Kidney and Blood Pressure Research

Research Article

Kidney Blood Press Res 2024;49:165–172
DOI: 10.1159/000535705

Received: December 2, 2022
Accepted: November 21, 2023
Published online: February 15, 2024

Clinical Characteristics and Outcomes of Patients with Heart Failure of Hypertensive Etiology: Analysis of Colombian Heart Failure Registry (RECOLFACA)

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Keywords
Heart failure · Registry · Hypertension · Mortality

Abstract
Introduction: Arterial hypertension represents one of the main comorbidities observed in patients with heart failure (HF) and one of the main risk factors for its development. Despite this, studies assessing this hypertensive etiology are scarce in Latin America. Our objective was to analyze the prevalence of HF of hypertensive etiology and evaluate its prognosis in patients enrolled in the Colombian Heart Failure Registry (RECOLFACA by its Spanish acronym). ***Methods:*** RECOLFACA recruited adult patients diagnosed with HF in 60 centers in Colombia between 2017 and 2019. The primary outcome was all-cause mortality. A Cox proportional hazards regression model was used to assess factors associated with primary

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outcomes in patients with hypertensive HF. A p value <0.05 was considered significant. All statistical tests were two-tailed. ***Results:*** Out of the total number of patients evaluated in RECOLFACA (n = 2,514), 804 had a diagnosis of HF with hypertensive etiology (31.9%). These patients were less frequently males and had a significantly older age and lower prevalence of comorbidities than those with HF of other etiologies. Additionally, patients with hypertensive HF had a higher prevalence of HF with preserved ejection fraction (HFpEF) (34.1% vs. 28.3%; p = 0.004). Finally, type 2 diabetes mellitus, chronic obstructive pulmonary disease diagnosis, and NYHA class IV were classified as independent mortality risk factors. ***Conclusions:*** Hypertensive HF represents about one-third of the total number of patients with HF in RECOLFACA. Compared with HF of other etiologies, it presents a differential clinical profile – older age and a higher prevalence of HFpEF. RECOLFACA has become a useful tool to characterize patients with HF in Colombia, with which it has been possible to carry out a more specific search and reach the diagnosis of this pathology in our population, and it has served as an example to stimulate registries of patients with HF in other countries in the region.

Introduction

Heart failure (HF) represents a chronic noncommunicable disease of high prevalence worldwide and is considered one of the most relevant public health problems today [1, 2]. In the USA, between 2013 and 2016, about 6.2 million people were living with HF, while in Latin America, its prevalence has been estimated at 1% – 95% confidence interval (95% CI), 0.1–2.7% [1, 3]. Although substantial advances have been made in its diagnosis and treatments, it still is one of the pathologies with the highest morbidity and mortality today [4, 5]. Similarly, hypertension (HTN) is a primary risk factor for cardiovascular diseases worldwide and one of the main conditions associated with morbidity and mortality [3, 6, 7]. It is estimated that, while in developed countries, the incidence of HTN has been decreasing since 1980, it may have been increasing in developing countries [7].

HTN is associated with structural and functional changes at a cardiac level, representing the individual risk factor with the highest attributable risk for developing HF – especially HF with preserved ejection fraction (HFpEF) [8]. Despite its importance, the exact mechanisms that favor the development of hypertensive HF are still unknown [9]. Additionally, studies in Latin America characterizing the population of patients with hypertensive HF are scarce and have included small sample sizes [10, 11]. This study aimed to describe laboratory analysis and clinical and echocardiographic characteristics of patients with hypertensive HF, as well as to evaluate their prognosis and identify potential risk factors for mortality in this population using the Colombian Heart Failure Registry (RECOLFACA).

Materials and Methods

Study Design and Population

This prospective cohort study used data collected by the RECOLFACA project which was conducted at 60 medical centers, HF clinics, and cardiology outpatient centers in Colombia. Patient enrollment for RECOLFACA started in February 2017 and ended in 2019, including all individuals older than 18 years old with a clinical diagnosis of HF of any etiology based on the guideline recommendations at the time of inclusion which had at least one HF hospitalization in the 12 months prior to enrollment. The specific inclusion and exclusion criteria, along with the additional methodological features of the registry, are described elsewhere [12, 13].

Data Collection

Information regarding sociodemographic, clinical, and laboratory variables was registered at baseline. The severity of HF was assessed using the New York Heart Association (NYHA) classification. In addition, an ischemic heart disease diagnosis was recorded if the patient underwent a coronary artery bypass procedure or had a history of previous myocardial infarction. Patients with left ventricular ejection fraction (LVEF) ≥50% were classified as HFpEF. In comparison, those with LVEF <40% were considered to have HF with reduced ejection fraction (EF). Individuals with an EF between 40% and 49% were labeled as having HF with a mid-range ejection fraction (HFmEF). Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 according to the MDRD formula.

Clinical comorbidities were described as follows:

- HTN (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg)
- Atrial fibrillation (diagnosed based on a 12-lead ECG or documented history of this condition)
- Anemia defined as the presence of a hemoglobin value <13 g/dL for men and <12 g/dL for women, and dyslipidemia defined as elevated total cholesterol (≥200 mg/dL) or low-density lipoprotein cholesterol (≥100 mg/dL), or triglycerides ≥150 mg/dL, or currently receiving lipid-lowering medications.

Clinical conditions such as valvular disease, chronic obstructive pulmonary disease (COPD), type 1 diabetes mellitus, cancer, liver failure, dementia, thyroid disease, and Chagas disease were used, as reported in the RECOLFACA database. In selected patients, additional echocardiographic variables were available, such as the systolic diameter of the left ventricle, among others.

Outcomes

The principal outcome of the study was all-cause mortality. Data on this outcome were collected using a questionnaire applied by each HF clinic and center twice a year. The current results represent the data of the first follow-up carried out after listing in the registry. Each center also reviewed each patient's clinical records to evaluate specific data on outcomes.

Statistical Analysis

Baseline characteristics were described as median and quartile – if the variable was continuous – or absolute counts and proportions – for categorical variables. Variables with a proportion of missing data less than 10% were imputed using *mice* statistical package available in R (R Core Team. 2022). For those variables with >10% missing data, no imputation approach was performed. Differences between patients with hypertensive HF versus those with HF of other etiologies were assessed using Pearson's χ^2 and Fisher's exact tests for categorical variables and the Mann-Whitney U test for continuous ones. The cumulative incidence of mortality events was calculated with their respective 95% CIs. Survival analyses were performed using the Kaplan-Meier method, the life table, and the Cox proportional hazard models. A univariate and multivariate analysis adjusted by age, sex, the New York Heart Association (NYHA) class, and HF medications was performed using the Cox proportional regression models to evaluate the association between hypertensive etiology and mortality. A p value <0.05 (two-tail test) was considered statistically significant. All analyses were performed using the STATA version 15 statistical package (Station College, TX, USA).

Results

RECOLFACA included 2,528 outpatients with chronic HF between February 2017 and October 2019. Of these, 2,514 had complete information on sociodemographic, clinical, and laboratory variables.

Sociodemographic and Clinical Characteristics

The population's average age was 69 years (Q1: 59; Q3: 78), mostly men (57.6%). 804 (31.9%) patients had a diagnosis of HF with hypertensive etiology. Table 1 summarizes the baseline characteristics of patients registered in RECOLFACA according to their etiological classification of the disease (hypertensive vs. non-hypertensive). On the one hand, Hypertensive HF was found less frequently among men, and more frequently in significantly older people than those diagnosed with cardiomyopathy of other etiologies. On the other hand, regarding the clinical characteristics, it was observed how patients in the hypertensive HF group presented a significantly lower prevalence in most of the comorbidities registered – highlighting type 2 diabetes mellitus, coronary heart disease, COPD, thyroid diseases, valvular heart diseases, dyslipidemia, and Chagas disease, among others (shown in Fig. 1).

It is important to note that in the registry our patients with hypertensive HF had a higher prevalence of HFpEF (34.1% vs. 28.3%; $p = 0.004$). Additionally, significant differences were observed in prescription drugs for HF – highlighting a greater use of angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (79.5% vs. 72.6%; $p < 0.001$). Meanwhile, the use of β-blockers (82.7% vs. 89.1%; $p < 0.001$), mineralocorticoid receptor antagonists (49.8% vs. 58.4%; $p < 0.001$), and ivabradine (3.7% vs. 7%; $p < 0.001$) was significantly lower in patients with hypertensive HF. Similarly, other drugs – such as nitrates, antiplatelets, statins, and anticoagulants – were significantly lower in the hypertensive cardiomyopathy group (shown in Fig. 2).

Ultimately, it was observed that patients with hypertensive HF had higher systolic blood pressure numbers and heart rates and a significantly lower median left ventricular end-diastolic diameter. They were accompanied by higher LVEF values, mirrored in a substantially lower prevalence of heart failure with reduced EF. Lastly, the hemoglobin level was significantly lower in patients with hypertensive HF – with a preponderance of anemia significantly higher in them (34.1% vs. 28.3% in patients with HF of other etiologies; $p = 0.004$) (shown in Table 1).

Mortality

The median follow-up in the present cohort was 215 days (Q1: 188; Q3: 254). Overall, 170 patients died during follow-up (6.76%), for a mortality rate of 0.30 per 1,000 person-years (95% CI 0.26–0.35). In contrast, patients diagnosed with HF caused by HTN had a mortality rate of 0.31 per 1,000 person-years (95% CI 0.24–0.39. $n = 58$), without statistically significant differences from patients of other etiologies (0.30 per 1,000 person-years [95% CI 0.25–0.37] $n = 112$). Consequently, the diagnosis of hypertensive HF was not associated with a differential risk of mortality during follow-up both in the unadjusted (HR 1.06; 95% CI 0.77–1.46) and adjusted (HR 1.02; 95% CI 0.73–1.42) multivariate models. Although multiple variables were associated with mortality outcomes in bivariate models, multivariate analysis of risk factors in patients diagnosed with hypertensive HF suggested that DM2, COPD diagnosis, and a NYHA class IV represent independent risk factors for this outcome (shown in Table 2).

Table 1. Baseline characteristics of patients with HF according to their etiological classification

	Hypertensive HF (*n* = 804)	HF of other etiologies (*n* = 1,710)	Total (*n* = 2,514)	*p* value
Men, *n* (%)	405 (50.4)	1,042 (60.9)	1,447 (57.6)	<0.001
Age, years	72 (62, 80)	68 (59, 77)	69 (59, 78)	<0.001
Alcoholism, *n* (%)	17 (2.1)	69 (4.0)	86 (3.4)	0.013
DM2, *n* (%)	170 (21.1)	450 (26.3)	620 (24.7)	0.005
Liver diseases, *n* (%)	3 (0.4)	8 (0.5)	11 (0.4)	0.737
CHD, *n* (%)	121 (15.0)	585 (34.2)	706 (28.1)	<0.001
COPD, *n* (%)	188 (23.4)	253 (14.8)	441 (17.5)	<0.001
Atrial fibrillation, *n* (%)	170 (21.1)	390 (22.8)	560 (22.3)	0.350
Thyroid Disease, *n* (%)	98 (12.2)	290 (17.0)	388 (15.4)	0.002
Chronic renal failure, chronic kidney disease, *n* (%)	143 (17.8)	291 (17.0)	434 (17.3)	0.634
Valvular heart disease, *n* (%)	73 (9.1)	356 (20.8)	429 (17.1)	<0.001
History of coronary bypass, *n* (%)	21 (2.6)	149 (8.7)	170 (6.8)	<0.001
Dyslipidemia, *n* (%)	167 (20.8)	480 (28.1)	647 (25.7)	<0.001
Chagas disease, *n* (%)	4 (0.5)	84 (4.9)	88 (3.5)	<0.001
Smoking, *n* (%)	128 (15.9)	324 (18.9)	452 (17.9)	0.065
NYHA classification, *n* (%)				0.043
I	76 (9.5)	222 (13.0)	298 (11.9)	
II	439 (54.6)	911 (53.3)	1,350 (53.7)	
III	255 (31.7)	492 (28.8)	747 (29.7)	
IV	34 (4.2)	85 (5.0)	119 (4.7)	
Diuretics, *n* (%)	551 (68.5)	1,142 (66.8)	1,693 (67.3)	0.383
ACE INHIBITOR/ARB, *n* (%)	639 (79.5)	1,241 (72.6)	1,880 (74.8)	<0.001
Beta-blockers	665 (82.7)	1,524 (89.1)	2,189 (87.1)	<0.001
ARNI	74 (9.2)	171 (10.0)	245 (9.7)	0.530
MRA	400 (49.8)	999 (58.4)	1,399 (55.6)	<0.001
Ivabradine	30 (3.7)	120 (7.0)	150 (6.0)	0.001
Nitrates	17 (2.1)	74 (4.3)	91 (3.6)	0.006
Antiplatelets	327 (40.7)	833 (48.7)	1,160 (46.1)	<0.001
Statins	389 (48.4)	1,002 (58.6)	1,391 (55.3)	<0.001
Anticoagulants	176 (21.9)	467 (27.3)	643 (25.6)	0.004
SBP, mm Hg	124 (110, 140)	118 (102, 130)	120 (106, 134)	<0.001
HR, bpm	74 (65.250, 82)	70 (64, 80)	72 (65, 81)	0.001
LVEF	35 (25, 45)	32 (25, 40)	33 (25, 42)	<0.001
HFrEF,* *n* (%)	403 (50.1)	972 (56.8)	1,375 (54.7)	0.002
HFpEF,** *n* (%)	274 (34.1)	484 (28.3)	758 (30.2)	0.004
HGB, mg/dL	12.700 (11.375, 14)	13.100 (11.7, 14.4)	13 (11.6, 14.3)	<0.001
NTproBNP	2,007 (777, 4,655)	2,377 (982, 6,685)	2,255.500 (954, 5,593.8)	0.193

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor and neprilysin inhibition; bpm, beats per minute; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; DM2, type 2 diabetes mellitus; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HGB, hemoglobin; HR, heart rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NTproBNP, N-terminal (NT)-pro hormone brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure. *HFrEF is defined as LVEF <40%. **HFpEF is defined as LVEF ≥50%.

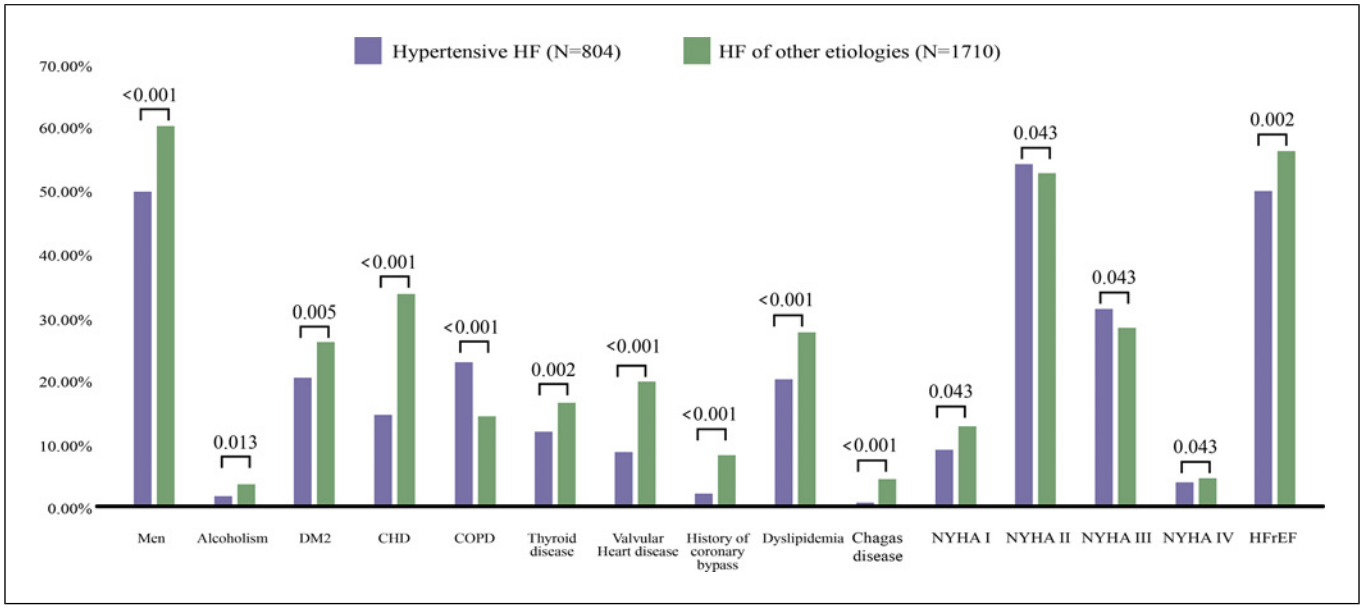

Fig. 1. Clinical characteristics of patients with HF of hypertensive etiology versus HF of other etiologies.

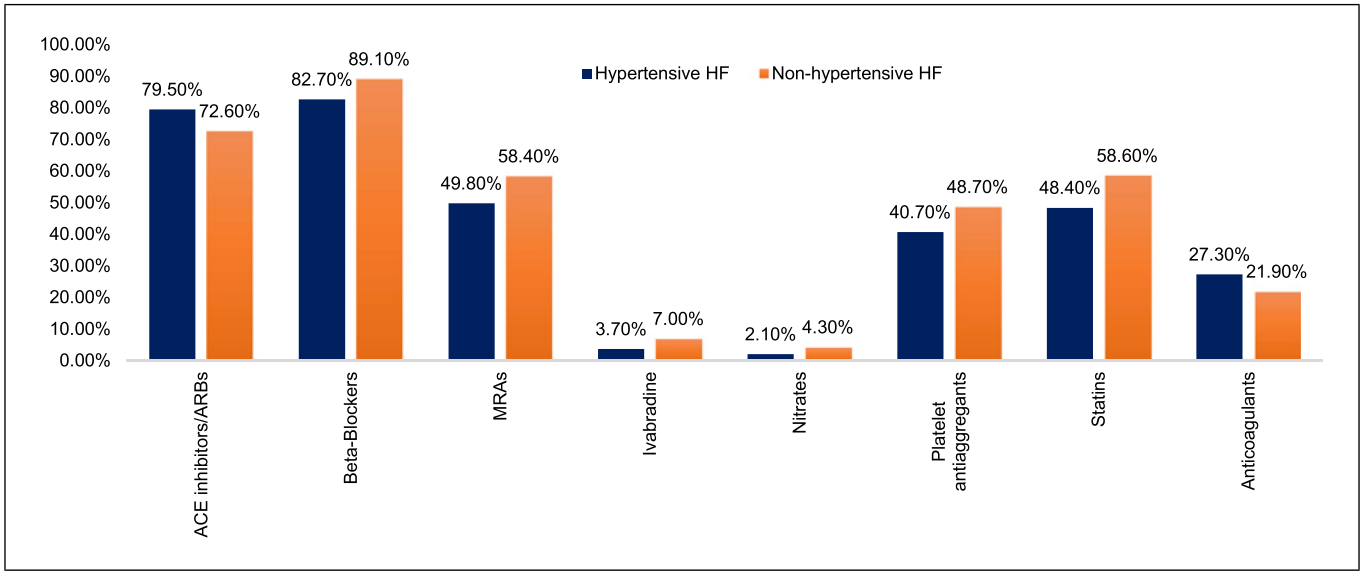

Fig. 2. Patterns of pharmacological prescription in patients with HF according to their etiological classification. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonists.

Discussion

This study represents the first comprehensive analysis of the clinical characteristics and outcomes of patients with HF of hypertensive etiology in Latin America. It emphasizes the significantly lower prevalence of comorbidities in patients with hypertensive HF compared to those with HF of other etiologies. In addition, substantial differences were observed in the prescription of drugs, with more frequent use of ACE inhibitors/

Table 2. Factors associated with mortality in patients with HF of hypertensive etiology

Variables	HR (bivariate)	HR (multivariate)
Male	0.74 (0.43–1.25, $p = 0.260$)	
Age	1.01 (0.99–1.03, $p = 0.326$)	
Alcoholism	0.51 (0.06–4.12, $p = 0.525$)	
DM2	2.06 (1.18–3.59, $p = 0.011$)	1.87 (1.03–3.41, $p = 0.041$)
Cancer	1.58 (0.49–5.08, $p = 0.443$)	
Dementia	2.47 (0.34–17.86, $p = 0.371$)	
CHD	0.98 (0.47–2.08, $p = 0.968$)	
COPD	1.94 (1.13–3.34, $p = 0.017$)	1.96 (1.10–3.49, $p = 0.023$)
Atrial fibrillation	0.86 (0.44–1.67, $p = 0.655$)	
Thyroid disease	1.70 (0.86–3.37, $p = 0.130$)	
Chronic renal failure	1.36 (0.73–2.53, $p = 0.339$)	
Valvular heart disease	0.77 (0.28–2.13, $p = 0.610$)	
History of coronary bypass	0.71 (0.10–5.15, $p = 0.736$)	
Dyslipidemia	0.88 (0.44–1.75, $p = 0.716$)	
Anemia	1.86 (1.06–3.25, $p = 0.031$)	1.45 (0.81–2.62, $p = 0.212$)
NYHA Rating		
I	Reference	
II	4.42 (0.60–32.65, $p = 0.145$)	3.17 (0.42–23.81, $p = 0.262$)
III	6.86 (0.92–50.81, $p = 0.060$)	4.21 (0.55–31.96, $p = 0.165$)
IV	16.86 (2.07–137.10, $p = 0.008$)	10.12 (1.19–85.78, $p = 0.034$)
ACE INHIBITOR/ARB	0.57 (0.32–1.01, $p = 0.053$)	0.73 (0.39–1.37, $p = 0.325$)
Diuretics	0.81 (0.47–1.41, $p = 0.461$)	
Beta-blockers	0.66 (0.36–1.24, $p = 0.199$)	
ARNI	0.57 (0.18–1.81, $p = 0.338$)	
MRA	0.52 (0.30–0.90, $p = 0.019$)	0.55 (0.30–1.00, $p = 0.052$)
Nitrates	0.89 (0.12–6.40, $p = 0.904$)	
Antiplatelets	0.84 (0.48–1.46, $p = 0.535$)	
Statins	0.47 (0.27–0.83, $p = 0.010$)	0.55 (0.30–1.00, $p = 0.051$)
Anticoagulants	0.93 (0.49–1.77, $p = 0.828$)	
SBP (mm Hg)	0.99 (0.98–1.01, $p = 0.342$)	
HR (bpm)	1.01 (0.99–1.02, $p = 0.356$)	
NTproBNP	1.00 (0.99–1.00, $p = 0.414$)	
LVEF	1.00 (0.98–1.02, $p = 0.885$)	
Use of implantable medical devices	0.74 (0.32–1.74, $p = 0.495$)	

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor and neprilysin inhibition; bpm, beats per minute; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; DM2, type 2 diabetes mellitus; HR, heart rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NTproBNP, N-terminal (NT)-prohormone brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

angiotensin II receptor blockers compared with the rest of the medications used to treat HF. Finally, the diagnosis of hypertensive cardiomyopathy was not associated with differential mortality risk. Among patients with hypertensive HF etiology, type 2 diabetes mellitus, COPD diagnosis, and NYHA class IV were associated with a higher risk of death.

HTN represents one of the most frequently observed comorbidities in patients with HF [14]. More importantly, this condition represents one of the leading individual risk factors for the development of HF. According to the results of the Framingham Heart Study cohort, the diagnosis of high blood pressure was associated with a 2-fold increased risk of HF in women and a 3-fold more prominent in men [15]. The progression from an isolated diagnosis of arterial HTN to the consequent development of HF comes from several mechanisms related to cardiac remodeling – with left ventricular (LV) volume overload – ending in an increase in myocardial mass at the expense of the volume of the chambers [16]. This remodeling differs from the volume overload observed, in which the myocardial mass and

chamber volumes are parallelly increased [17]. According to the present study's observations, patients with HF caused by HTN present HFpEF more frequently since the pressure overload leads directly to a process of diastolic dysfunction [18].

In this study, hypertensive cardiomyopathy accounted for approximately one-third of the total HF cases in the registry – slightly higher than those reported by other registries worldwide [19–21]. However, some reports indicate a similar preponderance [22]. Some have even higher ones, such as the Abuja registry conducted in Nigeria. It included 1,525 patients diagnosed with chronic HF – presenting a prevalence of hypertensive HF of 61% – the study highlights the wide geographical variability in the research body [23].

The clinical profile of the patient with hypertensive HF is heterogeneous, underlining conflicting results according to published studies so far. While some records (seem to) present a predominance of male patients, others report a majority of female patients in their studies [19, 22, 24, 25]. However, it seems there is more homogeneity concerning the prevalence of comorbidities. Most of them are significantly less frequent than those observed in patients with HF of other etiologies, which aligns with the findings reported in our Latin American population [19, 24, 26]. Furthermore, the use of HF drugs evidenced a higher prescription of mineralocorticoid receptor antagonists than written in similar studies [19, 26].

Besides, the risk factors for mortality in this population vary according to published reports – which are scarce. On the one hand, for example, the study by Ogah et al. [26] characterized the outcomes of 320 patients with hypertensive HF from the Abeokuta Heart Failure Clinical Registry in Nigeria. In this study's observations, the serum creatinine range was the only independent predictor of mortality [26]. On the other hand, the study by Peacock et al. [27] evaluated a cohort of patients with acute HF (AHF) resulting from a hypertensive emergency in the USA Patients with adverse outcomes have higher serum creatinine and brain natriuretic peptide (BNP) test levels [27]. More studies are required to evaluate the factors associated with adverse outcomes in HF patients to elucidate the profile of specific risk factors for this etiology entity – potentially improving therapeutic approaches and their follow-up.

Limitations

The present study is subject to considerable limitations. First, the participation of the different centers in the registry was voluntary; therefore, there could be a selection bias. Second, evaluating changes in blood pressure over time was unattainable, restricting a possible analysis assessing the relationship between the control of this parameter and mortality in this context. Third, RECOLFACA did not include information on pharmacological and non-pharmacological therapy of the comorbidities evaluated, limiting the possibility of including them in the risk factor analysis. Fourth, there was unavailable information on the severity and duration of the comorbidities assessed, which restrained a more detailed assessment of the impact of these conditions. Finally, despite the adjustments made, we must also recognize the possibility of residual confounding bias.

Conclusions

Hypertensive HF represents about one-third of the total number of patients with HF in RECOLFACA, posing a differential clinical profile, a higher prevalence of HFpEF, RECOLFACA has become a useful tool to characterize patients with HF in Colombia, with which it has been possible to carry out a more specific search and reach the diagnosis of this pathology in our population, and it has served as an example to stimulate registries of patients with HF in other countries in the region.

Statement of Ethics

This study protocol was reviewed and approved by the Biomedical Research Ethics Committee of the Fundación Valle del Lili, approval number 174-2017. Patient consent was waived by the Ethics Committee that revised the protocol considering that no intervention on the participants was intended. Furthermore, the anonymization of participants' personal information was guaranteed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding bodies had any role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript.

Author Contributions

Erika Martínez Carreño: investigation; roles/writing – original draft; writing – review and editing. Luis Eduardo Echeverría: conceptualization; formal analysis; funding acquisition; investigation; methodology; project administration; resources; validation;

visualization; roles/writing – original draft; writing – review and editing. Juan Esteban Gómez-Mesa: conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; roles/writing – original draft; and writing – review and editing. Alex Rivera Toquica: investigation; visualization; roles/writing – original draft; and writing – review and editing. Mario Hernán Zarama Márquez, Elkin Giovanni Ramírez Puentes, Rafael Ignacio Bustamante, Rolando Palacio, Luis Manuel Ávila Barros, Sebastián Campbell Quintero, Lisbeth Natalia Morales Rodríguez, Juan David López Ponce de León, Andrés Felipe Buitrago, and Jorge Alberto Sandoval-Luna: investigation and writing – review and editing. Clara Saldarriaga: conceptualization; formal analysis; funding acquisition; investigation; methodology; project administration; resources; validation; visualization; roles/writing – original draft; and writing – review and editing.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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