODUCTION

Review question / Objective Population (P): Patients with human leishmaniasis; Intervention (I): Molecular and serological diagnostic tests; Comparison (C): Different types of molecular and serological diagnostic tests; Outcome (O): Accuracy of diagnostic tests (sensitivity, specificity, etc.); Study Design (S): Systematic review and meta-analysis.

Rationale The study's rationale lies in addressing the imperative need for a comprehensive evaluation of the accuracy of diverse molecular and serological diagnostic tests for human leishmaniasis. With the existence of various diagnostic methods, understanding their performance is essential for clinicians to make informed decisions on the most reliable tools for timely and effective diagnosis. This systematic review and meta-analysis aim to fill critical gaps in the current understanding, informing healthcare practices, guiding future research, and ultimately contributing to improved diagnostic strategies for leishmaniasis, a disease of significant public health concern in specific regions. The study's findings hold the potential to enhance patient care, facilitate evidence-based decision-making, and impact public health initiatives aimed at controlling and preventing the spread of leishmaniasis.

Condition being studied Leishmaniasis, caused by protozoan parasites of the genus Leishmania, is a neglected tropical disease with over 20 species pathogenic to humans. The parasites are primarily transmitted through the bites of infected sandflies, with additional modes of transmission including vertical transmission, blood transfusion, and organ transplantation. Considered endemic in nearly 100 countries, the World Health Organization reports an

annual incidence of 700,000 to 1 million new cases and 20,000 to 30,000 deaths. Factors such as global warming, globalization, and conflict contribute to its global spread. Leishmaniasis presents a spectrum of clinical manifestations, including cutaneous leishmaniasis (CL), the most common form causing painless skin sores, mucocutaneous leishmaniasis (MCL) affecting mucous membranes and causing disfigurement, and visceral leishmaniasis (VL), the most severe form affecting internal organs and potentially leading to fatal complications if untreated. Post-kala-azar dermal leishmaniasis (PKDL) can develop as a sequela, serving as a reservoir of infection. The complexity and widespread prevalence of leishmaniasis underscore its status as a significant global public health concern.

METHODS

Search strategy The database employed for data collection was PubMed (https://pubmed.ncbi.nlm.nih.gov/). The search terms included Leishmaniasis[MeSH Terms], sensitivity and specificity[MeSH Terms], and “diagnostic technique”[MeSH Terms]. Within the "diagnostic technique" category, the following were considered: Intradermal Tests, ELISA, Fluorescent Antibody Technique, Hemagglutination Tests, rK39 protein, K26 protein, Agglutination Tests, Blotting, Western, Polymerase Chain Reaction, Real-Time Polymerase Chain Reaction, and LAMP assay. These searches covered the period from 1990 to2021.

Participant or population Humans affected by tegumentary and visceral leishmaniasis, as well as control groups without the disease.

Intervention In this review, our focus is on evaluating the utilization of molecular and serological diagnostic tests for leishmaniasis in patients affected by the disease in more intricate detail. Molecular testing encompasses techniques such as polymerase chain reaction (PCR), real-time PCR, and loop-mediated isothermal amplification (LAMP) testing. Conversely, serological tests include methods such as enzyme-linked immunosorbent assay (ELISA), fluorescent antibody techniques, and other agglutination or immunodiffusion tests. The comparison is specifically directed towards different variants of these diagnostic tests, with a comprehensive analysis of their respective advantages, limitations, and performance metrics, including sensitivity and specificity. The primary objective of this review is to furnish a thorough assessment of the effectiveness of these diagnostic tests in leishmaniasis diagnosis, thereby enhancing our understanding of their clinical applicability and offering guidance for the judicious selection of diagnostic methods within medical settings.

Comparator The comparative intervention applied to the target population, consisting of patients affected by leishmaniasis, involves an in-depth evaluation of various molecular and serological diagnostic tests. The comparison encompasses distinct types of these diagnostic methods, including polymerase chain reaction (PCR), real-time PCR, loop-mediated isothermal amplification (LAMP) testing for molecular diagnostics, and enzyme-linked immunosorbent assay (ELISA), fluorescent antibody techniques, and other agglutination or immunodiffusion tests for serological diagnostics. The review aims to systematically assess the advantages, limitations, and performance characteristics such as sensitivity and specificity of each diagnostic test variant. By undertaking this comprehensive comparison, the goal is to elucidate the relative effectiveness of these diagnostic approaches in the accurate and reliable detection of leishmaniasis. This analysis will inform the medical community about the most suitable diagnostic tools, contributing to enhanced clinical decision-making and optimized patient care for individuals affected byleishmaniasis.

Study designs to be included The study designs included to address the objective are those contributing to a systematic evaluation of the molecular and serological diagnostic tests for leishmaniasis. The primary study design is a systematic review, which involves a comprehensive and structured analysis of existing research literature on the topic. Additionally, a meta-analysis is incorporated, enabling the quantitative synthesis of data from multiple studies to provide a more robust and statistically supported assessment of the diagnostic tests' effectiveness.

Eligibility criteria The process of study selection for this review comprised three distinct phases. In the initial stage, known as the identification phase, only human studies published from 1990 to 2021 were considered. Exclusions encompassed duplicate articles, non-English publications, reviews, and meta-analyses. The second phase, denoted as the screening phase, involved assessing titles and abstracts of identified articles through the search method. Studies with full-text availability that were deemed highly relevant to the research question, specifically focusing on diagnostic methods and tests for leishmaniasis, were then retrieved. These selected studies were

distinguished from articles lacking the necessary information in their titles or abstracts to be considered, marking the eligibility and qualification phase of the review.

Information sources PubMed is a widely utilized biomedical literature database operated by the National Center for Biotechnology Information (NCBI), a branch of the United States National Library of Medicine (NLM). It serves as a comprehensive repository of peer-reviewed articles, research papers, and scholarly publications across various disciplines within the biomedical and life sciences fields. PubMed encompasses a vast collection of scientific literature, including articles from international journals, conference proceedings, and abstracts. The database is renowned for its user-friendly interface, robust search functionalities, and its commitment to providing open access to a wealth of biomedical information. Researchers, healthcare professionals, and the scientific community utilize PubMed to access authoritative and up-to-date literature, contributing significantly to advancements in medical research and practice.

Main outcome(s) A total of 156 publications meeting the established selection criteria were incorporated into the analysis. Polymerase chain reaction (PCR) demonstrates noteworthy sensitivity and specificity, rendering it a valuable diagnostic tool for both tegumentary leishmaniasis (TL) and visceral leishmaniasis (VL) in comparison to alternative molecular techniques like real-time PCR (qPCR) and loop-mediated isothermal amplification (LAMP). In the context of TL diagnosis, serological tests such as enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence assay (IFAT), and Western Blot (WB) exhibit relatively diminished sensitivity, while the Montenegro intradermal reaction (IDR) test distinguishes itself with heightened sensitivity. It is crucial to note, however, that all four tests demonstrate relatively low specificity. Concerning VL, IFAT and rapid diagnostic tests (RDT) manifest lower sensitivity when compared to ELISA and the direct agglutination test (DAT); moreover, they display relatively elevated specificity. The DAT emerges as the most effective choice for VL diagnosis, boasting the highest Area Under the Curve for Receiver Operating Characteristic (AUCFPR) at 0.966.

Quality assessment / Risk of bias analysis The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) method is a widely recognized and systematic approach used for conducting and reporting systematic reviews. In the context of quality assessment in primary studies, PRISMA emphasizes a rigorous and transparent process. The quality assessment is typically performed on individual studies included in the review to evaluate their methodological rigor and potential bias. PRISMA encourages the use of established tools, to systematically assess the quality of each primary study. By employing these standardized tools, PRISMA ensures a consistent and objective evaluation of the included studies, enhancing the reliability and validity of the systematic review findings. The transparent reporting guidelines provided by PRISMA also contribute to the overall quality and transparency of systematic reviews, facilitating a more thorough understanding of the evidence base by researchers, practitioners, and policymakers alike.

Strategy of data synthesis The results were input into a Microsoft Excel spreadsheet (version 19.0, Microsoft Corporation, Redmond, WA, USA) and analyzed using the "mada" package (version 0.5.11) in the R programming environment (version 4.2.3), accessible at https://cran.r-project.org/web/packages/mada/index.html (accessed on December 21, 2021). The "mada" package, employs a statistical approach to systematically combine and analyze multiple studies assessing the accuracy of diagnostic tests or procedures. This statistical tool considers variations between studies, explores potential sources of heterogeneity, and may incorporate techniques like subgroup analysis or meta-regression to explore factors influencing test performance. Initially, the count of true negatives (TN), false negatives (FN), true positives (TP), and false positives (FP) was individually analyzed for each diagnostic technique, and the evaluation of sensitivity and specificity was used to determine diagnostic performance.

Subgroup analysis The analysis involved the computation of several ratios: the positive likelihood ratio (LR+), the negative likelihood ratio (LR-), and the diagnostic odds ratio (DOR). The summary receiver operating characteristic (sROC) curve was fitted based on the "Reitsma" model parameters from the "mada" package to compare the diagnostic accuracy of leishmaniasis diagnostic methods. The sROC curve, synthesizing sensitivity and specificity data, visually represents the trade-off between sensitivity and specificity across various diagnostic thresholds. The area under the curve (AUC) in the sROC curve serves as a quantitative measure of overall test performance.

Sensitivity analysis All calculations were conducted with a 95% confidence level, employing a continuity correction of 0.5 when applicable.

Language restriction English.

Country(ies) involved Peru and Brazil.

Keywords Leishmaniasis; sensitivity; specificity; diagnostic accuracy; systematic review; meta-analysis.

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