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 planning 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%, is the most prevalent condition (>70% of cases) in patients older than 65 years. 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. Patients with HFpEF show elevations in plasma natriuretic peptide levels in response to increased end-diastolic wall stress, and may have a five-year survival of just 35% after hospitalization.

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. These patients show impairment in quality of life, high hospitalization and premature death rates, and one-year mortality rates of up to 6.3%, 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 Niterói, 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.

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).

The MEDLINE database was searched via PubMed for Brazilian studies published from the beginning of 2008 to December 10, 2018. The search strategies included...
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). HFrEF 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 HFrEF. 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. 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 HFrEF. 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) 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 HFrEF, and from 85 to 166 in studies involving patients with suspected HFrEF.

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 HF 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 HFrEF 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.

Mean LVEF and BNP values among patients with HFrEF, reported in the studies included, can be visualized in Figure 2.
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 mortality14-17 and hospitalization rates15,16 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, Silva16 evaluated 14-year retrospective data of 549 HF patients seen in a HF
outpatient clinic. Among HFrEF 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%).

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%). D’Almeida et al., in 2018, 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.
Sex distribution of Brazilian patients with HFrEF corroborates data from international studies, with higher proportion of women.\textsuperscript{19} We could not detect a clear pattern in terms of age ranges or mean age, which were similar between HFrEF patients and mixed HF patients.

According to available literature, HFrEF patients tend to be older,\textsuperscript{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 HFrEF. 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 HFrEF 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 HFrEF,\textsuperscript{25-27} data from Brazilian patients could add to the general knowledge about the subject.

Comorbidities like hypertension, coronary artery disease, atrial fibrillation, diabetes mellitus, chronic renal disease have been described\textsuperscript{18} as important influencing factors of the pathophysiology of HFrEF, and hence it is reasonable to expect that these diseases are addressed in studies on HFrEF. 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 HFrEF patients.

Data on mortality and hospitalization rates were also scarce. Also, some characteristics, the duration of follow-up, study design, and result definitions were widely different between the five studies reporting these data. Two studies comparing HFrEF with HFrEF reported lower one-year mortality and in-hospital mortality rates in the HFrEF groups. Although initial observational evidence on the relative risk of death in HFrEF versus HFrEF has yielded inconsistent conclusions,\textsuperscript{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 HFrEF as compared with HFrEF.\textsuperscript{28} The causes of death or hospitalization were not detailed in the studies included.

The PARADIGM-HF study involving HFrEF patients from Brazil and Latin America reported lower hospitalization rates in these populations as compared with North American patients.\textsuperscript{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 (ICSA 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 clinical-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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References


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