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ORIGINAL ARTICLE

Pulmonary artery elastance as a predictor of hospital mortality in heart failure cardiogenic shock

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Abstract

Aims The initial bundle of cares strongly affects haemodynamics and outcomes in acute decompensated heart failure cardiogenic shock (ADHF-CS). We sought to characterize whether 24 h haemodynamic profiling provides superior prognostic information as compared with admission assessment and which haemodynamic parameters best predict in-hospital death.

Methods and results All patients with ADHF-CS and with available admission and 24 h invasive haemodynamic assessment from two academic institutions were considered for this study. The primary endpoint was in-hospital death. Regression analyses were run to identify relevant predictors of study outcome. We included 127 ADHF-CS patients [65 (inter-quartile range 52–72) years, 25.2% female]. Overall, in-hospital mortality occurred in 26.8%. Non-survivors were older, with greater CS severity. Among admission variables, age [odds ratio (OR) = 1.06; 95% confidence interval (CI): 1.02–1.11; P_{adj} = 0.005] and CPI_{RAP} (OR = 0.62 for 0.1 increment; 95% CI: 0.39–0.95; P_{adj} = 0.034) were found significantly associated with in-hospital death. Among 24 h haemodynamic univariate predictors of in-hospital death, pulmonary elastance (PaE) was the strongest (area under the curve of 0.77; 95% CI: 0.68–0.86). PaE (OR = 5.98; 95% CI: 2.29–17.48; $P_{adj} < 0.001$), pulmonary artery pulsatility index (PAPi, OR = 0.77; 95% CI: 0.62–0.92; P_{adj} = 0.013) and age (OR = 1.06; 95% CI: 1.02–1.11; P_{adj} = 0.010) were independently associated with in-hospital death. Best cut-off for PaE was 0.85 mmHg/mL and for PAPi was 2.95; cohort phenotyping based on these PaE and PAPi thresholds further increased in-hospital death risk stratification; patients with 24 h high PaE and low PAPi exhibited the highest in-hospital mortality (56.2%).

Conclusions Pulmonary artery elastance has been found to be the most powerful 24 h haemodynamic predictor of in-hospital death in patients with ADHF-CS. Age, 24 h PaE, and PAPi are independently associated with hospital mortality. PaE captures ventricular (RV) afterload mismatch and PAPi provides a metric of RV adaptation, thus their combination generates four distinct haemodynamic phenotypes, enhancing in-hospital death risk stratification.

Keywords Cardiac power index; CPI; Cardiac power output; Cardiogenic shock; Pulmonary artery catheter; Haemodynamic monitoring; Pulmonary artery elastance; RV failure; Pulmonary artery pulsatility index

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Introduction

Acute decompensated heart failure (ADHF)-related cardiogenic shock (CS) accounts for approximately 50% of CS patient admissions in a contemporary cardiac intensive care unit (CICU).[1] In these patients, the invasive haemodynamic assessment provides incremental information over clinical evaluation and may affect both clinical decision making and prognosis.[2–5]

Several haemodynamic indexes measured on admission have been variably associated with in-hospital mortality in unselected CS patients, including cardiac index (CI), cardiac

power index (CPI), and right atrial pressure (RAP).[6–8] As a variable combination of vasoactive therapies, mechanical circulatory supports (MCS) and mechanical ventilation, affecting both right and left circulation, are generally initiated in the first 24 h from CICU admission, repeated haemodynamic assessment may potentially be a better gauge of the patient's prognosis than the index assessment. However, whether the haemodynamic trajectory after the initial bundle of cares has been implemented provides superior prognostic value remains poorly investigated.

Thus, we sought to characterize (i) whether haemodynamic assessment 24 h after admission provides superior prognostic information as compared with initial assessment, (ii) which haemodynamic parameters best predict in-hospital death in patients with ADHF-CS.

Methods

Study design

All data was obtained from clinical electronic records from two CICUs of large academic tertiary hospitals (IRCCS 'San Raffaele Hospital', Milan, Italy and Erasmus MC, Rotterdam, the Netherlands). Internal Review Board approval was waived due to the retrospective and anonymized nature of this analysis. Study years ranged from 2017 to 2022. We reviewed all patients admitted for CS in the pre-specified timespan and included only those with ADHF-CS. Patients meeting the Society for Cardiovascular Angiography and Interventions (SCAI) classification[9] B to E shock stages with available admission and 24 h pulmonary artery catheter (PAC) assessment were selected. Indication to PAC insertion was given by the treating physician based on clinical profile and concomitant need of MCS. All PAC assessments were prospectively registered in a dedicated database at each institution at the time of haemodynamic assessment, as per current clinical practice. Haemodynamic measures were performed at bedside by experienced operators, with the aim of obtaining complete haemodynamic profiling.[3] A detailed overview of PAC-derived indexes formulas is available in *Data S1*.

All patients had invasive arterial pressure monitoring. Laboratory tests were performed at time of PAC insertion and after 24 h. Medical records for clinical, imaging, and laboratory data were reviewed by two of the authors (C.A.D.U., G.F.) blinded to the selected study outcome and to the study design. Right ventricle (RV) dysfunction was categorized as follow: mild [tricuspid annular plane systolic excursion, tricuspid annular plane systolic excursion (TAPSE) $<$17 mm]; moderate (TAPSE $\leq$15 mm); severe (TAPSE $\leq$10 mm).[10]

The study outcome was in-hospital death.

Statistical analyses

Categorical variables are reported as proportions while continuous variables are reported as medians and inter-quartile range, as appropriate. Continuous variables from independent groups were compared by the Mann–Whitney *U* test and the categorical variables with the χ^2 test. Multiple comparisons were adjusted with the Benjamini and Hochberg method.[11]

A univariable logistic regression was obtained to identify variables significantly associated with the outcome of interest. Two multivariate models for the association of admission and 24 h haemodynamic variables, respectively, with in-hospital death were created. Considering the low number of events, the haemodynamic variables to be included in the multivariate models were selected as follow: all significant haemodynamic predictors ($P < 0.010$ at univariate analysis) were tested in bivariate models including the predictor with the highest *C*-statistic and each of the others. Only those remaining significantly associated with the outcome were retained in the final model. The clinical variables to be included as covariates in the haemodynamic models were selected by performing a multivariable logistic regression of the clinical variables significantly associated with the outcome ($P < 0.010$ at univariate analysis).

Receiver operating characteristic (ROC) curves were obtained to assess the discriminatory power of the haemodynamic predictors and of the multivariable models by calculation of the area under the curve (AUC). The 'Youden index' method was used to identify the optimal cut-off for each variable of interest for predicting the outcome. A formal comparison of the AUCs of different models was performed with the DeLong's test.

All analyses were performed with RStudio (Version 1.3.1093, RStudio, PBC).

Results

A total of 127 patients with ADHF-related SCAI B-E CS were included in this study. All patients had complete invasive haemodynamic assessment upon CICU admission and 24 h thereafter. Mean age was 65 (52, 73) years, and 32 (25.2%) were female. CS severity was SCAI B in 50 (39.4%), SCAI C in 68 (53.5%), SCAI D in 7 (5.5%), and SCAI E in 2 (1.6%). Mean body mass index was 25.45 (22.89, 29.00) kg/m^2. On admission, patients exhibited severe left ventricular (LV) and RV dysfunction: median LV ejection fraction (LVEF) was 20 (15, 30)% and median TAPSE was 14 (10, 15) mm. Intra-aortic balloon pump (IABP) was inserted in 54 (42.5%) patients. Invasive mechanical ventilation was required in 54 (42.5%). Median CICU stay was 10

(6, 16) days. In-hospital death occurred in 34 (26.8%). No deaths occurred in the first 24 h in this population. Baseline clinical characteristics and in-hospital events for the overall study population and according to in-hospital death are summarized in *Table 1*.

Admission clinical characteristics and haemodynamics

Several clinical characteristics were associated with in-hospital death, including age, diabetes mellitus, estimated

Table 1 Clinical characteristics on CICU admission and hospital outcomes according to in-hospital death

	Overall (n = 127)	Survivors (n = 93)	Non survivors (n = 34)	P value
Clinical characteristics				
Age (years)	65 (52, 73)	65 (52, 73)	69 (66, 75)	**0.005**
Female	32 (25.2)	20 (21.5)	12 (35.3)	0.113
BMI (kg/m^2)	25.45 (22.89, 29.00)	26.12 (23.19, 29.06)	24.00 (22.20, 26.67)	0.239
eGFR (mL/min/1.73 m^2)	45.14 (28.60, 62.41)	47.09 (32.44, 69.39)	30.86 (18.44, 50.17)	**0.041**
LVEF (%)	20 (15, 30)	20 (15, 26)	20.00 (15, 42)	0.175
TAPSE (mm)	14 (10, 15)	14 (10, 16)	14 (10, 15)	0.854
Moderate or severe RVF	87 (68.5)	61 (65.6)	26 (76.5)	0.243
Serum lactate (mmol/L)	1.90 (1.32, 3.30)	1.71 (1.20, 3.01)	2.79 (2.02, 4.52)	**0.020**
SCAI CS stage				**<0.001**
B	50 (39.4)	45 (48.4)	5 (14.7)	
C	68 (53.5)	46 (49.5)	22 (64.7)	
D	7 (5.5)	1 (1.1)	6 (17.6)	
E	2 (1.6)	1 (1.1)	1 (2.9)	
In-hospital outcome				
In-hospital death	34 (26.8)	0 (0)	34 (100)	-
LVAD implant	12 (9.4)	10 (10.8%)	2 (5.9)	0.406
CICU stay (days)	10.00 (5.50, 16.00)	10.00 (5.00, 14.25)	11.00 (8.00, 19.00)	0.146
IABP insertion	54 (42.5)	37 (39.8)	17 (50.0)	0.303
Need of CRRT	15 (11.8)	2 (2.2)	13 (38.2)	**<0.001**
Invasive mechanical ventilation	54 (42.5)	30 (32.3)	24 (70.6)	**<0.001**
Invasive haemodynamics				
MAP (mmHg)	77 (69, 86)	80 (70, 88)	75 (68, 78)	**0.013**
SAP (mmHg)	115 (95, 131)	116 (95, 134)	112 (91, 122)	0.252
DAP (mmHg)	59 (49, 69)	62 (54, 70)	52 (46, 62)	**0.011**
CPI (W/m^2)	0.36 (0.27, 0.48)	0.38 (0.28, 0.49)	0.30 (0.26, 0.39)	**0.017**
CPI_{RAP} (W/m^2)	0.30 (0.22, 0.39)	0.33 (0.22, 0.43)	0.25 (0.17, 0.35)	**0.012**
CI (L/min/m^2)	2.06 (1.67, 2.57)	2.16 (1.78, 2.63)	1.96 (1.53, 2.33)	0.157
HR (bpm)	90 (77, 105)	90 (77, 106)	90 (78, 105)	0.796
SVi (mL/m^2)	23 (18, 29)	24 (19, 31)	20 (17, 26)	0.187
SVR (WU)	16.39 (12.33, 22.34)	15.92 (12.50, 21.58)	18.76 (11.88, 23.46)	0.774
PVR (WU)	2.77 (1.58, 4.88)	2.75 (1.59, 4.74)	2.97 (1.71, 5.50)	0.927
SvO_2 (%)	54.0 (45.0, 66.5)	54.0 (43.5, 68.0)	54.0 (51.0, 64.0)	0.894
PCWP (mmHg)	21 (18, 26)	22 (18, 27)	25 (16,30)	0.529
mPAP (mmHg)	35 (26, 42)	34 (26, 41)	36 (27, 42)	0.873
sPAP (mmHg)	50 (38, 62)	50 (37, 60)	50 (40, 65)	0.572
dPAP (mmHg)	26 (20, 30)	25 (20, 31)	27 (19, 30)	0.994
PAPi	1.73 (1.20, 3.00)	1.70 (1.18, 2.83)	2.20 (1.30, 3.11)	0.479
API	2.40 (1.48, 3.65)	2.20 (1.57, 3.65)	2.59 (1.41, 3.19)	0.706
LVSWi (cJ/m^2)	20.07 (13.59, 27.46)	21.38 (16.10, 29.33)	15.45 (12.25, 22.34)	**0.022**
RVSWi (cJ/m^2)	6.18 (4.17, 8.68)	6.43 (4.21, 8.86)	5.80 (4.06, 8.04)	0.259
RAP (mmHg)	12 (9, 18)	12 (9, 18)	13 (9, 19)	0.580
RAP/PCWP	0.57 (0.44, 0.80)	0.57 (0.44, 0.86)	0.54 (0.43, 0.71)	0.664
PaC (mL/mmHg)	1.79 (1.24, 2.80)	1.90 (1.25, 3.29)	1.66 (1.11, 1.99)	**0.036**
PaE (mmHg/mL)	1.13 (0.70, 1.60)	1.33 (1.00, 1.89)	1.19 (0.75, 1.65)	0.397
PaE/RAP (1/mL)	0.09 (0.07, 0.15)	0.08 (0.06, 0.12)	0.11 (0.08, 0.17)	0.894
PaE/(RAP/WP) (mmHg/mL)	2.03 (1.15, 3.38)	1.75 (1.10, 3.15)	2.41 (1.44, 3.49)	0.876

API, arterial pulsatility index; BMI, body mass index; CI, cardiac index; CICU, cardiac intensive care unit; CPI, cardiac power index; CPI_{RAP}, RAP-adjusted cardiac power index; CRRT, continuous renal replacement therapy; CS, cardiogenic shock; dPAP, diastolic pulmonary artery pressure; eGFR estimated glomerular filtration rate; HR, heart rate; LVEF, left ventricle ejection fraction; LVSWi, left ventricular stroke work index; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; PaC, pulmonary compliance; PaE pulmonary elastance; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistances; RAP, right atrial pressure; RVF, right ventricular failure; RVSWi, right ventricular stroke work index; sPAP, systolic pulmonary artery pressure; SpO_2, peripheral oxygen saturation; SVi, stroke volume index; SvO_2, mixed venous oxygen saturation; SVR, systemic vascular resistances; TAPSE, tricuspid annular plane systolic excursion.

Categorical variables are expressed as count (proportions), continuous variable as medians (inter-quartile range), as appropriate. Bold emphasis denotes statistically significant P values.

glomerular filtration rate, and admission serum lactate. At bivariate analysis, only age remained significantly associated with in-hospital death. On admission, non-survivors demonstrated worse parameters of cardiac power but similar pulmonary pressures (*Table 1*). Among haemodynamic variables, only the RAP-corrected CPI (CPI_{RAP}) and pulmonary artery compliance (PaC) were associated with in-hospital mortality at the univariate analysis. Summary of these statistics are reported in *Data S1*. In the multivariable model, age (OR = 1.06 per year increment; 95% CI: 1.02–1.11; P_{adj} = 0.005), admission CPI_{RAP} (OR = 0.62 for 0.1 increment; 95% CI: 0.39–0.95; P_{adj} = 0.034), but not PaC (OR = 0.94 per mL/mmHg increment; 95% CI: 0.61–1.38; P_{adj} = 0.781) were independently associated with in-hospital death. The multivariable model had an AUC of 0.74 (95% CI: 0.64–0.83) (*Figure 1*).

Twenty-four-hour haemodynamics

At 24 h haemodynamic assessment, non-survivors demonstrated worse parameters of pulmonary congestion, including higher mean, diastolic, and systolic pulmonary pressures (mPAP, dPAP, sPAP), and worse flow and power indexes, including lower CPI, CPI_{RAP}, stroke volume index (SVi), left ventricle stroke work index (LVSWi). Non survivors also had higher systemic and pulmonary vascular resistances (SVR and PVR). Finally, non-survivors had worse measures of RV load and adaptation, including higher pulmonary artery elastance (PaE), lower pulmonary artery compliance (PaC), and higher RAP. These findings are summarized in *Table 2*.

Univariate analysis identified several 24 h variables associated with in-hospital death, including CI, SVi, CPI_{RAP}, mPAP, sPAP, dPAP, pulmonary artery wedge pressure (PAWP), RAP, SVR, pulmonary artery pulsatility index (PAPi), PaC, and PaE. Among haemodynamic indexes, PaE had the greatest AUC of 0.77 (95% CI: 0.68–0.86) and was selected for further modelling. At bivariate analyses, only PaE and PAPi resulted independently associated with in-hospital death. Summary statistics of these models are available in *Data S1*. At the multivariable analysis, PaE (OR = 5.98 per mmHg/mL increment; 95% CI: 2.29–17.48; $P_{adj} < 0.001$), PAPi (OR = 0.77 per unit increment; 95% CI: 0.62–0.92; P_{adj} = 0.013) and age (OR = 1.06 per year increment; 95% CI: 1.02–1.11; P_{adj} = 0.010) were significantly associated with the outcome of in-hospital death (*Table 3*).

Based on ROC analysis, the AUC of the multivariable model for the in-hospital death outcome was 0.82 (95% CI: 0.75–0.90) for the multivariable model (*Figure 1*). This AUC was significantly higher than that of admission model (0.82 vs. 0.74; P = 0.038). The Youden index method identified a PaE value of 0.85 mmHg/mL as the optimal threshold value

Figure 1 Receiver operating characteristic (ROC) curves for the multivariable models with admission variables (age and CPI_{RAP}, orange line) and for the 24 h variables (pulmonary elastance, pulmonary artery pulsatility index, and age; red line) for the endpoint of interest of in-hospital mortality. AUC, area under the curve.

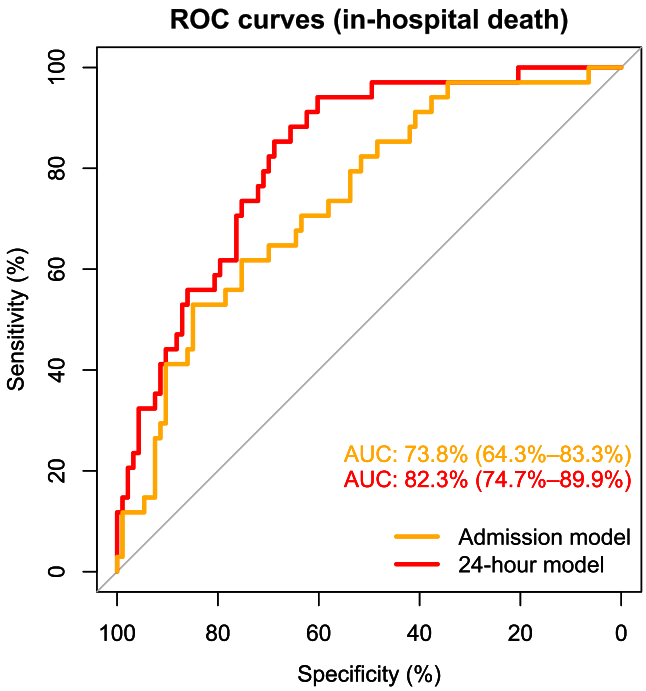


Table 2 Haemodynamics 24 h after CICU admission according to in-hospital death

	Overall (n = 127)	Survivors (n = 93)	Non-survivors (n = 34)	P value
MAP (mmHg)	79 (71, 86)	79 (73, 85)	75(68, 88)	0.367
SAP (mmHg)	123 (109, 136)	123 (109, 136)	125 (112, 128)	0.633
DAP (mmHg)	58 (48, 64)	59 (52, 64)	53 (41, 62)	0.059
CPI (W/m^2)	0.40 (0.33, 0.49)	0.42 (0.35, 0.50)	0.35 (0.27, 0.43)	**0.008**
CPI_{RAP} (W/m^2)	0.34 (0.28, 0.44)	0.36 (0.30, 0.45)	0.29 (0.25, 0.38)	**0.001**
CI (L/min/m^2)	2.30 (1.87, 2.74)	2.34 (1.97, 2.85)	2.00 (1.57, 2.51)	**0.035**
HR (bpm)	86 (77, 97)	86 (76, 95)	89 (78, 102)	0.183
SVi (mL/m^2)	26 (21, 32)	27 (22, 34)	21 (18, 30)	**0.021**
SVR (WU)	16.92 (13.21, 20.70)	16.06 (12.86, 18.93)	18.62 (14.01, 23.14)	**0.043**
PVR (WU)	2.41 (1.51, 3.91)	2.12 (1.43, 3.57)	3.42 (2.32, 4.51)	**0.045**
SvO_2 (%)	62.0 (54.5, 68.9)	63.0 (55.0, 69.3)	61.0 (54.5, 68.0)	0.964
PCWP (mmHg)	15 (10, 19)	16 (11, 21)	20 (13, 26)	**0.007**
mPAP (mmHg)	27 (22, 34)	26 (21, 30)	34 (25.00, 42)	<**0.001**
sPAP (mmHg)	40 (33, 53)	39 (31, 47)	50 (36, 62)	<**0.001**
dPAP (mmHg)	19 (15, 24)	17 (14, 22)	24 (18, 31)	<**0.001**
PAPi	2.86 (1.54, 5.00)	3.00 (1.61, 6.00)	2.33 (1.46, 3.76)	**0.028**
API	3.53 (0.00, 5.61)	3.60 (0.00, 5.71)	2.78 (0.28, 4.69)	0.270
LVSWi (cJ/m^2)	25.03 (19.31, 30.50)	26.85 (20.48, 31.96)	20.24 (15.21, 24.99)	< **0.001**
RVSWi (cJ/m^2)	6.06 (4.16, 9.00)	6.44 (4.29, 8.85)	5.27 (4.04, 9.70)	0.755
RAP (mmHg)	8 (5, 13)	7 (3, 12)	11 (6, 17)	**0.004**
RAP/PCWP	0.50 (0.30, 0.73)	0.45 (0.25, 0.72)	0.62 (0.43, 0.84)	0.954
PaC (mL/mmHg)	2.38 (1.51, 3.49)	2.83 (1.75, 3.93)	1.71 (1.19, 2.16)	**0.028**
PaE (mmHg/mL)	0.86 (0.59, 1.21)	0.74 (0.54, 0.99)	1.17 (0.91, 1.55)	<**0.001**
PaE/RAP (1/mL)	0.11 (0.07, 0.19)	0.11 (0.07, 0.20)	0.11 (0.08, 0.17)	0.231
PaE/(RAP/WP) (mmHg/mL)	1.77 (1.11, 3.11)	1.58 (0.95, 3.06)	2.22 (1.37, 3.26)	0.988

API, arterial pulsatility index; BMI, body mass index; CI, cardiac index; CICU, cardiac intensive care unit; CPI, cardiac power index; CPI_{RAP}, RAP-adjusted cardiac power index; CRRT, continuous renal replacement therapy; CS, cardiogenic shock; dPAP, diastolic pulmonary artery pressure; eGFR estimated glomerular filtration rate; HR, heart rate; LVEF, left ventricle ejection fraction; LVSWi, left ventricular stroke work index; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; PaC, pulmonary compliance; PaE pulmonary elastance; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistances; RAP, right atrial pressure; RVF, right ventricular failure; RVSWi, right ventricular stroke work index; sPAP, systolic pulmonary artery pressure; SpO_2, peripheral oxygen saturation; SVi, stroke volume index; SvO_2, mixed venous oxygen saturation; SVR, systemic vascular resistances; TAPSE, tricuspid annular plane systolic excursion.
Categorical variables are expressed as count (proportions), continuous variable as medians (inter-quartile range), as appropriate. Bold emphasis denotes statistically significant P values.

Table 3 Logistic regression analysis (in-hospital death outcome) for haemodynamic indexes at 24 h

	Univariate logistic regression		Multivariate logistic regression	
Variable	OR (95% CI)	P value	OR (95% CI)	P_{adj} value
Age (years)	1.05 (1.02–1.10)	**0.008**	1.06 (1.02–1.11)	**0.010**
PaE (mmHg/mL)	6.56 (2.76–17.11)	<**0.001**	5.98 (2.29–17.48)	<**0.001**
PAPi	0.84 (0.70–0.96)	**0.030**	0.77 (0.62–0.92)	**0.013**

CI, confidence interval; OR, odds ratio; PaE, pulmonary artery elastance; PAPi, pulmonary artery pulsatility index. Bold emphasis denotes statistically significant P values.

for the in-hospital death outcomes with a sensitivity of 0.88 and a specificity of 0.65; the optimal threshold value for PAPi was 2.95 with a sensitivity of 0.65 and a specificity of 0.54.

Phenotyping by pulmonary artery elastance and pulmonary artery pulsatility index

Based on the independent association of PaE and PAPi with in-hospital death, we divided the study cohort according to the respective threshold identified by the ROC curve analysis (*Figure 2*). Patients were then categorized in four phenotypes: (i) 'high PAPi–low PaE' (PAPi >2.95 and PaE ≤ 0.85 mmHg/mL; n = 29); (ii) 'lowPAPi–low PaE' (PAPi ≤2.95 and PaE ≤ 0.85 mmHg/mL; n = 33); (iii) 'high PAPi–high PaE' (PAPi >2.95 and PaE > 0.85 mmHg/mL; n = 33) and (iv) 'low PAPi–high PaE' (PAPi ≤2.95 and PaE > 0.85 mmHg/mL; n = 32). We observed a different mortality in the clusters identified by this classification (0 vs. 12.1 vs. 36.4 vs. 56.2%; P < 0.001, *Figure 3*). At pairwise comparisons, in-hospital death was significantly different in group 1 vs. 3 (P < 0.001), in group 1 vs. 4 (P < 0.001), in group 2 vs. 4 (P < 0.001), and marginally non-significant in group 2 vs. 3 (P = 0.064). As summarized in *Table 4*, patients in the 'high PAPi–low

Figure 2 Scatterplot of patients labelled by in-hospital death outcomes, according to the identified pulmonary elastance and pulmonary artery pulsatility index thresholds, assessed after 24 h from admission.

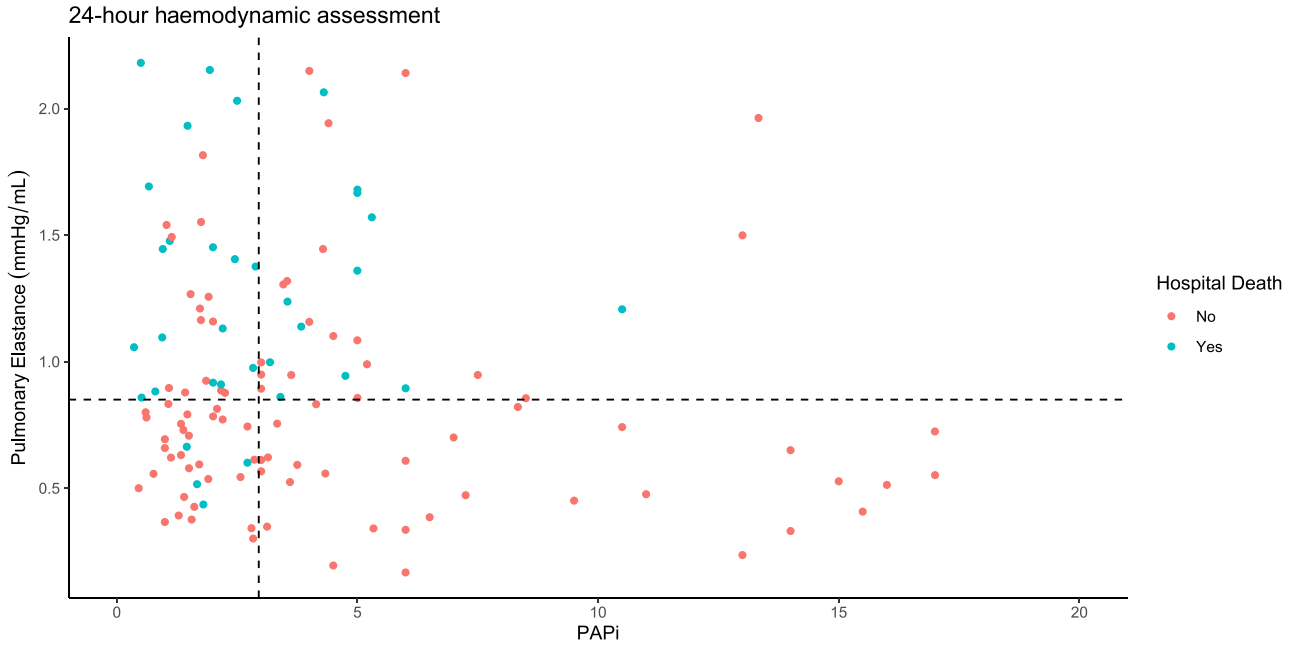
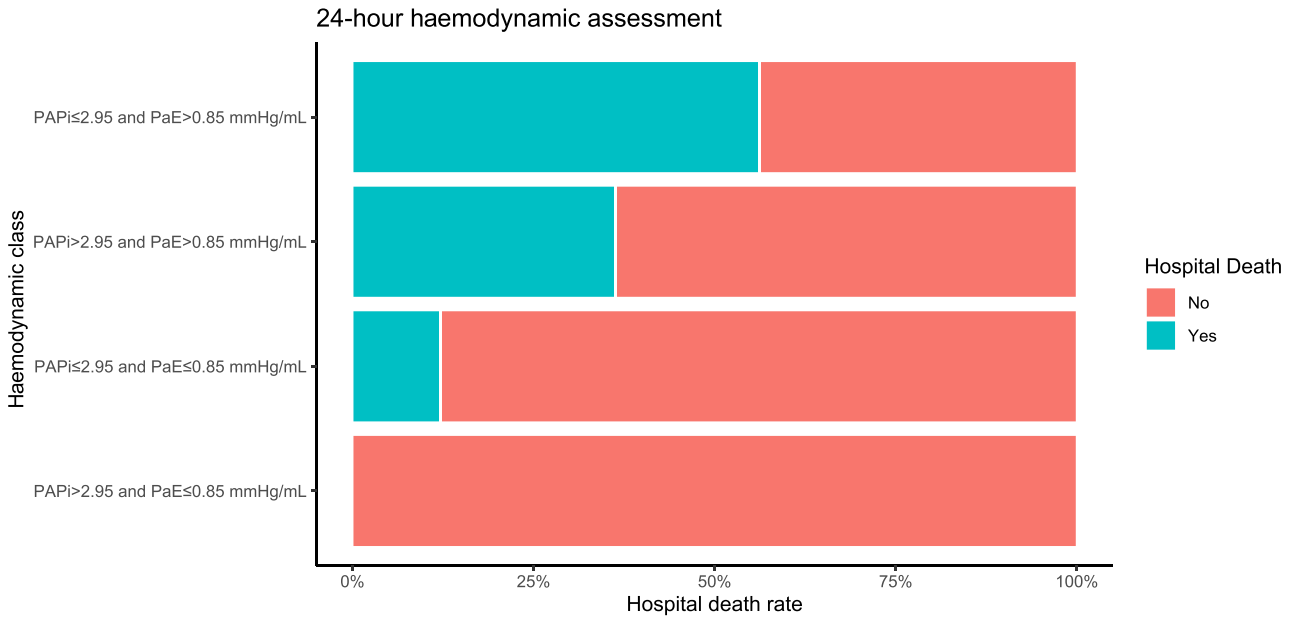


Figure 3 Observed in-hospital mortality for each cohort based on the identified pulmonary elastance and pulmonary artery pulsatility index thresholds, assessed after 24 h from admission.



PaE' group had the best parameters of (bi)ventricular function and lowest right and left filling pressures; patients in the 'lowPAPi–low PaE' group exhibited parameters of poor RV function, with prevalent RV dysfunction (high RAP/PAWP and high RAP); patients in the 'high PAPi–high PaE' had signs of prevalent LV dysfunction coupled with parameters of relatively preserved RV function; finally, patients in the 'low PAPi–high PaE' group exhibited worse parameters of LV and

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Table 4 Haemodynamics 24 h after CICU admission according to the identified PaE and PAPi thresholds

	High PAPi–low PaE (n = 29)	Low PAPi–low PaE (n = 33)	High PAPi–high PaE (n = 33)	Low PAPi–high PaE (n = 32)	P value
MAP (mmHg)	77 (75, 83)	84 (77, 87)	78 (70, 84)	78 (70, 88)	0.260
SAP (mmHg)	118 (109, 137)	125 (113, 136)	127 (105, 136)	122 (116, 127)	0.977
DAP (mmHg)	58 (51, 60)	61 (56, 72)	54 (46, 63)	57 (49, 66)	0.201
CPI (W/m^2)	0.48 (0.42, 0.56)	0.43 (0.37, 0.52)	0.36 (0.28, 0.39)	0.33 (0.27, 0.40)	**<0.001**
CPI_{RAP} (W/m^2)	0.47 (0.40, 0.55)	0.39 (0.31, 0.45)	0.31 (0.26, 0.36)	0.28 (0.20, 0.31)	**<0.001**
CI ($L/min/m^2$)	2.90 (2.38, 3.40)	2.50 (2.18, 2.75)	2.02 (1.64, 2.39)	1.89 (1.55, 2.28)	**<0.001**
HR (bpm)	85 (79, 90)	84 (70, 95)	86 (79, 95)	90 (79, 103)	0.226
SVi (mL/m^2)	35 (27, 43)	29 (26, 34)	22 (19, 28)	21 (18, 26)	**<0.001**
SVR (WU)	13.79 (10.48, 17.51)	15.71 (12.86, 17.43)	19.95 (16.28, 25.51)	18.26 (14.32, 21.65)	**<0.001**
PVR (WU)	1.50 (1.18, 2.05)	1.84 (1.23, 2.50)	4.27 (3.34, 5.71)	3.29 (2.37, 5.11)	**<0.001**
SvO_2 (%)	68.5 (53.5, 73.5)	64.0 (58.0, 67.0)	62.0 (52.0, 72.0)	61.0 (53.0, 65.0)	0.787
PAWP (mmHg)	12 (9, 17)	15 (11, 19)	15 (11, 20)	21 (17, 29)	**<0.001**
mPAP (mmHg)	21 (17, 24)	25 (21, 29)	29 (25, 36)	36 (30, 41)	**<0.001**
sPAP (mmHg)	33 (28, 39)	35 (28, 40)	52 (39, 65)	49 (39, 57)	**<0.001**
dPAP (mmHg)	14 (11, 17)	18 (15, 21)	20 (16, 24)	28 (22, 31)	**<0.001**
PAPi	6.50 (4.14, 13.00)	1.50 (1.12, 2.00)	4.75 (3.62, 6.00)	1.75 (1.07, 2.04)	**<0.001**
API	5.06 (3.35, 7.33)	3.00 (0.00, 4.81)	3.82 (2.60, 6.30)	1.97 (0.00, 3.64)	**<0.001**
LVSWi (cJ/m^2)	32.86 (26.93, 40.96)	28.75 (25.00, 32.11)	21.24 (19.08, 25.03)	18.91 (14.63, 22.26)	**< 0.001**
RVSWi (cJ/m^2)	8.22 (6.56, 10.22)	4.69 (3.59, 7.77)	7.15 (4.94, 10.72)	5.20 (4.00, 6.82)	**0.004**
RAP (mmHg)	2.00 (1.00, 4.00)	10.00 (8.00, 14.00)	6.00 (5.00, 10.00)	15.50 (11.00, 19.25)	**<0.001**
RAP/PAWP	0.20 (0.14, 0.32)	0.72 (0.60, 1.00)	0.38 (0.29, 0.64)	0.67 (0.48, 0.91)	**0.001**
PaC (mL/mmHg)	3.34 (2.92, 5.50)	3.56 (2.90, 4.56)	1.31 (1.05, 1.75)	1.74 (1.40, 2.13)	**<0.001**
PaE (mmHg/mL)	0.53 (0.39, 0.62)	0.61 (0.50, 0.74)	1.21 (0.95, 1.57)	1.23 (0.92, 1.50)	**<0.001**
PaE/RAP (1/mL)	0.20 (0.12, 0.33)	0.06 (0.04, 0.07)	0.20 (0.14, 0.29)	0.08 (0.07, 0.12)	**<0.001**
PaE/(RAP/PAWP) (mmHg/mL)	2.12 (1.43, 3.97)	0.77 (0.50, 1.24)	3.16 (1.95, 5.33)	1.90 (1.37, 2.47)	**<0.001**

API, arterial pulsatility index; BMI, body mass index; CI, cardiac index; CICU, cardiac intensive care unit; CPI, cardiac power index; CPI_{RAP}, RAP-adjusted cardiac power index; CRRT, continuous renal replacement therapy; CS, cardiogenic shock; dPAP, diastolic pulmonary artery pressure; eGFR estimated glomerular filtration rate; HR, heart rate; LVEF, left ventricle ejection fraction; LVSWi, left ventricular stroke work index; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; PaC, pulmonary compliance; PaE pulmonary elastance; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistances; RAP, right atrial pressure; RVF, right ventricular failure; RVSWi, right ventricular stroke work index; sPAP, systolic pulmonary artery pressure; SpO_2, peripheral oxygen saturation; SVi, stroke volume index; SvO_2, mixed venous oxygen saturation; SVR, systemic vascular resistances; TAPSE, tricuspid annular plane systolic excursion.
Categorical variables are expressed as count (proportions), continuous variable as medians (inter-quartile range), as appropriate. Bold emphasis denotes statistically significant P values.

RV functions, coupled with high degree of pulmonary circulation overload and high biventricular filling pressures.

In addition, when stratified by the admission SCAI stage, these phenotypes maintained a good association with mortality irrespectively of the admission SCAI class (*Figure S1*).

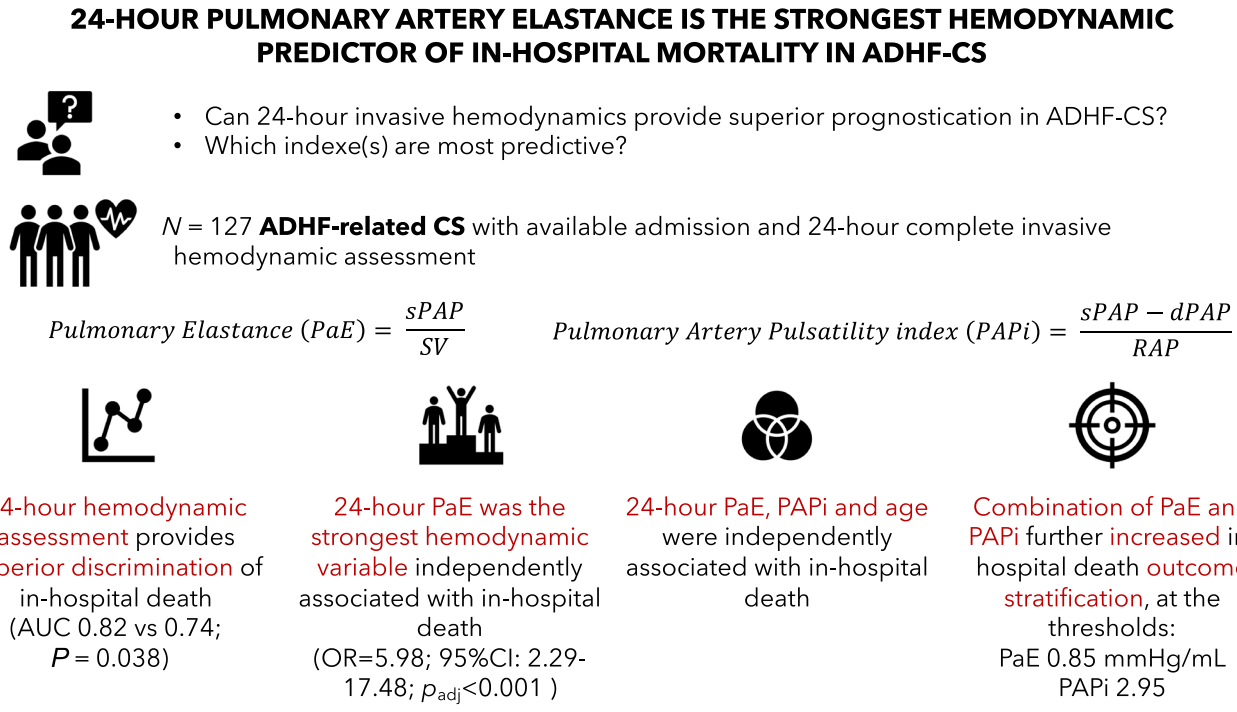
Discussion

The main findings of this study are summarized as follows (*Figure 4*):

- A 24 h haemodynamic assessment after the initial bundle of intensive cares provides superior discrimination of in-hospital death outcome in ADHF-CS patients.
- PaE was the strongest haemodynamic variable independently associated with in-hospital mortality after the first 24 h from admission in ADHF-CS patient.
- PaE at 24 h from admission was independently associated with in-hospital death when adjusted for multiple clinically relevant haemodynamic variables.
- Combination of PaE and PAPi at 24 h from admission generates four different haemodynamic phenotypes, further increasing in-hospital death outcome stratification.

Invasive haemodynamic monitoring in CS has been reappraised to improve risk stratification and prognostic assessment. Longitudinal repeated assessment with PAC has the potential to unveil the 'haemodynamic trajectory' of the patient[12] and thus further refine prognostic evaluation.[13] However, it is unclear what indexes provide prognostic information once supportive therapeutic measures have been initiated, and the majority of available data provides only admission haemodynamic phenotyping. The predictive value of the lumped measure of CPI upon patient admission has been demonstrated for the general CS population[14]: our findings reinforce this notion as baseline CPI_{RAP} was associated with in-hospital death and only differences in parameters of flow and power were observed between survivors and non-survivors upon admission. Of note, while the association of flow and power indexes with in-hospital death persisted, PaE exhibited the greatest discriminatory ability

Figure 4 Summary of study findings.



towards in-hospital death at the 24 h haemodynamic assessment in our cohort of ADHF-CS patients. The 24 h PaE index identified a population both with worse systemic perfusion parameters and with worse pulmonary congestion and RV overload markers. In addition, combination of PAPi with PaE provided incremental risk stratification.

This study reinforces the importance of continuous and serial patient reassessment, as the haemodynamic trajectory appears to play an important role in early CS prognosis.[12] The 24 h window is an important timepoint for reassessment as several treatments would already have been pursued and would have affected haemodynamics[12,15]: in our study, a relevant proportion of patients received IABP, reflecting real-world practice of the involved centres.[16,17] Our results also highlight important haemodynamics targets to be pursued with the initial bundle of intensive cares and suggest their potential usefulness to assess treatment efficacy and guide treatment modulation.

Several considerations may frame the findings of this study. The PaE index, combining a flow measure (stroke volume, SV) with static pulmonary pressure measure (sPAP), may represent an indirect index of decongestion: we recently reported that pulmonary decongestion after the first 24 h is firmly linked with in-hospital mortality in ADHF-CS.[12] In addition, PaE, calculated as the ratio between *sPAP* and *SV* as follows: $PaE = \frac{sPAP}{SV}$, is a lumped measure of passive, pulsatile, and resistive load to the RV.[18] The passive and pulsatile components of RV load increase at higher PAWP, and this makes PaE a sensible measure of RV afterload in case of concomitant LV dysfunction. Adding strength to this hypothesis, PaE was found the most reliable prognostic marker in pulmonary hypertension due to left heart disease.[19] The good approximation of global RV afterload by PaE, coupled with the exquisite afterload sensitivity of the RV, suggest that PaE may represent an haemodynamic marker of RV dysfunction secondary to increased afterload; indeed, high PaE has been shown to predict the occurrence of RV failure after LV assist device (LVAD) implantation.[20] In our patients sample, with a median LVEF of 20 (15, 30)%, each patient presented with a variable degree of LV dysfunction, and PaE thus successfully identifies patients at risk of or with overt RV afterload mismatch and biventricular failure. Indeed, patients with high PaE demonstrated worse parameters of systemic perfusion, pulmonary congestion, and RV afterload. To further explore this hypothesis, we tried to combine an index of RV load to an index of RV adaptation: in our cohort, both 24 h PaE and PAPi independently predicted in-hospital death after adjustment. The additive power of PAPi may be related to the inclusion of the RAP term as it provides a measure of RV involvement and adaptation.[10] We thus combined PaE (index of RV load) and PAPi (index of RV adaptation) at the identified respective thresholds of 0.85 mmHg/mL and 2.95, and we found a steep increase in mortality with worse classes of PaE, with high PaE and low PAPi associated with mortality rates above 50%. A conceptual framework to summarize

these findings may be that 'high PAPi–low PaE' patients at 24 h are those who achieve an early euvolaemic status, good biventricular function, and exhibit best prognosis; 'low PAPi–low PaE' patients suffer prevalent intrinsic RV dysfunction; 'high PAPi–high PaE' patients exhibit compensated RV afterload mismatch and highest pulmonary circulation overload; and 'low PAPi–high PaE' are those with decompensated RV afterload mismatch and worse parameters of biventricular function.

Phenotyping of CS patients has been consistently shown to segregate clusters at different risk of hospital death.[8,21,22] Our proposed classification adds to those currently available for the ADHF-CS, including one based on the number of 'heart chambers' involved in the disease process[8] and a more recent one that identified—with machine learning techniques—three clusters within the CS spectrum (i.e. 'non-congested', 'cardiorenal' and 'cardiometabolic' shock), that provided further prognostication at any given SCAI CS stage.[22] In line with the notion of CS as a systemic disease, the latter approach extends the clinical focus also on the end-organ function and the metabolic adaptation to the CS state, thereby providing a more holistic patient assessment. Notably, PAPi and PaE—and their combinations at the identified thresholds—might not just describe biventricular function and ventriculo-arterial coupling but might also reflect the effects of renal impairment, volaemic imbalance, respiratory performance, vascular resistances and multisystem involvement, all in just two haemodynamic parameters and four phenotypes.

The specific pathophysiology of the ADHF-CS population also underpins its different haemodynamics and hospital outcomes as compared with the myocardial infarction (MI)-related CS.[13,16] While the MI population warrants rapid normalization of cardiovascular power parameters, as demonstrated by the persistently strong prognostic value of power output measures at 24 h,[23,24] congestion measures and pulmonary circulation overload indexes are more central to the ADHF population ranging across the CS spectrum.[12,25] PaE, providing a combined measure of perfusion and pulmonary congestion coupled with a quantification of RV afterload, emerged as an important and independent 24 h haemodynamic predictor of in-hospital mortality in ADHF-CS patients.

Limitations

This study has some limitations, chiefly linked to its retrospective design. The 24 h haemodynamic invasive assessment mirrors the initial therapies that were instituted upon patient admission: as such, interaction between supportive measures and final haemodynamics at 24 h may have been variable in the study cohort depending on different treatment strategies. Nevertheless, this reinforces the powerful prognostication that PaE bears, across several different treatment strategies. The sample size is relatively small, as a consequence of selecting a population with a complete haemodynamic monitoring with PAC at two separate timepoints. The haemodynamic assessment was achieved by means of a PAC, and whether these findings apply also to echocardiographic non-invasive assessment remains uncertain. Finally, a prospective, multicentric validation will help to better understand whether the 24 h PaE is a simple prognostic marker of worse prognosis or rather an actionable prognostic driver.

Conclusions

Pulmonary artery elastance is the most powerful haemodynamic predictor of in-hospital death at 24 h in patients with ADHF-CS. Age, 24 h PaE, and PAPi are independently associated with hospital mortality. PaE captures RV afterload mismatch and PAPi provides a metric of RV adaptation: thus, their combination generates four distinct haemodynamic phenotypes, enhancing in-hospital death risk stratification.

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Conflict of interest

None of the authors has relevant conflict of interest to disclose.

Supporting information

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

Figure S1. In-hospital death rate according to admission SCAI CS stage and 24-hour hemodynamic phenotype (based on PaE and PAPi).

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