INPLASY PROTOCOL

To cite: Candia-Puma et al. Accuracy of the diagnostic tests for the detection of Chagas disease: a systematic review and meta-analysis. Inplasy protocol 202290132. doi: 10.37766/inplasy2022.9.0132

Received: 30 September 2022

Published: 30 September 2022

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Support: **grant 28048-R-2021 (UCSM).**

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

Conflicts of interest:
None declared.

Accuracy of the diagnostic tests for the detection of Chagas disease: a systematic review and meta-analysis

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Review question / Objective: **The objective of the current work is to systematically review and summarize the available literature on the diagnostic accuracy of diagnostic tests for Chagas Disease.**
Eligibility criteria: **The studies were selected in three stages. In the first, non-English language articles, duplicate articles, reviews, and meta-analyses were excluded, only articles published after 1990 and conducted on humans were included. In the second stage, the titles and ab-stracts of the articles selected through the search strategy were examined. Finally, the highly relevant full studies were retrieved and separated from the articles with a title or abstract that did not provide sufficient data to be included.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 September 2022 and was last updated on 30 September 2022 (registration number INPLASY202290132).

INTRODUCTION

Review question / Objective: **The objective of the current work is to systematically review and summarize the available literature on the diagnostic accuracy of diagnostic tests for Chagas Disease.**

Rationale: **Laboratory diagnostic tests for Chagas Disease depend largely on the clinical stage of the disease, while in the**

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acute phase, it allows the direct detection of the parasite using molecular biology (polymerase chain reaction and real-time polymerase chain reaction) or parasitological (xenodiagnoses) techniques; oppositely, in the chronic phase, parasitemia becomes low and intermittent; still, acute infection leads to seroconversion and anti-T. cruzi-specific immunoglobulins are detectable for years, so the infection can be indirectly identified by serological methods, such as enzyme-linked immunosorbent assay (ELISA), complement fixation test (CFT), immunofluorescent antibody technique (IFAT), hemag-glutination test (HmT), radioimmunoprecipitation assay (RIPA), and western blot (WB). However, at present, there is no gold standard diagnostic test, since commercial tests have shown a high rate of false-positive results, for this reason, the World Health Or-ganization (WHO) recommends that the diagnosis of CD should be carried out using two conventional tests based on the detection of different antigens; and in the case of am-biguous or discordant results, a third technique should be used. This situation reveals the urgent need for the development of new diagnostic tools for disease diagnosis. A satisfactory method will allow the establishment of a patient registry with CD, a useful tool to provide information on its epidemiology, characteristics, and treatment. Additionally, it must be considered that a behavioral design that allows establishing the rea-sons for people's refusal to participate in diagnostic campaigns for this disease can alter the internal and external validity of the diagnosis.

Condition being studied: Chagas disease is an anthropozoonosis caused by the protozoan parasite Tryp-anosoma cruzi, which is transmitted mainly by blood-sucking bugs (also known as “kiss-ing-bug”) from the subfamily Triatominiae. Other transmission forms are vertical transmission from mother to child or by blood transfusion, organ transplant, laboratory accident, oral contamination, and breastfeeding. Over six million people are affected by the disease in Latin America, being endemic in 21 countries. Additionally, it has been proposed that in the United States approximately 300,000 persons live with the in-fection, including 57,000 Chagas cardiomyopathy patients and 43,000 infected reproduc-tive-age women, even though only a small fraction are properly diagnosed and treated. Comparably, in the last decade, globalization has allowed the disease to spread through European countries, such as Austria, Belgium, France, Germany, Italy, Nether-lands, Portugal, Spain, Sweden, Switzerland, the United Kingdom, Australia, Japan, and Canada. In this scenario, at least 100 million people have a high risk of infection by living in endemic areas of disease, while the estimated annual global burden is $627.46 million in healthcare costs and 800,000 disability-adjusted life-years, be-sides that, approximately 10,000 deaths per year can be attributed to the disease, making CD a serious public health problem worldwide.

METHODS

Search strategy: PubMed database with Medical Subject Headings (MeSH) terms
"Chagas Disease" [MeSH Terms] AND "Sensitivity and Specificity" [MeSH Terms] AND "Polymerase Chain Reaction" [MeSH Terms]
"Chagas Disease" [MeSH Terms] AND "Sensitivity and Specificity" [MeSH Terms] AND "Real-Time Polymerase Chain Reaction" [MeSH Terms] for qPCR
"Chagas Disease" [MeSH Terms] AND "Sensitivity and Specificity" [MeSH Terms] AND "Xenodiagnosis" [MeSH Terms]
"Chagas Disease" [MeSH Terms] AND "Sensitivity and Specificity" [MeSH Terms] AND "Enzyme-Linked Immunosorbent Assay" [MeSH Terms]
"Chagas Disease" [MeSH Terms] AND "Sensitivity and Specificity" [MeSH Terms] AND "Complement Fixation Tests" [MeSH Terms]
"Chagas Disease" [MeSH Terms] AND "Sensitivity and Specificity" [MeSH Terms] AND "Fluorescent Antibody Technique" [MeSH Terms]
"Chagas Disease" [MeSH Terms] AND "Sensitivity and Specificity" [MeSH Terms]

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AND "Hemagglutination Tests" [MeSH Terms]
"Chagas Disease" [MeSH Terms] AND "Sensitivity and Specificity" [MeSH Terms] AND "Radioim-munoprecipitation Assay" [MeSH Terms]
"Chagas Disease" [MeSH Terms] AND "Sensitivity and Specificity" [MeSH Terms] AND "Blotting, Western" [MeSH Terms].

Participant or population: Humans with Chagas disease and control groups without the disease.

Intervention: The information consigned for each study chosen included the diagnostic technique, the number, type, and clinical characteristics of patients with CD and healthy controls. All studies evaluating the sensitivity and specificity of Chagas Disease diagnostic techniques have been included.

Comparator: Diagnostic techniques are compared by diagnostic accuracy (sensitivity and specificity).

Study designs to be included: Experimental studies.

Eligibility criteria: The studies were selected in three stages. In the first, non-English language articles, duplicate articles, reviews, and meta-analyses were excluded, only articles published after 1990 and conducted on humans were included. In the second stage, the titles and abstracts of the articles selected through the search strategy were examined. Finally, the highly relevant full studies were retrieved and separated from the articles with a title or abstract that did not provide sufficient data to be included.

Information sources: PubMed database; ScienceDirect; Springer; Wiley; MDPI.

Main outcome(s): The PubMed database was searched for studies published between 1990 and 2021 on CD diagnostic. Fifty-six published studies that met the criteria were analyzed and included in the meta-analysis, evaluating diagnostic accuracy through sensitivity and specificity. For Enzyme-Linked Immunosorbent Assay (ELISA), Fluorescent Antibody Technique (IFAT), Hemagglutination Test (HmT), Polymerase Chain Reaction (PCR) and Real-Time Polymerase Chain Reaction (qPCR) diagnosis methods, the sensitivity had a median of 99.0%, 78.0%, 75.0%, 76.0% and 94.0%, respectively; while specificity presented a median of 99.0%, 99.0%, 99.0%, 98.0% and 98.0%, respectively. The results of this meta-analysis showed that ELISA and qPCR techniques had a higher performance as compared to other methods of diagnosing CD in the chronic and acute phases, respectively.

Data management: Results were entered into Microsoft Excel (version 10.0, Microsoft Corporation, Red-mond, WA, USA).

Quality assessment / Risk of bias analysis: This systematic review is conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA).

Strategy of data synthesis: Data analyzed in the R programming environment (version 4.0.3) using the package "mada" (version 0.5.1); which em-ploys a hierarchical model that accounts for within and between-study (heterogeneity) and the correlation between sensitivity and specificity. Initially, the number of true negatives (TP), false negatives (FN), true positives (TP), and false positives (FP) were analyzed separately for each diagnostic technique; while the evaluation of sensitivity (Se) and specificity (Sp) made possible to determine the diagnostic performance.

Subgroup analysis: Additionally, the positive likelihood ratio (LR+), the negative likelihood ratio (LR-), the diagnostic likelihood ratio (DOR), and the 95% confidence interval (CI) were determined. Summary receiver operating characteristics (sROC) curves were fitted, according to the parameters of the "Reitsma" model of the "mada" package, and were used to compare the diagnostic

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accuracy of Chagas disease diagnostic techniques.

Sensitivity analysis: **The confidence level for all calculations was set to 95%, using a continuity correction of 0.5 if pertinent**

Language restriction: **English.**

Country(ies) involved: **Perú (Computational Biology and Chemistry Research Group, Vicerrectorado de Investigación, Universidad Católica de Santa María, Arequipa 04000, Perú).**

Keywords: **Chagas disease, Diagnostic Tests, Meta-analysis, Systematic review; Sensitivity and Specificity.**

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