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RESEARCH ARTICLE

Organ perfusion pressure predicts outcomes in cardiogenic shock patients

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Aims The diagnosis of cardiogenic shock (CS) relies upon signs and/or symptoms of end-organ hypoperfusion. The combination of hypoperfusion and systemic congestion identifies patients at particularly high risk. This study evaluated organ perfusion pressure (OPP), calculated as mean arterial pressure minus invasive central venous pressure, as a predictor of outcomes in CS.

Methods and results All consecutive patients with acute myocardial infarction-related CS (AMI-CS) or acutely decompensated heart failure-related CS (ADHF-CS) enrolled in the multicentre Altshock-2 registry between January 2020 and November 2023 were included. The primary outcome was in-hospital all-cause mortality. Overall, 316 patients were included (mean age: 64 ± 13 years, 62 [20%] female, median left ventricular ejection fraction: 22% [interquartile range, IQR 15–30%], 261 [85.9%] SCAI stage C or worse, median OPP at presentation: 57.0 mmHg [IQR 47.0–69.8 mmHg]). A total of 117 (37%) patients died during the hospitalization. Low OPP (i.e. <57.0 mmHg) was associated with significantly higher in-hospital all-cause mortality (hazard ratio [HR] 1.757, 95% confidence interval [CI] 1.208–2.556, $p = 0.003$), whereas low mean arterial pressure alone was not (HR 1.323, 95% CI 0.901–1.941, $p = 0.153$). After multivariable adjustment for significant clinical data available at first bedside assessment (age and Sequential Organ Failure Assessment score), low OPP still predicted significantly higher in-hospital all-cause mortality (HR per mmHg decrease: 1.016, 95% CI 1.004–1.029, $p = 0.010$). Low OPP appeared particularly powerful in predicting higher in-hospital all-cause mortality among ADHF-CS patients (HR 3.172, $p = 0.002$).

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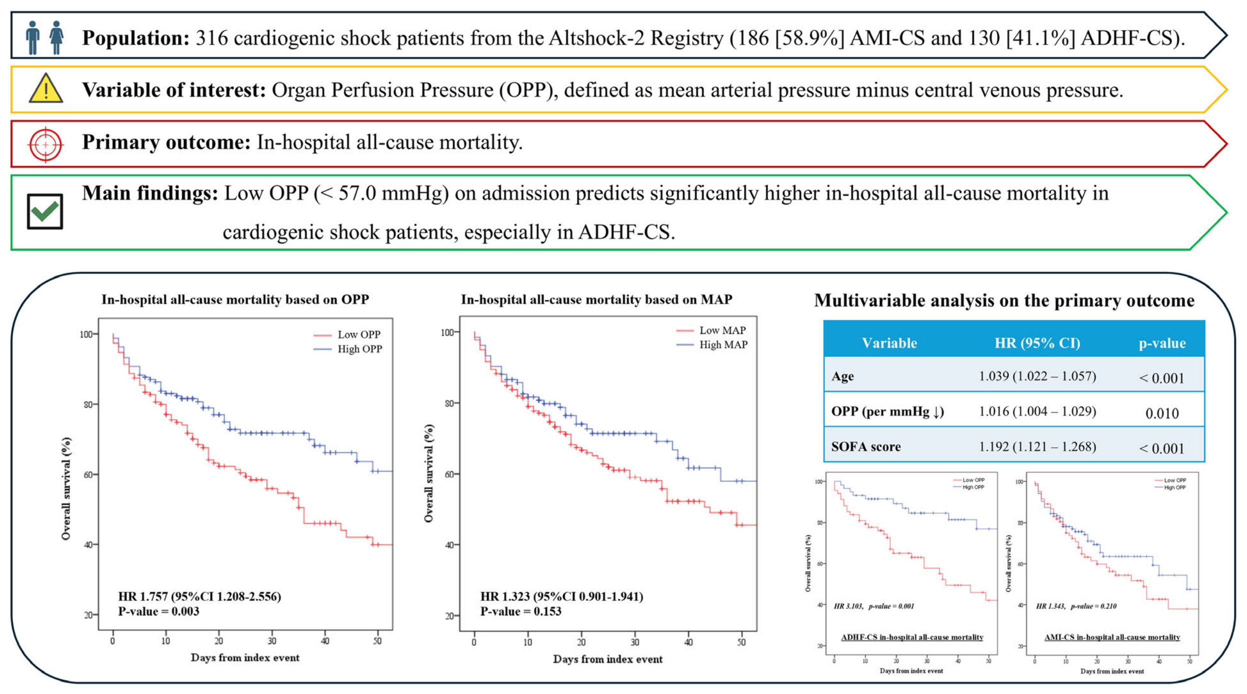
Conclusion In this multicentre, observational, prospective study on patients hospitalized for CS, lower OPP on admission was associated with significantly higher in-hospital all-cause mortality.

Graphical Abstract



Population: 316 cardiogenic shock patients from the Altshock-2 Registry (186 [58.9%] AMI-CS and 130 [41.1%] ADHF-CS).

Variable of interest: Organ Perfusion Pressure (OPP), defined as mean arterial pressure minus central venous pressure.

Primary outcome: In-hospital all-cause mortality.

Main findings: Low OPP (< 57.0 mmHg) on admission predicts significantly higher in-hospital all-cause mortality in cardiogenic shock patients, especially in ADHF-CS.

Multivariable analysis on the primary outcome

Variable	HR (95% CI)	p-value
Age	1.039 (1.022 – 1.057)	< 0.001
OPP (per mmHg ↓)	1.016 (1.004 – 1.029)	0.010
SOFA score	1.192 (1.121 – 1.268)	< 0.001

Organ perfusion pressure as a predictor of outcomes in cardiogenic shock: insights from the Altshock-2 registry. ADHF-CS, acutely decompensated heart failure-related cardiogenic shock; AMI-CS, acute myocardial infarction-related cardiogenic shock; CI, confidence interval; HR, hazard ratio; MAP, mean arterial pressure; OPP, organ perfusion pressure; SOFA, Sequential Organ Failure Assessment.

Keywords Organ perfusion pressure • Acute heart failure • Blood pressure • Central venous pressure • Cardiogenic shock

Introduction

Cardiogenic shock (CS) is characterized by end-organ hypoperfusion due to insufficient cardiac output, resulting in a life-threatening scenario.[1] Despite improvements in CS diagnosis and management, its prognosis is still ominous, with a 30% to 50% short-term mortality rate.[2] Hypotension refractory to volume resuscitation with features of end-organ hypoperfusion is a hallmark of CS diagnosis[1]; however, hypotension alone offers an inadequate gauge of peripheral perfusion, as the intricate interplay between anterograde cardiac output and systemic congestion more faithfully reflects end-organ perfusion status.[3] Indeed, the co-occurrence of hypoperfusion and systemic congestion, leading to kidney, liver, and gut impairment, was demonstrated to be associated with a worse prognosis in acute heart failure.[3,4] Organ perfusion pressure (OPP) combines measures associated with blood flow and volume load and was shown to predict patient outcomes in various clinical settings; however, its role in CS has not been explored.[5,6] The aim of this study was to investigate whether OPP can serve as a new accurate risk marker for CS patients.

Methods

This study was conducted on the Altshock-2 registry population. Details on the Altshock-2 registry have been previously described (www.ClinicalTrials.gov registration number: NCT04295252).[7,8] Briefly, this was a multicentre prospective, observational registry enrolling consecutive patients admitted for CS from 11 Italian centres since March 2020 (online supplementary *Appendix S1*). CS was diagnosed at each enrolling site according to the most recent definitions and all patients were stratified according to Society for Cardiovascular Angiography and Interventions (SCAI) stages.[2,9]

Only patients with acute myocardial infarction-related CS (AMI-CS) or acutely decompensated heart failure-related CS (ADHF-CS) enrolled until November 2023 were considered for the present analysis. Specifically, AMI-CS was defined as CS complicating an acute coronary syndrome, namely non-ST-elevation myocardial infarction or ST-elevation myocardial infarction. ADHF-CS was defined as CS due to acute decompensation of heart failure in a patient with or without (de novo) prior chronic heart failure.[7]

Organ perfusion pressure was calculated by subtracting central venous pressure (CVP) from mean arterial pressure (MAP). Blood pressure was measured through an arterial line, and CVP was obtained using a central venous catheter positioned at the junction of the superior cava vein with the right atrium, confirmed by X-ray. MAP and CVP were measured simultaneously to ensure accuracy; only patients with complete data on both assessments were included in the analysis.

The primary endpoint was to evaluate the prognostic performance of OPP in predicting in-hospital all-cause mortality; patients without data on the primary endpoint were excluded from the analysis. The secondary endpoint was all-cause mortality at longest follow-up.

All included patients' clinical, laboratory, haemodynamic, medication and device data, along with follow-up information, were collected electronically via the RedCap® platform. Written informed consent was obtained from all competent patients; for patients who lacked the capacity to consent due to their medical condition upon admission, a waiver was granted by the Ethics Committee. The study was conducted in accordance with ethical principles based on the Declaration of Helsinki, International Conference on Harmonization for Good Clinical Practice, and the current ethical rules.

Statistical analysis

Continuous variables are reported as mean (standard deviation) or median (interquartile range [IQR]), as appropriate, while categorical variables are reported as numbers and percentages. The presence of normal distribution was verified by the Shapiro–Wilk test.

Univariable analysis to assess predictors of in-hospital all-cause mortality was performed. Comparisons between baseline characteristics of in-hospital survivors and deceased patients were performed by means of Student's *t*-test for parametric continuous variables, Mann–Whitney U test for non-parametric continuous variables, and chi-square test or Fisher's exact test for categorical variables, as appropriate. Survival curves were generated according to the Kaplan–Meier method,[10] and univariable survival distributions were compared with Cox regression analysis. Hazard ratios (HR) and 95% confidence intervals (CI) for multivariable models were computed with the use of Cox regression to test OPP against predictors of the primary outcome. Different multivariable models for the primary outcome were evaluated: Model 1 was built adjusting for significant ($p < 0.05$) clinical data available at first bedside assessment, namely age and Sequential Organ Failure Assessment (SOFA) score; Model 2 investigated OPP alongside age, SOFA score and CVP; Model 3 evaluated haemodynamic parameters available at initial bedside assessment, namely OPP, systolic blood pressure, MAP and CVP. Multicollinearity among the variables included in Models 2 and 3 was assessed by calculating the variance inflation factors. When significant collinearity with OPP was detected (i.e. variance inflating factor greater than five), only OPP was retained in the model (online supplementary *Tables S1* and *S2*).

The OPP value with the highest accuracy was elaborated by means of the receiver-operating curve (ROC) analysis, and it was defined as the value with the highest Youden's index, best optimizing specificity and sensitivity, to detect in-hospital all-cause death.

Univariable analyses to assess predictors of in-hospital all-cause mortality were run in individual AMI-CS and ADHF-CS subgroups, separately; Kaplan–Meier curves were generated, and survival distributions were compared with univariable Cox regression analysis according to OPP in each subgroup. Due to the higher OPP values in AMI-CS as compared to ADHF-CS, a separate survival analysis was run according to OPP being higher or lower than its median value of each group.

A forest plot was drawn to assess OPP effects on in-hospital mortality across subgroups and identify significant interactions between OPP and covariates, which were further assessed with multivariable logistic regression analysis.

To account for the narrower range of CVP values compared to those of MAP, the prognostic role of adjusted OPP (adj-OPP), calculated as 'adj-OPP = MAP – (CVP × 3)', was assessed. Also, the difference between OPP at 24 h after hospital admission and baseline OPP (i.e. delta-OPP) was calculated and its predictive yield was evaluated. To further explore the relative weight of the individual components of OPP (i.e. MAP and CVP) on predicting the study primary outcome, a sensitivity analysis was run by dividing the study population into four groups according to different combinations of high or low MAP and high or low CVP; MAP and CVP were labelled as high or low according to their measurement being above or below the median value of the study population, respectively. Kaplan–Meier curves and the log-rank test were used to compare the univariable survival distributions of the four groups.

To correct the multivariable analysis for the potential effect of positive pressure ventilation on OPP calculation and predictive capability, a multivariable Cox regression model was built including age, OPP, positive pressure ventilation and SOFA score.

The association between OPP and lactate values was assessed by means of linear regression analysis; also, a separate multivariable Cox regression model on the primary outcome was conducted including OPP and lactate levels as independent variables.

Also, a sensitivity analysis was conducted to compare the characteristics of patients with versus without right ventricular dysfunction (RVD), defined as tricuspid annular plane systolic excursion (TAPSE) <17 mmHg,[11] and the predictive role of OPP in each subgroup.

A two-sided *p*-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS 26.0 (SPSS, Chicago, IL, USA).

Results

Among the 725 patients included in the Altshock-2 registry, 409 individuals were excluded according to the study exclusion criteria; a total of 316 patients were included in the present study. Detailed characteristics of the study population are reported in *Table 1*. Overall, mean age was 64 ± 13 years; 62 (19.7%) patients were female; mean body mass index was 26.6 ± 8.0 kg/m^2; 186 (58.9%) patients had AMI-CS and 130 (41.1%) had ADHF-CS. On admission, 261 (85.9%) patients had SCAI stage C or worse CS with a median lactate level of 2.3 mmol/L (IQR 1.5–5.2 mmol/L); median MAP was 70 mmHg (IQR 60–80 mmHg), median CVP was 11 mmHg (IQR 8–15 mmHg), median OPP was 57 mmHg

Table 1 **Baseline characteristics of the study population**

Variables	**All patients (*n* = 316)**	**In-hospital all-cause death**		***p*-value**
		Yes (*n* = 117)	**No (*n* = 199)**	
Age, years	64 ± 13	68 ± 11	62 ± 13	**<0.001**
Female sex, *n* (%)	62 (19.7)	27 (23.1)	35 (17.7)	0.075
Weight, kg	77.5 ± 15.7	76.8 ± 15.1	77.9 ± 16.1	0.554
Height, m	1.71 ± 9.01	1.70 ± 0.08	1.72 ± 0.10	**0.012**
BMI, kg/m^2	26.6 ± 8.0	26.7 ± 5.1	26.5 ± 9.3	0.838
NYHA class I–II, *n* (%)	183 (68.1)	68 (69.4)	115 (67.3)	0.694
Heart transplant candidate, *n* (%)	14 (4.4)	7 (6.0)	7 (3.5)	0.308
Smoking habit, *n* (%)	80 (25.5)	23 (19.8)	57 (28.8)	0.079
Arterial hypertension, *n* (%)	163 (51.6)	68 (58.1)	95 (47.7)	0.075
Diabetes mellitus, *n* (%)	108 (34.2)	46 (39.3)	62 (31.2)	0.140
Dyslipidaemia, *n* (%)	132 (41.8)	56 (47.9)	76 (38.2)	0.092
Prior stroke/TIA, *n* (%)	23 (7.3)	15 (12.8)	8 (4.0)	**0.004**
Chronic kidney disease, *n* (%)	75 (23.7)	44 (37.6)	31 (15.7)	**<0.001**
Cancer history, *n* (%)	39 (12.4)	15 (12.8)	24 (12.1)	0.856
Prior PCI, *n* (%)	79 (25.1)	34 (29.1)	45 (22.7)	0.210
Prior CABG, *n* (%)	30 (9.5)	14 (12.0)	16 (8.0)	0.250
Atrial fibrillation, *n* (%)	74 (23.6)	34 (29.1)	40 (20.3)	0.077
ICD[a], *n* (%)	57 (18.1)	20 (17.1)	37 (18.7)	0.723
CRT-D, *n* (%)	26 (8.3)	12 (10.3)	14 (7.0)	0.303
CS aetiology, *n* (%)				
ACS-CS	186 (58.9)	74 (63.2)	112 (56.3)	0.224
ADHF-CS	130 (41.1)	43 (36.8)	87 (43.7)	
ACS-CS type, *n* (%)				
STEMI	137 (79.7)	51 (73.9)	86 (83.5)	0.126
NSTEMI	35 (20.3)	18 (26.1)	17 (16.5)	
ADHF-CS type, *n* (%)				
Advanced ADHF-CS	85 (75.9)	35 (92.1)	50 (67.6)	**0.004**
De novo ADHF-CS	27 (24.1)	3 (7.9)	24 (32.4)	
Cardiocirculatory arrest, *n* (%)	71 (23.9)	28 (25.2)	43 (23.1)	0.680
Positive pressure ventilation, *n* (%)	249 (78.8)	90 (76.9)	159 (80.7)	0.423
SOFA score	7.1 ± 3.2	8.3 ± 3.0	6.4 ± 3.1	**<0.001**
SCAI shock stage, *n* (%)				
Stage A	9 (3.0)	2 (1.8)	7 (3.7)	
Stage B	34 (11.2)	10 (8.8)	24 (12.6)	
Stage C	160 (52.6)	45 (39.5)	115 (60.5)	**<0.001**
Stage D	75 (24.7)	46 (40.4)	29 (15.3)	
Stage E	26 (8.6)	11 (9.6)	15 (7.9)	
Haemodynamics				
Systolic blood pressure, mmHg	98 ± 22	94 ± 19	100 ± 23	**0.024**
MAP, mmHg	70 (60–80)	67 (60–75)	70 (60–83)	**0.027**
Diastolic blood pressure, mmHg	57 ± 15	55 ± 15	59 ± 15	**0.043**
Heart rate, bpm	92 ± 22	91 ± 23	92 ± 22	0.618
CVP, mmHg	11 (8–15)	14 (10–16)	10 (7–15)	**0.001**
Central venous oxygen saturation, %	61 ± 14	59 ± 15	61 ± 14	0.391
OPP, mmHg	57 (47–70)	54 (44–65)	61 (48–72)	**0.002**
Adjusted OPP, mmHg	35 (18–52)	28 (14–42)	40 (24–53)	**<0.001**
Shock index, bpm/mmHg	1.14 ± 0.41	1.13 ± 0.44	1.15 ± 0.39	0.613
Proportional differential pressure, %	41 ± 11	42 ± 11	41 ± 11	0.603
Laboratory tests				
Haemoglobin, g/dl	12.7 ± 2.5	12.1 ± 2.6	13.0 ± 2.4	**0.003**
Creatinine, mg/dl	1.80 ± 1.47	2.20 ± 1.69	1.56 ± 1.26	**0.001**
Total bilirubin, mg/dl	1.18 ± 1.15	1.27 ± 1.19	1.13 ± 1.14	0.347
Alanine transaminase, IU/L	253 ± 546	334 ± 704	206 ± 426	0.136

Table 1 (Continued)

Variables	**All patients ($n = 316$)**	**In-hospital all-cause death**		**p-value**
		Yes ($n = 117$)	**No ($n = 199$)**	
Aspartate transaminase, IU/L	338 ± 628	419 ± 718	291 ± 568	0.135
High-sensitivity troponin T, ng/ml	10 530 ± 29 151	16 647 ± 40 087	6452 ± 17 843	0.103
NT-proBNP, pg/ml	8044 (IQR 3928–21 056)	15 343 (IQR 7953–34 450)	5660 (IQR 3070–13 556)	**<0.001**
Hs-CRP, mg/L	12 ± 28	15 ± 32	11 ± 25	0.174
pH	7.11 ± 0.32	7.12 ± 0.33	7.11 ± 0.31	0.687
Lactate, mmol/L	2.3 (1.5–5.2)	3.1 (1.9–6.6)	2.0 (1.4–4.3)	**<0.001**
Heart failure home medications, *n* (%)				
Furosemide	121 (38.7)	49 (42.2)	72 (36.5)	0.318
Beta-blocker	140 (44.6)	59 (50.9)	81 (40.9)	0.087
ACEi or ARB	79 (35.1)	30 (12.8)	49 (12.5)	0.601
Sacubitril/valsartan	45 (14.4)	12 (10.3)	33 (16.8)	0.115
SGLT2i	16 (16.5)	5 (13.9)	11 (18.0)	0.595
MRA	91 (29.1)	36 (30.8)	55 (28.1)	0.610
Ivabradine	12 (3.8)	3 (2.6)	9 (4.6)	0.362
Echocardiographic data				
LVEDD, mm	61 ± 23	58 ± 16	63 ± 25	0.150
LV ejection fraction, %	22 (15–30)	25 (15–35)	22 (15–30)	0.343
Average E/e’	17.2 ± 6.5	19.0 ± 6.2	15.8 ± 6.5	**0.023**
At least moderate-to-severe mitral regurgitation, *n* (%)	109 (41.5)	38 (38.8)	71 (43.0)	0.957
TAPSE, mm	15.4 ± 3.9	14.3 ± 3.5	16.1 ± 3.9	**0.002**
At least moderate-to-severe tricuspid regurgitation, *n* (%)	72 (28.7)	33 (34.7)	39 (25.0)	0.267
Estimated PASP, mmHg	46 ± 13	48 ± 13	45 ± 14	0.260

Values are given as *n* (%), mean ± standard deviation, or median (interquartile range).
Percentages are calculated from the known data only.
ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ADHF, acutely decompensated heart failure; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CRT-D, cardiac resynchronization therapy with defibrillator; CS, cardiogenic shock; CVP, central venous pressure; hs-CRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NSTEMI, non-ST-elevation myocardial infarction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OPP, organ perfusion pressure; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; SCAI, Society for Cardiovascular Angiography and Interventions; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SOFA, Sequential Organ Failure Assessment; STEMI, ST-elevation myocardial infarction; TAPSE, tricuspid annular plane systolic excursion; TIA, transient ischaemic attack.
[a] This category includes either an ICD or CRT-D.

(IQR 47–70 mmHg), and mean heart rate was 92 ± 22 bpm. On echocardiography, median left ventricular ejection fraction was 22% (IQR 15–30%), mean TAPSE was 15.4 ± 3.9 mm, and mean estimated pulmonary artery systolic pressure was 46 ± 13 mmHg. Further details on patients’ baseline characteristics are provided in online supplementary *Tables S3–S5*.

Primary outcome

The primary outcome of in-hospital all-cause death occurred in 117 (37%) individuals (*Table 1*). At univariable analysis, compared to in-hospital survivors, those experiencing in-hospital all-cause death were significantly older (68 ± 11 vs. 62 ± 13 years, $p < 0.001$) and showed significantly greater prevalence of chronic kidney disease (37.6% vs. 15.7%, $p < 0.001$) and higher SOFA score (8.3 ± 3.0 vs. 6.4 ± 3.1, $p < 0.001$); patients dying in-hospital had significantly lower MAP (67 mmHg [IQR 60–75 mmHg] vs. 70 mmHg [IQR 60–83 mmHg], $p = 0.027$) and OPP (54 mmHg [IQR 44–65 mmHg] vs. 61 mmHg [48–72 mmHg], $p = 0.002$) and significantly higher CVP (14 mmHg [IQR 10–16 mmHg] vs. 10 mmHg [IQR 7–15 mmHg], $p = 0.001$), lactates (3.1 mmol/L [IQR 1.9–6.6 mmol/L] vs. 2.0 mmol/L [1.4–4.3 mmol/L], $p < 0.001$), creatinine ($p = 0.001$) and N-terminal pro-B-type natriuretic peptide ($p < 0.001$) on admission compared to in-hospital survivors. Non-survivors received more frequently dobutamine ($p < 0.001$), adrenaline ($p = 0.001$) or noradrenaline ($p < 0.001$), and less frequently levosimendan ($p = 0.003$) and sodium nitroprusside ($p < 0.001$) (online supplementary *Table S4*).

At univariable Cox regression analysis, low OPP (i.e. <57.0 mmHg) on admission was associated with significantly higher in-hospital all-cause mortality (HR 1.757, 95% CI 1.208–2.556, $p = 0.003$), whereas low MAP (i.e. <70 mmHg) was not associated with the primary outcome (HR 1.323, 95% CI 0.901–1.941, $p = 0.153$) (*Figure 1*).

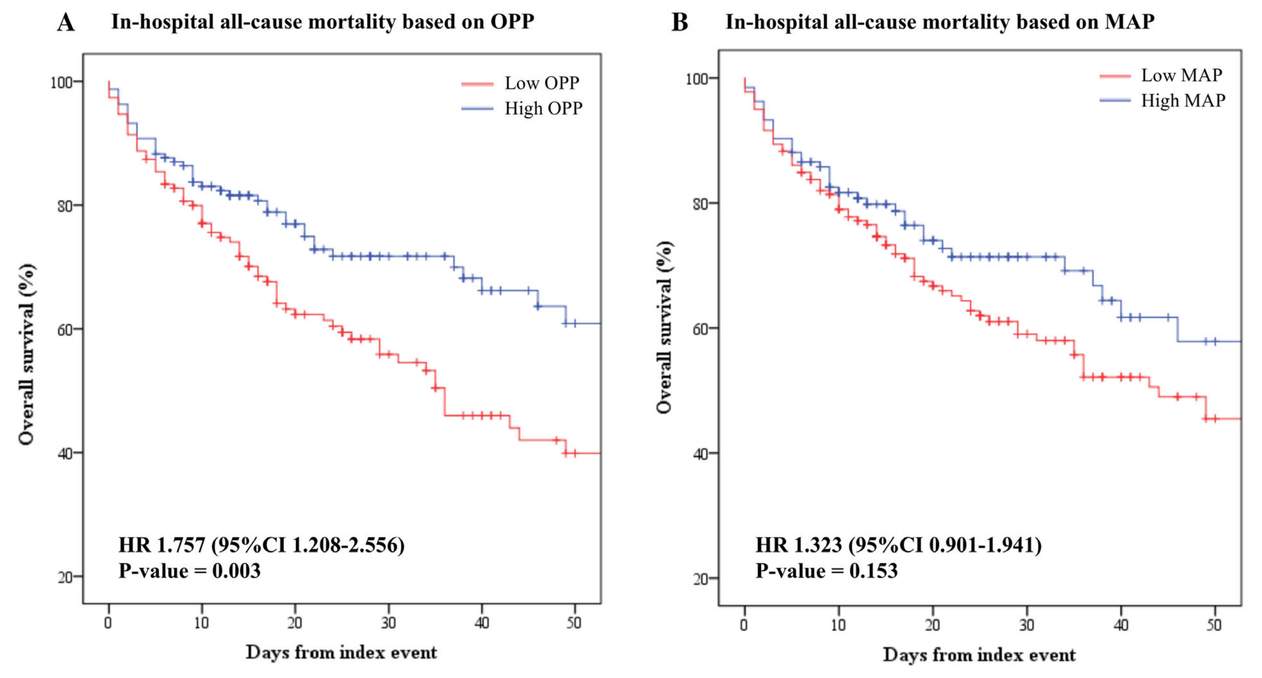


Figure 1 Kaplan–Meier estimates of in-hospital all-cause mortality according to organ perfusion pressure (OPP) (*A*) and mean arterial pressure (MAP) (*B*) on admission. CI, confidence interval; HR, hazard ratio.

At the multivariable Cox regression model on the primary outcome including clinical data available at first bedside assessment, namely age, OPP, and SOFA score (Model 1), lower OPP predicted significantly higher in-hospital all-cause mortality (HR per mmHg decrease: 1.016, 95% CI 1.004–1.029, $p = 0.010$; HR per 10 mmHg decrease: 1.153, 95% 1.023–1.300, $p = 0.019$) (*Table* 2 and online supplementary *Table S6*). Also, lower OPP on admission predicted significantly higher risk of in-hospital all-cause death in both Model 2 (HR per mmHg decrease: 1.013, 95% CI 1.001–1.027, $p = 0.048$) and Model 3 (HR per mmHg decrease: 1.014, 95% CI 1.001–1.027, $p = 0.030$) (*Table* 2). Systolic arterial pressure and MAP were not included in the models due to multicollinearity with OPP (online supplementary *Tables S1* and *S2*).

At ROC curves analysis, the OPP cut-off value which provided the best accuracy for predicting the primary outcome was 59.5 mmHg (specificity 66.4%, sensitivity 53.8%).

Table 2 Cox regression multivariable models on in-hospital all-cause mortality

Variable	HR (95% CI)	*p*-value
Model 1		
Age	1.039 (1.022–1.057)	**<0.001**
OPP[a]	1.016 (1.004–1.029)	**0.010**
SOFA score	1.192 (1.121–1.268)	**<0.001**
Model 2		
Age	1.039 (1.022–1.056)	**0.001**
OPP[a]	1.013 (1.001–1.027)	**0.048**
CVP	1.021 (0.982–1.062)	0.289
SOFA score	1.186 (1.115–1.262)	**<0.001**
Model 3		
OPP[a]	1.014 (1.001–1.027)	**0.030**
Heart rate	0.996 (0.988–1.005)	0.387
CVP	1.038 (1.004–1.072)	**0.027**

CI, confidence interval; CVP, central venous pressure; HR, hazard ratio; OPP, organ perfusion pressure; SOFA, Sequential Organ Failure Assessment.
[a] The HR for OPP is per unit of mmHg decrease.

Acute myocardial infarction- and acutely decompensated heart failure-related cardiogenic shock

Within the study population, 186 (58.9%) patients had AMI-CS and 130 (41.1%) patients had ADHF-CS. Among ADHF-CS patients, mean age was 61 ± 14 years, median OPP was 55 mmHg (IQR 45–64 mmHg), median lactate levels were 1.9 mmol/L (IQR 1.3–4.2 mmol/L) and median left ventricular ejection fraction was 20% (IQR 15–25%) (online supplementary *Table S7*). Among AMI-CS patients, mean age was 67 ± 12 years, median OPP was 59 mmHg (IQR 48–73 mmHg), median lactate levels were 2.8 mmol/L (IQR 1.7–5.7 mmol/L) and median left ventricular ejection fraction was 25% (IQR 20-–31%) (online supplementary *Table S8*). ADHF-CS patients had significantly lower MAP ($p = 0.026$), OPP ($p = 0.003$) and lactates ($p = 0.003$) and higher CVP ($p = 0.005$) as compared to AMI-CS patients (online supplementary *Table S9*). The relation between MAP and CVP for each CS aetiology is depicted in online supplementary *Figure S1*.

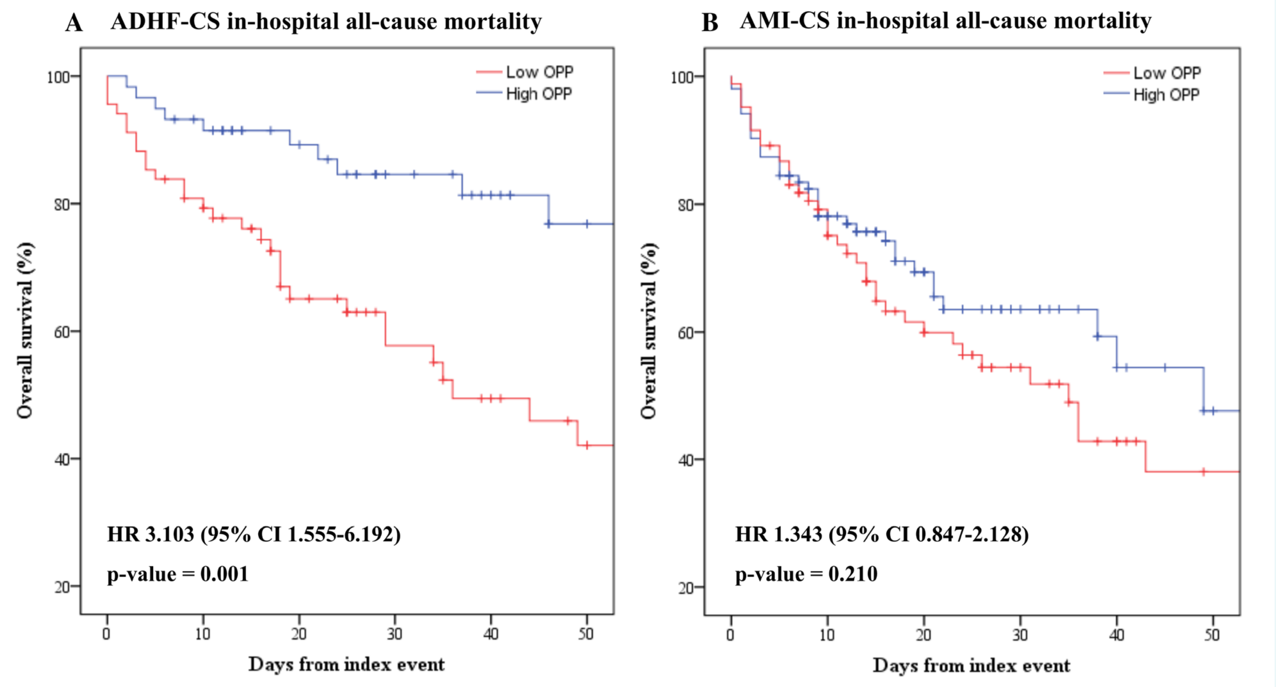


Figure 2 Kaplan–Meier estimates of in-hospital all-cause mortality according to cardiogenic shock (CS) aetiology and high or low organ perfusion pressure (OPP) on admission. ADHF, acutely decompensated heart failure; AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio.

At univariable Cox regression analysis, OPP <57.0 mmHg predicted significantly higher in-hospital all-cause mortality both among ADHF-CS patients (HR 3.103, 95% CI 1.555–6.192, $p = 0.001$) and among AMI-CS patients (HR 1.343, 95% CI 0.847–2.128, $p = 0.210$) with no significant interaction between subgroups (*Figures 2* and *3*).

In the ADHF-CS population, patients with OPP lower than its median value of 55 mmHg had significantly greater in-hospital all-cause mortality compared to those with higher OPP (HR 2.809, 95% CI 1.466–5.383, $p = 0.002$) (online supplementary *Figure S2*). Among AMI-CS patients, those with OPP lower than the median value of this subgroup (i.e. 59 mmHg) had non-significantly greater in-hospital all-cause mortality compared to those with higher OPP (HR 1.517, 95% CI 0.951–2.418, $p = 0.080$).

Secondary outcome

At a median follow-up of 58 days (IQR 14–248 days), 136 (43%) patients died. Low OPP on admission significantly predicted higher risk of all-cause mortality at latest follow-up (HR 1.777, 95% CI 1.260–2.505, $p < 0.001$) (online supplementary *Figure S3*).

Sensitivity analyses

When OPP was adjusted and adj-OPP was thus calculated, in-hospital survivors had significantly higher adj-OPP compared to patients dying during the hospitalization (28 mmHg [IQR 14–42 mmHg] vs. 40 mmHg [IQR 24–53 mmHg], $p < 0.001$) (*Table 1*). Median adj-OPP of the study population was 35.0 mmHg (IQR 18–52 mmHg). At univariable Cox regression analysis, low adj-OPP (i.e. <35.0 mmHg) predicted significantly greater in-hospital all-cause mortality (HR 1.260, 95% CI 1.114–2.356, $p = 0.011$). Among patients surviving beyond the first 24 h after hospital admission, OPP at 24 h was significantly lower in those experiencing in-hospital all-cause death compared to survivors (58 ± 12 mmHg vs. 65 ± 12 mmHg, $p < 0.001$), while delta-OPP was not significantly different between the two groups ($p = 0.487$) (online supplementary *Table S10*).

A total of 76 of the 180 patients with high MAP died in hospital, as did 74 of the 156 patients with high CVP and 70 of the 152 patients with low OPP (online supplementary *Table S11*). When the study population was divided into four groups according to different combinations of high/low MAP and high/low CVP, the study subjects with low MAP and high CVP had a significantly worse in-hospital overall survival compared to the other groups (log-rank $p < 0.001$) (online supplementary *Table S12* and *Figure S4*). When patients with high MAP and low CVP were excluded from the analysis, low OPP still significantly predicted in-hospital all-cause mortality (HR 2.314, 95% CI 1.380–3.880, $p = 0.001$) (online supplementary *Figure S5*).

In the multivariable model including age, OPP, positive pressure ventilation and SOFA score, OPP retained its prognostic yield to predict in-hospital all-cause mortality (HR per mmHg decrease 1.020, 95% CI 1.003–1.029, $p = 0.013$) (online supplementary *Table S13*).

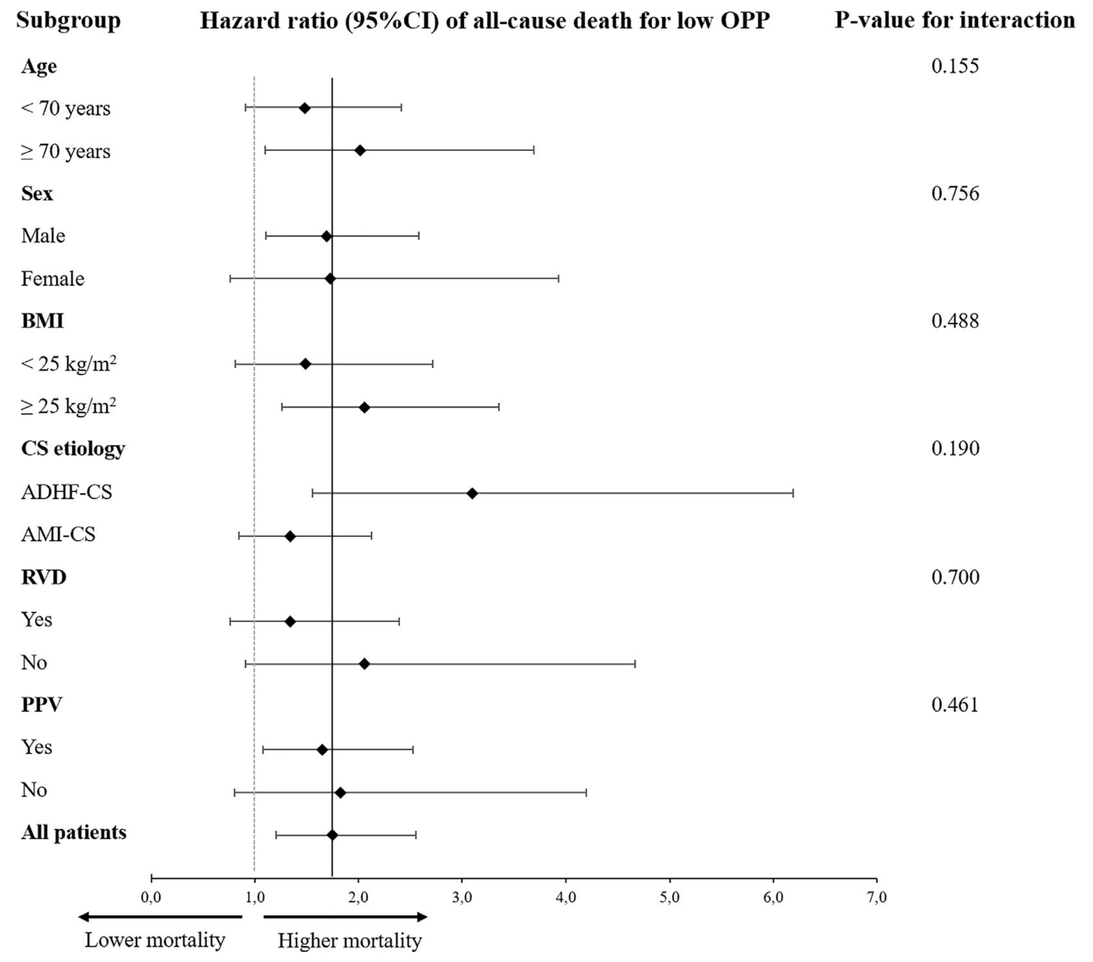


Figure 3 Overall and subgroup analysis on low organ perfusion pressure (OPP) (<57.0 mmHg) as a predictor of in-hospital all-cause mortality. The dotted line shows the no effect point, and the bold line shows the overall effect point. ADHF, acutely decompensated heart failure; AMI, acute myocardial infarction; BMI, body mass index; CI, confidence interval; CS, cardiogenic shock; PPV, positive pressure ventilation; RVD, right ventricular dysfunction.

A modest but statistically significant association was found between OPP and lactate levels in the overall population ($p = 0.006$) (online supplementary *Figure S6*) and in the AMI-CS cohort ($p = 0.008$), but not among ADHF-CS patients ($p = 0.125$) (online supplementary *Figure S7*). At multivariable Cox regression analyses on the primary outcome including both OPP and lactate levels on admission, both OPP and baseline lactates significantly predicted in-hospital all-cause mortality (HR per mmHg decrease: 1.015, 95% CI 1.003–1.027, $p = 0.014$, and HR 1.110, 95% 1.064–1.158, $p < 0.001$, respectively) (online supplementary *Table S14*).

Among the 209 patients with right ventricular function data available, RVD was found in 125 (59.8%). Patients with RVD had higher CVP ($p < 0.001$), creatinine ($p = 0.012$) and total bilirubin ($p = 0.014$) as compared to patients with preserved right ventricular function, while MAP ($p = 0.813$), OPP ($p = 0.074$) and lactate levels ($p = 0.078$) were not significantly different between the two groups (online supplementary *Table S15*). The prevalence of ADHF-CS was higher among patients with RVD as compared to those without RVD (69 [55.6%] vs. 34 [40.5%], $p = 0.032$). At univariable Cox regression analysis, OPP <57.0 mmHg predicted higher in-hospital all-cause mortality both among patients with RVD (HR 1.348, 95% CI 0.760–2.391, $p = 0.307$) and among patients without RVD (HR 2.061, 95% CI 0.910–4.667, $p = 0.083$) with no significant interaction between subgroups (*Figure 3* and online supplementary *Figure S8*). Similar results were obtained when OPP lower than its median value of each group was considered.

Discussion

This analysis on the multicentre prospective Altshock-2 registry cohort investigated on-admission OPP as a potential marker of prognosis in 316 consecutive patients hospitalized for CS. The main findings can be summarized as follows: (i) low OPP (i.e. <57.0 mmHg) on admission significantly predicted in-hospital all-cause mortality at univariable analysis, whereas low MAP did not; (ii) baseline OPP significantly predicted in-hospital all-cause mortality at multivariable analyses; and (iii) low OPP appeared particularly powerful in predicting higher in-hospital all-cause mortality among ADHF-CS patients (*Graphical Abstract*).

Cardiogenic shock is a critical condition defined by cardiac failure and systemic hypoperfusion, with a growing prevalence and persistently elevated mortality rates.[12] While low blood pressure itself may indicate poor cardiac output and inadequate peripheral perfusion, the gradient between MAP and CVP may better reflect end-organ capillary blood flow.[13] Notably, elevated CVP may jeopardize peripheral tissue perfusion, particularly in critical conditions like CS when MAP is already dangerously low. This complex interaction between abnormally low arterial and high venous pressures was termed the 'double-hit phenomenon' in patients with acute heart failure and adversely impacts organ function[14]; in fact, while reduced peripheral blood flow is a primary concern in CS, the concurrent backward pressure build-up may exacerbate congestion and further reduce end-organ perfusion. This combined effect can lead to kidney, liver, and intestinal failure. The resulting disastrous response intensifies fluid accumulation, worsens heart failure symptoms, and triggers a systemic inflammatory reaction, further damaging the heart and other vital organs.

Organ perfusion pressure is a straightforward and reliable measure that captures the intricate interplay between reduced blood flow and increased fluid accumulation. Previous research has demonstrated the predictive role of OPP in critically ill and cardiac surgery patients[15,16]; also, lower levels of OPP were significantly associated with in-hospital worsening heart failure in a multicentre study on 146 patients hospitalized for acute heart failure requiring intravenous sodium nitroprusside.[5] To our knowledge, this is the first study to demonstrate that lower levels of OPP are associated with increased in-hospital all-cause mortality in patients hospitalized for CS; this finding was confirmed in different multivariable models encompassing meaningful clinical and haemodynamic parameters, including baseline lactate levels, a well-known predictor of adverse events in CS,[17] thus reinforcing the consistency of the result. Even decreases of OPP as tiny as single units of mmHg yielded significant prognostic capability regarding in-hospital all-cause mortality, and this result was clinically emphasized when OPP variations of 5 to 10 units of mmHg were assessed. Conversely, low MAP alone could not reliably predict in-hospital mortality, stressing the need for a comprehensive and simultaneous evaluation of both anterograde perfusion and peripheral congestion in CS patients. The presence of low OPP, especially when resulting from the combination of low MAP and high CVP, may identify a subset of CS patients carrying a particularly poor prognosis in the short-term, necessitating prompt and aggressive treatment upfront. OPP retained its prognostic yield even after hospital discharge, suggesting that haemodynamic derangement on admission and propensity for either reduced forward flow or fluid accumulation or both portrays a precarious condition which needs strict monitoring also after the hospitalization period.

Low OPP appeared particularly powerful in predicting in-hospital all-cause mortality in ADHF-CS as compared to AMI-CS; this is likely due to the different underlying pathophysiology of these two CS phenotypes.[18] Over time, individuals with chronic heart failure develop compensatory mechanisms to accommodate the heart's declining pumping capacity, and even minor fluctuations in anterograde drive or fluid volume can trigger a rapid decline into subclinical or overt CS. Indeed, ADHF-CS patients present with higher baseline CVP, making them more sensitive to MAP decrease; OPP, representing the complex interplay between these critical factors, may reflect acute/subacute MAP reduction within the chronic congestive state of ADHF patients. In contrast, AMI-CS is an acute event primarily characterized by the heart's inability to produce sufficient cardiac output; consequently, reduced blood flow to peripheral tissues is predominantly caused by inadequate output rather than excessive fluid accumulation, and OPP may yield lower (albeit still significant) predictive capability. Indeed, the deterioration into ADHF-CS tends to be more insidious than in AMI-CS, as evidenced by greater fluid retention (i.e. increased CVP) and more pronounced decline in heart structure and function in ADHF-CS patients compared to AMI-CS patients.[7]

Limitations

Some limitations must be addressed. This was a post-hoc analysis on an observational study and all inherent limitations of such kind of study must be considered. OPP and outcome data were not available for the whole Altshock-2 registry cohort, and some selection bias might have occurred. Only ADHF-CS and AMI-CS were evaluated; thus, the results of the present research may not be generalizable to other types of shock. As this was a multicentre study, diagnosis and treatment algorithms may have been heterogeneous among different centres; on the other hand, the study multicentricity makes it all-encompassing and easily applicable to everyday clinical settings. Right ventricular function data were limited to TAPSE, so deficits of radial contractility (i.e. fractional area change) might have been missed.

Conclusion

In this multicentre, observational, prospective study on patients hospitalized for CS, lower OPP on admission was associated with a significantly higher risk of in-hospital all-cause death. This finding may aid in the early detection of very-high-risk CS individuals requiring prompt aggressive treatment, but requires validation in future randomized studies.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: none declared.

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