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ORIGINAL ARTICLE

The Prognostic Impact of Pulse Pressure in Acute Heart Failure: Insights from the HEARTS Registry

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Abstract

Background: **Low pulse pressure predicts long-term mortality in chronic heart failure, but its prognostic value in acute heart failure is less understood. The present study was designed to examine the prognostic value of pulse pressure in acute heart failure.**

Methods: **Pulse pressure was tested for its impact on short- and long-term mortality in all patients admitted with acute heart failure from October 2009 to December 2010 in eighteen tertiary centers in Saudi Arabia (n = 2609). All comparisons were based on the median value (50 mmHg). Heart failure with reduced ejection fraction was defined as less than 40%.**

Results: **Low pulse pressure was associated with increased short-term mortality in the overall population (OR = 1.61; 95 CI 1.17, 2.22; P 0.004 and OR = 1.51; 95% CI 1.13, 2.01; P = 0.005, for hospital and thirty-day mortality, respectively), and short-term and two-year mortality in the reduced ejection fraction group (OR = 1.81; 95% CI 1.19, 2.74; P = 0.005, OR = 1.69; 95% CI 1.17, 2.45; P = 0.006, and OR = 1.29; 95% CI 1.02, 1.61; P = 0.030 for hospital, thirty-day, and two-year mortality, respectively). This effect remained after adjustment for relevant clinical variables; however, pulse pressure lost its predictive power both for short-term and long-term mortality after the incorporation of systolic blood pressure in the model. Conversely, low pulse pressure was an independent predictor of improved survival at two and three years in heart failure with preserved ejection fraction (OR = 0.43; 95% CI 0.24, 0.78, P = 0.005 and OR = 0.49; 95% CI 0.28, 0.88; P = 0.016, respectively).**

Conclusion: **In acute heart failure with reduced ejection fraction, the prognostic value of low pulse pressure was dependent on systolic blood pressure. However, it inversely correlated with long-term survival in heart failure with preserved ejection fraction.**

Keywords: Acute heart failure, Pulse pressure, Mortality, Saudi Arabia

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1. Introduction

Pulse pressure (PP) is a blood pressure (BP) component that measures the pulsatility dynamics of the left ventricle (LV) throughout the cardiac cycle, and is influenced by two main parameters: stroke volume and aortic elasticity [1],[2]. In the Framingham study, elevated baseline PP carried a significant future risk for coronary artery disease [3] and heart failure (HF) [4]. In addition, it independently predicted an overall cardiovascular-related mortality in several studied populations [5−7].

The prognostication of PP across the spectrum of HF syndromes is variable. In chronic symptomatic HF with reduced ejection fraction (HFrEF), low PP was predictive of all-cause mortality [8−12]. A similar observation was found in HFrEF following acute coronary syndromes [13],[14]. However, post-hoc analyses from two recognized randomized trials revealed a reverse pattern in asymptomatic HFrEF [15],[16]. Moreover, PP in HF with preserved EF (HFpEF) is less understood owing to the lack of reports. Available evidence emerges from three large-scale registries with variable conclusions, where direct [9], U-shaped [11], and neutral [8] relationships with long-term survival were described.

Few reports have focused on PP and mortality rates following an acute HF (AHF) hospitalization, and as such, independent inverse relationships between PP and extended mortality rates were described, especially in HFrEF [9],[11],[17]. All evidence about PP in HF seems to emphasize on extended survival rates, and there remains a literature gap on the clinical utility of admission PP for predicting hospital mortality. The aim of this study is to examine the prognostic value of PP on short- and long-term outcomes in both phenotypes of AHF, using data from the Heart Function Assessment Registry Trial in Saudi Arabia (HEARTS). We hypothesized that low PP will be associated increased mortality in patients presenting with AHF.

Abbreviations

AHF	Acute Heart Failure
BP	Blood Pressure
DBP	Diastolic Blood Pressure
EF	Ejection Fraction
HF	Heart Failure
HF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HEARTS	Heart Function Assessment Registry Trial in Saudi Arabia
LV	Left Ventricle
OR	Odds Ratio
PP	Pulse Pressure
SBP	Systolic Blood Pressure

2. Methods

The HEARTS protocol had been previously described [18],[19]. Briefly, HEARTS is a prospective registry that enrolled 2609 consecutive patients aged 18 years and above with a primary admission diagnosis of AHF. Eighteen tertiary care centers in different regions of Saudi Arabia participated in this registry. Enrollment took place between October 2009 and December 2010, with clinical follow-up through January 2013. The definition of HF was based on the European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic HF [20]. The study was approved by the institutional review board at each participating hospital and complied with the Declaration of Helsinki. An informed written consent was obtained from all enrolled subjects.

BP was recorded on the first encounter in the emergency department. Measurements were done over the brachial artery with standard automated oscillometric devices or manual sphygmomanometers, depending on the practice of the participating institution. PP was calculated as the difference between systolic BP (SBP) and diastolic BP (DBP). Comparisons were assessed according to the PP median value (50 mmHg). LV systolic function was reported in categorical values as either normal (≥50%) or reduced (mild; 40−49%, moderate; 30−39%, and severe; < 30%), with the cutoff definition for HFrEF as 40%. We described patients' baseline characteristics, therapies, hospital course, and hospital outcomes. The primary endpoints were hospital, thirty-day, one-, two-, and three-year mortality. We obtained the vital status following hospital discharge by telephone interview, and then verified these data as needed with the use of hospital records.

2.1. Statistical Analysis

Categorical data were summarized with absolute numbers and percentages. Numeric data were summarized with mean and standard deviation or the median and interquartile range. Comparisons between the groups were performed using the Chi-square test or Fisher's exact test for categorical variables and the independent sample T-test or Mann−Whitney U test for continuous variables. We

Table 1. Baseline characteristics of all acute heart failure patients based on pulse pressure median value.

	Total, 2609	PP ≤ 50, 1360 (52.1%)	PP > 50, 1249 (47.9%)	P-value
Demographics				
Age, mean ± SD	61.3 ± 14.9	58.5 ± 16.1	64.4 ± 13.1	<0.001
Male, n (%)	1717 (65.8)	1002 (73.7)	715 (57.2)	<0.001
Body mass index, mean ± SD	29.2 ± 6.7	28.2 ± 6.0	30.2 ± 7.4	<0.001
Risk factors				
Diabetes mellitus, n (%)	1668 (64.1)	754 (55.7)	914 (73.3)	<0.001
Smoker/Ex-smoker, n (%)	872 (33.4)	537 (39.5)	335 (26.8)	<0.001
Hypertension, n (%)	1831 (70.6)	791 (58.6)	1040 (83.7)	<0.001
Dyslipidemia, n (%)	894 (36.4)	375 (29.1)	519 (44.5)	<0.001
History of cardiovascular diseases				
Heart failure, n (%)	1670 (64.2)	900 (66.3)	770 (62.0)	0.021
Ischemic heart disease, n (%)	1376 (53.3)	677 (50.3)	699 (56.5)	0.002
Percutaneous coronary intervention, n (%)	340 (13.1)	177 (13.0)	163 (13.1)	0.965
Coronary artery bypass graft, n (%)	261 (10.0)	134 (9.9)	127 (10.2)	0.792
Rheumatic heart disease, n (%)	183 (7.1)	111 (8.2)	72 (5.8)	0.016
Other valvular heart disease, n (%)	390 (15.0)	227 (16.7)	163 (13.2)	0.010
Atrial fibrillation, n (%)	408 (15.7)	223 (16.5)	185 (14.9)	0.267
Ventricular arrhythmias, n (%)	64 (2.5)	48 (3.5)	16 (1.3)	<0.001
Implantable cardioverter defibrillator, n (%)	229 (8.8)	166 (12.2)	63 (5.1)	<0.001
Cardiac resynchronization therapy, n (%)	85 (3.3)	62 (4.5)	23 (1.9)	<0.001
Transient ischemic attack/stroke, n (%)	252 (9.7)	111 (8.2)	141 (11.3)	0.007
Peripheral arterial disease, n (%)	99 (3.8)	45 (3.3)	54 (4.4)	0.170
History of other chronic medical illnesses				
Anemia, n (%)	1166 (44.9)	558 (41.2)	608 (49.1)	<0.001
Chronic renal insufficiency, n (%)	771 (29.7)	359 (26.5)	412 (33.2)	<0.001
Chronic lung disease, n (%)	185 (7.1)	82 (6.0)	103 (8.3)	0.027

used logistic regression models to estimate unadjusted and adjusted odds ratios (OR) for primary endpoints. We adjusted for age, gender, body mass index, diabetes mellitus, smoking, hypertension, dyslipidemia, history of HF, anemia, HF etiology, heart rate, and estimated glomerular filtration rate. Further, we applied stepwise adjustment by introducing BP components (SBP and DBP) to the models to test their effect on the predictive power of PP. Our multivariate analysis was done collectively for the overall population and repeated separately for each HF phenotype (EF < 40% vs. EF ≥ 40%). The Kaplan−Meier analysis was applied to plot the cumulative survival and differences between curves were assessed by the log-rank test. A two-sided P-value of <0.05 was considered statistically significant. All analyses were performed using [SAS/STAT] software, Version [9.2] (SAS Institute Inc., Cary, NC, USA.) and (R Foundation for Statistical Computing, Vienna, Austria).

Table 2. Etiologies and exacerbation factors of all acute heart failure patients based on pulse pressure median value.

	Total, 2609	PP ≤ 50, 1360 (52.1%)	PP > 50, 1249 (47.9%)	P-value
Heart failure etiology				
Ischemic heart disease, n (%)	1454 (55.7)	779 (57.3)	675 (54.0)	<0.001
Idiopathic dilated cardiomyopathy, n (%)	431 (16.5)	295 (21.7)	136 (10.9)	
Hypertensive heart disease, n (%)	307 (11.8)	52 (3.8)	255 (20.4)	
Primary valvular heart disease, n (%)	202 (7.7)	116 (8.5)	86 (6.9)	
Other etiologies, n (%)	215 (8.3)	118 (8.7)	97 (7.8)	
Decompensated heart failure exacerbation factors				
ST elevation myocardial infarction, n (%)	276 (10.6)	164 (12.1)	112 (9.0)	0.010
Non-ST elevation acute coronary syndromes, n (%)	711 (27.3)	355 (26.1)	356 (28.5)	0.169
Dietary noncompliance, n (%)	659 (25.3)	387 (28.5)	272 (21.8)	<0.001
Noncompliance to HF medications, n (%)	549 (21.0)	323 (23.8)	226 (18.1)	<0.001
Infections, n (%)	537 (20.6)	271 (19.9)	266 (21.3)	0.387
Uncontrolled hypertension, n (%)	516 (19.8)	77 (5.7)	439 (35.2)	<0.001
Worsening renal failure, n (%)	457 (17.5)	234 (17.2)	223 (17.9)	0.663
Arrhythmia, n (%)	284 (10.9)	165 (12.1)	119 (9.5)	0.033
Lung disease exacerbation, n (%)	101 (3.9)	37 (2.7)	64 (5.1)	0.001

Table 3. Clinical presentation and investigations of all acute heart failure patients based on pulse pressure median value.

	Total, 2609	PP ≤ 50, 1360 (52.1%)	PP > 50, 1249 (47.9%)	P-value
Hemodynamic parameters				
Systolic blood pressure, mean ± SD	128.7 ± 31.3	108.9 ± 18.0	150.2 ± 28.5	<0.001
Diastolic blood pressure, mean ± SD	74.1 ± 17.9	70.5 ± 15.6	78.0 ± 19.3	<0.001
Heart rate, mean ± SD	88.8 ± 21.0	89.4 ± 20.8	88.2 ± 21.2	0.134
Electrocardiography				
Wide QRS duration, n (%)	389 (15.0)	225 (16.6)	164 (13.1)	0.013
Left bundle branch block, n (%)	305 (11.7)	150 (11.0)	155 (12.4)	0.273
Left ventricular systolic function				
Normal (≥50%), n (%)	341 (13.7)	91 (6.9)	250 (21.2)	<0.001
Mild (40−49%), n (%)	334 (13.4)	117 (8.9)	217 (18.4)	
Moderate (30−39%), n (%)	632 (25.3)	320 (24.3)	312 (26.5)	
Severe (<30%), n (%)	1187 (47.6)	788 (59.9)	399 (33.9)	
Coronary angiogram (n = 749)				
Single vessel disease, n (%)	105 (13.7)	55 (12.7)	50 (15.2)	0.324
Double vessel disease, n (%)	116 (15.2)	55 (12.7)	61 (18.5)	0.027
Left main or triple vessel disease, n (%)	263 (34.4)	146 (33.6)	117 (35.5)	0.601
Nonsignificant coronary artery disease, n (%)	82 (10.7)	45 (10.4)	37 (11.2)	0.709
Normal, n (%)	183 (24.0)	123 (28.3)	60 (18.2)	0.001

3. Results

3.1. Baseline Demographics

Generally, patients with low PP were younger and had greater male predominance. Further, they were more likely to have a previous history of HF, and less likely to be diabetic, hypertensive, or dyslipidemic. On the other hand, the high PP patients had higher rates of previous atherosclerotic events, anemia, chronic renal insufficiency, and chronic lung diseases (P < 0.05 for all comparisons) (Table 1). Patients with elevated PP had a significantly higher prevalence of hypertensive cardiomyopathy and lower rates of idiopathic dilated cardiomyopathy (P < 0.001 for group comparison). Uncontrolled hypertension was the main exacerbating factor for AHF in the high PP group, while medication and dietary noncompliance were higher in the opposing group (P < 0.001 for all comparisons) (Table 2). The high PP group had higher average SBP and DBP values (150.2 vs. 108.9 mmHg; P < 0.001, and 78.0 vs. 70.5 mmHg; P < 0.001, respectively) and lower rates of severely reduced EF (P < 0.001 for group comparison). Among patients undergoing coronary angiogram in the same admission (n = 749), normal studies were more often reported in the low PP group (P = 0.001) (Table 3). Fig. 1 demonstrates all differences in medication use between the groups. There was a trend of higher use of statins and lower use of aldosterone antagonists in the high PP group on admission and at discharge (P < 0.01 for all comparisons). In addition, the requirement of inotropic support with dobutamine and dopamine was greater in patients with low PP, while the need for nitroglycerin infusions was higher in the other group (P < 0.001 for all comparisons).

3.2. Primary Endpoints

In crude analysis, patients having low PP experienced higher rates of hospital recurrence of HF, shock state, and ventricular arrhythmias (P < 0.001 for all comparisons), as well as higher requirements for intra-aortic balloon pumps, implantable cardioverter defibrillators, and cardiac resynchronization therapy (P < 0.05 for all comparisons). Furthermore, they had higher rates of hospital and thirty-day mortality (7.9 vs. 5.0%; P = 0.004, and 9.6 vs. 6.6%; P = 0.005, respectively), but not after one, two, or three years (Table 4). In univariate regression analysis, low PP was associated with greater short-term mortality in the overall population, and short-term and two-year mortality in HFrEF. Furthermore, initial multivariate analyses revealed PP was predictive of both short- and long-term mortality in the overall population and HFrEF, but not HFpEF. However, the stepwise introduction of SBP, but not DBP, to adjustment models eliminated this mortality association, but showed an independent inverse correlation with long-term mortality in HFpEF only (OR = 0.43; 95% CI 0.24, 0.78; P = 0.005 and OR = 0.49; 95% CI 0.28, 0.88; P = 0.016 for two- and three-year mortality, respectively) (Table 5 and Fig. 2). Of note, a subgroup analysis on HFpEF patients only showed higher rates of diabetes mellitus, hypertension, dyslipidemia, and chronic renal insufficiency in the high PP group (P < 0.001 for all comparisons) (See online supplementary material, Table S1).

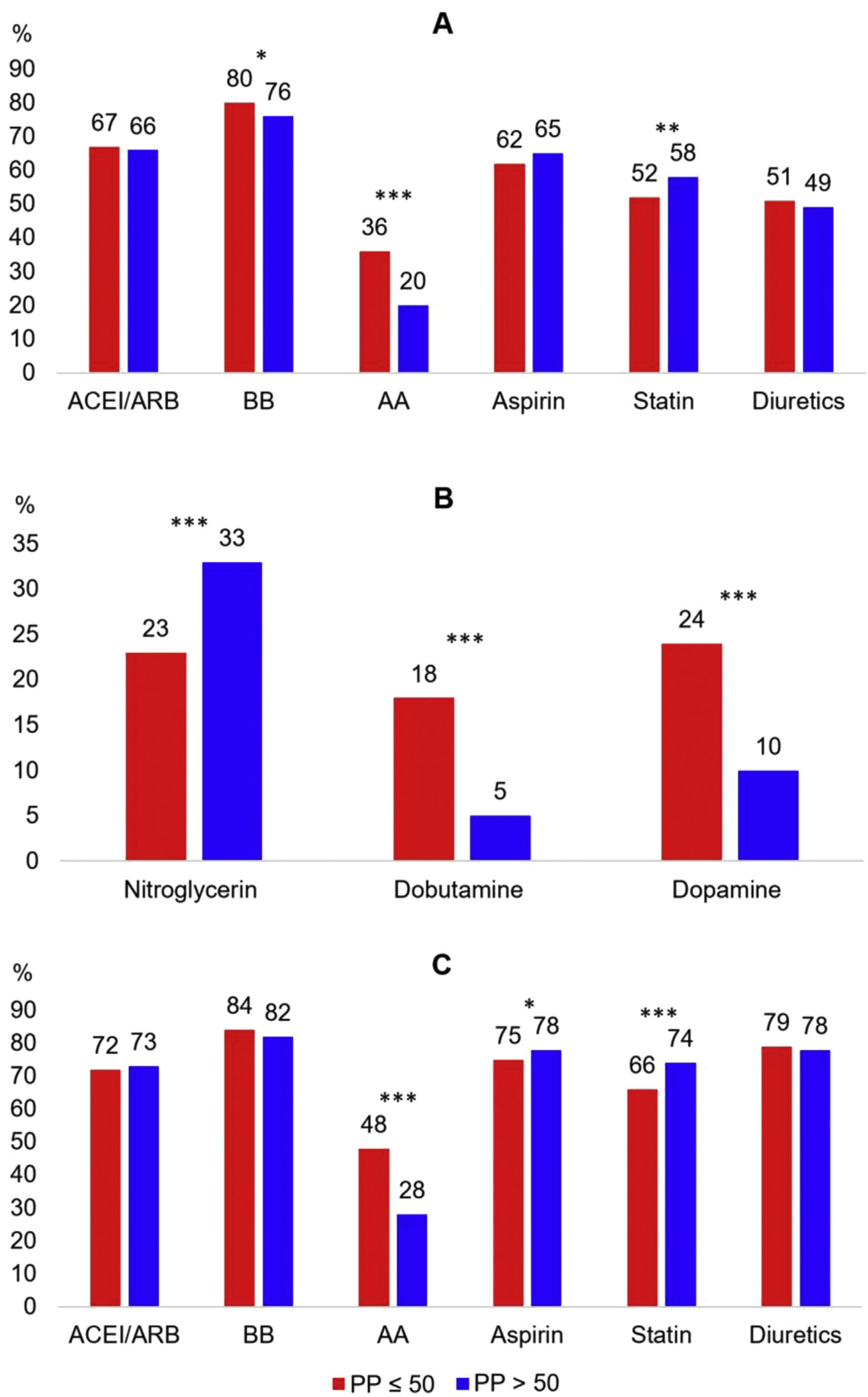

Fig. 1. Differences in evidence-based medical therapies used before admission (A), during hospital stay (B), and at discharge (C) based on pulse pressure median value. ***Abbreviations:*** *AA: aldosterone antagonists, ACEI: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blockers, BB: β-blockers, PP: pulse pressure. * P-value < 0.05. ** P-value < 0.01. *** P-value < 0.001.*

Table 4. Adverse hospital events and short- and long-term mortality rates of all acute heart failure patients based on pulse pressure median value.

	Total, 2609	PP ≤ 50, 1360 (52.1%)	PP > 50, 1249 (47.9%)	P-value
Hospital complications				
Recurrent heart failure, n (%)	816 (31.3)	493 (35.4)	323 (26.5)	<0.001
Sepsis, n (%)	196 (7.5)	109 (7.8)	87 (7.1)	0.503
Shock, n (%)	228 (8.7)	152 (10.9)	76 (6.2)	<0.001
Ventricular arrhythmias, n (%)	110 (4.2)	86 (6.2)	24 (2.0)	<0.001
Atrial fibrillation requiring therapy, n (%)	156 (6.0)	93 (6.7)	63 (5.2)	0.104
Major bleeding, n (%)	38 (1.5)	21 (1.5)	17 (1.4)	0.808
Transient ischemic attack/stroke, n (%)	48 (1.8)	29 (2.1)	19 (1.6)	0.320
Hospital procedures				
Dialysis, n (%)	125 (4.8)	69 (5.0)	56 (4.6)	0.665
Ventilation, n (%)	289 (11.1)	161 (11.6)	128 (10.5)	0.387
Intra-aortic balloon pumps, n (%)	86 (3.3)	66 (4.7)	20 (1.6)	<0.001
Pacing, n (%)	36 (1.4)	23 (1.6)	13 (1.1)	0.200
Hospital implantable cardioverter defibrillator, n (%)	150 (5.8)	110 (7.9)	40 (3.3)	<0.001
Hospital cardiac resynchronization therapy, n (%)	68 (2.6)	45 (3.2)	23 (1.9)	0.031
All-cause mortality				
Hospital mortality	170 (6.5)	107 (7.9)	63 (5.0)	0.004
Thirty-day mortality	212 (8.1)	130 (9.6)	82 (6.6)	0.005
One-year mortality	509 (19.5)	279 (20.5)	230 (18.4)	0.177
Two-year mortality	615 (23.6)	335 (24.7)	280 (22.4)	0.183
Three-year mortality	635 (24.4)	343 (25.2)	292 (23.4)	0.274

4. Discussion

In this report, we examined the prognostic value of PP in patients admitted with AHF. PP, when measured peripherally via conventional BP measurement devices on hospital arrival, was not an independent predictor of mortality in our overall population. However, the relationship between PP and HF outcomes represents a complex interaction between several factors, such as the HF phenotype, original BP components, and coexistent comorbidities. Our data showed that the predictive value of low PP for mortality in HFrEF was dependent on SBP, while long-term mortality rates correlated independently with elevated baseline PP in HFpEF.

PP was examined in multiple heterogeneous HF populations with various conclusions (Table 6). Low PP in chronic symptomatic HFrEF was consistently shown to correlate with decreased long-term survival [8–14]. Nonetheless, there was a reverse pattern seen in asymptomatic HF patients, as reported by the

Table 5. Crude and adjusted odds ratio and 95% confidence interval for mortality in acute heart failure based on pulse pressure median value (50 mmHg).

	Crude OR (95% CI)	P-value	Adjusted OR (95% CI) [a]	P-value	Adjusted OR (95% CI) [b]	P-value
Overall						
Hospital mortality	1.61 (1.17, 2.22)	0.004	1.86 (1.29, 2.67)	0.001	0.86 (0.54, 1.37)	0.515
Thirty-day mortality	1.51 (1.13, 2.01)	0.005	1.83 (1.32, 2.54)	<0.001	1.03 (0.68, 1.56)	0.908
One-year mortality	1.14 (0.94, 1.39)	0.177	1.46 (1.17, 1.83)	0.001	0.96 (0.72, 1.28)	0.783
Two-year mortality	1.13 (0.94, 1.36)	0.184	1.44 (1.17, 1.78)	0.001	0.96 (0.73, 1.26)	0.772
Three-year mortality	1.11 (0.92, 1.32)	0.274	1.42 (1.15, 1.75)	0.001	0.98 (0.75, 1.28)	0.854
Ejection fraction < 40%, N = 1819						
Hospital mortality	1.81 (1.19, 2.74)	0.005	2.06 (1.33, 3.19)	0.001	1.13 (0.65, 1.95)	0.675
Thirty-day mortality	1.69 (1.17, 2.45)	0.006	1.93 (1.31, 2.84)	0.001	1.33 (0.82, 2.16)	0.251
One-year mortality	1.26 (0.98, 1.60)	0.067	1.51 (1.16, 1.97)	0.002	1.11 (0.80, 1.56)	0.531
Two-year mortality	1.29 (1.02, 1.61)	0.030	1.62 (1.26, 2.08)	<0.001	1.19 (0.87, 1.63)	0.281
Three-year mortality	1.24 (0.99, 1.55)	0.057	1.59 (1.24, 2.03)	<0.001	1.16 (0.85, 1.58)	0.353
Ejection fraction > 40%, N = 675						
Hospital mortality	1.28 (0.65, 2.51)	0.480	1.61 (0.76, 3.41)	0.212	0.44 (0.16, 1.16)	0.095
Thirty-day mortality	1.18 (0.63, 2.20)	0.613	1.59 (0.79, 3.20)	0.191	0.49 (0.20, 1.20)	0.119
One-year mortality	0.84 (0.55, 1.30)	0.445	1.06 (0.64, 1.76)	0.829	0.55 (0.29, 1.02)	0.058
Two-year mortality	0.70 (0.46, 1.05)	0.087	0.81 (0.50, 1.31)	0.388	0.43 (0.24, 0.78)	0.005
Three-year mortality	0.69 (0.46, 1.03)	0.072	0.82 (0.51, 1.32)	0.414	0.49 (0.28, 0.88)	0.016

[a] Adjusted for age, gender, body mass index, diabetes mellitus, smoking, hypertension, dyslipidemia, history of heart failure, anemia, heart failure etiology, heart rate, and estimated glomerular filtration rate.

[b] Adjusted for age, gender, body mass index, diabetes mellitus, smoking, hypertension, dyslipidemia, history of heart failure, anemia, heart failure etiology, heart rate, estimated glomerular filtration rate, and systolic blood pressure.

Table 6. Comparison of populations and outcomes between all studies examining pulse pressure in heart failure.

#	Author	Study name	N	Population	Follow-up	EF	Conclusions	Notes
1	Aljohar, 2020	HEARTS	2609	Acute HF	36 months	All	**HFrEF:** Low PP showed trend towards short-term mortality. **HFpEF:** High PP associated with long-term mortality.	–
2	Laskey, 2016[9]	GWTG-HF	40,421	Acute HF	12 months	All	**HFrEF:** Low and high PP both associated with mortality; nadir of 50 mmHg. **HFpEF:** High PP associated with mortality if SBP >140 mmHg.	PP obtained at discharge.
3	Jackson, 2015[8]	MAGGIC	25,465	Acute and chronic HF	36 months	All	**HFrEF:** Low PP (<53 mmHg) associated with mortality. **HFpEF:** No association between mortality and PP.	Subgroup analysis (acute vs. chronic) showed no interaction.
4	Teng, 2018[11]	SwedeHF	36,770	Acute and chronic HF	12 months	All	**HFrEF:** Low PP (<40 mmHg) associated with mortality. **HFmrEF:** Trend towards higher mortality with PP > 70 mmHg. **HFpEF:** Low PP associated with mortality & trend towards higher mortality with PP > 75 mmHg.	In-hospital deaths excluded.
5	Voors, 2005[12]	PRIME	1901	Chronic symptomatic HFrEF	11 months	<35%	Low PP (<45 mmHg) associated with mortality.	–
6	Petrie, 2012[13]	CAPRICORN	1955	EF < 40% post-ACS	15 months	<40%	Low PP associated with mortality in Killip II-IV (17% increase in mortality for every 10-mmHg incremental decrease).	Comparison based on Killip classification.
7	Regnault, 2014[14]	EPHESUS	6613	EF < 40% post-ACS	16 months	<40%	Low PP associated with mortality (5% increase in mortality for every 5-mmHg incremental decrease).	PP impacted on mortality more than SBP and MAP.
8	Mitchell, 1997[16]	SAVE	2231	Asymptomatic HFrEF post-ACS	42 months	<40%	High PP associated with mortality (8% increase in mortality for every 10-mmHg incremental increase).	–
9	Domanski, 1999[15]	SOLVD	6781	Chronic HFrEF; 60% asymptomatic	40 months	<35%	High PP associated with mortality (5% increase in mortality for every 10-mmHg incremental increase).	Decreased MAP impacted more on poor outcomes.
10	Aronson, 2004[17]	VMAC	489	Acute HF	6 months	<35%	Low PP (<43 mmHg) associated with mortality.	SBP <90 mmHg excluded.

Abbreviations: ACS: acute coronary syndromes, CAPRICORN: Carvedilol Post Infarct Survival Control in LV Dysfunction, EPHESUS: Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, GWTG-HF: Get with the Guidelines-Heart Failure program, HEARTS: Heart Function Assessment Registry Trial in Saudi Arabia, HF: heart failure, HFmrEF: heart failure with mid-range ejection fraction, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction, MAGGIC: Meta-Analysis Global Group in Chronic Heart Failure, MAP: mean arterial pressure, PP: pulse pressure, PRIME: Prospective Randomized study of Ibopamine on Mortality and Efficacy, SAVE: Survival and Ventricular Enlargement study, SBP: systolic blood pressure, SOLVD: Study of Left Ventricular Dysfunction, SwedeHF: The Swedish Heart Failure Registry, VMAC: Vasodilation in the Management of Acute Congestive study.

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SOLVD (Study of Left Ventricular Dysfunction) [15] and SAVE (Survival and Ventricular Enlargement) [16] investigators. The exact explanation for these discrepant observations is not clear, although the presence of symptoms may be an indicator of an advanced state of HF with low cardiac output and hence lower PP. Few studies have looked into the association between PP and long-term outcomes in patients hospitalized for AHF and reported findings in line with the pattern seen with chronic symptomatic HFrEF [8],[9],[11],[17]. To the best of our knowledge, this is the first report to comment on *admission* PP and its correlation with *hospital* mortality. Our regression models revealed the predictive power of PP in HFrEF was not totally independent from original BP components, specifically SBP. The discrepancies between our study and others is likely due to several factors. Our patient population has a different ethnic background and has a younger mean age. Additionally, there were methodological differences that render our cohort incomparable, such as measuring PP at discharge [9], excluding in-hospital deaths [11], and using different PP cutoffs. Finally, the overall heterogeneity in HF syndromes may have also contributed to these differences.

Physiologically, PP is thought to be a measure of both stroke volume and vascular stiffness. In early systole, the ejected blood from the LV travels across the arterial tree from large and elastic to narrow and muscular vessels. This is followed by a reflected wave against the LV during late systole, mandating extra force generation (referred to as augmentation pressure) [21]. In advanced HF, the LV fails to exert this extra pressure, explaining why low PP correlates with poor outcomes in ambulatory HFrEF. Notwithstanding, the rapid disturbance of hemodynamics in a decompensated state and the emergent use of vasoactive and inotropic agents may have diminished the prognostic impact of PP. Nonetheless, we speculate it may have independently predicted hospital mortality, had values lower than 50 mmHg been tested in patients with worse LV dysfunction.

We observed greater long-term mortality rates in patients with HFpEF and elevated baseline PP, in agreement with others [9]. Our subgroup analysis of HFpEF patients showed that higher PP was significantly associated with hypertension, diabetes mellitus, dyslipidemia, and chronic renal insufficiency, all of which are known to be associated with accelerated atherosclerosis and worse outcomes. Arteriosclerosis plays an important role in the pathophysiology and prognosis of HF. In one HF trial, a subgroup of patients underwent measurements of pulse wave velocity, a direct indicator of vascular stiffness, with elevated readings at baseline

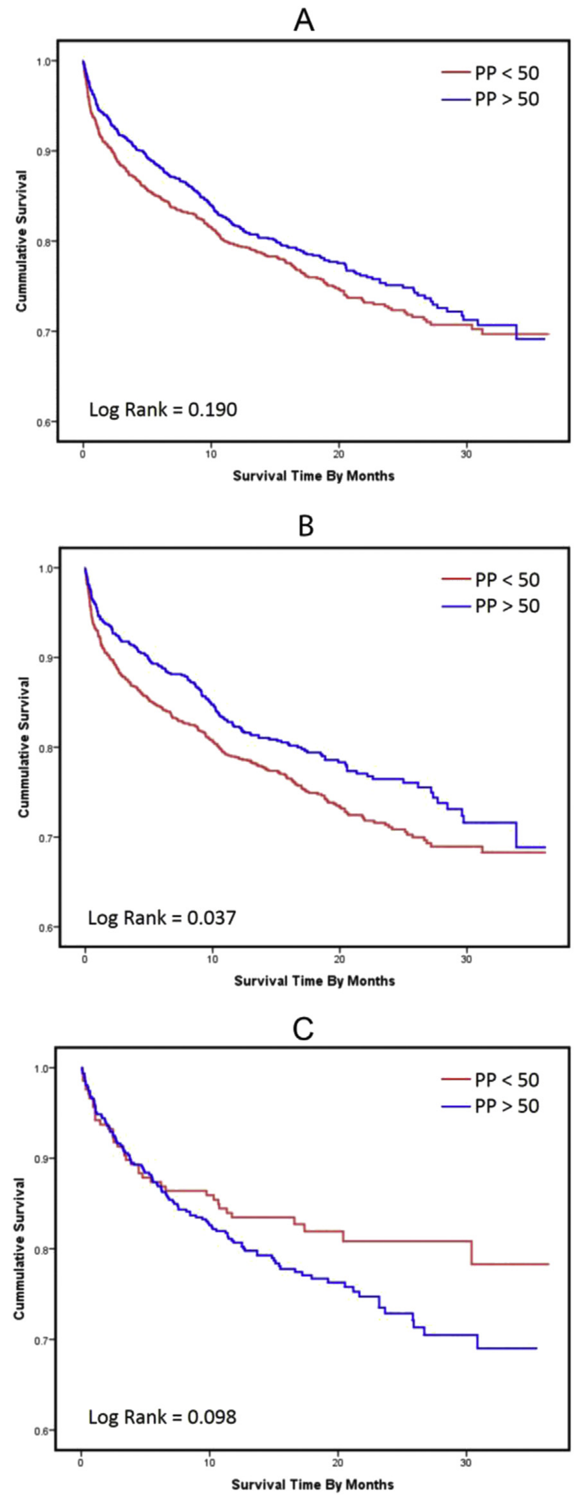

Fig. 2. Kaplan-Meier plot for all-cause mortality in all acute heart failure patients (A), heart failure with reduced ejection fraction (B), and heart failure with preserved ejection fraction (C) based on pulse pressure median value. ***Abbreviations:*** *PP: pulse pressure.*

predicting decreased survival during prolonged follow-up [14]. Nonetheless, it is worthwhile to explore other potential confounders in future research, which may have an influence on HF circulatory hemodynamics, such as advanced age [22], heart rate [23], LV end-diastolic volume and mass [24],[25], and anti-HF medications [26].

Central BP is the actual pressure exerted against the LV and the true determinant of renal and brain perfusion [27]. Hence, its predictability for future risk of major adverse cardiac events and end-organ damage is more accurate [24],[28]. How reliable estimating central PP from peripheral arteries is debatable [29]. The elasticity of peripheral vessels is relatively reduced [30]. PP amplification is a compensatory mechanism that exaggerates the forward flow of blood through these narrower lumens and may overestimate the actual central PP [21]. However, this difference diminishes with aging, as the aorta and its great branches gradually lose elasticity [31],[32]. Several commercial devices noninvasively measure central PP, but they lack standardization, providing ineffective alternatives to invasive methods.

Our study suffers from several limitations. Our classification of HF was based on the guidelines published during the enrollment period, which did not include the newly-defined HF with mid-range EF as a discrete entity. There was no predefined standard method of BP measurement during enrollment of the study cohort. Although this may generate inaccurate conclusions, it reflects 'real-life' practice and eases the generalizability of our findings. We did not record readmission rates and actual cause of death during the follow-up period, which are considered standard primary endpoints in large-scale registries in cardiovascular medicine. Our sample size, although large and representative, was not enough to study PP in quartiles or quintiles, or within different strata of SBP ranges.

5. Conclusion

PP is a noninvasive and inexpensive tool that is readily available. In this study, it did not independently correlate with morbidity and mortality in the overall AHF population. However, its prognostic value in this domain seems to be a function of phenotype. Whereas its predictive value in HFrEF was dependent on SBP, elevated baseline PP independently correlated with decreased long-term survival in HFpEF.

Author Contribution Statement

Aljohar: Conception, Design, Supervision, Analysis and/or interpretation, Literature review, Writer, Critical review; **Alhabib**: Conception, Design, Supervision, Materials, Data collection and/or processing, Analysis and/or interpretation, Critical review; **Alfaleh**: Conception, Design, Supervision, Materials, Data collection and/or processing, Analysis and/or interpretation, Critical review; **Hersi**: Conception, Design, Supervision, Materials, Data collection and/or processing, Analysis and/or interpretation, Critical review; **Al Habeeb**: Conception, Materials, Data collection and/or processing, Critical review; **Elasfar**: Conception, Materials, Data collection and/or processing, Critical review; **Almasood**: Conception, Materials, Data collection and/or processing, Critical review; **Ghabashi**: Conception, Materials, Data collection and/or processing, Critical review; **Mimish**: Conception, Materials, Data collection and/or processing, Critical review; **Alghamdi**: Conception, Materials, Data collection and/or processing, Critical review; **Abuosa**: Conception, Materials, Data collection and/or processing, Critical review; **Malik**: Conception, Materials, Data collection and/or processing, Critical review; **Hussein**: Conception, Materials, Data collection and/or processing, Critical review; **Al-Murayeh**: Materials, Conception, Data collection and/or processing, Critical review; **Kashour**: Conception, Design, Supervision, Materials, Data collection and/or processing, Analysis and/or interpretation, Literature review, wRiter, Critical review; **Ullah**: Design, Analysis and/or interpretation, Critical review.

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Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Supplementary Material

Table S1. Baseline characteristics of heart failure with preserved ejection fraction patients based on pulse pressure median value.

	Total, 675 (25.8%)	PP ≤ 50, 467 (69.2%)	PP > 50, 208 (30.8%)	P-value
Age, mean ± SD	64.3 ± 13.9	61.9 ± 16.7	65.4 ± 12.3	0.007
Male, n (%)	323 (47.9)	102 (49.0)	221 (47.3)	0.680
Body mass index, mean ± SD	31.5 ± 8.3	29.8 ± 7.3	32.2 ± 8.6	<0.001
Diabetes mellitus, n (%)	457 (67.8)	106 (51.2)	351 (75.2)	<0.001
Smoker/Ex-smoker, n (%)	153 (22.7)	54 (26.0)	99 (21.2)	0.172
Hypertension, n (%)	527 (78.3)	127 (61.4)	400 (85.8)	<0.001
Dyslipidemia, n (%)	273 (43.7)	61 (32.8)	211 (48.4)	<0.001
Heart failure, n (%)	389 (58.0)	115 (55.6)	274 (59.1)	0.397
Ischemic heart disease, n (%)	312 (46.6)	83 (40.3)	229 (49.5)	0.028
Anemia, n (%)	350 (52.2)	93 (45.1)	257 (55.4)	0.014
Chronic renal insufficiency, n (%)	208 (30.9)	45 (21.6)	163 (35.0)	0.001
Chronic lung disease, n (%)	71 (10.6)	16 (7.8)	55 (11.9)	0.111

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