Animal Diseases

REVIEW

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Clinicopathological alterations in wild mammals from the reservoir system of *Trypanosoma cruzi*: a scoping review

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Abstract

Trypanosoma cruzi is the etiologic agent of Chagas disease. This flagellated protozoan is transmitted to humans as well as different species of domestic and wild animals *via* vectors from the Reduviidae family (known as "kissing bugs"). Despite the fact that hundreds of species of wild mammals are part of the reservoir system, the morphological changes and clinical manifestations resulting from the pathogenesis of the infection have been largely neglected. The aim of this review is to systematically compile the available information regarding clinicopathological alterations in wild mammals due to natural infection by *T. cruzi*. Information was obtained from six online bibliographic data search platforms, resulting in the identification of 29 publications that met the inclusion criteria. Mortality was the most common clinical manifestation, cardiac damage was the main finding at necropsy, and lymphoplasmacytic inflammation was the most frequent microscopic injury. Thus, regardless of its role as a reservoir, *T. cruzi* has the potential to affect the health status of wild mammals, a situation that highlights the need for further research to analyze, measure, and compare its effects at both the individual and population levels.

Keywords *Trypanosoma cruzi*, Chagas disease, American trypanosomiasis, Clinicopathological alterations, Natural infection, Wild mammals

Introduction

Trypanosoma cruzi is the etiologic agent of Chagas disease or American trypanosomiasis and can infect humans as well as different species of domestic and wild animals. It is transmitted by blood-sucking triatome vectors (also known as "kissing bugs") of the family Reduviidae, specifically the subfamily Triatominae, and is distributed from Argentina to the southern United States of America (Cruz-Reyes and Pickering-López 2006; Salazar-Schettino et al. 2016; Hamer and Hodo 2019). Triatomines are most active during the night and feed on blood from their nymphal stages to their adult form (Hamer and Hodo 2019). The main infection route reported for wildlife is oral ingestion of infected triatomes or tissues of parasitemic prey and congenital transmission via the placenta (Gunn and Pitt 2012; Hamer and Hodo 2019; Beugnet and Halos 2018).

Chagas disease originated millions of years ago as an epizootic infection in wildlife. However, the continuous occupation of natural environments by humans has led to the inclusion of triatomine bugs as a source of blood,

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leading to anthropozoonosis. The interaction between the elements involved in the infection chain allows us to differentiate three interconnected transmission cycles: sylvatic, peridomestic and domestic (Fig. 1) (Hamer and Hodo 2019; Rodrigues Coura 2007).

These cycles can be characterized by vector–host interrelations. The sylvatic cycle is maintained by triatomine bugs and wild vertebrates in their natural habitats (e.g., armadillos, nonhuman primates, carnivores, etc.). The domestic cycle considers domiciliated triatome vectors, humans and companion animals (mainly dogs). Synanthropic species (such as rats, mice, raccoons, bats or opossums) and triatomines that migrate to urban environments as a result of habitat loss are involved in the peridomestic cycle (Fernandes and Andrews 2012; Jansen et al. 2018; Hamer and Hodo 2019).

T. cruzi is a pathogen with multiple hosts (Jansen et al. 2017a, b). To date, more than 150 species have been reported as part of the reservoir system of this parasite (Hamer and Hodo 2019), and all mammalian orders in the Americas are known to be part of one or more transmission cycles (Jansen et al. 2018; Coura and Junqueira 2015). Mammalian species can play different roles in the maintenance of the parasite depending on the host variables (species, sex, age, and behavioral patterns), parasite molecular and biochemical characteristics, and environmental conditions (stress, host coinfections, and availability of natural resources). In wild mammals, the infection rate is approximately 20%, with an average infectivity of 8%, indicating a high potential to maintain and disseminate the parasite (Jansen et al. 2017a, b, 2018).

Despite the evidence, research on these species has focused primarily on their importance in the maintenance and dispersion of Chagas disease, while the morphological changes and clinical manifestations resulting from the pathogenesis of the infection have been largely neglected. An integrated approach is crucial for predicting the impact of American trypanosomiasis on wildlife populations and for managing zoonotic risk (Jansen et al. 2017a, b; Hodo and Hamer 2017).

In the veterinary context, Chagas disease is described as a systemic parasitic disease that infects domestic and wild animals. In dogs, *T. cruzi* appears to exhibit increased pathogenicity, causing the potentially lethal cardiac failure reported in humans (Greene 2012; Desquesnes 2017). The clinicopathological alterations of American trypanosomiasis are related to genetic factors of both the parasite and the host, and different abnormalities develop depending on factors such as the affected species, health condition of the host, geographic location, parasite load, and *T. cruzi* strain (Gunn and Pitt 2012). According to this, Chagas disease can develop in two successive phases, acute and chronic (Rodrigues Coura 2007; Moncayo and Silveira 2017).

The acute phase is more common in young animals, which tend to die suddenly from cardiac failure during the first 2 to 4 weeks postinfection, during the peak of parasitaemia (Beugnet and Halos 2018). The main histopathological findings correspond to multifocal lymphoplasmacytic myocarditis and the presence of pseudocysts with amastigotes in the heart or lymph nodes. Additionally, there may be granulomatous myositis in the smooth muscle of

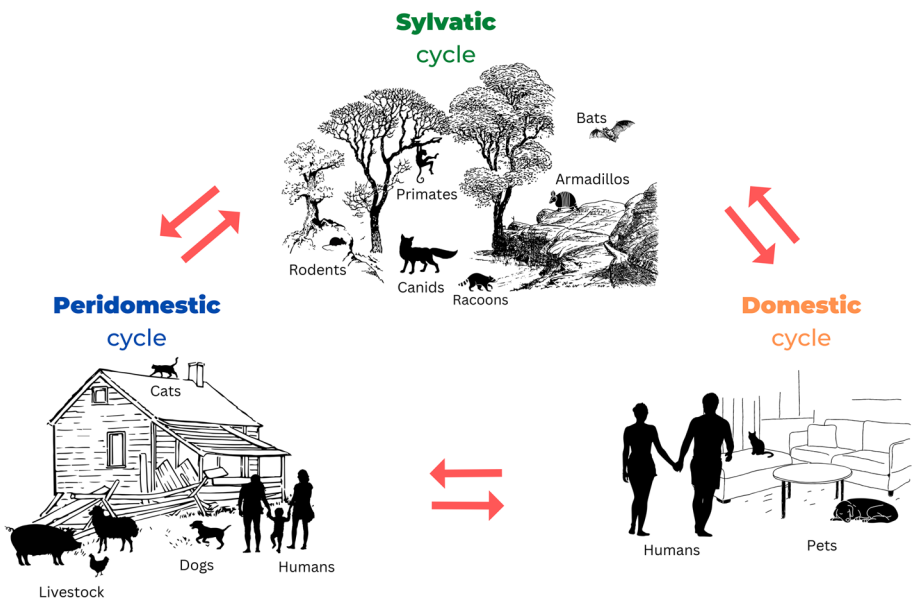

Fig. 1 Transmission cycles of *T. cruzi* (Modified from Hamer and Hodo 2019)

Table 1 Final search strategy established for the review

"*Trypanosoma cruzi*" *OR* "Chagas disease" *OR* Trypanosomiasis **AND** "Morphological findings" *OR* "Microscopic findings" *OR* "Pathological lesions" *OR* "Pathological changes" *OR* "Pathological alterations" *OR* Histopatholog* *OR* Necropsy **AND** Signs *OR* "Clinical manifestations" *OR* "Clinical changes" OR "Clinical findings" **AND** "Wild mammals" *OR* "Nondomestic Animals" *OR* "Wild Animals" *OR* Reservoir OR "Wild reservoir".

* Used as search command for partial words

the digestive tract, bladder, ureters, and skeletal muscle, as well as nonsuppurative encephalitis (Beugnet and Halos 2018; Gunn and Pitt 2012). As shown by necropsy, white spots or streaks can be found in the myocardium; pulmonary edema; and severe congestion in the liver, spleen, and kidneys. Moreover, laboratory test results tend to have little clinical relevance (Barr and Bowman 2012; Gunn and Pitt 2012). Common signs, such as lethargy, depression, weakness, hypothermia, anorexia, dyspnea, exercise intolerance, pale mucous membranes, delayed capillary refill, weak pulse, syncope, diarrhea and reproductive problems, are nonspecific. As in humans, this phase can be asymptomatic, and clinical manifestations may develop before the chronic phase (Gunn and Pitt 2012; Beugnet and Halos 2018; Barr and Bowman 2012).

The chronic course is characterized by adult or senile animals that may exhibit advanced signs or lesions beginning in the acute phase accompanied by ascites, paresis, ataxia, arrhythmia and ventricular tachycardia (Greene 2012). The macroscopic abnormalities typically observed are indicative of heart failure, such as bilateral dilated cardiomyopathy with thinning of the ventricular walls, serous exudate in the pleura and abdomen, hepatomegaly and splenomegaly (Barr and Bowman 2012; Beugnet and Halos 2018). Histopathological findings include evident loss of cardiac tissue and areas of lymphoplasmacytic myocarditis, along with extensive zones of necrosis and interstitial fibrosis (Barr and Bowman 2012). *T. cruzi* cannot be eliminated from the organism because its intracellular location enables it to avoid an immune response. Therefore, clinical manifestations can occur months or even several years post infection (Greene 2012; Beugnet and Halos 2018).

Although the confirmed presence of *T. cruzi* in several tissues of a wide range of wild reservoirs is known, information about morphological changes and clinical manifestations is scarce. The aim of this study was to methodologically determine the clinicopathological changes resulting from natural infection by *T. cruzi* in wild mammalian reservoirs. The focus is on the scope, nature and characteristics of the research conducted in this area.

Methodology

To the best of our knowledge, this is the first comprehensive review considering the clinicopathological alterations in wild mammals as a result of natural infection by *T. cruzi*. For this reason, a scoping review was conducted to systematically map, summarize and disseminate the research findings performed in this area (Arksey and O'Malley 2005). To achieve this goal, we followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis Extension for Scoping Reviews (PRISMA-ScR) (Tricco et al. 2018).

Eligibility criteria

Only free, open-access primary research studies were considered in the review without any timeframe restrictions. To be included, papers need to specify the morphological diagnosis, description of lesions and/or clinical manifestations, and method used for etiological diagnosis. Case reports and short communications were also included. Unpublished research (gray literature) and papers involving experimental infection protocols and/or any kind of therapeutic trial were excluded.

Information sources

The electronic databases selected were Scopus, PubMed, the Wiley Online Library, the Web of Science, and the Digital Library of the National Autonomous University of

Table 2 Examples of query formulas used in the electronic databases

Database	Formula
Scopus	(TITLE-ABS-KEY ("*Trypanosoma cruzi*" OR "Chagas disease" OR trypanosomiasis) AND TITLE-ABS-KEY ("Morphological findings" OR "Microscopic findings" OR "Pathological lesions" OR "Pathological changes" OR "Pathological alterations" OR histopatholog* OR necropsy) AND TITLE-ABS-KEY ("Wild mammals" OR sylvatic OR "Wild Animals" OR reservoir OR "Wild reservoir")) AND (LIMIT-TO (DOCTYPE, "ar"))
PubMed	((("*Trypanosoma cruzi*"[Title/Abstract] OR "Chagas disease"[Title/Abstract] OR Trypanosomiasis[Title/Abstract])) AND (("Morphological findings"[Title/Abstract] OR "Microscopic findings"[Title/Abstract] OR "Pathological lesions"[Title/Abstract] OR "Pathological changes"[Title/Abstract] OR "Pathological alterations"[Title/Abstract] OR Histopatholog*[Title/Abstract] OR Necropsy[Title/Abstract]))) AND (("Wild mammals"[Title/Abstract] OR Sylvatic[Title/Abstract] OR "Wild Animals"[Title/Abstract] OR Reservoir[Title/Abstract] OR "Wild reservoir"[Title/Abstract]))

* Used as a search command for partial words

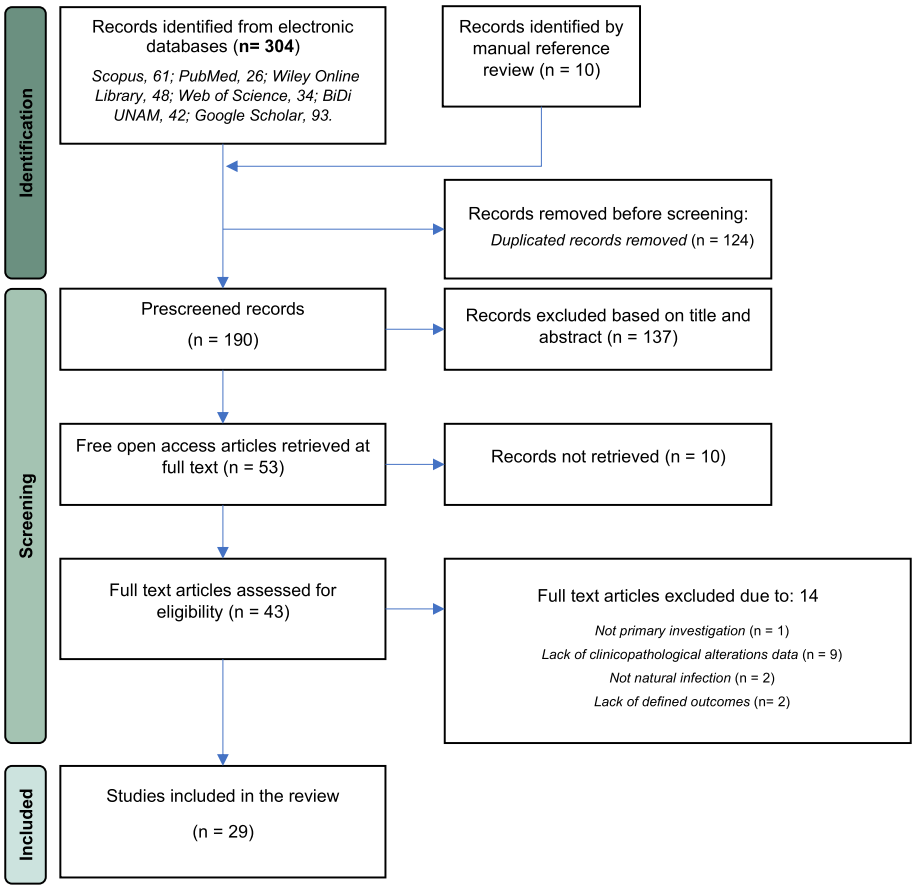

Fig. 2 PRISMA flow diagram for the selection of sources of evidence

Mexico (BiDi UNAM). Additionally, a web search engine (Google Scholar) was consulted to maximize the reach of the review. A search strategy was established by utilizing two structured vocabulary services indexing articles: DeCS (Health Sciences Descriptors) and MeSH (Medical Subject Headings) (Bramer et al. 2018). Subsequently, preliminary tests were carried out to refine and obtain the final search strategy (Table 1).

Search

This process was conducted during the months of April and May 2023. The fields selected for the search strategy were "title", "abstract", and/or "keywords". The filters available in each electronic database were used according to the eligibility criteria. In addition, a manual search was performed by reviewing the reference lists of the studies included to identify other relevant articles (Table 2).

Selection of sources of evidence

Before study selection, duplicate records were excluded. Subsequently, titles and abstracts were evaluated to identify potentially relevant publications, discarding those without free access to the full text. Finally, the preselected articles were read completely to verify compliance with the inclusion and exclusion criteria (Fig. 2). All the obtained records were saved and processed using Mendeley Reference Manager 2.89.0 (© 2023 Mendeley Ltd.).

Data charting process and synthesis of results

Relevant data from the included studies were extracted from the Microsoft Excel database, which included both the characteristics of the publication (main author, year, journal, electronic database, and language) and the wild reservoir (country, location, species, zootechnical purpose, affected organs, clinical manifestations, and morphological changes or pathologic lesions). Frequencies

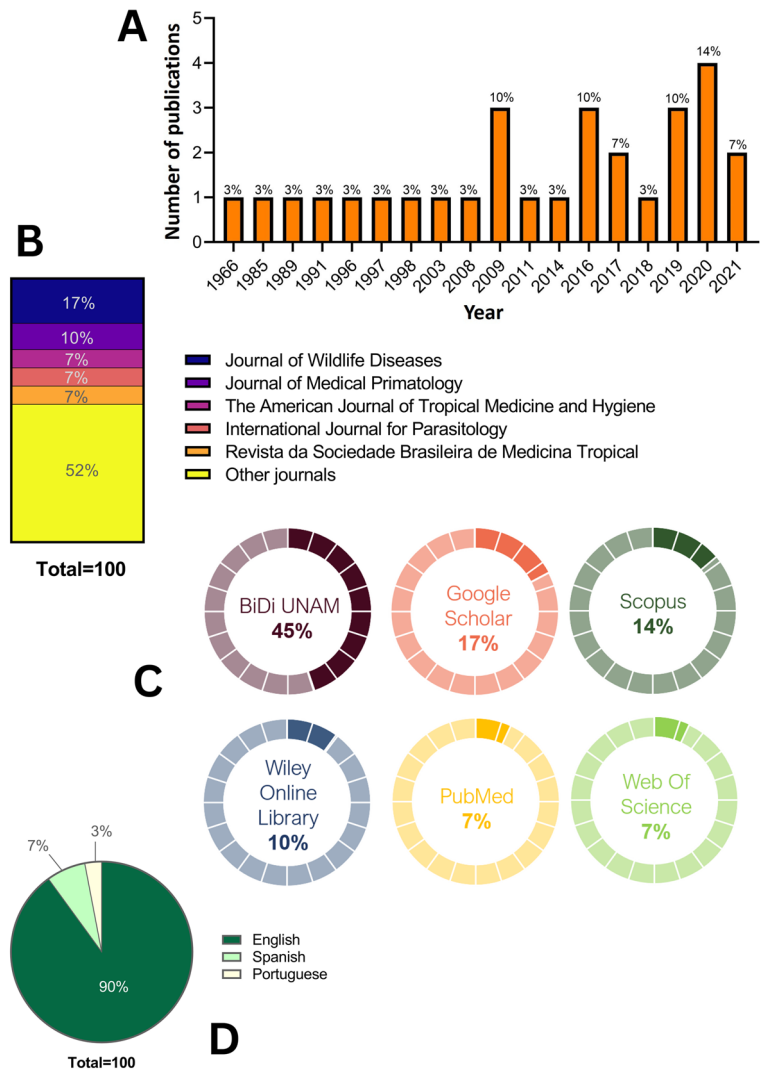

Fig. 3 Distribution of selected articles

A Frequency of articles by year of publication; **B** Percentage of articles by journal; **C** Proportion of articles by electronic database; **D** Distribution of publications by language

from every characteristic were obtained for graphic representation using Prism 9 (© 1992–2022 GraphPad, Software, LLC), ArcMap (© 1995–2022 Esri, Inc.) and Excel (Microsoft® Excel® 2016).

Results

Totally 29 publications and 21 wild mammals were selected

A total of 314 sources of evidence were assessed for eligibility, and after carrying out the selection process, 29 items were included in the review (Fig. 2). The publication languages were English (90%), Spanish (7%) and Portuguese (3%).

The 29 studies were published between 1966 and 2021. Most of the years (67%) had only one study recorded, while 2020 was the year with the highest number of publications (14%) (Fig. 3A). Five journals accounted for 48% of the publications, most of which (17%) were provided by the "Journal of Wildlife Diseases" (Fig. 3B). Furthermore, less than half (45%) of the papers included in this review were found in the "BiDi UNAM" electronic database. On the other hand, PubMed and Web of Science were the databases with the lowest number of publications, with 7% each (Fig. 3C). Moreover, 90% of the studies were published in English, while the remaining 10% were published in Spanish and Portuguese (Fig. 3D).

Table 3 Mammals of the reservoir system with data of clinicopathological alterations by natural infection of *T. cruzi*

Order	Family	Species	Items		Reference
Artiodactyla	Camelidae	*Llama glama*	1	3%	a
	Suidae	*Sus scofra*	1	3%	b
Diprotodontia	Macropodidae	*Macropus rufogriseus*	1	3%	c
		Petaurus breviceps	1	3%	d
Carnivora	Canidae	*Canis latrans*	2	6%	e, f
	Ailuridae	*Ailurus fulgens*	1	3%	g
	Felidae	*Leopardus pardalis*	1	3%	h
	Mephitidae	*Mephitis mephitis*	1	3%	i
	Procyonidae	*Procyon lotor*	3	9%	e, f, j
	Ursidae	*Ursus maritimus*	1	3%	k
Didelphimorphia	Didelphidae	*Didelphis marsupialis*	2	6%	l, m
		Didelphis virginiana	4	12%	n, o, p, q
		Philander frenatus	1	3%	r
		Philander opossum	1	3%	s
Primates	Hominidae	*Pan troglodytes*	1	3%	t
	Cercopithecidae	*Papio spp.*	3	9%	u, v, w
		Macaca fascicularis	4	12%	x, y, v, z
Rodentia	Caviidae	*Cavia porcellus*	1	3%	α
	Muridae	*Mus musculus*	1	3%	β
		Rattus rattus	1	3%	γ
Eulipotyphla	Erinaceidae	*Atelerix albiventris*	1	3%	d

a) Thompson, et al. 2021; b) Comeaux, et al. 2016; c) Diaz, et al. 2020; d) Latas – Reavill, 2019; e) Curtis, et al. 2016; f) Hodo, et al. 2020; g) Huckins, et al. 2019; h) Zecca, et al. 2021; i) Ryan, et al. 1985; j) Pietrzak - Pung, 1998; k) Jaime, et al. 1997; l) Araujo, et al. 1996; m) De brito – Deane, 1966; n) Villagrán, et. al. 2011; o) Zecca, et. al. 2020; p) Barr, et al. 1991; q) Carnevali, et al. 2017; r) Legey, et al. 2003; s) Barros, et al. 2020; t) Bommineni, et al. 2009; u) Andrade, et al. 2009; v) Mubiru, et al. 2014; w) Williams, et al. 2009; x) Grieves, et al. 2008; y) Henderson, et al. 2020; z) Vitelli, et al. 2017; α) Milei, et al. 1989; β) Torres – Hernández, 2016; γ) Ucan, et al. 2019

With respect to the wild reservoirs, we found 21 species of mammals with clinicopathological alterations caused by natural infection of *T. cruzi*. These species corresponded to seven orders and 15 families. Overall, "Carnivora" and "Didelphimorphia" had the highest number of studies, with 26% each. The most studied species were the crab-eating macaque (*Macaca fascicularis*) and the Virginia opossum (*Didelphis virginiana*), each with 12%, whereas 67% of the species had only one publication (Table 3).

These species were predominantly found in situ (55%). Conversely, 45% of the ex situ locations corresponded to wild mammals allocated for research, exhibition, or exotic pet purposes (Fig. 4B). Furthermore, 66% of the related research on these species was conducted in the U.S. Mexico, Argentina and Brazil had 17%, 14% and 3%, respectively, complete the list (Fig. 4A).

The proportion of affected organs was led by the heart, registering some kind of lesion in 41% of patients, followed by the gastrointestinal tract (tongue, esophagus, stomach, intestines and/or myenteric plexus) with 20%, the genitourinary tract (kidney, ureters, urinary bladder and testicles) with 14%, and the spleen and liver with 8% each (Fig. 5A).

The main research focus of the clinicopathological alterations was microscopic or histopathological lesions, which were addressed in 86% of the studies. Macroscopic lesions or necropsy findings were reported in 62% of the publications, and signs or clinical manifestations accounted for only 32% (Fig. 5B).

Clinical findings

Most of the wild mammals naturally infected by *T. cruzi* (88%) presented clinical manifestations. In 29% of the patients, sudden death was the main finding among the wild reservoirs with clinical signs. Other manifestations, such as inappetence (18%) and lethargy (12%), were also described, as were cardiac abnormalities, such as tachycardia; reproductive abnormalities, including abortion in the final phase of gestation; and digestive disorders, such as regurgitation problems and weight loss (Fig. 5C).

Macroscopic lesions

A great proportion of the wild reservoirs (77%) also developed macroscopic lesions. Representing 40% of the necropsy findings, organomegaly was the most common finding. This pathology was detected in a greater proportion of patients in the liver (11%), in other organs, such as

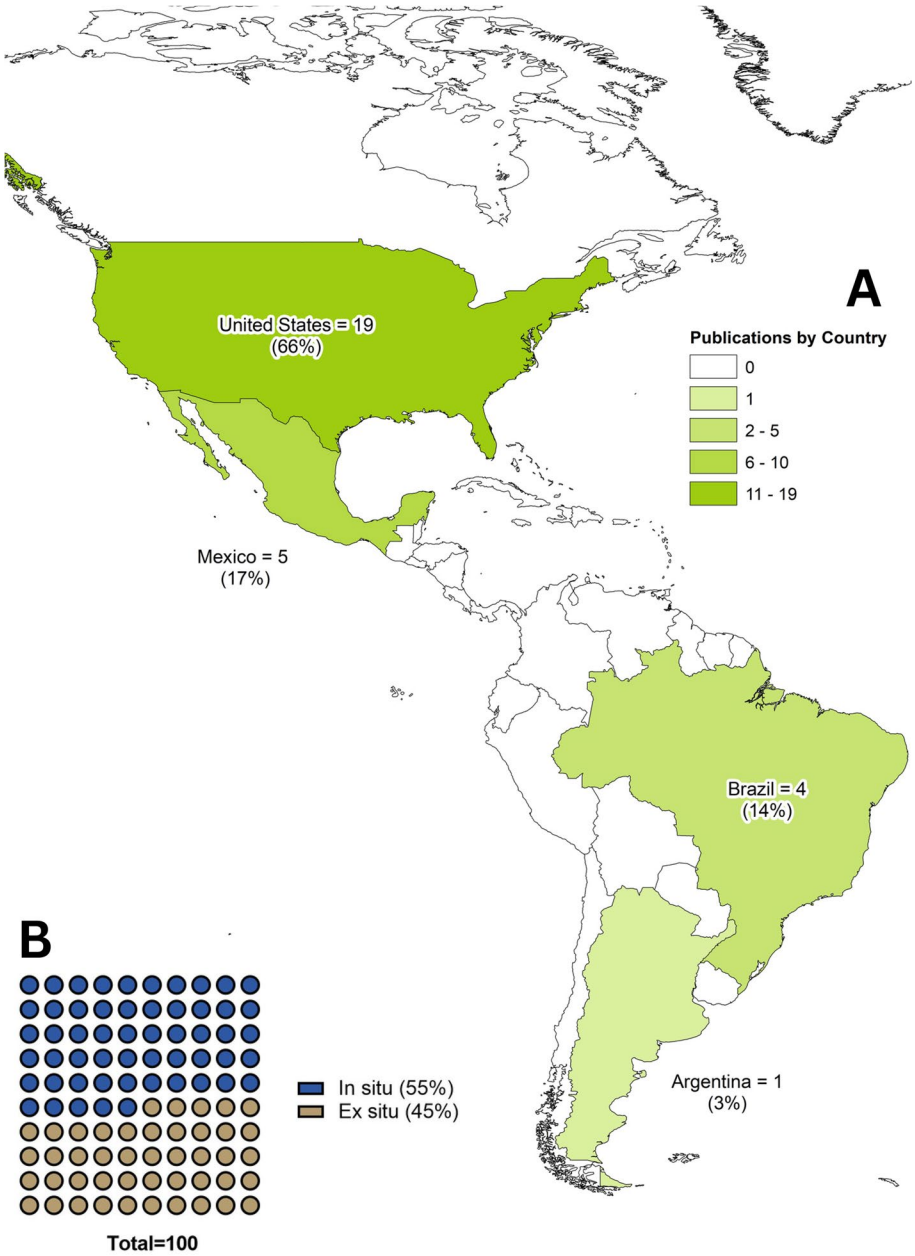

Fig. 4 Distribution of wild reservoirs

A Publications on wild reservoirs by country; **B** Location characteristics of the wild reservoirs

the spleen and esophagus (9% each), and in the heart and urinary bladder (6% each). Other important findings were heart damage, such as cardiac dilation, ventricular hypertrophy, and fibrinous pericarditis (14%), gastrointestinal injuries, such as gastric ulcers, and hemorrhagic gastrointestinal contents (9%). Notably, fetal maceration was reported at necropsy of the *Macaca fascicularis* macaques after abortion (Fig. 6A).

Microscopic lesions

In this case, almost all the infected animals reported histopathological lesions (98%). An inflammatory reaction was the primary microscopic finding (70%), corresponding to a nonsuppurative response characterized by the presence of mononuclear infiltrate in different organs and commonly associated with zones of edema, cellular degeneration, necrosis and/or fibrosis. The

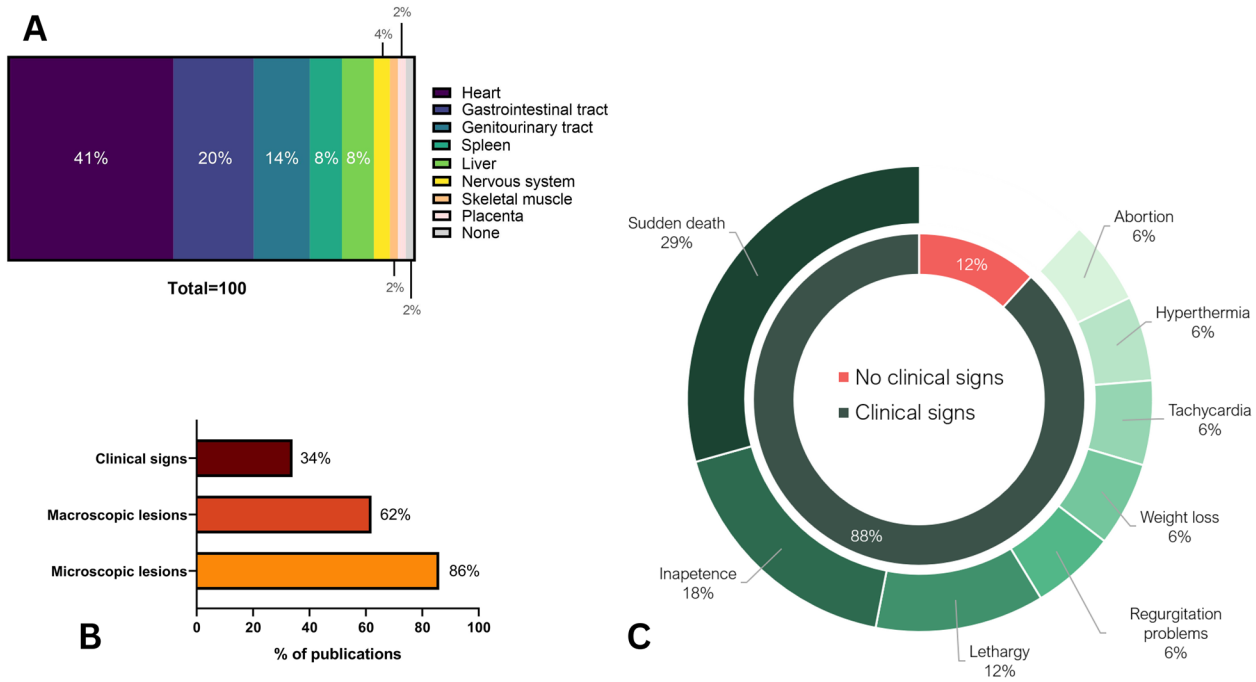

Fig. 5 Clinical findings of wild mammals infected by *T. cruzi*

A Proportion of organs affected by *T. cruzi* in wild reservoirs; **B** Percentage of publications with clinicopathological alteration data; **C** Distribution of the clinical manifestations reported in wild reservoirs

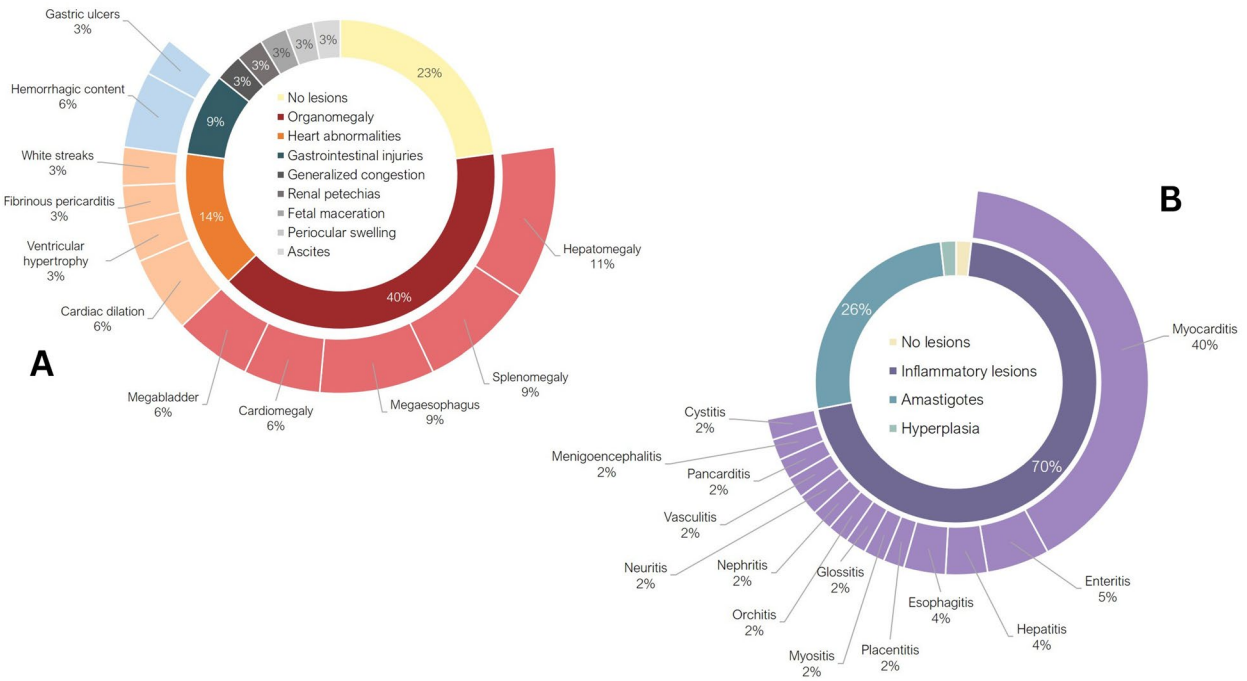

Fig. 6 Distribution of the macroscopic (**A**) and microscopic (**B**) lesions registered in wild reservoirs

cardiac muscle was the most relevant site for inflammatory lesions, resulting in the development of lymphoplasmacytic myocarditis in 40% of patients (Fig. 6B).

Amastigote pseudocysts were detected in 26% of the histological samples analyzed, and they spread to a variety of tissues and organs, including the smooth muscle of the esophagus and stomach, as well as the tongue, testicle, liver, kidney, brain, bladder, ureters, skeletal muscle, and placenta. Like for the other clinicopathological alterations, the heart was significantly different, accounting for 93% of the published cases of pseudocysts. Finally, follicular hyperplasia in the spleen and Kupffer cells of the liver completed the relevant microscopic lesions reported in the examined studies (Fig. 6B).

Discussion

In this scoping review, we identified a research background for at least the middle of the twentieth century, registering slight and unsustainable increases from 2009 onwards. Moreover, although Chagas disease is endemic in the Americas, no clinicopathological alterations have been documented in any of the four countries due to natural infection by *T. cruzi* in wild mammals. These results show the need to broaden and deepen the studies regarding wild reservoirs and the outcomes of being exposed to this pathogen. This is particularly true when there is evidence pointing to previously considered unlikely epidemiological interactions between wild reservoirs and *T. cruzi* (Martínez-Hernández et al. 2022).

Despite the high proportion (88%) observed among the wild reservoirs, the clinical signs were highly nonspecific. However, findings such as inappetence, weight loss, lethargy, and hyperthermia match those described for experimentally infected murine models (Rodrigues da Silva et al. 2016). Even for species considered natural reservoirs, mortality without previous clinical manifestations has been widely documented for both acute (Badra et al. 2008; Rojo et al. 2020) and chronic (Marinho et al. 2004) American trypanosomiasis. However, there are cases documenting the establishment of the infection and the development of pathological alterations, without lethal effects on the affected animals (Davis et al. 1980). The remaining clinical signs confirm the susceptibility of wild species to cardiomyopathies, which resemble the electrocardiographic and echocardiographic abnormalities described for domestic dogs (González-Vieyra et al. 2011). Likewise, abortions in wild species attributed to Chagas disease are thought to be related to the degenerative process in placental blood vessels that causes fetal mortality and low birth weight in the offspring of laboratory mice (Badra et al. 2008).

According to the macroscopic lesions referred to as American trypanosomiasis in wildlife, the pattern of enlargement in organs such as the heart, liver, spleen, and lymph nodes is a typical necropsy finding (Mbaya et al. 2009), possibly as part of the adaptive response to the infectious process. A further analysis of the lesions recorded in the heart showed that they were very similar to the characteristic cardiac damage mentioned for Chagas disease overall (Hamer and Hodo 2019) and causative of secondary circulatory disorders (such as edema, congestion, and fibrinous exudate) resulting from cardiac failure.

The inflammatory lesions detected in the included studies corresponded to two of the three histopathological patterns of inflammatory infiltration described in mice experimentally infected with *T. cruzi*. The first one has a predominance of lymphocytes with scarce macrophages, and the second has a mixed infiltrate with lymphocytes, macrophages, and occasional neutrophils (De Alba-Alvarado et al. 2020). The occurrence of inflammatory reactions in organs such as the liver, intestines, and kidney was also reported experimentally in *Thrichomys apereoides* and *Thrichomys pachyurus* (Rodrigues Roque et al. 2005). Histologic lesions in the heart were more frequent than those in any other organ, and this scenario tends to be similar to those described for Chagas disease under laboratory conditions (De Alba-Alvarado et al. 2020).

The capacity of *T. cruzi* to establish itself in a wide range of organs has been documented in naturally infected wild animals (Rojo et al. 2020). This could explain the consistent detection of pseudocysts in the different tissues examined. However, the tropism of this parasite for muscular tissues has been related to an actin-dependent cell invasion mechanism (Fernandes and Andrews 2012).

Conclusions

Our work demonstrated that wild mammals naturally infected with *T. cruzi* can cause clinicopathological alterations to occur in humans and domestic species, highlighting the need for complementary research to analyze, measure and compare not only the impact on the health of wild reservoirs but also epidemiological aspects, such as reemergence, disease outbreaks and the risk of zoonosis, especially when wild reservoirs have a critical role in the maintenance and dispersion of this pathogen in domestic, peridomestic, and wild environments.

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Authors' contributions
Conceptualization and Writing: Ricardo Sánchez Pérez; Review and critical comments: J. Manuel Aranda Coello, José A. De Fuentes Vicente and Oscar Rico Chávez; All the authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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