frontiers | Research Topics

The role of sex in heart failure and transplantation, volume II

Edited by
Manuel Martínez-Sellés, Ana Ayesta, Beatriz Diaz Molina, Antoni Bayes-Genis and Adrian Marco Baranchuk

Published in
Frontiers in Cardiovascular Medicine

ISSN 1664-8714
ISBN 978-2-83251-907-3
DOI 10.3389/978-2-83251-907-3

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

The role of sex in heart failure and transplantation, volume II

Topic editors

Manuel Martínez-Sellés — Gregorio Marañón Hospital, Spain
Ana Ayesta — Hospital Universitario Central de Asturias, Spain
Beatriz Diaz Molina — Servicio de Salud del Principado de Asturias (SESPA), Spain
Antoni Bayes-Genis — Hospital Germans Trias i Pujol, Spain
Adrian Marco Baranchuk — Queen's University, Canada

Citation

Martínez-Sellés, M., Ayesta, A., Molina, B. D., Bayes-Genis, A., Baranchuk, A. M., eds. (2023). *The role of sex in heart failure and transplantation, volume II*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83251-907-3

Table of contents

frontiers | Frontiers in Cardiovascular Medicine

TYPE Editorial
PUBLISHED 28 February 2023
DOI 10.3389/fcvm.2023.1141032

OPEN ACCESS

EDITED AND REVIEWED BY
Matteo Cameli,
University of Siena, Italy

*CORRESPONDENCE
Manuel Martínez-Sellés
✉ mmselles@secardiologia.es

SPECIALTY SECTION
This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 09 January 2023
ACCEPTED 13 February 2023
PUBLISHED 28 February 2023

CITATION
Ayesta A, Díaz-Molina B, Bayes-Genis A, Baranchuk A and Martínez-Sellés M (2023) Editorial: The role of sex in heart failure and transplantation, volume II.
Front. Cardiovasc. Med. 10:1141032.
doi: 10.3389/fcvm.2023.1141032

Editorial: The role of sex in heart failure and transplantation, volume II

Ana Ayesta[1], Beatriz Díaz-Molina[1], Antoni Bayes-Genis[2], Adrián Baranchuk[3] and Manuel Martínez-Sellés[4]*

[1]Área del Corazón, Servicio de Cardiología, Hospital Universitario Central de Asturias, Oviedo, Spain, [2]Servicio de Cardiología, Hospital Universitari Germans Trias i Pujol, CIBERCV, Universidad Autónoma de Barcelona, Badalona, Spain, [3]Kingston Health Science Center, Division of Cardiology, Queen's University, Kingston, ON, Canada, [4]Servicio de Cardiología, Hospital General Universitario Gregorio Marañón, Centro de Investigación Biomédica en Red. Enfermedad Cardiovascular (CIBERCV), Universidad Europea, Universidad Complutense, Madrid, Spain

KEYWORDS

heart failure, heart transplantation, frailty, sex, women

Editorial on the Research Topic
The role of sex in heart failure and transplantation, volume II

Heart failure (HF) is one of the main causes of hospitalization and death in developed countries. This is partly due to population aging but also due to increased survival in patients with heart disease (1). Differences between men and women with HF seem to be extremely relevant a several of them are still under investigation. This Research Topic is a continuation of the first volume previously published regarding this topic.

Den Ruijter summarizes the importance of cardiovascular disease in women and the role of sex in this relation. Most cardiovascular diseases at younger ages are more common in men, but under diagnosis in women might increase this difference. X chromosome seems to be related to inflammation and the Y chromosome to atherosclerosis. This fact might be one of the explanations to why men suffer more frequently from coronary artery disease and HF with left ventricular reduced ejection fraction, while women typically have stable atherosclerosis with non-obstructive coronary disease and HF with preserved left ventricular ejection fraction.

Women underrepresentation in clinical trials is still an issue that should be solved as sex-dependent mechanisms of cardiovascular diseases might modulate the effect of HF treatments. In fact, Sanromán Guerrero et al. conducted a systematic review of 29 randomized clinical trials in patients with HF with reduced ejection fraction. They observed that the proportion of women was low, there was not a pre-specified analysis of efficacy by sex, and the quality of evidence on the efficacy of medical treatment and devices in women was poor.

Dahlen et al. described a sex-specific association between parathyroid hormone and platelet indices in HF patients. The phenotypes of symptomatic HF varied depending on the interaction between parathyroid hormone and platelets in men and women. In women with symptomatic HF with reduced ejection fraction there was a positive association between parathyroid hormone and mean platelet volume, while platelet count was inversely associated with parathyroid hormone in males with HF with reduced ejection fraction and in both sexes with HF with preserved ejection fraction.

Some treatments may precipitate HF in women. Cheng et al. evaluated the risk of HF hospitalizations in patients suffering from gout under febuxostat and allopurinol. Febuxostat users had a higher risk of HF hospitalization than allopurinol users, irrespective of previous cardiovascular risk. Interestingly, the risk was higher in women than in men.

Bi et al. analyzed the effect of sex on left atrial remodeling and its relationship with myocardial fibrosis in 85 patients with hypertrophic obstructive cardiomyopathy treated with surgical septal myectomy. Left atrial function was evaluated using the early atrial peak of emptying rate and was normalized by left ventricular filling volume. These measurements were lower in patients with this entity compared with healthy controls, particularly in the case of female patients. This was attributed to a higher susceptibility to myocardial fibrosis in women, quantified by collagen volume fraction on magnetic cardiac resonance imaging. These would explain some previously evidence that suggests more severe diastolic dysfunction in women than in men. Gual-Capllonch et al. review sex differences in the prevalence of atrial mitral and tricuspid regurgitations. These valvular heart diseases occur mainly in patients with atrial fibrillation and HF with preserved ejection fraction. Women have a higher prevalence than men, especially in the case of atrial tricuspid regurgitation. Several potential mechanisms might explain these differences. Sex hormones may induce a proinflammatory state with different electrophysiological responses leading to a more advanced left atrial dysfunction and fibrosis in women. In addition, histopathological differences in the annuli and leaflets between women and men have been described. Finally, a later diagnosis of atrial fibrillation and of HF with preserved ejection fraction in women may lead to a less aggressive treatment increasing the prevalence of atrial mitral and tricuspid regurgitation in females.

Lozano-Jiménez et al. describe a cohort of 163 patients presenting with cardiogenic shock, 39 women (24%). Postcardiotomy and fulminant myocarditis were more frequent in women, while acute myocardial infarction was more common in male. The use of temporary mechanical circulatory support and its escalation was similar in women and men. The authors found no relevant sex-differences in hospital mortality, Society for Cardiovascular Angiography and Interventions risk stratification, and in the use of advanced HF therapies.

Two manuscripts focused on sex-differences in older patients with HF. Sun et al. presented a secondary analysis of *The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial* (TOPCAT) study (2) evaluating the impact of sex on baseline characteristics and outcomes of 1,619 patients with preserved ejection fraction older than 70 years, with 55.1% women. They found that, compared to males, females had worse cardiac diastolic function, worse New York Heart Association functional class and worse quality of life. However, outcomes in women were better than in men, with lower cardiovascular and all-cause mortality and less hospitalization due to HF. They found no association between sex and spironolactone effects. Díez-Villanueva et al. present a *post-hoc* analysis of 499 outpatients (28% women) with HF older than 75 years included in the FRAGIC registry (*impacto de la FRAGilidad y otros síndromes Geriátricos en el manejo clínico y pronóstico del paciente anciano ambulatorio con Insuficiencia Cardíaca)* (3). Compared to men, women were more frail and had more frequently other geriatric syndromes, as malnutrition, depression and poorer physical status. Interestingly, this was the case even despite the lower rates of comorbidities in women than in men. Frailty was less common in men but was only an independent predictor of mortality in males.

We would like to finish this Research Topic with a call for action to perform more studies on different aspects of HF in women and men. It is particularly important to address this issue in elderly patients with HF, as both women and advanced aged patients have been traditionally underrepresented in HF studies.

Author contributions

AA prepared the first draft of the manuscript. BD-M, AB-G, AB, and MM-S improved the manuscript with relevant content, contributed to the article, and approved the submitted version. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Emmons-Bell S, Johnson C, Roth G. Prevalence, incidence and survival of heart failure: a systematic review. *Heart*. (2022) 108:1351–60. doi: 10.1136/heartjnl-2021-320131

2. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. (2014) 370:1383–92. doi: 10.1056/NEJMoa1313731

3. Jiménez-Méndez C, Díez-Villanueva P, Bonanad C, Ortiz-Cortés C, Barge-Caballero E, Goirigolzarri J, et al. Frailty and prognosis of older patients with chronic heart failure. *Rev Esp Cardiol*. (2022) 75:1011–19. doi: 10.1016/j.rec.2022.04.016

frontiers in Cardiovascular Medicine

SPECIALTY GRAND CHALLENGE
published: 26 November 2020
doi: 10.3389/fcvm.2020.587888

Sex and Gender Matters to the Heart

*Hester Den Ruijter**

Laboratory of Experimental Cardiology, University Medical Center Utrecht, Utrecht, Netherlands

Keywords: sex, gender, cardiovasccular medicine, women, men, heart

Although it is clear that sex and gender play a role in the development and progression of cardiovascular disease, the integration of sex and gender is a real challenge in the field of cardiovascular medicine. The specialty section Gender Cardiovascular Medicine is a new section of Frontiers in Cardiovascular Medicine dedicated to transformative science in the field of sex differences and publishes peer-reviewed articles across clinical, translational, and basic cardiovascular medicine.

Thus far, prominent scientific journals and scientific funding organizations such as the European Commission, the Canadian Institutes of Health Research, and the US National Institutes of Health made huge efforts to integrate sex and gender not only in clinical research, but also in translational and basic research with the goal to promote transparency, inclusion, and better science (1). Online modules, courses and manuscripts are now available on how to integrate sex and gender in scientific design, in analyses and in reporting. Also, for the (bio)medical curriculum, sex and gender integration is gaining more attention. With this shift toward better integration of sex and gender in science, we launch a Specialty Section in Frontiers in Cardiovascular Medicine to advance the field even further.

In the next few lines, I briefly describe the knowledge gaps regarding cardiovascular disease in women, and discuss the rationale for integration of sex and gender in cardiovascular medicine studies.

SEX VS. GENDER

Although the terms sex and gender are often confused, "sex" refers to biological and physiologic traits characterizing maleness and femaleness. "Gender" refers to the roles and behaviors of men, women, and the continuum of gender diversities in our society. As recently elegantly summarized (2) whereas biological sex likely plays a more substantial role in disease etiology, onset, and progression, gender can differentially affect disease risk, symptom recognition, disease manifestations, access to care, quality of care, and adherence to treatment recommendations.

In cardiovascular disease our historical view on cardiovascular patients is seen in many textbooks in which pictures of male patients dominate. Indeed, men have outnumbered women in the majority of the cardiovascular diseases, specifically at younger ages. This pattern seems to reverse during aging with more women than men becoming affected with cardiovascular diseases. In recent years, a trend is emerging of women contributing more to the population of heart diseases at younger ages (3, 4). In addition, the question arises if heart disease in women has not been underestimated due to (previously) unrecognized pathophysiology such as coronary microvascular disease and coronary spasms. Therefore, the accurate diagnosis of heart disease in women warrants urgent attention.

WOMEN IN CLINICAL STUDIES, AND SEX-SPECIFIC PATHOLOGIES

The cornerstone of evidence-based medicine are randomized clinical trials that mostly evaluate drug efficacy and safety profiles. Cardiovascular trials are known for low enrollment of women, mostly attributed to exclusion of patients of older age and the presence of co-morbidities, such as diabetes. Despite awareness of the importance of including women in clinical trials in

OPEN ACCESS

Edited and reviewed by:
Hendrik Tevaearai Stahel,
Bern University Hospital, Switzerland

***Correspondence:**
Hester Den Ruijter
H.M.denRuijter-2@umcutrecht.nl

Specialty section:
This article was submitted to Sex and Gender in Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: *27 July 2020*
Accepted: *24 August 2020*
Published: *26 November 2020*

Citation:
Den Ruijter H (2020) Sex and Gender Matters to the Heart. Front. Cardiovasc. Med. 7:587888. doi: 10.3389/fcvm.2020.587888

cardiovascular disease, recent enrollment has not increased over time in trials that test novel therapeutic strategies for coronary artery disease and heart failure and remains at ∼25% women (5). Neither has reporting of data stratified by sex improved over time in studies reporting on efficacy and adverse drug reactions in HF (6, 7).

Despite the low number of women in studies, and the lack of sex stratification, the awareness that sex and gender differences exist are starting to emerge. For instance, men more often suffer from obstructive CAD and HF with reduced ejection fraction and other atherosclerosis-driven diseases while women more often develop stable atherosclerotic disease with plaque erosion as feature, non-obstructive CAD and heart failure (HF) with preserved ejection fraction (8, 9). Non-obstructive CAD and HFpEF may no longer be considered benign with multiple studies showing a poor prognosis, high prevalence in women, and hypothesize on sex and gender-dependent mechanisms (10–15). Most striking sex differences in terms of high prevalence in either men or women are found within diseases that are far less common such as Brugada syndrome in men, and sudden coronary artery dissection and Tsako-tsubo cardiomyopathy in women (16, 17). Tsako-tsubo seems to be triggered by psychological stress and mimics the features of acute myocardial infarction. It gives rise to severe left ventricular dysfunction while the coronary arteries are open. The unknown etiology of these rare cardiovascular events in either men or women allows us to fully explore new (sex-biased) pathophysiological processes and new opportunities for drug development.

IT IS NOT BETTER IN PRE-CLINICAL STUDIES

Similar trends of a male preference is also seen in pre-clinical studies, animal studies, and cellular studies (18). For animal studies, lack of female rodents is often attributed to the variable nature of the data caused by the reproductive cycle, yet this hypothesis has been studied in neuroscience and refuted (19, 20). High-throughput phenotype data comparing wildtype and mutant mice convincingly show that a large proportion of traits are influenced by sex (21). The current lack of sex-stratification in pre-clinical research may lead to unintended health risks. Drugs being retracted from the market due to unanticipated adverse drug reactions in women is an obvious health risk, but also for men this poses health risks, as their access to previously effective drugs are denied when taken from the market due to adverse drug reactions in women.

SEX-DEPENDENT MECHANISMS AND MANIFESTATIONS OF CARDIOVASCULAR DISEASES

Genetics and hormones play an important role, with sex chromosomes functioning in all cells containing global gene regulators that are present in different doses between the sexes (22). The X chromosome is of interest in diseases that have a different prevalence between sexes. Inactivation of the X chromosome in women entails the random silencing of one of the two X chromosomes to compensate for the fact that men have only one. The X chromosomes contain genes involved in inflammation, and are perceived to contribute largely to the occurrence of autoimmune diseases that are highly female-specific (23). Auto-immune diseases also set the stage for accelerated atherosclerosis, and the role of X chromosome-related mechanisms needs to be deciphered in more detail. Furthermore, the Y chromosome has received increasing attention due to its perceived role in inheritance of CAD risk and atherosclerosis (24, 25). Also, mosaic loss of chromosome Y in leukocytes has been associated with many different diseases, among which atherosclerotic diseases (26).

For sex hormones, estrogen and androgens are known to influence the cardiovascular system in multiple ways. Yet, the potential protection of exogenous sex hormone therapy on coronary artery disease remains under debate, and is nowadays thought to be dependent on timing, duration and dose. This highlights the need for more rigorous research to understand when and how sex hormones affect cardiovascular health in women and men.

CONCLUSIONS

For too long, researchers and clinicians have neglected sex and gender when reporting results related to cardiovascular disease. This is not necessarily due to sexism but rather to a lack of awareness that sex and gender can have such an impact on cardiovascular disease, whether in its development, progression, or treatment. We need to change this harmful misconception, and make research findings generalizable to everyone. Moreover, the potential of integrating sex and gender in cardiovascular studies is tremendous and can offer new perspectives on cardiovascular disease (mechanisms), inspire new research questions, and fill current knowledge gaps that society rightfully demands.

This new section comes at a time where we can leverage the momentum to call on our community to integrate sex and gender in cardiovascular studies to improve scientific quality. This will benefit the speed of translating research findings to the clinic, enhance equality between women and men, and thereby ultimately improve the cardiovascular health of both women and men.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

REFERENCES

1. Bartz, D, Chitnis T, Kaiser UB, Rich-Edwards JW, Rexrode KM, Pennell PB, et al. Clinical advances in sex- and gender-informed medicine to improve the health of all: a review. *JAMA Intern. Med.* (2020) 180:574–83. doi: 10.1001/jamainternmed.2019.7194
2. Arora S, Stouffer GA, Kucharska-Newton AM, Qamar A, Vaduganathan M, Pandey A, et al. Twenty year trends and sex differences in young adults hospitalized with acute myocardial infarction. *Circulation*. (2019) 139:1047–56. doi: 10.1161/CIRCULATIONAHA.118.037137
3. Gabet A, Danchin N, Juillière Y, Olié V. Acute coronary syndrome in women: rising hospitalizations in middle-aged French women, 2004–14. *Eur Heart J.* (2017) 38:1060–5. doi: 10.1093/eurheartj/ehx097
4. Scott PE, Unger EF, Jenkins MR, Southworth MR, McDowell TY, Geller RJ, et al. Participation of women in clinical trials supporting FDA approval of cardiovascular drugs. *J Am Coll. Cardiol.* (2018) 71:1960–9. doi: 10.1016/j.jacc.2018.02.070
5. Bots SH, Groepenhoff F, Eikendal ALM, Tannenbaum C, Rochon PA, Regitz-Zagrosek V, et al. Adverse drug reactions to guideline-recommended heart failure drugs in women: a systematic review of the literature. *JACC Heart Fail.* (2019) 7:258–66. doi: 10.1016/j.jchf.2019.01.009
6. Bots SH, den Ruijter Hester M. Recommended heart failure medications and adverse drug reactions in women. *Circulation*. (2019) 139:1469–71. doi: 10.1161/CIRCULATIONAHA.118.037585
7. Ventura-Clapier R, Dworatzek E, Seeland U, Kararigas G, Arnal JF, Brunelleschi S, et al. Sex in basic research: concepts in the cardiovascular field. *Cardiovasc Res.* (2017) 113:711–24. doi: 10.1093/cvr/cvx066
8. Becker JB, Prendergast BJ, Liang JW. Female rats are not more variable than male rats: a meta-analysis of neuroscience studies. *Biol Sex Diff.* (2016) 7:34. doi: 10.1186/s13293-016-0087-5
9. Prendergast BJ, Onishi KG, Zucker I. Female mice liberated for inclusion in neuroscience and biomedical research. *Neurosci Biobehav Rev.* (2014) 40:1–5. doi: 10.1016/j.neubiorev.2014.01.001
10. Karp NA, Mason J, Beaudet AL, Benjamini Y, Bower L, Braun RE, et al. Prevalence of sexual dimorphism in mammalian phenotypic traits. *Nat Commun.* (2017) 8:15475. doi: 10.1038/ncomms15475
11. Lam, CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, et al. Sex differences in heart failure. *Eur Heart J.* (2019) 40:3859–68. doi: 10.1093/eurheartj/ehz835
12. Waheed N, Elias-Smale S, Malas W, Maas AH, Sedlak TL, Tremmel J, et al. Sex differences in non-obstructive coronary artery disease. *Cardiovasc Res.* (2020) 116:829–40. doi: 10.1093/cvr/cvaa001
13. Sharaf B, Wood T, Shaw L, Johnson BD, Kelsey S, Anderson RD, et al. Adverse outcomes among women presenting with signs and symptoms of ischemia and no obstructive coronary artery disease: findings from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) angiographic core laboratory. *Am Heart J.* (2013) 166:134–41. doi: 10.1016/j.ahj.2013.04.002
14. Maddox TM, Stanislawski MA, Grunwald GK, Bradley SM, Ho PM, Tsai TT, et al. Nonobstructive coronary artery disease and risk of myocardial infarction. *J Am Med Assoc.* (2014) 312:1754–63. doi: 10.1001/jama.2014.14681
15. Lee BK, Lim HS, Fearon WF, Yong AS, Yamada R, Tanaka S, et al. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. *Circulation*. (2015) 131:1054–60. doi: 10.1161/CIRCULATIONAHA.114.012636
16. Pepine CJ, Ferdinand KC, Shaw LJ, Light-McGroary KA, Shah RU, Gulati M, et al. Emergence of nonobstructive coronary artery disease: a woman's problem and need for change in definition on angiography. *J Am Coll Cardiol.* (2015) 66:1918–33. doi: 10.1016/j.jacc.2015.08.876
17. Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman LO, Lerman A. Prevalence of coronary microvascular dysfunction among patients with chest pain and nonobstructive coronary artery disease. *JACC Cardiovasc Interv.* (2015) 8:1445–53. doi: 10.1016/j.jcin.2015.06.017
18. Wang ZJ, Zhang LL, Elmariah S, Han HY, Zhou YJ. Prevalence and prognosis of nonobstructive coronary artery disease in patients undergoing coronary angiography or coronary computed tomography angiography: a meta-analysis. *Mayo Clin Proc.* (2017) 92:329–46. doi: 10.1016/j.mayocp.2016.11.016
19. Lebrun S, Bond RM. Spontaneous coronary artery dissection (SCAD): the underdiagnosed cardiac condition that plagues women. *Trends Cardiovasc Med.* (2018) 28:340–5. doi: 10.1016/j.tcm.2017.12.004
20. Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of Takotsubo Syndrome. *Circulation.* (2017) 135:2426–41. doi: 10.1161/CIRCULATIONAHA.116.027121
21. Bellott DW, Hughes JF, Skaletsky H, Brown LG, Pyntikova T, Cho TJ, et al. Mammalian Y chromosomes retain widely expressed dosage-sensitive regulators. *Nature*. (2014) 508:494–9. doi: 10.1038/nature13206
22. Zhang Y, Li X, Gibson A, Edberg J, Kimberly RP, Absher DM. Skewed allelic expression on X-chromosome associated with aberrant expression of XIST on systemic lupus erythematosus lymphocytes. *Hum Mol Genet*. (2020) 29:2523–34. doi: 10.1093/hmg/ddaa131
23. Charchar FJ, Bloomer LD, Barnes TA, Cowley MJ, Nelson CP, Wang Y, et al. Inheritance of coronary artery disease in men: an analysis of the role of the Y chromosome. *Lancet*. (2012) 379:915–22. doi: 10.1016/S0140-6736(11)61453-0
24. Eales JM, Maan AA, Xu X, Michoel T, Hallast P, Batini C, et al. Chromosome exerts pleiotropic effects on susceptibility to atherosclerosis. *Arterioscler Thromb Vasc Biol.* (2019) 39:2386–401. doi: 10.1161/ATVBAHA.119.312405
25. Haitjema S, Kofink D, van Setten J, van der Laan SW, Schoneveld AH, Eales J, et al. Loss of Y chromosome in blood is associated with major cardiovascular events during follow-up in men after carotid endarterectomy. *Circ Cardiovasc Genet*. (2017) 10:e001544. doi: 10.1161/CIRCGENETICS.116.001544
26. Tannenbaum C, Ellis RP, Eyssel F, Zou J, Schiebinger F. Sex and gender analysis improves science and engineering. *Nature*. (2019) 575:137–46. doi: 10.1038/s41586-019-1657-6

Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 16 June 2021
doi: 10.3389/fcvm.2021.682521

Sex-Specific Relationship Between Parathyroid Hormone and Platelet Indices in Phenotypes of Heart Failure—Results From the MyoVasc Study

*Bianca Dahlen[1], Felix Müller[2,3], Sven-Oliver Tröbs[1,2,3], Marc William Heidorn[2,3], Andreas Schulz[1], Natalie Arnold[1,2], M. Iris Hermanns[1], Sören Schwuchow-Thonke[4], Jürgen H. Prochaska[1,2,3], Tommaso Gori[2,4], Hugo ten Cate[5], Karl J. Lackner[2,6], Thomas Münzel[2,4], Philipp S. Wild[1,2,3] and Marina Panova-Noeva[2,3]**

[1] Preventive Cardiology and Preventive Medicine, Department of Cardiology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany, [2] DZHK (German Center for Cardiovascular Research), Partner Site Rhine Main, Mainz, Germany, [3] Clinical Epidemiology and Systems Medicine, Center for Thrombosis and Hemostasis, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany, [4] Cardiology I, Department of Cardiology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany, [5] Laboratory for Clinical Thrombosis and Hemostasis, Department of Internal Medicine, Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, Maastricht, Netherlands, [6] Institute for Clinical Chemistry and Laboratory Medicine, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany

OPEN ACCESS

Edited by:
Georgios Kararigas,
University of Iceland, Iceland

Reviewed by:
Carrie Wiese,
University of California, Los Angeles, United States
Monika Gladka,
Academic Medical Center, Netherlands

***Correspondence:**
Marina Panova-Noeva
marina.panova-noeva@unimedizin-mainz.de

Specialty section:
This article was submitted to Sex and Gender in Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: 18 March 2021
Accepted: 10 May 2021
Published: 16 June 2021

Citation:
Dahlen B, Müller F, Tröbs S-O, Heidorn MW, Schulz A, Arnold N, Hermanns MI, Schwuchow-Thonke S, Prochaska JH, Gori T, ten Cate H, Lackner KJ, Münzel T, Wild PS and Panova-Noeva M (2021) Sex-Specific Relationship Between Parathyroid Hormone and Platelet Indices in Phenotypes of Heart Failure—Results From the MyoVasc Study. Front. Cardiovasc. Med. 8:682521. doi: 10.3389/fcvm.2021.682521

Background: Heart failure (HF) is a multifactorial syndrome with pathophysiological complexities still not fully understood. Higher mean platelet volume (MPV), a potential marker of platelet activation, and high concentrations of parathyroid hormone (PTH) have been implicated in the pathogenesis of HF.

Aim: This study aims to investigate sex-specifically the association between PTH concentrations and platelet indices in phenotypes of HF.

Methods and Results: PTH and platelet indices (MPV and platelet count) were available in 1,896 participants from the MyoVasc study in Mainz, Germany. Multivariable linear regression models, adjusted for age, sex, season, vitamin D status, cardiovascular risk factors, comorbidities, estimated glomerular filtration rate, and medication, were used to assess the associations between platelet indices and PTH. The results showed distinct sex-specific associations between PTH and platelet indices. A positive association between PTH and MPV was found in females with symptomatic HF with reduced ejection fraction (HFrEF) only [$\beta = 0.60$ (0.19; 1.00)]. Platelet count was inversely associated with PTH in male HFrEF individuals [$\beta = -7.6$ (-15; -0.30)] and in both males and females with HF with preserved ejection fraction (HFpEF).

Conclusion: This study reports differential, sex-specific relationships between PTH and platelet indices in HF individuals independent of vitamin D status and clinical profile. Particularly in phenotypes of symptomatic HF, distinct associations were observed, suggesting a sex-specific mechanism involved in the interaction between PTH and platelets.

Keywords: heart failure, MPV, platelet count, parathyroid hormone, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction

INTRODUCTION

Heart failure (HF) is one of the most common cardiovascular diseases (CVDs) accounting for substantial morbidity and mortality worldwide, with increasing incidence and prevalence especially among the elderly (1). As a heterogeneous condition, HF syndrome comprises predominantly two phenotypes (1). HF with preserved ejection fraction (HFpEF) is more frequent in females with cardiovascular comorbidities, whereas males with history of ischemic heart disease suffer more often from HF with reduced ejection fraction (HFrEF) (2, 3).

Recently, elevated parathyroid hormone (PTH) concentrations have been associated with all-cause and cardiovascular mortality in HF patients, suggesting a potential role for PTH in the pathogenesis and progression of HF (4, 5). PTH is physiologically released at low calcium concentrations to stimulate the synthesis of the active form of vitamin D, Calcitriol, which in turn suppresses PTH release as a negative feedback regulation of calcium homeostasis (6). Besides calcium concentrations, plasma PTH concentrations were also modulated by age and renal function (4, 7). Higher concentrations of PTH have been associated with advanced stages of HF according to categories of the New York Heart Association (NYHA) (8, 9), reduced left ventricular ejection fraction (LVEF) (8), and elevated brain natriuretic peptide (BNP) or N-terminal propeptide of BNP (NT-proBNP) (10–12). Different pathways have been proposed for the interaction of PTH with the heart. As a stimulator of hypertrophy, arrhythmia, and inflammation, PTH directly drives cardiomyocyte necrosis and thus accelerates the severity of HF (8, 11). In addition, PTH indirectly exacerbates HF by the activation of the renin–angiotensin–aldosterone system (RAAS), a key element of HF pathophysiology (13).

Platelet activation has been associated with traditional cardiovascular risk factors (CVRFs) and CVD including the HF syndrome (14, 15). Higher mean platelet volume (MPV), a potential marker of platelet activation, was reported in individuals with arterial hypertension, obesity, dyslipidemia, and diabetes mellitus (16). We have recently reported on sex-specific determinants of MPV in the general population with age, smoking, arterial hypertension, and high blood glucose concentrations linked with higher MPV in males, whereas oral contraceptives and menstrual bleeding were associated with higher MPV in females (14).

Platelet activation including higher MPV, increased whole blood aggregation tendency, and higher platelet-bound and soluble P-selectin has been associated with HF syndrome (14, 15). Positive associations between MPV and PTH were described in individuals with primary hyperparathyroidism and end-stage renal failure patients (17, 18). In addition, an experimental study showed an important enhancing effect of the PTH-related protein, a protein initially isolated from hypercalcemia-associated tumors, on agonist-induced platelet activation and aggregation (19). Individuals with coronary artery disease presenting with higher PTH concentrations showed increased ADP-mediated platelet aggregation and suboptimal response to clopidogrel, despite receiving a dual antiplatelet therapy (7).

The relation between platelet function and PTH plasma concentration has been poorly explored in individuals with HF. This analysis aimed to investigate sex-specifically the associations between PTH concentrations and the platelet indices, platelet count, and MPV, across phenotypes of HF in individuals enrolled in the MyoVasc study.

METHODS

Analysis Sample

As a large prospective cohort study at the University Medical Center of the Johannes Gutenberg-University Mainz in Germany, the MyoVasc Study was primarily conceptualized to investigate the development and progression of HF and its interaction with vascular disease (20). The study included 3,289 participants aged from 35 to 84 years. All subjects underwent an extensive, standardized clinical and laboratory investigation including sampling of biomaterials for biobanking at the MyoVasc study center. Platelet count, MPV, and PTH were available in the first 2,000 participants enrolled in the MyoVasc study at their baseline examination between January 2013 and January 2016. The assessment of CVRFs, comorbidities, and medication as well as echocardiography of cardiac structure and function are described in the **Supplementary Material (Part A)**. Written informed consent was obtained from all study participants prior to entering the study. The study complies with the principles outlined in the Declaration of Helsinki, Good Clinical Practice and Good Epidemiological Practice. An approval from the responsible ethics committee [reference number 837.319.12 (8420-F)] and data safety commissioner was obtained in 2012, before study initiation. The MyoVasc study was registered at http://clinicaltrials.gov (identifier: NCT04064450).

Definition of HF Phenotypes

Based on measurement of LVEF following a standardized echocardiographic assessment (**Supplementary Material Part A**), subjects with LVEF $\geq$ 50% were defined as having preserved ejection fraction (EF) and those with LVEF $<$ 50% as having reduced EF, independent of presence of HF symptoms. Individuals with symptomatic HF (i.e., HF, stage C or D according to AHA) were further categorized according to LVEF into (i) HF with preserved ejection fraction (HFpEF) with LVEF $\geq$ 50%, (ii) HF with reduced ejection fraction (HFrEF) with LVEF $\leq$ 40%, and (iii) HFpEF borderline with LVEF in the range of 41–49% according to the ACCF/AHA Guideline for the Management of Heart Failure (21).

Laboratory Assessment

Venous blood sampling was performed for laboratory markers of the present analysis by using tripotassium ethylenediaminetetraacetic acid (K3-EDTA) tubes. Platelet count (10^9/L) and MPV (femtoliter, fl) were automatically determined on an ADVIA 120 Hematology System (Siemens, Erlangen, Germany) within 30 to 90 min after blood withdrawal in the Central laboratory of the Institute for Clinical Chemistry and Laboratory Medicine, University Medical Center Mainz,

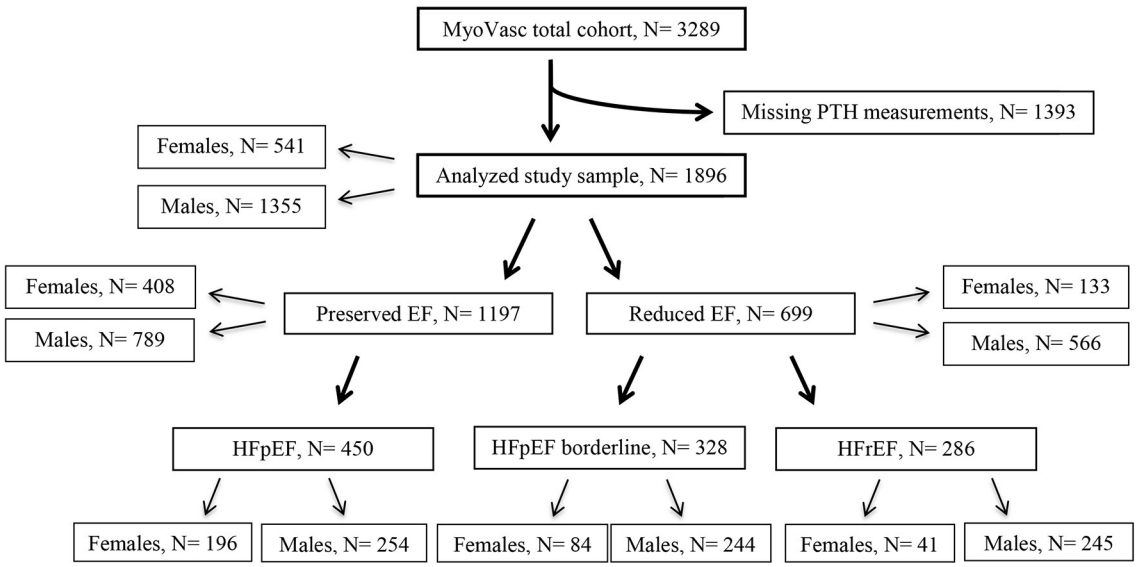


FIGURE 1 | Derivation of the analysis sample. Flow chart presenting the derivation of the analysis sample based on measurements of PTH and ejection fraction. *N*, number of individuals; PTH, parathyroid hormone; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFpEF borderline, heart failure with LVEF 41 to 49%; HFrEF, heart failure with reduced ejection fraction.

Germany. PTH was measured in pg/ml by an immunoassay with an automated chemiluminescence analyzer (Liaison XL, DiaSorin, Saluggia, Italy) in the Biomolecular Laboratory of the Clinical Epidemiology and Systems Medicine, Center for Thrombosis and Hemostasis, University Medical Center Mainz, Germany.

Data Management and Statistical Analysis

Statistical analysis was performed after data quality control including a review for correctness, completeness, representativeness, accuracy, and plausibility performed by the data management unit. Baseline characteristics of the analysis sample were presented according to phenotype of cardiac function. Normally distributed values were described by mean and standard deviation (SD), non-normally distributed variables were described by median and interquartile range. Associations between platelet indices (i.e., MPV and platelet count) and PTH were presented per phenotype of cardiac function by linear regression models, adjusted for the following variables in stepwise extended models: (i) age, sex, season, and vitamin D status; (ii) plus additionally with CVRFs (diabetes mellitus, arterial hypertension, smoking, dyslipidemia, obesity, and family history of myocardial infarction and stroke) and estimated glomerular filtration rate (eGFR); (iii) plus comorbidities subsuming CVD, venous thromboembolism (VTE), chronic obstructive pulmonary disease (COPD), cancer, and arthritis; and (iv) plus additionally medication (vitamin D supplements, calcium supplements, diuretics, beta-blockers, calcium channel blockers, RAAS antagonists, antiplatelet agents, antilipemic drugs, anti-inflammatory and rheumatic drugs, glucocorticoids, corticosteroids, antibacterial drugs, and immunosuppressant drugs). The subgroup analysis in males was conducted with adjustment for the same covariates as the whole analysis sample, whereas in females, it was additionally adjusted for oral contraceptives, hormone replacement therapy, and menstrual bleeding in the full model.

Because of the explorative character of the analysis, a significance threshold for *p*-values was not defined and *p*-values were interpreted as a continuous measure of statistical evidence. All statistical analyses were performed using R, version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

RESULTS

Baseline Characteristics of the Analysis Sample

After exclusion of individuals with missing data on PTH, 1,896 subjects were available for analysis (**Figure 1**). Baseline characteristics of the individuals in the analysis sample are reported in **Table 1** according to phenotype of cardiac function. Based on EF and irrespective of presence of symptoms, 1,197 individuals were characterized with preserved EF and 699 individuals with reduced EF. Symptomatic HF was present in 1,064 (56.1%) individuals, of whom 42.3% (450) had HFpEF, 30.8% (328) HFpEF borderline, and 26.9% (286) HFrEF. More than 80% of individuals with reduced EF and HFrEF were males with a higher frequency of smokers, dyslipidemia, coronary artery disease, and history of myocardial infarction compared to individuals with preserved EF and HFpEF, respectively. In the subgroup with preserved EF and HFpEF, there were more females comparatively to the other phenotypes, but overall still more males. Individuals with preserved EF and HFpEF had more often arterial hypertension and a history of VTE compared to

TABLE 1 | Baseline characteristics according to phenotype of cardiac function (*N*= 1,896).

	Phenotype of cardiac function				
	Preserved EF (*N* = 1,197)	**Reduced EF (*N* = 699)**	**HFpEF (*N* = 450)**	**HFpEF borderline (*N* = 328)**	**HFrEF (*N* = 286)**
Age [years]	67.2 ± 9.4	65.6 ± 10.6	70.7 ± 8.2	66.2 ± 10.6	65.6 ± 10.6
Sex (women)	34.1% (408)	19.0% (133)	43.6% (196)	25.6% (84)	14.3% (41)
CVRFs					
Arterial hypertension	84.0% (1,006)	74.8% (523)	86.2% (388)	78.7% (258)	75.9% (217)
Diabetes mellitus	25.1% (300)	30.3% (212)	32.7% (147)	28.7% (94)	33.9% (97)
Smoking	10.5% (126)	17.3% (121)	9.1% (41)	17.1% (56)	18.9% (54)
Obesity	34.4% (412)	35.2% (246)	38.7% (174)	38.4% (126)	36.0% (103)
Dyslipidemia	79.1% (947)	84.4% (590)	78.2% (352)	84.5% (277)	86.0% (246)
FH of MI/stroke	24.3% (290)	27.0% (189)	23.3% (105)	27.7% (91)	29.0% (83)
Comorbidities					
History of MI	30.7% (368)	39.3% (275)	28.4% (128)	37.5% (123)	43.7% (125)
History of Stroke	10.3% (123)	10.4% (73)	10.4% (47)	11.9% (39)	10.8% (31)
CAD	50.9% (609)	56.2% (393)	49.8% (224)	57.6% (189)	57.3% (164)
AF	26.9% (322)	37.6% (263)	36.9% (166)	38.7% (127)	40.2% (115)
History of VTE	11.2% (134)	9.3% (65)	14.2% (64)	10.1% (33)	8.7% (25)
History of Cancer	16.8% (201)	17.6% (123)	19.6% (88)	18.3% (60)	16.8% (48)
Echocardiographic parameters					
EF [%]	58.3 ± 5.2	39.5 ± 8.1	58.1 ± 5.4	45.2 ± 2.8	31.5 ± 5.9
E/E'	8.57 (6.65/11.30)	10.17 (7.26/14.47)	11.16 (8.76/14.62)	9.22 (7.05/12.74)	12.40 (8.34/18.02)
Lab parameters					
MPV [fl]	8.22 ± 0.86	8.36 ± 0.93	8.25 ± 0.84	8.31 ± 0.89	8.43 ± 0.99
Platelet count [10^9/L]	219 (182/260)	208 (173/251)	218 (179/261)	213 (177/260)	206 (170/244)
PTH [pg/ml]	30.0 (23.0/38.4)	34.0 (26.3/46.7)	32.1 (23.6/42.3)	32.7 (24.8/45.3)	38.6 (29.1/52.1)
eGFR [ml/min/1.73 m^2]	76.44 ± 18.62	71.98 ± 21.50	69.80 ± 19.42	73.80 ± 20.54	66.36 ± 22.36
Medication					
Vitamin D supplements (A11CC)	8.7% (104)	5.9% (41)	8.7% (39)	5.5% (18)	6.6% (19)
Calcium supplements (A12A)	1.9% (23)	1.9% (13)	3.1% (14)	2.7% (9)	1.0% (3)
Antihypertensiva (C02)	4.4% (53)	2.1% (15)	5.8% (26)	2.7% (9)	1.4% (4)
Diuretics (C03)	28.5% (341)	66.1% (462)	43.6% (196)	60.1% (197)	86.4% (247)
Beta-blockers (C07)	69.0% (826)	79.4% (555)	75.8% (341)	79.6% (261)	84.6% (242)
Calcium channel blockers (C08)	25.4% (304)	14.2% (99)	32.2% (145)	19.8% (65)	8.4% (24)
Renin–Angiotensin–Aldosterone system antagonsists (C09)	78.6% (941)	81.3% (568)	80.2% (361)	85.4% (280)	86.0% (246)
Lipid-modifying agents (C10)	60.4% (723)	60.9% (426)	58.9% (265)	64.3.% (211)	60.1% (172)
Antithrombotic agents (B01A)	80.6% (965)	85.6% (598)	85.1% (383)	88.4% (290)	86.0% (246)

Presented are baseline clinical characteristics, echocardiographic and laboratory parameters, including intake of medications according to cardiac function phenotype in 1,896 subjects. EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction (EF ≥ 50%); HFpEF borderline, heart failure with ejection fraction of 41%–49%; HFrEF, heart failure with reduced ejection fraction (EF ≤ 40%); CVRFs, cardiovascular risk factors; FH, family history; MI, myocardial infarction; CAD, coronary artery disease; AF, atrial fibrillation, PAD, peripheral artery disease, COPD, chronic obstructive pulmonary disease; VTE, venous thromboembolism; CKD, chronic kidney disease; EF, ejection fraction; MPV, mean platelet volume; PTH, parathyroid hormone.

other phenotypes. Subjects with HFpEF borderline had the lowest proportion of diabetes mellitus (28.7 vs. 32.7% in HFpEF and 33.9% in HFrEF).

Similarly to the clinical profile, differences between HF phenotypes were also evident in laboratory parameters: individuals with reduced EF presented with higher MPV and PTH concentrations, but lower platelet count as well as worse renal function (determined by eGFR), compared to individuals with preserved EF. Within the subsample with symptomatic HF, highest MPV and PTH and lowest platelet count and worst renal function were observed in individuals with HFrEF.

Individuals with preserved EF and particularly subjects with HFpEF were more frequently taking vitamin D supplements, antihypertensives, and calcium channel blockers compared to those with reduced EF, HFpEF borderline, and HFrEF. Intake of diuretics, beta-blockers, and antithrombotic agents were more often reported for subjects with reduced EF, HFpEF borderline, and HFrEF.

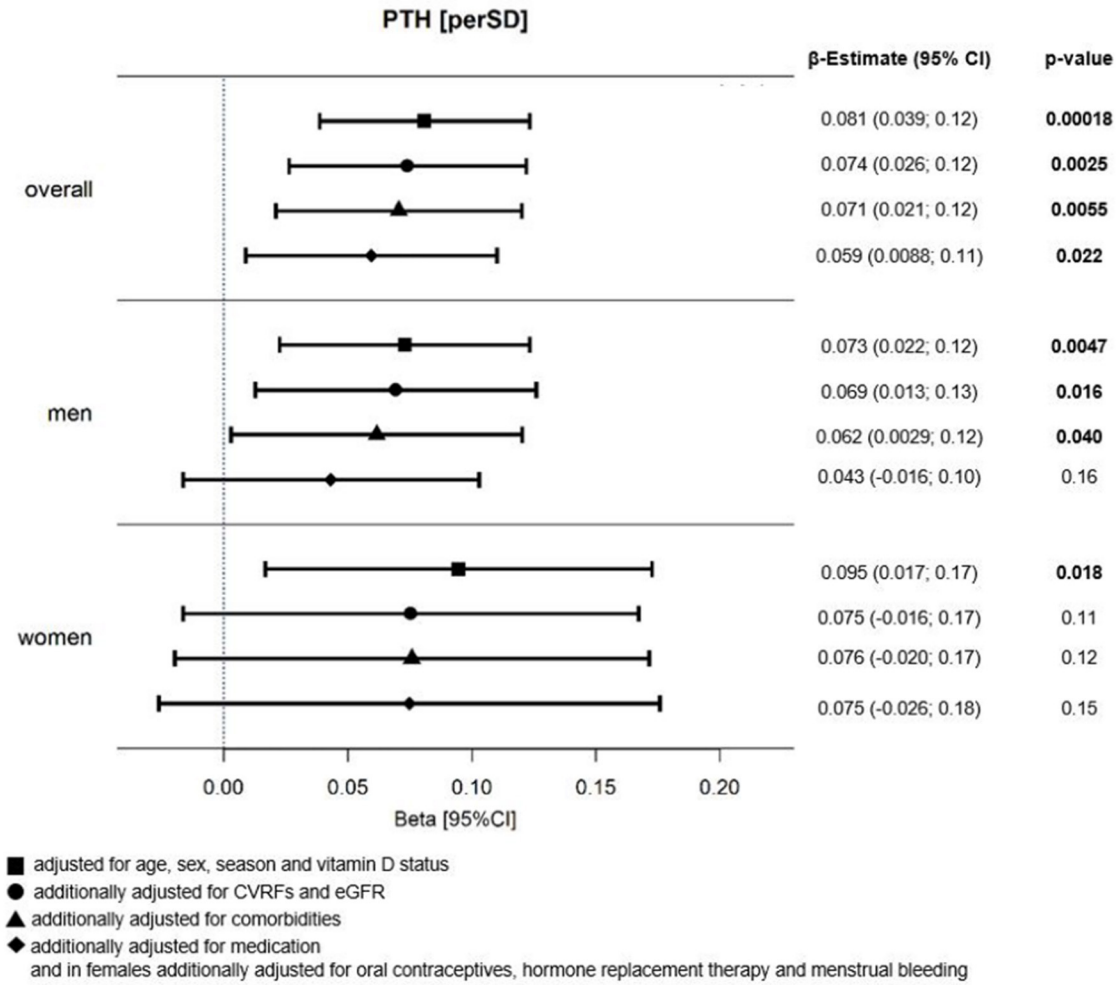


FIGURE 2 | Relation between MPV and PTH in HF individuals. Forest Plot of beta (β)-estimates with 95% confidence intervals (CIs) for the relation between MPV and PTH in all HF individuals and stratified by sex. $N = 1{,}861$; thereof $N = 532$ females and $N = 1{,}329$ males; adjustment for sex only in overall analysis sample; MPV, mean platelet volume; PTH, parathyroid hormone; CVRFs, cardiovascular risk factors; eGFR, estimated glomerular filtration rate.

Pearson's correlation sex-specific analysis between PTH levels and age and according to HF phenotype showed a weak correlation in both males and females across different HF phenotypes as presented in **Supplementary Table 1**.

Association Between MPV and PTH

In the whole sample, a positive association between MPV and SD change of PTH with beta estimate (β) = 0.081 (95% confidence interval: 0.039; 0.12) was observed after adjustment for age, sex, season, and vitamin D status, which corresponded in males to $\beta = 0.073$ (0.022; 0.12) and in females to $\beta = 0.095$ (0.017; 0.17). Results from a linear regression model for MPV are presented in **Figure 2**. Further adjustment for CVRFs plus eGFR, comorbidities, and medication did not significantly change this association in the whole sample. A sex-specific analysis showed a mildly stronger association between MPV and PTH in females compared to males. The analysis stratified for cardiac function showed important sex-specific differences between phenotypes (**Table 2**): there was a positive association between MPV and PTH independent of age, season, and vitamin D status in individuals with preserved EF [$\beta = 0.078$ (0.020; 0.14)], which was only present in male participants [$\beta = 0.11$ (0.034; 0.18)], whereas in reduced EF and HFrEF, MPV and PTH were associated in females only [$\beta_{\text{reducedEF}} = 0.21$ (0.043; 0.37); $\beta_{\text{HFrEF}} = 0.36$ (0.063; 0.67)] after the same adjustment. For HFpEF borderline, a weak association was only found in women. Interestingly, the strongest and most robust association was found in females in HFrEF, where it remained relevant even after adjustment for CVRFs and comorbidities.

Association Between Platelet Count and PTH

Results of the multivariable analysis for platelet count showed a strong inverse association per SD of PTH independent of

TABLE 2 | Relation between MPV and PTH according to cardiac function in a sex-specific analysis.

		MPV							
		Adjusted for age, sex[a], season, vitamin D status[b]		Additionally adjusted for CVRFs and eGFR		Additionally adjusted for comorbidities		Additionally adjusted for medication[c]	
	N	*β*-estimate (95% CI)	*P*-value	*β*-estimate (95% CI)	*P*-value	*β*-estimate (95% CI)	*P*-value	*β*-estimate (95% CI)	*P*-value
Preserved EF	1,174	0.078 (0.020; 0.14)	**0.0086**	0.077 (0.013; 0.14)	**0.019**	0.060 (−0.0066; 0.13)	0.078	0.043 (−0.025; 0.11)	0.21
Females	401	0.014 (−0.078; 0.11)	0.77	−0.023 (−0.13; 0.084)	0.67	−0.039 (−0.15; 0.073)	0.50	−0.046 (−0.17; 0.073)	0.45
Males	773	0.11 (0.034; 0.18)	**0.0044**	0.12 (0.037; 0.20)	**0.0045**	0.10 (0.016; 0.18)	**0.020**	0.074 (−0.011; 0.16)	0.090
Reduced EF	687	0.067 (0.0012; 0.13)	**0.046**	0.064 (−0.011; 0.14)	0.093	0.073 (−0.0051; 0.15)	0.067	0.071 (−0.0089;0.15)	0.082
Females	131	0.21 (0.043; 0.37)	**0.015**	0.26 (0.050; 0.46)	**0.016**	0.27 (0.055; 0.49)	**0.016**	0.25 (0.029; 0.47)	**0.029**
Males	556	0.030 (−0.041; 0.10)	0.41	0.021 (−0.061; 0.10)	0.62	0.025 (−0.061; 0.11)	0.57	0.023 (−0.065; 0.11)	0.61
HFpEF	442	0.075 (−0.0046; 0.15)	0.065	0.049 (−0.040; 0.14)	0.28	0.031 (−0.063; 0.12)	0.52	0.019 (−0.076; 0.11)	0.69
Females	191	0.033 (−0.086; 0.15)	0.59	−0.0011 (−0.15; 0.14)	0.99	−0.018 (−0.17; 0.13)	0.81	n.a.	n.a.
Males	251	0.10 (−0.0087; 0.21)	0.073	0.076 (−0.045; 0.20)	0.22	0.056 (−0.073; 0.18)	0.40	0.028 (−0.10; 0.16)	0.68
HFpEF borderline	324	0.046 (−0.051; 0.14)	0.35	0.040 (−0.070; 0.15)	0.48	0.038 (−0.076; 0.15)	0.51	0.029 (−0.090; 0.15)	0.63
Females	82	0.22 (0.0076; 0.44)	**0.046**	0.22 (−0.066; 0.50)	0.14	0.21 (−0.095; 0.51)	0.18	0.10 (−0.30; 0.50)	0.62
Males	242	−0.028 (−0.14; 0.080)	0.61	−0.036 (−0.16; 0.087)	0.57	−0.044 (−0.17; 0.084)	0.50	−0.051 (−0.19; 0.087)	0.47
HFrEF	279	0.11 (0.0062; 0.21)	**0.038**	0.11 (−0.0033; 0.23)	0.058	0.14 (0.016; 0.26)	**0.028**	0.12 (−0.0055; 0.24)	0.062
Females	41	0.36 (0.063; 0.67)	**0.024**	0.59 (0.19; 0.99)	**0.0071**	0.60 (0.19; 1.0)	**0.0089**	n.a.	n.a.
Males	238	0.072 (−0.036; 0.18)	0.19	0.059 (−0.065; 0.18)	0.35	0.083 (−0.049; 0.22)	0.22	0.079 (−0.056; 0.22)	0.25

Multivariable linear regression analysis with MPV as dependent variable and PTH as independent variable in phenotypes of cardiac function and sex-specific. Results are presented as beta (β)-estimates for change per 1 standard deviation in PTH. MPV, mean platelet volume; PTH, parathyroid hormone; N, number of individuals; eGFR, estimated glomerular filtration rate; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFpEF borderline, heart failure with ejection fraction of 41–49%; HFrEF, heart failure with reduced ejection fraction; n.a., not available due to low sample size [a]Sex-adjustment only in overall analysis sample; [b]Vitamin D status was determined by concentrations of Calcifediol and Calcitriol; [c]In females additionally adjusted for oral contraceptives, hormone replacement therapy and menstrual bleeding. P-value < 0.05 were highlighted in bold.

age, sex, season, and vitamin D status with $\beta = -6.42$ (−9.21; −3.63), which remained after further adjustment for CVRFs and eGFR [$\beta = -6.79$ (−9.94; −3.63)], comorbidities [$\beta = -6.52$ (−9.78; −3.27)], and medication [$\beta = -6.21$ (−9.53; −2.88)] in the whole analysis sample (**Figure 3**). This reciprocal association was observed in males and females independent of all potential confounders, but with higher estimates in females then in men [$\beta_{females} = -8.36$ (−15.44; −1.27) vs. $\beta_{males} = -4.50$ (−8.32; −0.67)].

The analysis according to cardiac phenotypes, as presented in **Table 3**, showed relevant associations between platelet count and PTH in both individuals with preserved [$\beta = -6.7$ (−11; −2.0)] and reduced ejection fraction [$\beta = -5.6$ (−11; −0.77)]. In HFpEF, the largest effect estimates for an inverse association between PTH and platelet count were found, and these remained robust after adjustment for age, sex, season, and vitamin D status [$\beta = -9.5$ (−15; −3.6)], but also further adjustment for CVRFs and eGFR [$\beta = -9.9$ (−17; −3.2)], comorbidities [$\beta = -9.4$ (−16; −2.4)], and medication [$\beta = -8.9$ (−16; −1.7)]. The sex-specific analysis in this phenotype showed stronger associations in females than in males. Differently, in HFrEF, the inverse association between PTH and platelet count was only found in male individuals and present independent of all considered confounders [$\beta = -7.6$ (−15; −0.30)]. No associations were observed between platelet count and PTH in individuals with HFpEF borderline.

DISCUSSION

PTH and platelet activation have been independently implicated in the pathogenesis of the HF syndrome (15, 22). However, the sex-specific interplay of these factors, as well as their specific relationship in phenotypes of HF, is currently largely unknown. This study demonstrated an important relation between platelet indices and PTH, which varied in phenotypes of cardiac function and particularly in individuals with symptomatic HF. In addition, the present analysis reports on distinct sex-specific differences in HF phenotypes.

Previous studies in individuals with primary hyperparathyroidism and end-stage renal failure patients have shown positive associations between MPV and PTH; however, sex-specific aspects were not addressed (17, 18). Other research has already demonstrated sex-specific differences for MPV in the general population that was also differentially associated with total mortality (14).

In contrast to the findings for MPV and PTH, an inverse association between PTH and platelet count was found in the total sample, which was present in both men and women. The inverse direction of the association between platelet count and PTH compared to MPV is explained by the fact that platelet count and MPV are physiologically inversely related to keep the overall platelet mass stable (23). Similarly, as for the MPV and PTH relation, sex-specific associations observed between platelet count and PTH were distinct for phenotypes of symptomatic

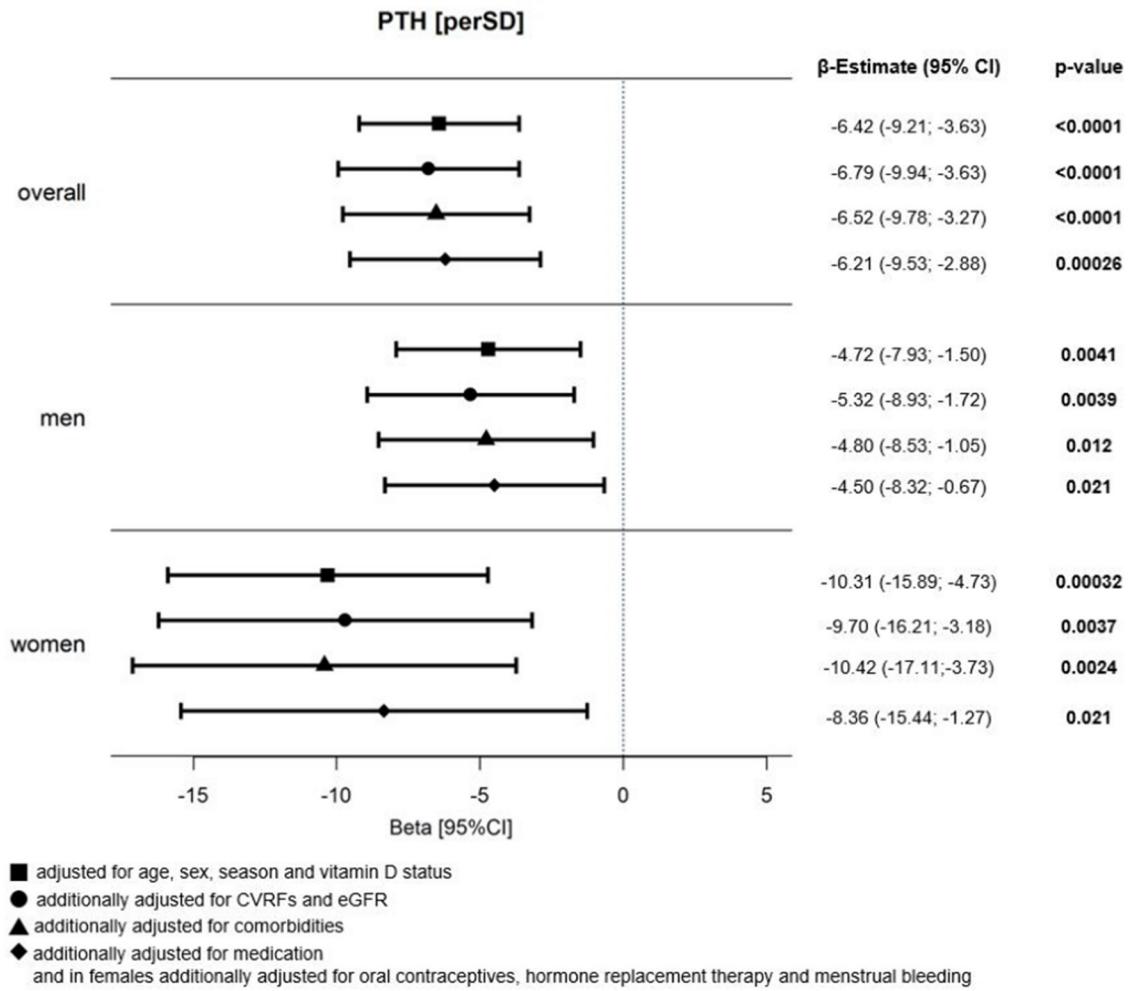


FIGURE 3 | Relation between platelet count and PTH in HF individuals. Forest Plot of beta (β)-estimates with 95% confidence intervals (CIs) for the relation between platelet count and PTH in all HF individuals and stratified by sex. *N* (total analysis sample) = 1,860, thereof *N* = 532 females and *N* = 1,328 males; adjustment for sex only in overall analysis sample; PTH, parathyroid hormone; CVRFs, cardiovascular risk factors; eGFR, estimated glomerular filtration rate.

HF: within HFpEF individuals, the inverse association was observed more consistent in females, whereas in HFrEF, the inverse association between PTH and platelet count was found in males only.

The etiology of HF differs between males and females regarding prevalence, risk factors, and comorbidities (2), and in part these differences could be explained by the sex-specific hormones, pregnancy, or preeclampsia (24). Also the pathophysiology differs between both sexes, as females tend to suffer more from a "microvascular" disease with vascular stiffness and systemic inflammation, whereas males tend to present with a more "macrovascular" pattern due to comorbidities such as MI or CAD (3, 25). Indeed, the results in the current analysis also differ between both sexes. The associations between MPV or platelet count, and PTH, if found, were with higher effect sizes in females compared to males. Notably, the association was also independent of known female factors influencing the platelet size, such as menstrual bleeding, hormone replacement therapy, and intake of oral contraceptives. Whether endogenous hormone levels influence the association between platelet indices and PTH in the HF syndrome requires further investigation. Genetically determined testosterone levels have been linked with development of HF, predominantly in men, as shown in a recent Mendelian randomization study (26). Post-menopause in women has been associated with an exponential increase in the incidence of HFpEF compared with men of the same age. Estrogen deprivation in post-menopause has been recognized as an important determinant of diastolic dysfunction as estrogen is shown to modulate many regulatory molecular pathways of cardiac diastolic function (27, 28). The present results further support the importance of hormones by showing an important effect of hormone-containing agents on the association between platelet count and PTH in female HF subjects.

TABLE 3 | Relation between platelet count and PTH according to cardiac function in a sex-specific analysis.

		Platelet count							
		Adjusted for age, sex[a], season, vitamin D status[b]		Additionally adjusted for CVRFs and eGFR		Additionally adjusted for comorbidities		Additionally adjusted for medication[c]	
	N	*β*-estimate (95% CI)	*P*-value	*β*-estimate (95% CI)	*P*-value	*β*-estimate (95% CI)	*P*-value	*β*-estimate (95% CI)	*P*-value
Preserved EF	1,173	−7.0 (−11; −3.0)	**0.00071**	−7.2 (−12; −2.8)	**0.0015**	−6.9 (−11; −2.3)	**0.0032**	−6.7 (−11;−2.0)	**0.0052**
Females	401	−11 (−18; −3.3)	**0.0046**	−10 (−19; −1.9)	**0.016**	−10 (−19; −1.7)	**0.019**	−8.0 (−17; 1.1)	0.084
Males	772	−5.0 (−9.8; −0.17)	**0.043**	−5.2 (−10; 0.060)	0.053	−4.8 (−10; 0.64)	0.084	−4.4 (−10; 1.1)	0.12
Reduced EF	687	−4.4 (−8.3; −0.41)	**0.031**	−5.7 (−10; −1.1)	**0.015**	−5.3 (−10; −0.52)	**0.030**	−5.6 (−11; −0.77)	**0.024**
Females	131	−5.9 (−14; 2.4)	0.17	−8.0 (−18; 2.4)	0.13	−9.1 (−20; 1.9)	0.11	−5.0 (−17; 6.8)	0.41
Males	556	−4.0 (−8.5; 0.41)	0.075	−5.1 (−10; 0.050)	0.053	−4.5 (−9.9; 0.94)	0.11	−4.7 (−10; 0.85)	0.098
HFpEF	442	−9.5 (−15; −3.6)	**0.0019**	−9.9 (−17; −3.2)	**0.0039**	−9.4 (−16; −2.4)	**0.0091**	−8.9 (−16; −1.7)	**0.015**
Females	191	−11 (−21; −0.96)	**0.033**	−12 (−23; −0.14)	**0.049**	−11 (−23; 1.4)	0.084	n.a.	n.a.
Males	251	−8.6 (−16; −1.2)	**0.024**	−8.3 (−17; 0.0084)	0.051	−7.7 (−17; 1.2)	0.090	−6.0 (−15; 3.2)	0.21
HFpEF borderline	324	−1.9 (−8.7; 4.8)	0.57	−3.0 (−11; 4.7)	0.44	−2.5 (−10; 5.4)	0.53	−3.9 (−12; 4.4)	0.35
Females	82	−11 (−23; 1.4)	0.086	−9.7 (−26; 6.5)	0.24	−12 (−29; 6.3)	0.21	−9.5 (−33; 14)	0.43
Males	242	0.71 (−7.2; 8.6)	0.86	−1.0 (−10; 8.1)	0.83	0.50 (−8.9; 9.9)	0.92	0.092 (−10; 10)	0.99
HFrEF	279	−5.4 (−11; −0.28)	**0.040**	−7.1 (−13; −1.2)	**0.019**	−7.0 (−13; −0.60)	**0.033**	−6.3 (−13; 0.18)	0.058
Females	41	−0.14 (−13; 13)	0.98	−10 (−27; 6.7)	0.25	−8.0 (−26; 10)	0.40	n.a.	n.a.
Males	238	−6.5 (−12; −0.79)	**0.027**	−7.4 (−14; −0.90)	**0.027**	−7.6 (−15; −0.49)	**0.037**	−7.6 (−15; −0.30)	**0.043**

Multivariable linear regression analysis with platelet count as dependent variable and PTH as independent variable in phenotypes of cardiac function and sex-specific. Results are presented as beta (β)-estimates for change per one standard deviation in PTH. PTH, parathyroid hormone; N, number of individuals; eGFR, estimated glomerular filtration rate; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFpEF borderline, heart failure with ejection fraction of 41–49%; HFrEF, heart failure with reduced ejection fraction; n.a., not available due to low sample size.

[a]Sex-adjustment only in overall analysis sample; [b]Vitamin D status was determined by concentrations of Calcifediol and Calcitriol; [c]In females additionally adjusted for oral contraceptives, hormone replacement therapy and menstrual bleeding. P-value < 0.05 were highlighted in bold.

The role of PTH according to HF severity has also been reported. A positive correlation between PTH and NYHA class and PTH and NT-proBNP levels as well as an inverse correlation between PTH and LVEF has been reported in different HF studies (8–11).

A positive relation between increasing age and PTH levels has been previously reported, primarily as a response to changes in serum calcium (29). The results from this study showed a weak positive correlation between age and PTH in males with predominantly HFpEF phenotype and in females with predominantly HFrEF phenotype.

In addition, patients with disorders of the parathyroid gland suffered more frequently from arterial hypertension, left ventricular hypertrophy, arrhythmia, and HF (13). Elevated PTH can stimulate cardiac myocyte hypertrophy, dysfunction of endothelium and vasculature, and hypercalcemia and activate aldosterone *via* RAAS (13). However, a community-based study in the Netherlands did not confirm PTH to be associated with a risk of developing HF or predicting new onset of HFpEF or HFrEF (30). Subjects with primary hyperparathyroidism and thus elevated concentrations of PTH presented with higher MPV compared to age- and sex-matched healthy controls (17). Higher MPV could suggest the presence of metabolically and enzymatically hyperactive platelets in HF individuals (17). Activated platelets release a plethora of different proinflammatory mediators that promote immune response, angiogenesis, and fibrosis (31, 32). Hypercalcemia can lead to oxidative stress and inflammation in the heart and finally contribute to cardiomyocyte necrosis (8). However, calcium is required as a cofactor in blood coagulation; a lack of calcium can also impair cardiac function and affect HF progression (33, 34). The presence of PTH-related protein and vitamin D receptors on platelets might lead to platelet activation after direct binding or after PTH-initiated increase of vitamin D or PTH-initiated increase of calcium (18, 19). The described pathways of platelet activation can result in a hypercoagulable state, an already recognized risk factor in HF syndrome (35). Vitamin D has been reported to have anti-inflammatory properties, and given the presence of vitamin D receptors in cardiac myocytes, vitamin D supplementation has been suggested as a possible supporting therapy in HF syndrome (36, 37). Indeed, the VINDICATE study showed the beneficial effects of Vitamin D supplementation on cardiac function and LV structure in patients with chronic HF and vitamin D deficiency for a duration of 1 year (38). On the other hand, suppressing PTH by vitamin D intake might present a potential therapeutic target to prevent PTH-driven endothelial dysfunction, atherosclerosis, and platelet activation as leading causes of cardiac ischemia and HF development (4, 39). In absence of robust experimental evidence for the direct interaction between PTH and platelets, it remains to understand if the observed relation depends on other PTH-dependent mechanisms such as plasma and platelet calcium level and vitamin D concentration and its association with platelet activation. Another hypothesis to be tested for the potential

improvement of the clinical outcome of individuals with HF syndrome, based on the present results on the interaction between PTH and platelets, could be the addition of antiplatelet agents in HF patients with higher PTH concentration. To increase the understanding of the interaction between PTH and platelet activation in HF phenotypes, a prospective investigation with specific platelet function tests depicting different aspects of platelet activation, that is, platelet aggregation and platelet procoagulant function, is needed. Furthermore, well-designed randomized controlled trials could importantly inform whether attenuating the levels of PTH intake and/or impeding platelet aggregation and procoagulant function by Vitamin D and antithrombotic agents, respectively, will decrease HF risk or mitigate its progression. Sex-related differences from biological mechanisms to treatment effects and prognosis have been already described in HF patients (40). Our findings for the sex differing association between PTH and platelet indices further support the recommendation to keep the sex-specific focus in future mechanistic, translational, and interventional studies.

CONCLUSION

The results of this analysis report important differences for the association between biomarkers of platelets and PTH that vary between sexes and with the phenotype of cardiac dysfunction. These differences are present independent of vitamin D status, CVRFs, and comorbidities. Particularly in phenotypes of symptomatic HF, distinct associations in males and females were observed, suggesting a sex-specific mechanism involved in the interaction between PTH and platelets. Further mechanistic studies are warranted to understand the effect of PTH at the molecular level of platelets, including the role of endogenous hormones in HF phenotypes.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee University Medical Centre Mainz, reference number 837.319.12 (8420-F). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BD, MP-N, and PW designed and performed research and wrote the manuscript. FM, S-OT, and MH contributed to discussion of results and to the critical review of the manuscript. AS performed the statistical analysis. NA, MH, SS-T, JP, TG, HC, KL, and TM contributed in critically reviewing the manuscript. All authors have read, critically reviewed, and approved the manuscript in its current form.

FUNDING

This work was supported by the German Center for Cardiovascular Research (DZHK) and the Center for Translational Vascular Biology (CTVB) of the University Medical Center of the Johannes Gutenberg-University Mainz.

ACKNOWLEDGMENTS

We thank all study participants and the team of the MyoVasc study and the co-workers of the Clinical Epidemiology Department of the University Medical Center Mainz for their support and commitment. Part of this work is part of the doctoral thesis of BD.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.682521/full#supplementary-material

REFERENCES

1. Savarese G, Lund LH. Global public health burden of heart failure. *Cardiac Fail Rev.* (2017) 3:7–11. doi: 10.15420/cfr.2016:25:2
2. De Bellis A, De Angelis G, Fabris E, Cannata A, Merlo M, Sinagra G. Gender-related differences in heart failure: beyond the "one-size-fits-all" paradigm. *Heart Fail Rev.* (2019) 25:245–55. doi: 10.1007/s10741-019-09824-y
3. Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, et al. Sex differences in heart failure. *Eur Heart J.* (2019) 40:3859–68c. doi: 10.1093/eurheartj/ehz835
4. Loncar G, Bozic B, Dimkovic S, Prodanovic N, Radojicic Z, Cvorovic V, et al. Association of increased parathyroid hormone with neuroendocrine activation and endothelial dysfunction in elderly men with heart failure. *J Endocrinol Invest.* (2011) 34:e78–85. doi: 10.1007/BF03347080
5. Schierbeck LL, Jensen TS, Bang U, Jensen G, Kober L, Jensen JE. Parathyroid hormone and vitamin D–markers for cardiovascular and all cause mortality in heart failure. *Eur J Heart Fail.* (2011) 13:626–32. doi: 10.1093/eurjhf/hfr016
6. Pyram R, Mahajan G, Gliwa A. Primary hyperparathyroidism: skeletal and non-skeletal effects, diagnosis and management. *Maturitas.* (2011) 70:246–55. doi: 10.1016/j.maturitas.2011.07.021
7. Verdoia M, Pergolini P, Rolla R, Nardin M, Barbieri L, Schaffer A, et al. Parathyroid hormone levels and high-residual platelet reactivity in patients receiving dual antiplatelet therapy with acetylsalicylic acid and clopidogrel or ticagrelor. *Cardiovasc Ther.* (2016) 34:209–15. doi: 10.1111/1755-5922.12188
8. Gruson D, Buglioni A, Burnett JC Jr. PTH: potential role in management of heart failure. *Clin Chim Acta.* (2014) 433:290–6. doi: 10.1016/j.cca.2014.03.029
9. Arakelyan KP, Sahakyan YA, Hayrapetyan LR, Khudaverdyan DN, Ingelman-Sundberg M, Mkrtchian S, et al. Calcium-regulating peptide hormones and blood electrolytic balance in chronic heart failure. *Regul Pept.* (2007) 142:95–100. doi: 10.1016/j.regpep.2007.02.001
10. Gandhi S, Myers RB. Can parathyroid hormone be used as a biomarker for heart failure? *Heart Fail Rev.* (2013) 18:465–73. doi: 10.1007/s10741-012-9336-9

11. Gruson D, Ahn SA, Rousseau MF. Multiple biomarker strategy based on parathyroid hormone and natriuretic peptides testing for improved prognosis of chronic heart failure. *Peptides.* (2015) 64:24–8. doi: 10.1016/j.peptides.2014.12.010
12. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol.* (2011) 8:30–41. doi: 10.1038/nrcardio.2010.165
13. Brown SJ, Ruppe MD, Tabatabai LS. The parathyroid gland and heart disease. *Methodist DeBakey Cardiovasc J.* (2017) 13:49–54. doi: 10.14797/mdcj-13-2-49
14. Panova-Noeva M, Schulz A, Hermanns MI, Grossmann V, Pefani E, Spronk HM, et al. Sex-specific differences in genetic and nongenetic determinants of mean platelet volume: results from the Gutenberg Health Study. *Blood.* (2016) 127:251–9. doi: 10.1182/blood-2015-07-660308
15. Chung I, Lip GY. Platelets and heart failure. *Eur Heart J.* (2006) 27:2623–31. doi: 10.1093/eurheartj/ehl305
16. Wang R, Cao Z, Li Y, Yu K. Mean platelet volume provides an additive value in differentiating congestive heart failure from chronic obstructive pulmonary disease. *Int J Cardiol.* (2015) 179:201–2. doi: 10.1016/j.ijcard.2014.11.078
17. Arpaci D, Kuzu F, Emre A, Karadeniz G, Unal M, Uygun SI, et al. Elevated mean platelet volume in patients with primary hyperparathyroidism. *Int J Clin Exp Med.* (2016) 6330–5.
18. Baradaran AaHN. Impact of parathormone hormone on platelet count and mean volume in end-stage renal failure patients on regular hemodialysis. *J Med Sci.* (2005) 266–71. doi: 10.3923/jms.2005.266.271
19. Ortega A, Perez de Prada MT, Mateos-Caceres PJ, Ramos Mozo P, Gonzalez-Armengol JJ, Gonzalez Del Castillo JM, et al. Effect of parathyroid-hormone-related protein on human platelet activation. *Clin Sci.* (2007) 113:319–27. doi: 10.1042/CS20070010
20. Gobel S, Prochaska JH, Trobs SO, Panova-Noeva M, Espinola-Klein C, Michal M, et al. Rationale, design and baseline characteristics of the MyoVasc study: a prospective cohort study investigating development and progression of heart failure. *Eur J Prev Cardiol.* (2020). doi: 10.1177/2047487320926438. [Epub ahead of print].
21. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation.* (2013) 128:e240–327. doi: 10.1016/j.jacc.2013.05.019
22. Sugimoto T, Tanigawa T, Onishi K, Fujimoto N, Matsuda A, Nakamori S, et al. Serum intact parathyroid hormone levels predict hospitalisation for heart failure. *Heart.* (2009) 95:395–8. doi: 10.1136/hrt.2008.147652
23. Thompson C, Jakubowski J. The pathophysiology and clinical relevance of platelet heterogeneity. *Blood.* (1988) 72:1–8. doi: 10.1182/blood.V72.1.1.1
24. Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM. Sex differences in cardiovascular pathophysiology: why women are overrepresented in heart failure with preserved ejection fraction. *Circulation.* (2018) 138:198–205. doi: 10.1161/CIRCULATIONAHA.118.034271
25. Sickinghe AA, Korporaal SJA, den Ruijter HM, Kessler EL. Estrogen contributions to microvascular dysfunction evolving to heart failure with preserved ejection fraction. *Front Endocrinol.* (2019) 10:442. doi: 10.3389/fendo.2019.00442
26. Luo S, Au Yeung SL, Zhao JV, Burgess S, Schooling CM. Association of genetically predicted testosterone with thromboembolism, heart failure, and myocardial infarction: mendelian randomisation study in UK Biobank. *BMJ.* (2019) 364:l476. doi: 10.1136/bmj.l476
27. Maslov PZ, Kim JK, Argulian E, Ahmadi A, Narula N, Singh M, et al. Is cardiac diastolic dysfunction a part of post-menopausal syndrome? *JACC Heart Fail.* (2019) 7:192–203. doi: 10.1016/j.jchf.2018.12.018
28. Sabbatini AR, Kararigas G. Menopause-related estrogen decrease and the pathogenesis of HFpEF: JACC review topic of the week. *J Am Coll Cardiol.* (2020) 75:1074–82. doi: 10.1016/j.jacc.2019.12.049
29. Haden ST, Brown EM, Hurwitz S, Scott J, El-Hajj Fuleihan G. The effects of age and gender on parathyroid hormone dynamics. *Clin Endocrinol.* (2000) 52:329–38. doi: 10.1046/j.1365-2265.2000.00912.x
30. Meems LMG, Brouwers FP, Joosten MM, Lambers Heerspink HJ, de Zeeuw D, Bakker SJL, et al. Plasma calcidiol, calcitriol, and parathyroid hormone and risk of new onset heart failure in a population-based cohort study. *ESC Heart Fail.* (2016) 3:189–97. doi: 10.1002/ehf2.12089
31. Vinholt PJ, Hvas AM, Frederiksen H, Bathum L, Jorgensen MK, Nybo M. Platelet count is associated with cardiovascular disease, cancer and mortality: a population-based cohort study. *Thromb Res.* (2016) 148:136–42. doi: 10.1016/j.thromres.2016.08.012
32. Jenne CN, Kubes P. Platelets in inflammation and infection. *Platelets.* (2015) 26:286–92. doi: 10.3109/09537104.2015.1010441
33. Gorski PA, Ceholski DK, Hajjar RJ. Altered myocardial calcium cycling and energetics in heart failure–a rational approach for disease treatment. *Cell Metab.* (2015) 21:183–94. doi: 10.1016/j.cmet.2015.01.005
34. Johnson DM, Mugelli A, Cerbai E. Editorial: the role of calcium handling in heart failure and heart failure associated arrhythmias. *Front Physiol.* (2019) 10:1. doi: 10.3389/fphys.2019.00001
35. Jafri SM. Hypercoagulability in heart failure. *Semin Thromb Hemost.* (1997) 23:543–5. doi: 10.1055/s-2007-996133
36. Amin A, Minaee S, Chitsazan M, Naderi N, Taghavi S, Ardeshiri M. Can vitamin D supplementation improve the severity of congestive heart failure? *Congest Heart Fail.* (2013) 19:E22–8. doi: 10.1111/chf.12026
37. Moretti HD, Colucci VJ, Berry BD. Vitamin D3 repletion versus placebo as adjunctive treatment of heart failure patient quality of life and hormonal indices: a randomized, double-blind, placebo-controlled trial. *BMC Cardiovasc Disord.* (2017) 17:274. doi: 10.1186/s12872-017-0707-y
38. Witte KK, Byrom R, Gierula J, Paton MF, Jamil HA, Lowry JE, et al. Effects of Vitamin D on Cardiac Function in Patients With Chronic HF: The VINDICATE Study. *J Am Coll Cardiol.* (2016) 67:2593–603. doi: 10.1016/j.jacc.2016.03.508
39. Fitzpatrick LA, Bilezikian JP, Silverberg SJ. Parathyroid hormone and the cardiovascular system. *Curr Osteoporos Rep.* (2008) 6:77–83. doi: 10.1007/s11914-008-0014-8
40. Regitz-Zagrosek V, Kararigas G. Mechanistic pathways of sex differences in cardiovascular disease. *Physiol Rev.* (2017) 97:1–37. doi: 10.1152/physrev.00021.2015

Conflict of Interest: PW received research funding from Boehringer Ingelheim, Bayer Healthcare, Daiichi Sankyo Europe, Novartis, AstraZeneca, Evonik, Sanofi-Aventis, Bayer Vital, AstraZeneca, DiaSorin and Evonik and received nonfinancial support from DiaSorin and I.E.M. JH. JP reports personal fees from Bayer AG and Boehringer Ingelheim. S-OT has received personal fees from Philips Health Care for a lecture outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 04 October 2021
doi: 10.3389/fcvm.2021.721850

Sex Differences in Characteristics and Outcomes in Elderly Heart Failure Patients With Preserved Ejection Fraction: A *Post-hoc* Analysis From TOPCAT

Jiaxing Sun[1†], Shi Tai[1†], Yanan Guo[1], Liang Tang[1], Hui Yang[1], Xuping Li[1], Zhenhua Xing[1], Liyao Fu[2] and Shenghua Zhou[1]*

[1] Department of Cardiovascular Medicine, The Second Xiangya Hospital of Central South University, Changsha, China,
[2] Department of Blood Transfusion, The Second Xiangya Hospital of Central South University, Changsha, China

OPEN ACCESS

Edited by:
Saskia C. A. De Jager,
Utrecht University, Netherlands

Reviewed by:
Nobuyuki Ohte,
Nagoya City University, Japan
Micha Tobias Maeder,
Kantonsspital St. Gallen, Switzerland
Loek Van Heerebeek,
Onze Lieve Vrouwe Gasthuis (OLVG), Netherlands

***Correspondence:**
Shenghua Zhou
zhoushenghua@csu.edu.cn

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Sex and Gender in Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: 07 June 2021
Accepted: 30 August 2021
Published: 04 October 2021

Citation:
Sun J, Tai S, Guo Y, Tang L, Yang H, Li X, Xing Z, Fu L and Zhou S (2021) Sex Differences in Characteristics and Outcomes in Elderly Heart Failure Patients With Preserved Ejection Fraction: A Post-hoc Analysis From TOPCAT. Front. Cardiovasc. Med. 8:721850. doi: 10.3389/fcvm.2021.721850

Introduction: Although the impact of sex on patient outcomes for heart failure (HF) with preserved ejection fraction (HFpEF) has been reported, it is still unclear whether this impact is applicable for elderly patients with HFpEF. This study was conducted as a secondary analysis from a large randomized controlled trial—The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT)—to evaluate the impact of sex differences on the baseline characteristics and outcomes of HFpEF patients who were older than 70 years.

Methods: Baseline characteristic of elderly patients were compared between men and women. Primary outcomes were cardiovascular (CV) mortality and HF-related hospitalization, whereas secondary outcomes were all-cause mortality and all-cause hospitalization. Cox regression models were used to determine the effect of sex differences on patient outcomes.

Results: A total of 1,619 patients were included in the study: 898 (55.5%) women and 721 (44.5%) men. Age was similar between women and men. Women had fewer comorbidities but worse cardiac function than men. The rate of primary outcomes was lower in women than in men (18.4 vs. 27.5%; $p < 0.001$), including rate of CV mortality (8.9 vs. 14.8%; $p < 0.001$) and HF-related hospitalization (13.4 vs. 18.2%; $p = 0.008$). All-cause mortality was also lower in women than in men (15.6 vs. 25.4%; $p < 0.001$). After adjustment for baseline characteristics, Cox regression analysis showed that female sex was a protective factor for CV mortality [hazard ratio (HR): 0.53; 95% confidence interval (CI): 0.40–0.73], HF-related hospitalization (HR: 0.71; 95% CI: 0.55–0.93), and all-cause mortality (HR: 0.59; 95% CI: 0.47–0.75). Although spironolactone significantly reduced the rate of all-cause mortality in women even after adjusting for baseline characteristics (HR: 0.68; 95% CI: 0.48–0.96; $p = 0.028$), no significant multivariate association was noted between sex and treatment effects ($p = 0.190$).

Conclusion: Among elderly patients with HFpEF, women had worse cardiac function but better survival and lower HF-related hospitalization rate than men.

Clinical Trial Registration: NCT00094302 (TOPCAT). Registered October 15, 2004, https://www.clinicaltrials.gov/ct2/show/NCT00094302.

Keywords: sex differences, HFpEF, baseline characteristics, mortality, HF-related hospitalization, elderly patients

INTRODUCTION

The incidence and prevalence of heart failure (HF) with preserved ejection fraction (HFpEF) increase exponentially with advancing age (1). And clinical and echocardiographic characteristics, quality of life, and patient outcomes differ between young and old HFpEF patients (2). Most of the recently completed large randomized clinical trials on HFpEF did not specifically set an age limit for participants, and elderly patients whose clinical features, event rates, and response to treatments may be different from those of young patients are underrepresented in randomized clinical trials.

Sex differences exist in almost every facet of HF (both HF with reduced ejection fraction and HFpEF), including baseline characteristics, risk factors, pathophysiology, drug response, and patient outcomes (3–5). Community-based studies indicated that women are substantially different from men in terms of clinical features and event rates (6, 7). The Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial demonstrated a lower mortality or hospitalization rate for both cardiovascular (CV) and non-CV diseases in women with HFpEF, suggesting a better overall prognosis in women (8). The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT) reported no significant interactions between spironolactone and sex in terms of primary outcomes in a pre-specified subgroup analysis (9), whereas a secondary analysis of this trial, which was restricted to the Americans, has shown that women have a significantly decreased all-cause mortality rate associated with spironolactone (10); however, this was not observed in men, suggesting sex differences in patient outcomes. But information about sex differences on patient outcomes and spironolactone response in elderly patients with HFpEF is limited. To address this, our study conducted a *post-hoc* exploratory subgroup analysis in elderly patients with HFpEF from TOPCAT to determine sex differences in baseline characteristics, outcomes, and spironolactone response.

MATERIALS AND METHODS

Study Design and Patients

For this *post-hoc* analysis, clinical data from TOPCAT were collected from the National Heart, Lung, and Blood Institute's Biological Specimen and Data Repository Information Coordinating Center (BioLINCC, Calverton, Maryland, USA). Patients who were diagnosed with symptomatic HF and left ventricular ejection fraction of ≥45% and were hospitalized for HF within 12 months prior to enrollment or had elevated natriuretic peptide levels (brain natriuretic peptide level (BNP) of ≥100 pg/ml or N-terminal pro-BNP level of ≥360 pg/ml) within 60 days prior to inclusion were eligible. The age of the patients had to be 50 years or above, with controlled blood pressure (systolic blood pressure of <140 mmHg or ≤160 mmHg if three or more drugs were used to control blood pressure) and serum potassium level of <5.0 mmol/L. Patients whose life expectancy was <3 years, estimated glomerular filtration rate was <30 ml/min/1.73 m^2 of body surface area, or serum creatinine level was ≥2.5 mg/dl were excluded. The details can be found in the main study publications (9, 11). All included patients were randomly assigned to receive spironolactone or placebo treatment according to a double-blind design. For the purposes of our study, we selected 1,619 elderly patients (age ≥70 years) (12, 13) from TOPCAT to conduct a *post-hoc* secondary analysis.

Definitions of Outcomes

The follow-up time was about 3.3 years. Primary outcomes were cardiovascular (CV) mortality and HF-related hospitalization, and secondary outcomes were all-cause mortality (CV and non-CV mortality) and all-cause hospitalization.

Statistical Analysis

Descriptive statistical data were obtained for all variables of interest. Baseline clinical characteristics of patients were expressed as mean ± standard deviation for normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables, and frequencies and percentages for categorical variables. Data were stratified by sex and treatment arms. Sex differences in outcomes were compared within the entire cohort, the placebo arm, and the spironolactone arm. All continuous variables were compared using the *t*-test or Mann–Whitney *U*-test, and categorical variables were compared using Fisher's exact test or the χ^2 test. The Kaplan–Meier method was performed for time-to-event analysis. Associations between sex and patient outcomes were determined using univariate and multivariate Cox proportional hazards regression models. Adjusted variables included race, New York Heart Association (NYHA) class, myocardial infarction, atrial fibrillation, hypertension, dyslipidemia, chronic obstructive pulmonary disease, percutaneous coronary intervention, coronary artery bypass grafting, systolic blood pressure, diastolic blood pressure, heart rate, body mass index, baseline estimated

Abbreviations: CV, cardiovascular; HF, heart failure; NYHA, New York Heart Association; HFpEF, heart failure with preserved ejection fraction; BNP, brain natriuretic peptide.

glomerular filtration rate, and baseline potassium level. Stata/S.E. version 15.0 software (Stata Corp., College Station, TX, USA) was used for statistical analyses. Empower Stats was used to analyze sex–treatment interactions. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Baseline Characteristics According to Sex in the Elderly

Baseline characteristics of the overall cohort ($n = 1{,}619$) according to sex are summarized in **Table 1**. Of the 1,619 elderly patients, 898 (55.5%) were women, and 721 (44.5%) were men. All the patients were ≥70 years, and their mean age was similar between women and men. There were 533 (59.4%) women from the Americas (including the United States, Canada, Brazil, and Argentina) and 365 (40.6%) from Russia/Georgia. The baseline characteristics of each group are presented in **Table 1**. Women had fewer comorbidities than men: atrial fibrillation (41.4 vs. 47.4%; $p = 0.016$), myocardial infarction (18.7 vs. 30.9%; $p < 0.001$), coronary artery bypass grafting (7.6 vs. 22.3%; $p < 0.001$), percutaneous coronary intervention (12.5 vs. 18.9%; $p < 0.001$), dyslipidemia (57.3 vs. 66.2%; $p = 0.001$), and chronic obstructive pulmonary disease (9.24 vs. 47.4%; $p = 0.001$). However, women had a higher prevalence of hypertension (93.0 vs. 89.2%; $p = 0.007$), higher rate of NYHA functional classes III–IV (38.5 vs. 31.5%; $p = 0.003$), and higher body mass index (30.9 ± 6.2 vs. 30.1 ± 5.8 kg/m^2; $p = 0.011$) than men, whereas serum potassium (4.2 ± 0.43 vs. 4.3 ± 0.48 mmol/l; $p = 0.010$), blood urea nitrogen (16.2 ± 14.2 vs. 20.1 ± 14.3 mg/dl; $p = 0.001$), hemoglobin (12.6 ± 1.8 vs. 13.3 ± 2.4 g/dl; $p = 0.001$), and creatinine (1.0 ± 0.3 vs. 1.3 ± 0.31 mg/dl; $p < 0.001$) levels were lower in women than in men, and women had lower Kansas City Cardiomyopathy Questionnaire scores (54.1 ± 19.9 vs. 61.9 ± 21.3, $p < 0.001$) than men. Furthermore, elderly women with HFpEF had significantly higher left ventricular ejection fraction (63.3 ± 0.5 vs. 58.9 ± 0.6%, $p = 0.001$) and late mitral inflow velocity (81.5 ± 25.2 vs. 71.1 ± 26.8 cm/s, $p < 0.001$). Left ventricular filling pressure (E/Em) (12.5 ± 6.4 vs. 11.5 ± 5.9, $p = 0.142$) and E-wave deceleration time (210.4 ± 65.2 vs. 201.6 ± 67.1 s, $p = 0.154$) were higher in women than in men, but the differences in these parameters were not significant. Furthermore, plasma BNP [245 (148, 431) vs. 302 (165, 483) pg/ml, $p = 0.039$] was lower in women than in men, but there was no significant difference in the N-terminal pro-BNP [889 (485, 1,914) vs. 901 (532, 1,908) pg/ml, $p = 0.787$] level.

Regarding the use of medications, no significant differences were noted for angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, or diuretics between men and women. Men were significantly more likely to take statins, warfarin, any hypoglycemic drug, other antihypertensives, or CV medications. Moreover, in both the placebo and spironolactone arms, differences in the use of drugs between women and men were the same as the differences in the entire cohort.

Differences in Outcomes Between Elderly Women and Men

The rates of primary and secondary outcomes according to sex between the placebo and spironolactone arms are summarized in **Table 2**. In the entire cohort, the rates of primary outcome (18.4 vs. 27.5%, $p < 0.001$), CV mortality (8.9 vs. 14.8%, $p < 0.001$), HF-related hospitalization (13.4 vs. 18.2%, $p = 0.008$), all-cause mortality (15.6 vs. 25.4%, $p < 0.001$), and all-cause hospitalization (47.0 vs. 52.3%, $p = 0.012$) were all significantly lower in women than in men. In the placebo arm, women had lower rates of composite primary outcomes (18.9 vs. 28.1%; $p = 0.002$), CV mortality (10.6 vs. 15.4%; $p = 0.039$), HF-related hospitalization (13.5 vs. 19.0%; $p = 0.033$), and all-cause mortality (31.5 vs. 50.4%; $p < 0.001$) than men. The rate of all-cause hospitalization was lower in women than in men (48.5 vs. 53.2%, $p = 0.191$), but the difference was not statistically significant. In patients treated with spironolactone, the rates of composite primary outcomes (17.9 vs. 26.8%; $p = 0.002$), CV mortality (7.3 vs. 14.2%; $p = 0.001$), all-cause mortality (13.0 vs. 25.7%; $p < 0.001$), and all-cause hospitalization (45.5 vs. 53.4%; $p = 0.026$) were significantly lower in women than in men. The HF-related hospitalization rate was lower in women than in men (13.2 vs. 17.3%, $p = 0.107$), but the difference was not statistically significant. Kaplan–Meier curves for primary and secondary outcomes stratified by sex are shown in **Figures 1**, **2**. Sex-specific univariate analysis showed that women had lower rates of all outcomes in the entire cohort and in the placebo arm. In patients treated with spironolactone, no significant statistical differences were noted in HF-related hospitalization [hazard ratios (HR): 0.73; 95% confidence interval (CI): 0.51–1.04; $p = 0.083$] and all-cause hospitalization (HR: 0.71; 95% CI: 0.50–1.01; $p = 0.058$) between women and men, but primary outcome, CV mortality, and all-cause mortality were significantly lower in women than in men. Sex-specific multivariate HRs in the placebo and spironolactone arms for all outcomes adjusted for race, NYHA class, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, atrial fibrillation, hypertension, dyslipidemia, chronic obstructive pulmonary disease, systolic blood pressure, diastolic blood pressure, heart rate, body mass index, baseline estimated glomerular filtration rate, and baseline potassium levels are detailed in **Supplementary Table 1** and **Figure 3**. In the entire cohort, the risk of primary outcomes, CV mortality, HF-related hospitalization, and all-cause mortality was significantly lower in women after adjusting for covariates. Also, both in the placebo and spironolactone arms, women were more likely to have significantly reduced risks of composite primary outcomes, CV mortality, and all-cause mortality compared with men.

Treatment Effect in Elderly Women and Men

Univariate HR for all outcomes is shown in **Table 3**. In women, primary outcomes occurred in 84 patients (10.4%) treated with placebo and in 81 patients (10.0%) treated with spironolactone (HR: 0.95; 95% CI: 0.70–1.29). The rates of CV mortality,

TABLE 1 | Characteristics of the patients according to treatment arm.

	All			Placebo arm			Spironolactone arm		
	Women (*n* = 898)	**Men (*n* = 721)**	***p***	**Women (*n* = 445)**	**Men (*n* = 363)**	***p***	**Women (*n* = 453)**	**Men (*n* = 358)**	***p***
Age, years	77.0 ± 5.3	77.1 ± 5.1	0.458	76.6 ± 0.2	77 ± 0.3	0.116	77.4 ± 0.3	77.2 ± 0.3	0.621
Region	533 (59.4)	498 (69.1)	<0.001	255 (56.0)	252 (69.4)	<0.001	278 (61.4)	246 (68.7)	0.03
Americas, *n (%)*									
Russia/Georgia, *n (%)*	365 (40.6)	223 (30.9)	<0.001	190 (42.7)	111 (30.6)	<0.001	175 (38.6)	112 (31.3)	0.03
Atrial fibrillation, *n (%)*	371 (41.4)	341 (47.4)	0.016	188 (42.2)	164 (45.2)	0.399	183 (40.4)	177 (49.4)	0.01
Coronary artery disease									
Angina, *n (%)*	363 (40.4)	316 (43.9)	0.166	193 (43.4)	164 (45.2)	0.602	170 (37.5)	152 (42.5)	0.154
MI, *n (%)*	168 (18.7)	223 (30.9)	<0.001	86 (19.3)	120 (33.1)	<0.001	82 (18.1)	103 (28.8)	<0.001
CABG, *n (%)*	68 (7.6)	161 (22.3)	<0.001	41 (9.2)	89 (24.5)	<0.001	27 (6.0)	72 (20.1)	<0.001
PCI, *n (%)*	11 2(12.5)	136 (18.9)	<0.001	49 (11.0)	76 (20.9)	<0.001	63 (13.9)	60 (16.8)	0.261
Hypertension, *n (%)*	835 (93.0)	643 (89.2)	0.007	417 (93.7)	326 (89.8)	0.042	418 (92.3)	317 (88.5)	0.071
Diabetes mellitus, *n (%)*	252 (28.1)	229 (31.2)	0.105	117 (26.3)	123 (33.9)	0.019	135 (29.8)	106 (29.6)	0.953
Dyslipidemia, *n (%)*	515 (57.3)	477 (66.2)	<0.001	258 (58.0)	250 (68.9)	0.001	257 (56.7)	227 (63.4)	0.054
Tobacco use, *n (%)*	224 (24.8)	482 (66.9)	<0.001	114 (25.6)	236 (65.0)	<0.001	110 (24.3)	246 (67.8)	<0.001
COPD, *n (%)*	83 (9.24)	118 (47.4)	<0.001	39 (8.6)	63 (17.6)	<0.001	44 (9.7)	55 (15.4)	0.015
Heart rate, beats/min	69.0 ± 10.4	67.2 ± 10.2	0.002	69.0 ± 0.5	67.5 ± 0.5	0.049	69.1 ± 0.5	66.8 ± 0.6	0.013
SBP, mmHg	130.5 ± 14.3	126.8 ± 13.5	<0.001	131.1 ± 0.7	126.6 ± 0.7	<0.001	129.9 ± 0.7	127.1 ± 0.7	0.009
DBP, mmHg	74.5 ± 11.1	71.9 ± 10.7	<0.001	74.5 ± 0.6	71.6 ± 0.6	<0.001	72.5 ± 0.5	72.1 ± 0.6	0.006
Body mass index, kg/m^2	30.9 ± 6.2	30.1 ± 5.8	0.011	31.0 ± 0.3	30.0 ± 0.3	0.024	30.7 ± 0.3	30.1 ± 0.3	0.164
Serum potassium, mmol/L	4.2 ± 0.4	4.3 ± 0.5	0.01	4.3 ± 0.0	4.29 ± 0.0	0.108	4.2 ± 0.2	4.3 ± 0.0	0.349
Blood urea nitrogen, mg/dl	16.2 ± 14.2	20.1 ± 14.3	<0.001	16.9 ± 0.7	18.8 ± 0.7	0.005	15.4 ± 0.6	21.4 ± 0.8	<0.001
Creatinine, mg/dl	1.0 ± 0.3	1.3 ± 0.3	<0.001	1.0 ± 0.0	1.2 ± 0.0	<0.001	1.0 ± 0.0	1.3 ± 0.0	<0.001
Estimated GFR, ml/min/1.73 m^2	60.8 ± 17.6	64.2 ± 17.5	<0.001	60.0 ± 0.8	65.1 ± 1.0	<0.001	61.5 ± 0.8	63.3 ± 0.9	0.073
Hemoglobin, g/dL	12.6 ± 1.8	13.3 ± 2.4	<0.001	12.8 ± 0.1	13.2 ± 0.1	<0.001	12.5 ± 0.1	13.4 ± 0.1	<0.001
NYHA functional classes III–IV, *n (%)*	346 (38.5)	227 (31.5)	0.003	172 (38.7)	104 (28.7)	0.003	174 (38.4)	123 (34.4)	0.234
LVEF (%)	63.3 ± 0.5	58.9 ± 0.6	0.001	61.3 ± 0.7	59.3 ± 0.8	0.031	61.4 ± 0.6	58.5 ± 0.9	0.012
E (cm/s)	86.3 ± 26.9	86.7 ± 29.1	0.37	85.2 ± 24.8	88.6 ± 29.1	0.381	87.2 ± 28.7	84.6 ± 29.0	0.727
A (cm/s)	81.5 ± 25.2	71.1 ± 26.8	<0.001	83.9 ± 25.1	7.6 ± 26.0	0.001	79.3 ± 25.3	71.9 ± 27.9	0.11
E/A	1.1 ± 0.7	1.2 ± 0.7	0.108	1.1 ± 0.7	1.3 ± 0.7	0.064	1.2 ± 0.7	1.2 ± 0.7	0.712
EDT (s)	210.4 ± 65.2	201.6 ± 67.1	0.154	210 ± 73.5	198.5 ± 63.9	0.381	210.8 ± 57.3	205.1 ± 70.8	0.249
E/Em septal	16.5 ± 6.7	15.9 ± 7.7	0.262	16.3 ± 5.8	15.8 ± 7.5	0.345	16.6 ± 7.5	15.8 ± 8.0	0.513
E/Em lateral	12.5 ± 6.4	11.5 ± 5.9	0.142	12.6 ± 5.3	11.8 ± 6.3	0.149	12.4 ± 7.2	11.2 ± 5.5	0.436
BNP (pg/ml)	245 [148, 431]	302 [165, 483]	0.039	241.5 [147.5, 389.5]	307 [159, 454]	0.094	245 [151, 472]	284.5 [170,502]	0.234
NT-proBNP (pg/ml)	889 [485,1914]	901 [532, 1,908]	0.787	971 [560, 2,276]	904.5 [540.5, 2,025]	0.437	802 [435, 1,650]	901 [517, 1,790]	0.378
KCCQ overall score	54.1 ± 19.9	61.9 ± 21.3	<0.001	53.8 ± 0.9	61.8 ± 1.1	<0.001	54.3 ± 1.0	62.0 ± 1.2	<0.001
PHQ-9 score	5.3 ± 9.2	4.8 ± 8.8	0.065	5.5 ± 0.6	4.1 ± 0.8	0.078	5.0 ± 0.7	5.4 ± 0.3	0.377
Any antihypertensive drugs, *n (%)*	892 (99.4)	713 (99.0)	0.334	441 (99.1)	360 (99.2)	0.825	451 (99.6)	353 (98.6)	0.144
ACEI or ARB, *n (%)*	730 (81.4)	568 (78.9)	0.21	365 (82.0)	282 (77.7)	0.126	365 (80.6)	286 (80.0)	0.807
Beta-blocker, *n (%)*	670 (74.7)	558 (77.5)	0.189	333 (74.8)	286 (78.8)	0.18	337 (74.4)	272 (76.0)	0.604
CCB, *n (%)*	356 (39.7)	256 (35.6)	0.089	186 (41.8)	125 (34.4)	0.033	170 (37.5)	131 (36.6)	0.784
Diuretic, *n (%)*	754 (84.1)	604 (83.9)	0.927	378 (84.9)	309 (85.1)	0.929	376 (83.0)	295 (82.4)	0.822

(Continued)

TABLE 1 | Continued

	All			Placebo arm			Spironolactone arm		
	Women (*n* = 898)	**Men (*n* = 721)**	***p***	**Women (*n* = 445)**	**Men (*n* = 363)**	***p***	**Women (*n* = 453)**	**Men (*n* = 358)**	***p***
Other antihypertensive drugs, *n (%)*	110 (12.3)	115 (16.0)	0.032	56 (12.6)	55 (15.2)	0.29	54 (11.9)	60 (16.8)	0.049
Aspirin, *n (%)*	552 (61.5)	460 (63.9)	0.332	278 (62.5)	233 (64.2)	0.608	274 (60.5)	227 (63.4)	0.395
Nitrate, *n (%)*	143 (15.9)	113 (15.7)	0.892	73 (16.4)	57 (15.7)	0.789	70 (15.5)	56 (15.6)	0.941
Any hypoglycemic, *n (%)*	202 (22.5)	195 (27.1)	0.034	93 (20.9)	103 (28.4)	0.013	109 (24.1)	92 (25.7)	0.592
Statin, *n (%)*	420 (46.8)	445 (61.8)	<0.001	204 (45.8)	220 (60.6)	<0.001	216 (47.7)	225 (62.8)	<0.001
Warfarin, *n (%)*	231 (25.8)	229 (31.8)	0.007	116 (26.1)	115 (31.7)	0.078	115 (25.4)	114 (31.8)	0.043
Other CV medication, *n (%)*	396 (44.1)	410 (56.9)	<0.001	192 (43.1)	207 (57.0)	<0.001	204 (45.0)	203 (56.7)	0.001
Selective serotonin reuptake inhibitor, *n (%)*	78 (8.7)	50 (6.9)	0.195	39 (87.6)	26 (7.2)	0.406	39 (8.6)	24 (6.7)	0.314

Values are mean ± SD or n (%).

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; PHQ-9, Patient Health Questionnaire 9th edition; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CV, cardiovascular; E, early mitral inflow velocity; A, late mitral inflow velocity; E/A, early to late mitral inflow velocity ratio; EDT, E wave deceleration time; E/Em, mitral inflow to mitral relaxation velocity ratio.

TABLE 2 | Differences in outcomes between women and men.

	All			Placebo arm			Spironolactone arm		
	Women (*n* = 898)	**Man (*n* = 721)**	***p***	**Women (*n* = 445)**	**Men (*n* = 363)**	***P***	**Women (*n* = 453)**	**Men (*n* = 358)**	***p***
Primary outcome, *n (%)*	165 (18.4)	198 (27.5)	<0.001	84 (18.9)	102 (28.1)	0.002	81 (17.9)	96 (26.8)	0.002
CV mortality, *n (%)*	80 (8.9)	107 (14.8)	<0.001	47 (10.6)	56 (15.4)	0.039	33 (7.3)	51 (14.2)	0.001
HF hospitalization, *n (%)*	120 (13.4)	131 (18.2)	0.008	60 (13.5)	69 (19.0)	0.033	60 (13.2)	62 (17.3)	0.107
All-cause mortality, *n (%)*	140 (15.6)	183 (25.4)	<0.001	140 (31.5)	183 (50.4)	<0.001	59 (13.0)	92 (25.7)	<0.001
All-cause hospitalization, *n (%)*	422 (47.0)	384 (52.3)	0.012	216 (48.5)	193 (53.2)	0.191	206 (45.5)	191 (53.4)	0.026

*Values are n (%). Chi-square tests for women vs. men. Abbreviations as in **Table 1**.*

HF-related hospitalization, all-cause mortality, and all-cause hospitalization were also lower in patients taking spironolactone, but the differences were not statistically significant ($p > 0.05$ for all outcomes). The effects of spironolactone treatment were similar among men.

Multivariate HR and interaction terms between sex and treatment response are summarized in **Supplementary Figure 1** and **Table 3**. No significant reduction was observed in the rate of primary outcomes associated with spironolactone in women (HR: 0.91; 95% CI: 0.67–1.25; $p = 0.580$) and men (HR: 0.88; 95% CI: 0.66–1.17; $p = 0.377$). The rates of CV mortality, HF-related hospitalization, and all-cause hospitalization were not significantly different between the placebo and spironolactone arms in both women and men ($p > 0.05$). Although women treated with spironolactone had a decreased rate of all-cause mortality (10.0 vs. 7.3%; HR: 0.68; 95% CI: 0.48–0.96, $p = 0.028$) compared with that noted in men treated with spironolactone, sex–treatment interactions were not significant (p for interaction = 0.190).

DISCUSSION

Patients older than 70 years from TOPCAT were included in the present study, and the following sex differences in baseline characteristics and outcomes were found: (1) elderly women with HFpEF had fewer comorbidities but worse cardiac function than men; (2) elderly women had a lower rate of primary outcomes, CV mortality, HF-related hospitalization, all-cause mortality, and all-cause hospitalization than men; and (3) although elderly women taking spironolactone had a lower rate of all-cause mortality than women taking placebo, there was no significant multivariate sex–treatment interaction.

Sex Differences in Baseline Characteristics in Elderly Patients

Most of the HF cases happens in elderly patients, and more than half of patients hospitalized with HF are older than 75 years (14). It is reported that the prevalence of HF doubles for each decade of life. The prevalence is <1 and 10% for those

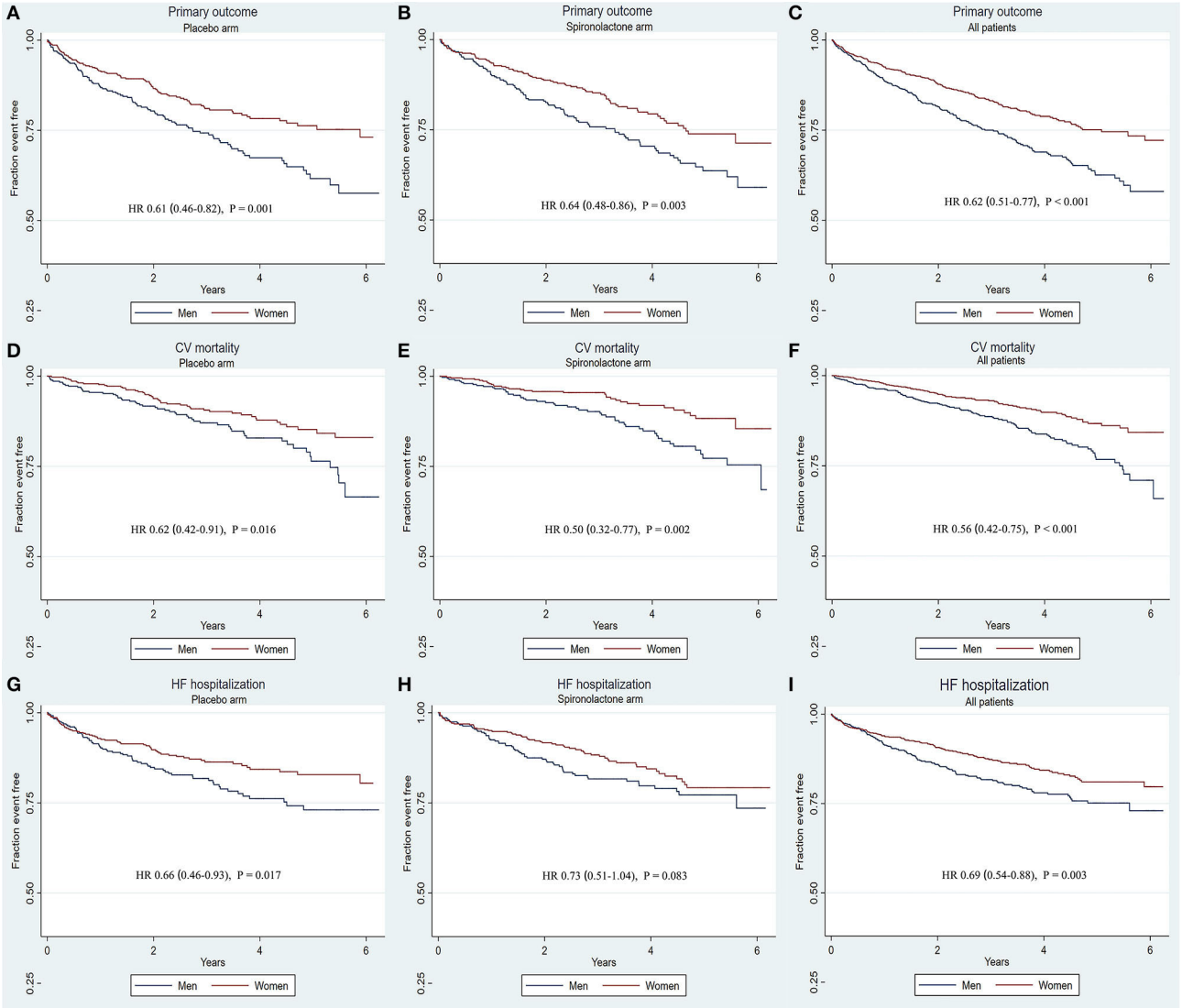


FIGURE 1 | Kaplana–Meier survival curves for primary outcomes and components stratified by sex according to treatment. There was a significant association between sex and the primary outcome, CV mortality in either placebo arm or spironolactone arm. Women had a significantly lower rate of all the primary outcomes in all patients. **(A–C)** Primary outcome in placebo arm, spironolactone arm, all patients; **(D–F)** CV mortality in placebo arm, spironolactone arm, all patients; **(G–I)** HF-related hospitalization in placebo arm, spironolactone arm, all patients. CV, cardiovascular diseases; HF, heart failure; HR, hazard ratio.

younger than 40 years and older than 80 years, respectively (15). Moreover, a recent prospective study demonstrated that patients from different age groups have different clinical characteristics and outcomes (2). Previous HF trials examined sex differences for different age groups, such as age of ≥60 years in the I-PRESERVE study (8), age of ≥21 years in the DIG (Digitalis Investigation Group)—PEF (preserved ejection fraction) study (16), and age of ≥50 years in the TOPCAT—Americas study (17). Although significant sex differences in the baseline characteristics of patients with HFpEF have been reported, only a few studies have specifically focused on sex differences in elderly patients with HFpEF. Moreover, elderly HFpEF patients are underrepresented in large-scale randomized clinical trials. Thus, it is of great significance to emphasize sex difference in these elderly patients.

In the present study, we focused on elderly patients from TOPCAT. We observed that hypertension, higher body mass index, and lower hemoglobin levels were more prevalent in elderly women. Men were more likely to be smokers and have coronary artery disease, atrial fibrillation, and chronic obstructive pulmonary disease. These findings were consistent with the data derived from the I-PRESERVE (8) and TOPCAT studies (17), and were also consistent with another meta-analysis (10) of the CHARM-Preserved (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity), I-PRESERVE, and TOPCAT—Americas studies: female HFpEF patients are older and more likely to have obesity and hypertension but less likely to have coronary artery disease or atrial fibrillation. Pepine et al. reported in a recent study that the higher prevalence of obesity,

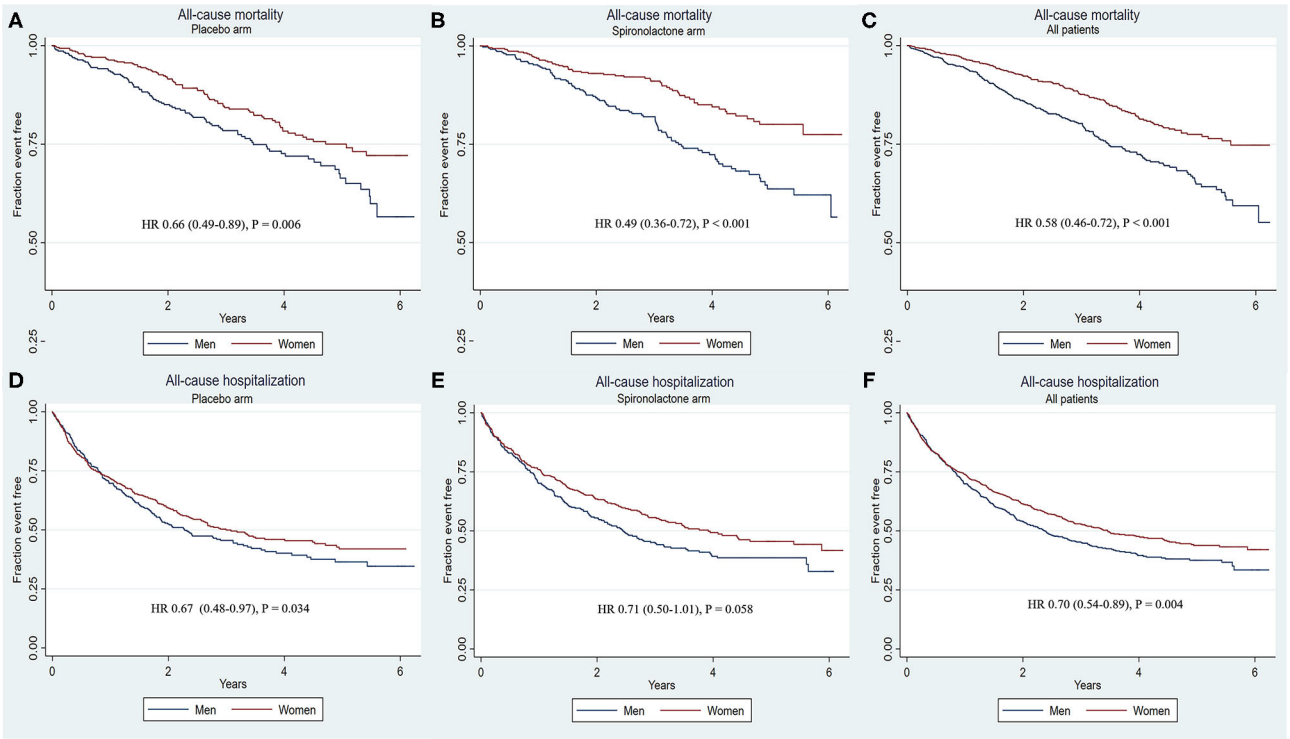


FIGURE 2 | Kaplana–Meier survival curves for secondary outcomes and components stratified by sex according to treatment. Women were associated with a significantly reduced likelihood of all-cause mortality in the placebo arm, spironolactone arm, and all patients. No significant result was observed for all-cause hospitalization. **(A–C)** All-cause mortality in placebo arm, spironolactone arm, all patients; **(D–F)** All-cause hospitalization in placebo arm, spironolactone arm, all patients.

hypertension, and other comorbidities in older women increases the prevalence of HFpEF in this group, which might explain that older women are more likely to develop HFpEF (18).

Furthermore, we observed that elderly women with HFpEF had worse NYHA functional classes and lower Kansas City Cardiomyopathy Questionnaire (19) scores (0–100, the higher scores, the fewer symptoms and physical limitations) than elderly men with HFpEF. The results suggested that elderly women were prone to have higher left ventricular ejection fraction, worse NYHA functional classes, more symptoms, and worse quality of life. We speculated that the worse NYHA functional classes and more symptoms in elderly women were attributable to impaired diastolic function. Women presented significantly higher late mitral inflow velocity (A) than men. Left ventricular filling pressure (E/Em) and E-wave deceleration time were numerically higher in women than in men but did not reach statistical significance, possibly due to the fact that many patients were without echo data. Consistent with previous studies, women with HFpEF had worse cardiac diastolic dysfunction than men. The possibility that diastolic cardiac function is more frequently abnormal in women is in agreement with the findings of previous studies (20–22): women with HFpEF have more prominent diastolic dysfunction than men with HFpEF. In contrast to the impaired diastolic function in women, lower BNP level was observed in elderly women with HFpEF. It was reported that women have higher plasma BNP level (23) in the general population but have lower BNP level in HFpEF due to the left ventricular concentric remodeling and hypertrophy among HFpEF patients (24). However, another study also reported that female HFpEF patients have a higher BNP level (21). Thus, the sex difference of BNP in HFpEF is still unclear and warrants further exploration.

Although women with HFpEF were more likely to have comorbid hypertension, no significant sex differences in the use of antihypertensive drugs, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, or diuretics were observed. Based on previous studies (25–28), we speculated that these findings are attributed to different pharmacokinetics and pharmacodynamics: women taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers had higher plasma drug concentrations than men. Men were more likely to taking statins, warfarin, or hypoglycemic drugs than women, which could be explained by the fact that more men in our study had atrial fibrillation, diabetes, and dyslipidemia.

Sex Differences in Outcomes in Elderly Patients

In the entire cohort, women not only had a lower rate of death including both CV mortality and all-cause mortality but also had a significantly lower rate of HF hospitalization. This result

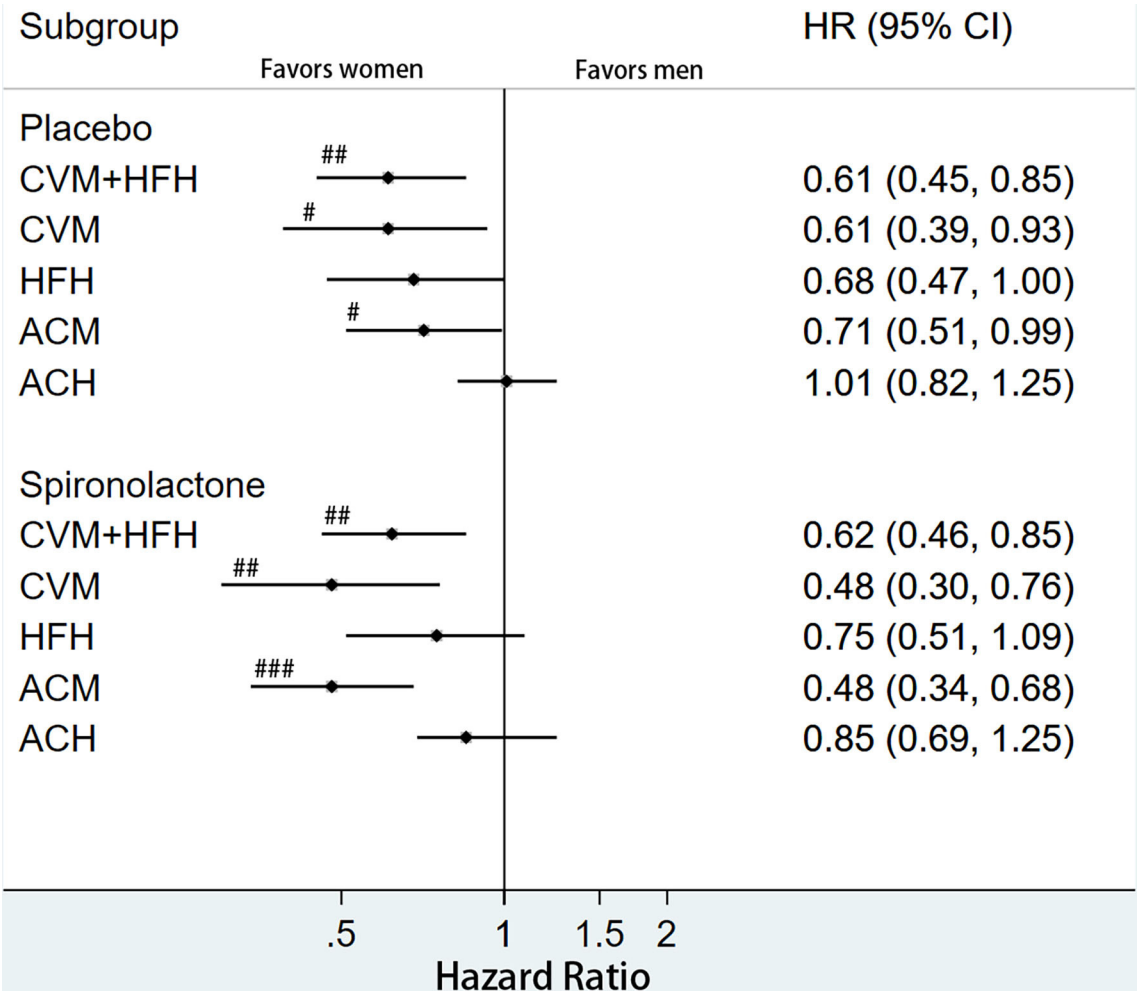


FIGURE 3 | Multivariate hazard ratios for primary and secondary outcomes according to treatment arm and stratified by sex. $^{\#}p < 0.05$, $^{\#\#}p < <0.01$, $^{\#\#\#}p < 0.001$. ACM, all-cause mortality; CVH, cardiovascular hospitalization; CVM, cardiovascular mortality; HFH, heart failure hospitalization; ACH, all-cause hospitalization.

was inconsistent with a previous meta-analysis (10) involving 4,174 patients ≤70 years and 4,294 patients >70 years: women had better survival conditions than men but had similar rates of hospitalization. Another secondary analysis using data from the I-PRESERVE study (patients ≥60 years old) also indicated that women had significantly lower mortality rates and HF hospitalization than men (8). These results may suggest that the difference in the rate of HF-related hospitalization becomes more obvious with aging.

We also found that elderly women had significantly lower rates of composite primary outcome, CV mortality, and all-cause mortality than men both in the placebo arm and in the spironolactone arm. The rate of HF-related hospitalization in women were lower in women than in men even without a statistical significance. While in the study of Merrill (17), women and men present with similar clinical outcomes in the placebo arm, in the spironolactone arm, although women had better survival rate than men, the HF-related hospitalization was similar. The discrepant results might be caused by different age groups. Our study strictly selected patients ≥70 years, while the result of Merrill also included patients <70 years. The results might further confirm that men will have a higher rate of HF-related hospitalization with aging.

Interestingly, upon examining the differences in quality of life and outcomes between female and male HFpEF patients, we found that women, who had more symptoms and more physical limitations than men, had better outcomes. An observational study in 2018 has reported a similar result (21), such that quality of life was associated with HF severity and outcomes in men but not in women, whose quality of life was determined more by other unknown factors instead of HF itself. More evidence is needed to investigate the relationship between quality of life and outcomes in women with HFpEF. Combined with these studies, ways to improve quality of daily life are more pivotal for female patients, while exploring ways to improve outcomes for elderly male patients is more urgent even though they have fewer symptoms.

TABLE 3 | Univariate and multivariate hazard ratios and interaction terms between sex and treatment response for all outcomes.

Outcome	Placebo ($n = 808$)	Spironolactone ($n = 811$)	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	*p*	*P* interaction
Primary outcome							*0.781*
Women, *n* (%)	84 (10.4)	81 (10.0)	0.95 (0.70–1.29)	0.73	0.91 (0.67–1.25)	0.58	
Men, *n* (%)	102(12.6)	96 (11.8)	0.90 (0.68–1.19)	0.475	0.88 (0.66–1.17)	0.377	
CV mortality							0.525
Women, *n* (%)	47 (5.8)	33 (4.1)	0.70 (0.45–1.09)	0.117	0.66 (0.42–1.03)	0.068	
Men, *n* (%)	102 (12.6)	96 (11.8)	0.87 (0.60–1.28)	0.483	0.81 (0.55–1.20)	0.287	
HF hospitalization							0.699
Women, *n* (%)	60 (7.4)	60 (7.4)	0.98 (0.67–1.40)	0.921	0.93 (0.68–1.33)	0.683	
Men, *n* (%)	69 (8.5)	62 (7.6)	0.87 (0.62–1.23)	0.436	0.87 (0.61–1.24)	0.449	
All-cause mortality							0.19
Women, *n* (%)	81 (10.0)	59 (7.3)	0.73 (0.52–1.01)	0.062	0.68 (0.48–0.96)	0.028	
Men, *n* (%)	91 (11.3)	92 (11.3)	0.97 (0.73–1.30)	0.857	0.95 (0.70–1.28)	0.72	
All-cause hospitalization							0.325
Women, *n* (%)	216 (26.7)	206 (25.4)	0.89 (0.73–1.07)	0.212	0.84 (0.69–1.02)	0.086	
Men, *n* (%)	193 (23.9)	191 (23.6)	0.97 (0.80–1.19)	0.783	0.97 (0.79–1.19)	0.779	

Values are n (%). Cox proportional hazards model to explore the associations between sex and the outcomes. Abbreviations as in ***Table 1****.*

Apart from the fact of the different outcomes in elderly women and men with HFpEF, digging the causes is more important. Another secondary analysis from TOPCAT has reported that outcomes are influenced by key physiological factors that vary according to sex, such as ventricular vascular stiffening, which was the most significant determinant of outcomes in women, whereas in men, overall survival was influenced by heart rate and BNP levels (29). Thus, according to the varied determinants, controlling hypertension is key to improve outcomes in women while heart rate control may be beneficial to improve outcomes in men.

Sex Differences of Spironolactone Treatment in Elderly Heart Failure With Preserved Ejection Fraction Patient

A previous meta-analysis (30) demonstrated that although mineralocorticoid receptor antagonists reduce morbidity and mortality rates in elderly patients with HFpEF more significantly. It also has the same effect on HFpEF, while in the current study, spironolactone therapy failed to reduce the rate of CV mortality or HF-related hospitalization in elderly patients with HFpEF. Moreover, after stratification by sex, there was no significant reduction in the rate of CV mortality and HF-related hospitalization associated with spironolactone in elderly women and men. This result is consistent with the findings of a previous study stating that the interaction between spironolactone and sex was not significant for CV mortality and HF-related hospitalization in the entire TOPCAT cohort (9) and the TOPCAT study restricted to the Americas (17). Although there was no significant sex–treatment interaction, spironolactone treatment had a significantly lower multivariate risk of the all-cause mortality in elderly women, suggesting a possible sex difference in spironolactone treatment concerning all-cause mortality.

Limitations

First, all results are just hypotheses based on *post-hoc*, subgroup analysis selecting subjects older than 70 years from TOPCAT. Second, in order to make the sample size larger, we also included patients from Russia and Georgia, wherein the dose and treatments could vary between the Americas and other regions (Russia and Georgia) (31, 32), which might influence researchers to analyze treatment response. Finally, the *post-hoc* analysis was underpowered to assess sex differences in outcomes and response to treatment above the age of 75 years.

Perspectives and Significance

This study showed that elderly women with HFpEF had worse clinical symptoms but better outcomes including both better survival and lower HF-related hospitalization than elderly men with HFpEF. Although the results were almost similar with studies that were not strictly limited to elderly patients, it did give an implication to us that men were more likely to have worse HF-related hospitalization with aging and provide stronger evidence for gender differences in HFpEF. Exploring the in-depth mechanism of HFpEF prognostic differences caused by sex differences is emergent and may help discover new targets for HFpEF treatment according to sex in the future.

In conclusion, our results showed that elderly women with HFpEF had fewer comorbidities but were more likely to have worse NYHA functional classes and worse quality of life than men. Importantly, elderly women not only had a better survival but also a lower rate of HF-related hospitalization than elderly men. It is worth noting that spironolactone is possibly associated with a reduced rate of all-cause mortality in elderly women.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: the datasets used or analyzed during the current study are available from the National Heart, Lung, and Blood Institute's Biological Specimen and Data Repository Information Coordinating Center (BioLINCC, Calverton, Maryland). NCT00094302 (TOPCAT). https://www.clinicaltrials.gov/ct2/show/NCT00094302.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

The work presented here was carried out in collaboration with all authors. SZ defined the study theme and methods. JS and ST collected clinical data, analyzed the data, interpreted the results, and wrote the paper. YG, LT, HY, XL, ZX, and LF are the attending doctor responsible for reviewing and giving suggestions to the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This research was partly supported by the Natural Science Foundation of China (NSFC) Projects 81670269 (to SZ) and 81801394 (to ST) and Natural Science Foundation of Hunan Province 2019JJ50878 (to ST).

ACKNOWLEDGMENTS

The authors thank the TOPCAT investigators for conducting the research and making the data available for the public. The TOPCAT trial was funded by the National Heart Lung and Blood Institute (NHLBI), Bethesda, MD (N01 HC45207).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.721850/full#supplementary-material

REFERENCES

1. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol.* (2017) 14:591–602. doi: 10.1038/nrcardio.2017.65
2. Tromp J, MacDonald MR, Tay WT, Teng TK, Hung CL, Narasimhan C, et al. Heart failure with preserved ejection fraction in the young. *Circulation.* (2018) 138:2763–73. doi: 10.1161/CIRCULATIONAHA.118.034720
3. Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, et al. Sex differences in heart failure. *Eur Heart J.* (2019) 40:3859–68c. doi: 10.1093/eurheartj/ehz835
4. Savarese G, D'Amario D. Sex differences in heart failure. *Adv Exp Med Biol.* (2018) 1065:529–44. doi: 10.1007/978-3-319-77932-4_32
5. López-Vilella R, Marqués-Sulé E, Laymito Quispe RDP, Sánchez-Lázaro I, Donoso Trenado V, Martínez Dolz L, et al. The female sex confers different prognosis in heart failure: same mortality but more readmissions. *Cardiovasc Med.* (2021) 8:618398. doi: 10.3389/fcvm.2021.618398
6. Gomez-Soto FM, Andrey JL, Garcia-Egido AA, Escobar MA, Romero SP, Garcia-Arjona R, et al. Incidence and mortality of heart failure: a community-based study. *Int J Cardiol.* (2011) 151:40–5. doi: 10.1016/j.ijcard.2010.04.055
7. Brouwers FP, de Boer RA, van der Harst P, Voors AA, Gansevoort RT, Bakker SJ, et al. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. *Eur Heart J.* (2013) 34:1424–31. doi: 10.1093/eurheartj/eht066
8. Lam CS, Carson PE, Anand IS, Rector TS, Kuskowski M, Komajda M, et al. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: the irbesartan in heart failure with preserved ejection fraction (I-PRESERVE) trial. *Circ Heart Fail.* (2012) 5:571–8. doi: 10.1161/CIRCHEARTFAILURE.112.970061
9. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med.* (2014) 370:1383–92. doi: 10.1056/NEJMoa1313731
10. Dewan P, Rorth R, Raparelli V, Campbell RT, Shen L, Jhund PS, et al. Sex-related differences in heart failure with preserved ejection fraction. *Circ Heart Fail.* (2019) 12:e006539. doi: 10.1161/CIRCHEARTFAILURE.119.006539
11. Desai AS, Lewis EF, Li R, Solomon SD, Assmann SF, Boineau R, et al. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. *Am Heart J.* (2011) 162:966–72.e10. doi: 10.1016/j.ahj.2011.09.007
12. Vidán MT, Blaya-Novakova V, Sánchez E, Ortiz J, Serra-Rexach JA, Bueno H. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. *Eur J Heart Fail.* (2016) 18:869–75. doi: 10.1002/ejhf.518
13. Gironés R. Desire for information in the elderly: interactions with patients, family, and physicians. *J Cancer Educ.* (2015) 30:766–73. doi: 10.1007/s13187-014-0760-5
14. Chen J, Dharmarajan K, Wang Y, Krumholz HM. National trends in heart failure hospital stay rates, 2001 to 2009. *J Am Coll Cardiol.* (2013) 61:1078–88. doi: 10.1016/j.jacc.2012.11.057
15. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. heart disease and stroke statistics-2016 update: a report from the American heart association. *Circulation.* (2016) 133:e38–360. doi: 10.1161/CIR.0000000000000350
16. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC, McMurray JJ. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-preserved, and I-PRESERVE? *J Am Coll Cardiol.* (2012) 60:2349–56. doi: 10.1016/j.jacc.2012.04.064
17. Merrill M, Sweitzer NK, Lindenfeld J, Kao DP. Sex Differences in outcomes and responses to spironolactone in heart failure with preserved ejection fraction: a secondary analysis of TOPCAT trial. *JACC Heart failure.* (2019) 7:228–38. doi: 10.1016/j.jchf.2019.01.003
18. Pepine CJ, Merz CNB, El Hajj S, Ferdinand KC, Hamilton MA, Lindley KJ, et al. Heart failure with preserved ejection fraction: similarities and differences between women and men. *Int J Cardiol.* (2020) 304:101–8. doi: 10.1016/j.ijcard.2020.01.003
19. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas city cardiomyopathy questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol.* (2000) 35:1245–55. doi: 10.1016/S0735-1097(00)00531-3

20. Gori M, Lam CS, Gupta DK, Santos AB, Cheng S, Shah AM, et al. Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. *Eur J Heart Fail.* (2014) 16:535–42. doi: 10.1002/ejhf.67
21. Faxén UL, Hage C, Donal E, Daubert JC, Linde C, Lund LH. Patient reported outcome in HFpEF: sex-specific differences in quality of life and association with outcome. *Int J Cardiol.* (2018) 267:128–32. doi: 10.1016/j.ijcard.2018.04.102
22. Beale AL, Nanayakkara S, Segan L, Mariani JA, Maeder MT, van Empel V, et al. Sex Differences in heart failure with preserved ejection fraction pathophysiology: a detailed invasive hemodynamic and echocardiographic analysis. *JACC Heart failure.* (2019) 7:239–49. doi: 10.1016/j.jchf.2019.01.004
23. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol.* (2002) 40:976–82. doi: 10.1016/S0735-1097(02)02059-4
24. Harada E, Mizuno Y, Kugimiya F, Shono M, Maeda H, Yano N, et al. Sex differences in heart failure with preserved ejection fraction reflected by B-type natriuretic peptide level. *Am J Med Sci.* (2018) 356:335–43. doi: 10.1016/j.amjms.2018.06.009
25. Israili ZH. Clinical pharmacokinetics of angiotensin II (AT1) receptor blockers in hypertension. *J Hum Hypertens.* (2000) 14(Suppl.1):S73–86. doi: 10.1038/sj.jhh.1000991
26. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet.* (2009) 48:143–57. doi: 10.2165/00003088-200948030-00001
27. Jochmann N, Stangl K, Garbe E, Baumann G, Stangl V. Female-specific aspects in the pharmacotherapy of chronic cardiovascular diseases. *Eur Heart J.* (2005) 26:1585–95. doi: 10.1093/eurheartj/ehi397
28. Eugene AR. Gender based dosing of metoprolol in the elderly using population pharmacokinetic modeling and simulations. *Int J Clin Pharmacol Toxicol.* (2016) 5:209–15. doi: 10.19070/2167-910X-1600035
29. Beale AL, Nanayakkara S, Kaye DM. Impact of sex on ventricular-vascular stiffness and long-term outcomes in heart failure with preserved ejection fraction: TOPCAT trial substudy. *J Am Heart Assoc.* (2019) 8:e012190. doi: 10.1161/JAHA.119.012190
30. Ferreira JP, Rossello X, Eschalier R, McMurray JJV, Pocock S, Girerd N, et al. MRAs in elderly hf patients: individual patient-data meta-analysis of RALES, EMPAHSIS-HF, and TOPCAT. *JACC Heart Fail.* (2019) 7:1012–21. doi: 10.1016/j.jchf.2019.08.017
31. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, et al. Regional variation in patients and outcomes in the treatment of preserved cardiac function heart failure with an aldosterone antagonist (TOPCAT) trial. *Circulation.* (2015) 131:34–42. doi: 10.1161/CIRCULATIONAHA.114.013255
32. Bristow MR, Enciso JS, Gersh BJ, Grady C, Rice MM, Singh S, et al. Detection and management of geographic disparities in the topcat trial: lessons learned and derivative recommendations. *JACC Basic Transl Sci.* (2016) 1:180–9. doi: 10.1016/j.jacbts.2016.03.001

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Cardiovascular Medicine

MINI REVIEW
published: 13 June 2022
doi: 10.3389/fcvm.2022.877592

Atrial Mitral and Tricuspid Regurgitation: Sex Matters. A Call for Action to Unravel the Differences Between Women and Men

Francisco Gual-Capllonch[1]*, *José Ignacio Sáenz de Ibarra*[1,2], *Antoni Bayés-Genís*[3,4,5] and *Victoria Delgado*[3]

[1] Heart Institute, Clínica Rotger, Palma, Spain, [2] Cardiac Surgery Department, Clínica Rotger, Palma, Spain, [3] Heart Institute, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain, [4] Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain, [5] CIBERCV, Instituto de Salud Carlos III, Madrid, Spain

Atrial functional regurgitation is caused by atrioventricular annulus dilation, with normal leaflets and ventricular dimensions and function within the normal range. Its occurrence, in both mitral and tricuspid valves, implies a worse prognosis due to the hemodynamic derangement they produce, but also constitutes a marker of greater comorbidity and more advanced disease. Predisposing conditions for these heart valve dysfunctions are mainly atrial fibrillation and heart failure with preserved ejection fraction. However, other factors like female sex also may be involved and influence their incidence, especially for atrial tricuspid regurgitation. In the present review, we analyze sex differences in the reported prevalence of atrial mitral and tricuspid regurgitation, and suggest possible mechanisms involved. Finally, we underline potential therapeutic and preventive strategies to reduce the burden of these heart valve disorders and discuss research gaps.

Keywords: female sex, atrial mitral regurgitation, atrial tricuspid regurgitation, heart failure, atrial fibrillation

OPEN ACCESS

Edited by:
Matteo Cameli,
University of Siena, Italy

Reviewed by:
Maria Concetta Pastore,
Università del Piemonte Orientale, Italy

***Correspondence:**
Francisco Gual-Capllonch
fgualc@gmail.com

Specialty section:
This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine

Received: *16 February 2022*
Accepted: *23 May 2022*
Published: *13 June 2022*

Citation:
Gual-Capllonch F, Sáenz de Ibarra JI, Bayés-Genís A and Delgado V (2022) Atrial Mitral and Tricuspid Regurgitation: Sex Matters. A Call for Action to Unravel the Differences Between Women and Men. Front. Cardiovasc. Med. 9:877592. doi: 10.3389/fcvm.2022.877592

Secondary regurgitation of atrioventricular valves is characterized by geometric changes of the valvular apparatus secondary to dilation and/or dysfunction of the ventricles or atria. In contrast to primary atrioventricular regurgitation, the leaflets of the mitral and tricuspid valves are structurally normal. Accordingly, the management of secondary atrioventricular valve regurgitation differs significantly from that of primary regurgitation since it needs to target the underlying mechanism first rather than fixing directly the anatomy and competence of the atrioventricular valve (1). Secondary atrioventricular valve regurgitation due to dilation and dysfunction of the left or right ventricles are associated with an excess of mortality (2–5). Additionally, it is increasingly recognized a specific type of secondary atrioventricular regurgitation caused by mitral or tricuspid valve annulus dilation but with left and right ventricular dimensions and function within the normal range. This type of secondary atrioventricular valve regurgitation is known as atrial mitral regurgitation (AMR) (6) and atrial tricuspid regurgitation (ATR) (7), and is characterized by normal leaflet motion -type I of the Carpentier classification- and a diminished coaptation surface caused by atrial and subsequent atrioventricular annulus valve dilation. The characteristics of the patients with significant AMR and ATR have been described in a few cohort-based studies (6, 7). Patients are characterized for being elderly, having a high prevalence of atrial fibrillation (AF) (8, 9) and heart failure with preserved ejection fraction (HFpEF) (10, 11). Both AF and HFpEF are associated with atrial cardiomyopathy and/or atrial failure (12)

and increased pressure overload of the atria leading to dilation and dysfunction of these cardiac chambers (13). Furthermore, the volume overload imposed by atrioventricular regurgitation may aggravate the atrial and atrioventricular valvular annulus dilation, leading to more advanced atrial myopathy and impairment of atrioventricular valve regurgitation. The excess of mortality and heart failure complications associated to the presence of significant AMR and ATR has been demonstrated in patients with AF and HFpEF (14–17).

While it is well known that women with AF and/or HFpEF (which are associated with AMR and ATR) present at a more advanced course of the disease as compared to men and the implementation of the available therapies may differ between the two sexes (18, 19), the sex differences in AMR and ATR have not been extensively investigated. In the present review article we provide an overview of the sex differences in the prevalence and pathophysiology of AMR and ATR and discuss the potential gaps in knowledge from the diagnostic and therapeutic point of view that need further research in order to improve the outcomes of men and women (**Figure 1**).

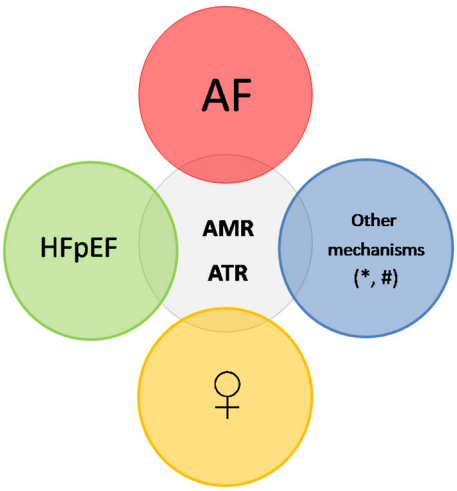


FIGURE 1 | Differents factors contribute to the occurrence of AMR and ATR. The most frequent substrate is AF, which leads to atrial and atrioventricular annulus dilation. HFpEF also elicits AMR and ATR, due to left and right atrial dilation as a result of pressure overload, and also constitutes a frequent trigger for AF. *denotes other variables or mechanisms, which may contribute to the occurrence of AMR, like hypervolemia, hamstringing of the posterior mitral leaflet or insufficient leaflet growth. # denotes other variables or mechanisms, which may contribute to the occurrence of ATR, like older age, hypervolemia, pulmonary hypertension, intracardiac lead or insufficient leaflet growth. Prevalence data and suggested pathophysiologic mechanisms indicate that female patients are at higher risk for these heart valve disorders. AMR, atrial mitral regurgitation; ATR, atrial tricuspid regurgitation; AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; PH, pulmonary hypertension.

DIFFERENCES IN PREVALENCE OF AMR BETWEEN WOMEN AND MEN

Women have a distinct etiologic spectrum of mitral valve disease compared to men, with a higher prevalence of mitral valve prolapse and rheumatic mitral valve regurgitation and lower prevalence of ischemic mitral regurgitation (20, 21). However, differences in prevalence of AMR between sexes is not clearly established, since the definition of AMR is relatively new and not consistent across the various observational studies and there are potential selection biases inherent to the design of the studies. Nonetheless, a number of studies have shown a higher frequency of AMR in women as compared to men. In a community study from Olmsted County, 67% of patients with AMR were women whereas only 41% of patients with secondary mitral regurgitation due to left ventricular dilation and/or dysfunction (ventricular functional regurgitation) and 49% of patients with primary mitral regurgitation were women (22). In a study evaluating the etiology of mitral valve regurgitation of patients referred for surgical mitral valve repair, Glower et al observed that 78% of the patients with isolated mitral annular dilation causing significant mitral regurgitation (surrogate definition of AMR) were women (23). Additionally, a study of 378 consecutive patients with significant secondary mitral regurgitation demonstrated a higher frequency of women with AMR compared to women with ventricular functional regurgitation (64 vs. 35%, $p < 0.001$) (24). In an attempt to understand the efficacy of transcatheter edge-to-edge mitral valve repair, various studies have analyzed the subgroups of patients with AMR and have shown that the frequency of women with AMR was larger than the frequency of men with AMR (25–27).

When analyzing the frequency of AMR from the underlying pathophysiology point of view, the sex differences are less clear. A substudy of the Atherosclerosis Risk in Communities (ARIC) Study investigating the association between AF and mitral regurgitation among patients hospitalized for acute decompensated heart failure showed that among 9,104 patients with HFpEF, 2,501 had significant mitral regurgitation and 4,437 had AF. Although the mechanism of mitral regurgitation was not specified, most probably the majority of the patients had AMR since patients with primary mitral regurgitation would have been excluded as per study design. The proportion of female was comparable among patients with and without AF (67 vs. 65%, respectively) and the frequency of AF increased with increasing severity of mitral regurgitation (28). Therefore, it could be inferred that the prevalence of AMR would be higher in women than in men. In the prospective All Nippon AF In the Elderly (ANAFIE) registry, the echocardiographic substudy including 1,494 elderly patients with non-valvular AF showed that 41% of patients were female and that the proportion of significant AMR was 14%. However, it was not specified if among patients with significant AMR there were more women than men (29).

DIFFERENCES IN PREVALENCE OF ATR BETWEEN WOMEN AND MEN

Several observational studies have shown that tricuspid regurgitation is more prevalent in women than in men (30–32). It was also demonstrated in a retrospective cohort

study of 1,552 patients (49% of women), in which female sex, as well as age, AF, heart failure and right ventricular systolic pressure were significantly associated with tricuspid regurgitation progression (33). Specifically, the association of ATR to female sex has also been recognized (9, 34). Zhao et al analyzed factors involved in determining the severity of ATR in 170 patients with AF (56% of women), and found a female predominance in severe ATR (percentage of women 70 vs. 43% of women in non-severe ATR group, $p < 0.001$) (35). It was also observed in an echocardiographic study of 251 patients (53% of women), in which AF was strongly associated with the occurrence of significant ATR in women (OR 10.1, $p < 0.001$) but not in men (OR 0.91, $p < 0.87$) (36). This was confirmed in a non-selected population of 432 patients (49.1% of women) with AF and without primary valve disease or LV abnormalities. Significant ATR was present in 14.8% of patients, and the associated factors were female sex (OR 2.61, $p < 0.001$), LA dilation and increasing pulmonary artery systolic pressure (37). Regarding ATR in the context of HFpEF, a retrospective observational study of 328 patients detected 8% of significant ATR, with 58% of female patients among this group (11).

POTENTIAL CAUSES FOR THE DIFFERENT FREQUENCY OF AMR AND ATR BETWEEN WOMEN AND MEN

The possible causes for the higher proportion of women with AMR and ATR as compared to men are not completely understood and remain speculative. First, some studies point to distinct factors that may lead to more advanced LA dysfunction and more atrial fibrosis in women than in men (38), higher levels of the inflammatory markers (39, 40), or different electrophysiological properties (41, 42), which may be modulated by sex hormones (43, 44). In addition, the atrioventricular annuli may have differences in composition and cellularity according to sex. In a post-mortem study, El-Busaid et al. analyzed 5-mm sections from the anterior and posterior mitral and tricuspid valve annuli and demonstrated that the myocardium was consistently present in all atrioventricular valve annuli of men but it was nearly absent in women, whereas the atrioventricular valve annuli of women were less elastic and had relatively scattered cells within the collagen matrix compared to the atrioventricular valve annuli of men (45). Insufficient compensatory leaflet remodeling in response to mitral and tricuspid annulus dilation has been demonstrated to play a role in the pathophysiology of AMR (46, 47) and ATR (48, 49). A distinct pattern of leaflet remodeling between sexes cannot be inferred from these studies yet. However, different response of fibroblasts has been demonstrated according to sex (50, 51) and could explain different prevalence of AMR and ATR between men and women. Finally, it is possible that more advanced stage of AF (18) and HFpEF (19) at the time of diagnosis and less aggressive treatment approach may also account for this greater prevalence of AMR and ATR in women.

CLINICAL PERSPECTIVE AND FORWARD THINKING. A CALL FOR ACTION

As a result of this higher susceptibility of women for this type of atrioventricular valve regurgitation as compared to men, strategies aimed at reducing the occurrence of AMR and ATR may have a greater impact in women than in men. The development of AMR and ATR has been associated to worse prognosis, as it entails volume overload and decreased stroke volume, but also because they are both markers of more advanced atrial remodeling due to increased AF burden, diastolic dysfunction, LA failure and pulmonary hypertension. Therefore, early diagnosis and adequate treatment of related conditions may impact on the burden of AMR and ATR, particularly in women. For instance, it is acknowledged that women with AF are diagnosed later and received less rhythm control as compared to men, as demonstrated in the EORP-AF Pilot survey (52). Subsequently, this late diagnosis and underutilization of effective therapies in women with AF may lead to a higher prevalence of significant AMR and ATR. Furthermore, successful pulmonary vein ablation for AF has been associated with lower rates of significant AMR (8) and ATR (53) during follow-up. Earlier detection of HFpEF would also be expected to reduce atrial dilation and dysfunction, and decrease the incidence of AMR. On the other side, timely diagnosis and effective treatment of pulmonary hypertension would reverse right atrial and ventricular dilation and consequently, ATR and secondary tricuspid regurgitation. Additionally, an intracavitary lead may predispose to tricuspid regurgitation (54), or worsen its severity when there are other pathogenic factors like tricuspid annular remodeling or right ventricular dilatation (55). Therefore, mode of pacing should be carefully pondered in women with high risk of tricuspid regurgitation, taking into account that leadless pacing has been also unexpectedly associated with tricuspid regurgitation progression (56). When surgery for AMR is indicated, it has been advocated to perform simultaneously a tricuspid annuloplasty in all patients to prevent future regurgitation, since right atrial enlargement is expected to continue as long as AF or HFpEF persist (57). In the setting of other left-sided valve surgery, tricuspid repair for mild or moderate tricuspid regurgitation with a dilated tricuspid annulus is advocated (class IIa) (1), and should be particularly recommended in women with additional risk factors, in order to prevent more severe forms of ATR. Furthermore, the use of surgical ablation techniques should be considered at the time of mitral valve repair/replacement in patients who are symptomatic and may be considered in patients who are asymptomatic, if feasible and if it does not increase the risk of pacemaker implantation (58). It is conceivable to hypothesize that effective rhythm control may help to halt the progression of atrial remodeling and reduce the risk of failure of mitral valve repair at long-term follow-up, although this has not been demonstrated.

The use of new percutaneous transcatheter therapies may increase in the future for the treatment of symptomatic and refractory significant AMR (25) and ATR (59), which

may be preferred over valve surgery due to old age or comorbidities of these patients. In this regard, early diagnosis and treatment may be imperative in order to ensure that these therapies are effective and the patients are not referred too late when the remodeling process of the atria has reached a point of no return. Finally, echocardiographic follow-up is warranted to evaluate the development of significant AMR or ATR in patients considered at risk, for instance, those with permanent AF, HFpEF, severely dilated atria, mild-to-moderate AMR or ATR, pulmonary hypertension or those with an intracavitary lead.

There is currently a growing interest in the field of AMR and ATR due to their increasing prevalence, prognostic implications and novel therapeutic strategies. In this regard, research on sex differences in pathophysiology, clinical presentation and treatment approach is warranted and could help to better understand these heart valve diseases. On the other hand, a closer attention is required to prevent sex inequity in diagnosis and treatment of AF and HFpEF (18, 60, 61), the underlying conditions of AMR and ATR. Additionally, prompt referral to echocardiography is necessary for an earlier diagnosis, when treatment or preventive strategies may modify the natural history of these heart valve diseases.

CONCLUSIONS

AMR and ATR occur mainly in patients with AF and HFpEF and are associated with higher rates of heart failure and mortality. Observational data demonstrate a higher prevalence of these heart valve diseases in women, especially for ATR. Mechanisms involved in this sex distribution are not well-understood, and may be related to differences in histopathological characteristics of the atrio-ventricular annuli and leaflets and different time-course or treatment strategies of the predisposing conditions in women compared to men. Research gaps include pathophysiological determinants and unbiased incidence of both heart valve diseases, as well as differential treatment strategies. Awareness of these sex-related differences from the clinical ground to the echocardiography laboratories and the investigational setting may contribute to improve the knowledge and better management of these valve disorders in both sexes.

AUTHOR CONTRIBUTIONS

FG-C and VD contributed to the conception and design of the paper. FG-C drafted the manuscript. JS, AB-G, and VD contributed to the critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J.* (2021) 43:561–632. doi: 10.1093/eurheartj/ehab626
2. Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. *J Am Coll Cardiol.* (2015) 65:1231–48. doi: 10.1016/j.jacc.2015.02.009
3. O'Gara PT, Mack MJ. Secondary mitral regurgitation. *N Engl J Med.* (2020) 383:1458–67. doi: 10.1056/NEJMcp1903331
4. Benfari G, Antoine C, Miller WL, Thapa P, Topilsky Y, Rossi A, et al. Excess mortality associated with functional tricuspid regurgitation complicating heart failure with reduced ejection fraction. *Circulation.* (2019) 140:196–206. doi: 10.1161/CIRCULATIONAHA.118.038946
5. Gerçek M, Rudolph V. Secondary tricuspid regurgitation: pathophysiology, incidence and prognosis. *Front Cardiovasc Med.* (2021) 8:701243. doi: 10.3389/fcvm.2021.701243
6. Deferm S, Bertrand PB, Verbrugge FH, Verhaert D, Rega F, Thomas JD, et al. Atrial functional mitral regurgitation: JACC review topic of the week. *J Am Coll Cardiol.* (2019) 73:2465–76. doi: 10.1016/j.jacc.2019.02.061
7. Silbiger JJ. Atrial functional tricuspid regurgitation: an underappreciated cause of secondary tricuspid regurgitation. *Echocardiography.* (2019) 36:954–7. doi: 10.1111/echo.14327
8. Gertz ZM, Raina A, Saghy L, Zado ES, Callans DJ, Marchlinski FE, et al. Evidence of atrial functional mitral regurgitation due to atrial fibrillation: reversal with arrhythmia control. *J Am Coll Cardiol.* (2011) 58:1474–81. doi: 10.1016/j.jacc.2011.06.032
9. Utsunomiya H, Itabashi Y, Mihara H, Berdejo J, Kobayashi S, Siegel RJ, et al. Functional tricuspid regurgitation caused by chronic atrial fibrillation: a real-time 3-dimensional transesophageal echocardiography study. *Circ Cardiovasc Imaging.* (2017) 10:e004897. doi: 10.1161/CIRCIMAGING.116.004897
10. Tamargo M, Obokata M, Reddy YNV, Pislaru SV, Lin G, Egbe AC, et al. Functional mitral regurgitation and left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail.* (2020) 22:489–98. doi: 10.1002/ejhf.1699
11. Harada T, Obokata M, Omote K, Iwano H, Ikoma T, Okada K, et al. Functional tricuspid regurgitation and right atrial remodeling in heart failure with preserved ejection fraction. *Am J Cardiol.* (2022) 162:129–35. doi: 10.1016/j.amjcard.2021.09.021
12. Bisbal F, Baranchuk A, Braunwald E, Bayés de. Luna A, Bayés-Genís A. Atrial failure as a clinical entity. *J Am Coll Cardiol.* (2020) 75:222–32. doi: 10.1016/j.jacc.2019.11.013
13. Omote K, Borlaug BA. Left atrial myopathy in heart failure with preserved ejection fraction. *Circ J.* (2021). doi: 10.1253/circj.CJ-21-0795
14. Abe Y, Akamatsu K, Ito K, Matsumura Y, Shimeno K, Naruko T, et al. Prevalence and prognostic significance of functional mitral and tricuspid regurgitation despite preserved left ventricular ejection fraction in atrial fibrillation patients. *Circ J.* (2018) 82:1451–8. doi: 10.1253/circj.CJ-17-1334
15. Saito C, Minami Y, Arai K, Haruki S, Yagishita Y, Jujo K, et al. Prevalence, clinical characteristics, and outcome of atrial functional mitral regurgitation in hospitalized heart failure patients with atrial fibrillation. *J Cardiol.* (2018) 72:292–9. doi: 10.1016/j.jjcc.2018.04.002
16. Prapan N, Ratanasit N, Karaketklang K. Significant functional tricuspid regurgitation portends poor outcomes in patients with atrial fibrillation and preserved left ventricular ejection fraction. *BMC Cardiovasc Disord.* (2020) 20:433. doi: 10.1186/s12872-020-01716-6
17. Wang TKM, Akyuz K, Mentias A, Kirincich J, Duran Crane A, Xu S, et al. contemporary etiologies, outcomes, and novel risk score for isolated tricuspid regurgitation. *JACC Cardiovasc Imaging.* (2021) 15:731–44. doi: 10.1016/j.jcmg.2021.10.015
18. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. *Nat Rev Cardiol.* (2016) 13:321–32. doi: 10.1038/nrcardio.2016.45
19. Dewan P, Rørth R, Raparelli V, Campbell RT, Shen L, Jhund PS, et al. Sex-related differences in heart failure with preserved ejection fraction. *Circ Heart Fail.* (2019) 12:e006539 doi: 10.1161/CIRCHEARTFAILURE.119.006539

20. Vakamudi S, Jellis C, Mick S, Wu Y, Gillinov AM, Mihaljevic T, et al. Sex differences in the etiology of surgical mitral valve disease. *Circulation.* (2018) 138:1749–51. doi: 10.1161/CIRCULATIONAHA.118.035789
21. Martínez-Sellés M, García-Fernández MA, Moreno M, Larios E, García-Robles JA, Pinto A. Influence of gender on the etiology of mitral regurgitation. *Rev Esp Cardiol.* (2006) 59:1335–8. doi: 10.1016/S1885-5857(07)60091-7
22. Dziadzko V, Dziadzko M, Medina-Inojosa JR, Benfari G, Michelena HI, Crestanello JA, et al. Causes and mechanisms of isolated mitral regurgitation in the community: clinical context and outcome. *Eur Heart J.* (2019) 40:2194–202. doi: 10.1093/eurheartj/ehz314
23. Glower DD, Bashore TM, Harrison JK, Wang A, Gehrig T, Rankin JS. Pure annular dilation as a cause of mitral regurgitation: a clinically distinct entity of female heart disease. *J Heart Valve Dis.* (2009) 18:284–8.
24. Okamoto C, Okada A, Nishimura K, Moriuchi K, Amano M, Takahama H, et al. Prognostic comparison of atrial and ventricular functional mitral regurgitation. *Open Heart.* (2021) 8:e001574. doi: 10.1136/openhrt-2021-001574
25. Popolo Rubbio A, Testa L, Grasso C, Sisinni A, Tusa M, Agricola E, et al. Transcatheter edge-to-edge mitral valve repair in atrial functional mitral regurgitation: insights from the multi-center MITRA-TUNE registry. *Int J Cardiol.* (2022) 349:39–45 doi: 10.1016/j.ijcard.2021.11.027
26. Claeys MJ, Debonnaire P, Bracke V, Bilotta G, Shkarpa N, Vanderheyden M, et al. Clinical and hemodynamic effects of percutaneous edge-to-edge mitral valve repair in atrial vs. ventricular functional mitral regurgitation. *Am J Cardiol.* (2021) 161:70–5. doi: 10.1016/j.amjcard.2021.08.062
27. Benito-González T, Carrasco-Chinchilla F, Estévez-Loureiro R, Pascual I, Arzamendi D, Garrote-Coloma C, et al. Clinical and echocardiographic outcomes of transcatheter mitral valve repair in atrial functional mitral regurgitation. *Int J Cardiol.* (2021) 345:29–35. doi: 10.1016/j.ijcard.2021.09.056
28. Arora S, Brown ZD, Sivaraj K, Hendrickson MJ, Mazzella AJ, Chang PP, et al. The relationship between atrial fibrillation, mitral regurgitation, and heart failure subtype: the ARIC study. *J Card Fail.* (2021). doi: 10.1016/j.cardfail.2021.10.015. [Epub ahead of print].
29. Hiasa KI, Kaku H, Kawahara G, Inoue H, Yamashita T, Akao M, et al. Echocardiographic structure and function in elderly patients with atrial fibrillation in Japan-The ANAFIE echocardiographic substudy. *Circ J.* (2022) 86:222–32. doi: 10.1253/circj.CJ-21-0180
30. Ong K, Yu G, Jue J. Prevalence and spectrum of conditions associated with severe tricuspid regurgitation. *Echocardiography.* (2014) 31:558–62. doi: 10.1111/echo.12420
31. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol.* (1999) 83:897–902. doi: 10.1016/S0002-9149(98)01064-9
32. Mutlak D, Aronson D, Lessick J, Reisner SA, Dabbah S, Agmon Y. Functional tricuspid regurgitation in patients with pulmonary hypertension: is pulmonary artery pressure the only determinant of regurgitation severity? *Chest.* (2009) 135:115–21. doi: 10.1378/chest.08-0277
33. Mutlak D, Khalil J, Lessick J, Kehat I, Agmon Y, Aronson D. risk factors for the development of functional tricuspid regurgitation and their population-attributable fractions. *JACC Cardiovasc Imaging.* (2020) 13:1643–51. doi: 10.1016/j.jcmg.2020.01.015
34. Topilsky Y, Nkomo VT, Vatury O, Michelena HI, Letourneau T, Suri RM, et al. Clinical outcome of isolated tricuspid regurgitation. *JACC Cardiovasc Imaging.* (2014) 7:1185–94. doi: 10.1016/j.jcmg.2014.07.018
35. Zhao SX, Soltanzad N, Swaminathan A, Ogden WD, Schiller NB. Frequency and associated clinical features of functional tricuspid regurgitation in patients with chronic atrial fibrillation. *Am J Cardiol.* (2017) 119:1371–7 doi: 10.1016/j.amjcard.2017.01.037
36. Gual-Capllonch F, Cediel G, Ferrer E, Teis A, Juncà G, Vallejo N, et al. Sex-related differences in the mechanism of functional tricuspid regurgitation. *Heart Lung Circ.* (2021) 30:e16–22. doi: 10.1016/j.hlc.2020.06.018
37. Gual-Capllonch F, Cediel G, Teis A, Ferrer-Sistach E, Borrellas A, Juncà G, et al. Prevalence and factors associated with atrial mitral and tricuspid regurgitation in patients with atrial fibrillation. *Echocardiography.* (2021) 38:2043–51. doi: 10.1111/echo.15257
38. Cochet H, Mouries A, Nivet H, Sacher F, Derval N, Denis A, et al. Age, atrial fibrillation, and structural heart disease are the main determinants of left atrial fibrosis detected by delayed-enhanced magnetic resonance imaging in a general cardiology population. *J Cardiovasc Electrophysiol.* (2015) 26:484–92. doi: 10.1111/jce.12651
39. Khera A, McGuire DK, Murphy SA, Stanek HG, Das SR, Vongpatanasin W, et al. Race and gender differences in C-reactive protein levels. *J Am Coll Cardiol.* (2005) 46:464–9. doi: 10.1016/j.jacc.2005.04.051
40. Ix JH, Katz R, Kestenbaum BR, de Boer IH, Chonchol M, Mukamal KJ, et al. Fibroblast growth factor-23 and death, heart failure, and cardiovascular events in community-living individuals: CHS (Cardiovascular Health Study). *J Am Coll Cardiol.* (2012) 60:200–7. doi: 10.1016/j.jacc.2012.03.040
41. Takigawa M, Kuwahara T, Takahashi A, Watari Y, Okubo K, Takahashi Y, et al. Differences in catheter ablation of paroxysmal atrial fibrillation between males and females. *Int J Cardiol.* (2013) 168:1984–91. doi: 10.1016/j.ijcard.2012.12.101
42. Kim JS, Shin SY, Kang JH, Yong HS, Na JO, Choi CU, et al. influence of sex on the association between epicardial adipose tissue and left atrial transport function in patients with atrial fibrillation: a multislice computed tomography study. *J Am Heart Assoc.* (2017) 6:e006077. doi: 10.1161/JAHA.117.006077
43. Yang PC, Kurokawa J, Furukawa T, Clancy CE. Acute effects of sex steroid hormones on susceptibility to cardiac arrhythmias: a simulation study. *PLoS Comput Biol.* (2010) 6:e1000658. doi: 10.1371/journal.pcbi.1000658
44. Tsai WC, Chen YC, Lin YK, Chen SA, Chen YJ. Sex differences in the electrophysiological characteristics of pulmonary veins and left atrium and their clinical implication in atrial fibrillation. *Circ Arrhythm Electrophysiol.* (2011) 4:550–9. doi: 10.1161/CIRCEP.111.961995
45. El-Busaid H, Hassan S, Odula P. Ogeng'o J, Ndung'u B. Sex variations in the structure of human atrioventricular annuli. *Folia Morphol.* (2012) 71:23–7.
46. Kim DH, Heo R, Handschumacher MD, Lee S, Choi YS, Kim KR, et al. Mitral valve adaptation to isolated annular dilation: insights into the mechanism of atrial functional mitral regurgitation. *JACC Cardiovasc Imaging.* (2019) 12:665–77. doi: 10.1016/j.jcmg.2017.09.013
47. Kagiyama N, Hayashida A, Toki M, Fukuda S, Ohara M, Hirohata A, et al. Insufficient leaflet remodeling in patients with atrial fibrillation: association with the severity of mitral regurgitation. *Circ Cardiovasc Imaging.* (2017) 10:e005451. doi: 10.1161/CIRCIMAGING.116.005451
48. Afilalo J, Grapsa J, Nihoyannopoulos P, Beaudoin J, Gibbs JS, Channick RN, et al. Leaflet area as a determinant of tricuspid regurgitation severity in patients with pulmonary hypertension. *Circ Cardiovasc Imaging.* (2015) 8:e002714. doi: 10.1161/CIRCIMAGING.114.002714
49. Van Rosendael PJ, Joyce E, Katsanos S, Debonnaire P, Kamperidis V, van der Kley F, et al. Tricuspid valve remodelling in functional tricuspid regurgitation: multidetector row computed tomography insights. *Eur Heart J Cardiovasc Imaging.* (2016) 17:96–105. doi: 10.1093/ehjci/jev140
50. Dworatzek E, Mahmoodzadeh S, Schriever C, Kusumoto K, Kramer L, Santos G, et al. Sex-specific regulation of collagen I and III expression by 17β-Estradiol in cardiac fibroblasts: role of estrogen receptors. *Cardiovasc Res.* (2019) 115:315–27. doi: 10.1093/cvr/cvy185
51. Walker CJ, Schroeder ME, Aguado BA, Anseth KS, Leinwand LA. Matters of the heart: cellular sex differences. *J Mol Cell Cardiol.* (2021) 160:42–55. doi: 10.1016/j.yjmcc.2021.04.010
52. Lip GY, Laroche C, Boriani G, Cimaglia P, Dan GA, Santini M, et al. Sex-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Observational Research Programme Pilot survey on Atrial Fibrillation. *Europace.* (2015) 17:24–31. doi: 10.1093/europace/euu155
53. Markman TM, Plappert T, De Feria Alsina A, Levin M, Amankwah N, Sheth S, et al. Improvement in tricuspid regurgitation following catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol.* (2020) 31:2883–8. doi: 10.1111/jce.14707
54. Chang JD, Manning WJ, Ebrille E, Zimetbaum PJ. Tricuspid valve dysfunction following pacemaker or cardioverter-defibrillator implantation. *J Am Coll Cardiol.* (2017) 69:2331–41. doi: 10.1016/j.jacc.2017.02.055
55. Riesenhuber M, Spannbauer A, Gwechenberger M, Pezawas T, Schukro C, Stix G, et al. Pacemaker lead-associated tricuspid regurgitation in patients with or without pre-existing right ventricular dilatation. *Clin Res Cardiol.* (2021) 110:884–94. doi: 10.1007/s00392-021-01812-3

56. Beurskens NEG, Tjong FVY, de Bruin-Bon RHA, Dasselaar KJ, Kuijt WJ, Wilde AAM, et al. Impact of leadless pacemaker therapy on cardiac and atrioventricular valve function through 12 months of follow-up. *Circ Arrhythm Electrophysiol.* (2019) 12:e007124. doi: 10.1161/CIRCEP.118.007124
57. Shibata T, Takahashi Y, Fujii H, Morisaki A, Abe Y. Surgical considerations for atrial functional regurgitation of the mitral and tricuspid valves based on the etiological mechanism. *Gen Thorac Cardiovasc Surg.* (2021) 69:1041–9. doi: 10.1007/s11748-021-01629-x
58. Gillinov AM, Gelijns AC, Parides MK, DeRose JJ Jr, Moskowitz AJ, Voisine P, et al. Surgical ablation of atrial fibrillation during mitral-valve surgery. *N Engl J Med.* (2015) 372:1399–409. doi: 10.1056/NEJMoa1500528
59. Lurz P. Stephan von Bardeleben R, Weber M, Sitges M, Sorajja P, Hausleiter J, et al. Transcatheter Edge-to-Edge Repair for Treatment of Tricuspid Regurgitation. *J Am Coll Cardiol.* (2021) 77:229–39. doi: 10.1016/j.jacc.2020.11.038
60. Sotomi Y, Hikoso S, Nakatani D, Mizuno H, Okada K, Dohi T, et al. Sex differences in heart failure with preserved ejection fraction. *J Am Heart Assoc.* (2021) 10:e018574. doi: 10.1161/JAHA.120.018574
61. Farrero M, Bellumkonda L, Gómez Otero I, Díaz Molina B. Sex and heart failure treatment prescription and adherence. *Front Cardiovasc Med.* (2021) 8:630141. doi: 10.3389/fcvm.2021.630141

Conflict of Interest: VD received speaker fees from Abbott Vascular, Edwards Lifesciences, GE healthcare, Medtronic, MSD and Novartis.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 13 July 2022
doi: 10.3389/fcvm.2022.912802

Gender Differences in Cardiogenic Shock Patients: Clinical Features, Risk Prediction, and Outcomes in a Hub Center

Sara Lozano-Jiménez[1,2†], Reyes Iranzo-Valero[3†], Javier Segovia-Cubero[1], Manuel Gómez-Bueno[1], Mercedes Rivas-Lasarte[1], Cristina Mitroi[1], Juan Manuel Escudier-Villa[1], Juan Francisco Oteo-Dominguez[1], Jose María Vieitez-Florez[1], Susana Villar-García[4] and Francisco José Hernández-Pérez[1†]*

[1] Department of Cardiology, Hospital Puerta de Hierro, Madrid, Spain, [2] Centre of Biomedical Research in Cardiovascular Diseases (CIBERCV), Carlos III, Madrid, Spain, [3] Department of Anesthesiology, Hospital Puerta de Hierro, Madrid, Spain, [4] Department of Cardiovascular Surgery, Hospital Puerta de Hierro, Madrid, Spain

Introduction: There is scarce knowledge about gender differences in clinical presentation, management, use of risk stratification tools and prognosis in cardiogenic shock (CS) patients.

Purpose: The primary endpoint was to investigate the differences in characteristics, management, and in-hospital mortality according to gender in a cohort of CS patients admitted to a tertiary hub center. The secondary endpoint was to evaluate the prognostic performance of the Society of Cardiovascular Angiography and Interventions (SCAI) classification in predicting in-hospital mortality according to sex.

Methods: This is a retrospective single-Center cohort study of CS patients treated by a multidisciplinary shock team between September 2014 and December 2020. Baseline characteristics and clinical outcomes according to gender were registered. Discrimination of SCAI classification was assessed using the area under the receiver operating characteristic curve (AUC).

Results: Overall, 163 patients were included, 39 of them female (24%). Mean age of the overall cohort was 55 years (44–62), similar between groups. Compared with men, women were less likely to be smokers and the prevalence of COPD and diabetes mellitus was significantly lower in this group ($p < 0.05$). Postcardiotomy (44 vs. 31%) and fulminant myocarditis (13 vs. 2%) were more frequent etiologies in females than in males ($p = 0.01$), whereas acute myocardial infarction was less common among females (13 vs. 33%). Regarding management, the use of temporary mechanical circulatory support, mechanical ventilation, or renal replacement therapy was frequent and no different between the groups (88, 87, and 49%, respectively, in females vs. 42, 91, and 41% in males, $p > 0.05$). In-hospital survival in the overall cohort was 53%, without differences between groups (52% in females vs. 55% in males, $p = 0.76$).

OPEN ACCESS

Edited by:
Manuel Martínez-Sellés,
Gregorio Marañón Hospital, Spain

Reviewed by:
Vojko Kanic,
Maribor University Medical Centre, Slovenia
Vjekoslav Tomulic,
Clinical Hospital Centre Rijeka, Croatia

***Correspondence:**
Sara Lozano-Jiménez
sara12s@hotmail.com

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine

Received: 04 April 2022
Accepted: 22 June 2022
Published: 13 July 2022

Citation:
Lozano-Jiménez S, Iranzo-Valero R, Segovia-Cubero J, Gómez-Bueno M, Rivas-Lasarte M, Mitroi C, Escudier-Villa JM, Oteo-Dominguez JF, Vieitez-Florez JM, Villar-García S and Hernández-Pérez FJ (2022) Gender Differences in Cardiogenic Shock Patients: Clinical Features, Risk Prediction, and Outcomes in a Hub Center. Front. Cardiovasc. Med. 9:912802. doi: 10.3389/fcvm.2022.912802

Most of the patients (60.7%) were in SCAIE at presentation without differences between sexes. The SCAI classification showed a moderate ability for predicting in-hospital mortality (overall, AUC: 0.653, 95% CI 0.582–0.725). The AUC was 0.636 for women (95% CI 0.491–0.780) and 0.658 for men (95% CI 0.575–0.740).

Conclusions: Only one in four of patients treated at a dedicated CS team were female. This may reflect differences in prevalence of severe heart disease at young (<65) ages, although a patient-selection bias cannot be ruled out. In this very high-risk CS population of multiple etiologies, overall, in-hospital survival was slightly above 50% and showed no differences between sexes. Treatment approaches, procedures, and SCAI risk stratification performance did not show gender disparities among treated patients.

Keywords: cardiogenic shock, gender, SCAI classification, heart failure, prognosis, mortality

INTRODUCTION

Cardiogenic shock (CS) is a life-threatening condition. In spite of recent advances in its management, morbidity and mortality remains high (1) and only emergency revascularization in CS complicating acute myocardial infraction (AMI) has shown a significant survival benefit (2).

There is scarce knowledge about gender differences in clinical presentation and prognosis of CS. Previous studies in this field are based on AMI-related CS and women tended to have a higher mortality (3–5). However, it has been argued that this fact might be explained by an older age in female patients. Furthermore, results among the different authors are conflicting and there is a lack of consensus on whether gender is associated with outcomes in CS (6).

On the other hand, a classification of the Society of Cardiovascular Angiography and Interventions (SCAI) has been recently proposed. It can be easily obtained at bedside and stratifies CS in 5 stages from least to greatest severity (A: "at risk"; B: "beginning"; C: "Classic"; D: "Deteriorating" or E: "Extremis") (7). There are insufficient data regarding to gender-associated differences for this risk stratification tool.

Therefore, the primary end-point of this study was to investigate the influence of gender on in-hospital mortality. Secondary end-points were to evaluate differences between gender regarding comorbidities, clinical presentation and treatment approaches for CS. Finally, we analyzed the yield of SCAI classification in both sexes.

Abbreviations: ACS, Acute coronary syndrome; AMI, Acute Myocardial infarction; AUC, Area under the curve; CHF, Chronic heart failure; COPD, Chronic obstructive pulmonary disease; CS, Cardiogenic shock; ECMO, venoarterial extracorporeal membrane oxygenation; LVAD, Left ventricular assist device; MCS, Mechanical circulatory support; ROC curves, Receiver operating characteristic; SCAI, Society of Cardiovascular Angiography and Interventions; VIS, Vasoactive inotropic score.

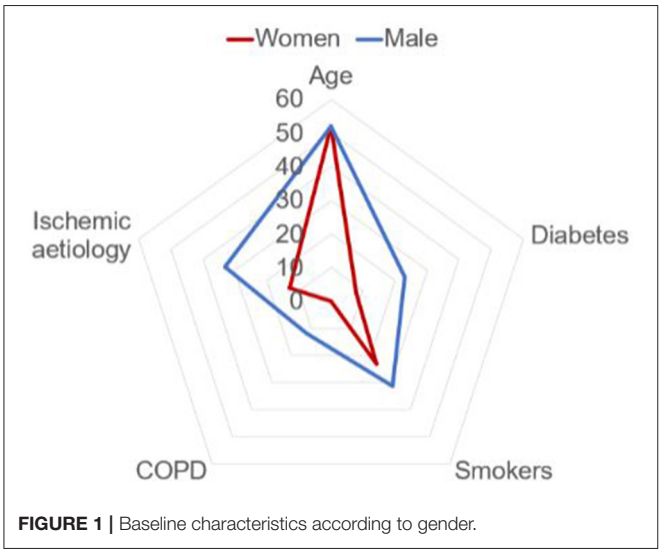


FIGURE 1 | Baseline characteristics according to gender.

MATERIALS AND METHODS

Study Design, Inclusion Criteria and Data Collection

We performed a retrospective observational study of a cohort of CS patients managed by a multidisciplinary team in a hub center between September 2014 and December 2020. It has been considered to be managed in this Unit those patients with refractory cardiogenic shock and/or patients who are candidates for advanced heart failure therapies, such as transplantation or LVAD (8).

Baseline characteristics and clinical outcomes according to gender were registered. Mean age of the overall cohort was 55 years (44–62). CS was defined by a systolic blood pressure < 90 mmHg for more than 30 min or inotropes required to maintain a mean blood pressure > 65 mmHg and signs of impaired organ perfusion with at least one of the following: altered mental status, urine output <30 ml/h or serum lactate > 2 mmol/l. Patients were assigned to one of the five SCAI stages by two independent cardiologists, who were blind to each other's classification. SCAI CS subgroups were interpreted considering the recent consensus statement (7); based on clinical, laboratory, and hemodynamic parameters. In our case, due to the nature of the CS Unit, all the patients fulfilled at least

TABLE 1 | Baseline characteristics, treatment, and outcomes according to gender.

		Male ($n = 124$)	Female ($n = 39$)	*P*-value
Mean age (years)		52 (44–62)	53 (43–62)	0.91
Comorbidities: *n* (%)				
Hypertension		48 (39)	12 (31)	0.37
Dyslipidemia		44 (35)	8 (21)	0.07
Diabetes mellitus		29 (23)	3 (8)	0.03
Smoking		38 (31)	9 (23)	0.01
Chronic kidney disease		14 (11)	2 (5)	0.25
COPD		15 (12)	0 (0)	0.02
Prior stroke		9 (7)	6 (15)	0.12
Previous heart disease		73 (59)	23 (59)	0.09
Etiology of CS: *n* (%)				
ADHF	Overall	36 (30)	9 (23)	0.01
	- Ischemic	10 (28)	2 (22)	0.01
	- Non ischemic	26 (72)	7 (78)	
Acute myocardial infarction		40 (33)	5 (13)	
Postcardiotomy	Overall	37 (31)	17 (44)	
	- CABG	15 (41)	4 (23)	
	- Valvular heart surgery	12 (32)	8 (47)	
	- Acute MI	0	0	
	- PGD	9 (24)	4 (23)	
	- Other causes	1 (3)	1 (7)	
Myocarditis		3 (2)	5 (13)	
Other causes		8 (6)	3 (8)	
Clinical presentation: *n* (%)				
SCAI C		6 (5)	3 (8)	0.42
SCAI D		45 (36)	10 (26)	
SCAI E		73 (59)	26 (67)	
Prior cardiac arrest		43 (35)	10 (26)	0.29
Mean blood pressure (mmHg)		81 ± 17	73 ± 17	0.86
Treatment and procedures: *n* (%)				
Vasoactive-inotropic score in the first 24 h		44 ± 5	50 ± 10	0.74
Intra-aortic balloon pump		73 (59)	22 (56)	0.78
Mechanical circulatory support (MCS)		99 (80)	33 (85)	0.24
VA-ECMO		52 (42)	24 (62)	
Levitronix Centrimag		30 (24)	7 (18)	
Impella		17 (14)	2 (5)	
Mechanical ventilation		113 (91)	34 (87)	0.47
Renal replacement therapy		51 (41)	19 (49)	0.40
Outcome				
Initial mortality due to CS		52 (42%)	17 (43%)	0.88
Recovery		35 (28%)	12 (31%)	
Heart replacement (Heart transplant or LVAD)		37 (30%)	10 (26%)	
Overall in-hospital survival		67 (55%)	20 (52%)	0.76

ADHF, Acute decompensation of chronic heart failure; CABG, Coronary Artery Bypass Graft surgery; COPD, Chronic obstructive pulmonary disease; CS, Cardiogenic shock; LVAD, Left ventricular assist device; MCS, Mechanical circulatory support; MI, Myocardial infarction; PGD, Primary Graft Dysfunction; SCAI, Society of Cardiovascular Angiography and Interventions; VA- ECMO, venoarterial extracorporeal membrane oxygenation. Categorical variables are expressed as No. (%) and continuous variables as mean ± standard deviation or median (interquartile range).

stage C. Most patients were classified as stage D due to clinical and/or biochemical worsening in the first hours, addition of 2 or more vasoactive drugs, and/or need or change of mechanical circulatory support (MCS). Those classified as stage E had combinations of some or all of the following characteristics: cardiac arrest requiring cardiopulmonary resuscitation and/or venoarterial extracorporeal membrane oxygenation (ECMO), mechanical ventilation, profound acidosis (pH $<$ 7.2) and/or lactate $>$ 5 mmol/l, refractory ventricular arrhythmias or sustained hypotension despite maximum support.

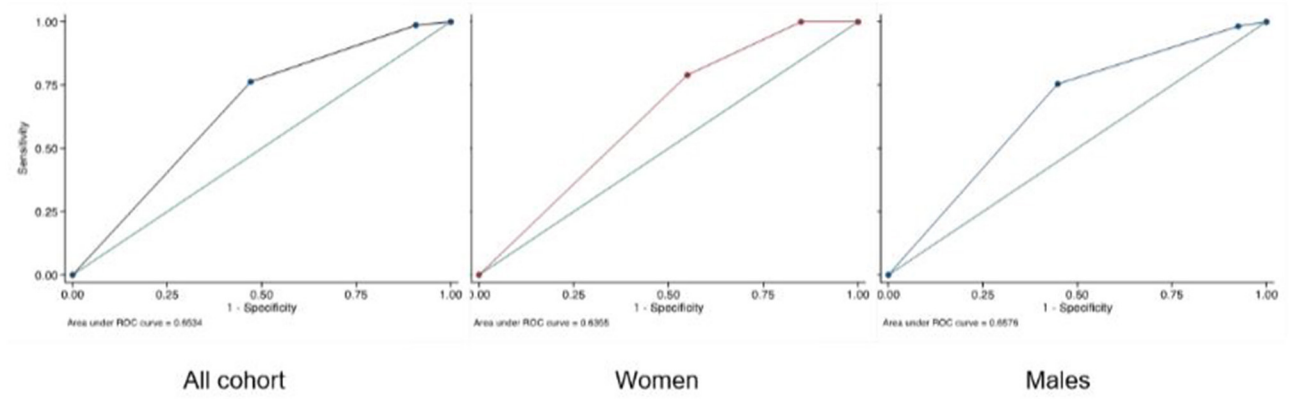


FIGURE 2 | AUC of SCAI classification.

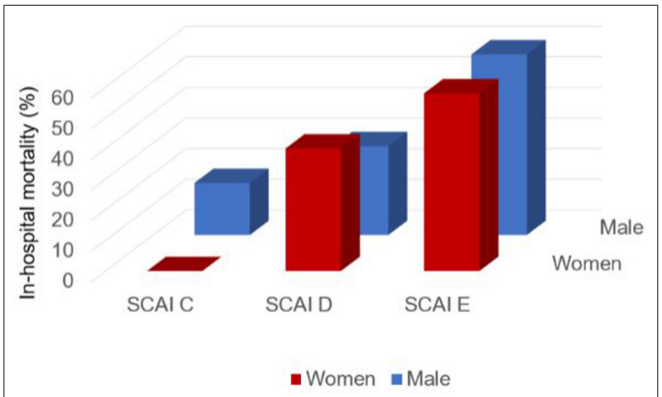


FIGURE 3 | In-hospital mortality according to SCAI and gender.

The study was approved by Local Institutional Ethics Committee.

Statistical Analysis

Continuous variables are reported as mean (standard deviation) or median (interquartile range) as appropriate. For categorical variables, frequencies and percentages are presented. Statistical differences were analyzed using T-student (for continuous variables) or the χ^2 test/fisher's exact test (for categorical variables). Discrimination of the SCAI classification was assessed with the area under the receiver-operating characteristic curve (AUC) and its calibration with the Hosmer-Lemeshow test. Two-tailed $p < 0.05$ were considered statistically significant. All analyses were performed using statistical software STATA IC/13 (Stata corp, College Station, TX, USA).

RESULTS

Sex-Differences in Baseline Characteristics of the Study Population

Overall, 163 patients were included and 39 of them female (24%). Mean age of the overall cohort was 55 years (44–62), similar between groups. Compared with men, women were less likely to be smokers, and the prevalence of COPD and diabetes mellitus was significantly lower in this group ($p < 0.05$). Postcardiotomy (44 vs. 31%) and fulminant myocarditis (13 vs. 2%) were more frequent etiologies in females than in males, whereas CS was less often related to AMI in women (13 vs. 33%) (**Figure 1**). However, other relevant characteristics did not differ between both sexes (**Table 1**).

Management and Outcomes According to Sex

Regarding management, the use of temporary MCS was high and no different between the groups (female 33/39 [84%] vs. male 99/124 [80%]; $p = 0.24$). The vast majority of patients required only one MCS procedure (138/163; 85%). However, 25 patients (15%) needed two or more devices. Most of them were converted to Levitronix Centrimag® (21/25; 84%). Likewise, escalation of MCS did not differ according to gender (13% in female patients vs. 19% in male, $p = 0.61$).

Furthermore, the use of mechanical ventilation (87 vs. 91%) and renal replacement therapy (49 vs. 41%) were not significantly different either.

In-hospital survival rate in the overall cohort was 53%, without differences between the groups (female 20/39 [52%] vs. male 67/124 [55%], $p = 0.76$). Likewise, use of advanced heart failure therapies such as heart transplantation or left ventricular assist device (LVAD) did not differ according to gender (26 vs. 30%, $p = 0.96$).

Performance of the SCAI Classification in Predicting In-hospital Mortality

No significant differences were observed regarding SCAI classification according to gender ($p = 0.42$), with the highest proportion of patients in SCAI class E (60.7%).

The SCAI classification showed a moderate ability for predicting in-hospital mortality AUC: 0.653 (95% CI 0.582–0.725). The AUC was 0.636 in women (95% CI 0.491–0.780) and 0.658 in men (95% CI 0.575–0.740) (**Figure 2**). **Figure 3** shows

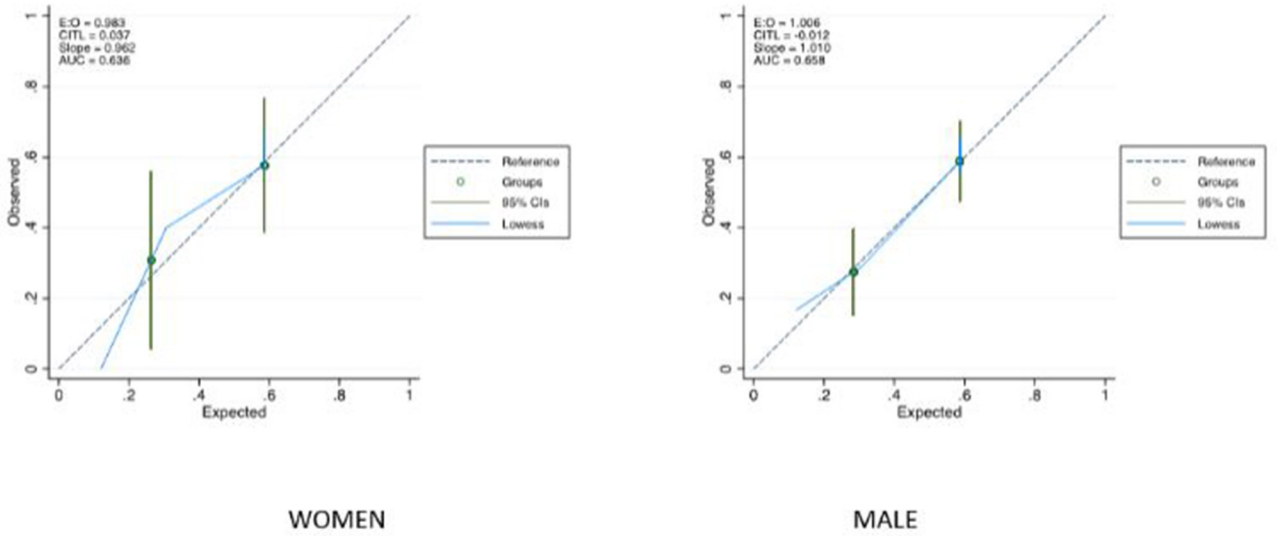


FIGURE 4 | Calibration of SCAI classification.

in-hospital mortality in each stage according to gender. It was 0, 25, and 42% in stages C, D, and E respectively in female patients and 13, 26, and 54% in stages C, D and E respectively in male ($p = 0.06$). Calibration of the SCAI classification was good (Hosmer-Lemeshow $p = 0.92$) and similar between sexes (**Figure 4**).

There were no differences in performance between SCAI categorization in the overall cohort and VIS score. This last stratification tool had an AUC of 0.67 (CI 95% 0.57–0.74).

DISCUSSION

This study concluded that there is a high (47%) in-hospital mortality in patients with cardiogenic shock of any etiology in our population and mortality risk did not vary significantly between sexes. Treatment approaches and procedures performed in our center were equitable and no sex disparities were observed.

Clinical evidence in this field is scarce. There are only few divergent observational studies addressing CS complicating AMI (3, 4) whose results cannot be extrapolated to any other different etiology. In addition, the proportion of ACS-related CS is significantly lower in women (9). In contrast, our cohort of patients includes a wide range of underlying conditions and provides valuable insight into this complex area.

Moreover, women are underrepresented, as the proportion of women included in previous series is relatively low (ranging from 25 to 45%) as it happened in our case. It is also remarkable that they are usually older and suffer from more comorbidities (9–11) which might be associated with a worse prognosis. Conversely, our cohort is quite balanced with respect to baseline characteristics and prognostic factors. However, it is remarkable that only 24% of our cohort are women. We hypothesize that this low percentage may reflect a low prevalence of severe heart disease at young ages in female patients, although a patient-selection bias cannot be ruled out.

Some authors suggest that management disparities may also play a crucial role in ACS-related CS (12). Vallabhajosyula et al. described that young women are treated less aggressively with coronary angiography and experience higher in-hospital mortality than men (13). On the other hand, this inequity seems to be less noticeable in patients requiring advanced support treatment. The use of temporary mechanical circulatory support, mechanical ventilation or renal replacement therapy was not significantly different in both groups in the vast majority of studies (14, 15).

The major limitation of our single-center study is its observational retrospective design, with a modest sample size, which makes necessary further validation in a prospective trial. It is of paramount importance to highlight that our results must be contextualized in a CS cohort of high severity and complexity, with a high accessibility to heart transplantation in an urgent code.

Noteworthy is also the modest ability of SCAI classification for predicting in-hospital mortality, similar in both sexes. To our knowledge, this fact has not been previously described in the literature. Despite the limitations mentioned above, we strongly believe that SCAI classification is easy to apply in clinical practice and provides useful baseline information about the prognosis of patients in CS.

CONCLUSIONS

The management of cardiogenic shock remains a clinical challenge even in hub centers. Almost one in four patients in this series are women. In- hospital mortality risk is still high (47%

in our population) and did not differ significantly between both sexes. Treatment approaches and procedures performed were equitable and no sex disparities were observed in our cohort. The yield of SCAI risk classification was only fair and similar in both genders.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hospital Puerta de Hierro. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SL and RI wrote the manuscript and collaborated in data collection. FH and JS conceived of the presented idea and supervised the findings of this work. CM and MR developed the theory, performed the computations, and verified the analytical methods. SV, JE, JO, and JV verified the numerical results and support the results. All authors discussed the results and contributed to the final manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by Fundación Investigación Puerta de Hierro.

REFERENCES

1. Berg DD, Bohula EA, van Diepen S, Katz JN, Alviar CL-, Baird-Zars V, et al. Epidemiology of shock in contemporary cardiac intensive care units. *Circ Cardiovasc Qual Outcomes.* (2019) 12:e005618. doi: 10.1161/CIRCOUTCOMES.119.005618
2. Hochman JS, Sleeper LA, Webb JG, Sanborn T, Harvey MD, White DS, et al. Early revascularization in acute myocardial infarction complicate by cardiogenic shock. SHOCK investigators should we emergently revascularize occluded coronaries for cardiogenic shock. *N Engl J Med.* (1999) 341:625–34. doi: 10.1056/NEJM199908263410901
3. Rubini Gimenez M, Zeymer U, Desch S, Waha-Thiele S, Ouarrak T, Poess J, et al. Sex-specific management in patients with acute myocardial infarction and cardiogenic shock: a substudy of the CULPRIT-SHOCK trial. *Circulation.* (2020) 13:e008537. doi: 10.1161/CIRCINTERVENTIONS.119.008537
4. Abdel-Qadir HM, Ivanov J, Austin PC, Tu J, Džavík V. Sex differences in the management and outcomes of Ontario patients with cardiogenic shock complicating acute myocardial infarction. *Can J Cardiol.* (2013) 29:691–6. doi: 10.1016/j.cjca.2012.09.020
5. Holger Thiele MD, Uwe Zeymer MD, Franz-Josef Neumann MD, Miroslaw Ferenc MD, Hans-Georg Olbrich MD, Jörg Hausleiter MD, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med.* (2012) 367:1287–96. doi: 10.1056/NEJMoa1208410
6. Isorni MA, Aissaoui N, Angoulvant D, Bonello L, Lemesle G, Delmas C, et al. Temporal trends in clinical characteristics and management according to sex in patients with cardiogenic shock after acute myocardial infarction: the FAST-MI programme. *Arch Cardiovasc Dis.* (2018) 111:555–63. doi: 10.1016/j.acvd.2018.01.002
7. Baran DA, Grines GL, Bailey S, Burkhoff D, A Hall S, Henry TD, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock. *Catheter Cardiovasc Interv.* (2019) 94:29–37. doi: 10.1002/ccd.28329
8. Hernández-Pérez FJ, Álvarez-Avelló JM, Forteza A, Gómez-Bueno M, González A, et al. Resultados iniciales de un programa multidisciplinario de atención a pacientes en shock cardiogénico en red. *Rev Española de Cardiol.* (2020) 74:33–43. doi: 10.1016/j.recesp.2020.01.019
9. Collado-Lledó E, Llaó I, Rivas-Lasarte M, González-Fernández V, Noriega FJ, Hernández-Perez FJ, et al. Clinical picture, management and risk stratification in patients with cardiogenic shock: does gender matter? *BMC Cardiovasc Disord.* (2020) 20:189. doi: 10.1186/s12872-020-01467-4
10. Yan I, Schrage B, Weimann J, Dabboura S, Hilal R, Beer BN, et al. Sex differences in patients with cardiogenic shock. *ESC Heart Fail.* (2021) 8:1775–83. doi: 10.1002/ehf2.13303
11. Fengler K, Fuernau G, Desch S, Eitel I, Neumann FJ, Olbrichet HG, et al. Gender differences in patients with cardiogenic shock complicating myocardial infarction: a substudy of the IABP-SHOCK II-trial. *Clin Res Cardiol.* (2015) 104:71–8. doi: 10.1007/s00392-014-0767-2
12. Mahmoud AN, Elgendy IY. Gender impact on 30-day readmissions after hospitalization with acute myocardial infarction complicated by cardiogenic shock (from the 2013 to 2014 National Readmissions Database). *Am J Cardiol.* (2018) 121:523–8. doi: 10.1016/j.amjcard.2017.11.023
13. Vallabhajosyula S, Ya'Qoub L, Singh M, Bell MR, Gulati R, Cheungpasitporn W, et al. Sex disparities in the management and outcomes of cardiogenic shock complicating acute myocardial infarction in the young. *Circ Heart Fail.* (2020) 13:e007154. doi: 10.1161/CIRCHEARTFAILURE.120.007154
14. Redfors B, Angerås O, Råmunddal T, Petursson P, Haraldsson I, Dworeck C, et al. Trends in gender differences in cardiac care and outcome after acute myocardial infarction in Western Sweden: a report from the Swedish web system for enhancement of evidence-based Care in Heart Disease Evaluated According to recommended therapies (SWEDEHEART). *J Am Heart Assoc.* (2015) 4:e001995. doi: 10.1161/JAHA.115.001995
15. Joseph SM, Brisco MA, Colvin M, Grady KL, Walsh MN, Cook JL, et al. Women with cardiogenic shock derive greater benefit from early mechanical circulatory support: an update from the cVAD registry. *J Interv Cardiol.* (2016) 29:248–56. doi: 10.1111/joic.12298

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Cardiovascular Medicine

TYPE Systematic Review
PUBLISHED 25 July 2022
DOI 10.3389/fcvm.2022.921378

OPEN ACCESS

EDITED BY
Manuel Martínez-Sellés,
Gregorio Marañón Hospital, Spain

REVIEWED BY
Hani Sabbour,
Cleveland Clinic Abu Dhabi, United Arab Emirates
Barbara Dominik,
University Hospital of Zielona Gora, Poland

*CORRESPONDENCE
Jesús Álvarez-García
jalvarezg82@gmail.com

SPECIALTY SECTION
This article was submitted to Sex and Gender in Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 15 April 2022
ACCEPTED 27 June 2022
PUBLISHED 25 July 2022

CITATION
Sanromán Guerrero MA, Antoñana Ugalde S, Hernández Sánchez E, del Prado Díaz S, Jiménez-Blanco Bravo M, Cordero Pereda D, Zamorano Gómez JL and Álvarez-García J (2022) Role of sex on the efficacy of pharmacological and non-pharmacological treatment of heart failure with reduced ejection fraction: A systematic review. *Front. Cardiovasc. Med.* 9:921378. doi: 10.3389/fcvm.2022.921378

Role of sex on the efficacy of pharmacological and non-pharmacological treatment of heart failure with reduced ejection fraction: A systematic review

María Ascensión Sanromán Guerrero, Sonia Antoñana Ugalde, Elena Hernández Sánchez, Susana del Prado Díaz, Marta Jiménez-Blanco Bravo, David Cordero Pereda, José Luis Zamorano Gómez and Jesús Álvarez-García*

Department of Cardiology, Ramón y Cajal University Hospital, IRYCIS, Centro de Investigación en Red en Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain

Background: Heart Failure (HF) is a growing epidemic with a similar prevalence in men and women. However, women have historically been underrepresented in clinical trials, leading to uneven evidence regarding the benefit of guideline-directed medical therapy (GDMT). This review aims to outline the sex differences in the efficacy of pharmacological and non-pharmacological treatment of HF with reduced ejection fraction (HFrEF).

Methods and results: We conducted a systematic review *via* Medline from inception to 31 January 2022, including all randomized clinical trials published in English including adult patients suffering HFrEF that reported data on the efficacy of each drug. Baseline clinical characteristics, primary outcomes, and sex-specific effects are summarized in tables. The systemic review has been conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. In total, 29 articles were included in the systematic review. We observed that the proportion of women enrolled in clinical trials was generally low, the absence of a prespecified analysis of efficacy by sex was frequent, and the level of quality of evidence on the efficacy of GDMT and implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT-) in women was relatively poor.

Conclusions: Sex influences the response to treatment of patients suffering from HFrEF. All the results from the landmark randomized clinical trials are based on study populations composed mainly of men. Further studies specifically designed considering sex differences are warranted to elucidate if GDMT and new devices are equally effective in both sexes.

KEYWORDS

sex differences, gender, heart failure, women, sex

Introduction

Heart failure (HF) is a global epidemic that is growing every year, with a similar prevalence and incidence in men and women (1, 2). During the last 30 years, there has been a significant advance in the treatment of HF, in particular in those patients suffering from HF with reduced ejection fraction (HFrEF) (3). Thus, current guidelines recommend several saving-life therapies, such as drugs and devices, based on the positive results of randomized clinical trials (4, 5).

However, women have been underrepresented in every landmark study, preventing us from concluding if the benefit of these therapies is unequivocally observed in both sexes (6). There are also sex differences in demographics and pathophysiology which may modulate the response to HF treatments (7). Moreover, some social factors historically linked to gender have determined distinct patterns in clinical presentation, workup, and management in HF that, in turn, also could play a role in the treatment of women (8). In consequence, greater awareness about the relevance of closing these gaps and implementing strategies that consider a sex perspective is rising from the scientific community to medical societies (9, 10).

The purpose of this systematic review is to describe the sex-specific differences in the efficacy of pharmacological and non-pharmacological treatment of HFrEF.

Methods

This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (11).

Search strategy

An electronic systematic review of the literature was conducted in the Medline database (National Library of Medicine Bethesda, Maryland). The keywords used were chosen according to the MESH terminology: (sex OR gender OR female OR male OR women OR men) AND (beta-blocker OR Nebivolol OR Bisoprolol OR Metoprolol OR Carvedilol OR sacubitril OR sacubitril-valsartan OR angiotensin neprylisin inhibitor receptor OR sodium glucose cotransporter inhibitor OR SGLT2 inhibitor OR dapagliflozin OR empagliflozin OR sotagliflozin OR mineralocorticoid receptor antagonist OR MRA OR eplerenone OR spironolactone OR ivabradine OR implantable cardioverter defibrillator OR ICD OR cardiac resynchronization therapy OR CRT). These terms were restricted to "Title/Abstract" and "English" (Language). The search was conducted from inception to 31 January 2022. In addition, we conducted a hand-searching of reference lists of all included studies and guidelines to identify further studies.

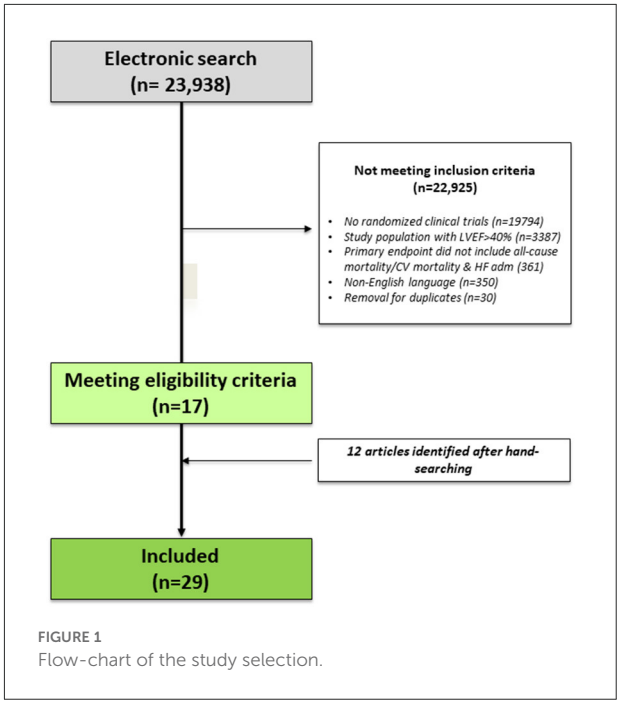


FIGURE 1
Flow-chart of the study selection.

Eligibility criteria for study selection and validity assessment

The inclusion criteria were the following: (i) randomized clinical trials including adult patients (≥18 years of age) suffering from HFrEF and (ii) studies that reported data on the efficacy of each drug. There was no restriction on the publication date. We excluded animal studies, abstracts, editorials, commentaries, systematic reviews, and narrative reviews. Once duplicates were removed, all authors independently screened titles and abstracts to ensure the capture of all relevant studies. Disagreements were resolved by discussion to achieve consensus.

Data extraction and outcomes of interest

Data were extracted by the authors into predetermined tables using a standardized protocol. The data extracted were drug name, study name, year of publication, characteristics of the study population, number of included patients, number of women included, left ventricular ejection fraction (LVEF), efficacy primary endpoint, sex-specific outcomes, and *p*-value for interaction when available. The primary outcomes of interest were all-cause mortality or the combined endpoint of mortality and HF hospitalization. This systematic review was restricted to data published in manuscript or abstract form. We expressed study results as relative risk (*RR*) or hazard ratio (*HR*) with 95% confidence intervals (*CI*) when available.

Results

Study selection

Our electronic search retrieved 23,938 articles. After the removal of duplicates and those which did not fulfill inclusion criteria, 17 articles were identified. After hand-searching, 12 articles were identified. Finally, 29 articles were included in our systematic review. Figure 1 illustrates the flowchart of the study selection. The main characteristics of the included studies are summarized in Table 1. The specific results of the studies are presented in chronological order of appearance by drug class.

Angiotensin-converting enzyme inhibitors

Two studies were reviewed according to the inclusion criteria (12, 13). The Cooperative North Scandinavian Enalapril Survival (CONSENSUS) study was conducted in 1987 to evaluate the impact of Enalapril vs. placebo in 253 patients with the New York Heart Association (NYHA) IV congestive HF. Only 74 (30%) patients were women and, interestingly, LVEF was not measured. After a 6-month follow-up period, enalapril significantly reduce all-cause mortality, but a sex-based analysis was not performed (12). After 4 years, the Studies of Left Ventricular Dysfunction (SOLVD) analyzed the effect of Enalapril vs. placebo in 2,569 patients with mostly NYHA II-III congestive HF and LVEF $\leq$35% (505 women, 20%), showing a significant 14% risk reduction of death at 4-year. However, an analysis stratified by sex was not performed either (13).

Two meta-analyses including the CONSENSUS and SOLVD study populations together with smaller studies showed that the mortality benefit of ACEI showed only a trend for benefit in women, without reaching statistical significance (14, 15).

Beta-blockers

Five studies were finally selected according to our selection criteria (16–20). The U.S. Carvedilol of HF study was conducted in 1996 in 1,094 patients (256 women, 23%) suffering from chronic HF with LVEF $\leq$ 35% and showed that carvedilol significantly reduced the risk of death by 65% after a median follow-up of 6.5 months. The analysis stratified by sex showed similar benefits in both sexes (16). The CIBIS II was a trial performed in 1999 to assess bisoprolol vs. placebo on all-cause mortality in 2,564 patients (515 women, 19%) with advanced HF and LVEF $<$ 35% already treated with ACEI (17). It was also stopped early because a clear benefit was observed in the group assigned to beta-blockers. Women differed from men with regard to age, the NYHA functional classification, the primary cause of HF, and risk factors, such as left bundle-branch block. In a *post-hoc* analysis, bisoprolol reduced the mortality rates for both men and women after adjustment for baseline differences (21). The MERIT-HF was another clinical trial conducted in 1999 in 3,991 (898 women, 23%) patients with advanced HF and LVEF $\leq$ 40% to investigate whether metoprolol-controlled release/extended release (CR/XL) once daily added to optimum standard therapy lowered mortality (18). After a median follow-up of 1 year, a 34% decrease in death risk was observed in the metoprolol arm. In a *post-hoc* analysis, treatment with metoprolol CR/XL in women resulted in a 21% reduction in the primary combined endpoint of all-cause mortality/all-cause hospitalizations (164 vs. 137 patients; $p = 0.044$) (22). In the Beta-blocker Evaluation of Survival Trial (BEST), it was evaluated bucindolol vs. placebo in 2,708 patients (593 women, 23%) with NYHA III or IV HF and LVEF $\leq$ 35% (19). The primary endpoint to evaluate was death from any cause and the results showed no improvement in survival. In a prespecified analysis by sex, no differences were observed among men and women (23). The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial was designed to evaluate the effects of carvedilol in 2,289 patients (465 women, 20%) with severe chronic HF and LVEF $\leq$ 25% (20). Carvedilol reduced the combined endpoint of death or hospitalization among the 469 women studied, mostly driven by a reduction in hospitalization, but the significant reduction in all-cause death was only achieved in men.

In a pooling-data analysis of total mortality by sex from CIBIS II, MERIT-HF, and COPERNICUS, beta-blockers showed very similar and statistically significant survival benefits in women (*RR* 0.69; 95% *CI* 0.51–0.93) and men (0.66; 95% *CI* 0.58–0.75) (22).

Antagonist receptor blockers

Three studies were reviewed according to the inclusion criteria (24–26). The Valsartan Heart Failure Trial (Val-HeFT) was conducted in 2001 to evaluate the effect of valsartan vs. placebo on mortality in 5,010 patients (1,003 women, 20%) with NYHA II-IV HF and LVEF $<$ 40% (24). On top of ACEI, diuretics, digoxin, and beta-blocker treatment, valsartan significantly reduced the combined endpoint of mortality or cardiac arrest, HF hospitalization, or need for intravenous therapy. There was a clear benefit in men and a trend toward benefit in women, although it did not reach statistical significance. In a *post-hoc* analysis adjusted for NYHA class, LVEF, use of ACEI and beta-blockers, and HF etiology, valsartan reduced the adjusted *RR* for the combined endpoint in women (0.84; 95% *CI*: 0.67–1.06; $p = 0.044$), but not in men (0.872; 95% *CI*: 0.779–0.975; $p = 0.053$) (27). The Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity (CHARM) program was specifically designed as

TABLE 1 Randomized clinical trials for drugs in HFrEF included in the systematic review.

Intervention	Study name	Year	Study population	*N*	Women (%)	LVEF	Primary endpoint	Overall treatment effect (95% CI)	Sex-specific effect	*P* value for sex interaction
Enalapril	CONSENSUS	1987	NYHA IV Congestive HF	253	74 (30)	–	All-cause mortality	RR 0.56 (0.34–0.91)	Not performed	–
Enalapril	SOLVD	1991	NYHA I-IV Congestive HF (90% NYHA II-III)	2569	504 (20)	≤35%	All-cause mortality	RR 0.86 (0.74–0.95)	Not performed	–
Carvedilol	US Carvedilol HF	1996	NYHA I–IV	1094	256 (23)	≤35%	All-cause mortality	HR 0.35 (0.20–0.61)	HR 0.41 (0.22–0.80) in men; HR 0.23 (0.07-0.69) in women	Not reported
Bisoprolol	CIBIS II	1999	NYHA III–IV	2647	515 (19)	≤35%	All-cause mortality	HR 0.66 (0.54–0.81)	HR 0.53 (0.42–0.67) in men; HR 0.37 (0.19–0.69) in women	Not reported
Metoprolol	MERIT-HF	1999	NYHA II–IV	3991	898 (23)	≤40%	All-cause mortality	RR 0.66 (0.53–0.81)	HR 0.61 in men ($p < 0.001$); HR 0.92 in women (p = NS)	0.14
Bucindolol	BEST	2001	NYHA III–IV	2708	593 (22)	≤35%	All-cause mortality	HR 0.90 (0.78–1.02)	No differences among sexes	Not reported
Carvedilol	COPERNICUS	2001	NYHA III–IV	2289	469 (20)	<25%	All-cause mortality	HR 0.65 (0.52–0.81)	Significant benefit in men, trend toward benefit in women	Not reported
Valsartan	Val-HeFT	2001	NYHA II–IV	5010	1003 (20)	<40%	Mortality or cardiac arrest or HF admission or need for iv therapy	RR 0.87 (0.77–0.97)	Significant benefit in men, trend toward benefit in women	Not reported
Candesartan	CHARM added	2003	NYHA II–IV + ACEI	2548	542 (21)	≤40%	CV death or HF admission	HR 0.85 (0.75–0.96)	No differences among sexes	0.87
Candesartan	CHARM alternative	2003	NYHA II-IV, intolerant to ACEI	2028	646 (32)	≤40%	CV death or HF admission	HR 0.77 (0.67–0.89)	No differences among sexes	0.87
Spironolactone	RALES	1999	NYHA III-IV	1663	446 (27)	≤35%	All-cause mortality	RR 0.70 (0.60–0.82)	No differences among sexes	Not reported
Eplerenone	EPHESUS	2003	Acute MI and HF or diabetes mellitus	6632	1918 (29)	≤40%	All-cause mortality	RR 0.85 (0.75–0.96)	Significant benefit in women, trend toward benefit in men	0.44
Eplerenone	EMPHASIS-HF	2011	NYHA II and older than 55 years old	2737	610 (22)	≤35%	CV death/HF admission	HR 0.63 (0.54–0.74)	No differences among sexes	0.36
Ivabradine	SHIFT	2010	NYHA II-IV	6505	1535 (24)	≤35%	CV death/HF admission	HR 0.82 (0.75–0.90)	No differences among sexes	0.26
Sacubitril-valsartan vs enalapril	PARADIGM	2014	NYHA II-IV	8399	1832 (22)	≤40%	CV death/HF admission	HR 0.80 (0.73–0.87)	No differences among sexes	0.63
Dapagliflozin	DAPA-HF	2019	NYHA II-IV	4744	1109 (23)	≤40%	CV death/Worsening HF	HR 0.74 (0.65–0.85)	HR 0.73 (0.63–0.85) in men, HR 0.79 (0.59–1.06) in women	0.67
Empagliflozin	EMPEROR-Reduced	2020	NYHA II–IV	3730	893 (24)	≤40%	CV death/Worsening HF	HR 0.75 (0.65–0.86)	HR 0.80 (0.68–0.93) in men, HR 0.59 (0.44–0.80) in women	Not reported

HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; HF, heart failure; RR, relative risk; HR, hazard ratio; CV, cardiovascular; ACEI, angiotensin-converter enzyme inhibitor; MI, myocardial infarction.

10.3389/fcvm.2022.921378

three double-blind, placebo-controlled, clinical trials comparing candesartan vs. placebo in three distinct populations with symptomatic HF. In those two trials including subjects with LVEF $\leq$ 40% (being treated with an ACEI -CHARM-Added- or intolerant to ACEI -CHARM-Alternative-), candesartan significantly reduced the combined endpoint of cardiovascular death or HF readmission (25, 26). This reduction was similar in men and women (28).

Mineraloid receptor antagonists

Three studies met the established search criteria for drugs (29–31). The Randomized Aldactone Evaluation Study (RALES) was a trial to test the hypothesis that daily treatment with spironolactone would significantly reduce the risk of all-cause death among 1,663 patients (446 women, 27%) who had severe HF and LVEF $\leq$ 35% who were receiving standard therapy, such as ACEI. The RALES accomplished the primary endpoint, with a similar benefit in both sexes, and a good safety profile (29). The Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) was a trial to evaluate the effect of eplerenone—an aldosterone blocker that selectively blocks the mineralocorticoid receptor—on overall mortality in 6,632 patients (1,918 women, 29%) with acute myocardial infarction complicated by left ventricular dysfunction and HF who were receiving optimal medical therapy. Eplerenone also met the primary endpoint for efficacy, but regarding sex-specific effects, women presented a higher benefit than men for mortality risk reduction (30). Lastly, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) was designed to investigate the effects of eplerenone, added to evidence-based therapy, on clinical outcomes in 2,737 patients (610 women, 22%) with NYHA II HF and LVEF $\leq$ 35% (31). After a median follow-up of 21 months, patients allocated in the drug arm showed a significant 37% reduction in the primary endpoint composed by cardiovascular death or HF admission and a significant 24% reduction in all-cause mortality. Similar benefits were observed among men and women.

Ivabradine

The Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT) study reported a significant reduction in the composite endpoint of cardiovascular death or HF hospitalization with ivabradine vs. placebo (*HR* 0.82, 95% *CI* 0.75–0.90, $p < 0.0001$) in 6,505 patients (1,535 women, 24%) with symptomatic HF and LVEF $\leq$ 35%, in sinus rhythm and with heart rate $\geq$70 beats per minute (bpm) (32). The effects were driven mainly by hospital admissions for worsening HF (*HR* 0.74, 0.66–0.83; $p < 0.0001$) and deaths due to HF (*HR* 0.74, 0.58–0.94, $p = 0.014$). This lower rate of the composite endpoint with ivabradine was similar in both sexes (*p*-value for interaction = 0.260).

Angiotensin receptor neprylisin inhibitor

Only the Prospective Comparison of Angiotensin receptor neprylisin inhibitor (ARNI) with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trials (PARADIGM-HF) met the inclusion criteria (33). This was a clinical trial conducted in 2014 which evaluated sacubitril-valsartan (SV) vs. enalapril in 8,399 patients (1,832 women, 22%) with NYHA II–IV, LVEF $\leq$ 40% and increased natriuretic peptides. After a median follow-up of 27 months, patients allocated in the SV arm showed a significant 20% reduction in the primary endpoint composed by cardiovascular death or HF admission and a significant 16% reduction in all-cause mortality. Similar benefits were observed in both sexes.

Sodium-glucose cotransporter 2 inhibitors

Two clinical trials met the search criteria (34, 35). The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) prospectively evaluated the efficacy and safety of dapagliflozin in 4,744 patients (1,109 women, 23%) with NYHA II–IV and LVEF $\leq$ 40%, regardless of the presence of diabetes (34). Over a median of 18 months, the primary outcome (worsening HF or CV death) occurred in 386 of 2,373 patients (16.3%) in the dapagliflozin group and in 502 of 2,371 patients (21.2%) in the placebo group (*HR*, 0.74; 95% *CI* 0.65–0.85; $p < 0.001$). Moreover, a total of 276 patients (11.6%) in the dapagliflozin group and 329 patients (13.9%) in the placebo group died from any cause (*HR* 0.83; 95% *CI*, 0.71–0.97). In a prespecified subgroup analysis of the DAPA-HF, dapagliflozin reduced the risk of worsening HF, CV death, and all-cause death and improved symptoms, physical function, and health-related quality of life similarly in men and women with HFrEF. In addition, dapagliflozin was safe and well-tolerated irrespective of sex (36). The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) evaluated empagliflozin in 3,730 patients (893 women, 24%) with NYHA II–IV and LVEF $\leq$ 40%, regardless of the presence of diabetes (35). After a median follow-up of 16 months, the primary outcome event occurred in 361 of 1,863 patients (19.4%) in the empagliflozin group and in 462 of 1,867 patients (24.7%) in the placebo group (*HR* for CV death or hospitalization for HF, 0.75; 95% *CI* 0.65–0.86; $p < 0.001$). The effect of empagliflozin on the primary outcome was consistent in patients of both sexes.

Implantable converter defibrillators and cardiac resynchronization therapy

In total, 12 clinical trials were reviewed according to inclusion criteria (37–48). Table 2 summarizes the main characteristics of the randomized clinical trials in HfrEF for implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT).

Several randomized trials have proven the efficacy of ICD to prevent all-cause death. As in most HF drug therapy trials, women were underrepresented in these studies, accounting for less than one-third of the total population (37–43). Overall, subgroup analyses of each study were consistent and did not show statistically significant differences between both sexes.

On the other hand, CRT studies included a wide variety of patients (with NYHA classes ranging from I to IV), but less than one-third of them were women. The subgroup analysis of most trials did not show a significant difference in outcomes between men and women (44–48). An exception to this is the MADIT-CRT trial, in which ICD plus CRT therapy was associated with a greater benefit in women (p for interaction = 0.01) (49).

Discussion

Main findings

In this systematic review including 28 randomized clinical trials evaluating pharmacological and non-pharmacological treatment of HFrEF, we observed that: (1) the proportion of women enrolled was generally low, (2) the absence of a prespecified analysis of efficacy by sex was frequent, and (3) the level of quality of evidence on the efficacy of GDMT and ICD or CRT in women is relatively poor.

Role of sex on HFrEF treatment

Over the last 30 years, many significant advances have been made in the treatment of patients suffering from HFrEF. Thus, the main HF guidelines that have been recently published recommend starting neurohormonal drugs and SGLT2 inhibitors at the same level to achieve the maximum mortality risk reduction (4, 5). Once GDMT is implemented at the highest tolerated dose and LVEF is again assessed, ICD and CRT have to be considered in those patients with an estimated survival greater than 1 year according to HF etiology, morphology, and duration of QRS complex.

However, this "foundational therapy" approach is not supported by the same level of quality of evidence when sex is considered. After reviewing the principal landmark trials involving drugs, we observed that women were repeatedly underrepresented and prespecified sex-based analyses were not performed. Only in the case of the most recent families, sacubitril-valsartan and SGLT2 inhibitors, we should be confident that the sex interaction was not significant when assessing the efficacy of the drug (33–36).

This uneven supporting evidence is particularly relevant when epidemiological, physiological, and pharmacological differences by sex are known. The HF incidence increases over time with aging in both sexes and the overall lifetime risk for developing HF is also similar (50, 51). Nevertheless, women tend to be older, with a higher prevalence of comorbidities than men when HFrEF appears (52). In addition, the presence of risk factors is different according to sex (less smoking and more diabetes in women) and the social determinants of health can also be especially unique in women (7). Regarding to pathophysiological differences by sex, the predisposition to macrovascular coronary artery disease and myocardial infarction in men may only explain a part of the higher risk of HFrEF compared with women (6). As we said, HFrEF in women is more likely to be present with aging and non-cardiac comorbidities, and distinct immune responses can be particularly important when inflammation and microvascular disease are pointed out to develop HF (53, 54). Specific etiologies of HFrEF, such as Takotsubo syndrome, peripartum cardiomyopathy, or cardiotoxicity (whether related to chemotherapy or alcohol abuse) also involve different consequences by sex (7, 55). Lastly, there are relevant sex-differences in pharmacokinetics and pharmacodynamics based on differences in body composition (with women usually having lower weight and height, a higher proportion of body fat, and a lower peripheral distribution volume) and lower renal and hepatic filtration rate (56). Several studies have suggested that the maximum benefit of GDMT may be achieved in women at doses lower than those recommended by the guidelines (57).

In relation to devices, women are less likely to receive an ICD than men, but they have higher rates of device implantation-related complications. Instead, women are more likely to respond favorably to CRT than men, which can result in an improvement of survival rates. The reasons for this are not clear still but include differences in vascular access, higher hemorrhagic risk, QRS duration cutoff, and less ischemic HF origin (58).

Limitations

Our systematic review has some limitations. First, we only included randomized clinical trials in our study. Although publication and selection bias may arise because we selected those published in English, the main pivotal studies are usually published in this language. Second, since only aggregated data were available, it was not possible to perform a more granular analysis of clinical outcomes.

TABLE 2 Randomized clinical trials for ICD/CRT in HFrEF included in the systematic review.

Intervention	Study name	Year	Study population	N	Women (%)	LVEF	Primary endpoint	Overall treatment effect (95% CI)	Sex-specific effect	*P* value for sex interaction
ICD	MADIT II	2002	Prior MI	1232	192 (16)	≤30%	All-cause mortality	HR 0.69 (0.51–0.93)	HR 0.66 (0.48–0.91) in men, HR 0.57 (0.28–1.18) in women	0.72
ICD	AMIOVIRT	2003	NIDCM and asymptomatic NSVT	103	30 (29)	≤35%	All-cause mortality	1- and 3-year survival rates did not differ between both arms ($p = 0.8$)	Not performed	–
ICD	DINAMIT TRIAL	2004	Post-acute MI patients	694	160 (24)	≤35%	All-cause mortality	HR 1.08 (0.76–1.55)	Not reported	0.82
ICD	DEFINITE TRIAL	2004	Non-ischemic dilated cardiomyopathy with PVB	458	264 (29)	≤35%	All-cause mortality	HR 0.65 (0.40–1.06)	HR 0.49 (0.27–0.90) in men, HR 1.14 (0.50–2.64) in women	0.18
ICD	SCD HeFT	2005	NYHA class II or III	2521	588 (23)	≤35%	All-cause mortality	HR 0.77 (0.62–0.96)	HR 0.73 (0.57–0.93) in men, HR 0.96 (0.56–1.61) in women	0.54
ICD	IRIS TRIAL	2009	Post-acute MI patients with HR ≥ 90 bpm	898	209 (23)	≤40%	All-cause mortality	HR 1.04 (0.81–1.35)	Not reported	0.85
ICD	DANISH	2016	NIDCM	1160	307 (28)	≤35%	All-cause mortality	HR 0.87 (0.68–1.12)	HR 0.85 (0.64–1.12) in men, HR 1.03 (0.57–1.87) in women	0.66
CRT	COMPANION	2004	NYHA III-IV and a QRS ≥ 120 ms	1520	493 (33)	≤35%	Time to death from or hospitalization for any cause	CRT vs OMT: HR 0.81 ($p = 0.014$) ICD-CRT vs OMT: HR 0.80 ($p = 0.01$)	Not reported	Not reported
CRT	MADIT-CRT	2005	Cardiomyopathy with QRS≥130 msec and NYHA I-II	1820	453 (25)	≤30%	All-cause mortality and HF events	HR 0.66 (0.52–0.84)	HR 0.76 (0.59–0.97) in men, HR 0.37 (0.22–0.60) in women	0.01
CRT	CARE HF	2005	NYHA III-IV and cardiac desynchrony	813	216 (27)	≤35%	Time to death from any cause or an unplanned hospitalization for a major cardiovascular event	HR 0.63 (0.51–0.77)	HR 0.62 (0.49–0.79) in men, HR 0.64 (0.42–0.97) in women	Not reported
CRT	RAFT	2010	NYHA II-III, QRS ≥120 ms or a paced QRS duration ≥ 200 ms	1798	308 (18)	≤30%	Death from any cause or hospitalization for HF	HR 0.75 (0.64–0.87)	Not reported	0.09
CRT	ECHO-CRT	2013	NYHA III-IV, QRS<130 ms and desynchrony	809	227 (28)	≤35%	Death from any cause or first hospitalization for HF	HR 1.20 (0.92–1.57)	HR 1.31 (0.95–1.80) in men, HR 0.93 (0.56–1.56) in women	0.43

ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; HF, heart failure; NIDCM, non-ischemic dilated cardiomyopathy; NSVT, non-sustained ventricular tachycardia; PVB, premature ventricular beats; RR, relative risk; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction.

10.3389/fcvm.2022.921378

Conclusion

Sex influences in the response to treatment of patients suffering from HFrEF. All results from the landmark randomized clinical trials are based on study populations composed mainly of men. Further studies specifically designed to consider sex-differences are warranted to elucidate if GDMT and new devices are equally effective in both sexes.

Data availability statement

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

Author contributions

MS and JÁ-G drafted the work. All authors made substantial contributions to the conception, design of the work, data acquisition, analysis, and interpretation of data for the work. All authors contributed to the article and approved the submitted version.

Publisher's note

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Seferović PM, Vardas P, Jankowska EA, Maggioni AP, Timmis A, Milinković I, et al. The heart failure association atlas: heart failure epidemiology and management statistics 2019. *Eur J Heart Fail.* (2021) 23:906–14. doi: 10.1002/ejhf.2143

2. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet.* (2018) 391:572–80. doi: 10.1016/S0140-6736(17)32520-5

3. Tromp J, Ouwerkerk W, Veldhuisen DJ. van, Hillege HL, Richards AM, Meer P van der, et al. A systematic review and network meta-analysis of pharmacological treatment of heart failure with reduced ejection fraction. *JACC Heart Fail.* (2022) 10:73–84. doi: 10.1016/j.jchf.2021.09.004

4. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* (2021) 42:3599–726.

5. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure. *J Card Fail.* (2022) 28:810–30. doi: 10.1016/j.cardfail.2022.02.009

6. Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, et al. Sex differences in heart failure. *Eur Heart J.* (2019) 40:3859–68. doi: 10.1093/eurheartj/ehz835

7. Lala A, Tayal U, Hamo CE, Youmnas Q, AlL-Khatib SM, Bozkurt B, et al. Sex differences in heart failure. *J Card Fail.* (2022) 28:477–98. doi: 10.1016/j.cardfail.2021.10.006

8. DeFilippis EM, Blumer V, Morris AA, Cogswell R. Referring women for advanced heart failure therapies: too little, too late. *J Card Fail.* (2022). doi: 10.1016/j.cardfail.2021.12.022

9. Spall HGC. Van, Lala A, Deering TF, Casadei B, Zannad F, Kaul P, et al. Ending gender inequality in cardiovascular clinical trial leadership: JACC Review Topic of the Week. *J Am Coll Cardiol.* (2021) 77:2960–72. doi: 10.1016/j.jacc.2021.04.038

10. Han JK, Belardo D, Ibrahim NE, Capers Q, Grines CL, Smith SC, et al. A look back, a path forward: moving toward diversity and inclusion in cardiovascular society presidents. *JACC Case Rep.* (2022) 4:247. doi: 10.1016/j.jaccas.2021.12.022

11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* (2021). 372. doi: 10.1136/bmj.n71

12. Swedberg K, Kjekshus J, CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med.* (1987) 316:1429–35. doi: 10.1056/NEJM198706043162301

13. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med.* (1991) 325:67. doi: 10.1056/NEJM199108013250501

14. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA.* (1995) 273:1450–6. doi: 10.1001/jama.273.18.1450

15. Shekelle PG, Rich MW, Morton SC, Atkinson SW, Tu W, Maglione M, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. *J Am Coll Cardiol.* (2003) 41:1529–38. doi: 10.1016/S0735-1097(03)00262-6

16. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. US Carvedilol Heart Failure Study Group. *N Engl J Med.* (1996) 334:1349–55. doi: 10.1056/NEJM199605233342101

17. Dargie HJ, Lechat P. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. *Lancet.* (1999) 353:9–13. doi: 10.1016/S0140-6736(98)11181-9

18. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure (MERIT-HF). *Lancet.* (1999) 353:2001–7. doi: 10.1016/S0140-6736(99)04440-2

19. Eichhorn EJ, Domanski MJ, Krause-Steinrauf H, Bristow MR, Lavori BW, A. trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med.* (2001) 344:1659–67. doi: 10.1056/NEJM200105313442202

20. Packer M, Coats AJS, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med.* (2001) 344:1651–8. doi: 10.1056/NEJM200105313442201

21. Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P. Sex differences in the prognosis of congestive heart failure: results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). *Circulation.* (2001) 103:375–80. doi: 10.1161/01.CIR.103.3.375

22. Ghali JK, Piña IL, Gottlieb SS, Deedwania PC, Wikstrand JC. Metoprolol CR/XL in female patients with heart failure: analysis of the experience in Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). *Circulation.* (2002) 105:1585–91. doi: 10.1161/01.CIR.0000012546.20194.33

23. Ghali JK, Krause-Steinrauf HJ, Adams KF, Khan SS, Rosenberg YD, Yancy CW, et al. Gender differences in advanced heart failure: insights from the BEST study. *J Am Coll Cardiol.* (2003) 42:2128–34. doi: 10.1016/j.jacc.2003.05.012

24. Cohn JN, Tognoni G, A. randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med.* (2001) 345:1667–75. doi: 10.1056/NEJMoa010713

25. McMurray JJV, Östergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet.* (2003) 362:767–71. doi: 10.1016/S0140-6736(03)14283-3

26. Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet.* (2003) 362:772–6. doi: 10.1016/S0140-6736(03)14284-5

27. Majahalme SK, Baruch L, Aknay N, Goedel-Meinen L, Hofmann M, Hester A, et al. Comparison of treatment benefit and outcome in women versus men with chronic heart failure (from the Valsartan Heart Failure Trial). *Am J Cardiol.* (2005) 95:529–32. doi: 10.1016/j.amjcard.2004.10.026

28. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet.* (2003) 362:759–66. doi: 10.1016/S0140-6736(03)14282-1

29. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med.* (1999) 341:709–17. doi: 10.1056/NEJM199909023411001

30. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* (2003) 348:1309–21. doi: 10.1056/NEJMoa030207

31. Zannad F, McMurray JJV, Krum H, Veldhuisen DJ. van, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med.* (2011) 364:11–21. doi: 10.1056/NEJMoa1009492

32. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet.* (2010) 376:875–85. doi: 10.1016/S0140-6736(10)61198-1

33. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* (2014) 371:132–3. doi: 10.1056/NEJMoa1409077

34. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* (2019) 381:1995–2008. doi: 10.1056/NEJMoa1911303

35. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med.* (2020) 383:1413–24.

36. Butt JH, Docherty KF, Petrie MC, Schou M, Kosiborod MN, O'Meara E, et al. Efficacy and safety of dapagliflozin in men and women with heart failure with reduced ejection fraction: a prespecified analysis of the dapagliflozin and prevention of adverse outcomes in heart failure trial. *JAMA Cardiol.* (2021) 6:678–89. doi: 10.1001/jamacardio.2021.0379

37. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* (2002) 346:877–83. doi: 10.1056/NEJMoa013474

38. Strickberger SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL, et al. Amiodarone versus implantable cardioverter-defibrillator:randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia—AMIOVIRT. *J Am Coll Cardiol.* (2003) 41:1707–12. doi: 10.1016/S0735-1097(03)00297-3

39. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NAM, Anderson KP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med.* (2004) 350:2151–8. doi: 10.1056/NEJMoa033088

40. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med.* (2004) 351:2481–8. doi: 10.1056/NEJMoa041489

41. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med.* (2005) 352:225–37. doi: 10.1056/NEJMoa043399

42. Steinbeck G, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, et al. Defibrillator implantation early after myocardial infarction. *N Engl J Med.* (2009) 361:1427–36. doi: 10.1056/NEJMoa0901889

43. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med.* (2016) 375:1221–30. doi: 10.1056/NEJMoa1608029

44. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, Marco T De, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* (2004) 350:2140–50. doi: 10.1056/NEJMoa032423

45. Cleland JGF, Daubert J-C, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* (2005) 352:1539–49. doi: 10.1056/NEJMoa050496

46. Tang ASL, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med.* (2010) 363:2385–95. doi: 10.1056/NEJMoa1009540

47. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med.* (2013) 369:38. doi: 10.1056/NEJMoa1306687

48. Moss AJ, Brown MW, Cannom DS, Daubert JP, Estes M, Foster E, et al. Multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT): design and clinical protocol. *Ann Noninvasive Electrocardiol.* (2005) 10:34–43. doi: 10.1111/j.1542-474X.2005.00073.x

49. Arshad A, Moss AJ, Foster E, Padeletti L, Barsheshet A, Goldenberg I, et al. Cardiac resynchronization therapy is more effective in women than in men: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. *J Am Coll Cardiol.* (2011) 57:813–20.

50. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation.* (2002) 106:3068–72. doi: 10.1161/01.CIR.0000039105.49749.6F

51. Bleumink GS, Knetsch AM, Sturkenboom MCJM, Straus SMJM, Hofman A, Deckers JW, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J.* (2004) 25:1614–9. doi: 10.1016/j.ehj.2004.06.038

52. Swaraj S, Kozor R, Arnott C, Bartolo BA Di A, Figtree G. Heart failure with reduced ejection fraction-does sex matter? *Curr Heart Fail Rep.* (2021) 18:345–52. doi: 10.1007/s11897-021-00533-y

53. Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol.* (2016) 16:626–38. doi: 10.1038/nri.2016.90

54. Stolfo D, Uijl A, Vedin O, Strömberg A, Faxén UL, Rosano GMC, et al. Sex-based differences in heart failure across the ejection fraction spectrum: phenotyping, and prognostic and therapeutic implications. *JACC Hear Fail.* (2019) 7:505–15. doi: 10.1016/j.jchf.2019.03.011

55. Sans-Roselló J, Fernández-Peregrina E, Duran-Cambra A, Carreras-Mora J, Sionis A, Álvarez-García J, et al. Coronary microvascular dysfunction in takotsubo syndrome assessed by angiography-derived index of microcirculatory resistance: a pressure-wire-free tool. *J Clin Med.* (2021). 10:4331. doi: 10.3390/jcm10194331

56. Rosano GMC, Lewis B, Agewall S, Wassmann S, Vitale C, Schmidt H, et al. Gender differences in the effect of cardiovascular drugs: a position document of the Working Group on Pharmacology and Drug Therapy of the ESC. *Eur Heart J.* (2015) 36:2677–80. doi: 10.1093/eurheartj/ehv161

57. Santema BT, Ouwerkerk W, Tromp J, Sama IE, Ravera A, Regitz-Zagrosek V, et al. Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. *Lancet Elsevier.* (2019) 394:1254–63. doi: 10.1016/S0140-6736(19)31792-1

58. Hsich EM. Sex differences in advanced heart failure therapies. *Circulation Circulation.* (2019) 139:1080–93. doi: 10.1161/CIRCULATIONAHA.118.037369

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 11 August 2022
DOI 10.3389/fcvm.2022.891606

OPEN ACCESS

EDITED BY
Beatriz Diaz Molina,
Servicio de Salud del Principado de Asturias (SESPA), Spain

REVIEWED BY
Stefano Coiro,
Hospital of Santa Maria della Misericordia in Perugia, Italy
James Cheng-Chung Wei,
Chung Shan Medical University Hospital, Taiwan

*CORRESPONDENCE
Yea-Huei Kao Yang
yhkao@mail.ncku.edu.tw

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 08 March 2022
ACCEPTED 03 June 2022
PUBLISHED 11 August 2022

CITATION
Cheng C-L, Yen C-T, Su C-C, Lee C-H, Huang C-H and Yang Y-HK (2022) Sex difference in heart failure risk associated with febuxostat and allopurinol in gout patients. *Front. Cardiovasc. Med.* 9:891606. doi: 10.3389/fcvm.2022.891606

Sex difference in heart failure risk associated with febuxostat and allopurinol in gout patients

Ching-Lan Cheng[1,2,3†], Chi-Tai Yen[4†], Chien-Chou Su[2], Cheng-Han Lee[5], Chien-Huei Huang[1,2] and Yea-Huei Kao Yang[1,3*]

[1]School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [2]Department of Pharmacy, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [3]Health Outcome Research Center, National Cheng Kung University, Tainan, Taiwan, [4]Department of Nephrology, Ministry of Health and Welfare, Tainan Hospital, Tainan, Taiwan, [5]Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Background: Gout or rapid reduction in serum uric acid level may increase the incidence of heart failure (HF). To compare the risk of HF between febuxostat and allopurinol in gout patients with coexisting cardiovascular (CV) diseases, the varying severity would be likely to confound the risk estimation. Gout and HF are both sex-related diseases, and the risk difference from the urate-lowering agents between women and men remains unknown.

Aims: To evaluate the HF hospitalisations risk of febuxostat and allopurinol in gout patients in real-world settings.

Methods: A population-based cohort enrolled patients with allopurinol or febuxostat initiation from 2011 to 2018. Participants were grouped into, without (low CV risk group) or with (high CV risk group) a history of recent major CV admission. The primary outcome was HF hospitalization. The secondary outcomes were composite CV events, all-cause mortality, and the cause of CV mortality. We used the 'as-treated' analysis and Cox proportional hazards model after propensity score (PS) matching. Patients were further stratified into men and women to evaluate the gender differences.

Results: Febuxostat users had a significantly higher risk of HF hospitalization than allopurinol users in gout patients either with low CV risk [hazard ratio (HR) 1.39; 95% confidence interval (CI) 1.25–1.55] or high CV risk [HR 1.36; 95% CI 1.22–1.52]. Particularly, women with gout had a higher risk of HF hospitalization than men.

Conclusion: The HF hospitalization risk was highest in gout women with high CV risk and febuxostat use. Monitoring of HF is warranted in these patients.

KEYWORDS

heart failure, febuxostat, allopurinol, gout, sex difference, Taiwan

Introduction

Heart failure (HF) hospitalisations were reported to occur more frequently than myocardial infarction or stroke in gout patients in previous studies (1). Because uric acid lowering agents would be indicated for gout patients, the risk associated with HF should not be ignored (2, 3). The risk of HF hospitalization event rate was higher in febuxostat users than in allopurinol users (4.3 vs. 3.9%) in the trial of Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) (4). However, all patients enrolled in the CARES study had cardiovascular (CV) history but might be different in severity, that would confound the risk of HF hospitalization events.

In addition, results of previous observational studies comparing the HF risk between febuxostat and allopurinol were inconsistent (5–7).

Gout and HF are both considered sex-dependent diseases (8). Earlier studies have shown that hyperuricemia-associated risks of HF, and cardiovascular mortality are both greater in women than in men (9, 10). Some studies showed that women had more sex-specific CV comorbidities than men with HF (11, 12). In addition, women who were hospitalized with CV disease had a higher risk of readmission for heart failure than men. Some prescription drugs were withdrawn from the market due to greater health risks for women than for men (11). It would be critical to assess the sex difference of HF in gout patients receiving uric acid lowing agents.

Therefore, considering patients receiving uric acid lowering agents would pose various severity of CV disease, we stratified the gout patients into low- and high-risk groups to compare the risk difference of HF between febuxostat and allopurinol exposure. We also compared the HF hospitalization risk between febuxostat and allopurinol in female and male gout patients.

Methods

Data source

The National Health Insurance Database (NHID) and Cause of Death Data from 2011 to 2018, provided by the Ministry of Health and Welfare, were used for this study. The databases were accessed at the Health and Welfare Data Science Center in Taipei City, Taiwan (13). The NHID is derived from the claims data of Taiwan's national health insurance program, which covers nearly the entire population (23 million people). The NHID includes registries for beneficiaries, ambulatory care claims, inpatient claims, and prescriptions dispensed at pharmacies. Each medical encounter in the claims data contains diagnosis and procedure codes ([International Classification of Diseases, Ninth Edition, Clinical Modification [ICD-9-CM, up to 2015] and Tenth Edition [ICD-10-CM, after 1/1/2016]), and details regarding drug information (e.g., date of prescription, days of supply for all drugs covered by the program). The cause of death data were derived from the death certificates, which included date of birth, sex, date of death, and cause of death (ICD diagnosis codes: ICD-9-CM until 2008 and ICD-10-CM after 2008). These databases can be linked with personal identification numbers to provide details of patient-level information regarding demographics, clinical data, and cause of death information. This study was approved by the Institutional Review Board of the National Cheng Kung University Hospital (IRB certificate number B-EX-107-018). Informed consent from the study participants was waived because patient-level information from the NHID was anonymous.

Study design and study population

The present study used a retrospective cohort study with a new user design. We identified a study cohort aged >20 years who had used CV-related drugs and initiated treatment with allopurinol or febuxostat, between 2012 and 2017 (patients had at least one year of follow-up). The CV-related drugs in this study were defined as alpha-blockers, antiplatelets, antithrombotics, antiarrhythmics, beta-blockers, calcium channel blockers, diuretics, or renin-angiotensin–aldosterone system inhibitors. We also estimated nitrates from use with other CV-related drugs. The index date was defined as the date of allopurinol or febuxostat initiation, and a new user was defined as a patient who had not received any febuxostat or allopurinol within 1 year before the index date. Patients were excluded if they met any of the following criteria: (1) cancer history; (2) history of acquired immune deficiency syndrome; (3) pregnancy within the one-year period prior to the index date; (4) prescription of cyclosporine, tacrolimus, rifampicin, pyrazinamide, ethambutol, or isoniazid within 180 days prior to the index date (Figure 1).

Exposure and high/low CV risk definition

We performed an "as-treated" analysis to estimate whether heart failure occurred within the exposure period. The medication exposure to allopurinol or febuxostat was counted from the date of the first prescription to discontinuation during the study period. Discontinuation was defined as the last day of continuous supply, allowing for a gap of 90 days to account for delayed refills.

We aimed to divide patients into high and low CV risk groups. High CV risk was defined as a history of major CV admission during the 3-year look-back period prior to the index date. Low CV risk was defined as patients who did not have a history of major CV admission during the 3-year look-back period prior to the index date. Major CV admission was defined

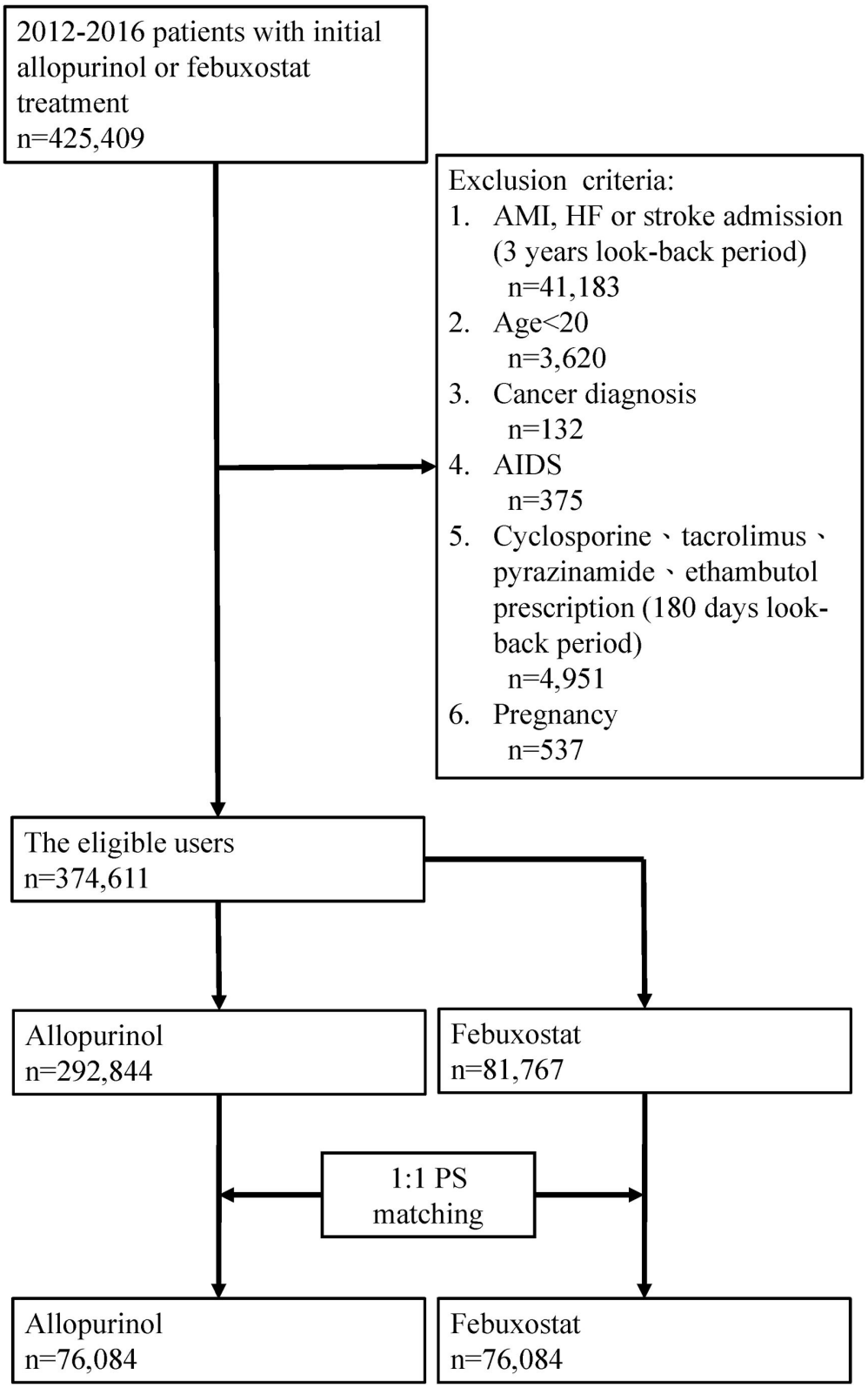


FIGURE 1
Assembly of the study population.

TABLE 1 Baseline characteristics of the study population.

Variable (%)	Low CV risk group			High CV risk group		
	Allopurinol ($n = 61,424$)	Febuxostat ($n = 61,424$)	SMD[a]	Allopurinol ($n = 12,795$)	Febuxostat ($n = 12,795$)	SMD[a]
Demographics						
Sex, male	69.9	69.1	−0.02	64.6	64.3	−0.01
Age, mean (SD)	66.8 (13.6)	66.7 (14.4)	−0.01	72.7 (12.7)	72.6 (13.3)	0.00
Age, %			0.08			0.08
20–29	0.6	0.8		0.2	0.3	
30–39	2.8	3.6		1.1	1.6	
40–49	7.6	8.2		3.7	4.3	
50–59	18.1	16.9		11.3	10.8	
60–69	25.1	24.9		19.6	19.9	
70–79	26.4	24.3		29.4	27.6	
80+	19.4	21.2		34.8	35.7	
Comorbidities						
Hypertension	82.4	82.1	−0.01	85.5	85.5	0.00
Gout	51.4	50.4	−0.02	39.2	39.0	0.00
Hyperlipidaemia	48.1	47.1	−0.02	39.4	39.5	0.00
Diabetes mellitus	44.6	44.6	0.00	56.3	56.5	0.01
Osteoarthritis	26.0	26.0	0.00	28.0	28.3	0.01
Ischaemic heart disease	23.8	23.9	0.00	50.1	50.1	0.00
Liver disease	14.1	13.9	−0.01	11.5	11.6	0.00
Kidney disease			0.09			0.04
CKD	36.0	34.2		42.7	41.2	
Pre-ESRD	12.8	14.5		15.2	16.4	
ESRD	2.8	2.6		4.6	4.4	
Stroke	11.8	11.8	0.00	41.9	42.3	0.01
COPD	10.5	10.5	0.00	18.6	18.0	−0.02
Heart failure	9.1	9.4	0.01	54.9	54.4	−0.01
Kidney stone	8.8	8.5	−0.01	5.4	5.2	−0.01
Atrial fibrillation	3.4	3.4	0.00	16.8	16.7	0.00
Peripheral artery disease	2.1	2.0	0.00	3.1	2.9	−0.02
Rheumatoid arthritis	1.9	1.8	−0.01	1.8	1.9	0.00
Acute myocardial infarction	1.0	1.0	0.01	12.7	12.6	0.00
Co-medications						
RAAS inhibitors	65.5	64.4	−0.02	62.1	61.3	−0.01
CCBs	45.4	46.1	0.01	48.4	48.6	0.00
NSAIDs	45.4	45.9	0.01	41.8	41.6	0.00
Antidiabetics	40.5	40.3	0.00	52.3	52.4	0.00
Beta blockers	40.2	40.4	0.01	53.0	53.0	0.00
Antiplatelets	38.8	38.5	−0.01	65.2	65.3	0.00
Statins	36.9	36.2	−0.02	38.1	38.4	0.01
Diuretics	35.4	36	0.01	68.3	68.4	0.00
Colchicine	34.5	34.5	0.00	34.6	34.7	0.00
Systemic steroids	24.3	24.6	0.01	33.2	32.5	−0.02
Analgaesics	14.1	14.3	0.01	23.4	23.1	−0.01
Benzbromazone	12.3	12.4	0.00	13.3	13.5	0.01

(Continued)

TABLE 1 Continued

Variable (%)	Low CV risk group			High CV risk group		
	Allopurinol ($n = 61,424$)	Febuxostat ($n = 61,424$)	SMD[a]	Allopurinol ($n = 12,795$)	Febuxostat ($n = 12,795$)	SMD[a]
Nitrates	12.1	12.3	0.01	38.5	37.9	−0.01
Alpha blockers	10.8	11	0.01	13.7	13.7	0.00
Antithrombotics	6.8	7.1	0.01	22.2	22.1	0.00
Antiarrhythmics	4.1	4.2	0.00	12.6	12.3	−0.01
Sulfinpyrazone	1.1	1.1	0.00	1.2	1.3	0.00
Probenecid	0.0	0.0	0.00	0.0	0.0	0.01

[a]SMD, standardized mean difference.
Low CV risk: No admission for AMI, HF, or stroke prior to the 3-year look-back period.
High CV risk: Admission for AMI, HF, or stroke prior to the 3-year look-back period.

as patients being admitted for acute myocardial infarction (AMI, ICD-9 code: 410), HF (ICD-9 code: 428), or stroke (ICD-9 code: 430-434 and 436).

Outcomes, follow-up, and covariates definition

The primary outcome was hospitalization for HF (ICD-9 code: 428). The secondary outcomes were composite CV events, defined as any hospitalization with AMI (ICD-9 code: 410), HF (ICD-9 code: 428), stroke (ICD-9 code: 430–434, and 436), all-cause mortality, and cause of CV mortality. CV mortality was defined as death due to AMI, HF, or stroke. We followed up with patients until the date of one of the following outcomes: death, the end of the study period, or discontinuation of allopurinol or febuxostat, whichever came first. The covariates included in the analyses were age, sex, comorbidities, and concomitant medications. Baseline comorbidities were retrieved during the 1-year look-back period prior to the index date. Patients diagnosed with old myocardial infarction, HF, and stroke from outpatient visits were retrieved as baseline comorbidities. Concomitant medications were retrieved during the 30-day period both before and after the index date. The details of the covariates are shown in Table 1.

Statistical analysis

Continuous variables were described as means and standard deviations and categorical variables as numbers and proportions. The distribution of time to event or death since prescription initiation was estimated using the Kaplan-Meier survival analysis. Propensity score (PS) matching was used to adjust for confounding effects. The PS was derived from multiple logistic regression models, and the degree of multicollinearity for all covariates was tested using the PS model. The allopurinol group was matched to the febuxostat group at a 1:1 ratio using a greedy algorithm. The standardized mean difference (SMD) was used to evaluate the degree of different proportions of baseline characteristics between the two groups. In order to consider competing risk, that is, death as a competing risk of CV events, Fine and Gray's sub-distribution hazard model was used (14). For gender analysis, we stratified the study population into male and female groups to estimate the primary and secondary outcomes within low or high CV risk. All statistical analyses were performed using SAS 9.4 version software (SAS Institute, Cary, NC, USA).

Sensitivity analyses

We conducted two sensitivity analyses to validate the results. First, whether long-term use of allopurinol or febuxostat influences the treatment effect was investigated by including patients who were exposed to allopurinol or febuxostat for at least 1 year and comparing the risk of heart failure, composite endpoints, all-cause mortality, and cause of CV death between allopurinol and febuxostat. Second, serum uric acid level is an important factor associated with the occurrence of CV events and is not available in claim databases. To evaluate the effect of this unmeasured confounding factor, we used the "rule-out approach" based on the method developed by Schneeweiss (15). Two data would be required in this approach, the association between drug use category and confounder (OR_{EC}) and the association between confounders and disease outcome (RR_{CD}). Then, the apparent relative risk could be calculated to plot the curve within OR_{EC} and RR_{CD}.

Results

The NHID showed that there were 269,580 patients who had used CV-related drugs and had been prescribed allopurinol

TABLE 2 Hazard ratios of heart failure, composite of end points, all-cause mortality, and cause of CV death between patients taking allopurinol and febuxostat.

Variable	Allopurinol		Febuxostat		HR (febuxostat vs. allopurinol)	95 % CI	
	No. of event	Incidence (per 1,000 person-year	No. of event	Incidence (per 1,000 person-year		Lower	Upper
Low CV risk group							
Primary outcome							
Heart failure	541	11.4	947	15.8	1.39	1.25	1.55
Secondary outcome							
Composite of end points	1,199	25.2	1,744	29.0	1.15	1.07	1.24
All-cause mortality	656	13.8	869	14.5	1.08	0.97	1.19
Cause of CV death	65.0	1.4	104	1.7	1.35	0.98	1.85
High CV risk group							
Primary outcome							
Heart failure	523	69.2	840	89.2	1.36	1.22	1.52
Secondary outcome							
Composite of end points	886	117.2	1,308	138.9	1.26	1.15	1.37
All-cause mortality	309	40.9	425	45.1	1.11	0.95	1.28
Cause of CV death	56	7.4	83	8.8	1.16	0.83	1.64

or febuxostat from 2012 to 2017. After PS matching, 61,424 and 12,795 patients initiated allopurinol/febuxostat at low CV and high CV risk, respectively. The mean age was higher in the high CV risk group than in the low CV risk group. The proportion of male patients was higher than that of female patients in both groups, particularly in gout patients with low CV risk. The baseline characteristics were similar and more comparable in the two groups after PS matching (SMD <0.1) (Table 1).

Low CV risk group

For the primary outcome, febuxostat users had a significantly higher risk for HF hospitalization than allopurinol users [hazard ratio (HR) 1.39; 95% confidence interval (CI) 1.25–1.55] (Table 2). For secondary outcomes, febuxostat users had a significantly higher risk for composite endpoints than allopurinol users (HR 1.15; 95% CI 1.07–1.24) (Table 2). There was no significant difference between the allopurinol and febuxostat groups in all-cause mortality risk (HR 1.08; 95% CI 0.97–1.19) and cause of CV mortality risk (HR 1.35; 95% CI 0.98–1.85) (Table 2).

Stratified by gender, women (HR 1.24; 95% CI 1.05–1.47) and men (HR 1.47; 95% CI 1.28–1.69) among febuxostat users also had a higher risk of HF hospitalization than allopurinol users (Figure 2). The association of composite endpoint and febuxostat was also found in men (HR 1.20; 95% CI 1.10–1.32) but not in women (HR 1.04; 95% CI 0.91–1.18) (Figure 2).

High CV risk group

The incidence of HF hospitalization was fivefold higher in the high CV risk group than in the low CV risk group (Figure 3). For the primary outcome, the febuxostat users had a higher risk for HF hospitalization than the allopurinol users (HR 1.36; 95% CI 1.22–1.52) (Table 2). With regards to the secondary outcomes, febuxostat users also had a significantly higher risk for composite endpoints than allopurinol users (HR 1.26; 95% CI 1.15–1.37). There was no significant difference between the allopurinol and febuxostat groups in all-cause mortality risk (HR 1.11; 95% CI 0.95–1.28) and cause of CV mortality risk (HR 1.16; 95% CI 0.83–1.64) (Table 2). The primary and secondary outcomes were the same in both women and men (Figure 2).

Sensitivity analyses

In the sensitivity analysis, we also found that febuxostat had an increased risk of HF hospitalization in gout patients with high CV risk (HR 2.00; 95% CI 1.59–2.51) or low CV risk (HR 1.65; 95% CI 1.40–1.96) for long-term use of medication (Table 3). With regards to the effects of unmeasured confounders (high levels of serum uric acid) in association with allopurinol, febuxostat, and HF hospitalization risk, we found that when the effect of high levels of serum uric acid had a very strong association with allopurinol or febuxostat exposure (odds ratio >10), the observed association of CV risk between allopurinol and febuxostat tended to be negligible (relative risk = 1).

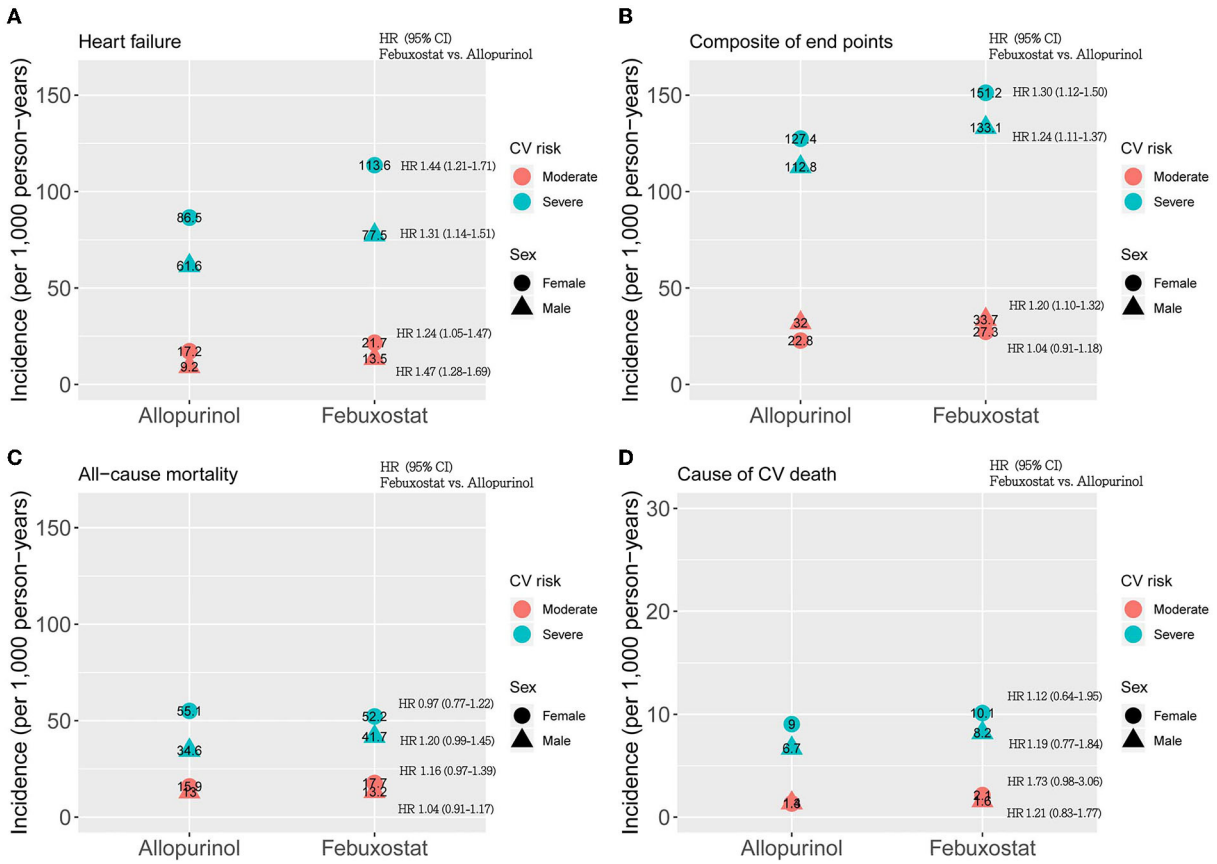


FIGURE 2
Gender analysis for CV risk-specific hazard ratios of **(A)** heart failure, **(B)** composite of end points, **(C)** all-cause mortality, and **(D)** cause of CV death between patients taking allopurinol and febuxostat. The x-axis shows two drugs: allopurinol and febuxostat, and the y-axis shows the incidence rate per 1,000 person-years. The circles and triangles represent female and male patients, respectively. The red dots represent moderate CV risk, and the blue dots represent severe CV risk. HR represents the hazard ratio. The hazard ratios were estimated in the same strata (the same sex and CV risk groups) for febuxostat users compared to allopurinol users.

However, the chance of a strong association with allopurinol or febuxostat is much lower. Therefore, the effect of high levels of serum uric acid as a confounder might be ruled out because its results were not significant enough to explain this observed association (Supplementary Figures 1A,B).

Discussion

Our study found that febuxostat use had a significantly higher risk of HF hospitalization, but similar mortality compared to allopurinol use in gout patients with low or high CV risk. In gout patients, women were more likely to experience HF hospitalization than men, and the HF hospitalization risk was highest in women with high CV risk and febuxostat use.

Gout is related to a variety of cardiovascular diseases, such as myocardial infarction, stroke, and HF. In the studies in younger populations with mean a age og <50 years old, urate-lowering therapy was associated with lowered coronary artery disease and stroke hospitalization, but not heart failure hospitalization, compared to non-urate lowering therapy in gout patients (16, 17). In particular, gout was associated with an increased risk of HF, rather than an increased incidence of coronary heart disease, stroke, or all-cause mortality, in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort study (18). Meanwhile, serum uric acid level was known to be associated with incident cardiovascular events and could be an important prognostic factor for patients with HF (19–21). Animal studies demonstrated that high serum UA increased HF and worse the prognosis, with a possible mechanism *via* its effects on oxidative stress and endothelial dysfunction (22–25). Therefore, it is suggested that lowering uric acid therapy has a beneficial effect on the prognosis of HF (26, 27). However, other studies have reported that individuals whose serum UA was too low might have an increased incidence of cardiovascular disease or mortality (28, 29). In addition, rapid reduction of serum UA

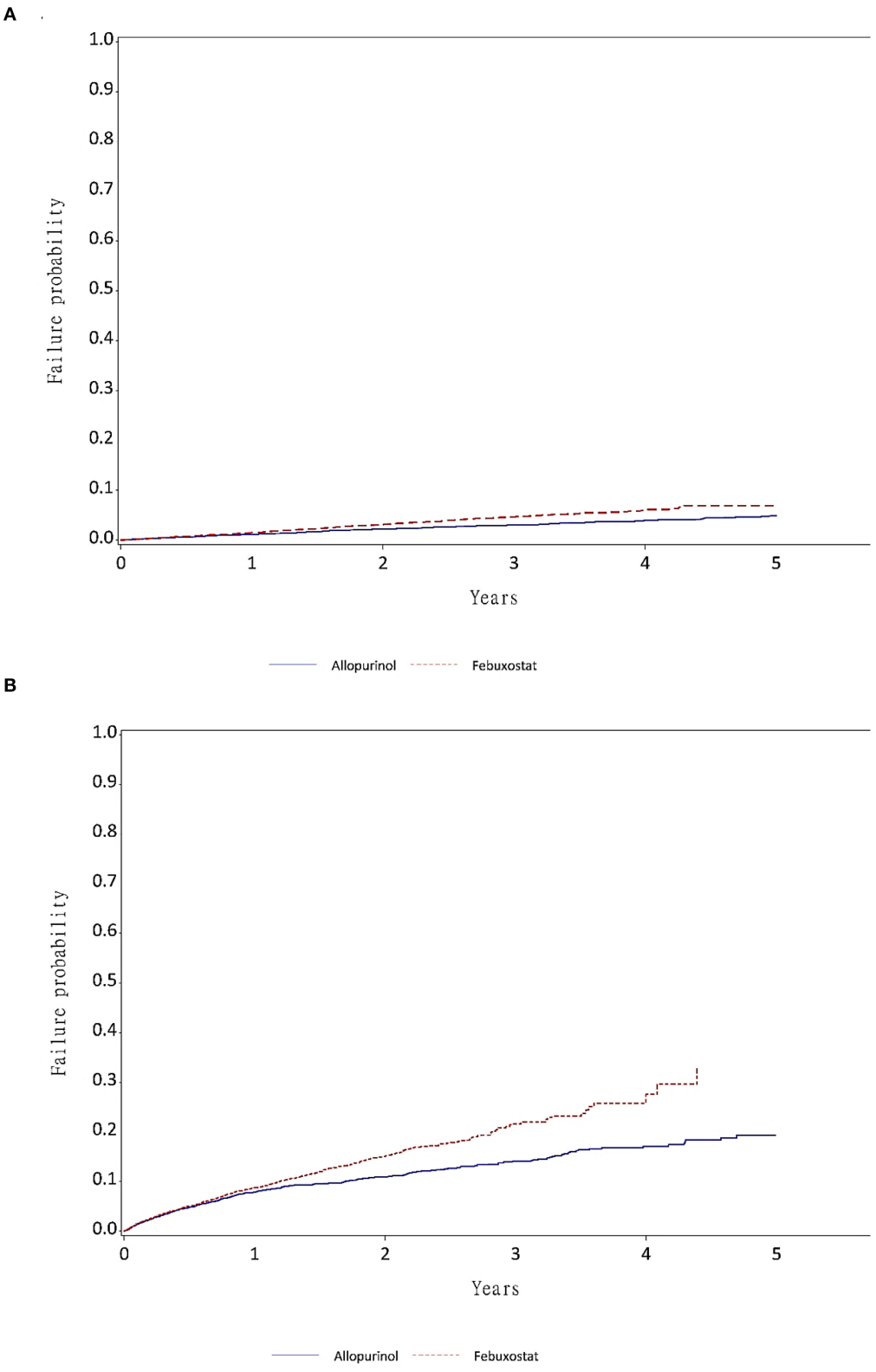


FIGURE 3
The failure function by year of medication exposure. **(A)** Failure function of time to heart failure in patients without admission for AMI, HF, or stroke prior to the 3-year look-back period (low CV risk group). **(B)** Failure function of time to heart failure in patients admitted for AMI, HF, or stroke prior to the 3-year look-back period (high CV risk group).

TABLE 3 Heart failure, composite of end points, all-cause mortality, and cause of CV death between patients taking allopurinol and febuxostat for more than 1-year.

Variable	Allopurinol		Febuxostat		HR*a* (febuxostat vs. allopurinol)	95% CI	
	No. of event	Incidence (per 1,000 person-year	No. of event	Incidence (per 1,000 person-year		Lower	Upper
Low CV risk group							
Primary outcome							
Heart failure	218	5.9	407	8.3	1.65	1.4	1.96
Secondary outcome							
Composite of end points	480	12.9	713	14.6	1.35	1.19	1.52
All-cause mortality	207	5.6	246	5.0	1.16	0.95	1.4
Cause of CV death	24	0.6	32	0.7	1.45	0.84	2.5
High CV risk group					0	0	0
Primary outcome							
Heart failure	112	20.6	248	35.4	2.00	1.59	2.51
Secondary outcome							
Composite of end points	204	37.6	363	51.8	1.64	1.37	1.95
All-cause mortality	55	10.1	76	10.9	1.26	0.88	1.81
Cause of CV death	7	1.3	18	2.6	2.22	0.90	5.48

[a]HR: The hazard ratios were adjusted by propensity score.

levels was associated with readmission of HF (30). In particular, a potent uric acid lowering drug, febuxostat, was found to have higher rates of all-cause mortality and CV mortality than allopurinol in clinical trials (4). In the CARES study, a large and randomized control study enrolled patients with major CV disease. All-cause mortality and cardiovascular mortality were higher with febuxostat use than with allopurinol use. They also found that the HF hospitalization event rate was higher in febuxostat users than in allopurinol users (4.3 vs. 3.9%) (4). The main limitations of the CARES study were the high attrition rate of 45% (lost to follow-up) and high drug discontinuation rate (56%). A population cohort study from Taiwan similarly reported increased adverse CV events in febuxostat users, compared to allopurinol users, and subgroup analysis showed that elevated risk of HF hospitalization (HR, 1.22; 95% CI, 1.13–1.36) (5). However, the mean follow-up duration of the above-mentioned studies were <1 year. In contrast, in a population study using US Medicare claims data with a mean follow-up duration of 1.1–1.2 years, febuxostat users had similar rates of new-onset HF, compared to allopurinol users (6). A trend toward a lower risk for HF hospitalisations in febuxostat users, compared to allopurinol users, was noted in a cohort study from Hong Kong, but the study population was relatively small (7). In the recently published randomized FAST trial, no risk difference of MACEs or HF hospitalisations between febuxostat and allopurinol use was found (31). However, the enrolled population had fewer comorbidities, lower adverse CV event rates, and total mortality than the population from our study, which might not be representative of the real-world setting. Compared to these conflicting results, our national population-based cohort study from the NHID, which covered more than 99.9% of the total population of 23 million in Taiwan with extremely few barriers to medical accessibility, had the advantage of assessing the CV risk of febuxostat in the general population with gout. We identified gout patients with CV risk from the National Health Insurance database by using CV-related drugs, to elucidate the risk of HF hospitalization between febuxostat and allopurinol users in real-world settings. We further divided gout patients into low or high CV risk to evaluate the risk of HF at different CV risk profiles. Moreover, we restricted our analysis to patients, who had received febuxostat or allopurinol treatment for more than 1 year. These analyses yielded consistent results with the elevated HF hospitalization risk of febuxostat, compared to allopurinol. Assuming the follow-up duration was fixed, we estimated the attributable risk of febuxostat in the low and high CV risk groups are 42.87 and 37.7%, respectively. Our study provided valuable information to illustrate the HF hospitalizations risk of febuxostat use as stratified by low or high CV risk in the Asian population.

The mechanism underlying the cardiovascular risk of febuxostat vs. allopurinol was uncertain. Previous evidence has suggested that high levels of uric acid represent an independent CV risk factor and that the use of xanthine oxidase inhibitor (XOI) may reduce the risk of major adverse CV events (MACEs) (32, 33). On the other hand, accumulating evidence suggests that increased xanthine oxidase activity contributes to increased

vascular oxidative stress and endothelial dysfunction in HF patients (25). The CV protective effects of allopurinol might be attributed to the anti-oxidant effect by inhibiting the production of reactive oxygen species released during the activity of xanthine oxidase or improving endothelium function along with the reduction of uric acid levels (34, 35). Compared with febuxostat, the CV protective effect of allopurinol might be due to the difference in chemical activities of purine (allopurinol) and non-purine-like (febuxostat) medication and was only seen in patients with allopurinol dosage ≤300 mg/day (32). In patients with HF and gout, lower dose allopurinol (≤100 mg/day) was found to have reduced HF hospitalizations or death (36). In contrast, in the EXACT-HF study, allopurinol with a target dosage of 300–600 mg/day in heart failure patients failed to improve clinical status (35). This might possibly explain the relatively beneficial effect of lower dose allopurinol in our study.

Our study found that compared to men, women with gout were substantially more likely to experience HF hospitalisations, which was independent of low or high CV risk. This result might be due to the fact that women with gout arthritis had onset of gout at an older age, had increased comorbidities with hypertension or renal insufficiency, and had more frequent use of diuretics (8). Gender differences were observed in the prevalence of heart disease, comorbidities, mortality, and treatment response to HF (11). In the general population, men have a higher incidence of HF, but the overall prevalence rate is similar in both sexes due to better long-term survival after the onset of HF in women (37). HF occurs at an older age and with fewer ischaemic causes in women compared to men. In addition, hypertension and diabetes predispose older women to HF to a greater extent than men (11). In HF patients, some comorbidities were clearly sex-specific, such as arthritis, depression, and hypothyroidism were higher in women, while arrhythmias, ischaemic heart disease, and chronic COPD were higher in men (12). Febuxostat users had an increased risk of HF hospitalisations and similar mortality in both sexes compared to allopurinol users. Interestingly, there was no significant difference between febuxostat and allopurinol users in composite CV outcomes for female gout patients with low CV risk (HR 1.04; 95% CI 0.91–1.18), and further investigation is needed. Therefore, our study reinforced the importance of HF monitoring and management in gout patients, particularly in females and patients taking febuxostat.

Our study had several strengths. First, this was a national population-based cohort study using a claims database to estimate the HF risk of febuxostat compared with allopurinol, adjusted for many known confounders. We also provided safety information regarding febuxostat, which is widely used in Asia where allopurinol hypersensitivity is common (38–40). Second, we divided our patients into low or high CV risk to further analyse the complete risk profiles in general practice. Third, we restricted our analysis to patients with more than 1 year of febuxostat or allopurinol treatment to assess the safety of long-term use. Since febuxostat at usual doses is more potent in lowering uric acid than allopurinol, it is probable that patients who started on febuxostat had higher baseline uric acid than those on allopurinol. Physicians would likely switch allopurinol to febuxostat if uric acid levels were uncontrolled. Not only in as-treated analysis, but also in the cohort of long-term use, we found that the heart failure risk was higher in febuxostat than in allopurinol users. However, there were some limitations to our study. First, unlike hospitalization of AMI or stroke which had been validated in previous studies, the coding of HF hospitalisations was not validated (41, 42). However, the Bureau of NHI regularly performs auditing reviews on a random sample of one per every 100 ambulatory claims and one per 20 inpatient claims quarterly and false reporting of diagnostic information results in a severe penalty from the Bureau. The coding validity of HF would be acceptable and misclassification of HF hospitalisations between febuxostat and allopurinol should be non-differential in this comparative study design. Second, the CV-related mortality was not been validated from death certificates, but the in-hospital mortality for AMI and stroke cases was validated, with a positive predictive value of 0.79 (43). Third, unmeasured confounding factors, such as uric acid level, blood pressure, BMI, and renal function, were not available in our study. Febuxostat was usually reimbursed when allopurinol or uricosuric treatment was ineffective in achieving target uric acid levels and in individuals who were intolerant to allopurinol. Gout patients who were resistant or intolerant to allopurinol or uricosuric treatment might be at higher risk of hyperuricemia than those who achieved effective control with allopurinol alone (44). Thus, we used a new-users design to minimize this confounding bias, as patients did not receive any study drug before 1 year on the index date. In addition, we used the rule-out sensitivity approach to estimate the extent of high levels of serum uric acid in association with allopurinol, febuxostat, and HF hospitalization risk. Further, we found it cannot possibly be strong enough confounders to explain the observed association obtained between allopurinol and febuxostat. Therefore, the effect of uric acid levels might be negligible in this study. Although we did not measure blood pressure or renal function, the baseline characteristics on renal disease and antihypertensive drugs were similar between febuxostat and allopurinol even before PS matching.

Conclusion

Febuxostat use was associated with an increase in HF hospitalization risk compared to allopurinol use in gout patients, which was independent of low or high CV risk. Considering the risk of HF hospitalization would be highest in female gout patients with high CV risk who use febuxostat, HF monitoring is particularly warranted in these patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

This study was approved by the Institutional Review Board of the National Cheng Kung University Hospital (IRB certificate number B-EX-107-018). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

C-LC and C-TY carried out this population studies, participated in study design, interpretation of data, and drafting the manuscript. C-CS participated in the design of the study, performed the statistical analysis, and drafting the manuscript. C-HH participated in study design and drafting the manuscript. C-HL participated in interpretation of the data. Y-HY conceived of the study, participated in its design and coordination, and helped to draft the manuscript. All authors have read and approved the final manuscript.

Funding

This work was supported by the Ministry of Science and Technology, Taiwan (MOST 104-2321-B-006—036 -) and National Cheng Kung University Hospital (NCKUH-10609002).

Acknowledgments

The authors thank the Health Data Science Center, National Cheng Kung University Hospital, for providing administrative and technical support, and Dr. Swu-Jane Lin for her helpful review and advice regarding manuscript preparation.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.891606/full#supplementary-material

References

1. Cox P, Gupta S, Zhao SS, Hughes DM. The incidence and prevalence of cardiovascular diseases in gout: a systematic review and meta-analysis. *Rheumatol Int.* (2021) 41:1209–19. doi: 10.1007/s00296-021-04876-6

2. Palazzuoli A, Ruocco G, De Vivo O, Nuti R, McCullough PA. Prevalence of hyperuricemia in patients with acute heart failure with either reduced or preserved ejection fraction. *Am J Cardiol.* (2017) 120:1146–50. doi: 10.1016/j.amjcard.2017.06.057

3. Piepoli MF, Salvioni E, Corra U, Doni F, Bonomi A, La Gioia R, et al. Increased serum uric acid level predicts poor prognosis in mildly severe chronic heart failure with reduced ejection fraction. An analysis from the MECKI score research group. *Eur J Intern Med.* (2020) 72:47–52. doi: 10.1016/j.ejim.2019.11.003

4. White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med.* (2018) 378:1200–10. doi: 10.1056/NEJMoa1710895

5. Su CY, Shen LJ, Hsieh SC, Lin LY, Lin FJ. Comparing cardiovascular safety of febuxostat and allopurinol in the real world: a population-based cohort study. *Mayo Clin Proc.* (2019) 94:1147–57. doi: 10.1016/j.mayocp.2019.03.001

6. Zhang M, Solomon DH, Desai RJ, Kang EH, Liu J, Neogi T, et al. Assessment of cardiovascular risk in older patients with gout initiating febuxostat versus allopurinol: population-based cohort study. *Circulation.* (2018) 138:1116–26. doi: 10.1161/CIRCULATIONAHA.118.033992

7. Ju C, Lai RWC, Li KHC, Hung JKF, Lai JCL, Ho J, et al. Comparative cardiovascular risk in users versus non-users of xanthine oxidase inhibitors and febuxostat versus allopurinol users. *Rheumatology.* (2020) 59:2340–9. doi: 10.1093/rheumatology/kez576

8. Dirken-Heukensfeldt KJ, Teunissen TA, van de Lisdonk H, Lagro-Janssen AL. Clinical features of women with gout arthritis. A systematic review. *Clin Rheumatol.* (2010) 29:575–82. doi: 10.1007/s10067-009-1362-1

9. Ekundayo OJ, Dell'Italia LJ, Sanders PW, Arnett D, Aban I, Love TE, et al. Association between hyperuricemia and incident heart failure among older adults: a propensity-matched study. *Int J Cardiol.* (2010) 142:279–87. doi: 10.1016/j.ijcard.2009.01.010

10. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National health and nutrition examination survey. *JAMA.* (2000) 283:2404–10. doi: 10.1001/jama.283.18.2404

11. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, Brinton RD, Carrero JJ, DeMeo DL, et al. Sex and gender: modifiers of health, disease, and medicine. *Lancet.* (2020) 396:565–82. doi: 10.1016/S0140-6736(20)31561-0

12. Gracia Gutierrez A, Poblador-Plou B, Prados-Torres A, Ruiz Laiglesia FJ, Gimeno-Miguel A. Sex differences in comorbidity, therapy, and health services' use of heart failure in spain: evidence from real-world data. *Int J Environ Res Public Health*. (2020) 17:2136. doi: 10.3390/ijerph17062136

13. MOHW 2018; Pages. *Accessed at Health and Welfare Data Science Center*. Available online at: https://dep.mohw.gov.tw/DOS/lp-2506-113.html2022 (accessed March 2, 2022).

14. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* (1999) 94:496–509. doi: 10.1080/01621459.1999.10474144

15. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf.* (2006) 15:291–303. doi: 10.1002/pds.1200

16. Yen FS, Hsu CC, Li HL, Wei JC, Hwu CM. Urate-lowering therapy may prevent the development of coronary artery disease in patients with gout. *Front Med.* (2020) 7:63. doi: 10.3389/fmed.2020.00063

17. Yen FS, Hsu CC Li HL, Wei JC, Hwu CM. Urate-lowering therapy may mitigate the risks of hospitalized stroke and mortality in patients with gout. *PLoS ONE.* (2020) 15:e0234909. doi: 10.1371/journal.pone.0234909

18. Colantonio LD, Saag KG, Singh JA, Chen LG, Reynolds RJ, Gaffo A, et al. Gout is associated with an increased risk for incident heart failure among older adults: the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort study. *Arthritis Res Ther*. (2020) 22:86. doi: 10.1186/s13075-020-02175-2

19. Coiro S, Carluccio E, Biagioli P, Alunni G, Murrone A, D'Antonio A, et al. Elevated serum uric acid concentration at discharge confers additive prognostic value in elderly patients with acute heart failure. *Nutr Metab Cardiovasc Dis.* (2018) 28:361–8. doi: 10.1016/j.numecd.2017.12.009

20. Ambrosio G, Leiro MGC, Lund LH, Coiro S, Cardona A, Filippatos G, et al. Serum uric acid and outcomes in patients with chronic heart failure through the whole spectrum of ejection fraction phenotypes: analysis of the ESC-EORP heart failure long-term (HF LT) Registry. *Eur J Intern Med.* (2021) 89:65–75. doi: 10.1016/j.ejim.2021.04.001

21. Carluccio E, Coiro S, Ambrosio G. Unraveling the relationship between serum uric acid levels and cardiovascular risk. *Int J Cardiol.* (2018) 253:174–5. doi: 10.1016/j.ijcard.2017.11.035

22. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the framingham heart study. *Ann Intern Med.* (1999) 131:7–13. doi: 10.7326/0003-4819-131-1-199907060-00003

23. Wu AH, Gladden JD, Ahmed M, Ahmed A, Filippatos G. Relation of serum uric acid to cardiovascular disease. *Int J Cardiol.* (2016) 213:4–7. doi: 10.1016/j.ijcard.2015.08.110

24. Pagidipati NJ, Hess CN, Clare RM, Akerblom A, Tricoci P, Wojdyla D, et al. An examination of the relationship between serum uric acid level, a clinical history of gout, and cardiovascular outcomes among patients with acute coronary syndrome. *Am Heart J.* (2017) 187:53–61. doi: 10.1016/j.ahj.2017.02.023

25. Landmesser U, Spiekermann S, Dikalov S, Tatge H, Wilke R, Kohler C, et al. Vascular oxidative stress and endothelial dysfunction in patients with chronic heart failure: role of xanthine-oxidase and extracellular superoxide dismutase. *Circulation.* (2002) 106:3073–8. doi: 10.1161/01.CIR.0000041431.57222.AF

26. Hare JM, Mangal B, Brown J, Fisher C Jr, Freudenberger R, Colucci WS, et al. Impact of oxypurinol in patients with symptomatic heart failure Results of the OPT-CHF study. *J Am Coll Cardiol.* (2008) 51:2301–9. doi: 10.1016/j.jacc.2008.01.068

27. Nagayama D, Yamaguchi T, Saiki A, Imamura H, Sato Y, Ban N, et al. High serum uric acid is associated with increased cardio-ankle vascular index (CAVI) in healthy Japanese subjects: a cross-sectional study. *Atherosclerosis.* (2015) 239:163–8. doi: 10.1016/j.atherosclerosis.2015.01.011

28. Lee SY, Park W, Suh YJ, Lim MJ, Kwon SR, Lee JH, et al. Association of serum uric acid with cardiovascular disease risk scores in Koreans. *Int J Environ Res Public Health*. (2019) 16:4632. doi: 10.3390/ijerph16234632

29. Cho SK, Chang Y, Kim I, Ryu S. U-shaped association between serum uric acid level and risk of mortality: a cohort study. *Arthritis Rheumatol.* (2018) 70:1122–32. doi: 10.1002/art.40472

30. Lee JS, Oh JS, Kim YG, Lee CK, Yoo B, Hong S. Rapid reduction in uric acid by a urate-lowering agent is associated with recurrent cardiovascular events. *Med Hypotheses*. (2020) 141:109740. doi: 10.1016/j.mehy.2020.109740

31. Mackenzie IS, Ford I, Nuki G, Hallas J, Hawkey CJ, Webster J, et al. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. *Lancet.* (2020) 396:1745–57. doi: 10.1016/S0140-6736(20)32234-0

32. Bredemeier M, Lopes LM, Eisenreich MA, Hickmann S, Bongiorno GK, d'Avila R, et al. Xanthine oxidase inhibitors for prevention of cardiovascular events: a systematic review and meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord.* (2018) 18:24. doi: 10.1186/s12872-018-0757-9

33. Bove M, Cicero AF, Veronesi M, Borghi C. An evidence-based review on urate-lowering treatments: implications for optimal treatment of chronic hyperuricemia. *Vasc Health Risk Manag.* (2017) 13:23–8. doi: 10.2147/VHRM.S115080

34. Doehner W, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation.* (2002) 105:2619–24. doi: 10.1161/01.CIR.0000017502.58595.ED

35. Givertz MM, Anstrom KJ, Redfield MM, Deswal A, Haddad H, Butler J, et al. Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients: the xanthine oxidase inhibition for hyperuricemic heart failure patients (EXACT-HF) study. *Circulation.* (2015) 131:1763–71. doi: 10.1161/CIRCULATIONAHA.114.014536

36. Thanassoulis G, Brophy JM, Richard H, Pilote L. Gout, allopurinol use, and heart failure outcomes. *Arch Intern Med.* (2010) 170:1358–64. doi: 10.1001/archinternmed.2010.198

37. Stromberg A, Martensson J. Gender differences in patients with heart failure. *Eur J Cardiovasc Nurs.* (2003) 2:7–18. doi: 10.1016/S1474-5151(03)00002-1

38. Lu N, Rai SK, Terkeltaub R, Kim SC, Menendez ME, Choi HK. Racial disparities in the risk of stevens-johnson syndrome and toxic epidermal necrolysis as urate-lowering drug adverse events in the United States. *Semin Arthritis Rheum.* (2016) 46:253–8. doi: 10.1016/j.semarthrit.2016.03.014

39. Kang DY, Yun J, Lee SY, Koh YI, Sim DW, Kim S, et al. A nationwide study of severe cutaneous adverse reactions based on the multicenter registry in Korea. *J Allergy Clin Immunol Pract.* (2021) 9:929–36.e7. doi: 10.1016/j.jaip.2020.09.011

40. Yang CY, Chen CH, Deng ST, Huang CS, Lin YJ, Chen YJ, et al. Allopurinol use and risk of fatal hypersensitivity reactions: a nationwide population-based study in Taiwan. *JAMA Intern Med.* (2015) 175:1550–7. doi: 10.1001/jamainternmed.2015.3536

41. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the national health insurance research database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf.* (2011) 20:236–42. doi: 10.1002/pds.2087

42. Cheng CL, Lee CH, Chen PS, Li YH, Lin SJ, Yang YH. Validation of acute myocardial infarction cases in the national health insurance research database in taiwan. *J Epidemiol.* (2014) 24:500–7. doi: 10.2188/jea.JE20140076

43. Cheng CL, Chien HC, Lee CH, Lin SJ, Yang YHK. Validity of in-hospital mortality data among patients with acute myocardial infarction or stroke in national health insurance research database in Taiwan. *Int J Cardiol.* (2015) 201:96–101. doi: 10.1016/j.ijcard.2015.07.075

44. Mankad R. Cardiovascular safety of febuxostat versus allopurinol in the real world: old reliable comes out on top. *Mayo Clin Proc.* (2019) 94:1128–30. doi: 10.1016/j.mayocp.2019.05.012

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 12 September 2022
DOI 10.3389/fcvm.2022.1000700

OPEN ACCESS

EDITED BY
Matteo Pagnesi,
ASST Spedali Civili di Brescia, Italy

REVIEWED BY
Dario Cani,
ASST Spedali Civili, Italy
Deirdre M. Mooney,
Maine Medical Center, United States

*CORRESPONDENCE
Pablo Díez-Villanueva
pablo_diez_villanueva@hotmail.com

†These authors share first authorship
‡These authors share last authorship

SPECIALTY SECTION
This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 22 July 2022
ACCEPTED 26 August 2022
PUBLISHED 12 September 2022

CITATION
Díez-Villanueva P, Jiménez-Méndez C, Bonanad C, Ortiz-Cortés C, Barge-Caballero E, Goirigolzarri J, Esteban-Fernández A, Pérez-Rivera A, Cobo M, Sanz-García A, Formiga F, Ariza-Solé A, Martínez-Sellés M and Alfonso F (2022) Sex differences in the impact of frailty in elderly outpatients with heart failure. *Front. Cardiovasc. Med.* 9:1000700. doi: 10.3389/fcvm.2022.1000700

Sex differences in the impact of frailty in elderly outpatients with heart failure

Pablo Díez-Villanueva[1*†], César Jiménez-Méndez[1†], Clara Bonanad[2], Carolina Ortiz-Cortés[3], Eduardo Barge-Caballero[4,5], Josebe Goirigolzarri[6], Alberto Esteban-Fernández[7], Angel Pérez-Rivera[8], Marta Cobo[5,9], Ancor Sanz-García[10], Francesc Formiga[11], Albert Ariza-Solé[12], Manuel Martínez-Sellés[13‡] and Fernando Alfonso[1‡]

[1]Cardiology Department, Hospital Universitario de la Princesa, Universidad Autónoma de Madrid, CIBERCV, IIS-IP, Madrid, Spain, [2]Cardiology Department, Hospital Clínico Universitario de Valencia, Instituto de Investigación Sanitaria (INCLIVA), Valencia, Spain, [3]Cardiology Department, Hospital Universitario San Pedro de Alcántara, Cáceres, Spain, [4]Cardiology Department, Complejo Hospitalario Universitario de a Coruña, A Coruña, Spain, [5]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain, [6]Cardiology Department, Hospital Clínico Universitario San Carlos, Madrid, Spain, [7]Cardiology Department, Hospital Universitario Severo Ochoa, Leganés, Spain, [8]Cardiology Department, Hospital Universitario de Burgos, Universidad Isabel I, Burgos, Spain, [9]Cardiology Department, Hospital Universitario Puerta de Hierro, Madrid, Spain, [10]Unidad de Análisis de Datos, Instituto de Investigación Sanitaria del Hospital Universitario de la Princesa, Madrid, Spain, [11]Servicio de Medicina Interna, Hospital Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain, [12]Cardiology Department, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain, [13]Cardiology Department, Hospital Universitario Gregorio Marañón, CIBERCV, Universidad Europea, Universidad Complutense, Madrid, Spain

Introduction: Frailty is common among patients with heart failure (HF). Our aim was to address the role of frailty in the management and prognosis of elderly men and women with HF.

Methods and results: Prospective multicenter registry that included 499 HF outpatients ≥75 years old. Mean age was 81.4 ± 4.3 years, and 193 (38%) were women. Compared with men, women were older (81.9 ± 4.3 vs. 81.0 ± 4.2 years, $p = 0.03$) and had higher left ventricular ejection fraction (46 vs. 40%, $p < 0.001$) and less ischemic heart disease (30 vs. 57%, $p < 0.001$). Women had a higher prevalence of frailty (22 vs. 10% with Clinical Frailty Scale, 34 vs. 15% with FRAIL, and 67% vs. 46% with the mobility visual scale, all p-values < 0.001) and other geriatric conditions (Barthel index ≤90: 14.9 vs. 6.2%, $p = 0.003$; malnutrition according to Mini Nutritional Assessment Short Formulary ≤11: 55% vs. 42%, $p = 0.007$; Pfeiffer cognitive test's errors: 1.6 ± 1.7 vs. 1.0 ± 1.6, $p < 0.001$; depression according to Yesavage test; $p < 0.001$) and lower comorbidity (Charlson index ≥4: 14.1% vs. 22.1%, $p = 0.038$). Women also showed worse self-reported quality of life (6.5 ± 2.1 vs. 6.9 ± 1.9, on a scale from 0 to 10, $p = 0.012$). In the univariate analysis, frailty was an independent predictor of mortality in men [Hazard ratio (HR) 3.18, 95% confidence interval (CI) 1.29–7.83, $p = 0.012$; HR 4.53, 95% CI 2.08–9.89, $p < 0.001$; and HR 2.61, 95% CI 1.23–5.43, $p = 0.010$, according to FRAIL,

Clinical Frailty Scale, and visual mobility scale, respectively], but not in women. In the multivariable analysis, frailty identified by the visual mobility scale was an independent predictor of mortality (HR 1.95, 95% CI 1.04–3.67, $p = 0.03$) and mortality/readmission (HR 2.06, 95% CI 1.05–4.04, $p = 0.03$) in men.

Conclusions: In elderly outpatients with HF frailty is more common in women than in men. However, frailty is only associated with mortality in men.

KEYWORDS

frailty, heart failure, elderly, sex, prognosis

Introduction

Heart failure (HF) is one of the main causes of morbimortality in older patients (1). Both its incidence and prevalence are increasing due, in part, to population aging (2, 3). However, elderly patients are still frequently underrepresented in clinical trials (4), and a better understanding of the clinical factors associated with prognosis in this population is needed (5). Frailty, which is common in elderly patients with HF, is an age-associated clinical syndrome characterized by a decrease in physiological reserve that entails an increased vulnerability to stressors (6–8). As such, frailty should be adequately both identified and addressed in HF patients (9).

Besides, sex-related differences in men and women with HF have been identified, not only from a pathophysiological point of view, but also regarding the different impact of traditional risk factors, together with specific sex-related factors and different prognosis in men and women (10, 11).

Our aim was to address the role of frailty and sex differences in the management and prognosis of elderly outpatients with HF.

Methods

The FRAGIC registry (*impacto de la FRAGilidad y otros síndromes Geriátricos en el manejo clínico y pronóstico del paciente anciano ambulatorio con Insuficiencia Cardíaca)* is an prospective observational multicenter study. The rationale of this study has been previously reported (12). Briefly, ambulatory patients ≥75 years with chronic HF treated according to current guidelines (13) were prospectively included between March and September 2019. Baseline clinical characteristics and laboratory and echocardiographic parameters were collected. Functional status and functional class as well as comorbidity and a systematic and comprehensive geriatric evaluation were registered in all patients at the first visit. Medical treatment was optimized according to clinical practice guidelines recommendations in all patients. Follow-up was carried out *via* clinical visit, electronic medical records review and/or telephone contacts at 1 year follow up. Total mortality and the need for hospitalization for any cause (duration >24 h) were recorded. The ethics committee of Hospital Universitario de La Princesa (Madrid, Spain) approved the study and the protocol was redacted according to the Declaration of Helsinki. All patients included in this study willingly completed the informed consent.

Statistical analysis

For the purpose of this analysis, patients were divided by sex. Percentages were used to represent categorical variables, and the mean and standard deviation were used for continuous variables. The univariate comparison between each independent variable and sex, was assessed by Log-Rank test, from which *p*-values and Hazard ratios (HR) were obtained. Next, a predictive model was fitted using Cox Regression (multivariate analysis) by selecting those variables from the univariate analysis ($p < 0.05$ for women, and $p < 0.001$ for men, this difference is due to the high number of statistically significant variables in univariate analysis in men); this analysis was performed separately for women and men by considering as outcome mortality or the combination of mortality and readmission. Disease-specific survival or the cumulative event of readmission for any cause and mortality was obtained using the Kaplan-Meier method. Comparison of survival distributions was performed using a Log-Rank test. Data were analyzed using our own codes and basic functions in R, version 4.0.3 (http://www.R-project.org; the R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics and geriatric syndromes according to sex

A total of 499 ambulatory patients with chronic HF were included. Mean age was 81.4 ± 4.3 years, and 38% were women. Compared with men, women were older (81.9 ±

4.3 vs. 81.0 ± 4.2 years, $p = 0.03$) and had significantly higher left ventricular ejection fraction as well as less previous ischemic heart disease. Baseline variables are depicted in Table 1. Comorbidity prevalence was higher in men. Women had a higher prevalence of frailty and other geriatric conditions. Frailty was always more common in women irrespective of the scale (all p values< 0.001). Physical status according to short physical performance battery (SSPB) was also lower in women, in whom malnutrition and depression, as well as worse self-reported quality of life, were also more frequent (Table 1).

Clinical outcomes during follow-up according to sex

During a mean follow up of 371 (361–387) days, 58 patients (11.6%) died (32 men and 26 women). The leading cause of mortality was non-cardiovascular mortality (58%). Table 2 shows the variables associated with 1-year mortality according to sex in univariate analysis. In men, lower values of hemoglobin, lymphocytes, albumin and sodium, as well as urea and renal dysfunction were associated with mortality, whilst a lower platelet count was associated with prognosis in women. Data related to more advanced HF were associated with worse prognosis in women. Higher doses of diuretics, higher levels of natriuretic peptides and reduced right ventricular function were the only parameters independently associated with mortality in men and women. Frailty was associated with mortality only in men, although a trend toward higher mortality was observed in women according to some scales. Figure 1 shows the differential impact of frailty according to sex in mortality

During follow up, 202 patients (40%) fulfilled the 1-year composite endpoint of mortality and readmission for any cause:117 (38%) men and 85 (44.5%) women. Table 3 shows the variables associated with this endpoint according to sex in univariate analysis. Atrial fibrillation, physical signs of congestion, lower hemoglobin or lymphocytes levels, and a more advanced HF, were associated with mortality and readmission in men and women. Comorbidity and geriatric syndromes, were associated with worse prognosis in men, but not in women (except frailty estimated by Clinical Frailty Scale). Figure 2 shows the different impact of frailty in men and women in the composite endpoint.

In the multivariable analysis, frailty identified by the visual mobility scale was an independent predictor of mortality (HR 1.95, 95% CI 1.04–3.67, $p = 0.03$) and mortality/readmission (HR 2.06, 95% CI 1.05–4.04, $p = 0.03$) in men (Tables 4, 5). In women, higher doses of diuretics and higher levels of natriuretic peptides were the only factors significantly associated with mortality, while hemoglobin, right ventricular dilatation and higher diuretic doses were independently associated with mortality/readmission during follow-up (Tables 6, 7).

Discussion

To the best of our knowledge, this is the first study addressing sex differences in the impact of frailty in elderly ambulatory patients with chronic HF followed by cardiologists. Main findings of our study are: (1) elderly men and women with chronic HF show a different baseline and clinical profile; (2) frailty and other geriatric syndromes are more common in women, although they only associate worse prognosis in men; (3) some parameters common in advanced stages of HF entail worse prognosis in men and women, but differ between them.

There are several sex differences in patients with HF previously reported, as traditional risk factors, pathophysiology and response to treatment differs between men and women (10, 11, 14, 15). In a large multicentre study, including >80,000 hospitalized patients, Hsich et al. described, more than a decade ago, that women with HF were usually older than men, more likely to have hypertension and depression and less likely to have coronary or peripheral artery disease. However, in-hospital mortality rates were similar irrespective of sex (16). Our study showed similar results, since HF women were older, and had less frequently a previous history of coronary or peripheral artery disease. However, patients included in our study were all ambulatory patients with chronic HF (i.e., not hospitalized), and mean age was much higher. Besides, our study adds novel evidence with valuable data from the late clinical follow up, unlike the study by Hsich et al.

In FRAGIC study, women presented with better LVEF compared with men, as previously reported (10). Such differences regarding the subtype of HF have been suggested to be partially explained due to inherent physiological distinctions between men and women (17, 18). Regarding clinical presentation, some studies suggest women usually present with worse functional class and more advanced symptoms (10, 11, 14). Interestingly, in our study key issues like NTproBNP levels or NYHA functional class did not differ at baseline between men and women, unlike other previous studies, in which female sex had been associated with worse functional class and even higher NTproBNP levels regardless of LVEF (14, 19). In FRAGIC study, higher levels of natriuretic peptides and diuretics doses were significantly associated with higher mortality in women at 1 year follow-up. On the other hand, lower hemoglobin and sodium levels and higher NTproBNP levels independently associated poorer prognosis in men, together with the presence of frailty identified by the visual mobility scale.

Regarding geriatric conditions, HF commonly coexists with frailty, especially in the elder population, yet the prevalence

10.3389/fcvm.2022.1000700

TABLE 1 Baseline characteristics.

	Overall $n = 499$	Men (308, 61.7%)	Women (191, 38.3%)	*p*-value
Mean age (years)	81.4 ± 4.3	81.0 ± 4.2	81.9 ± 4.3	0.03
>85 years	25.9%	28.3%	24.3%	0.33
Body mass index (kg/m^2)	27.6 ± 4.6	27.5 ± 4.1	27.7 ± 5.4	0.719
Hypertension	400 (80.3%)	241 (78.5%)	159 (83.2%)	0.238
Diabetes mellitus	199 (40%)	125 (40.7%)	74 (38.7%)	0.732
Dyslipidaemia	334 (67.3%)	210 (68.6%)	124 (65.3%)	0.498
Past smoker	166 (33.4%)	147 (47.9%)	19 (10%)	<0.001
Prior stroke	60 (12.1%)	38 (12.4%)	22 (11.5%)	0.758
Prior peripheral artery disease	55 (11.0%)	46 (14.9%)	9 (4.74%)	0.001
Atrial fibrillation	263 (52.7%)	163 (52.9%)	100 (52.4%)	0.975
Chronic obstructive pulmonary disease	74 (14.8%)	60 (19.5%)	14 (7.33%)	<0.001
Chronic renal failure	210 (42.1%)	128 (41.6%)	82 (42.9%)	0.835
Left ventricular ejection fraction (%)	42 ± 13	40 ± 12	46 ± 15	<0.001
NYHA ≥II	422 (84.5%)	255 (82.8%)	167 (87.4%)	0.106
Ischemic HF	161 (48.2%)	130 (56.8%)	31 (29.5%)	<0.001
Idiopathic HF	121 (36.2%)	70 (30.6%)	51 (48.6%)	<0.001
Systolic blood pressure (mmHg)	123 ± 19	122 ± 19	126 ± 19	0.028
Heart rate (bpm)	69 ± 12	69 ± 12	71 ± 12	0.027
Laboratory findings				
Hemoglobin (g/dl)	13.3 ± 1.7	13.7 ± 1.8	12.7 ± 1.4	<0.001
Platelet count (×10^3/mm^3)	187 ± 54	179 ± 50	202 ± 59	<0.001
Leucocytes (×10^3/mm^3)	7.1 ± 2.2	7.09 ± 2.0	7.07 ± 2.4	0.916
Lymphocytes (×10^3/mm^3)	1.9 ± 1.3	1.87 ± 1.1	2.01 ± 1.5	0.254
Estimated glomerular filtration rate (eGFR, ml/min/1.72 m^2)	52.1 ± 17.5	53.6 ± 17.4	49.6 ± 17.6	0.015
Sodium (mEq/L)	140 (3.1)	141 (3.1)	141 (3.1)	0.501
Potassium (mEq/L)	4.5 (0.5)	4.52 (0.5)	4.48 (0.5)	0.486
Brain natriuretic peptide NT proBNP (pg/ml)	2817 ± 3803	2940 ± 4032	2617 ± 3381	0.341
Ultrasensitive troponin (ng/ml)	26 ± 28	28 ± 32	20 ± 18	0.019
Cholesterol (mg/dl)	151 ± 35	145 ± 33	162 ± 36	<0.001
LDL-cholesterol (mg/dl)	80 ± 29	76 ± 27	88 ± 30	<0.001
Albumin (g/dl)	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.4	0.514
Ferritin (ng/ml)	194 ± 18	200 ± 17	184 ± 22	0.424
Transferrin (mg/dl)	232 ± 47	229 ± 47	237 ± 48	0.126
Transferrin saturation (%)	24 ± 10	25 ± 10	23 ± 9	0.072
Geriatric assessment and comorbidity				
Comorbidity (Charlson index ≥4)	95 (19.0%)	68 (22.1%)	27 (14.1%)	0.038
Dependency (Barthel index ≤90)	96 (19.2%)	46 (14.9%)	50 (26.2%)	0.003
Dependency for daily activities (Lawton-Brody index ≤5)	183 (36.7%)	116 (37.7%)	67 (35.1%)	0.627
Pfeiffer cognitive test	1.22 ± 1.7	1.01 ± 1.6	1.57 ± 1.7	<0.001
Frailty (clinical frailty scale ≥4)	73 (14.6%)	32 (10.4%)	41 (21.5%)	0.001
Frailty (FRAIL)	111 (22.2%)	47 (15.3%)	64 (33.5%)	<0.001
Frailty (mobility visual scale ≥2)	269 (53.9%)	141 (45.8%)	128 (67.0%)	<0.001
Frailty (SPPB ≤9)	372 (74.5%)	211 (68.5%)	161 (84.3%)	<0.001
Nutrition status (MNA-SF ≤11)	235 (47.1%)	130 (42.2%)	105 (55.0%)	0.007
Yesavage test				
(v-15)	133 (26.6%)	59 (19.2%)	74 (38.7%)	<0.001
(v-5)	201 (40.3%)	101 (32.8%)	100 (52.4%)	
Self-reported quality of life (0–10)	6.8 ± 2	6.94 ± 1.91	6.47 ± 2.08	0.012
Average prescribed drugs	9.6 ± 3.2	9.6 ± 3.2	9.6 ± 3.3	0.93

TABLE 2 Variables significantly associated with 1-year mortality according to sex.

	Men				Women			
	No event ($n = 276$)	Event ($n = 32$)	HR CI 95%	*p*-value	No event ($n = 165$)	Event ($n = 26$)	HR CI 95%	*p*-value
Malignancy*	55 (19%)	13 (40.6%)	2.66 [1.31; 5.39]	0.007	28 (17.0%)	6 (23.1%)	1.51 [0.60; 3.76]	0.377
Hemoglobin (g/dl)*	13.9 (1.66)	12.1 (2.01)	0.56 [0.47; 0.68]	<0.001	12.8 (1.32)	12.3 (1.83)	0.77 [0.58; 1.02]	0.072
Platelets ($\times 10^3$ /μl)[y]	178 (48.0)	187 (64.8)	1.00 [1.00; 1.01]	0.331	205 (59.9)	184 (52.9)	0.99 [0.99; 1.00]	0.035
Lymphocites ($\times 10^3$/μl)*	1.92 (1.09)	1.42 (0.59)	0.38 [0.21; 0.69]	0.001	2.08 (1.65)	1.59 (0.76)	0.64 [0.40; 1.02]	0.058
eGFR (ml/min/1.72 m^2)*	54.6 (17.1)	45.0 (17.3)	0.97 [0.95; 0.99]	0.002	49.8 (17.5)	48.3 (18.1)	0.99 [0.97; 1.02]	0.562
Urea (mg/dl)*	64.3 (30)	81.5 (42)	1.01 [1.00; 1.02]	0.002	66.9 (31)	77.1 (37)	1.01 [1.00; 1.02]	0.095
Sodium (mEq/L)*	141 (3)	139 (4)	0.81 [0.74; 0 0.91]	<0.001	141 (3)	141 (3)	1.00 [0.88; 1.13]	0.968
NT-proBNP (pg/ml)*†	2586 (3272)	6202 (7567)	1.00 [1.00; 1.00]	<0.001	2437 (3388)	3725 (3178)	1.00 [1.00; 1.00]	0.014
Albumin (mg/dl)*	4.15 (0.41)	3.92 (0.50)	0.27 [0.11; 0.65]	0.003	4.10 (0.42)	4.06 (0.44)	0.55 [0.16; 1.92]	0.348
Non-dilated right ventricle (%)†	224 (83.6%)	25 (80.6%)	0.80 [0.33; 1.95]	0.626	146 (89.6%)	12 (57.1%)	0.20 [0.08; 0.47]	<0.001
Systolic pulmonary artery pressure (mmHg)†	38.6 (11.8)	42.3 (12.2)	1.03 [1.00; 1.06]	0.072	38.8 (12.9)	49.8 (20.1)	1.03 [1.01; 1.05]	0.004
Significant tricuspid regurgitation†	29 (10.7%)	4 (12.9%)	1.45 [0.51; 4.16]	0.487	22 (13.6%)	11 (42.3%)	3.94 [1.80; 8.63]	0.001
Significant mitral regurgitation†	39 (14.3%)	8 (25.8%)	1.91 [0.85; 4.27]	0.116	18 (11.1%)	8 (30.8%)	4.31 [1.80; 10.3]	0.001
TAPSE (mm)*,†	18.3 (4.1)	16 (2.8)	0.88 [0.79; 0.97]	0.012	18.7 (3.7)	16.7 (4.3)	0.88 [0.79; 0.99]	0.032
Diuretic mean dose (mg of furosemide)*,†	55.1 (36.2)	80.8 (45.1)	1.01 [1.01; 1.02]	0.001	57.9 (32.3)	78.0 (45.8)	1.01 [1.00; 1.02]	0.004
Frailty (FRAIL)*	37 (13.4%)	10 (31.2%)	3.18 (1.29–7.83)	0.012	54 (32.7%)	10 (38.5%)	5.79 (0.74—45.3)	0.094
Frailty (CFS)*	23 (8.33%)	9 (28.1%)	4.53 (2.08–9.89)	<0.001	36 (21.8%)	5 (19.2%)	0.84 (0.32- 2.24)	0.732
Frailty (mobility visual scale ≥2)*	120 (43.5%)	21 (65.6%)	2.61 (1.26–5.43)	0.010	107 (64.8%)	21 (80.8%)	2.35 (0.88–6.24)	0.086
Malnutrition (MNA-SF ≤11)*	109 (39.5%)	21 (65.6%)	2.86 (1.38–5.94)	0.005	87 (52.7%)	18 (69.2%)	1.98 (0.86–4.57)	0.107

CFS, Clinical Frailty Scale; eGFR, estimated glomerular filtration rate; MNA-SF, Mini Nutritional Assessment Short Formulary; TAPSE, tricuspid annular plane systolic excursion.

*Variables significantly associated with 1-year mortality in men.

†Variables significantly associated with 1-year mortality in women.

10.3389/fcvm.2022.1000700

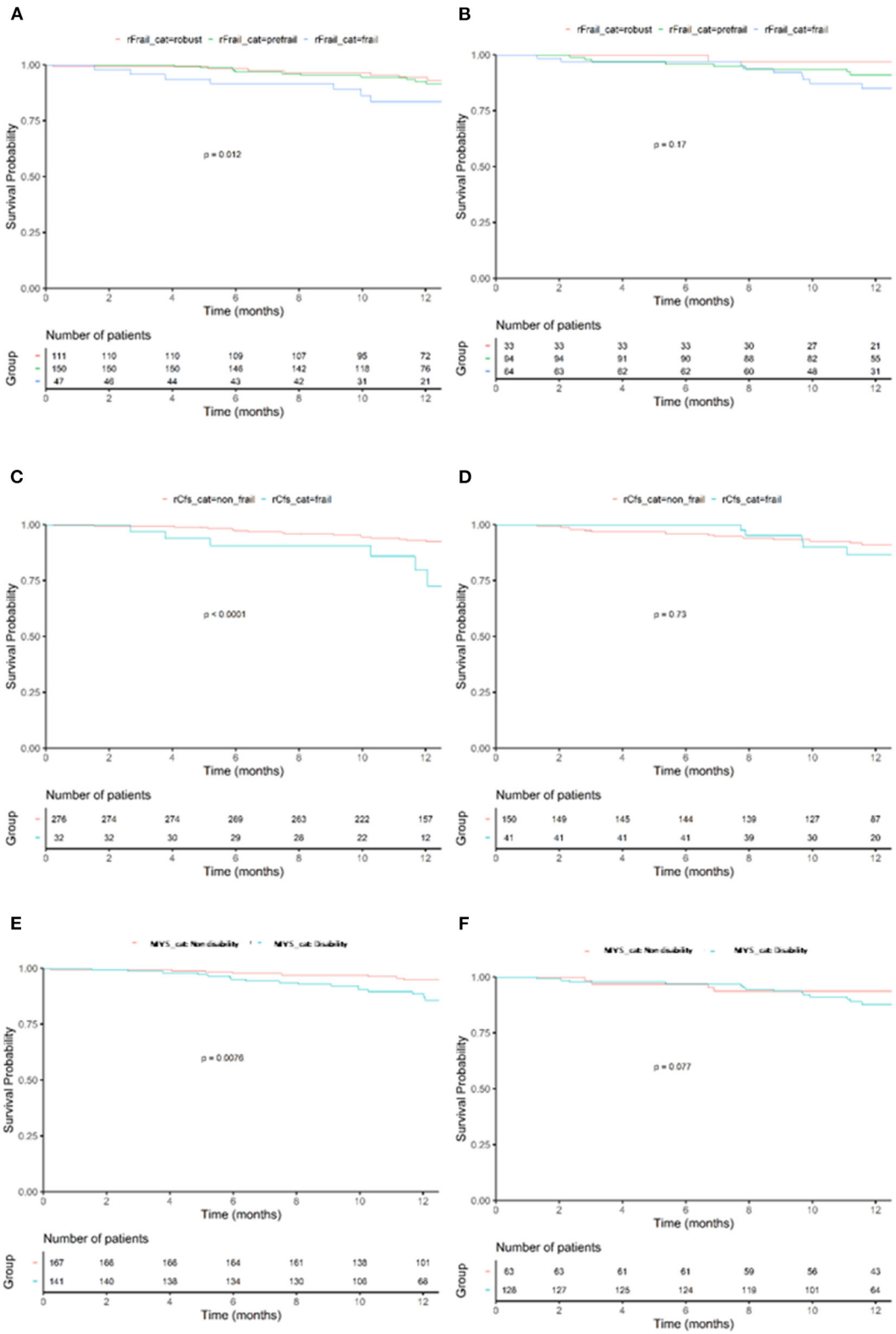


FIGURE 1
Kaplan–Meyer for 1-year mortality according to frailty category. Effects of frailty (FRAIL scale) in mortality in men **(A)** and women **(B)**. Effects of frailty (Clinical Frailty scale) in mortality in men **(C)** and women **(D)**. Effects of frailty (mobility visual scale) in mortality in men **(E)** and women **(F)**. *p*-value shows comparison by Log-Rank.

TABLE 3 Variables significantly associated with 1-year mortality or readmission according to sex.

	Men				Women			
	No event ($n = 191$)	Event ($n = 117$)	HR CI 95%	*p*-value	No event ($n = 106$)	Event ($n = 85$)	HR CI 95%	*p*-value
Atrial fibrillation*,†	88 (46.1%)	75 (64.1%)	1.83 [1.25; 2.67]	0.002	50 (47.2%)	50 (58.8%)	1.62 [1.05; 2.51]	0.028
Number of previous HF admissions*	0.36 (0.59)	0.56 (0.87)	1.44 [1.15; 1.80]	0.001	0.53 (1.27)	0.56 (0.68)	1.02 [0.84; 1.23]	0.874
NYHA class ≥II*	150 (78.5%)	105 (89.7%)	2.07 [1.14; 3.77]	0.017	89 (84.0%)	78 (91.8%)	1.62 [0.75; 3.52]	0.220
Chronic pulmonary obstructive disease*	27 (14.1%)	33 (28.2%)	1.99 [1.33; 2.99]	0.001	6 (5.66%)	8 (9.41%)	1.30 [0.63; 2.69]	0.485
Chronic oxygen supply†	4 (2.09%)	3 (2.56%)	1.57 [0.50; 4.94]	0.444	4 (3.77%)	11 (12.9%)	1.99 [1.05; 3.75]	0.034
Peripheral artery disease*	19 (9.95%)	27 (23.1%)	1.87 [1.22; 2.88]	0.004	6 (5.71%)	3 (3.53%)	0.73 [0.23; 2.31]	0.593
Malignancy*	35 (18.3%)	33 (28.2%)	1.55 [1.04; 2.33]	0.032	18 (17.0%)	16 (18.8%)	1.08 [0.62; 1.86]	0.792
Peripheral congestion*	21 (11.1%)	26 (22.2%)	1.97 [1.28; 3.06]	0.002	13 (12.3%)	10 (11.8%)	1.08 [0.56; 2.10]	0.817
Pulmonary rales*,†	9 (4.74%)	14 (12.0%)	2.46 [1.40; 4.32]	0.002	2 (1.89%)	13 (15.3%)	4.13 [2.26; 7.52]	<0.001
Jugular venous distention*,†	6 (3.14%)	9 (7.69%)	2.19 [1.11; 4.33]	0.024	1 (0.95%)	6 (7.06%)	3.43 [1.47; 7.97]	0.004
Hemoglobin (g/dl)*,†	13.9 (1.63)	13.3 (1.97)	0.84 [0.76; 0.93]	0.001	12.9 (1.34)	12.6 (1.46)	0.86 [0.73; 1.00]	0.047
Lymphocites ($\times 10^3/\mu l$)*,†	1.97 (1.18)	1.70 (0.81)	0.70 [0.55; 0.91]	0.007	2.23 (1.90)	1.75 (0.97)	0.76 [0.60; 0.97]	0.025
Creatinine (mg/dl)*	1.30 (0.41)	1.46 (0.75)	1.39 [1.11; 1.73]	0.004	1.21 (0.80)	1.19 (0.41)	1.00 [0.72; 1.38]	0.994
Urea (mg/dl)*,†	62.8 (30.7)	71.2 (34.9)	1.01 [1.00; 1.01]	0.011	63.3 (28.0)	74.2 (36.5)	1.01 [1.00; 1.01]	0.030
Estimated glomerular filtration rate (eGFR, ml/min/1.72 m^2)*	55.1 (16.7)	51.2 (18.2)	0.99 [0.98; 1.00]	0.030	50.4 (17.8)	48.7 (17.3)	1.00 [0.98; 1.01]	0.561
Sodium (mEq/L)*	141 (3.05)	140 (3.29)	0.92 [0.87; 0.98]	0.005	141 (3.27)	141 (2.95)	0.98 [0.92; 1.05]	0.647
Albumin (mg/dl)*	4.17 (0.38)	4.05 (0.48)	0.48 [0.29; 0.78]	0.003	4.11 (0.39)	4.09 (0.45)	0.68 [0.35; 1.30]	0.239
NT-proBNP (pg/ml)*	2356 (3092)	3911 (5102)	1.00 [1.00; 1.00]	<0.001	2686 (3993)	2536 (2487)	1.00 [1.00; 1.00]	0.781
Transferrin (mg/dl)*	235 (45.6)	219 (48.1)	0.99 [0.99; 1.00]	0.014	238 (45.1)	237 (51.9)	1.00 [0.99; 1.00]	0.798
Left ventricle hypertrophy*	84 (45.4%)	66 (58.4%)	1.67 [1.14; 2.43]	0.008	43 (41.7%)	39 (47.6%)	1.35 [0.87; 2.09]	0.178
Non-dilated right ventricle (%)†	157 (85.3%)	92 (80.0%)	0.71 [0.45; 1.12]	0.138	98 (94.2%)	60 (75.0%)	0.34 [0.21; 0.57]	<0.001
Systolic pulmonary artery pressure (mmHg)*,†	37.1 (11.0)	42.2 (12.7)	1.03 [1.01; 1.05]	0.001	37.7 (12.6)	43.9 (16.2)	1.02 [1.00; 1.03]	0.022
Significant tricuspid regurgitation†	21 (11.2%)	12 (10.4%)	1.07 [0.59; 1.95]	0.819	12 (11.5%)	21 (25.0%)	1.97 [1.20; 3.23]	0.008
Diuretic mean dose (mg of furosemide)*,†	50.7 (33.0)	67.4 (42.1)	1.01 [1.00; 1.01]	<0.001	53.8 (31.6)	69.3 (37.9)	1.01 [1.00; 1.01]	0.005
Comorbidity (Charlson index)*	3.03 (1.89)	3.80 (2.07)	1.16 [1.06; 1.26]	0.001	2.65 (1.59)	3.02 (1.85)	1.06 [0.94; 1.20]	0.319
Independency (Barthel index ≥90) *	168 (88.0%)	94 (80.3%)	0.59 [0.37; 0.93]	0.022	80 (75.5%)	61 (71.8%)	0.86 [0.54; 1.38]	0.540
Frailty (FRAIL)*	20 (10.5%)	27 (23.1%)	2.57 [1.55; 4.26]	<0.001	33 (31.1%)	31 (36.5%)	1.54 [0.79; 3.01]	0.201
Frailty (CFS ≥4)*,†	11 (5.76%)	21 (17.9%)	3.07 [1.91; 4.94]	<0.001	17 (16.0%)	24 (28.2%)	1.78 [1.11; 2.86]	0.018
Frailty (mobility visual scale ≥2)*	77 (40.3%)	64 (54.7%)	1.68 [1.17; 2.42]	0.005	68 (64.2%)	60 (70.6%)	1.22 [0.77; 1.95]	0.396
Depression*	55 (28.8%)	46 (39.3%)	1.50 [1.03; 2.17]	0.034	52 (49.1%)	48 (56.5%)	1.29 [0.84; 1.99]	0.239
Average prescribed drugs*	9.28 (3.09)	10.2 (3.31)	1.07 [1.01; 1.13]	0.015	9.27 (3.33)	10.1 (3.22)	1.05 [0.99; 1.11]	0.135

CFS, Clinical Frailty Scale; MNA-SF, Mini Nutritional Assessment Short Formulary.

*Variables significantly associated with 1-year mortality in men.

† Variables significantly associated with 1-year mortality in women.

10.3389/fcvm.2022.1000700

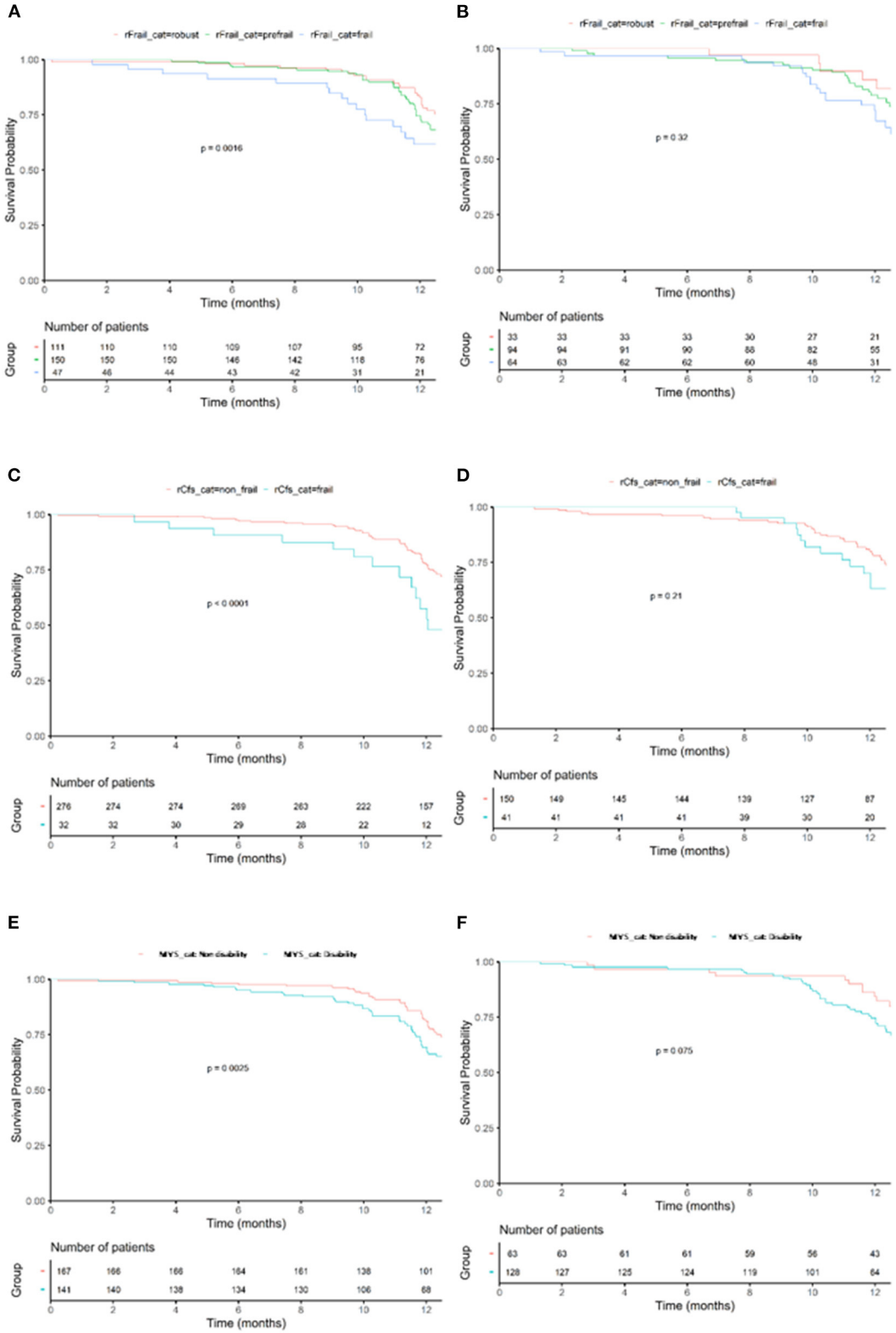


FIGURE 2
Kaplan–Meyer for 1-year mortality or readmission according to frailty category. Effects of frailty (FRAIL scale) in mortality or readmission in men **(A)** and women **(B)** Effects of frailty (Clinical Frailty scale) in mortality or readmission in men **(C)** and women **(D)**. Effects of frailty (mobility visual scale) in mortality or readmission in men **(E)** and women **(F)**. *p*-value shows comparison by Log-Rank.

10.3389/fcvm.2022.1000700

TABLE 4 Independent predictors of 1-year mortality in men.

	HR	CI 95%	*p*-value
Hemoglobin (g/dl)	0.68	0.57–0.80	<0.001
Sodium (mEq/L)	0.94	0.86–1.02	0.17
NT-proBNP (pg/ml)	1.00	1.00–1.00	<0.001
Frailty (FRAIL)	1.45	0.81–2.59	0.20
Hemoglobin (g/dl)	0.67	0.56–0.79	<0.001
Sodium (mEq/L)	0.95	0.87–1.03	0.24
NT-proBNP (pg/ml)	1.00	1.00–1.00	<0.001
Frailty (CFS)	1.36	0.71–2.58	0.34
Hemoglobin (g/dl)	0.68	0.58–0.80	< 0.001
Sodium (mEq/L)	0.94	0.87–1.03	0.21
NT-proBNP (pg/ml)	1.00	1.00–1.00	0.001
Frailty (mobility visual scale ≥2)	1.95	1.04–3.67	0.03

A Cox regression was performed for each of the different frailty scales to avoid collinearity between them: in each case, the significant variables ($p < 0.001$) were included in the log-rank test and the corresponding frailty scale.

TABLE 5 Independent predictors of 1-year mortality and readmission in men.

	HR	CI 95%	*p*-value
NT-proBNP (pg/ml)	1.00	1.00–1.00	<0.001
Diuretic mean dose (mg of furosemide)	1.01	1.01–1.02	<0.001
Frailty (FRAIL)	1.59	0.86–2.95	0.13
NT-proBNP (pg/ml)	1.00	1.00–1.00	<0.001
Diuretic mean dose (mg of furosemide)	1.01	1.01–1.02	<0.001
Frailty (CFS ≥4)	1.99	0.95–4.14	0.06
NT-proBNP (pg/ml)	1.00	1.00–1.00	0.002
Diuretic mean dose (mg of furosemide)	1.01	1.01–1.02	< 0.001
Frailty (mobility visual scale ≥2)	2.06	1.05–4.04	0.03

CFS, Clinical Frailty Scale.
A Cox regression was performed for each of the different frailty scales to avoid collinearity between them: in each case, the significant variables ($p < 0.001$) were included in the log-rank test and the corresponding frailty scale.

TABLE 6 Independent predictors of 1-year mortality in women.

	HR	CI 95%	*p*-value
Platelets ($\times 10^3/\mu l$)	1.00	0.99–1.00	0.91
NT-proBNP (pg/ml)	1.00	1.00–1.00	< 0.001
TAPSE (mm)	0.96	0.87–1.06	0.45
Non-dilated right ventricle (%)	0.75	0.32–1.75	0.51
Systolic pulmonary artery pressure (mmHg)	1.02	0.99–1.04	0.09
Diuretic mean dose (mg of furosemide)	1.01	1.00–1.01	0.04
Significant mitral regurgitation	1.26	0.56–2.78	0.56
Significant tricuspid regurgitation	1.39	0.55–3.55	0.48

TAPSE, tricuspid annular plane systolic excursion.

of frailty varies according to the scale used. Both conditions when present together lead to worse outcomes (3, 20). Thus, it is recommended to properly assess its presence (9, 21), since the greater accumulation of deficits in frailty domains, the greater the mortality (22). Notably, frailty affects women significantly more than men in HF, as demonstrated in a recent meta-analysis including 29 studies, in which the relative risk of frailty was found to be 26% higher in women compared with men (23). As expected, the relative risk of frailty in women was higher when defined with a physical approach. In this regard, Denfeld et al. performed a small prospective single-center study (including 115 patients, mean age 63.6 ± 15.7 years, 49% women) aimed to characterize sex differences in physical frailty in HF. Authors found that women with HF were significantly more likely to be physically frail than men. Frailty was related with higher overall comorbidity burden in both men and women although frail women had a worse symptom profile (24). However, such population was significantly younger than that in our study (mean age 63.6 vs. 81.4 years) and had different baseline characteristics: 71% had reduced LVEF and almost 50% had NYHA III-IV functional status (which may, in part, explain the discrepant findings). In our study, women were more commonly frail than men, irrespective of the scale. Hence, it could be hypothesized that these differences may rely on the fact that frailty scales might not adequately identify (or even overestimate) the presence of frailty in women. However, the FRAIL scale was developed in a cohort of 4,000 patients, 50% women and this scale was later validated in a mostly-women community population (25, 26). FRAIL scale has been also validated in a sample of 703 patients, 40% women (27), whereas the CFS was developed in a prospective cohort of 2305 patients, 61% women, from the Canadian Study of Health and Aging (CSHA) (28). Interestingly, in our study, women showed significantly worse self-reported quality of life. This finding has been previously reported in some studies, closely related to HF status (10), though it has also been found to be higher in frail patients (Souza).

Concerning the prognosis of frailty in HF patients, a recent metanalysis showed it was associated with an approximately 1.5-fold increase risk of death and hospitalization in HF

10.3389/fcvm.2022.1000700

TABLE 7 Independent predictors of 1-year mortality and readmission in women.

	HR	CI 95%	*p*-value
Atrial fibrillation	0.81	0.38–1.71	0.58
Chronic oxygen supply	0.69	0.17–2.72	0.59
Pulmonary rales	1.43	0.41–5.00	0.56
Jugular venous distention	1.62	0.47–5.55	0.43
Hemoglobin (g/dl)	0.76	0.60–0.97	0.03
Lymphocites ($\times 10^3/\mu l$)	0.68	0.46–1.01	0.05
Urea (mg/dl)	0.99	0.98–1.00	0.47
Non-dilated right ventricle (%)	0.45	0.20–0.99	0.04
Systolic pulmonary artery pressure (mmHg)	1.01	0.98–1.03	0.35
Diuretic mean dose (mg of furosemide)	1.01	1.00–1.01	0.04
Frailty (CFS $\geq$4)	1.46	0.56–3.79	0.43
Significant tricuspid regurgitation	1.55	0.69–3.48	0.28

CFS, Clinical Frailty Scale.

patients, although differences between men and women were not explored (29). However, results of this study should be taken with caution, since the sample had high heterogeneity, with some studies including patients during an acute HF episode, and frailty was not uniformly defined. On the other hand, in a recent study including nearly 600 patients admitted with decompensated HF (mean age 76.6 years, 45% women), patients with higher CFS score showed a worse clinical profile and had higher probability of all-cause death and rehospitalisation in both men and women (30). Besides, it is recommended to assess frailty in an ambulatory fashion, and not in the setting of an acute HF event, as in those studies (9). In our study, frailty identified by the mobility visual scale was independently associated with mortality/readmission in men.

Recently, St Sauver et al. (31), demonstrated the negative relationship between inflammation, multi-morbidity and biologic aging, in such a way that men and elderly people, especially with higher comorbidity, had significantly higher levels of inflammatory biomarkers. This, in turn, has been linked with the concept of "*inflammaging*," key component of the aging process. Soysal et al. (32) have associated this concept with the development of cardiovascular disease and frailty. Thus, although the prevalence of frailty was lower in men in our study, it could be hypothesized that a greater proinflammatory state might explain, at least in part, why it had a greater prognostic impact in older men with heart failure.

Our study, despite its prospective design, has some limitations that merit discussion. First, it is an observational study so we cannot rule out the possibility of selection bias. On the other hand, the sample size was modest, and the percentage of women included lower than that in other similar studies. Also, the 1-year event rate was relatively low, therefore results should be extrapolated with caution, particularly to other settings, since our study only included elderly ambulatory patients with chronic HF followed by cardiologists. In spite of these limitations, we think that this study provides new and interesting information on gender differences in the impact of frail in older patients from a large cohort of consecutive unselected elderly HF patients. Further studies will be required to elucidate the underlying reasons explaining a distinct effect of frailty according to gender.

Conclusion

Elderly women with HF present frailty and other geriatric conditions more often than men, although frailty is only associated with worse prognosis in men.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by CEIm Hospital Universitario de La Princesa, Madrid, Spain. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PD-V and CJ-M prepared the first draft of the manuscript. All authors improved the manuscript with relevant content, contributed to the article, and approved the submitted version.

Acknowledgments

To the Geriatric Section of the Spanish Society of Cardiology, for its support.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet.* (2018) 391:572–80. doi: 10.1016/S0140-6736(17)32520-5

2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* (2021) 42:3599–726. doi: 10.1093/eurheartj/ehab368

3. Heckman GA, McKelvie RS, Rockwood K. Individualizing the care of older heart failure patients. *Curr Opin Cardiol.* (2018) 33:208–16. doi: 10.1097/HCO.0000000000000489

4. Cherubini A, Oristrell J, Pla X, Ruggiero C, Ferretti R, Diestre G et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med.* (2011) 171:550–6. doi: 10.1001/archinternmed.2011.31

5. Díez-Villanueva P, Jiménez-Méndez C, Alfonso F. Heart failure in the elderly. *J Geriatr Cardiol.* (2021) 18:219–32. doi: 10.11909/j.issn.1671-5411.2021.03.009

6. Rodríguez-Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. *J Gerontol A Biol Sci Med Sci.* (2013) 68:62–7. doi: 10.1093/gerona/gls119

7. Chaudhry SI, McAvay G, Chen S, Whitson H, Newman AB, Krumholz HM, et al. Risk factors for hospital admission among older persons with newly diagnosed heart failure: findings from the Cardiovascular Health Study. *J Am Coll Cardiol.* (2013) 61:635–42. doi: 10.1016/j.jacc.2012.11.027

8. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet.* (2013) 381:752–62. doi: 10.1016/S0140-6736(12)62167-9

9. Díez-Villanueva P, Arizá-Solé A, Vidán MT, Bonanad C, Formiga F, Sanchis J, et al. Recommendations of the geriatric cardiology section of the spanish society of cardiology for the assessment of frailty in elderly patients with heart disease. *Rev Esp Cardiol.* (2019) 72:63–71. doi: 10.1016/j.rec.2018.06.035

10. Lala A, Tayal U, Hamo CE, Youmans Q, Al-Khatib SM, Bozkurt B, et al. Sex differences in heart failure. *J Card Fail.* (2022) 28:477–98. doi: 10.1016/j.cardfail.2021.10.006

11. Postigo A, Martínez-Sellés M. Sex influence on heart failure prognosis. *Front Cardiovasc Med.* (2020) 7:616273. doi: 10.3389/fcvm.2020.616273

12. Díez-Villanueva P, Salamanca J, Ariza-Solé A, Formiga F, Martín-Sánchez FJ, Bonanad Lozano C, et al. Impacto de la FRAgilidad y otros síndromes Geriátricos en el manejo clínico y pronóstico del paciente anciano ambulatorio con Insuficiencia Cardiaca (FRAGIC). Estudio prospectivo y multicéntrico. *Rev Esp Geriatr Gerontol.* (2020) 55:29–33. doi: 10.1016/j.regg.2019.08.005

13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* (2016) 37:2129–200. doi: 10.1093/eurheartj/ehw128

14. Dewan P, Rørth R, Raparelli V, Campbell RT, Shen L, Jhund PS, et al. Sex-related differences in heart failure with preserved ejection fraction. *Circ Heart Fail.* (2019) 12:e006539. doi: 10.1161/CIRCHEARTFAILURE.119.006539

15. Vicent L, Guerra J, Vazquez-García R, Gonzalez-Juanatey JR, Dolz LM, Segovia J, et al. Ischemic etiology and prognosis in men and women with acute heart failure. *J Clin Med.* (2021) 10:1713. doi: 10.3390/jcm10081713

16. Hsich EM, Grau-Sepulveda MV, Hernandez AF, Peterson ED, Schwamm LH, Bhatt DL, et al. Sex differences in in-hospital mortality in acute decompensated heart failure with reduced and preserved ejection fraction. *Am Heart J.* (2012) 163:430–7, 437.e1–3. doi: 10.1016/j.ahj.2011.12.013

17. Ravera A, Santema BT, de Boer RA, Anker SD, Samani NJ, Lang CC, et al. Distinct pathophysiological pathways in women and men with heart failure. *Eur J Heart Fail.* (2022). doi: 10.1002/ejhf.2534. [Epub ahead of print].

18. Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM. Sex differences in cardiovascular pathophysiology: why women are overrepresented in heart failure with preserved ejection fraction. *Circulation.* (2018) 138:198–205. doi: 10.1161/CIRCULATIONAHA.118.034271

19. Stolfo D, Uijl A, Vedin O, Strömberg A, Faxén UL, Rosano GMC, et al. Sex-based differences in heart failure across the ejection fraction spectrum: phenotyping, and prognostic and therapeutic implications. *JACC Heart Fail.* (2019) 7:505–15. doi: 10.1016/j.jchf.2019.03.011

20. Pandey A, Kitzman D, Reeves G. Frailty is intertwined with heart failure: mechanisms, prevalence, prognosis, assessment, and management. *JACC Heart Fail.* (2019) 7:1001–101. doi: 10.1016/j.jchf.2019.10.005

21. Vitale C, Jankowska E, Hill L, Piepoli M, Doehner W, Anker SD, et al. Heart Failure Association/European Society of Cardiology position paper on frailty in patients with heart failure. *Eur J Heart Fail.* (2019) 21:1299–305. doi: 10.1002/ejhf.1611

22. Kleipool EEF, Wiersinga JHI, Trappenburg MC, Rossum AC, Dam CS, Liem SS, et al. The relevance of a multidomain geriatric assessment in older patients with heart failure. *ESC Heart Fail.* (2020) 7:1264–72. doi: 10.1002/ehf2.12651

23. Davis MR, Lee CS, Corcoran A, Gupta N, Uchmanowicz I, Denfeld QE. Gender differences in the prevalence of frailty in heart failure: a systematic review and meta-analysis. *Int J Cardiol.* (2021) 333:133–40. doi: 10.1016/j.ijcard.2021.02.062

24. Denfeld QE, Habecker BA, Camacho SA, Roberts Davis M, Gupta N, Hiatt SO, et al. Characterizing sex differences in physical frailty phenotypes in heart failure. *Circ Heart Fail.* (2021) 14:e008076. doi: 10.1161/CIRCHEARTFAILURE.120.008076

25. Woo J, Leung J, Morley JE. Comparison of frailty indicators based on clinical phenotype and the multiple deficit approach in predicting mortality and physical limitation. *J Am Geriatr Soc.* (2012) 1478–86. doi: 10.1111/j.1532-5415.2012.04074.x

26. Woo J, Yu R, Wong M, Yeung F, Wong M, Lum C. Frailty screening in the community using the FRAIL Scale. *J Am Med Dir Assoc.* (2015) 16:412–9. doi: 10.1016/j.jamda.2015.01.087

27. Morley JE, Malmstrom TK, Miller DK, A. simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging.* (2012) 16:601–8. doi: 10.1007/s12603-012-0084-2

28. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ.* (2005) 173:489–95. doi: 10.1503/cmaj.050051

29. Yang X, Lupón J, Vidán MT, Ferguson C, Gastelurrutia P, Newton PJ, et al. Impact of frailty on mortality and hospitalization in chronic heart failure: a systematic review and meta-analysis. *J Am Heart Assoc.* (2018) 7:e008251. doi: 10.1161/JAHA.117.008251

30. Kanenawa K, Isotani A, Yamaji K, Nakamura M, Tanaka Y, Hirose-Inui K, et al. The impact of frailty according to Clinical Frailty Scale on clinical outcome in patients with heart failure. *ESC Heart Fail.* (2021) 8:1552–61. doi: 10.1002/ehf2.13254

31. St Sauver J, Rocca W, LeBrasseur N, Chamberlain A, Olson J, Jacobson D, et al. Inflammatory biomarkers, multi-morbidity, and biologic aging. *J Int Med Res.* (2022) 50:3000605221109393. doi: 10.1177/03000605221109393

32. Soysal P, Arik F, Smith L, Jackson SE, Isik AT. Inflammation, frailty and cardiovascular disease. *Adv Exp Med Biol.* (2020) 1216:55–64. doi: 10.1007/978-3-030-33330-0_7

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 30 November 2022
DOI 10.3389/fcvm.2022.947975

OPEN ACCESS

EDITED BY
Beatriz Diaz Molina,
Servicio de Salud del Principado de Asturias (SESPA), Spain

REVIEWED BY
Xiaoyue Zhou,
Siemens Healthineers Digital Technology (Shanghai) Co., Ltd., China
Ferenc Imre Suhai,
Semmelweis University, Hungary

*CORRESPONDENCE
Shubin Qiao
qsbfw@sina.com
Shihua Zhao
cjrzhaoshihua1011@163.com

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Sex and Gender in Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 19 May 2022
ACCEPTED 07 November 2022
PUBLISHED 30 November 2022

CITATION
Bi X, Song Y, Yang C, Song Y, Zhao S, Qiao S and Zhang J (2022) Sex differences in atrial remodeling and its relationship with myocardial fibrosis in hypertrophic obstructive cardiomyopathy.
Front. Cardiovasc. Med. 9:947975.
doi: 10.3389/fcvm.2022.947975

Sex differences in atrial remodeling and its relationship with myocardial fibrosis in hypertrophic obstructive cardiomyopathy

Xuanye Bi[1,2†], Yanyan Song[3†], Chengzhi Yang[2], Yunhu Song[2], Shihua Zhao[3*], Shubin Qiao[2*] and Jinying Zhang[1]

[1]Henan Province Key Laboratory of Cardiac Injury and Repair, Department of Cardiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, [2]State Key Laboratory of Cardiovascular Disease, Department of Cardiovascular Disease, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [3]State Key Laboratory of Cardiovascular Disease, Department of Magnetic Resonance Imaging, Cardiovascular Imaging and Intervention Center, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: This study aimed to explore the effect of sex on left atrial (LA) remodeling and its relationship with myocardial fibrosis in patients with hypertrophic obstructive cardiomyopathy (HOCM).

Methods and results: A total of 85 patients with HOCM were enrolled. Myocardial fibrosis was quantified by the collagen volume fraction (CVF) in myocardial samples. The early atrial peak of emptying rate (PER-E) was assessed by LA volume/time (V/t) curves derived from cardiac magnetic resonance (CMR) imaging analysis. The PER-E index was PER-E normalized by left ventricular (LV) filling volume. Patients with HOCM showed a lower PER-E index than healthy controls ($P = 0.027$). Compared with men, the PER-E ($P < 0.001$) and the PER-E indexes ($P = 0.012$) in women were lower. In CVF-stratified subgroups, a sex difference in the PER-E index was eliminated ($P > 0.05$). The CVF was correlated with the PER-E and PER-E indexes in both sexes (all P-values were <0.05). In multivariate regression analysis, sex ($P = 0.007$) and CVF ($P < 0.001$) were independently correlated with PER-E (all P-values were <0.05).

Conclusion: Patients with HOCM presented LA reverse remodeling. Impaired LA function was more common in female patients with HOCM due to their susceptibility to myocardial fibrosis.

KEYWORDS

hypertrophic cardiomyopathy, myocardial fibrosis, magnetic resonance imaging, left atrial function, sex differences

Introduction

Hypertrophic cardiomyopathy (HCM) is a complex and relatively common genetic cardiac disorder (1). Many patients remain free of clinically significant symptoms and adverse events (2). However, patients with hypertrophic obstructive cardiomyopathy (HOCM) usually present with exertional dyspnea or angina and may experience severe functional limitation and higher HCM-related death risk (3). Left ventricular (LV) diastolic dysfunction (LVDD) is a major reason for these clinical manifestations in HOCM, with myocardial fibrosis as the pathological basis (4, 5). An enlargement of the left atrium (LA), an established marker of LVDD, acts as a compensatory mechanism to modulate LV filling pressure (6). However, recent studies have shown that functional LA changes became evident at the earliest stages of LVDD (7). Despite the increased knowledge of LA function in HCM, its exact relationship with myocardial fibrosis needs further research to be elucidated.

Sex is an important factor contributing to disease heterogeneity. Interestingly, female patients with HCM have been described to show less ventricular remodeling compared with male patients (8, 9), whereas several studies reported more severe diastolic dysfunction, greater likelihood of heart failure progression, and higher mortality in female patients than in male patients with HCM (10, 11). The possible mechanism might be the susceptibility to myocardial fibrosis in female patients with HCM (12). Although LVDD and myocardial fibrosis are closely related to sex, the sex differences in LA remodeling in patients with HOCM remain undetermined.

Therefore, the current study aimed to investigate the effect of sex on LA remodeling and the association between LA remodeling and myocardial fibrosis in patients with HOCM.

Materials and methods

Study population

This study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient. The study protocol was approved by the Ethics Committee.

We consecutively recruited 85 symptomatic adult patients with HOCM who underwent surgical myectomy consecutively from 2016 to 2019. All patients underwent a detailed cardiovascular evaluation, including medical history, clinical examination, 12-lead ECG, and cardiac magnetic resonance (CMR) imaging.

Hypertrophic cardiomyopathy was diagnosed by the presence of a non-dilated and hypertrophied LV on CMR imaging in the absence of other diseases that could account for the hypertrophy. Obstructive HCM was defined as a left ventricular outflow tract (LVOT) gradient either $\geq$40 mmHg at rest and/or $\geq$50 mmHg during provocation using Doppler echocardiography (13). Patients with severe valvular disease, stages 3–5 of chronic kidney disease (CKD), connective tissue disease, and osteoarthropathy were excluded from the study.

Control myocardium from the LV septal wall was collected at autopsy of nine individuals (6 men/3 women; mean age 45.4 $\pm$ 14.3 years) who died from accidents without any cardiac medical history and their hearts showed no signs of macroscopic or microscopic cardiac lesions. CMR images from 35 age- and gender-matched healthy people (21 men/14 women; mean age 45.2 $\pm$ 8.5 years) were used as control subjects.

Cardiovascular MRI

Cardiac magnetic resonance was performed on a 1.5-T magnetic resonance scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany). All imaging acquisitions were captured under breath control. CMR images were analyzed using the standard ventricular analysis software (Medis Medical Imaging systems, Leiden, Netherlands). For all patients, septal wall thickness, and posterior and LV end-diastolic dimensions were all determined in the short-axis view (at the midpapillary level). To evaluate functional parameters, cine images were acquired in three long-axis views (LV 2-chamber, 4-chamber, and LV outflow tract) and continuous short-axis planes encompassing the entire LV using a balanced steady-state free precession sequence. Typical parameters include field of view: 320 $\times$ 320 mm; matrix: 192 $\times$ 224; slice thickness: 8 mm; slice gap: 2 mm; repetition time: 2.8–3.0 ms; echo time: 1.1–1.5 ms; flip angle: 60–70°; bandwidth: 930 Hz; views per segment: 12–20; temporal resolution: 30–55 ms (depending on the heart rate); cardiac phases: 25; SENSE factor: $\times$2. Epicardial and endocardial borders of the LV myocardium were manually traced during the whole cardiac phase on each cine short-axis image to obtain LV end-diastolic and end-systolic volumes, ejection fractions, and myocardial mass. Myocardial mass was calculated by multiplying the volume of the myocardium calculated at end-diastole by the specific gravity of the myocardium (1.05 g/ml). The end-diastolic volume index, end-systolic volume index, and mass index were indexed to body surface area (BSA). Late gadolinium enhancement (LGE, %) was performed on 67 patients. LGE images were acquired 15 min after intravenous administration of 0.2 mmol/kg gadolinium-DTPA (Magnevist, Schering, Berlin, Germany) using a phase-sensitive inversion recovery-spoiled gradient echo sequence. LGE images were determined automatically by computer counting all hyper-enhanced pixels in the LV myocardium on each of the short-axis images. LGE images were defined as those with image intensities of 6 SDs above the mean of image intensities in a remote myocardial region in the same image.

Image post-processing was performed using the Tracking Tool software (QStrain version 2.0; Medis Medical Imaging Systems bv). LA endocardial contour was manually traced at the phase of the maximal LA volume before mitral valve opening and at the phase of the minimum LA volume after atrial contraction in the two-chambered and four-chambered views. The atrial and ventricular volume/time (V/t) and dV/dt curves were obtained by plotting the cavity volumes over time (**Figures 1d,h,l**). From atrial curves, we measured maximum LA volume (LAV max; ml; **Figures 1b,f,j**) at the end of ventricular systole, and minimum LA volume (LAV min; ml; **Figures 1a,e,i**) at the end of atrial systole. The left atrial stroke volumes (LASVs; ml) were defined as the difference between the maximal and minimal atrial volumes (i.e., LASV = LAV max-LAV min); the left atrial ejection fraction (LAEF; %) was measured as the ratio in percentage between atrial stroke volumes and maximal atrial volumes (i.e., LAEF = LASV/LAV max × 100%). Peaks of the atrial dV/dt curves were defined as follows: the first negative peak was defined as the early peak empty rate (PER-E; ml/s), and the second peak was defined as the atrial peak empty rate (PER-A; ml/s) representing maximal emptying during the conduit phase and the booster phase, respectively. To be more comparable, LAV max and LAV min were indexed to BSA (m^2). PER-E and PER-A were also normalized by the LV filling volume (difference between LV end-diastolic and end-systolic volumes), obtaining the PER-E index and the PER-A index. The isovolumetric pulmonary vein transit (IPVT; ml) was defined as the amount of LV filling volume flowing directly from the pulmonary veins into the LV cavity without significant change in LA volume (i.e., IPVT = LV filling volume-LASV). The isovolumetric pulmonary vein transit ratio (IPVTR) was defined as the ratio between IPVT and the atrial emptying volume (i.e., IPVTR = IPVT/LASV), as previously described (14).

Histomorphological studies

The septal myocardium samples were immediately fixed in 10% buffered formalin and embedded in paraffin. The samples were sectioned and stained with Masson's trichrome staining for evaluating myocardial fibrosis (**Figures 1c,g,k**). Four images of every section were acquired with a projection microscope (200×). Subsequent image analysis was performed using the Image-Pro Plus version 6.0 image analysis software (Media

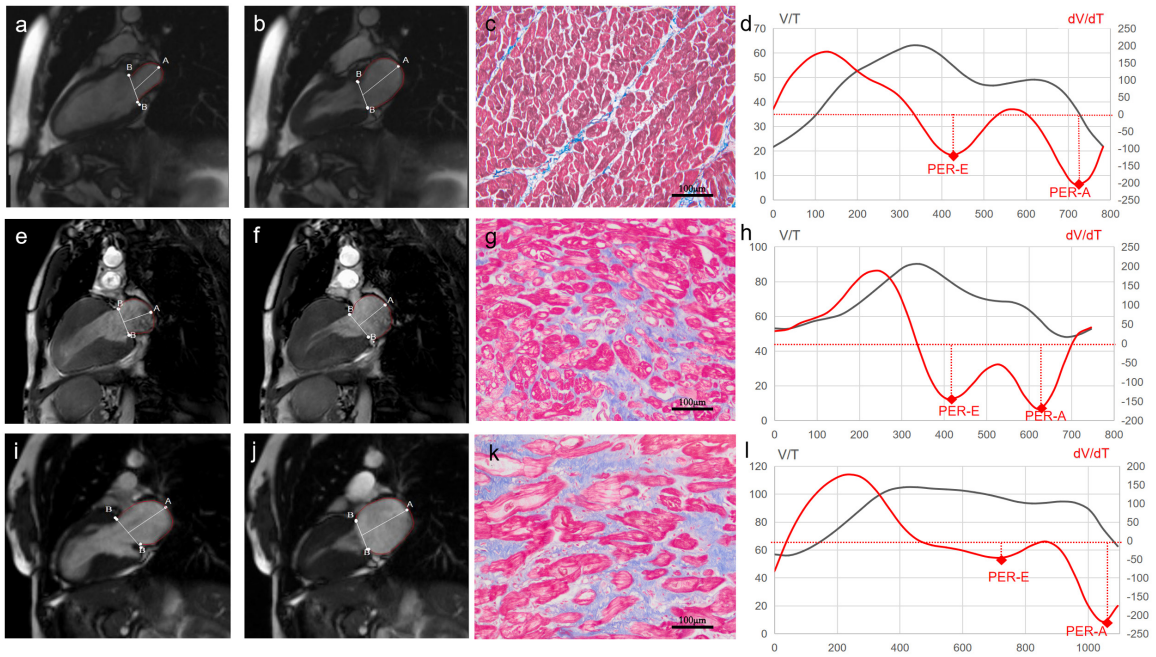


FIGURE 1
Cardiac magnetic resonance (CMR) images of left atrial (LA) and histological images of myocardium from a control subject (the top panel), a male patient with hypertrophic obstructive cardiomyopathy (HOCM) (the middle panel), and a female patient with HOCM (the bottom panel). The first column is CMR images of the minimum LA volume after atrial contraction in the two-chambered view (Control: **a**, Male: **e**, Female: **i**). The second column is CMR images of the maximal LA volume before the mitral valve opening in the two-chambered view (Control: **b**, Male: **f**, Female: **j**). The third column is the images of myocardial fibrosis (blue) stained with Masson's trichrome (Control: **c**, Male: **g**, Female: **k**). The fourth column is volume-time curves (black) and their first derivatives (red) of the left atrium (Control: **d**, Male: **h**, Female: **l**). LA V/T curves after the first peak and dV/dt curves under the coordinate axis represent the process of LA emptying. The first negative peak, representing maximal emptying during the conduit phase, is identified as the early atrial peak emptying rate (PER-E). The second peak, during the booster phase, is identified as the late atrial peak emptying rate (PER-A).

Cybernetics Inc., Buckinghamshire, UK) by a cardiovascular pathologist. The extent of myocardial fibrosis was expressed as collagen volume fraction (CVF; %). CVF was calculated as the ratio of collagen-specific staining to the total area of the myocardium in each myocardium sample. The endocardium was excluded from the analysis.

Statistical analysis

Continuous variables are shown as mean ± SD. Categorical variables are presented as frequencies (percentages). Patients with HOCM were divided into two subgroups according to the upper limit of CVF normality (established as mean + 2 SDs obtained in control subjects and equal to 6%). Of these patients, 51 patients showed high CVF (23 men and 28 women) and 34 patients showed normal CVF (26 men and 8 men). Comparisons of the groups for continuous variables were performed with the unpaired *t*-test or the Mann–Whitney *U* test, whereas the chi-squared test or Fisher's exact test was used for categorical variables. Pearson's correlation test or Spearman's correlation test was used to examine correlations between two continuous variables when indicated. A multivariate analysis was performed with logistic regression analysis using block entry to evaluate if the variables were independent predictors for PER-E, provided to have a *p*-value of <0.1 in a univariate analysis. All *p*-values were two-sided. Statistical analysis was performed using the SPSS software package (version 20; IBM Corp., Armonk, NY, USA).

Results

A total of 85 patients were enrolled in our study. The baseline clinical characteristics of patients with HOCM are summarized in Table 1.

Assessment of myocardial fibrosis in patients with hypertrophic obstructive cardiomyopathy

The CVF values were significantly higher in patients with HOCM than in controls (7.4 ± 3.8% vs. 3.8 ± 1.1%, $P = 0.002$). Women showed more extensive fibrosis than men (8.7 ± 4.2% vs. 6.4 ± 3.3%, $P = 0.012$, Figure 2A). However, no difference in the extent of LGE was found between the two sexes. In subgroups stratified by fibrotic status, there was no difference in CVF between the two sexes (Figure 2D).

Left atrial structure and function in patients with hypertrophic obstructive cardiomyopathy

Compared with healthy controls, patients with HOCM showed greater septal wall thickness, LV mass index (LVMI), LV end-diastolic diameter (LVEDD), and LV end-diastolic volume index (LVEDVI) (all *P*-values were <0.05). LA diameters, LAV max, and LAV min indices were larger (all *P*-values were <0.005) in patients with HOCM than in the controls. In addition, patients with HOCM had a lower PER-E index and LAEF (1.2 ± 0.6/s vs. 1.6 ± 1.2/s, $P = 0.027$; 41.2 ± 12.2% vs. 59.4 ± 6.6%, $P < 0.001$) than the controls.

As shown in Table 2, LVEDD and septal thickness were lower in women than in men (43.9 ± 4.1 mm vs. 46.3 ± 3.8 mm, $P = 0.006$; 23.9 ± 4.9 mm vs. 26 ± 4.8 mm, $P = 0.048$). However, women showed lower PER-E, PER-E index, and PER-E/PER-A than men (86.3 ± 47.4 ml/s vs. 130.6 ± 58.6 ml/s, $P < 0.001$, Figure 2B; 1 ± 0.5 ml/s vs. 1.3 ± 0.6 ml/s, $P = 0.012$, Figure 2C; 0.64 ± 0.42 vs. 0.97 ± 0.86, $P = 0.025$). The results of the CVF-stratified analyses revealed that female patients with high CVF showed lower LVEDD (43.9 ± 4.4 mm vs. 46.7 ± 3.9 mm,

TABLE 1 Baseline clinical characteristics of patients with hypertrophic obstructive cardiomyopathy (HOCM).

	Patients with HOCM			
	All patients ($n = 85$)	**Males ($n = 49$)**	**Females ($n = 36$)**	***P*-value**
Age, years	48.4 ± 13.2	46.2 ± 11.6	51.3 ± 14.7	0.074
Dyspnea, %	79 (92.9)	46 (93.9)	33 (91.7)	1.000
NYHA III/IV, %	30 (35.3)	16 (32.7)	14 (38.9)	0.552
AF, %	13 (15.3)	10 (20.4)	3 (8.3)	0.126
History of hypertension, %	19 (22.4)	8 (16.3)	11 (30.6)	0.12
History of diabetes mellitus, %	8 (9.4)	2 (4.1)	6 (16.7)	0.122
Family history of HCM or SCD, %	6 (7.1)	5 (10.2)	1 (2.8)	0.372
Calcium antagonist, %	24 (28.2)	17 (34.7)	7 (19.4)	0.123
Beta blocker, %	68 (80)	36 (73.5)	32 (88.9)	0.079

AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; NYHA, new york heart association; SCD, sudden cardiac death.

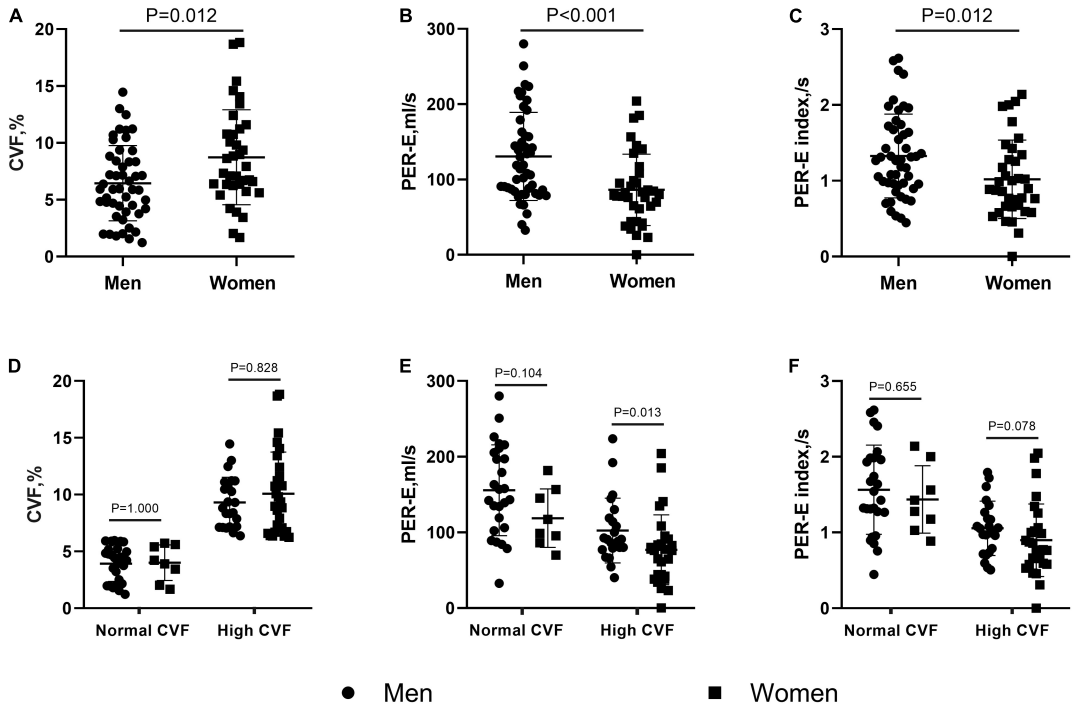


FIGURE 2
Sex differences in collagen volume fraction (CVF) and left atrial (LA) deformation rates in patients with hypertrophic obstructive cardiomyopathy (HOCM). Female patients showed higher CVF **(A)**, but lower peak of emptying rate (PER-E) **(B)**, and PER-E index **(C)** than males. When stratifying patients by the CVF values, the sex differences in CVF **(D)** and PER-E index **(F)** were eliminated in the subgroups with normal and high CVF, but in PER-E **(E)**, the sex differences remained significant in the subgroup with high CVF.

$P = 0.021$), LVMI (89.5 ± 30.6 g/m^2 vs. 111.1 ± 38.1 g/m^2, $P = 0.036$), and PER-E (77 ± 46 ml/s vs. 102.3 ± 42.8 ml/s, $P = 0.013$, Figure 2E) than male patients with high CVF. PER-E index (0.9 ± 0.5 ml/s vs. 1.1 ± 0.4 ml/s, $P = 0.078$, Figure 2F), septal thickness (24.1 ± 5 mm vs. 26.4 ± 4.3 mm, $P = 0.076$), and IVPTR (1 ± 0.5 vs. 1.4 ± 1, $P = 0.082$) were lower in female patients than in male patients with high CVF, although the difference was not significant between the two sexes. However, there was no sex-specific difference in CMR parameters in the subgroup with normal CVF.

The associations between left atrial cardiac magnetic resonance parameters and myocardial fibrosis in patients with hypertrophic obstructive cardiomyopathy

The CVF value was inversely correlated with PER-E (whole cohort: $r = -0.604$, $P < 0.001$; women: $r = -0.727$, $P < 0.001$, Figure 3B; men: $r = -0.482$, $P < 0.001$, Figure 3A), PER-E index (whole cohort: $r = -0.568$, $P < 0.001$; women: $r = -0.653$, $P < 0.001$, Figure 3D; men: $r = -0.460$, $P = 0.001$, Figure 3C), and PER-E: PER-A ratio (whole cohort: $r = -0.464$, $P = 0.008$; women: $r = -0.693$, $P < 0.001$; men: $r = -0.269$, $P = 0.061$). However, the extent of LGE was not correlated with any LA remodeling parameters.

A univariate regression analysis showed that age ($P = 0.033$), sex ($P < 0.001$), EDVI ($P = 0.098$), ESVI ($P = 0.071$), and CVF ($P < 0.001$) were associated with PER-E. After multivariate adjustment, only sex ($P = 0.007$), EDVI ($P = 0.012$), and CVF ($P < 0.001$) remained significant (Table 3).

Discussion

The major findings can be summarized as follows. (1) Compared with the healthy controls, patients with HOCM showed worse LA remodeling. (2) Female patients were more likely to develop impaired LA deformation rates than male patients. (3) The female sex and myocardial fibrosis were independent predictors for LA deformation rate after adjusting for clinical confounders in patients with HOCM.

Patients with HOCM are characterized by early LVDD, mitral regurgitation, and outflow tract obstruction (15). The abnormal hemodynamics could increase LV filling pressure, leading to LA reverse remodeling. LA function has three phases, serving as a reservoir in systole, a conduit in early diastole, and a

TABLE 2 Cardiac magnetic resonance (CMR) parameters in patients with hypertrophic obstructive cardiomyopathy (HOCM).

				High CVF			Normal CVF		
	Males ($n = 49$)	**Females ($n = 36$)**	***P*-value**	**Males ($n = 23$)**	**Females ($n = 28$)**	***P*-value**	**Males ($n = 26$)**	**Females ($n = 8$)**	***P*-value**
Left atrium diameter, mm	43.3 ± 8.7	40.6 ± 6.7	0.122	42.3 ± 10.1	41.3 ± 6.3	0.691	44.2 ± 7.4	38.1 ± 8	0.053
LAV max index, ml/m^2	67.4 ± 26.5	67.1 ± 17.2	0.491	64 ± 25.1	68.5 ± 14.4	0.125	70.3 ± 27.8	62.2 ± 25.5	0.291
LAV min index, ml/m^2	41.4 ± 23.5	40.5 ± 16.8	0.676	39.3 ± 20.3	41.1 ± 14.3	0.472	43.2 ± 26.3	38.2 ± 24.7	0.372
PER-E, ml/s	**130.6 ± 58.6**	**86.3 ± 47.4**	**<0.001**	**102.3 ± 42.8**	**77 ± 46**	**0.013**	155.7 ± 60	118.7 ± 38.7	0.104
PER-A, ml/s	178.7 ± 85.4	169.9 ± 84.5	0.341	173.4 ± 88.6	175.3 ± 87.8	0.514	183.3 ± 83.8	151 ± 73.7	0.31
PER-E index, /s	**1.3 ± 0.6**	**1 ± 0.5**	**0.012**	1.1 ± 0.4	0.9 ± 0.5	0.078	1.6 ± 0.6	1.4 ± 0.4	0.655
PER-A index, /s	1.8 ± 0.7	2 ± 1.0	0.471	1.8 ± 0.8	2.1 ± 1	0.394	1.8 ± 0.7	1.8 ± 0.8	0.839
PER-E/PER-A	0.97 ± 0.86	0.64 ± 0.42	0.025	0.95 ± 1.1	0.56 ± 0.4	0.135	0.98 ± 0.53	0.91 ± 0.39	0.871
LASV, ml	48.3 ± 18	43.6 ± 13	0.249	45.4 ± 16.3	44.7 ± 13.5	0.985	50.9 ± 19.3	39.9 ± 11.3	0.113
222 LAEF, %	41.1 ± 12.4	41.3 ± 12.2	0.925	41 ± 11.1	41.3 ± 12.1	0.929	41.1 ± 13.6	41.4 ± 13.5	0.957
IPVTR	1.3 ± 0.9	1.1 ± 0.6	0.259	1.4 ± 1	1 ± 0.5	0.082	1.2 ± 0.9	1.2 ± 0.7	0.903
Septal thickness, mm	**26 ± 4.8**	**23.9 ± 4.9**	**0.048**	26.4 ± 4.3	24.1 ± 5	0.076	25.7 ± 5.3	23.1 ± 4.7	0.271
LV end-diastolic diameter, mm	**46.3 ± 3.8**	**43.9 ± 4.1**	**0.006**	**46.7 ± 3.9**	**43.9 ± 4.4**	**0.021**	46 ± 3.8	43.9 ± 3.2	0.165
LVEDVI, ml/m^2	82.1 ± 19.9	85.3 ± 17.9	0.335	85.9 ± 25.1	83.6 ± 16.8	0.91	78.7 ± 13.6	90.9 ± 21.6	0.208
LVESVI, ml/m^2	31.5 ± 17.7	30 ± 11.8	0.855	30.8 ± 12.6	29.3 ± 11.3	0.733	32.2 ± 21.4	32.7 ± 14	0.871
LVMI, g/m^2	99 ± 35.4	91.5 ± 31.4	0.449	**111.1 ± 38.1**	**89.5 ± 30.6**	**0.036**	88.3 ± 29.5	98 ± 35.1	0.626
LVEF, %	64.2 ± 9.8	65.7 ± 8	0.452	64.6 ± 7.7	65.9 ± 8.2	0.586	63.8 ± 11.6	65.1 ± 7.7	0.772
LGE	6.64 ± 4.76	7.08 ± 5.12	0.876	7.18 ± 4.69	8.29 ± 5.36	0.664	6.27 ± 4.86	3.99 ± 2.82	0.227

IPVTR, isovolumetric pulmonary vein transit ratio, defined as the ratio between the PRVT and the atrial emptying volume; LA, left atrial; LAEF, left atrial ejection fraction; LASV, left atrial stroke volume; LAV, left atrial volume; LGE, late gadolinium enhancement; LV, left ventricular; LVEDVI, left ventricle end diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricle end systolic volume index; LVMI, left ventricle mass index; PER-A, atrial peak emptying rate; PER-A, index atrial peak emptying rate A normalized by LV filling volume; PER-E, early peak emptying rate; PER-E, index early peak emptying rate normalized by LV filling volume. Bold values mean $P < 0.05$.

booster pump in late diastole. LA reservoir function represents LA relaxation and compliance (16). LA conduit function is reliant on LV diastolic function, including both the suction force dependent on LV relaxation and LV chamber stiffness, whereas LA booster function is based on intrinsic LA contractility and LV end-diastolic compliance and pressure (17, 18). Thereby, there is a close relationship between LA and LV functions.

Cardiovascular magnetic resonance imaging-feature tracking (CMR-FT) is a new quantitative method for wall motion assessment, with a high spatial resolution and large field of view. The details for the change rates of LAV during conduit (i.e., PER-E and PER-E indexes) and booster phases (i.e., PER-A and PER-A indexes) can be provided by the analysis of LA dV/dt curves plotting by CMR-FT. In this study, patients with HOCM showed a lower PER-E index in the conduit phase than controls, but there was no difference in the booster phase. A previous study has also found that patients with non-obstructive HCM were likely to have LA conduit dysfunction, compared to healthy controls (19). The possible explanation is that during early LVDD, increased ventricular stiffness and abnormal relaxation reduce the passive suction effect on LA, which decreases the empty rate in the conduit phase. In contrast, increased atrial stretching results in a more powerful contraction of the LA during the booster phase (6). Therefore, we believed that parameters in the conduit phase are superior as an estimate of the LA function.

In addition, our study showed that the PER-E and PER-E index of female patients is lower than male patients. A previous study has demonstrated that female patients presented more severe atrial stiffness than male patients with heart failure, which was assessed with pulse wave analysis of the radial artery and carotid-femoral pulse wave velocity using commercially available radial artery tonometry. The effect of atrial stiffness can increase LV afterload and impair LV relaxation, which may contribute to a greater susceptibility to heart failure with preserved LV ejection fraction in female patients (20). To explore the relationship between LA remodeling and myocardial fibrosis, we stratified patients with HOCM into two subgroups according to the upper limit of CVF normality. In both subgroups with high and normal CVF, female patients

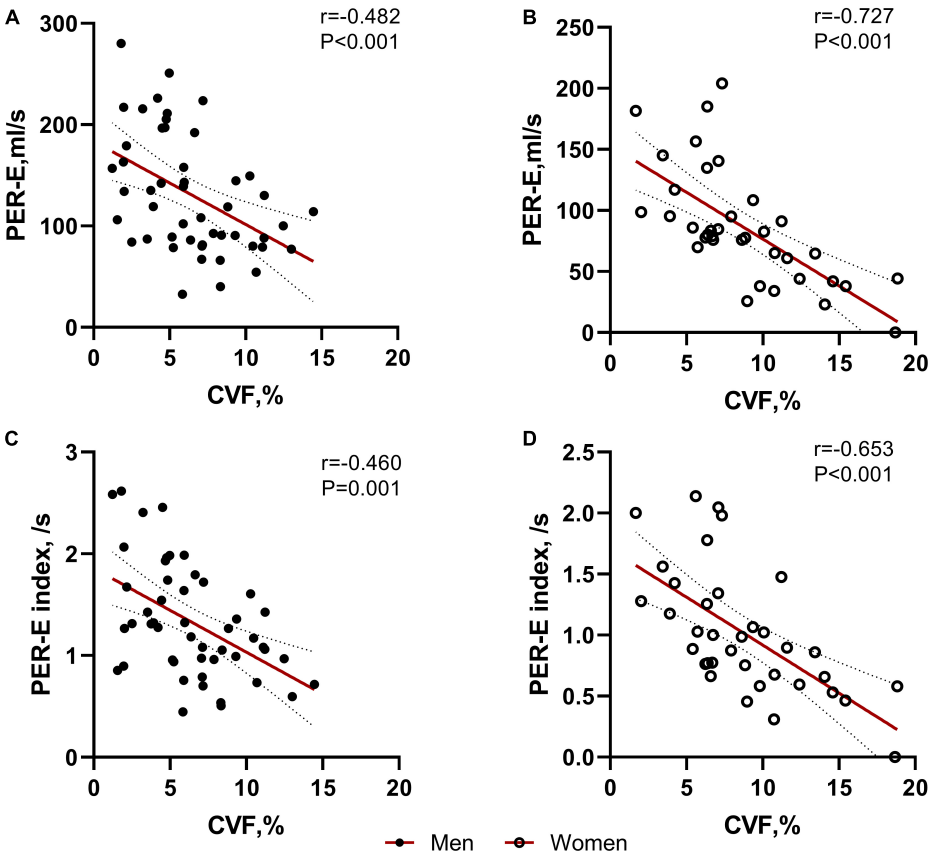


FIGURE 3
Correlations between collagen volume fraction (CVF) and left atrial (LA) deformation rates in both sexes. CVF was significantly correlated with PER-E and PER-E index in males **(A,C)** and females **(B,D)**.

TABLE 3 Univariate and multivariate regression analyses for peak of emptying rate (PER-E) in patients with hypertrophic obstructive cardiomyopathy (HOCM).

	Univariate		Multivariate	
	β (95%CI)	*P*-value	β (95%CI)	*P*-value
Age	−1.022 (−1.959– −0.084)	0.033		
Sex	44.347 (20.707–67.986)	<0.001	28.341 (8.016–48.666)	0.007
EDVI	0.551 (−0.104–1.207)	0.098	0.658 (0.151–1.165)	0.012
ESVI	0.744 (−0.064–1.552)	0.071		
CVF	−8.914 (−11.582– −6.646)	<0.001	−7.927 (−10.547– −5.308)	<0.001

CVF, collagen volume fraction; HOCM, hypertrophic obstructive cardiomyopathy; LVMI, left ventricular mass index; PER-E, early peak emptying rate.

had a similar extent of myocardial fibrosis to male patients. The sex difference in PER-E remained significant in patients with high CVF, but the sex differences in PER-E index were eliminated in both subgroups with normal CVF and high CVF. The multivariate analysis also suggested that sex and myocardial fibrosis were independently correlated with PER-E when adjusting for clinical confounders. This indicated that a higher fibrotic burden in female patients might be one of the factors that led to their worse LA remodeling. Interestingly, at present, LGE imaging is a standard non-invasive approach to evaluate myocardial fibrosis. However, this sex-related difference in myocardial fibrosis could not be found in the LGE analysis, and no correlation was found between the LA function and the extent of LGE. This might be explained by the drawback of detecting diffuse fibrosis in LGE imaging. In patients with aortic stenosis, female patients presented with a larger extent of diffuse myocardial fibrosis but a similar amount of replacement myocardial fibrosis (LGE), which was possible

due to the aggressive nature of the response to increasing the LV filling pressure (21). The interaction of sex with myocardial fibrosis was significant in pathological studies (22), but was easily ignored with the use of LGE (23).

The mechanisms underlying sex-specific differences in myocardial fibrosis are unknown, but in our study, despite worse LA function in female patients, they showed smaller LV diameters and lower septal wall thickness. The LV geometry in female patients could underlie a greater prevalence of obstructive hemodynamics (24), which was negatively correlated with LGE (25). Sex hormones and different responses to the renin-angiotensin-aldosterone system may also play a role in the process of fibrosis development (26, 27).

Our study still has several limitations. First, owing to the observational nature of our study, there may be less insight into the causality between LA function and myocardial fibrosis, and it is still unclear how sex modifies the relationship. Second, we only enrolled patients with HOCM, which limited the appliance to other morphological types of HCM. Third, this study is a cross-sectional analysis and may have inherent limitations; the findings must be confirmed by further studies with a longitudinal design.

Conclusion

Patients with HOCM presented LA reverse remodeling. Impaired LA function was more common in female patients with HOCM due to their susceptibility to myocardial fibrosis.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Fuwai Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

XB, YYS, and CY contributed to the conception and design of the study and wrote the first draft of the manuscript. XB organized the database and performed data analysis. All authors contributed to the interpretation of the results and manuscript revision, read, and approved the submitted version.

Funding

This study was partly supported by the National Natural Science Foundation of China (81370327).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.947975/full#supplementary-material

References

1. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, et al. American College of Cardiology/European society of cardiology clinical expert consensus document on hypertrophic cardiomyopathy. *J Am Coll Cardiol.* (2003) 42:1687–713.

2. Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. *N Engl J Med.* (2018) 379:655–68. doi: 10.1056/NEJMra1710575

3. Pelliccia F, Pasceri V, Limongelli G, Autore C, Basso C, Corrado D, et al. Long-term outcome of nonobstructive versus obstructive hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Int J Cardiol.* (2017) 243:379–84. doi: 10.1016/j.ijcard.2017.06.071

4. Varnava AM, Elliott PM, Sharma S, McKenna WJ, Davies MJ. Hypertrophic cardiomyopathy: the interrelation of disarray, fibrosis, and small vessel disease. *Heart.* (2000) 84:476. doi: 10.1136/heart.84.5.476

5. Avegliano G, Politi MT, Costabel JP, Kuschnir P, Trivi M, Ronderos R. Differences in the extent of fibrosis in obstructive and nonobstructive hypertrophic cardiomyopathy. *J Cardiovasc Med*. (2019) 20:389–96. doi: 10.2459/JCM.0000000000000800

6. Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left atrial structure and function, and left ventricular diastolic dysfunction: JACC state-of-the-art review. *J Am Coll Cardiol*. (2019) 73:1961–77. doi: 10.1016/j.jacc.2019.01.059

7. Boyd AC, Richards DA, Marwick T, Thomas L. Atrial strain rate is a sensitive measure of alterations in atrial phasic function in healthy ageing. *Heart*. (2011) 97:1513–9. doi: 10.1136/heartjnl-2011-300134

8. Leinwand LA. Sex is a potent modifier of the cardiovascular system. *J Clin Invest*. (2003) 112:302–7. doi: 10.1172/JCI200319429

9. Schuster A, Backhaus SJ, Stiermaier T, Navarra J, Uhlig J, Rommel K, et al. Left atrial function with MRI enables prediction of cardiovascular events after myocardial infarction: insights from the AIDA STEMI and TATORT NSTEMI Trials. *Radiology*. (2019) 293:292–302. doi: 10.1148/radiol.2019190559

10. Borlaug BA, Redfield MM, Melenovsky V, Kane GC, Karon BL, Jacobsen SJ, et al. Longitudinal changes in left ventricular stiffness: a community-based study. *Circ Heart Fail*. (2013) 6:944–52. doi: 10.1161/CIRCHEARTFAILURE.113.000383

11. Chen Y, Qiao S, Hu F, Yuan J, Yang W, Cui J, et al. Left ventricular remodeling and fibrosis: sex differences and relationship with diastolic function in hypertrophic cardiomyopathy. *Eur J Radiol*. (2015) 84:1487–92. doi: 10.1016/j.ejrad.2015.04.026

12. Nijenkamp L, Bollen I, van Velzen HG, Regan JA, van Slegtenhorst M, Niessen H, et al. Sex differences at the time of myectomy in hypertrophic cardiomyopathy. *Circ Heart Fail*. (2018) 11:e4133. doi: 10.1161/CIRCHEARTFAILURE.117.004133

13. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. (2014) 35:2733–79. doi: 10.1093/eurheartj/ehu284

14. Aquaro GD, Pizzino F, Terrizzi A, Carerj S, Khandheria BK, Di Bella G. Diastolic dysfunction evaluated by cardiac magnetic resonance: the value of the combined assessment of atrial and ventricular function. *Eur Radiol*. (2019) 29:1555–64. doi: 10.1007/s00330-018-5571-3

15. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA*. (2002) 287:1308–20. doi: 10.1001/jama.287.10.1308

16. Barbier P, Solomon SB, Schiller NB, Glantz SA. Left atrial relaxation and left ventricular systolic function determine left atrial reservoir function. *Circulation*. (1999) 100:427–36. doi: 10.1161/01.CIR.100.4.427

17. Manning WJ, Silverman DI, Katz SE, Douglas PS. Atrial ejection force: a noninvasive assessment of atrial systolic function. *J Am Coll Cardiol*. (1993) 22:221–5. doi: 10.1016/0735-1097(93)90838-r

18. Toma Y, Matsuda Y, Moritani K, Ogawa H, Matsuzaki M, Kusukawa R. Left atrial filling in normal human subjects: relation between left atrial contraction and left atrial early filling. *Cardiovasc Res*. (1987) 21:255–9. doi: 10.1093/cvr/21.4.255

19. Yang Y, Yin G, Jiang Y, Song L, Zhao S, Lu M. Quantification of left atrial function in patients with non-obstructive hypertrophic cardiomyopathy by cardiovascular magnetic resonance feature tracking imaging: a feasibility and reproducibility study. *J Cardiovasc Magn Reson*. (2020) 22:1. doi: 10.1186/s12968-019-0589-5

20. Shim CY, Park S, Choi D, Yang W, Cho I, Choi E, et al. Sex differences in central hemodynamics and their relationship to left ventricular diastolic function. *J Am Coll Cardiol*. (2011) 57:1226–33. doi: 10.1016/j.jacc.2010.09.067

21. Tastet L, Kwiecinski J, Pibarot P, Capoulade R, Everett RJ, Newby DE, et al. Sex-related differences in the extent of myocardial fibrosis in patients with aortic valve stenosis. *JACC Cardiovasc Imaging*. (2020) 13:699–711. doi: 10.1016/j.jcmg.2019.06.014

22. Lu DY, Ventoulis I, Liu H, Kudchadkar SM, Greenland GV, Yalcin H, et al. Sex-specific cardiac phenotype and clinical outcomes in patients with hypertrophic cardiomyopathy. *Am Heart J*. (2020) 219:58–69. doi: 10.1016/j.ahj.2019.10.004

23. Haukilahti MAE, Holmström L, Vähätalo J, Kenttä T, Tikkanen J, Pakanen L, et al. Sudden cardiac death in women. *Circulation*. (2019) 139:1012–21. doi: 10.1161/CIRCULATIONAHA.118.037702

24. Nogales-Romo MT, Cecconi A, Olivera MJ, Caballero P, Hernández S, Jiménez-Borreguero LJ, et al. Sex differences in cardiac magnetic resonance features in patients with hypertrophic cardiomyopathy. *Int J Cardiovasc Imaging*. (2020) 36:1751–9. doi: 10.1007/s10554-020-01880-y

25. Liu J, Zhao S, Yu S, Wu G, Wang D, Liu L, et al. Patterns of replacement fibrosis in hypertrophic cardiomyopathy. *Radiology*. (2022) 302:298–306. doi: 10.1148/radiol.2021210914

26. Greiten LE, Holditch SJ, Arunachalam SP, Miller VM. Should there be sex-specific criteria for the diagnosis and treatment of heart failure? *J Cardiovasc Transl Res*. (2014) 7:139–55. doi: 10.1007/s12265-013-9514-8

27. Patten RD, Pourati I, Aronovitz MJ, Baur J, Celestin F, Chen X, et al. 17beta-estradiol reduces cardiomyocyte apoptosis in vivo and in vitro via activation of phospho-inositide-3 kinase/Akt signaling. *Circ Res*. (2004) 95:692–9. doi: 10.1161/01.RES.0000144126.57786.89

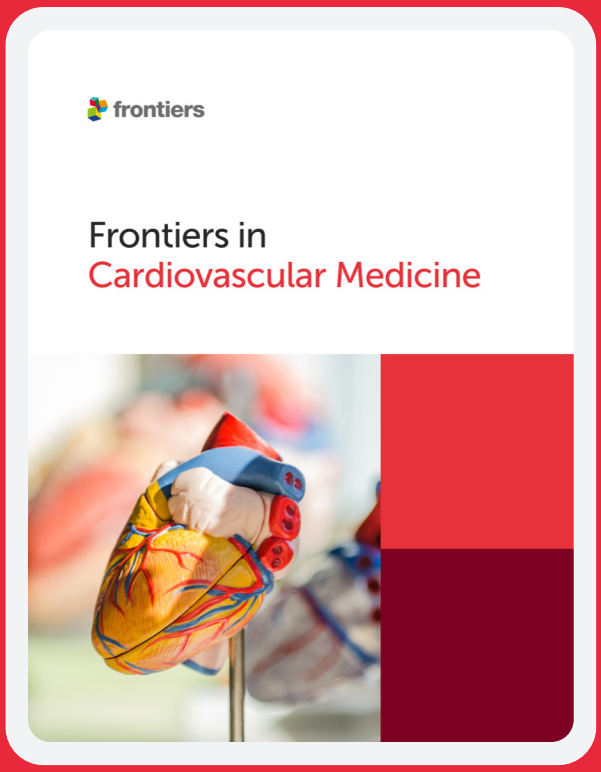
Frontiers in
Cardiovascular Medicine

Innovations and improvements in cardiovascular treatment and practice

Focuses on research that challenges the status quo of cardiovascular care, or facilitates the translation of advances into new therapies and diagnostic tools.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact