Revista Clínica Española 223 (2023) 231–239

Revista Clínica Española

www.elsevier.es/rce

Prognostic utility of pulse pressure in patients with heart failure with preserved ejection fraction: The RICA Registry

I. Bravo Candela[a], N. Moya González[a], P. Salamanca Bautista[a,b,*], J. Pérez Silvestre[c], A. Conde Martel[d], S. Carrascosa García[c], M. Sánchez Marteles[e], J.M. Cerqueiro González[f], J. Casado Cerrada[g], M. Montero-Pérez-Barquero[h], on behalf of the investigators of the RICA Registry

[a] *Medicina Interna, Hospital Universitario Virgen Macarena, Sevilla, Spain*
[b] *Universidad de Sevilla, Sevilla, Spain*
[c] *Medicina Interna, Consorcio Hospital General Universitario de Valencia, Valencia, Spain*
[d] *Medicina Interna, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain*
[e] *Medicina Interna, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain*
[f] *Medicina Interna, Hospital Universitario Lucus Augusti, Lugo, Spain*
[g] *Medicina Interna, Hospital Universitario de Getafe, Madrid, Spain*
[h] *Medicina Interna, IMIBIC/Hospital Universitario Reina Sofía, Córdoba, Spain*

Received 22 November 2022; accepted 31 January 2023
Available online 17 March 2023

KEYWORDS
Heart failure;
Pulse pressure;
Left ventricular ejection fraction;
Arterial stiffness;
Mortality

Abstract
Background and aims: The prognostic role of pulse pressure (PP) in heart failure (HF) patients with preserved left ventricular ejection fraction (LVEF) is not well understood. Our aim was to evaluate it in acute and stable HF.
Material and methods: This work is a retrospective observational study of patients included in the RICA registry between 2008 and 2021. Blood pressure was collected on admission (decompensation) and 3 months later on an outpatient basis (stability). Patients were categorized according to whether the PP was greater or less than 50 mmHg. All-cause mortality was assessed at 1 year after admission.
Results: A total of 2291 patients were included, with mean age 80.1 ± 7.7 years. 62.9% were women and 16.7% had a history of coronary heart disease. In the acute phase, there was no difference in mortality according to PP values, but in the stable phase PP < 50 mmHg was independently associated with all-cause mortality at 1-year follow-up (HR 1.57, 95% CI 1.21–2.05, $p = 0.001$), after adjusting for age, sex, *New York Heart Association* functional class, previous HF, chronic kidney disease, valvular heart disease, cerebrovascular disease, score on the Barthel and Pfeiffer scales, hemoglobin and sodium levels.

* Corresponding author.
E-mail address: msalamanca2@us.es (P. Salamanca Bautista).

https://doi.org/10.1016/j.rceng.2023.01.006

Conclusions: Low stable-phase PP was associated with increased all-cause mortality in HF patients with preserved LVEF. However, PP was not useful as a prognostic marker of mortality in acute HF. Further studies are needed to assess the relationship of this variable with mortality in HF patients.

PALABRAS CLAVE
insuficiencia cardiac;
Presión de pulso;
Fracción de eyección del ventrículo izquierdo;
Rigidez arterial;
Mortalidad

Utilidad pronóstica de la presión de pulso en pacientes con insuficiencia cardiaca con fracción de eyección preservada: Registro RICA

Resumen
Antecedentes y objetivo: El papel pronóstico de la presión de pulso (PP) en pacientes con insuficiencia cardiaca (IC) con fracción de eyección de ventrículo izquierdo (FEVI) preservada no es bien conocido. Nuestro objetivo fue evaluarlo en fases de descompensación y de estabilidad.
Material y métodos: Estudio observacional retrospectivo de pacientes incluidos en registro RICA entre 2008 y 2021. La presión arterial se recogió al ingreso (descompensación) y a los 3 meses (estabilidad). Se calculó la PP y los pacientes se categorizaron según PP mayor/igual vs menor de 50 mmHg. Se evaluó la mortalidad por todas las causas al año del ingreso.
Resultados: Se incluyeron 2.291 pacientes, con edad media 80,1 ± 7,7 años. El 62,9% eran mujeres y un 16,7% tenían antecedentes de cardiopatía isquémica. En fase aguda, no hubo diferencias en la mortalidad según los valores de PP, pero en fase estable una PP < 50 mmHg se asoció de forma independiente con mortalidad por todas las causas al año de seguimiento (HR 1,57, IC 95% 1,21-2,05; $p = 0,001$), una vez controlado por edad, sexo, NYHA, IC previa, enfermedad renal crónica, valvulopatía, enfermedad cerebrovascular, Barthel, Pfeiffer, hemoglobina y sodio.
Conclusiones: Una PP baja en fase estable se asoció con mayor mortalidad por todas las causas en pacientes con IC con FEVI preservada. Sin embargo, la PP no demostró ser un factor pronóstico en fase de descompensación. Se necesitan más estudios que valoren la relación de esta variable con la mortalidad en los pacientes con IC.

Introduction

Heart failure (HF) is the leading cause of hospitalization in individuals older than 65 years.[1] Although its prognosis has improved in recent years, it continues to be associated with high morbidity and mortality. Therefore, it is important to determine factors that help identify patients with a worse prognosis. This is especially relevant in HF with preserved left ventricular ejection fraction (pLVEF), a population on which there are fewer studies.

Pulse pressure (PP), defined as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP), is an easy measurement to determine. High PP is related to increased arterial stiffness, greater cardiovascular mortality, and onset of HF. On the other hand, a low PP seems to reflect a decrease in systolic volume.[2–6] However, the prognostic role of PP in HF is complex. Studies provide data depending on the left ventricular ejection fraction (LVEF) spectrum. In patients with HF with reduced LVEF (HFrEF), previous studies have observed greater mortality associated with a low PP[2–6] whereas in patients with HF with pLVEF, the data are less consistent.[2–4,7,8] The ideal PP cut-off point for predicting mortality either in the decompensation phase or in stable condition is also not clear.

This study aims to assess the prognostic value of PP with a cut-off point of 50 mmHg, analyzing the outcome variable of all-cause mortality in patients with HFpEF in both the acute and stable phases included in a real-world registry (RICA Registry).

Materials and methods

Study population

This work is a retrospective study of data from the National Heart Failure Registry (RICA, for its initials in Spanish) conducted by the Heart Failure and Atrial Fibrillation Working Group of the Spanish Society of Internal Medicine. The RICA Registry is a prospective, multicenter, nation-wide registry that included patients older than 50 years hospitalized for HF according to European Society of Cardiology criteria from 52 hospitals between 2008 and 2021. The exclusion criteria were HF secondary to pulmonary hypertension, refusing to participate in the study, or death during the index admission. After discharge, the patients were followed-up on as outpatients at three months and one year and data on readmissions and all-cause mortality were recorded.

The study was conducted according to the Declaration of Helsinki and was approved by Reina Sofía University Hospital ethics committee (Córdoba, Spain). All participating patients signed an informed consent form.

Variables

Descriptive data such as age, sex, comorbidities, and New York Heart Association (NYHA) functional class in the previous month were collected upon inclusion. SBP and DBP were gathered at the index admission when the patient was decompensated (first value recorded in the admission) and at three months when the patient was in stable condition. With these values, the PP was calculated.

Previously, the literature was reviewed to determine the PP cut-off point with the greatest prognostic yield. Although there is variability among different works, the great majority of studies showed that the cut-off point with the greatest prognostic value was around 50 mmHg.[2–4] Therefore, the population in this work was categorized according to whether the PP value was lesser than or greater than/equal to said value. Pfeiffer's Short Portable Mental Status Questionnaire and Barthel Index were calculated for patients upon inclusion. Laboratory tests were performed in the first 48 h of admission. Given that some hospitals determined NT-proBNP and others measured BNP, patients' results were analyzed in three groups: one included patients with an NT-proBNP value greater than 1800 pg/mL or BNP above 400 pg/mL, another included patients with values below the aforementioned cut-off points, and a third included patients without a peptide determination.[9] The glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD-4) formula. A patient was considered to have chronic kidney disease (CKD) if they had eGFR <60 mL/min/1.73 m^2 at least three months prior to admission. LVEF was determined by echocardiogram. Patients with LVEF $\geq$ 50% and diagnostic criteria of HF with pLVEF according to the current European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure for each data collection period were included.[10–13] The dependent variable (outcome measure) was all-cause mortality at one year of follow-up.

Statistical analysis

Variables were expressed as means (standard deviation), medians (interquartile range), and frequencies (percentage). Categorical variables were compared using the chi-square test. Continuous variables were compared using Student's *t*-test if they followed a normal distribution or the non-parametric Mann–Whitney *U* test Kaplan–Meier curves (with log-rank) were used to evaluate the impact of PP on mortality. Two analyses were performed: one in patients with acute HF (decompensation) and another at three months of admission (stable). Lastly, a mortality analysis was conducted via a univariate and multivariate Cox regression (forward stepwise selection method), evaluating each variable's relationship to mortality. All variables that were statistically significant ($p < 0.05$) in the univariable analysis were included in the multivariable model. Natriuretic peptides were not able to be included because there were many missing values. The statistical study was conducted using the IBM SPSS Statistics for Windows package, version 26.0, Armonk, NY: IBM Corp, licensed by the University of Seville.

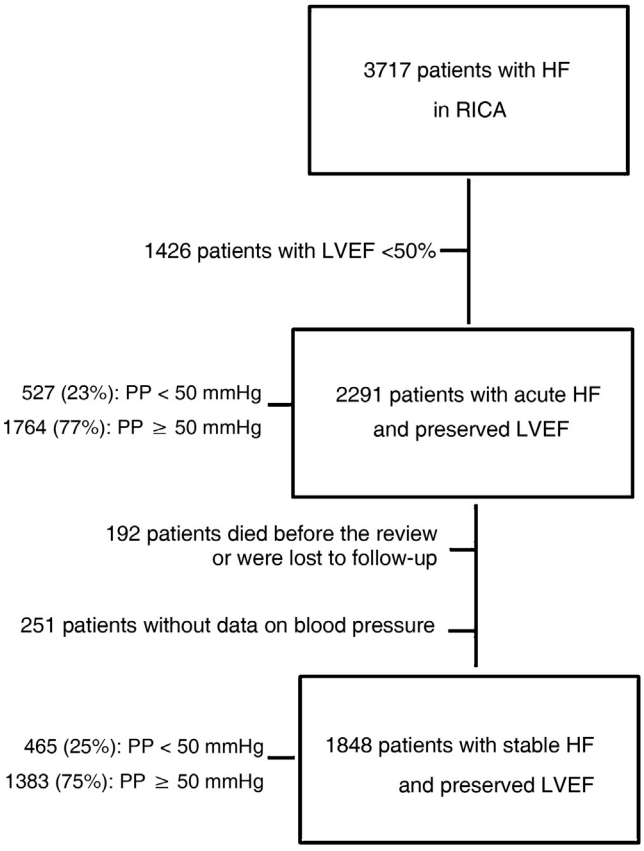

Figure 1 Flow chart of patients included in the study.

Results

Of the 3717 patients included in the RICA registry who were followed-up on for one year, 2291 (61.6%) had pLVEF. Of them, 192 were lost to follow-up or died before three months and 251 did not have blood pressure data. These 443 patients who were excluded were older (81.2 ± 7.9 years); more had a medical history of previous AMI (22.6%), CKD (44.9%), and dyslipidemia (57.1%); and fewer had valvular disease (59.8%). They also had a greater degree of dependence (Barthel <60 points 23.7%), lower hemoglobin (11.5 ± 2.1 g/dl) and sodium levels (138 ± 5.5 mEq/L), and higher potassium (4.5 ± 0.6 mEq/L) and NT-proBNP levels (median 3758 (1772–8690) pg/mL) compared to the patients included in the stable phase, which were 1848 (Fig. 1).

Baseline characteristics of patients in the acute phase

Table 1 shows the characteristics of patients according to PP values in the acute phase. The PP $\geq$ 50 mmHg group had a greater proportion of patients with hypertension, diabetes mellitus, dyslipidemia, and CKD and higher SBP values

Table 1 Characteristics of the study population in the acute phase according to pulse pressure values.

	Total population (n = 2291)	PP < 50 mmHg (n = 527, 23%)	PP ≥ 50 mmHg (n = 1,764, 77%)	*p*
Demographic and examination data				
Age, years	80.1 ± 7.7	79.7 ± 8.4	80.2 ± 7.5	0.23
Women (%)	1441 (62.9)	319 (60.5)	1122 (63.6)	0.20
SBP, mmHg	140.5 ± 27.2	114.5 ± 16.4	148.2 ± 24.9	**<0.001**
DBP, mmHg	75.2 ± 16.2	75.6 ± 15.4	75.1 ± 16.4	0.49
Baseline PP, mmHg	65.3 ± 22.0	38.9 ± 7.93	73.2 ± 18.4	**<0.001**
Heart disease				
Prior AMI	382 (16.7)	79 (15.0)	303 (17.2)	0.24
Valvular heart disease	812 (35.4)	196 (37.2)	616 (34.9)	0.34
Prior heart failure	1395 (60.9)	310 (58.8)	1085 (61.5)	0.27
Other comorbidities				
Diabetes mellitus	1039 (45.3)	183 (34.7)	856 (48.5)	**<0.001**
Hypertension	2045 (89.3)	441 (83.7)	1604 (90.9)	**<0.001**
Dyslipidemia	1147 (50.1)	240 (45.5)	907 (51.4)	**0.02**
Cerebrovascular disease	296 (12.9)	59 (11.2)	237 (13.4)	0.18
Chronic kidney disease	777 (33.9)	140 (26.6)	637 (36.1)	**<0.001**
Electrocardiogram				
Sinus rhythm	759 (33.1)	114 (21.6)	645 (36.6)	**<0.001**
Atrial fibrillation/flutter	1372 (59.9)	381 (72.3)	991 (56.2)	**<0.001**
Functional evaluation				
Prior NYHA functional class III-IV	798 (34.8)	200 (37.9)	598 (33.9)	0.08
Barthel <60 points	341 (14.9)	80 (15.2)	261 (14.8)	0.83
Pfeiffer >2 errors	718 (31.3)	172 (32.6)	546 (30.9)	0.46
Laboratory tests				
Hemoglobin, mg/dl	11.9 ± 2.1	12.3 ± 1.9	11.7 ± 2.0	**<0.001**
Creatinine, mg/dl	1.30 ± 0.7	1.36 ± 0.7	1.31 ± 0.7	0.20
Sodium, mEq/L	138.9 ± 4.9	138.6 ± 4.9	138.9 ± 4.9	0.33
Potassium, mEq/L	4.3 ± 0.6	4.2 ± 0.5	4.3 ± 0.6	**0.02**
NT-proBNP, median (pg/mL)	2926 (1370—6335)	3577 (1642—7249)	2710 (1302—5995)	**0.01**
Low natriuretic peptides	459 (20.0)	90 (17.1)	369 (20.9)	**0.01**
High natriuretic peptides	887 (38.7)	237 (45.0)	650 (36.8)	
No peptides	943 (41.2)	200 (37.9)	743 (42.3)	
Follow-up				
Readmissions at one year	962 (42.0)	218 (41.4)	744 (42.2)	0.74
Mortality at one year	489 (21.3)	124 (23.5)	365 (20.7)	0.17

The qualitative data are shown as frequencies and percentages, n (%). The quantitative data are shown as means (standard deviation) or median (interquartile range).
AMI: acute myocardial infarction; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York Heart Association; DBP: diastolic blood pressure; SBP: systolic blood pressure; PP: pulse pressure.

than the PP < 50 mmHg group. In addition, NT-proBNP and hemoglobin figures were lower in this group and there were more patients with sinus rhythm.

Effect of PP on mortality on patients with HFpEF in the acute phase

At one year of follow-up, 489 patients (21.3%) had died. In the univariable analysis of the acute phase, PP < 50 mmHg was not related to one-year mortality and therefore not included into the multivariable model. In the multivariable model, age, sex, presence of prior HF, CKD, NYHA, score <60 on the Barthel index, more than two errors on the Pfeiffer scale, and potassium figures were demonstrated to be independent prognostic factors of mortality (Table 2).

Fig. 1S (supplementary material) shows survival curves according to PP < 50 vs >50 mmHg in the acute phase. In patients with acute HF, there were no differences in mortality according to PP values (log-rank 0.116).

Characteristics of patients in the acute phase

Table 3 describes the characteristics of patients upon follow-up at three months. Patients with PP ≥ 50 mmHg had more cardiovascular risk factors (hypertension, diabetes, dyslipidemia, etc.) and comorbidities such as CKD. As in the acute phase, they had lower levels of hemoglobin and natriuretic

Table 2 Predictors of mortality at 12 months of hospitalization in patients with acute HF.

	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Demographic and examination data				
Age	1.04 (1.03–1.05)	<0.001	1.03 (1.01–1.04)	**0.01**
Female sex	0.81 (0.68–0.97)	0.03	0.64 (0.53–0.78)	**0.001**
PP < 50 mmHg in the acute phase	1.18 (0.96–1.44)	0.12		
Heart disease				
Prior AMI	1.14 (0.91–1.44)	0.25		
Valvular heart disease	1.40 (1.17–1.68)	<0.001	1.19 (0.98–1.44)	0.08
Prior heart failure	1.76 (1.44–2.14)	<0.001	1.29 (1.04–1.60)	**0.02**
Other comorbidities				
Diabetes mellitus	1.06 (0.88–1.26)	0.54		
Hypertension	0.94 (0.71–1.25)	0.68		
Dyslipidemia	1.13 (0.95–1.35)	0.17		
Cerebrovascular disease	1.23 (0.96–1.57)	0.10		
Chronic kidney disease	1.89 (1.58–2.26)	<0.001	1.54 (1.27–1.88)	**<0.001**
Electrocardiogram				
Sinus rhythm	0.78 (0.64–0.95)	0.02	1.17 (0.96–1.43)	0.13
Atrial fibrillation/flutter	1.07 (0.90–1.29)	0.44		
Functional evaluation				
Prior NYHA functional class III-IV	1.78 (1.49–2.13)	<0.001	1.46 (1.21–1.76)	**<0.001**
Barthel <60 points	2.50 (2.05–3.06)	<0.001	1.98 (1.59–2.47)	**<0.001**
Pfeiffer > 2 errors	1.74 (1.46–2.09)	<0.001	1.38 (1.13–1.68)	**0.01**
Laboratory tests				
Hemoglobin, mg/dl	0.90 (0.86–0.94)	<0.001	0.96 (0.91–1.01)	0.08
Sodium, mEq/L	0.98 (0.97–1.00)	0.04	0.99 (0.97–1.01)	0.44
Potassium, mEq/L	1.31 (1.15–1.31)	<0.001	1.18 (1.02–1.37)	**0.03**

HR: hazard ratio; AMI: acute myocardial infarction; CI: confidence interval; NYHA: New York Heart Association; PP: pulse pressure.

peptides. Potassium levels were also higher in the greater PP group.

Effect of PP on mortality in patients with HFpEF in the stable phase

In the stable phase, after performing the multivariable analysis, the independent variables predictive of mortality were age, male sex, CKD, score <60 points on the Barthel scale, NYHA, and PP < 50 mmHg (HR 1.57; 95 %CI 1.21–2.05) (Table 4).

In the stable phase, significantly more patients with PP < 50 mmHg died at one year than those with PP ≥ 50 mmHg (log-rank <0.001) (Fig. 2S).

Discussion

This work aimed to determine the prognostic value of PP in patients with HFpEF in the decompensated and stable phases. In the acute phase, PP did not demonstrate value as a prognostic marker, but in the stable phase, PP < 50 mmHg was independently associated with all-cause mortality at one year of follow-up.

The main strength of our study is that it is a real-life registry of a large number of patients with HFpEF who have been admitted for decompensation on at least one occasion. Therefore, it is representative of patients who are usually treated in internal medicine departments. However, the results also have some limitations. First, it is a retrospective study. Second, recruitment took place between 2008 and 2021 and there are patients who were not able to be treated with the disease-modifying drugs that have become available in recent years. Third, only patients older than 50 years in functional class II-IV were included. Therefore, the results are not able to be extrapolated to patients who do not have these characteristics. Between the acute and stable phases, there was a significant loss of patients who had a more unfavorable profile. What's more, natriuretic peptide figures, a known prognostic marker of HF, were not able to be included in the univariable and multivariable analyses because these values were missing for many patients. Logically, these limitations could have introduced bias in the study.

PP fundamentally depends on systolic volume and the elastic properties of the arterial wall. Arterial stiffness increases with age and begins to rise starting in the fifth decade of life.[14,15] This increase in stiffness translates into greater SBP and, to a lesser extent, a decrease in DBP, which leads to greater PP values.[7]

A low PP seems to reflect a decrease in systolic volume.[1–3] Different studies have highlighted this relationship in patients with HF. Ferreira et al. conducted a retrospective study of 914 decompensated patients

Table 3 Characteristics of the study population in the stable phase according to pulse pressure values.

	Total population (n = 1848, 100)	PP < 50 mmHg (n = 465, 25.2%)	PP ≥ 50 mmHg (n = 1,383, 74.8%)	*p*
Demographic and examination data				
Age, years	79.8 ± 7.7	80.1 ± 8.1	79.7 ± 7.5	0.31
Women (%)	1152 (62.3)	278 (59.8)	874 (63.2)	0.19
SBP, mmHg	132.4 ± 20.6	112.4 ± 13.5	139.0 ± 18.2	**<0.001**
DBP, mmHg	72.0 ± 12.2	73.1 ± 12.2	71.6 ± 12.2	**0.02**
PP in the stable phase, mmHg	60.4 ± 18.0	39.4 ± 6.6	67.4 ± 14.9	**<0.001**
Heart diseases				
Prior AMI	282 (15.3)	56 (12.0)	226 (16.3)	**0.03**
Valvular heart disease	634 (34.3)	171 (36.8)	463 (33.5)	0.19
Prior heart failure	1108 (60.0)	282 (60.6)	826 (59.7)	0.72
Other comorbidities				
Diabetes mellitus	832 (45.0)	163 (35.1)	669 (48.4)	**<0.001**
Hypertension	1646 (89.1)	386 (83.0)	1260 (91.1)	**<0.001**
Dyslipidemia	894 (48.4)	197 (42.4)	697 (50.4)	**0.01**
Cerebrovascular disease	249 (13.5)	64 (13.8)	185 (13.4)	0.83
Chronic kidney disease	578 (31.3)	119 (25.6)	459 (33.2)	**0.01**
Electrocardiogram				
Sinus rhythm	620 (33.8)	102 (22.2)	518 (37.7)	**<0.001**
Atrial fibrillation/flutter	1098 (59.9)	335 (72.8)	763 (55.6)	**<0.001**
Functional evaluation				
Prior NYHA functional class III-IV	627 (34.1)	178 (38.5)	449 (32.6)	**0.02**
Barthel <60 points	236 (12.8)	74 (15.9)	162 (11.7)	**0.02**
Pfeiffer > 2 errors	564 (30.5)	154 (33.1)	410 (29.6)	0.16
Laboratory tests				
Hemoglobin, mg/dl	12.3 ± 1.7	12.6 ± 1.8	12.3 ± 1.7	**0.01**
Creatinine, mg/dl	1.28 ± 0.6	1.26 ± 0.5	1.29 ± 0.6	0.24
Sodium, mEq/L	139.9 ± 4.0	140.1 ± 3.9	139.8 ± 4.1	0.21
Potassium, mEq/L	4.5 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	0.59
NT-proBNP, median (pg/mL)	1484 (703—3206)	1851 (832—3599)	1332 (624—2995)	0.03
Low natriuretic peptides	391 (21.1)	92 (19.7)	299 (21.6)	**0.02**
High natriuretic peptides	256 (13.9)	84 (18.1)	172 (12.5)	
No peptides	1201 (65.0)	289 (62.2)	912 (65.9)	
Follow-up				
Readmission at 9 months	777 (42.6)	198 (42.4)	574 (41.9)	0.79
Mortality at 9 months	253 (13.7)	87 (18.7)	166 (12.0)	**<0.001**

The qualitative data are shown as frequencies and percentages, n (%). The quantitative data are shown as means (standard deviation) or median (interquartile range).
AMI: acute myocardial infarction; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York Heart Association; DBP: diastolic blood pressure; SBP: systolic blood pressure; PP: pulse pressure.

with advanced HF (NYHA III-IV), observing that those with PP < 40 mmHg had lower LVEF values.[14] Said systolic dysfunction translated into a decreased systolic volume, favoring a lower SBP and, therefore, lower PP values. These results confirm what was previously observed by Voors et al.[16] However, a lower systolic volume may not only be linked to reduced LVEF, it can also be found in patients with HFpEF, valvular disease, or severe diastolic dysfunction.[17]

The results of previous studies on PP as a prognostic marker in patients with HF vary according to the patients' characteristics and clinical situation. In HFrEF, greater mortality has been described among patients with a low PP, observing a direct relationship between lower PP values and lower systolic volume.[2–6] Few studies have demonstrated an association between elevated PP in patients with HFrEF and greater mortality.[3,5,6]

In studies on patients with HFpEF, the results are disparate. Some describe a greater risk of adverse events in patients with elevated PP in acute condition,[3] with similar results observed in patients in stable condition in a recently published subanalysis of the PARAGON-HF trial.[18] On the contrary, the SWEDEHF study,[4] like this work, analyzed patients in acute and stable condition and found that presence of a low PP was related to a worse prognosis.[4] On their part, Tokitsu et al. observed a relationship on the U curve between PP and cardiovascular events and HF-associated events; they found greater rate of events with low PP (<44 mmHg) and elevated PP (>75 mmHg).[7] In

Table 4 Predictors of mortality at 12 months in patients with stable HF.

	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Demographic and examination data				
Age	1.03 (1.01–1.04)	<0.001	1.02 (1.00–1.04)	**0.03**
Female sex	0.68 (0.54–0.86)	0.01	0.62 (0.48–0.80)	**<0.001**
PP < 50 mmHg	1.62 (1.25–2.11)	<0.001	1.57 (1.21–2.05)	**0.01**
Heart disease				
Prior AMI	1.14 (0.85–1.53)	0.39		
Valvular heart disease	1.30 (1.03–1.64)	0.03	0.95 (0.73–1.24)	0.72
Prior heart failure	1.95 (1.50–2.52)	<0.001	1.65 (1.22–2.23)	**<0.001**
Other comorbidities				
Diabetes mellitus	1.04 (0.83–1.31)	0.75		
Hypertension	0.95 (0.67–1.38)	0.82		
Dyslipidemia	1.09 (0.87–1.37)	0.44		
Cerebrovascular disease	1.42 (1.05–1.91)	0.03	1.18 (0.85–1.63)	0.34
Chronic kidney disease	1.69 (1.34–2.12)	<0.001	1.40 (1.07–1.81)	**0.02**
Electrocardiogram				
Sinus rhythm	0.82 (0.64–1.05)	0.11		
Atrial fibrillation/flutter	1.03 (0.82–1.29)	0.82		
Functional evaluation				
Prior NYHA functional class III-IV	1.58 (1.25–1.98)	<0.001	1.38 (1.07–1.78)	**0.02**
Barthel <60 points	2.27 (1.74–2.96)	<0.001	1.82 (1.32–2.49)	**<0.001**
Pfeiffer > 2 errors	1.47 (1.16–1.85)	0.01	1.20 (0.92–1.58)	0.18
Laboratory tests				
Hemoglobin, mg/dl	0.79 (0.74–0.84)	<0.001	0.95 (0.890–1.01)	0.12
Glucose, mg/dl				
Sodium, mEq/L	0.93 (0.97–1.000)	<0.001	0.99 (0.97–1.02)	0.64
Potassium, mEq/L	0.95 (0.77–1.17)	0.64		

HR: hazard ratio; AMI: acute myocardial infarction; CI: confidence interval; NYHA: New York Heart Association; PP: pulse pressure.

the MAGGIC study, the PP was measured in either acute or stable condition, without later distinguishing the prognostic value of PP in each of these situations; no relationship was found between mortality and PP.

Of note in the RICA Registry are a high proportion of patients with HFpEF, patients who are older, and female patients as well as a greater prevalence of hypertension, atrial fibrillation, and CKD and a lower probability of coronary disease.

When comparing the characteristics of patients with HFpEF with the studies, the patients included in this study are more similar to those included in GWTG-HF,[3] as they are older and have more comorbidities. One-year mortality in patients with HFpEF in GWTG-HF[3] was higher (31.8%) than what was observed in this study (21.3%) as well as compared to the MAGGIC, SWEDEHF, and PARAGON-HF studies. This increase in mortality could be due to the fact that GWTG-HF[3] analyzed patients only during hospitalization, measuring PP at the time of discharge, while in this study and in the MAGGIC[2], SWEDHF,[4] and PARAGON-HF studies,[18] patients were analyzed both in the acute and stable phases.

In addition to LVEF, there are other factors that may influence the prognostic value of PP, such as the patient's baseline condition. In the SAVE[19] and SOLVD studies,[20] elevated PP was demonstrated to be a negative prognostic factor in patients with asymptomatic or mild HF, with the increase in PP values being attributed to greater arterial stiffness and arteriosclerosis and thus a worse prognosis. In addition, in patients with advanced HF, lower PP values are related to a lower systolic volume and are linked to a greater number of adverse events.[14]

One possible explanation of this study's results in the acute phase is that hemodynamic abnormalities that affect SBP and DBP during the decompensation phase would not allow for adequately evaluating PP. It is likely that a PP < 50 mmHg in the stable phase implies established lower SBP values or a lower systolic volume; these are markers of poor prognosis in patients with HF.

In regard to the external validity of this study, the fact that it was conducted in real-world patients hospitalized due to decompensated HF in internal medicine departments makes it representative of patients who are usually treated in this setting. Therefore, these results would be applicable for this type of patients, but caution should be taken when extrapolating it to other populations. Future lines of research in this field include attempting to validate these data in other types of patients, such as those cared for in cardiology or emergency departments.

Conclusions

In patients with HFpEF drawn from a real-world registry, low PP (<50 mmHg) measured in the stable phase was related to greater all-cause mortality at one year of follow-up. PP during the decompensation phase of HF was not shown to be a prognostic factor.

Funding

The RICA Registry belongs to the Spanish Society of Internal Medicine and is led by the Heart Failure and Atrial Fibrillation Working Group. This study has not received any funding from public or private entities.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgments

We would like to thank all researchers who form part of the RICA Registry. The authors declare that they do not have any conflicts of interest.

Appendix A. Members of the RICA Registry

Álvarez Rocha P, Anarte L, Aramburu-Bodas O, Arévalo-Lorido JC, Arias Jiménez JL, Carrascosa García S, Carrasco Sanchez FJ, Carretero-Gómez J, Casado Cerrada J, Cepeda Rodrigo JM, Cerqueiro Gonzalez JM, Chivite Guillén D, Conde-Martel A, Dávila Ramos MF, Díaz de Castellví S, Epelde F, Formiga Pérez F, García Campos A, García Moreno C, González Franco A, Guisado Espartero ME, Guzmán García M, León Acuña A, López Castellanos G, Lorente Furió O, Manzano Espinosa L, Montero-Pérez-Barquero M, Moreno García MC, Ormaechea Gorricho G, Quesada Simón MA, Quirós López R, Salamanca Bautista MP, Silvera G, Trullàs Villa JC.

Irene Bravo Candela, Natalia Moya González, Prado Salamanca Bautista designed the study, analyzed the data, and wrote the manuscript. The rest of authors participated in data collection and reviewed and approved the manuscript.

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.rceng.2023.01.006.

References

1. Sayago-Silva I, García-López F, Segovia-Cubero J. Epidemiología de la insuficiencia cardiaca en España en los últimos 20 años. Rev Esp Cardiol. 2013;66:649–56.
2. Jackson CE, Castagno D, Maggioni AP, Køber L, Squire IB, Swedberg K, et al. Differing prognostic value of pulse pressure in patients with heart failure with reduced or preserved ejection fraction: results from the MAGGIC individual patient meta-analysis. Eur Heart J. 2015;36:1106–14.
3. Laskey WK, Wu J, Schulte PJ, Hernandez AF, Yancy CW, Heidenreich PA, et al. Association of arterial pulse pressure with long-term clinical outcomes in patients with heart failure. JACC Heart Fail. 2016;4:42–9.
4. Teng THK, Tay WT, Dahlstrom U, Benson L, Lam CSP, Lund LH. Different relationships between pulse pressure and mortality in heart failure with reduced, mid-range and preserved ejection fraction. Int J Cardiol. 2018;254:203–9.
5. Petrie CJ, Voors AA, Robertson M, Van Veldhuisen DJ, Dargie HJ. A low pulse pressure predicts mortality in subjects with heart failure after an acute myocardial infarction: a post-hoc analysis of the CAPRICORN study. Clin Res Cardiol. 2012;101:29–35.
6. Regnault V, Lagrange J, Pizard A, Safar ME, Fay R, Pitt B, et al. Opposite predictive value of pulse pressure and aortic pulse wave velocity on heart failure with reduced left ventricular ejection fraction: insights from an Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) substudy. Hypertension. 2014;63:105–11.
7. Tokitsu T, Yamamoto E, Hirata Y, Kusaka H, Fujisue K, Sueta D, et al. Clinical significance of pulse pressure in patients with heart failure with preserved left ventricular ejection fraction. Eur J Heart Fail. 2016;18:1353–61.
8. Suzuki K, Claggett B, Minamisawa M, Nochioka K, Mitchell GF, Anand IS, et al. Pulse pressure, prognosis, and influence of sacubitril/valsartan in heart failure with preserved ejection fraction. Hypertension. 2021;77:546–56.
9. Mueller C, McDonald K, De Boer RA, Maisel A, Cleland JGF, Kozhuharov N, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail. 2019;21:715–31.
10. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, Poole-Wilson PA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail. 2008;10:933–89.
11. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33:1787–847.
12. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016;37:2129–200.
13. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599–726.
14. Ferreira AR, Mendes S, Leite L, Monteiro S, Pego M. Pulse pressure can predict mortality in advanced heart failure. Rev Port Cardiol. 2016;35:225–8.
15. Angeli F, Reboldi G, Verdecchia P. Heart failure, pulse pressure and heart rate: refining risk stratification. Int J Cardiol. 2018;271:206–8.
16. Voors A, Petrie C, Petrie M, Charlesworth A, Hillege AL, Zijlstra F, et al. Low pulse pressure is independently related to elevated natriuretic peptides and increased mortality in advanced chronic heart failure. Eur Heart J. 2005;26:1759–64.
17. Naka KK, Ikonomidis I. Brachial pulse pressure in heart failure: simple to measure but complex to interpret. Eur Heart J. 2019;40:E8–10.

18. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med. 2019;381:1609–20.
19. Mitchell GF, Moye LA, Braunwald E, Rouleau JL, Bernstein V, Geltman EM, et al. Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. SAVE investigators. Survival and ventricular enlargement. Circulation. 1997;96:4254–60.
20. Domanski MJ, Mitchell GF, Norman JE, Exner DV, Pitt B, Pfeffer MA. Independent prognostic information provided by sphygmomanometrically determined pulse pressure and mean arterial pressure in patients with left ventricular dysfunction. J Am Coll Cardiol. 1999;33:951–8.