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Original article

A systematic review and meta-analysis of mortality in chronic Chagas cardiomyopathy versus other cardiomyopathies: higher risk or fiction?

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A B S T R A C T

Introduction and objectives: Although multiple studies suggest that chronic Chagas cardiomyopathy (CCC) has higher mortality than other cardiomyopathies, the absence of meta-analyses supporting this perspective limits the possibility of generating robust conclusions. The aim of this study was to systematically evaluate the current evidence on mortality risk in CCC compared with that of other cardiomyopathies.
Methods: PubMed/Medline and EMBASE were searched for studies comparing mortality risk between patients with CCC and those with other cardiomyopathies, including in the latter nonischemic cardiomyopathy (NICM), ischemic cardiomyopathy, and non-Chagas cardiomyopathy (nonCC). A random-effects meta-analysis was performed to combine the effects of the evaluated studies.
Results: A total of 37 studies evaluating 17 949 patients were included. Patients with CCC had a significantly higher mortality risk compared with patients with NICM (HR, 2.04; 95%CI, 1.60-2.60; I^2, 47%; 8 studies) and non-CC (HR, 2.26; 95%CI, 1.65-3.10; I^2, 71%; 11 studies), while no significant association was observed compared with patients with ischemic cardiomyopathy (HR, 1.72; 95%CI, 0.80-3.66; I^2, 69%; 4 studies) in the adjusted-measures meta-analysis.
Conclusions: Patients with CCC have an almost 2-fold increased mortality risk compared with individuals with heart failure secondary to other etiologies. This finding highlights the need for effective public policies and targeted research initiatives to optimally address the challenges of CCC.

Revisión sistemática y metanálisis de la mortalidad en la miocardiopatía chagásica crónica frente a otras miocardiopatías: ¿mayor riesgo o ficción?

Palabras clave:
Enfermedad de Chagas
Miocardiopatía chagásica
Insuficiencia cardiaca
Mortalidad

R E S U M E N

Introducción y objetivos: Aunque múltiples estudios indican una mayor mortalidad en la miocardiopatía de Chagas crónica (MCC) en comparación con otras miocardiopatías, la ausencia de metanálisis que respalden esta perspectiva limita la posibilidad de generar conclusiones robustas respecto a este fenómeno. El objetivo de este estudio es evaluar de manera sistemática la evidencia actual respecto al riesgo de mortalidad en la MCC respecto a otras miocardiopatías.
Métodos: Se realizaron búsquedas en PubMed/Medline y EMBASE de estudios que compararan el riesgo de mortalidad entre pacientes con MCC y con otras miocardiopatías, como la miocardiopatía no isquémica (MNI), la miocardiopatía isquémica y la miocardiopatía no chagásica (MNC). Se realizó un metanálisis de efectos aleatorios para combinar los efectos de los estudios evaluados.
Resultados: Se incluyeron 37 estudios que evaluaron a 17.949 pacientes. Los pacientes con MCC presentaron un riesgo de mortalidad significativamente mayor en comparación con los pacientes con MNI (HR = 2,04; IC95%, 1,60-2,60; I^2, 47%; 8 estudios) y MNC (HR = 2,26; IC95%, 1,65-3,10; I^2, 71%; 11 estudios). Sin embargo, no se observó ningún efecto significativo entre los grupos con MCC y con miocardiopatía isquémica (HR = 1,72; IC95%, 0,80-3,66; I^2, 69%; 4 estudios) en el metanálisis de efectos ajustados.

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Conclusiones: Los pacientes con MCC se enfrentan a un riesgo de mortalidad casi 2 veces mayor en comparación con los individuos con otras etiologías de miocardiopatía isquémica. Este resultado pone de relieve la necesidad de políticas públicas eficaces e iniciativas de investigación centradas en abordar de manera óptima los retos de la MCC.

Abreviations

CCC: chronic Chagas cardiomyopathy
NICM: nonischemic cardiomyopathy
ICM: ischemic cardiomyopathy
Non-CC: non-Chagas cardiomyopathy

INTRODUCTION

Chagas disease, caused by the parasite *Trypanosoma cruzi*, currently affects 6 to 8 million people, primarily in endemic areas in Latin America.[1] However, migration has turned Chagas disease into a worldwide public health issue, with nearly 300 000 cases estimated in the USA and 50 000 in Europe.[1] During the course of the disease, 30% of the patients will develop chronic Chagas cardiomyopathy (CCC), characterized by rapid heart failure (HF) progression and a high incidence of stroke and fatal ventricular arrhythmias.[2] Although the prognosis of HF patients ha significantly improved with the advent of neurohormonal blockade therapies during the last 4 decades, multiple studies indicate a persistent higher risk of adverse cardiovascular outcomes in the CCC population than in other cardiomyopathies (OC).[3] Nonetheless, evidence supporting this association is mainly derived from individual original studies and reviews not focused on HF patients, leaving a substantial knowledge gap in this area.[4,5] Therefore, this study aimed to systematically assess the evidence comparing the mortality risk in CCC with that of OC.

METHODS

Data sources and search strategy

This study was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (table 1 of the supplementary data). We searched the PubMed/Medline (National Library of Medicine, United States) and EMBASE (Elsevier, Netherlands) databases from inception to October 3, 2023, to identify longitudinal studies comparing the incidence of mortality in adult ambulatory patients with CCC and OC. No language restrictions were applied. We used the following search terms: Chagas cardiomyopathy, Chagas disease, *Trypanosoma cruzi*, *American trypanosomiasis*, mortality, and outcomes, among others. The complete search strategy is described in the supplementary data.

Study selection and eligibility criteria

We included clinical trials and all observational studies (eg, cross-sectional, cohort, and case-control studies), except for case reports and case-series. We also excluded systematic reviews and meta-analyses. Studies that assessed adult patients with CCC and compared the mortality risk with those with OC were considered. The follow-up of included studies also had to be performed in an outpatient setting. We excluded studies in the pediatric population or animals.

Data screening and extraction

The selection process was carried out using Rayyan.[6] Two independent reviewers screened the titles and abstracts, while considering the selection criteria. Any disagreements were resolved by a third reviewer. After this stage, full texts were reviewed to determine whether each study fulfilled the selection criteria. Relevant data from included studies was extracted using an Excel form. For studies reporting only medians and ranges (interquartile range, range, and maximum-minimum values), these values were converted into means and standard deviations using the method explained by Hozo, et al.[7]

Risk of bias assessment

The study quality was independently evaluated by 2 authors employing the Newcastle-Ottawa Scale. In instances where a consensus was elusive, a third author arbitrated to reach a resolution. The quality of each study was analyzed on a 10-point scale, stratified into "low risk of bias" for 9 to 10 points, "medium risk of bias" for 6 to 8 points, and "high risk of bias" for scores less than 6.

Data synthesis and analysis

The summary measures for continuous variables are reported as the mean ± standard deviation, while categorical variables are expressed as proportions. Participants were classified into 4 groups, initially: *a)* chronic Chagas cardiomyopathy (CCC); *b)* nonischemic cardiomyopathy (NICM), and *c)* ischemic cardiomyopathy (ICM). In addition, a fourth non-Chagas cardiomyopathy (non-CC) group was included for studies that did not characterize individuals in the comparator population (without Chagas cardiomyopathy) with respect to their etiology. Data synthesis was conducted by employing random effect models using the inverse variance method to estimate the pooled size effects, while the Paule-Mandel estimator was used to account for random error. In addition, the Hartung-Knapp adjustment was applied. Pooled unadjusted risk ratios (RR) were calculated from the mortality information reported, while adjusted hazard ratios (HR) were directly extracted from the multivariate models of the studies. Heterogeneity was assessed using the I^2 statistic. Value higher than 75% were considered to indicate high heterogeneity, those between 25% and 75% as moderate, and those less than 25% as low. Meta-regression analysis was performed in contrasts with more than 10 studies to assess variables that might explain heterogeneity in the observed associations. A meta-regression analysis was also performed in contrasts with more than 10 studies to assess variables that might explain the heterogeneity in the observed associations, while a sensitivity analysis comparing studies published before and after 2016 was performed to explore the potential influence of the use of the more recently introduced angiotensin receptor-neprilysin inhibitors. Finally, publication bias was assessed using funnel plots and

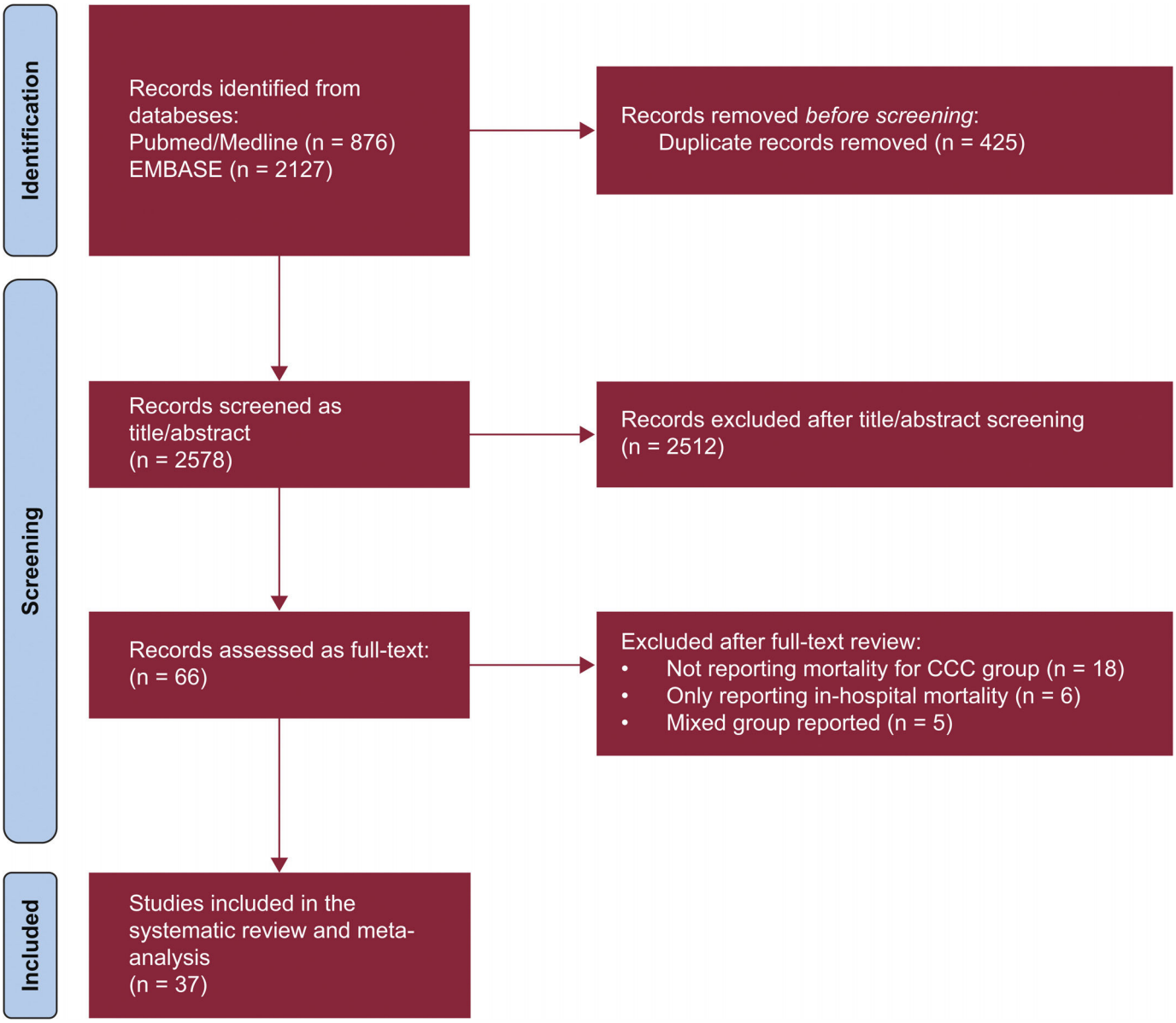

Figure 1. Central illustration. Flowchart of included studies.

Egger's test. If potential publication bias was identified, the trim-and-fill method was employed using the metafor package to calculate an adjusted effect size, accounting for the presence of this bias. Statistical significance was set at a $P < .05$. All analyses were conducted using R Statistical Software (v4.2.3; R Core Team 2023) and the meta and metafor packages.

RESULTS

Study and patient characteristics

Out of 2134 screened studies, 37 met the selection criteria and were included in the meta-analysis (figure 1 and table 1).[3,8–43] These studies were performed predominantly in Brazil (n = 32, 86.5%) and were primarily prospective cohorts (64.9%). A total of 17 949 patients (4258 with CCC and 13 691 with OC) were analyzed. CCC patients were younger (mean difference, −2.35 years; 95% confidence interval [95%CI], −4.05 to −.65 years; I^2, 93%) and less frequently male (odds ratio [OR], 0.74; 95%CI, 0.63-0.87; I^2, 40%) compared with patients with OC, with no significant differences in the proportion of patients in New York Heart Association class III-IV status (OR, 0.88; 95%CI, 0.70-1.09; I^2, 44.3%) or left ventricular ejection fraction (mean difference, 0.77%; 95%CI, −0.79% to 2.33%; I^2, 90%). The mean follow-up times in the assessed studies ranged from 100 days to 1970 days (median, 758 days). Finally, most of the studies (86.5%) were classified as having a low risk of bias (figure 2A,B).

Mortality risk meta-analysis

In the unadjusted analyses, CCC patients had a significantly higher risk of mortality during follow-up compared with patients with NICM (RR, 1.44; 95%CI, 1.21-1.71; I^2, 65%; 12 studies), ICM (RR, 1.34; 95%CI; 1.11-1.63; I^2, 65%; 10 studies), and non-CC (RR,

Table 1
General characteristics of the included studies and the evaluated population

First author	Year	Country/ Region	Quality (NOS)	Study type	Total patients	Total CCC patients	Total OC patients	Median follow-up	Multivariate analysis of mortality*
Areosa CMN, et al.[8]	2007	Brazil	5	Retrospective cohort study	330	94	236	1780	Yes
Ayub-Ferreira SM, et al.[9]	2013	Brazil	7	Post-hoc trial analysis	342	55	287	1284	Yes
Barbosa AP, et al.[11]	2011	Brazil	6	Prospective cohort study	352	246	106	851	Yes
Barbosa MPT, et al.[10]	2013	Brazil	7	Retrospective cohort study	135	65	70	266	No
Bertolino ND, et al.[12]	2010	Brazil	4	Retrospective cohort study	103	46	57	100	Yes
Bestetti RB, et al.[13]	1997	Brazil	6	Prospective cohort study	125	75	50	NR	No
Bestetti RB, et al.[14]	2013	Brazil	6	Prospective cohort study	374	244	130	1003	Yes
Bradfield J, et al.[15]	2014	USA	6	Prospective cohort study	36	18	18	1970	No
Braga JCV, et al.[16]	2008	Brazil	7	Prospective cohort study	191	89	102	365	Yes
Cardoso J, et al.[17]	2010	Brazil	7	Prospective cohort study	110	33	77	760	No
Cerqueira-Silva T, et al.[18]	2021	Brazil	7	Retrospective cohort study	404	210	194	1305	Yes
de Albuquerque DC, et al.[19]	2023	Brazil	7	Prospective cohort study	3013	262	2751	346	No
De Campos Lopes CB, et al.[20]	2006	Brazil	7	Prospective cohort study	458	98	360	730	Yes
de Melo RMV, et al.[21]	2019	Brazil	6	Retrospective cohort study	108	52	56	478	Yes
Oliveira Jr MT, et al.[22]	2005	Brazil	6	Prospective cohort study	126	56	70	NR	No
Dubner S, et al.[23]	2005	Latin America	7	Prospective cohort study	507	201	306	213	Yes
Echeverría LE, et al.[24]	2023	Colombia	7	Prospective cohort study	2514	86	2428	215	Yes
Femenía F, et al.[25]	2012	Argentina	6	Retrospective cohort study	179	72	107	NR	No
Freitas HFG, et al.[26]	2005	Brazil	8	Prospective cohort study	866	242	624	170	Yes
Freitas HFG, et al.[27]	2009	Brazil	7	Retrospective cohort study	280	144	136	1043	Yes
Heringer-Walther S, et al.[28]	2006	Brazil	7	Prospective cohort study	82	32	50	955	No
Issa VS, et al.[3]	2009	Brazil	7	Post-hoc trial analysis	456	68	388	1326	No
Martinelli M, et al.[29]	2017	Brazil	6	Prospective cohort study	426	115	311	365	Yes
Nadruz W, et al.[30]	2018	Brazil	7	Prospective cohort study	944	159	785	730	No
Nakazone MA, et al.[31]	2020	Brazil	7	Prospective cohort study	677	368	309	1459	Yes
Nunes MC, et al.[32]	2010	Brazil	7	Prospective cohort study	287	224	63	1201	Yes
Nunes VL, et al.[33]	2006	Brazil	4	Prospective cohort study	45	26	19	1825	No
Ochiai ME, et al.[34]	2011	Brazil	6	Retrospective cohort study	350	92	258	523	Yes
Olivera MJ, et al.[35]	2022	Colombia	6	Prospective cohort study	80	40	40	365	No
Passos LCS, et al.[36]	2019	Brazil	6	Retrospective cohort study	54	13	41	456	No
Pereira FTM, et al.[37]	2016	Brazil	8	Prospective cohort study	153	65	88	821	No
Rassi S, et al.[38]	2005	Brazil	8	Prospective cohort study	204	57	147	1399	No
Shen L, et al.[39]	2017	Latin America	7	Post-hoc trial analysis	2552	195	2357	973	Yes
Silva, et al.[40]	2008	Brazil	5	Prospective cohort study	354	122	232	365	No
Traina MI, et al.[41]	2015	USA	6	Prospective cohort study	135	25	110	1307	No
Vilas-Boas, LGC, et al.[42]	2013	Brazil	7	Prospective cohort study	301	222	79	638	Yes
Ferreira SMA, et al.[43]	2010	Brazil	5	Post-hoc trial analysis	296	47	249	758	Yes

CCC, chronic Chagas cardiomyopathy; NOS, Newcastle-Ottawa Scale; NR, not reported; OC, other cardiomyopathies.
* Studies reporting adjusted effect measures derived from multivariate Cox proportional-hazards models assessing mortality as the dependent variable and CCC as an independent variable.

1.42; 95%CI, 1.30-1.55; I^2, 37%; 22 studies) (figure 2A). Twenty studies provided adjusted effect measures for the risk of mortality, mainly including age, sex, New York Heart Association class, left ventricular ejection fraction, and HF medications as adjustment covariates. The meta-analysis of adjusted measures reported a significantly higher mortality risk in the CCC group compared with the NICM (HR, 2.04; 95%CI, 1.60-2.60; I^2, 47%; 8 studies) and the non-CC (HR 2.26; 95%CI, 1.65-3.10; I^2, 71%; 11 studies) groups, while no significant effect was observed when patients with CCC and ICM were compared (HR, 1.72; 95%CI, 0.80-3.66; I^2, 69%; 4 studies) (figure 2B). Of note, some studies reported information for more than one comparator group (ICM /NICM/non-CC), and consequently the total number of contrasts performed was higher than the number of articles included.

Meta-regression and publication bias

The results of meta-regression analysis revealed that none of the evaluated study characteristics (age, sex, New York Heart Association class, left ventricular ejection fraction, publication year, and follow-up time) was a significant source of heterogeneity ($P > .05$) (table 2 of the supplementary data). Moreover, a sensitivity analysis by publication year (before 2016 and after 2016) showed no significant differences in the effects between groups among the different contrasts (table 3 of the supplementary data). At the same time, Egger's test did not suggest publication bias in most of the performed analyses ($P > .05$), except for the unadjusted contrast between CCC and non-CC patients, which showed a potential bias toward reporting of larger effects ($P = .024$)

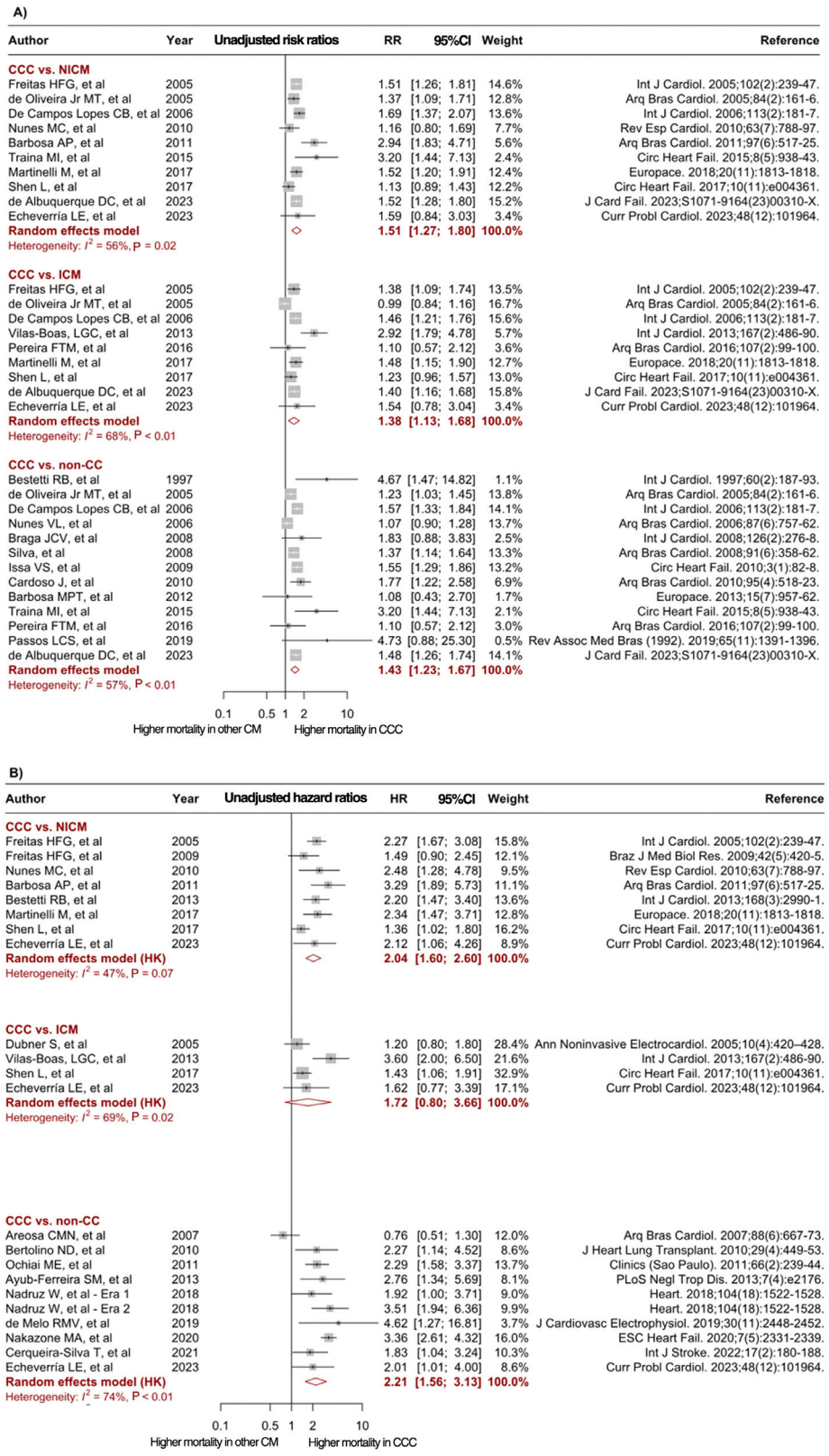

Figure 2. Forest plots comparing mortality risk between CCC and heart failure of other etiologies. **A:** unadjusted RR for CCC vs NICM, ICM, and non-CC. **B:** adjusted HR derived from multivariable Cox proportional-hazards models for CCC vs NICM, ICM, and non-CC. 95%CI, 95% confidence interval; CCC, chronic Chagas cardiomyopathy; CM; cardiomyopathy; HR, hazard ratio; ICM, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; NICM, nonischemic cardiomyopathy; non-CC, nonchagasic cardiomyopathy; NOS, Newcastle-Ottawa Scale; RR, risk ratio. The bibliographic references cited in the figure correspond to: Issa et al.,[3] Areosa et al.,[8] Ayub-Ferreira et al.,[9] Barbosa et al.,[11] Barbosa et al.,[10] Bertolino et al.,[12] Bestetti et al.,[13] Bestetti et al.,[14] Bradfield et al.,[15] Braga et al.,[16] Cardoso et al.,[17] Cerqueira-Silva et al.,[18] de Albuquerque et al.,[19] De Campos Lopes et al.,[20] de Melo et al.,[21] Oliveira Jr et al.,[22] Dubner et al.,[23] Echeverría et al.,[24] Femenía et al.,[25] Freitas et al.,[26] Freitas et al.,[27] Heringer-Walther et al.,[28] Martinelli et al.,[29] Nadruz et al.,[30] Nakazone et al.,[31] Nunes et al.,[32] Nunes et al.,[33] Ochiai et al.,[34] Olivera et al.,[35] Passos et al.,[36] Pereira et al.,[37] Rassi et al.,[38] Shen et al.,[39]Silva et al.,[40]Traina et al.,[41]Vilas-Boas et al.,[42] Ferreira et al.[43]

(Figure 1 of the supplementary data). Nonetheless, after implementing the trim-and-fill method for this contrast, the adjusted estimates showed a consistently higher risk of mortality in the CCC group (RR, 1.39; 95%CI, 1.26-1.52; I^2, 44%) (Figure 2 of the supplementary data).

DISCUSSION

In the present meta-analysis, which evaluated more than 17 000 patients with HF, we observed that HF secondary to CCC was associated with a significantly higher mortality risk than HF arising from other causes. This result was evident in both unadjusted and adjusted models. Notably, we found a similar mortality risk in the meta-analysis of adjusted effects when comparing CCC and ICM. However, this finding was limited by a smaller number of studies (n = 4) compared with the other adjusted contrasts (CCC vs NICM [n = 8] and CCC vs non-CC [n = 10]). Overall, our findings confirm the previously reported trend in individual studies and provide valuable information on the estimates for each etiologic group and the magnitude of the mortality risk associated with the diagnosis of CCC in HF patients. Interestingly, we observed a lower prevalence of male sex in the CCC group compared with the OC group. Current evidence suggests that male sex is associated with greater progression from the indeterminate form of Chagas disease to CCC[44]; however, there is also evidence suggesting that male sex is significantly associated with the development of OC, and the effect of this variable is potentially greater in other HF etiologies than in CCC.[45–48]

CCC represents a rapidly progressive form of cardiac involvement with a unique pathophysiology, characterized by severe immune cell infiltration to the myocardium, leading to extensive myocardial remodeling, intense fibrotic involvement, and a dilated cardiomyopathy phenotype.[49] Moreover, transmural replacement of the myocardium by scar tissue is frequent in CCC and has been associated with the development of fatal arrhythmias, making sudden cardiac death the second cause of mortality in this population after worsening HF.[50] In addition, systemic embolisms are highly incident in CCC due to the high prevalence of structural abnormalities, such as ventricular aneurysms and atrial fibrillation, as well as the presence of coagulation disorders intrinsic to chronic *Trypanosoma cruzi* infection.[49,51] Finally, the neuroendocrine involvement observed during the course of the disease, marked by compromised adrenal and thymus gland function coupled with more pronounced parasympathetic denervation, may potentially explain the more severe clinical profile of this cardiomyopathy compared with other etiologies.[52,53] Despite these insights, targeted therapeutic solutions that take into account the intricate pathophysiology of CCC remain elusive. Equally, there have been no dedicated randomized controlled trials evaluating the benefit of neurohormonal blockade in this patient population. Consequently, it is unknown whether patients with CCC benefit similarly from these therapies or continue to be at increased risk of mortality and adverse cardiovascular outcomes despite receiving optimal HF treatment.[54,55] Therefore, the results of the PARACHUTE trial are eagerly anticipated, as they will compare sacubitril-valsartan with enalapril in patients with CCC, focusing on mortality risk and other cardiovascular outcomes. The results of this clinical trial may define the future of the pharmacological management of CCC and have the potential to set a new trend regarding mortality in this vulnerable population.[56]

Limitations

Despite its comprehensiveness, our study has several limitations. First, the moderate to high heterogeneity among the included studies in some comparisons, including various populations, methodologies, and clinical settings, could have introduced potential biases. Although difficult to determine, the observed interstudy heterogeneity may be due to multiple factors. These factors include the year of study publication. Although the year of publication was not significantly associated with the impact of CCC diagnosis on mortality in the meta-regression analyses, the relatively low sensitivity of this approach does not allow us to rule out the presence of a significant effect. This is because the diagnostic and therapeutic approaches to HF varied significantly between the publication of the first included study (1997) and the last study (2023). Other important factors include the type and stage of cardiac involvement, since some studies did not clarify the etiologies of the comparator groups or whether the individuals included had a diagnosis of HF or were in earlier stages of cardiomyopathy, as well as the mean follow-up time, which, although not significant in the meta-regression analysis, could also have influenced the differences observed. Finally, although most of the studies were performed in Brazilian populations, 7 studies (19%) were conducted in other countries, mainly Colombia and the United States. Differences in the distribution of *Trypanosoma cruzi* discrete typing units and other variables could have also influenced the observed results.

Second, we identified a potential publication bias in the studies reporting unadjusted risks for CCC vs non-CC groups. However, a significant effect was still observed after we adjusted by this type of bias using a trim-and-fill method. Moreover, the potential confounders included in the multivariate-adjusted models varied significantly among studies, as different covariate selection approaches were used. Nevertheless, the absence of significant results in the meta-regression analyses supports the accuracy of our results. Furthermore, the absence of patient-level data restricted our ability to conduct more refined subgroup analyses or assess the influence of individual patient characteristics on outcomes.

Of note, patients with CCC represent a vulnerable population, with limited access to health services and, therefore, to HF medications and therapies that reduce mortality, such as neurohormonal blockade and implantable cardioverter-defibrillators, which may influence their survival. However, we were unable to include data on socioeconomic status, access to HF therapies, or adherence to these drugs in our analyses, representing an important limitation.

Finally, assessment of all-cause mortality allowed the inclusion of a larger number of studies, not discriminating between the different causes of mortality (HF, sudden cardiac death, stroke, among others).

CONCLUSIONS

This meta-analysis indicates that CCC patients have an almost 2-fold increase in mortality risk during follow-up compared with their counterparts with HF secondary to OC. This finding underscores the pressing need to increase awareness of CCC prognosis and encourage the performance of large RCTs evaluating the benefit of HF therapies in this special population. Furthermore, our results invite further investigation of the factors potentially associated with the worse prognosis observed in patients with CCC, potentially highlighting access to HF therapies, treatment adherence, and early diagnosis of cardiomyopathy. Such insights are critical for shaping effective public policies and focusing research initiatives to better address the challenges of CCC and enhance outcomes for this vulnerable patient group.

WHAT IS KNOWN ABOUT THE TOPIC?

- CCC is characterized by a unique pathophysiology that differentiates it from other etiologies of HF, potentially limiting the benefit of conventional diagnostic and therapeutic approaches to HF.
- CCC has been characterized by rapid progression and high mortality rate. Despite multiple studies highlighting worse clinical outcomes compared with other cardiomyopathies, there is lack of aggregated evidence analyzing whether diagnosis of CCC is associated with an increased risk of mortality.

WHAT DOES THIS STUDY ADD?

- In this meta-analysis of 17 949 patients, those with CCC showed a consistently higher risk of mortality when compared with patients with other cardiomyopathies even after adjustment by relevant confounding covariates.

FUNDING

The present study did not require funding.

ETHICAL CONSIDERATIONS

The present work is exempt from approval by the institutional ethics committee because it corresponds to a systematic review of the literature and meta-analysis, which did not require patient recruitment or access to disaggregated information on individuals, since it was based on scientific publications freely available in the medical literature. Possible sex and gender biases have been taken into account in the preparation of this article.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tools were used for the design or preparation of this study.

AUTHORS' CONTRIBUTIONS

S.A. Gómez-Ochoa participated in the study design, data collection, systematic review, study selection, methodology, statistical analysis, and manuscript review and editing. A.Y. Serrano-García oversaw the study design, data collection, systematic review, study selection, methodology, statistical analysis, and manuscript review and editing. A. Hurtado-Ortiz and A. Aceros were in charge of data collection, systematic review, study selection, and manuscript review. L.Z. Rojas and L.E. Echeverría oversaw the study design, study selection, and manuscript review and editing. All authors are responsible for reviewing the original manuscript and approving the final version.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2024.02.014.

REFERENCES

1. Gómez-Ochoa SA, Rojas LZ, Echeverría LE, Muka T, Franco OH. Global, Regional, and National Trends of Chagas Disease from 1990 to 2019: Comprehensive Analysis of the Global Burden of Disease Study. *Glob Heart.* 2022;17:59.
2. Echeverria LE, Morillo CA. American Trypanosomiasis (Chagas Disease). *Infect Dis Clin North Am.* 2019;33:119–134.
3. Issa VS, Amaral AF, Cruz FD, et al. Beta-blocker therapy and mortality of patients with Chagas cardiomyopathy: a subanalysis of the REMADHE prospective trial. *Circ Heart Fail.* 2010;3:82–88.
4. Cucunubá ZM, Okuwoga O, Basáñez M-G, Nouvellet P. Increased mortality attributed to Chagas disease: a systematic review and meta-analysis. *Parasit Vectors.* 2016;9:42.
5. Linetzky B, Konfino J, Castellana N, et al. Risk of cardiovascular events associated with positive serology for Chagas: a systematic review. *Int J Epidemiol.* 2012;41:1356–1366.
6. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan. A web and mobile app for systematic reviews. *Systematic Reviews.* 2016;5:210.
7. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol.* 2005;5:13.
8. Areosa CMN, Almeida DR, Carvalho ACCd, de Paola AAV. Evaluation of heart failure prognostic factors in patients referred for heart transplantation. *Arq Bras Cardiol.* 2007;88:667–673.
9. Ayub-Ferreira SM, Mangini S, Issa VS, et al. Mode of death on Chagas heart disease: comparison with other etiologies. a subanalysis of the REMADHE prospective trial. *PLoS Negl Trop Dis.* 2013;7:e2176.
10. Barbosa AP, Cardinalli Neto A, Otaviano AP, Rocha BF, Bestetti RB. Comparison of outcome between Chagas cardiomyopathy and idiopathic dilated cardiomyopathy. *Arq Bras Cardiol.* 2011;97:517–525.
11. Barbosa MPT, da Costa Rocha MO, de Oliveira AB, Lombardi F, Ribeiro ALP. Efficacy and safety of implantable cardioverter-defibrillators in patients with Chagas disease. *Europace.* 2013;15:957–962.
12. Bertolino ND, Villafanha DF, Cardinalli-Neto A, et al. Prognostic impact of Chagas' disease in patients awaiting heart transplantation. *J Heart Lung Transplant.* 2010;29:449–453.
13. Bestetti RB, Muccillo G. Clinical course of Chagas' heart disease: a comparison with dilated cardiomyopathy. *Int J Cardiol.* 1997;60:187–193.
14. Bestetti RB, Otaviano AP, Fantini JP, Cardinalli-Neto A, Nakazone MA, Nogueira PR. Prognosis of patients with chronic systolic heart failure: Chagas disease versus systemic arterial hypertension. *Int J Cardiol.* 2013;168:2990–2991.
15. Bradfield J, Woodbury B, Traina M, et al. Repolarization parameters are associated with mortality in chagas disease patients in the United States. *Indian Pacing Electrophysiol J.* 2014;14:171–180.
16. Braga JCV, Reis F, Aras R, et al. Is Chagas cardiomyopathy an independent risk factor for patients with heart failure? *Int J Cardiol.* 2008;126:276–278.
17. Cardoso J, Novaes M, Ochiai M, et al. [Chagas cardiomyopathy: prognosis in clinical and hemodynamic profile C]. *Arq Bras Cardiol.* 2010;95:518–523.
18. Cerqueira-Silva T, Gonçalves BM, Pereira CB, et al. Chagas disease is an independent predictor of stroke and death in a cohort of heart failure patients. *Int J Stroke.* 2022;17:180–188.
19. de Albuquerque DC, de Barros E, Silva PGM, Lopes RD, et al. In-Hospital Management and Long-term Clinical Outcomes and Adherence in Patients With Acute Decompensated Heart Failure: Primary Results of the First Brazilian Registry of Heart Failure (BREATHE). *J Card Fail.* 2023 https://doi.org/10.1016/j.cardfail.2023.08.014.
20. de Campos Lopes CB, Yamada AT, Araújo F, Pereira Barreto AC, Mansur AJ. Socioeconomic factors in the prognosis of heart failure in a Brazilian cohort. *Int J Cardiol.* 2006;113:181–187.
21. Vieira de Melo RM, de Azevedo DFC, Lira YM, Cardoso de Oliveira NF, Passos LCS. Chagas disease is associated with a worse prognosis at 1-year follow-up after implantable cardioverter-defibrillator for secondary prevention in heart failure patients. *J Cardiovasc Electrophysiol.* 2019;30:2448–2452.
22. Oliveira MTd., Canesin MF, Munhoz RT, et al. Major clinical characteristics of patients surviving 24 months or more after hospitalization due to decompensated heart failure. *Arq Bras Cardiol.* 2005;84:161–166.
23. Dubner S, Valero E, Pesce R, et al. A Latin American registry of implantable cardioverter defibrillators: the ICD-LABOR study. *Ann Noninvasive Electrocardiol.* 2005;10:420–428.
24. Echeverría LE, Saldarriaga C, Rivera-Toquica AA, et al. Characterization of Patients With Heart Failure of Chagas Etiology in Colombia: An Analysis Based on the Colombian Registry of Heart Failure (RECOLFACA). *Curr Probl Cardiol.* 2023;48:101964.
25. Femenía F, Arce M, Arrieta M, McIntyre W, Baranchuk A. ICD implant without defibrillation threshold testing: patients with Chagas disease versus patients with ischemic cardiomyopathy. *J Innov Card Rhythm Manag.* 2012;3:662–667.
26. Freitas HFG, Chizzola PR, Paes AT, Lima ACP, Mansur AJ. Risk stratification in a Brazilian hospital-based cohort of 1220 outpatients with heart failure: role of Chagas' heart disease. *Int J Cardiol.* 2005;102:239–247.

27. Freitas HFG, Barbosa EA, Rosa FHFP, Lima ACP, Mansur AJ. Association of HDL cholesterol and triglycerides with mortality in patients with heart failure. *Braz J Med Biol Res.* 2009;42:420–425.
28. Heringer-Walther S, Moreira M, da CV, Wessel N, et al. Does the C-type natriuretic peptide have prognostic value in chagas disease and other dilated cardiomyopathies? *J Cardiovasc Pharmacol.* 2006;48:293–298.
29. Martinelli Filho M, de Lima Peixoto G, de Siqueira SF, et al. A cohort study of cardiac resynchronization therapy in patients with chronic Chagas cardiomyopathy. *Europace.* 2018;20:1813–1818.
30. Nadruz W, Gioli-Pereira L, Bernardez-Pereira S, et al. Temporal trends in the contribution of Chagas cardiomyopathy to mortality among patients with heart failure. *Heart.* 2018;104:1522–1528.
31. Nakazone MA, Otaviano AP, Machado MN, Bestetti RB. The use of the CALL Risk Score for predicting mortality in Brazilian heart failure patients. *ESC Heart Fail.* 2020;7:2331–2339.
32. Pereira Nunes Md.., Barbosa MM, Ribeiro ALP, Amorim Fenelon LM, Rocha MOC. Predictors of mortality in patients with dilated cardiomyopathy: relevance of chagas disease as an etiological factor. *Rev Esp Cardiol.* 2010;63:788–797.
33. Nunes VL, Ramires FJA, Pimentel Wd.., Fernandes F, Ianni BM, Mady C. The role of storage of interstitial myocardial collagen on the overlife rate of patients with idiopathic and Chagasic dilated cardiomyopathy. *Arq Bras Cardiol.* 2006;87:757–762.
34. Ochiai ME, Cardoso JN, Vieira KRN, Lima MV, Brancalhao ECO, Barretto ACP. Predictors of low cardiac output in decompensated severe heart failure. *Clinics (Sao Paulo).* 2011;66:239–244.
35. Olivera MJ, Arévalo A, Muñoz L, Duque S, Bedoya J, Parra-Henao G. Comparison of 1-year healthcare resource utilization and related costs for patients with heart failure in the Chagas and non-Chagas matched cohorts. *Ther Adv Infect Dis.* 2022;9:20499361221114270.
36. Passos LCS, Melo RMVd, Lira YM, et al. Chagas disease is associated with a poor outcome at 1-year follow-up after cardiac resynchronization therapy. *Rev Assoc Med Bras (1992).* 2019;65:1391–1396.
37. Pereira FTM, Rocha EA, Monteiro Md.., Lima Nd.., Rodrigues Sobrinho CRM, Pires Neto Rd... Clinical Course After Cardioverter-Defibrillator Implantation: Chagasic Versus Ischemic Patients. *Arq Bras Cardiol.* 2016;107:99–100.
38. Rassi S, Barretto ACP, Porto CC, Pereira CR, Calaça BW, Rassi DC. Survival and prognostic factors in systolic heart failure with recent symptom onset. *Arq Bras Cardiol.* 2005;84:309–313.
39. Shen L, Ramires F, Martinez F, et al. Contemporary Characteristics and Outcomes in Chagasic Heart Failure Compared With Other Nonischemic and Ischemic Cardiomyopathy. *Circ Heart Fail.* 2017;10:e004361.
40. Silva CP, Del Carlo CH, de Oliveira Junior MT, et al. Why do patients with chagasic cardiomyopathy have worse outcomes than those with non-chagasic cardiomyopathy? *Arq Bras Cardiol.* 2008;91:358–362.
41. Traina MI, Sanchez DR, Hernandez S, et al. Prevalence and Impact of Chagas Disease Among Latin American Immigrants With Nonischemic Cardiomyopathy in Los Angeles, California. *Circ Heart Fail.* 2015;8:938–943.
42. Vilas Boas LGC, Bestetti RB, Otaviano AP, Cardinalli-Neto A, Nogueira PR. Outcome of Chagas cardiomyopathy in comparison to ischemic cardiomyopathy. *Int J Cardiol.* 2013;167:486–490.
43. Ferreira SMA, Guimarães GV, Cruz FD, et al. Anemia and renal failure as predictors of risk in a mainly non-ischemic heart failure population. *Int J Cardiol.* 2010;141:198–200.
44. Cutshaw MK, Sciaudone M, Bowman NM. Risk Factors for Progression to Chronic Chagas Cardiomyopathy: A Systematic Review and Meta-Analysis. *Am J Trop Med Hyg.* 2023;108:791–800.
45. Chen Y-T, Vaccarino V, Williams CS, Butler J, Berkman LF, Krumholz HM. Risk factors for heart failure in the elderly: a prospective community-based study. *Am J Med.* 1999;106:605–612.
46. Caponetti AG, Rapezzi C, Gagliardi C, et al. Sex-Related Risk of Cardiac Involvement in Hereditary Transthyretin Amyloidosis: Insights From THAOS. *JACC Heart Fail.* 2021;9:736–746.
47. Jain A, Norton N, Bruno KA, Cooper LT, Atwal PS, Fairweather D. Sex Differences, Genetic and Environmental Influences on Dilated Cardiomyopathy. *J Clin Med.* 2021;10:2289.
48. Rastogi T, Ho FK, Rossignol P, et al. Comparing and contrasting risk factors for heart failure in patients with and without history of myocardial infarction: data from HOMAGE and the UK Biobank. *Eur J Heart Fail.* 2022;24:976–984.
49. Nunes MCP, Beaton A, Acquatella H, et al. Chagas Cardiomyopathy: An Update of Current Clinical Knowledge and Management: A Scientific Statement From the American Heart Association. *Circulation.* 2018;138:e169–e209.
50. Duran-Crane A, Rojas CA, Cooper LT, Medina HM. Cardiac magnetic resonance imaging in Chagas' disease: a parallel with electrophysiologic studies. *Int J Cardiovasc Imaging.* 2020;36:2209–2219.
51. Echeverría LE, Rojas LZ, Gómez-Ochoa SA. Coagulation disorders in Chagas disease: A pathophysiological systematic review and meta-analysis. *Thromb Res.* 2021;201:73–83.
52. González FB, Villar SR, Pacini MF, Bottasso OA, Pérez AR. Immune-neuroendocrine and metabolic disorders in human and experimental T. cruzi infection: New clues for understanding Chagas disease pathology. *Biochim Biophys Acta Mol Basis Dis.* 2020;1866:165642.
53. Machado CR, Camargos ER, Guerra LB, Moreira MC. Cardiac autonomic denervation in congestive heart failure: comparison of Chagas' heart disease with other dilated cardiomyopathy. *Hum Pathol.* 2000;31:3–10.
54. Bocchi EA, Rassi S, Guimarães GV; Argentina, Chile, and Brazil SHIFT Investigators. Safety profile and efficacy of ivabradine in heart failure due to Chagas heart disease: a post hoc analysis of the SHIFT trial. *ESC Heart Fail.* 2018;5:249–256.
55. Ramires FJA, Martinez F, Gómez EA, et al. Post hoc analyses of SHIFT and PARADIGM-HF highlight the importance of chronic Chagas' cardiomyopathy Comment on: ''Safety profile and efficacy of ivabradine in heart failure due to Chagas heart disease: a post hoc analysis of the SHIFT trial'' by Bocchi et al. *ESC Heart Fail.* 2018;5:1069–1071.
56. Lopes RD, Gimpelewicz C, McMurray JJV. Chagas disease: still a neglected emergency? *Lancet.* 2020;395:1113–1114.