Bibliometric and visual analysis of coronary microvascular dysfunction

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Background: Coronary microvascular dysfunction (CMD) may play an important role in various cardiovascular diseases, including HFrEF and both obstructive and non-obstructive coronary artery disease (CAD). To date, there has been no bibliometric analysis to summarize this field. Here, we aim to conduct a bibliometric analysis of CMD to determine the current status and frontiers in this field.

Materials and methods: Publications about CMD were taken from the Web of Science Core Collection database (WOSCC). WOSCC’s literature analysis wire, the VOSviewer 1.6.16, and CiteSpace 5.1.3 were used to conduct the analysis.

Results: A total of 785 publications containing 206 reviews and 579 articles are included in the sample. The leading authors are Iacopo Olivotto, Paolo G. Camici, and Carl J. Pepine. The most productive institutions are the University of Florence, Cedars Sinai Medical Center, and Harvard University. The most productive countries are the USA, Italy, and England. There are a total of 237 journals that contribute to this field, and the leading journals in our study were the International Journal of Cardiology, the European Heart Journal and the JACC. From 2012 to 2021, the top three most-cited articles focused on the association between HFrEF and CMD. The important keywords are heart failure, hypertrophic cardiomyopathy, chest pain, women, coronary flow reserve (CFR), endothelial dysfunction and prognostic value. “Positron emission tomography” shows the strongest burst strength, followed by “blood flow” and “artery.” The keywords that started to burst from 2015 are particularly emphasized, including “heart failure,” “coronary flow reserve,” and “management.”

Conclusion: Studies about CMD are relatively limited, and the largest contribution comes from the USA, Italy and England. More studies are needed, and publications from other countries should be enhanced. The main research hotspots in the CMD field include CMD in patients with HFrEF, sex differences, the new methods of diagnosis for CMD, and the effective treatment of CMD.
Attention should be given to CMD in patients with HFrEF, and untangling the association between CMD and HFrEF could be helpful in the development of physiology-stratified treatment for patients with CMD and HFrEF.

KEYWORDS
coronary microvascular dysfunction (CMD), bibliometric analysis, visual maps, HFrEF, treatment

Introduction

Coronary microvascular dysfunction (CMD) is an underdiagnosed and underrecognized condition that is related to an increased incidence of adverse cardiac events (1–4). CMD could present as chest pain with imaging abnormalities and/or electrocardiographic changes evident in stress testing but without obstructive coronary artery disease on angiography. The risk factors for CMD are similar to those for coronary artery disease (CAD), including chronic inflammation, hyperlipidemia, hyperglycemia, hypertension, and aging (1, 5–7). CMD could be diagnosed by the use of non-invasive coronary assessment via PET, CMR, or echocardiography and invasive coronary assessment via doppler or thermodilution. The treatment of CMD encompasses antianginal medications including ranolazine, ivabradine, and nicorandil, anti-atherosclerotic drugs including statins, ACEIs, and calcium-channel blockers, and some non-pharmacological treatments including a well-balanced diet, lifestyle modifications, cognitive behavioral therapy (CBT) and enhanced external counterpulsation (5).

Coronary microvascular dysfunction can be divided into four types including dysfunction in the presence of obstructive CAD, dysfunction due to myocardial diseases, dysfunction in the absence of myocardial and CAD diseases, and iatrogenic dysfunction. CMD is prevalent across various cardiovascular diseases (CVDs) including non-ischemic cardiomyopathies, angina with and without obstructive CAD, takotsubo syndrome, myocardial infarction, and heart failure (HF). Among them, CMD in heart failure with HFrEF has drawn increasing attention. In Shah’s study, the high prevalence of CMD in HFrEF (75%) was demonstrated (8). Taqueti et al. found that impaired CFR in symptomatic patients without overt CAD was independently associated with adverse events such as HFrEF hospitalization (9). In specific populations, CMD may have a pathophysiological and prognostic role. Previous studies have shown that CMD may play an important role in different cardiovascular diseases including HFrEF, obstructive and non-obstructive CAD. To date, there has been no bibliometric analysis to summarize this field. We aim to conduct a bibliometric analysis of CMD to determine the current status and frontiers in this field.

Materials and methods

Search strategy

The WoSCC has been widely used for bibliometric analysis widely (10, 11). In our study, publications about CMD were taken from the WoSCC. The search term used was TS = “coronary microvascular dysfunction” OR “Coronary Microvascular Endothelia Inflammation” OR “Coronary Microvascular Rarefaction” OR “coronary microvascular endothelial dysfunction.” The search results were narrowed by publication data including a date range of: 1 January 2000 to 31 December 2021, a publication language of English and the article types of reviews and articles.

Data collection and analysis

The VOSviewer 1.6.16 (Rotterdam, Netherlands), CiteSpace 5.1.3 (Philadelphia, PA, USA), and WoSCC literature analysis wire were used to conduct the our study’s analysis (12, 13). The h-index was used to evaluate the citations of the selected publications. In our study, VOSviewer1.6.16 software was used to determine co-authorship keywords, authors, countries/regions, and institutions. Publication year, document type, categories, the distribution of authors, country/region, institutions, and h-index were analyzed by the WoSCC literature analysis wire. CiteSpace 5.1.3 was used to the burst detection analysis of keywords. Total link strength (TLS) was used to evaluate the cooperation relationship.

Results

Publication output

A total of 785 publications containing 206 reviews and 579 articles were included (Figure 1). The publications generally showed an upward trend from 2006. The major subject categories were cardiac cardiovascular systems (505 publications), peripheral vascular disease (103 publications),
radiology nuclear medicine medical imaging (99 publications), medicine general internal (43 publications), and pharmacology pharmacy (38 publications), which is shown in Figure 2.

**Distribution of authors**

From this field, a total of 4,207 authors were included. Among them, Iacopo Olivotto was the leading author from Italy with 45 publications, followed by Paolo G Camici with 40 publications, Carl J Pepine with 32 publications, Janet Wei with 27 publications, and C Noel Bairey Merz with 26 publications. Paolo G Camici, Filippo Crea, and Iacopo Olivotto were the most highly cited authors. The uppermost h-index value was for Paolo G Camici (h-index: 29), followed by Iacopo Olivotto (h-index: 23), Filippo Crea (h-index: 15) and Amir Lerman (h-index: 15). The coauthorship map of authors is shown in Figure 3A. The top three coauthorship triads of authors were C Noel Bairey Merz (TLS = 238), Janet Wei (TLS = 196) and Carl J. Pepine (TLS = 175).

**Distribution by countries/regions and institutions**

All publications were taken from 48 countries/regions and 1,064 organizations. The most productive institutions were the University of Florence (52 publications with 2,536 citations), the Cedars Sinai Medical Center (51 publications with 2,867 citations), Harvard University (50 publications with 2,654 citations), the Azienda Ospedaliero Universitaria Careggi (48 publications with 2,395 citations), and Imperial College London (42 publications with 4,510 citations). The coauthorship map of institutions is shown in Figure 3B. The top three institutions involved in coauthorship were the University of Florida, Careggi University Hospital and Cedars Sinai Medical Center. For countries/regions, the USA had the most publications (301 documents), followed by Italy (178 documents), England (111 documents), Netherlands (72 documents), and Japan (67 documents). The top three countries/regions involved in coauthorship were the USA, Italy, and England. The coauthorship map of countries/regions and the top 10 high-yield countries/regions, institutions and authors are summarized in Figure 3C and Table 1.

**Distribution by journal**

A total of 237 journals contribute to this field. Among them, the International Journal of Cardiology was the leading journal with 55 documents, followed by EHJ with 25 documents and JACC with 23 documents. The coauthorship map of journals and the top 10 high-yield journals are summarized in Figure 4A and Table 2.
Analysis of high-cited references

The characteristics of publications were summarized in Table 3 (1, 14–32). The most-cited reference was published in the JACC and authored by Paulus W. J. and Tschope C. The second most-cited reference was published in NEJM and authored by Paolo G. Camici and Filippo Crea in 2007. The third most-cited reference was published in the JACC and authored by Piero O. Bonetti et al in 2004. To explore the hotspots in this field over recent years, we summarize the top three most highly cited articles in the last decade (2012–2021) The most highly cited article was published in the JACC by Paulus W. J. in 2013 (26). In this article, Paulus first proposed the association between CMD and HFpEF, which differs from that between HFpEF and HFrEF. Attention should be given to this new HFpEF paradigm of CMD with potential important diagnostic and therapeutic implications. The second most highly cited article was published by Shah S. J. in 2016 (31). Shah believed that CMD played an important role in HFpEF and proposed personalized therapeutic strategies. The third most cited article was published by Mohammed SF in 2015, who found that patients with HFpEF had coronary microvascular rarefaction compared with controls following autopsy. The citation map of documents is shown in Figure 4B.

Analysis of keywords co-occurrence clusters

Figure 5 shows the co-occurrence map of keywords, and four research directions are also shown. The green cluster includes heart failure, hypertrophic cardiomyopathy, and disease. The red cluster includes artery disease, chest pain, women, and cardiac syndrome. The blue cluster includes coronary flow reserve (CFR), endothelial dysfunction, and inflammation. The yellow cluster includes blow flow, PET, and prognostic value.

Burst detection of keywords

CiteSpace 5.1.3 is used to perform burst detection of keywords. The burst detection analysis of keywords can predict frontier research directions, reflect emerging academic trends, and display the hotspots in a field. Twenty prominent words were obtained by the burst detection analysis. "Positron
 FIGURE 3
Visualization knowledge maps of the co-authorship. (A) The co-authorship map of authors which indicates the authors that cooperate in the field of CMD. (B) The co-authorship map of organizations. The institution with the strongest total link strength is the University of Florida. (C) The co-authorship map of countries. The number of collaborators with the USA is 300 and the total link strength is 230. Different colors indicate different clusters and the size of nodes indicates the number of publications. The thickness of the lines represents the link strength of the countries.

emission tomography” shows the strongest burst strength, followed by “blow flow” and “artery.” The keywords that started to burst from 2015 are particularly emphasized, including “heart failure” (burst strength 4.98), “coronary flow reserve” (burst strength 4.79), and “management” (burst strength 4.47), which is shown in Figure 6.

Discussion
General information
To the best of our knowledge, this is the first bibliometric study in the field of CMD. A total of 785 publications are included. The leading authors are Iacopo Olivotto, Paolo G Camici and Carl J Pepine. The uppermost h-index value is for Paolo G. Camici, followed by Iacopo Olivotto, Filippo Crea, and Amir Lerman. The top three authors involved in coauthorship are C. Noel Bairey Merz, Janet Wei and Carl J. Pepine. All publications are taken from 48 countries/regions and 1,064 organizations. The most productive institutions are the University of Florence, the Cedars Sinai Medical Center, and Harvard University. The most productive countries are the USA, Italy, and England. The top three institutions involved in coauthorship are the University of Florida, Careggi University Hospital and Cedars Sinai Medical Center, and the top three countries/regions involved in coauthorship are the USA, Italy, and England. A total of 237 journals contribute to this field, and the leading journals are the International Journal of Cardiology, EHJ and JACC. From 2012 to 2021, the top three most-cited articles focused on the association between HFpEF and CMD. The important keywords used in this study are heart failure, hypertrophic cardiomyopathy, chest pain, women, CFR, endothelial dysfunction and prognostic value. “Positron
TABLE 1  Ranking of the top 10 authors, institutions, and countries based on publications.

| Items | Publications | Co-authorship maps |
|-------|--------------|--------------------|
|       | Rank | Name | Number | Citations | H-index | Rank | Name | Total link strength |
| Country | 1 | USA | 301 | 13,574 | 55 | 1 | USA | 230 |
|         | 2 | Italy | 178 | 8,531 | 44 | 2 | Italy | 182 |
|         | 3 | England | 111 | 6,985 | 38 | 3 | England | 149 |
|         | 4 | Netherlands | 72 | 5,125 | 28 | 4 | Netherlands | 114 |
|         | 5 | Japan | 67 | 1,343 | 19 | 5 | Germany | 77 |
|         | 6 | People’s Republic of China | 58 | 477 | 12 | 6 | Australia | 61 |
|         | 7 | Germany | 51 | 4,248 | 26 | 7 | Japan | 47 |
|         | 8 | Turkey | 36 | 561 | 12 | 8 | Scotland | 39 |
|         | 9 | Denmark | 31 | 565 | 12 | 9 | Spain | 34 |
|         | 10 | Australia | 29 | 1,104 | 18 | 10 | Belgium | 32 |
| Institution | 1 | University of Florida | 52 | 2,536 | 26 | 1 | University of Florida | 105 |
|         | 2 | Cedars Sinai Medical Center | 51 | 2,867 | 19 | 2 | Careggi University Hospital | 103 |
|         | 3 | Harvard University | 50 | 2,654 | 24 | 3 | Cedars Sinai Medical Center | 92 |
|         | 4 | Azienda Ospedaliero Universitaria Careggi | 48 | 2,395 | 24 | 4 | Università Vita-Salute San Raffaele MILANO | 84 |
|         | 5 | Imperial College London | 42 | 4,510 | 26 | 5 | Erasmus Medical Center | 75 |
|         | 6 | Mayo Clinic | 39 | 3,648 | 23 | 6 | Yale University | 67 |
|         | 7 | Brigham Women’s Hospital | 38 | 2,461 | 23 | 7 | St George’s University of London | 66 |
|         | 8 | State University System of Florida | 38 | 2,069 | 17 | 8 | Imperial College London | 60 |
|         | 9 | University of Florida | 38 | 2,069 | 17 | 9 | University of Michigan | 59 |
|         | 10 | Catholic University of the Sacred Heart | 32 | 3,391 | 18 | 10 | Emory University | 58 |
| Author | 1 | Iacopo Olivotto | 45 | 2,187 | 23 | 1 | C. Noel Bairey Merz | 238 |
|         | 2 | Paolo G. Camici | 40 | 5,623 | 29 | 2 | Janet Wei | 196 |
|         | 3 | Carl J. Pepine | 32 | 1,485 | 13 | 3 | Carl J. Pepine | 175 |
|         | 4 | Janet Wei | 27 | 475 | 9 | 4 | Puja K. Mehta | 146 |
|         | 5 | C. Noel Bairey Merz | 26 | 1,392 | 13 | 5 | Chrisandra Shufelt | 116 |
|         | 6 | Filippo Crea | 24 | 3,177 | 15 | 6 | Iacopo Olivotto | 113 |
|         | 7 | Eileen Handberg | 21 | 825 | 8 | 7 | Galen Cook-Wiens | 111 |
|         | 8 | Eva Prescott | 21 | 408 | 9 | 8 | Eileen Handberg | 110 |
|         | 9 | Amir Lerman | 21 | 1,027 | 15 | 9 | Eva Prescott | 110 |
|         | 10 | Puja K. Mehta | 21 | 483 | 10 | 10 | Daniel S. Berman | 94 |

“emission tomography” shows the strongest burst strength, followed by “blow flow” and “artery.” The keywords that started to burst from 2015 are particularly emphasized, including “heart failure,” “coronary flow reserve,” and “management.”

Most of the included publications come from the USA, Italy, and England (590/785, 75.2%). Of the top 10 productive authors, six were from the USA, and the remaining four were from Italy. Of the top 10 institutions, 6 were from the USA, 3 were from Italy, and 1 was from England. Among cooperative relationships of authors, institutions and countries/regions, the USA, Italy and England were also prominent. The prominent countries in this field were again the USA, Italy, and England. Studies from and cooperation among other countries should be enhanced.

**Hotspots and frontiers**

In accordance with the most cited references and the important keywords, the research frontiers and hotspots were found to be as follows: (1) The first relates to sex difference among CMD patients. Among the most-cited references, three explored sex differences in CMD patients (25, 28, 29). The
Figure 4 Visualization knowledge maps of citation. (A) Citation map of Journal; (B) citation map of documents. Different color indicates different clusters. The size of the nodes represents the counts of citations. The distance between the two nodes indicates their correlation.

Table 2 Ranking of the top 10 journals based on publications.

| Ranking | Journal name                                      | Country | Counts | Citation | H-index |
|---------|---------------------------------------------------|---------|--------|----------|---------|
| 1       | International Journal of Cardiology              | Ireland | 55     | 919      | 14      |
| 2       | European Heart Journal                           | England | 25     | 2,852    | 20      |
| 3       | Journal of the American College of Cardiology    | USA     | 23     | 4,934    | 20      |
| 4       | Cardiovascular Research                          | England | 20     | 885      | 16      |
| 5       | Journal of Nuclear Cardiology                    | USA     | 19     | 192      | 8       |
| 6       | Circulation                                      | USA     | 18     | 3,390    | 18      |
| 7       | Atherosclerosis                                   | USA     | 15     | 339      | 10      |
| 8       | Journal of The American Heart Association        | USA     | 15     | 243      | 8       |
| 9       | Microcirculation                                  | USA     | 15     | 174      | 6       |
| 10      | American Journal of Physiology Heart and Circulatory Physiology | USA     | 12     | 373      | 9       |

The keyword of women was in the red cluster. In the Women’s Ischemia Syndrome Evaluation (WISE) study (29, 33, 34). The keyword “women” occurred in the red cluster. The results of the Women’s Ischemia Syndrome Evaluation (WISE) study demonstrated that CMD was present in approximately 50% of women with NOCAD and chest pain. Murthy et al. showed that CMD was highly prevalent in both men and women who were at-risk, and was associated with adverse outcomes irrespective of sex (25). Kobayashi et al. found that the microvascular function was similar in men and women (35). Recently, Chandramouli et al. found that the drivers of CMD may differ by sex, but the prevalence of CMD in HFpEF was similar in women and men. They demonstrated that fibrosis and derangement in ventricular remodeling potentially predominate in women while the inflammatory paradigm of CMD seems to play a more important role in men (36). Based on recent evidence, the prevalence of CMD were similar in both women and men, but the mechanisms might be different, which should be considered in future therapeutic interventions. (2) The next hotspot involves the new methods of diagnosis for CMD. Among the most-cited references, four explored the diagnosis of CMD (1, 14, 15, 17). The keywords of coronary flow reserve, blow flow, PET, and prognostic value occur in the blue and yellow clusters. The diagnosis of CMD is usually made by the measurement of CFR or IMR with invasive coronary assessment via Doppler or thermodilution or CFR with non-invasive coronary assessment via PET, CMR, or echocardiography (37). The approaches of diagnosis for CMD are limited, and new methods are needed. A recent systematic review and meta-analysis showed that CFR was related to the rate of major adverse cardiovascular events (MACE) and all-cause mortality, and suggested that, CFR should be measured more routinely in clinical practice.
| Rank | Title                                                                 | Journals                      | Total citations | Publication year | First author         |
|------|-----------------------------------------------------------------------|-------------------------------|-----------------|------------------|----------------------|
| 1    | A novel paradigm for heart failure with preserved ejection fraction   | JACC                          | 1,739           | 2013             | Paulus, WJ           |
|      | comorbidities drive myocardial dysfunction and remodeling through     |                               |                 |                  |                      |
|      | coronary microvascular endothelial inflammation                      |                               |                 |                  |                      |
| 2    | Medical progress - Coronary microvascular dysfunction                 | NEJM                          | 1,082           | 2007             | Camici, PG           |
| 3    | Non-invasive identification of patients with early coronary           | JACC                          | 713             | 2004             | Bonetti, PO          |
|      | atherosclerosis by assessment of digital reactive hyperemia           |                               |                 |                  |                      |
| 4    | Coronary microvascular dysfunction and prognosis in hypertrophic      | NEJM                          | 507             | 2003             | Cecchi, F            |
|      | cardiomyopathy                                                        |                               |                 |                  |                      |
| 5    | Phenotype-specific treatment of heart failure with preserved ejection | Circulation                   | 488             | 2016             | Shah, SJ             |
|      | fraction a multiorgan roadmap                                        |                               |                 |                  |                      |
| 6    | Coronary microvascular reactivity to adenosine predicts adverse       | JACC                          | 460             | 2010             | Pepine, CJ           |
|      | outcome in women evaluated for suspected ischemia results from the    |                               |                 |                  |                      |
|      | national heart, lung and blood institute WISE (Women's Ischemia     |                               |                 |                  |                      |
|      | Syndrome Evaluation) study                                           |                               |                 |                  |                      |
| 7    | Coronary microvascular rarefaction and myocardial fibrosis in heart   | Circulation                   | 404             | 2015             | Mohammed, SF         |
|      | failure with preserved ejection fraction                              |                               |                 |                  |                      |
| 8    | The global burden of ischemic heart disease in 1990 and 2010         | Circulation                   | 400             | 2014             | Moran, AE            |
| 9    | Coronary microvascular dysfunction: an update                         | European heart journal        | 383             | 2014             | Crea, F              |
| 10   | The pathophysiology of acute myocardial infarction and strategies of | European heart journal        | 378             | 2017             | Heusch, G            |
|      | protection beyond reperfusion: a continual challenge                  |                               |                 |                  |                      |
| 11   | Coronary microvascular dysfunction is highly prevalent in women with  | American heart journal        | 365             | 2001             | Reis, SE             |
|      | chest pain in the absence of coronary artery disease: Results from the|                               |                 |                  |                      |
|      | NHLBI WISE study                                                      |                               |                 |                  |                      |
| 12   | From endothelial dysfunction to atherosclerosis                       | Autoimmunity reviews          | 318             | 2010             | Sitia, S             |
| 13   | Role of chronic hyperglycemia in the pathogenesis of coronary         | JACC                          | 318             | 2003             | Di Carlo, MF         |
|      | microvascular dysfunction in diabetes                                 |                               |                 |                  |                      |
| 14   | Effects of sex on coronary microvascular dysfunction and cardiac      | Circulation                   | 308             | 2014             | Murthy, VL           |
|      | outcomes                                                              |                               |                 |                  |                      |
| 15   | Hemodialysis-induced cardiac dysfunction is associated with an acute  | Clinical journal of the       | 305             | 2008             | McIntyre, CW         |
|      | reduction in global and segmental myocardial blood flow               | American society of           |                 |                  |                      |
|      |                                                                      | nephrology                    |                 |                  |                      |
| 16   | Clinical diabetic cardiomyopathy: a two-faced disease with restrictive| European heart journal        | 290             | 2015             | Seferovic, PM        |
|      | and dilated phenotypes                                                |                               |                 |                  |                      |
| 17   | Ischemia and no obstructive coronary artery disease (INOCA)           | Circulation                   | 286             | 2017             | Merz, CNB            |
|      | developing evidence-based therapies and research agenda for the next  |                               |                 |                  |                      |
|      | decade                                                                |                               |                 |                  |                      |
| 18   | Primary coronary microvascular dysfunction clinical presentation,      | Circulation                   | 286             | 2010             | Lanza, GA            |
|      | pathophysiology, and management                                       |                               |                 |                  |                      |
| 19   | Pathophysiology of takotsubo syndrome                                 | Circulation                   | 277             | 2017             | Pelliccia, F         |
| 20   | Coronary microvascular dysfunction: mechanisms and functional         | Nature reviews cardiology     | 239             | 2015             | Camici, PG           |
|      | assessment                                                             |                               |                 |                  |                      |

(38). In addition, coronary flow velocity reserve (CFVR) as assessed by echocardiography to evaluate the CMD is feasible and could predict the adverse outcomes in women with no obstructive CAD and angina (39). More diagnostic approaches are being developed. (3) The next hotspot involves the effective treatment of CMD, which was explored by five of the most cited references (15, 17, 20, 22, 31). The treatment of CMD includes the use of antiangiinal drugs, anti-atherosclerotic medication, and new therapeutic strategies such as phosphodiesterase-5 inhibitors and ivabradine (40–43). It is necessary to explore more effective treatments for CMD in further studies. In this regard, it is essential to distinguish between endothelium-independent and endothelium-dependent CMD since they may require different treatments. (4) The final hotspot involves CMD in HFP EF. Among the most-cited references, three explored the association between CMD and HFP EF (23, 26, 31), and all
FIGURE 5
Visualization of keyword co-occurrence analysis. The size of nodes indicates the frequency of occurrences of the keywords. The lines between the nodes represent their co-occurrence in the same publication. The shorter the distance between two nodes, the larger the number of co-occurrence of the two keywords.

FIGURE 6
Top 20 Keywords with the strongest citation bursts. The blue indicates the timeline. The red segment indicates the start year, end year, and duration of the burst.
The top three most-cited articles over recent 10 years were about it (23, 26, 31). The keyword of heart failure occurs in the green cluster. In 2013, the association between CMD and HFP EF was first proposed. In 2016, Kato et al conducted the first study and showed that the prevalence of CMD diagnosed with non-invasive coronary assessment was 76%, while Dryer et al demonstrated that the prevalence CMD diagnosed with invasive measurement in patients with HFP EF was 73.4% (44, 45). The largest multi-national study (PROMIS-HFP EF) showed that the prevalence of CMD was 75% (8). In 2022, a study conducted by Arnold et al demonstrated that the prevalence of CMD was 70% in patients with HFP EF, and it was the first study to explore the association between the CMR-measured indexes of microvascular function and clinical outcomes (46). Several studies have explored the prevalence and correlation of CMD in patients with HFP EF. The prevalence of CMD was high in patients with HFP EF (over 70%) (8, 46–49). At present, all large-scale clinical trials had neutral results regarding the efficacy of pharmaceutical treatments for HFP EF with the exception of SGLT2 inhibitors (50–75), and even the effect of empagliflozin was attenuated in patients with an ejection fraction >65% (76). The heterogeneity of HFP EF may be the reason behind the failure of previous clinical trials to determine effective treatment for patients with HFP EF. Some patients could benefit from certain interventions, while others might not benefit or even be harmed by the same treatment. When these patients are mixed and treated together, it is difficult to identify an effective treatment. Untangling the association between CMD and HFP EF may be helpful to the development of physiology-stratified treatment for patients with CMD and HFP EF.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

XL, GW, and BG were responsible for data collection, investigation, figures and tables construction, and writing the original draft. JH and SW contributed to the discussion and final review and editing. All authors reviewed and edited the final manuscript.

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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.

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Irbesartan in patients with heart failure and preserved ejection fraction.

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