Review Article

Heart Failure with Preserved Ejection Fraction in Brazil: A Systematic Review

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is the most common condition of heart failure (HF) in patients over 65 years of age and is associated with high morbidity and mortality. Epidemiological data on this condition are still scarce in Brazil and these data are relevant for a better understanding of the impact and unmet needs in HFpEF and for the planning of actions to improve prevention, diagnosis, and treatment of this disease.

The objective of the study was to identify evidence on the epidemiology and clinical characteristics of Brazilian patients with HFpEF.

We systematically reviewed observational and clinical studies evaluating epidemiological and clinical data of Brazilian patients with HFpEF in the Pubmed/MEDLINE and LILACS databases, following PRISMA guidelines.

The prevalence of HFpEF in patients with confirmed HF ranged from 28.2 to 59.0% in the outpatient setting and from 20.0% to 53.1% in the hospital setting. Among patients with suspected HF, the prevalence of patients with LVEF>50% ranged from 29.0 to 37.6%. The most frequently reported comorbidities were systemic arterial hypertension and diabetes, with a prevalence of 57.4 to 100.0% in studies involving only patients with HFpEF, and from 10.2 to 49.1% in studies on patients with HF with normal ejection fraction (n = 14). Data on mortality and hospitalization rates were scarce.

Despite few and heterogeneous data on the prevalence of HFpEF in Brazil, the prevalence of this condition in primary care patients and in hospitalized patients was relatively high.

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF), defined as an ejection fraction (EF) ≥ 50%,[1] is the most prevalent condition (>70% of cases) in patients older than 65 years.[2] It is a complex, heterogenous clinical syndrome, with high morbidity and mortality, characterized by symptoms associated with a reduced capacity of the heart to pump blood adequately at normal cardiac filling pressures during diastole.[2] Patients with HFpEF show elevations in plasma natriuretic peptide levels in response to increased end-diastolic wall stress,[2] and may have a five-year survival of just 35% after hospitalization.[3]

The prevalence of HFpEF in the general population is estimated at 1-3% and further increments are expected with aging, improved diagnosis, and increased comorbidities such as diabetes, hypertension, obesity and atrial fibrillation.[4] These patients show impairment in quality of life, high hospitalization and premature death rates,[5,6] and one-year mortality rates of up to 6.3%,[1] similar to HFpEF patients after hospitalization.

In Brazil, epidemiological data on HFpEF are still scarce. In 2016, a cross sectional epidemiological study was conducted to evaluate the prevalence of HF and its phenotypes in individuals attending primary care clinics in the city of Niteroi, Brazil. In this sample, 59% of patients had HFpEF, and 41% HF with reduced EF (HFrEF). HFpEF was more prevalent among women, elderly, and in obese patients, with a higher proportion of hypertension and diabetes than in those with HFrEF.[7]

To better understand the impact and unmet needs in HFpEF, it is essential to produce epidemiological data that will guide physicians and decision makers in the planning of preventive, diagnostic and therapeutic interventions. Therefore, the aim of this review was to identify available evidence on clinical and epidemiological characteristics of Brazilian patients with HFpEF.

Methods

The protocol of the systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42019122380). We systematically reviewed observational and clinical studies evaluating epidemiological and clinical characteristics of Brazilian patients with HFpEF, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[8]

The MEDLINE database was searched via PubMed for Brazilian studies published from the beginning of 2008 to December 10, 2018. The search strategies included

Keywords

Heart Failure; Heart Failure with Preserved Ejection Fraction; Epidemiology; Comorbidity; Mortality.

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Medical Subject Headings (MeSH)/ Health Sciences Descriptors and general terms, without restrictions for language or year, and were divided into two groups, "diseases and conditions" and "population (country)".

The MEDLINE search strategy (via PubMed) for "diseases and conditions" was: ((Heart Failure[Mesh] OR "Heart Failure, Diastolic"[Mesh] OR heart failure[Text Word] OR Heart Failure Preserved Ejection Fraction (HfpEF) and Heart Failure Normal Ejection Fraction OR cardiac failure[Text Word] OR cardiac insufficiency[Text Word] OR diastolic heart failure[Text Word] OR "Atrial Fibrillation"[Mesh] OR atrial fibrillation[Text Word] OR "Natriuretic Peptide, Brain"[Mesh] OR BNP[Text Word]) OR (("Hypertrophy, Left Ventricular"[Mesh] OR Left Ventricular Hypertrophy[Text Word] OR LVH[Text Word] OR "Cardiomyopathy, Hypertrophic"[Mesh]) AND (Hypertension[Mesh] OR hypertension[Text Word] OR Blood Pressure[Mesh])) OR ("Amyloidosis"[Mesh] AND (cardio*[tw] OR cardia*[tw])). For "population (country)", the MEDLINE strategy (via PubMed) was: (Brazil[Mesh] OR Brazil*[All Fields] OR Brasil*[All Fields] OR Portuguese[LA] OR Brazil[PL] OR São Paulo[All Fields] OR Rio de Janeiro[All Fields] OR Brasília[All Fields] OR Salvador[All Fields] OR Niterói[All Fields] OR Goiânia[All Fields] OR Porto Alegre[All Fields] OR Belo Horizonte[All Fields] OR Recife[All Fields] OR Campinas[All Fields] OR Ribeirão Preto[All Fields]). This same strategy was used for the LILACS database, including all significant words related to the terms previously described for "diseases and conditions" and "population (country)".

After applying the search strategy to the databases, the titles and abstracts were screened for relevant records, and full texts of the abstracts selected were retrieved for a detailed analysis. The screening was conducted by four reviewers.

Eligible articles were those reporting primary data about any of the following: 1) prevalence or incidence of HFpEF; 2) mortality or hospitalization rates for HF, or 3) clinical characteristics of patients with HFpEF.

The selected studies also met the following eligibility criteria: observational or experimental studies including Brazilian patients only or describing data exclusively from Brazilian patients, with sample size of at least 25, and published in the last 10 years (2008-2018). HFpEF was defined as presence of EF ≥ 50%. Studies with EF ≥ 45% were also considered, since at the time of the search, this cutoff was used to define HFpEF in five of the articles selected (Table 1).

Today it is known that, in addition to clinical history, physical examination, and basic tests such as chest X-ray, electrocardiogram, pulmonary function tests and biochemical and hematological tests, the measurement of B-type natriuretic peptide (BNP) or pro-BNP levels is of great value in the diagnosis of HFpEF. When elevated, BNP has a high specificity for the diagnosis of the disease and, when this review was conducted, most studies did not include this parameter. Studies that included the measurement of BNP levels are listed in Figure 1

Case reports, case series with n<25, editorials, letters to the editors, comments, narrative reviews, studies published as abstracts, studies on animals and *in vitro* studies were excluded.

Data were extracted from eligible full-text articles by two independent reviewers; summarized data included year of publication, author, study design, EF cut-off values, sample size, sample characteristics (demographic data, comorbidities, clinical features) and outcome measures. The Joanna Briggs Institute Critical Appraisal Checklist for Prevalence Studies was used for bias assessment.[9] The risk assessment tool is descriptive and does not provide a score or equivalent.

The combination of results by meta-analysis was not planned due to the usual heterogeneity in methods, outcomes and sample characteristics of observational studies. The aim of this review was to describe the epidemiology of a condition with few available data. Thus, the results were grouped and described by categories defined by study design and sample characteristics.

Results

Study selection was performed according to the PRISMA guidelines and can be visualized in Figure 2.

The search strategy yielded 3,175 records (PubMed: 2,524, LILACS: 651), and 424 duplicates were removed. The title and abstract screening yielded 61 potentially eligible reports that were selected for full-text reading. After screening of the full texts, 24 studies were included for data extraction.

Table 1 shows the main characteristics of the studies included according to the population – patients with diagnosed HF, suspected HF, and suspected HFpEF. Most were cross-sectional studies (13 of 24), using an EF cut-off of 50% (18 of 24).

In studies that evaluated patients with suspected HF (*i.e.*, without non-cardiac causes of dyspnea)[10] or confirmed HF, the number of patients with suspected HF varied from 75 to 2056 regardless of EF. Studies including patients with preserved EF only had considerably smaller sample sizes, varying from 25 to 60 in studies with patients with confirmed HFpEF, and from 85 to 166 in studies involving patients with suspected HFpEF.

The proportion of women in the samples varied from 34.0 to 91.0% in patients with suspected or confirmed HF, regardless of HF, and from 54.0% to 81.0% in patients with preserved EF. In these studies, age ranges were 52.2-74.7 and 56.0-76.9 years, respectively. Prevalence rates of patients with confirmed HF varied from 28.2% to 59.0% in the outpatient setting, and from 20.0% to 53.1% in the hospital setting. Among patients with suspected HF, the prevalence varied from 24.6% to 46.5% in studies involving patients regardless of their EF, and from 29.0% to 37.6% in studies involving only patients with EF >50%. The prevalence of HFpEF was higher among outpatients with HF. Three studies also reported the prevalence of HF and intermediate EF, varying from 14.2% to 18.9% in patients with confirmed HF.[11-13]

Mean LVEF and BNP values among patients with HFpEF, reported in the studies included, can be visualized in Figure 2.

Table 1 – Characteristics of the studies included in the meta-analysis

First author	Year	Study design	Treatment setting	Cut-off value	Sample size	% Women	Mean age
Patients diagnosed with heart failure, regardless of ejection fraction values							
Abuhab[19]	2012	Retrospective	Hospital	45%	577	39.3%	69.0*
Balieiro[30]	2009	Cross-sectional	Outpatient	50%	166	63.0%	59.0
Borges dos Reis[14]	2013	Prospective	Outpatient	45%	383	55.8%	52.2
Cardoso[11]	2018	Prospective	Hospital	50%	260	45.8%	66.1
Goldraich[20]	2010	Prospective	Hospital	50%	721	50.2%	66.0
Gripp[31]	2009	Retrospective	Hospital	40%	322	34.0%	63.5
Jorge[7]	2016	Cross-sectional	Outpatient	50%	633	74.0%	72.5
Mangini[32]	2008	Prospective	Hospital	45%	212	44.0%	59.9
Nogueira[33]	2010	Cross-sectional	Hospital	45%	144	45.8%	61.0
Oliveira[11]	2018	Prospective	Outpatient	50%	75	44.0%	61.8
Rycembel[34]	2013	Cross-sectional	Outpatient	50%	155	60.4%	64.7
Silva[16]	2012	Retrospective	Outpatient	50%	549	49.0%	NR
Villacorta[35]	2010	Retrospective	Outpatient	50%	209	66.4%	61.7
Wajner[13]	2017	Retrospective	Outpatient	50%	2056	49.0%	71.0*
Patients with suspected heart failure, regardless of ejection fraction values							
Jorge[36]	2012	Cross-sectional	Outpatient	50%	142	91.0%	73.6
Jorge[37]	2013a	Cross-sectional	Outpatient	50%	161	80.0%	74.7
Moutinho[15]	2008	Cross-sectional	Outpatient	45%	239	60.8%	61.5
Patients with suspected HFpEF							
Jorge[38]	2014	Cross-sectional	Outpatient	50%	166	72.0%	67.9
Jorge[39]	2010	Cross-sectional	Outpatient	50%	118	78.9%	75.0
Jorge[40]	2013b	Cross-sectional	Outpatient	50%	85	81.0%	76.9
HFpEF patients only							
Pereira[21]	2018	Cross-sectional	Outpatient	50%	60	54.0%	56.0
D'Almeida[17]	2018	RCT	Hospital	50%	53	67.9%	72.3
Garcia[22]	2015	Cross-sectional	Outpatient	50%	28	71.4%	60.0
Messias[23]	2016	Cross-sectional	Outpatient	50%	25	76.0%	57.0

*NR: not reported; *mean age; HFpEF: Heart failure with preserved ejection fraction; RCT: randomized clinical trial.*

Table 2 describes the clinical parameters of HFpEF patients. Data on the New York Heart Association (NYHA) functional classes were described in detail in one study. Patients with NYHA III-IV corresponded to 15.2%-43.2% of the sample in three studies investigating this variable.[14-16] The absence of the use of functional classes in most studies suggests that there is still inappropriate care for many patients.

Left ventricular ejection fraction (LVEF) is the most commonly assessed clinical parameter in studies on HFpEF, followed by the body mass index (BMI), left atrial volume, BNP and serum creatinine. Detailed data on LVEF and BNP are also presented in Figure 2.

Studies that included HFpEF patients only and those reporting specific data on HFpEF (n=14) reported data on 10 of the comorbidities selected (Table 2). The most frequently reported comorbidities were hypertension and diabetes, with prevalence varying from 57.4% to 100.0% and from 10.2 to 49.1%, respectively.

Five studies reported data on mortality[14-17] and hospitalization rates[15,16] in patients with HFpEF. Only one study presented in-hospital mortality data.[18] Since these studies used different methods and follow-up periods, their results will be presented in a descriptive manner only. In 2008, Moutinho et al. assessed 170 patients with suspected HF who underwent echocardiography at primary care centers, and found that 79 (46.5%) were diagnosed with HFpEF, and 16.5% of these patients were hospitalized during the last year.[15] In 2012, Silva,[16] evaluated 14-year retrospective data of 549 HF patients seen in a HF

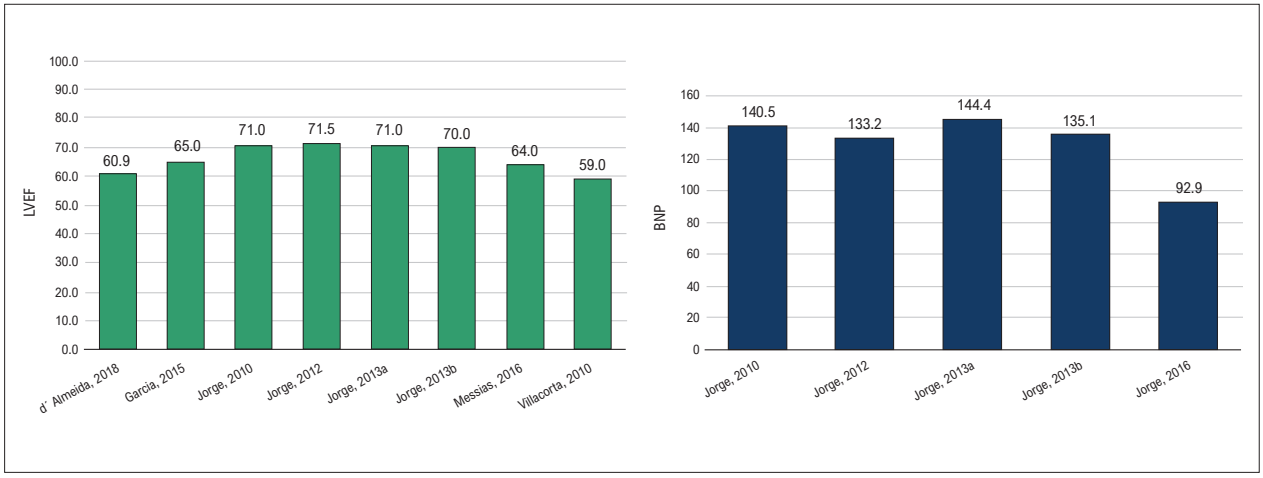

Figure 1 – *Mean left ventricular ejection fraction (LVEF) and brain natriuretic peptide (BNP) in patients with heart failure and preserved ejection fraction.*

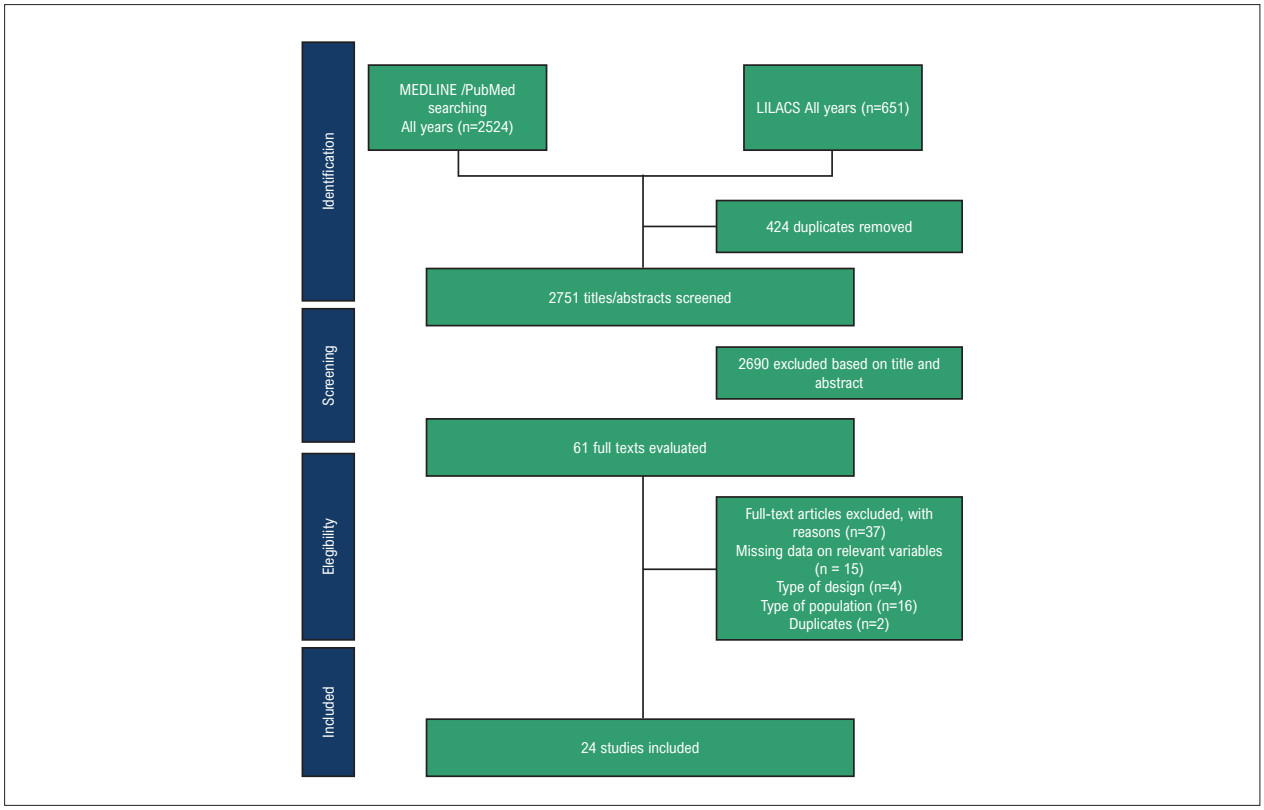

Figure 2 – *PRISMA flowchart of study selection.*

outpatient clinic. Among HFpEF patients (n=155, 28.2%), 20.0% had at least one HF-related hospitalization, 25.8% of them had two or more events, and 8.4% died during the follow-up period. Abuhab, in 2012, analyzed data of 577 HF-related hospitalizations and found an in-hospital mortality rate of 24.0% among patients with LVEF > 45%, which was significantly lower than in patients with LVEF ≤45% (34.0% for LVEF 30-45 % and 41% for LVEF <30%).[19] Reis et al., in 2013, followed 138 patients with HFpEF (44.2% with Chagas disease) for one year and found that mortality rate (10.2%) among patients with HFpEF was significantly lower than in patients with systolic dysfunction (23.6%).[14] D'Almeida et al., in 2018,[17] conducted a randomized study with inpatients evaluating the effects of aggressive fluid and sodium restriction on decompensated HFpEF. Thirty-day mortality rate after hospitalization was 7.5% in the sample (n=53). None of the studies reported the causes of death or hospitalization.

Table 2 – Prevalence of clinical characteristics and comorbidities in patients with heart failure and preserved ejection fraction

Variable	Number of studies	Minimum	Maximum
Clinical parameters			
LVEF (mean)	8	59.0	71.5
BMI (mean)	6	28.1	32.8
Left atrial volume	5	32.6	44.6
BNP (mean)*	5	92.9	144.4
Creatinine (mean)	5	0.92	0.99
NYHA III-IV	3	15.2%	43.2%
NYHA I	1	0.0%	0.0%
NYHA II	1	9.5%	9.5%
NYHA III	1	50.9%	50.9%
NYHA IV	1	39.6%	39.6%
NYHA II-III	1	100.0%	100.0%
Right atrial diameter (mm) (mean)	1	27	27
Comorbidities			
Hypertension	13	57.4%	100.0%
Diabetes mellitus	13	10.2%	49.1%
Atrial fibrillation	6	2.5%	49.1%
BMI > 30	4	34.0%	72.9%
Coronary disease	4	17.7%	28.4%
COPD	3	0.0%	13.9%
Anemia	3	0.0%	21.3%
Chronic renal disease	2	3.8%	16.8%
Previous stroke	2	8.9%	15.4%
Previous myocardial infarction	1	10.9%	10.9%

**One study reported mean brain natriuretic peptide (BNP) values. LVEF: left ventricular ejection fraction; BMI: body mass index; COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association.*

Discussion

To our knowledge, this is the first systematic review of the epidemiology of HFpEF in Brazil. Our results revealed a scarcity of data, particularly related to the incidence, population-based prevalence, and clinical characteristics of the patients. Available data were extracted from studies with different methods and sample sizes obtained from different groups of patients (confirmed/suspected HF or HFpEF), making it difficult to compare results and conclusions, and extrapolate them to other contexts and clinical situations.

Although it was not possible to determine the prevalence of HFpEF in the general population, it is reasonable to assume that the condition affects a significant proportion of HF patients, with estimates greater than 50%. As expected, estimates of HFpEF prevalence were higher in samples of outpatients and in one study with primary care patients.[7,10,11,20-23]

Sex distribution of Brazilian patients with HFpEF corroborates data from international studies, with higher proportion of women.[18] We could not detect a clear pattern in terms of age rages or mean age, which were similar between HFpEF patients and mixed HF patients.

According to available literature, HFpEF patients tend to be older,[24] although clear differences in designs and methods of sample selection between the studies included may have hampered our ability to detect the same tendency. Clinical parameters such as LVEF, BNP, creatine and BMI were not evaluated in a homogeneous manner in studies that included patients with HFpEF. Only eight of 24 studies reported LVEF data, and only five presented mean BNP values; both variables are important to better understand the characteristics of HFpEF patients. Natriuretic peptides (BNP, N-terminal-pro-BNP, and midregional pro-atrial natriuretic peptide) are well established criteria for the diagnosis of HF in the clinical guidelines. Despite uncertainties on the diagnostic and prognostic value of these peptides in HFpEF,[25-27] data from Brazilian patients could add to the general knowledge about the subject.

Comorbidities like hypertension, coronary artery disease, arial fibrillation, diabetes mellitus, chronic renal disease have been described[18] as important influencing factors of the pathophysiology of HFpEF, and hence it is reasonable to expect that these diseases are addressed in studies on HFpEF. The prevalence of diabetes and hypertension was described in most of the studies selected (13/24). In contrast, atrial fibrillation, obesity, coronary artery disease and chronic renal disease were rarely reported in the studies. Besides, the high variability in the prevalence of comorbidities precludes any robust inferences about their frequencies among Brazilian HFpEF patients.

Data on mortality and hospitalization rates were also scarce. Also, sample characteristics, the duration of follow-up, study design, and result definitions were widely different between the five studies reporting these data. Two studies comparing HFpEF with HFrEF reported lower one-year mortality and in-hospital mortality rates in the HFpEF groups. Although initial observational evidence on the relative risk of death in HFpEF versus HFrEF has yielded inconsistent conclusions,[5] most studies have found relatively higher mortality rates in HFrEF patients. More recently, a meta-analysis of experimental and observational studies concluded in favor of a lower risk of death in HFpEF as compared with HFrEF.[28] The causes of death or hospitalization were not detailed in the studies included.

The PARADIGM-HF study involving HFpEF patients from Brazil and Latin America reported lower hospitalization rates in these populations as compared with North American patients.[29]

Limitations

This systematic review was conducted using a reproducible methodology according to a prespecified protocol included in the PROSPERO database. The results are based on published data from independent studies that adopted different methods and included different samples. Therefore,

the main limitations of this study concern the variability between the studies included, inherent to observational studies. Today, it is very clear the importance of determining BNP concentrations in the diagnosis of HFpEF. At the time of this review, only five of the studies included assessed BNP. In the last years, progresses have been made in the understanding of the pathophysiology of HFpEF, with the emergence of new diagnostic options and a diagnostic algorithm for suspicion of HFpEF.[10]

Despite these limitations, this is the first effort to systematically present the available knowledge about demographic and clinical data, and hospitalization and mortality rates of Brazilian patients with HFpEF. These observations reinforce the need for methodological standards for future studies on hospitalizations for primary care sensitive conditions (ICSAP project), such as standardized diagnostic criteria, and collection of relevant exposure variables (e.g., comorbidities, natriuretic peptides, echocardiographic parameters), and prespecified outcomes.

Conclusions

Our findings reflect the dimension and the importance of epidemiological information for the generation of evidence on HFpEF in Brazil. The systematization of these data points to the fact that the population-based prevalence is still unknown and the prevalence of HFpEF among patients with confirmed or suspected HF varies widely in the literature available. Studies with outpatients were predominant and, consequently, they have brought the greater volume of information about HFpEF. However, the lack of reporting of HF functional classes evidenced potential gaps and poor health care in the healthcare system.

Also, our study highlights that improvements in health information systems are still lacking in Brazil, especially regarding hospital data, leading to limitations in evaluating the actual prevalence and incidence of HFpEF in hospitalized patients. This review gathers information that may serve as an instrument of monitoring and characterizing the clinic-epidemiological profile of HFpEF patients, the impact on the prognosis and the costs of this heterogeneous clinical syndrome, associated with different comorbidities and aging.

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Contribuição dos autores

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