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Research paper

Prospective registry of heart failure with preserved ejection fraction in México: EDIFICE-Mx

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ABSTRACT

Background and aims: Heart failure with preserved ejection fraction (HFpEF) is an increasingly common clinical syndrome, estimated to constitute approximately 50 % of all heart failure (HF) cases. Nonetheless, registries from specific geographic areas, as Latin America, are lacking. The present study aims to report the underlying causes, comorbidities, treatment patterns and outcomes of patients with HFpEF in a large cardiovascular center in Mexico City.

Methods: The present is a prospective, longitudinal, observational study, including female and male patients over 18 years of age, who presented to the emergency department, coronary care unit or outpatient department of the National Institute of Cardiology Ignacio Chavez in Mexico City with HFpEF. Patients were classified according to different phenotypes and current literature. The primary outcome was the composite total HFpEF hospitalization and all-cause mortality.

Results: Within a median follow-up of 472 (IQR 425–518) days, total mortality was 14.56 %, with 10.68 % attributed to cardiovascular causes. HF hospitalization was 7.77 %. Atrial fibrillation showed a notable association with outcomes (adjusted HR 2.87, P = 0.028). Beta-blocker showed a non-significant trend towards benefit, while mineralocorticoid receptor antagonists (MRA) significantly influenced outcomes (adjusted HR 3.30, P = 0.018). The primary composite endpoint occurred in 19.42 % of patients, with no significant difference among phenotypes (P = 0.536).

Conclusions: We observed a substantial comorbidity burden impacting quality of life, as indicated by KCCQ scores. There was a high incidence of hard endpoints, including cardiovascular death and hospitalizations, alongside significant variability in treatment utilization. Future research should focus on elucidating individual healthcare trajectories in HFpEF patients and promoting wider adoption of evidence-based therapies.

1. Introduction

Heart failure with preserved ejection fraction (HFpEF) is an increasingly common clinical syndrome, estimated to constitute approximately 50 % of all heart failure (HF) cases [1]. While long term cardiovascular mortality in patients with HFpEF is lower than in those with HF with reduced ejection fraction (HFrEF), all-cause mortality is similar. In addition, hospital admissions are frequent and lead to increased healthcare costs, loss of disability adjusted life year (DALYs) and a decreased quality of life in patients with HFpEF.

A great heterogeneity in patient profiles, phenotypes and clinical course has been observed in patients with HFpEF. In addition, registries from specific geographic areas (as Latin America) that report comorbidities, underlying causes, patterns of treatment and outcomes are lacking.

The present study aims to report the underlying causes,

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comorbidities, treatment patterns and outcomes in a prospectively enrolled cohort of patients with HFpEF in a large cardiovascular center in Mexico.

2. Material and methods

The present is a prospective, single center, longitudinal, observational study (cohort), including female and male patients over 18 years of age, who presented to the emergency department, coronary care unit or outpatient department of the National Institute of Cardiology Ignacio Chavez in Mexico City, with a diagnosis of HFpEF, including signs and symptoms of heart disease, elevated level natriuretic peptides and a LVEF >45 % or higher within the previous 6 months from March 2020 to July 2022.

Eligibility requirements at screening included age of 18 years or older, an ejection fraction of 45 % or greater at screening or in the previous 6 months, signs and symptoms of HF that required treatment with intravenous or oral diuretics during the last 30 days (or that would require starting from the enrolment visit), elevated concentrations of natriuretic peptides (>200 pg/mL if the patient had been hospitalized for HF within the past 9 months or >300 pg/mL without a recent hospitalization, considering that NT-proBNP requirement is tripled if patients were in atrial fibrillation at screening in the index visit or documented in the last 6 months before the recruitment visit in the absence of other potential causes of elevation), and evidence of structural heart abnormality including either left ventricular hypertrophy (i.e., septal or posterior wall thickness ≥1.1 cm) or left auricular enlargement (i.e., width ≥3.8 cm, length ≥5.0 cm, area ≥20 cm^2, volume ≥55 mL, or volume index ≥29 mL/m^2) documented by echocardiogram.

Individuals who had any prior echocardiogram measurement of left ventricular ejection fraction (LVEF) <40 %, severe valvular heart disease (aortic or mitral stenosis greater than moderate, aortic or mitral insufficiency greater than moderate), acute coronary syndrome, including myocardial infarction (MI), cardiac surgery, other major cardiovascular surgery, or urgent percutaneous coronary intervention (PCI) within the 3 months prior to visit 1 or an elective PCI within 30 days prior to visit 1, any clinical event within the 6 months prior to visit 1 that could have reduced the LVEF (e.g., MI, CABG), unless an echocardiographic measurement was performed after the event confirming the LVEF to be ≥45 % were excluded.

Also, probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (i.e., dyspnoea, fatigue), such as significant pulmonary disease (including primary pulmonary hypertension), moderate to severe anaemia according to WHO classification (Hb <10 g/dL), were excluded. Specifically, patients with the following: severe pulmonary disease including COPD (i.e., requiring home oxygen, chronic nebulizer therapy, or chronic oral steroid therapy or hospitalized for pulmonary decompensation within 12 months), haemoglobin <10 g/dL.

The current research received approval from the study site research and ethics committee, with a reference number "INCAR-DG-DI-CI-467-2019", and all participants provided written informed consent before participating in the study. This study was funded by a research grant from Novartis (IIT - CLCZ696AMX01T). The sponsor did not participate in the enrolment or conduction of the study, nor in the final analysis or in the writing and approval of the present study.

2.1. Acquisition of data

Data collected during recruitment, hospital visits and telephone calls was stored directly to a digital platform for analysis, while frequent backups (every 7 days) were secured in the cloud and once a month on an external hard disk copy. The database was protected with username and password, and sensitive information was censored anonymously to protect patient information and identity. All investigators who manipulate the database signed a professional confidentiality agreement.

Two follow-up visits were scheduled at month 6 and month 12 after patient recruitment, to evaluate functional class, quality of life by Kansas City Cardiomyopathy Questionnaire (KCCQ), biomarker levels and physical exam. Also, two telephone calls at months 3 and 9 were made using established questions to investigate the quality of life, occurrence of hospitalization or death of the patient.

2.2. Definition of phenotypes

Since patients with HFpEF have a wide-ranging clinical profile, we classified patients according the different phenotypes of heart failure based on the scientific statement of the Heart Failure Association, the European Heart Rhythm Association of the European Society of Cardiology and the European Society of Hypertension and current literature [2–5], as ischaemic (prior MI or coronary occlusion of >70 %), obesity as a BMI ≥30, elderly as age greater than or equal to 75 years old and hypertensive phenotype as history of hypertension plus hypertensive cardiomyopathy, defined as diastolic dysfunction grade II or III, or concentric hypertrophy (RWT >0.42 and index mass >115 g for men and >95 g for women). We made separate groups for each type of phenotype and a different individual group for patients who had combined of two or more phenotypes.

2.3. Study endpoints

The primary outcome of this study was the composite total HFpEF hospitalization and all-cause mortality. Heart failure hospitalization definition was based on the International Cardiovascular Endpoints Definitions for Clinical Trials [6], defined as an unscheduled in-hospital stay or in the emergency service for a minimum of 24 h for a primary diagnosis of HF, and also have typical signs, symptoms, and diagnostic testing results consistent with the diagnosis of HF.

For the statistical analysis the binary variables are described as frequencies and proportions and analysed with the Pearson independence test (χ^2) or Fisher's exact test, according to the number of individuals. Quantitative variables were analysed first with the Shapiro-Wilk's normality test and described as parametric (mean, standard deviation, minimum-maximum) or non-parametric (median, interquartile range, minimum-maximum) accordingly. Univariate Cox regression was performed to assess associations between variables of interest and the primary composite endpoint, and multivariable Cox regression models were performed based on hazard ratio and P value of the univariate analysis. For the baseline characteristics analysis by phenotype the Kruskal-Wallis test was performed for non-normal continuous variables, and for categorical data chi-square test was used. Kaplan-Meier curves were used for time to the first event of composite and independent outcomes. To provide an accuracy of +/−5 % to describe an observed 10 % mortality per year (according to previous reports) with a 99 % confidence level, a sample size of 259 patients is estimated. A final sample of 330 patients is chosen, which is estimated to record approximately 33 (17–42) death events from all causes during 12 months of follow-up. However, due to a slow recruitment rate, especially during COVID-19 pandemic, enrolment was terminated at 103 patients.

3. Results

During the study period a total of 143 patients were screened for diagnosis of HFpEF who presented to the emergency room with signs and symptoms of HF, of whom 103 were included in the study. Due to slow recruitment and the COVID-19 pandemic, the decision to halt recruitment and stop the study was taken by the study committee and the first author who verified with the study center's research committee. The Fig. 1 shows the study flowchart. The main reasons to exclude patients were loss of follow-up and individuals who did not meet the NT-

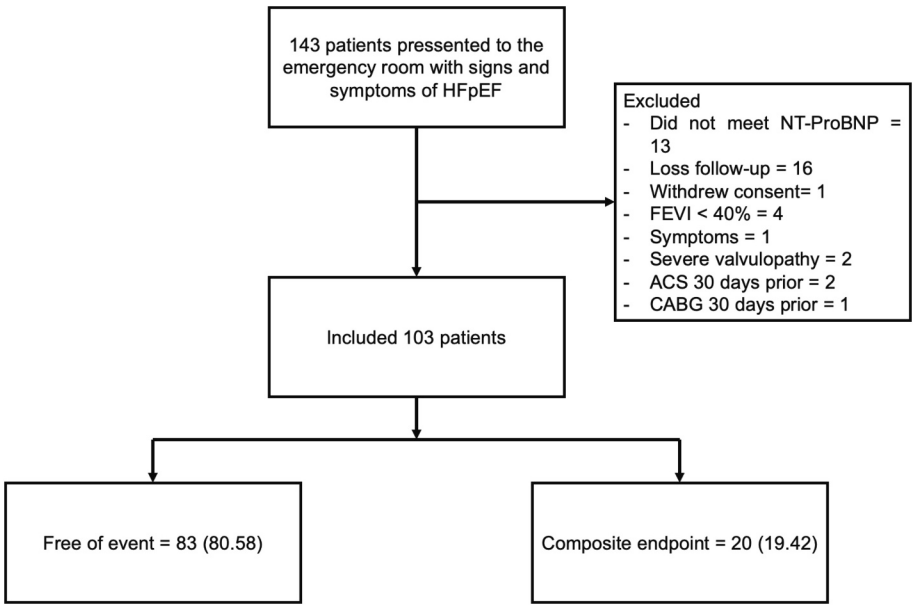

Fig. 1. Study flowchart.

ProBNP cut-off value according to age.

3.1. HFpEF comorbidities

The baseline characteristics of the population are shown in the Table 1. The median age was 65 (57–76) years, 62.14 % had high blood pressure (HBP), 42.72 % had type 2 diabetes (T2D), and 24.7 % were obese; 29.13 % had a previous myocardial infarction (MI), 28.16 % of patients had a history of hospitalization for heart failure (HF), with a mean LVEF of 57.81 ± 7.82, 58.25 % of patients were in functional class II. In our study, the median score on the KCCQ was 41 (IQR 31–56), indicating a moderate impact on the quality of life due to HF symptoms. The distribution of KCCQ scores among participants was as follows: 14 (15.5 %) scored between 0 and 24, reflecting severe symptomatology; 48 individuals (53.33 %) had scores ranging from 25 to 49, indicating a significant impact on daily life; 20 participants (22.22 %) scored between 50 and 74, suggestive of a moderate effect; and 8 subjects (8.88 %) achieved scores >75, indicative of a mild impact on their quality of life. According to initial routine clinical assessment, 51 (49.5 %) of patients were classified as low socio-economic status.

3.2. HFpEF causes and phenotypes

The distribution of phenotypes among the study population classified 14 (13.59 %) patients within the obese phenotype, 11 (10.68 %) in the elderly phenotype, 12 (11.65 %) with the ischaemic phenotype, 8 (7.77 %) with hypertensive phenotype, and 28 (27.18 %) with one or more combined phenotypes, of whom 18 patients (50 %) shared the hypertensive phenotype. Baseline characteristics by phenotype were significantly different for age, hypertension, MI, CKD, and beta blocker use (Table 2).

3.3. Treatment patterns

At time of recruitment ACE inhibitors (ACEI) with captopril (19.61 %) and enalapril (13.73 %), loop diuretics including furosemide (62.75 %), beta-blockers such as metoprolol (36.27 %), spironolactone (17.65 %), and acetylsalicylic acid (41.18 %) were the main therapeutic agents found. However, a notable proportion of patients were not receiving optimal guideline-recommended therapies. Additionally, due temporality, SGLT-2 inhibitors were not part of the standard of care during the conception and development of the present registry, and therefore, we do not provide data regarding their use.

3.4. HFpEF outcomes

Within a median of 472 (IQR 425–518) days of follow up, a total mortality rate of 14.56 % was observed of which 10.68 % of morality events were of cardiovascular aetiology. There was an incidence of 7.77 % of hospitalizations due to HF. In Cox regression analyses (Table 3) for the composite primary endpoint, age did not significantly influence outcomes in either univariate (HR 1.01, 95 % CI 0.98–1.047, P = 0.396) or multivariate models (HR 1.01, 95 % CI 0.98–1.05, P = 0.455). Atrial fibrillation showed a notable association with the endpoint, with adjusted HR 2.87 (95 % CI 1.12–7.36, P = 0.028). While beta-blocker use suggested a non-significant trend towards benefit, mineralocorticoid receptor antagonists (MRA) usage was significantly linked to outcomes in both models (adjusted HR 3.30, 95 % CI 1.23–8.89, P = 0.018).

The primary composite endpoint, which included all-cause mortality and HF hospitalizations, occurred in 19.42 % of patients (Table 4). A Kaplan-Meier analysis was conducted to assess the primary composite endpoint according to phenotypes (Fig. 2), with no statistically significant difference (P = 0.536) according to log-rang test. A second survival analysis was performed for the composite of cardiovascular death and HF hospitalization, demonstrating rate of 17.48 %. Fig. 3 summarizes the study outcomes.

4. Discussion

We found a significant relationship between MRA usage and the primary composite endpoint, although the use of MRA was not associated with more renal replacement therapy or less rate of HF hospitalization. Our findings are in line with the outcomes of the controversial TOPCAT trial, where there was no reduction in mortality with MRA treatment. It remains challenging to justify the use of MRA for all patients with HFpEF [7]. Furthermore, our findings also align with those of the recent REDUCE-AMI trial, regarding the use of beta blockers for the primary composite endpoint, total mortality, and HF hospitalization [8].

Despite several phenotypes and multisystem disorders involved in the pathophysiology support a proinflammatory state, HBP, T2D, and obesity have been described as the most common comorbidities [1,9], consistent with the findings in our study. Whereas we did not find any

Table 1
Baseline characteristics of the population.

	n = 103
Age, median (IQR)	65 (57–76)
Sex m, n (%)	50 (48.54)
Sex f, n (%)	53 (51.46)
Days of follow-up, median (IQR)	472 (425–518)
Hypertension, n (%)	64 (62.14)
Type 2 diabetes, n (%)	44 (42.72)
Atrial fibrillation (AF), n (%)	18 (17.48)
Passive smoking, n (%)	13 (12.62)
Active smoking, n (%)	18 (17.48)
Moderate to severe anaemia (<10 g/dL), n (%)	4 (3.88)
Myocardial infarction (MI), n (%)	30 (29.13)
Percutaneous coronary intervention (PCI), n (%)	25 (24.27)
Cerebrovascular accident, n (%)	2 (1.94)
Chronic kidney disease (CKD), n (%)	14 (13.59)
Cancer, n (%)	5 (4.85)
History of hospitalization for heart failure, n (%)	29 (28.16)
Left ventricular ejection fraction, mean (SD)	57.81 (±7.82)
Heart rate, median (IQR)	67 (59–77)
Systolic blood pressure, median (IQR)	120 (110–135)
Diastolic blood pressure, median (IQR)	75 (65–80)
SpO2, median (IQR)	95 (92–96)
Respiratory rate, median (IQR)	18 (16–18)
Rales, n (%)	34 (33.01)
Oedema, n (%)	46 (44.66)
S3, n (%)	11 (10.68)
S4, n (%)	2 (1.96)
Jugular vein distension, n (%)	22 (21.57)
NTproBNP, median (IQR)	554 (211–1550.5)
TnI, median (IQR)	40.5 (5.4–260)
Functional class, n (%)	
I	14 (13.59)
II	60 (58.25)
III	21 (20.39)
IV	6 (5.83)
KCCQ, median (IQR)	41 (31–56)
0–24, n (%)	14 (15.5)
25–49, n (%)	48 (53.33)
50–74, n (%)	20 (22.22)
≥75, n (%)	8 (8.88)
Phenotypes, n (%)	
Obesity	14 (13.59)
Age ≥ 75	11(10.68)
Ischemic	12 (11.65)
Hypertensive	8 (7.77)
Combined	28 (27.18)
Other	30 (29.13)
Treatment (at recruitment)	
ACE inhibitors (ACEI), n (%)	34 (33.01)
Captopril, n (%)	20 (19.61)
Enalapril, n (%)	14 (13.73)
Angiotensin II receptor antagonists (ARB), n (%)	20 (19.42)
Losartan	13 (12.75)
Telmisartan	7 (6.86)
Sacubitril/valsartan, n (%)	3 (2.94)
Beta-blocker, n (%)	54 (52.93)
Metoprolol	37 (36.27)
Carvedilol	11 (10.78)
Bisoprolol	6 (5.88)
Spironolactone, n (%)	18 (17.65)
Other anti-hypertensive treatment, n (%)	
Calcium channel blocker	24 (23.53)
Thiazide diuretic	7 (6.86)
Loop diuretic, n (%)	
Furosemide	64 (62.75)
Bumetanide	10 (9.80)
Type 2 diabetes treatment, n (%)	
Metformin	30 (29.41)
SGLT2 inhibitors	3 (2.94)
DPP4 inhibitors	1 (0.98)
Insulin, n (%)	14 (13.73)
Acetylsalicylic acid, n (%)	42 (41.18)
Dual antiplatelet therapy, n (%)	23 (22.55)
Oral anticcoagulants, n (%)	
Low molecular weight heparin	22 (21.57)
Vitamin K antagonists	6 (5.88)
Apixaban	1 (0.98)
Statin, n (%)	
Atorvastatin	48 (47.06)
Rosuvastatin	2 (1.96)
Antiarrhythmic medications, n (%)	
Digoxin	6 (5.88)
Amiodarone	7 (6.86)
Other	1 (0.98)
Renal replacement therapy, n (%)	3 (2.94)

IQR, interquartile range; SpO2, peripheral oxygen saturation; SD, standard deviation; S3, third heart sound; S4, fourth heart sound; KCCQ, Kansas City Cardiomyopathy Questionnaire; SLGT2, sodium-glucose cotransporter-2; DPP4, Dipeptidyl peptidase 4.

significant difference in our study between phenotypes and mortality, this may be because of our limited number of participants, which could explain why other studies did find higher mortality with different phenotypes [2].

It is estimated that the prevalence of HF in the United States (US) is 6 million people, with significant variability between American and European reports, ranging from 1 % to 12 %, being lower in the European population. HFpEF accounts for up to 50 % of all HF cases and is the most common form of HF in patients over 65 years of age. Moreover, this population experiences a high rate of adverse cardiovascular events, which represents a substantial cost to the healthcare system [10,11]. However, there is limited information about HFpEF epidemiology in Latin America. Mendez et al. identified that 37 % of patients with HF had preserved ejection fraction [12], and according to a review by Bocchi et al., reports from Latin America show a prevalence of HFpEF ranging from 0 % to 37 % in outpatient settings, while in hospitalized patients, it ranges from 20 % to 45.7 % [13]. A cohort study in the Brazilian population reported an incidence of 199 cases per 100,000 persons per year (while in the US, an incidence of 310 cases per 100,000 persons per year is reported) [14]. These differences in prevalence and incidence could be due to variations in diagnostic approaches, age, and population heterogeneity.

Limited data are available regarding mortality and hospitalizations in Latin America. Mendez et al. reported a combined mortality rate of HF with reduced and preserved ejection fraction of 11 % at one-year follow-up, while Ciapponi et al. estimated an in-hospital mortality of 11.67 % and 15.38 % in HFrEF [12,14]. The results of our study demonstrate a higher total mortality rate in HFpEF (14.56 %) than previously described in other Latin American reports, which better aligns with mortality rates from international reports (15 %) [15].

The hospitalization rate in patients with HFpEF is high; however, the proportion of cardiovascular and non-cardiovascular causes varies depending on the study and its design, with some studies slightly favouring non-cardiovascular causes of hospitalization. It is estimated that, on average, these patients are hospitalized 1.4 times per year, although there is controversy over whether HFpEF carries a higher risk of hospitalization than HFrEF [3,16]. In our results, we observed a slight difference, with non-cardiovascular causes being more prevalent (9.71 % vs. 7.77 %). Furthermore, we found a high rate of the primary composite endpoint at 19.42 %, which could indicate an underestimation of the severity of this disease in Latin American countries, thus adding to the limited literature in this region.

Results of our study must be accounted as exploratory rather than conclusive. The present study does not address the socioeconomic and environmental factors, as well as the genetic and molecular mechanisms and their impact on HFpEF outcomes. The main limitation of our registry is the early halt in recruitment, motivated by slow recruitment during COVID-19 pandemic. Therefore, our sample size was not reached and arguable, our results may be submitted to bias and underpowered to

Table 2
Baseline characteristics & outcomes by phenotype.

	Other n = 30	Obesity n = 14	Elderly n = 11	Ischemic n = 12	Hypertensive n = 8	Combined n = 28	P value
Age, median (IQR)	59.5 (49–65)	61.5 (57–70)	81 (78–85)	59.5 (54.5–64)	62.5 (59.5–67.5)	76.5 (67.5–84.5)	0.0001
Sex f, n (%)	14 (46.67)	11 (78)	5 (45)	3 (25)	6 (75)	14 (50)	0.084
Hypertension, n (%)	10 (33.33)	10 (71.43)	8 (72.73)	4 (33.33)	8 (100)	24 (85.71)	<0.0001
T2D, n (%)	12 (40)	6 (42.86)	2 (18.18)	10 (83.33)	3 (37.50)	11 (39.29)	0.049
AF, n (%)	5 (16.67)	3 (21.43)	1 (9.09)	0 (0)	3 (37.5)	6 (21.43)	0.316
MI, n (%)	1 (3.33)	0 (0)	0 (0)	12 (100)	0 (0)	17 (60.71)	<0.0001
CKD, n (%)	0 (0)	2 (14.29)	1 (9.09)	1 (8.33)	2 (25)	8 (28.57)	0.015
LVEF, mean (SD)	59.57 (5.94)	59.1 (10.13)	55.52 (9.09)	53.25 (4.1)	61.12 (12.84)	57.36 (6.63)	0.138
NTproBNP, median (IQR)	1322 (450–2801)	1317.5 (675–4026)	1821 (411–7618)	907 (520.5–1405.5)	2138 (1126–6241.5)	2250.5 (682–7251)	0.3149
MRA, n (%)	8 (26.67)	3 (21.43)	2 (18.18)	2 (16.67)	0 (0)	3 (10.71)	0.526
Beta blocker, n (%)	11 (36.67)	5 (35.71)	4 (36.36)	12 (100)	3 (37.5)	19 (67.86)	<0.0001
Renal replacement therapy, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (12.5)	2 (7.14)	0.212
Composite endpoint, n (%)	8 (26.67)	3 (21.43)	3 (27.27)	1 (8.33)	2 (25)	3 (10.71)	0.559
Total mortality, n (%)	7 (23.33)	1 (7.14)	3 (27.27)	1 (8.33)	1 (12.5)	2 (7.14)	0.353

IQR, interquartile range; T2D, type 2 diabetes; AF, atrial fibrillation; MI, myocardial infarction; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; SD, standard deviation; MRA, mineralocorticoid receptor antagonists.

Table 3
Composite primary endpoint - Cox regression.

Variable	Model 1 (crude)		Model 2 (multivariate)	
	HR (95 % CI)	P value	HR (95 % CI)	P value
Age	1.01 (0.98–1.047)	0.396	1.01 (0.98–1.05)	0.455
AF	3.25 (1.33–7.95)	0.010	2.87 (1.12–7.36)	0.028
Beta-blocker	0.47 (0.19–1.19)	0.111	0.52 (0.2–1.35)	0.177
MRA	3.117 (1.24–7.85)	0.016	3.308 (1.23–8.89)	0.018
NTproBNP	1 (1.000002–1.000017)	0.015	1.00001 (1.00002–1.000018)	0.018

AF, atrial fibrillation; MRA mineralocorticoid receptor antagonists.
Univariate Cox regression analysis was performed of all variables and multivariable Cox regression models were performed based on hazard ratio and P value of the univariate analysis. Only models with a high hazard ratio and/or significant P value based on the univariate analysis were included in this table.

Table 4
Outcomes.

Total mortality, n (%)	15 (14.56)
Cardiovascular mortality, n (%)	11 (10.68)
High blood pressure	2 (1.94)
HF	3 (2.91)
Renal	1 (0.97)
Type 2 diabetes	1 (0.97)
Arrythmia	2 (1.94)
Cerebrovascular accident	1 (0.97)
Non-cardiovascular mortality, n (%)	4 (3.88)
HF hospitalization, n (%)	8 (7.77)
Non-cardiovascular hospitalization, n (%)	10 (9.71)
- Gastrointestinal bleeding	2 (1.94)
- Renal	2 (1.94)
- Other	6 (5.83)
Cardiovascular mortality and HF hospitalization, n (%)	18 (17.48 %)
Composite primary endpoint, n (%)	20 (19.42)

HF, heart failure.

detect actual differences among groups. In addition, changes of care during COVID-19 pandemic may have also altered patterns of care for patients with HF, and therefore, may have an influence in our event rate. HFpEF has been defined recently by the ESC guidelines using a cut-off of >50 % [17,18]; however, recent trials such as EMPEROR-Preserved [19], DELIVER [20] & FINEARTS [21] have used a cut-off point of >40 %. Our definition and LVEF cut-off (>45 %) were based in the design of PARAGON [22], a trial assessing the role of sacubitril valsartan in patients with HFpEF.

The present study highlights the need for further research regarding HFpEF particularly in underserved geographical areas like Latin-American. Future research should focus on personalizing treatment strategies and exploring phenotype specific management approaches.

5. Conclusions

In this prospective observational study including patients with HFpEF in México, we found a high comorbidity burden among patients with HFpEF, an important limitation to quality of life assessed by KCCQ, a high rate of hard endpoints (including cardiovascular death and hospitalizations) and a great heterogeneity in the use of treatments. Further research aimed to better understand the individual healthcare trajectory of patients with HFpEF, in addition to initiatives to improve the adoption of evidence-based therapies is needed.

CRediT authorship contribution statement

Diego Araiza-Garaygordobil: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Oscar-Ulises Preciado-Gutierrez:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jorge Daniel Sierra-Lara Martinez:** Writing – review & editing, Validation. **Hector Gonzalez-Pacheco:** Writing – review & editing, Formal analysis. **Rodrigo Gopar-Nieto:** Writing – review & editing, Formal analysis. **Ximena Latapi-Ruiz Esparza:** Visualization, Data curation. **Sarai Hernandez-Pastrana:** Writing – review & editing, Data curation. **Braiana-Angeles Diaz-Herrera:** Data curation. **Amada Alvarez-Sangabriel:** Writing – review & editing, Validation, Supervision, Conceptualization. **Antonio Jordan-Rios:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources,

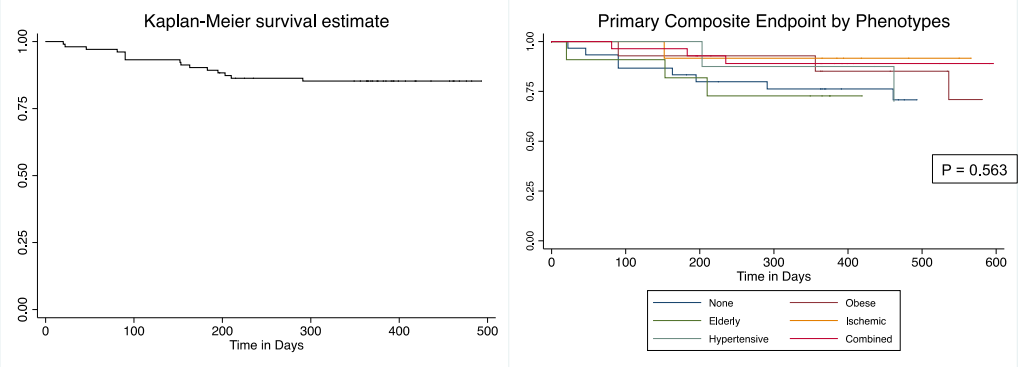

Fig. 2. Kaplan-Meier survival estimate (A). Primary composite endpoint, of all-cause mortality and heart failure hospitalization, by phenotype (B).

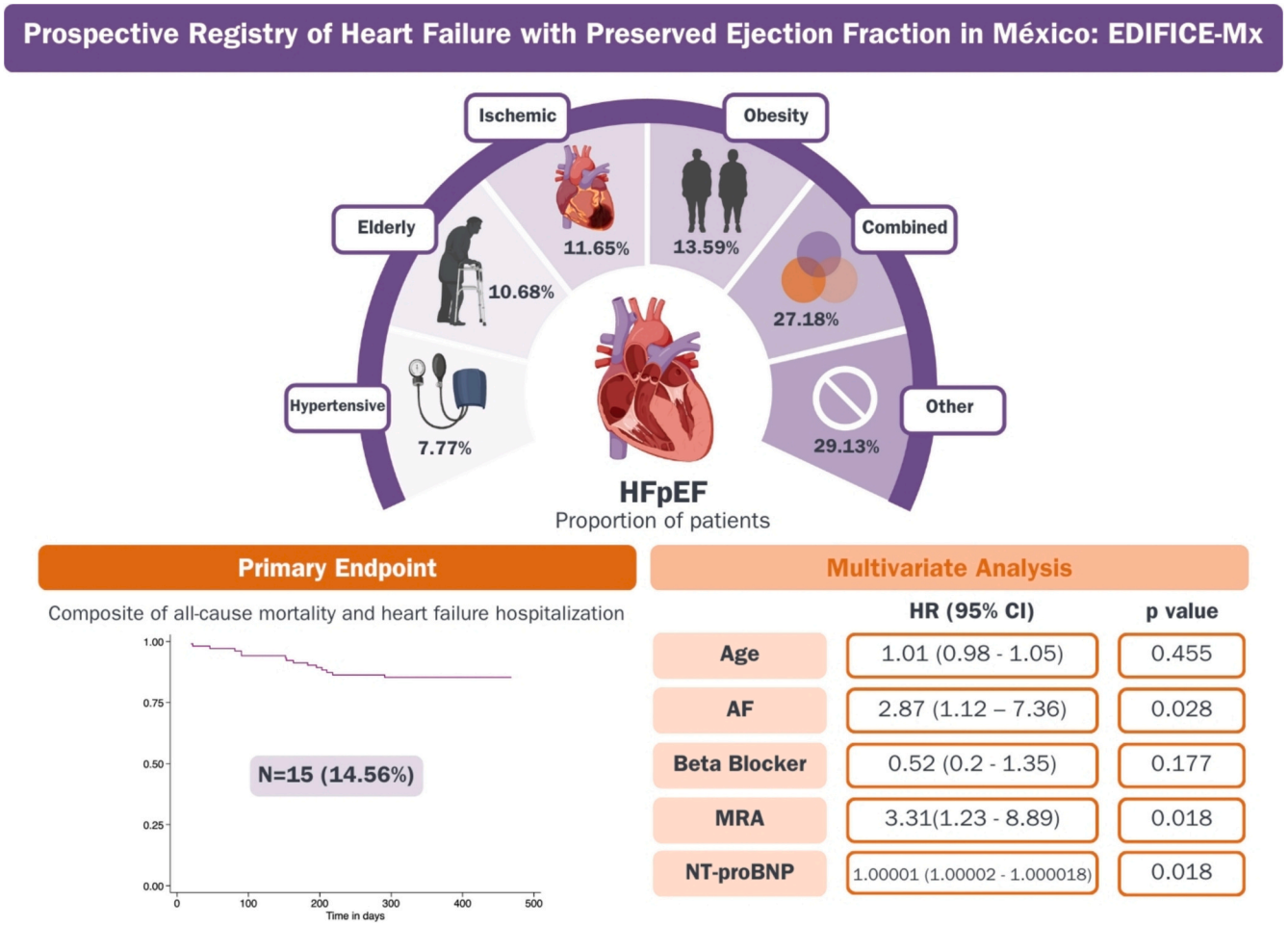

Fig. 3. Central illustration. The study findings highlight the heterogeneity of patient phenotypes in HFpEF in our population, the relationship between the use of beta blockers and MRA with the outcome. The primary composite endpoint of all-cause mortality and heart failure hospitalization showed a high incidence rate.

Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Alexandra Arias-Mendoza:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Conceptualization.

Ethical statement

The current research received approval from the study site research and ethics committee, with a reference number "INCAR-DG-DI-CI-467-2019", and all participants provided written informed consent before participating in the study. This study was funded by a research grant from Novartis (IIT - CLCZ696AMX01T). The sponsor did not participate in the enrolment or conduction of the study, nor in the final analysis or in the writing and approval of the present study.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: this work was supported by a research grant from Novartis [grant number IIT - CLCZ696AMX01T]. The sponsor did not participate in the enrolment or conduction of the study, nor in the final analysis or in the writing and approval of the present study.

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