

Ventilation strategies in cardiogenic shock: Insights from the AltShock-2 registry

Alice Sacco¹, Andrea Montisci^{2*}, Giovanni Tavecchia¹, Simone Frea³, Davide Bernasconi⁴, Costanza N.J. Colombo^{5,6}, Stephanie Bertolin⁷, Giovanna Viola¹, Luca Villanova¹, Martina Briani⁸, Lisa Patrini⁵, Pier Paolo Bocchino³, Carlotta Sorini Dini⁹, Nicoletta D'Ettore¹⁰, Maurizio Bertaina¹¹, Mario Iannaccone¹¹, Luciano Potena¹², Letizia Bertoldi⁸, Serafina Valente⁹, Rita Camporotondo¹³, Marco Marini¹⁴, Matteo Pagnesi¹⁵, Marco Metra¹⁵, Gaetano De Ferrari³, Fabrizio Oliva¹, Nuccia Morici¹⁶, Federico Pappalardo^{17,18}, and Guido Tavazzi^{5,6}, on behalf of AltShock-2 Investigators

¹Cardiac Intensive Care Unit, De Gasperis Cardio Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; ²Division of Cardiothoracic Intensive Care, ASST Spedali Civili, Brescia, Italy; ³Intensive Cardiac Care Unit, Città della Salute e della Scienza di Torino, Turin, Italy; ⁴Bicocca Bioinformatics Biostatistics and Bioimaging Centre - B4, School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy and Functional Department for Higher Education, Research, and Development, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; ⁵Department of Clinical-Surgical, Diagnostic and Paediatric Sciences University of Pavia, Pavia, Italy; ⁶Anestesia e Rianimazione I, Fondazione Policlinico San Matteo Hospital IRCCS, Pavia, Italy; ⁷Cardiothoracic and Vascular Anesthesia and Intensive Care, AO SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; ⁸Humanitas Research Hospital IRCCS Rozzano, Milan, Italy; ⁹Division of Cardiology, Department of Medical Biotechnologies, University of Siena, Siena, Italy; ¹⁰Cardiologia, Ospedale San Giacomo, Novi Ligure, Italy; ¹¹Division of Cardiology, San Giovanni Bosco Hospital, ASL Città di Torino, Turin, Italy; ¹²Cardiology Unit, Cardio-Thoraco-Vascular Department, University Hospital of Bologna, Policlinico S. Orsola-Malpighi, Bologna, Italy; ¹³Cardiology Unit, Fondazione Policlinico San Matteo Hospital IRCCS, Pavia, Italy; ¹⁴Department of Cardiovascular Sciences, Clinic of Cardiology, Ospedali Riuniti, Ancona, Italy; ¹⁵Cardiology, ASST Spedali Civili, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; ¹⁶IRCCS S. Maria Nascente - Fondazione Don Carlo Gnocchi ONLUS, Milan, Italy; ¹⁷Kore University, Enna, Italy; and ¹⁸Centro Cuore GB Morgagni, Catania, Italy

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Aims

To describe the use and the relation to outcome of different ventilation strategies in a contemporary, large, prospective registry of cardiogenic shock patients.

Methods and results

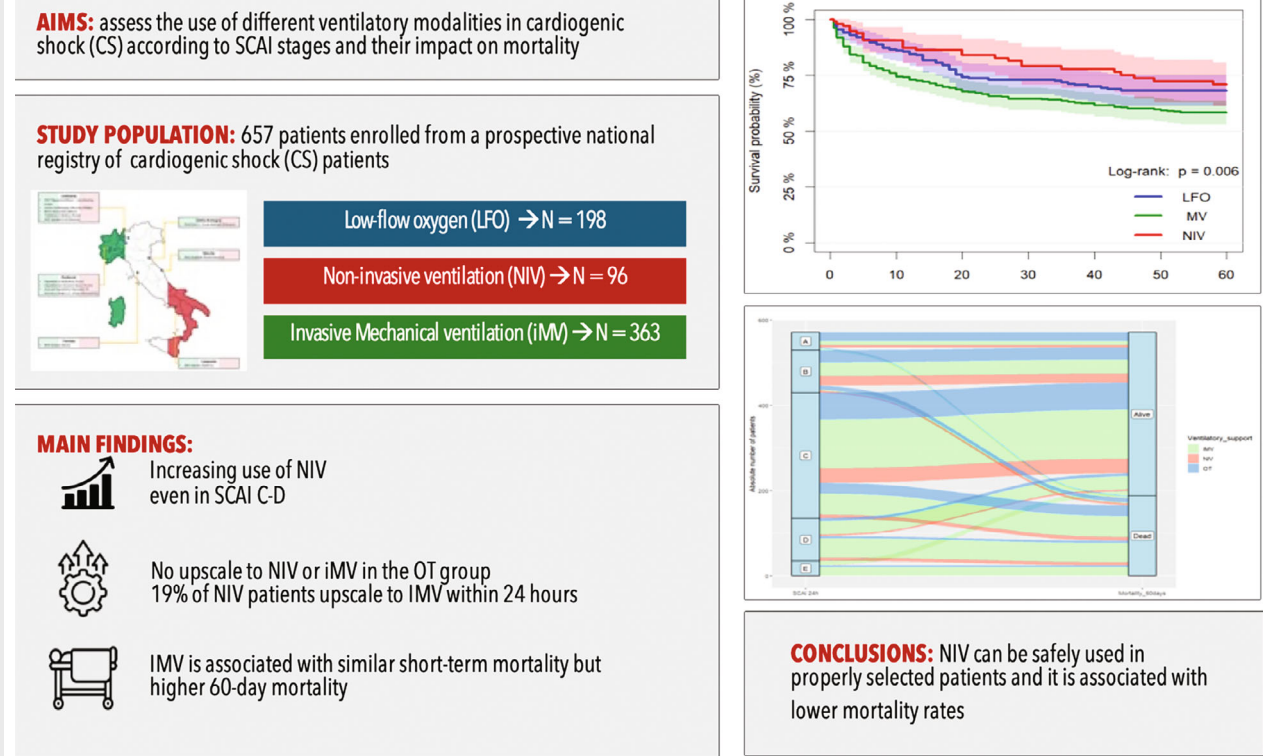
Among 657 patients enrolled from March 2020 to November 2023, 198 (30.1%) received oxygen therapy (OT), 96 (14.6%) underwent non-invasive ventilation (NIV), and 363 (55.3%) underwent invasive mechanical ventilation (iMV). Patients in the iMV group were significantly younger compared to those in the NIV and OT groups (63 vs. 69 years, $p < 0.001$). There were no significant differences between groups regarding cardiovascular risk factors. Patients with SCAI B and C were more frequently treated with OT and NIV compared to iMV (65.1% and 65.4% vs. 42.6%, respectively, $p > 0.001$), while the opposite trend was observed in SCAI D patients (12% and 12.2% vs. 30.9%, respectively, $p < 0.001$). All-cause mortality at 24 h did not differ amongst the three groups. The 60-day mortality rates were 40.2% for the iMV group, 26% for the OT group, and 29.3% for the NIV group ($p = 0.005$), even after excluding patients with cardiac arrest at presentation. In the multivariate analysis including SCAI stages, NIV was not associated with worse mortality compared to iMV (hazard ratio 1.97, 95% confidence interval 0.85–4.56), even in more severe SCAI stages such as D.

Conclusions

Compared to previous studies, we observed a rising trend in the utilization of NIV among cardiogenic shock patients, irrespective of aetiology and SCAI stages. In this clinical scenario, NIV emerges as a safe option for appropriately selected patients.

*Corresponding author. Division of Cardiothoracic Intensive Care, ASST Spedali Civili, 25123 Brescia, Italy. Email: montisci.andrea@yahoo.it

Graphical Abstract



Ventilatory modalities in cardiogenic shock: insights from the AltShock-2 registry.

Keywords

Cardiogenic shock • Mechanical ventilation • Positive pressure ventilation • Invasive mechanical ventilation • Non-invasive ventilation

Introduction

Cardiogenic shock (CS) remains a critical condition potentially leading to multiorgan failure associated with significant morbidity and mortality. Recently, the early implantation of temporary mechanical circulatory supports (tMCS), alongside invasive haemodynamic monitoring within a 'shock team' framework, has demonstrated improved outcomes.¹⁻⁴ Respiratory failure is common in the CS population, representing the most common organ failure and being significantly associated with worse outcome.^{5,6} Data from recent registries showed that the rate of CS patients treated with positive pressure ventilation (PPV) is up to 70%.^{7,8} PPV plays a crucial role in the management of CS by providing adequate oxygenation, improving haemodynamics, and reducing myocardial workload.⁹⁻¹²

Despite the large use of PPV, the optimal ventilation strategy remains unclear, and haemodynamic profiles and underlying aetiologies present unique challenges for clinical decision making.¹⁰⁻¹²

The present study aims to evaluate the use of different ventilation strategies and their impact in a contemporary, large, prospective registry of CS patients with different aetiologies.

Methods

Study design

All patients within the AltShock-2 registry, a multicentre prospective study ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT04295252), were included. The registry, operating across 12 Italian tertiary centres, has been enrolling patients with CS since March 2020. CS was diagnosed at each enrolling site according to the most recent definitions¹³ and all patients were stratified according to the Society for Cardiovascular Angiography and Interventions (SCAI) stages.¹⁴

Only adult (age ≥ 18 years) patients with known clinical outcomes were considered for analyses.

The assessment of the need for ventilatory support and the selection of ventilatory mode (non-invasive ventilation [NIV], including continuous positive airway pressure and bilevel positive airway pressure, or

invasive mechanical ventilation [iMV]) were at the discretion of the treating physician, who followed standard indications and contraindications for NIV and iMV treatment.

We categorized patients into three groups according to the highest intensity of ventilatory support throughout their hospitalization: oxygen therapy (OT), NIV, and iMV. IMV was started as a consequence of (a) cardiac arrest; (b) deterioration of neurologic function; (c) NIV failure, defined as requirement for endotracheal intubation due to gas exchanges deterioration despite NIV, or fatigue, or impending respiratory arrest; (d) periprocedural reasons, wherein iMV was required only during an invasive procedure, with an iMV duration of <24 h. High-flow nasal cannula ventilation was included in the OT group.

The primary endpoint was the cumulative probability of time to all-cause death at 60 days. Escalation to NIV and iMV was also documented. We examined differences in aetiology, clinical and laboratory characteristics, haemodynamic, echocardiographic findings and prognostic scores on admission and at 24 h. Mortality at 24 h and mid-term survival were reported for each treatment cohort.

The vasopressor-inotropic score (VIS) was calculated for the overall population. This quantitative measure assesses the pharmacological adrenergic support provided to patients by summing the dosages of various cardiovascular medications.¹⁵ We prospectively assigned SCAI stages to individual patients according to the updated classification.¹⁶ A further refinement of the patients' shock stage was independently performed by two authors (NM, GT) during data analysis using the updated SCAI shock stages classification.^{14,17}

The investigation conforms with the principles outlined in the Declaration of Helsinki.¹⁸

Statistical analysis

The distribution of categorical variables was summarized using counts and percentages, while median and interquartile range (IQR) were used for continuous variables. Comparison between respiratory support groups was performed using Chi-square test for categorical variables and with Kruskal–Wallis test for continuous variables. Holm adjustment to Chi-square test for categorical variables and Mann–Whitney test for continuous variables was applied to pairwise comparisons between groups. Survival probability until day 60 after cardiac intensive care unit (CICU) admission was estimated using Kaplan–Meier curves. Multivariable Cox regression analysis was used to assess the association of several risk factors (respiratory support group, age, MCS, lactates) with 60-day mortality. Covariates included in the model were chosen as the most relevant to adjust the association of respiratory support groups with mortality based on clinical knowledge. A regression analysis with Cox model was also performed on subgroups of SCAI at 24 h. Statistical analyses were performed using R (version 4.3.2, R Foundation for Statistical Computing, Vienna, Austria).

Results

We analysed 657 patients with complete follow-up information, out of a total of 725 patients consecutively admitted from March 2020 to November 2023 with a diagnosis of CS.

The main demographics and clinical characteristics of the study population are shown in *Table 1*.

Overall, 198 patients (30%) were treated with OT, 119 (16.4%) were supported with NIV and 363 (55%) with iMV. No one in the OT group experienced a step up to either NIV or iMV, whereas 23

of the NIV group were escalated to iMV within the first 24 h and were included in the latter group for analysis.

Patients in the iMV group were significantly younger compared to the NIV and OT group (63, 69 and 69 years, respectively, $p < 0.001$). There were no significant differences between groups in terms of cardiovascular risk factors (*Table 1*). Patients with acute myocardial infarction (AMI)-CS showed a higher rate of iMV compared to non-AMI-CS patients, particularly acute decompensated heart failure (ADHF)-CS (54.3% vs. 45.7%, $p = 0.001$).

The three groups were comparable in terms of systolic blood pressure, heart rate, oxygen saturation, left ventricular ejection fraction and tricuspid annular plane systolic excursion (*Table 1*). The NIV group exhibited a more severe congestive profile (right atrial pressure compared to the iMV group, 14 vs. 11 mmHg, $p = 0.006$).

N-terminal pro-B-type natriuretic peptide levels were not significantly different between the iMV and NIV group, but appeared to be significantly higher in the OT group compared to the iMV group (17 057.5 vs. 6177.5 ng/L, $p < 0.001$).

Thirty-eight patients (5%) had pneumonia or ventilator-associated pneumonia, 37 (10%) in the iMV group and one in the NIV group. Notably, iMV patients with this respiratory complication had a longer CICU stay compared to those without (median [IQR]: 25 [12–38] vs. 10 [5–17] days, $p < 0.001$).

At admission, 10% of patients were classified as SCAI B. Specifically, 17% of patients in the OT group, 16% in the NIV group, and 6% in the iMV group were classified as SCAI B ($p < 0.001$). Patients classified as SCAI C were also more frequently treated with OT and NIV compared to iMV (65.1% and 65.4% vs. 42.6%, respectively, $p > 0.001$), while the opposite trend was observed in SCAI D patients (12% and 12.2% vs. 30.9%, respectively, $p < 0.001$) (*Table 1*).

Pharmacologic, ventilatory and MCS settings are shown in *Table 2*.

The iMV group, as compared to the NIV and OT groups, had lower PaO₂ (PaO₂/FiO₂ ratio 215 vs. 278 and 310 mmHg, $p < 0.001$) and higher PaCO₂ (paCO₂ 37 vs. 32.5 and 31 mmHg, $p < 0.001$). PEEP levels during the first 24 h were similar in the iMV and NIV groups, but the duration of ventilatory support was significantly higher in the iMV group compared to the NIV group (96 vs. 48 h, $p < 0.001$).

The iMV patients had higher pharmacologic support (VIS 20 vs. 9 and 8 points, $p < 0.001$, in the iMV group compared to the NIV and OT groups), and a significantly greater proportion of NIV patients were treated with sodium nitroprusside (53.1% vs. 32.8% in the OT group and 24.2% in the iMV group, $p < 0.001$).

The time from CICU admission to tMCS was longer in the OT and NIV groups compared to the iMV group (median [IQR]: 0 [0–1] days [69.4% 0 days] and 0 [0–1] days [64.8% 0 days] vs. 0 [0–0] days [86.2% 0 days], $p < 0.001$).

Venoarterial extracorporeal membrane oxygenation and Impella were more frequently implanted in the iMV group (*Table 2*), whereas intra-aortic balloon pump (IABP) was the most common device used in the OT and NIV groups compared to the iMV group (92.7% and 88.9% vs. 73.7%, $p < 0.001$) (*Table 2*).

Table 1 Comparison of demographic and clinical characteristics between patients categorized by respiratory support

Characteristics	Overall (n = 657)	OT (n = 198)	NIV (n = 96)	iMV (n = 363)	p-value*
Age, years	66 [56–75]	69 [57–80]	69 [60.5–78]	63 [55–72]	<0.001 ^{b,c}
Male sex, n (%)	499 (76.1)	142 (71.7)	80 (83.3)	277 (76.5)	0.087
Risk factors, n (%)					
Smoking	162 (24.9)	43 (21.8)	27 (28.4)	92 (25.7)	0.418
Hypertension	362 (55.2)	106 (53.8)	58 (60.4)	198 (54.5)	0.529
Diabetes	202 (30.8)	57 (28.8)	35 (36.5)	110 (30.4)	0.397
CS aetiology, n (%)					0.001 ^{b,c}
AMI	329 (50.1)	88 (44.4)	44 (45.8)	197 (54.3)	
ADHF	190 (28.9)	71 (35.9)	39 (40.6)	80 (22.0)	
Acute myocarditis	17 (2.6)	3 (1.5)	0 (0.0)	14 (3.9)	
PE	16 (2.4)	5 (2.5)	0 (0.0)	11 (3.0)	
Other	105 (16.0)	31 (15.7)	13 (13.5)	61 (16.8)	
Resuscitated	156 (25.4)	10 (5.8)	4 (4.3)	142 (40.6)	<0.001 ^{b,c}
Clinical findings					
SBP, mmHg	95 [80–110]	93 [83.50–107.25]	95.50 [84.25–115.50]	96 [80–112]	0.597
Heart rate, bpm	90 [75.5–110]	90 [75–110]	90 [78–110]	91 [77.5–110]	0.926
Heart rate 24 h, bpm	86.00 [74–100]	88 [73–100]	86.5 [74.5–104.25]	86 [75–99.75]	0.624
SpO ₂ , %	97 [95–99]	97 [95–98]	97.50 [95–99]	98 [95–100]	0.067
SpO ₂ 24 h, %	98 [96–100]	98 [96–99]	98 [96–99]	98 [97–100]	0.001 ^b
RAP, mmHg	12 [8–15]	12 [7–17]	14 [9–18]	11 [8–14]	0.006 ^c
RAP 24 h, mmHg	10 [6–12]	10 [5–14]	9 [5.25–12]	9 [6–12]	0.237
LVEF, %	25 [17–33.75]	25 [18–34.50]	25 [18–30]	25 [15–34.75]	0.711
TAPSE, mm	15 [12–18]	15 [13–18]	15 [13–18]	15 [11–18]	0.067
Biochemistry					
Haemoglobin, g/dl	12.70 [10.80–14.50]	12.45 [10.97–14.40]	12 [10–13.80]	12.90 [11–14.80]	0.009 ^c
Creatinine, mg/dl	1.33 [1–1.90]	1.30 [1–2.20]	1.40 [1.02–2.55]	1.29 [1–1.80]	0.149
ALT, U/L	68 [27–188]	57 [27–181]	28.50 [19.25–79.50]	89 [36.50–227]	<0.001 ^{a,c}
Bilirubin, mg/dl	0.80 [0.50–1.40]	1 [0.60–1.70]	1 [0.60–1.80]	0.80 [0.50–1.30]	0.001 ^{b,c}
NT-proBNP, ng/L	8560 [4377.50–22 244]	17 057.50 [6373.75–27 451]	8674 [4998–24 945]	6177.50 [3101.25–10 033.75]	<0.001 ^{b,c}
NT-proBNP 24 h, ng/L	6996 [3667–19 050]	10 484 [4747–22 943]	9418.50 [5028.75–21 422.75]	4723 [2279.25–8978.25]	<0.001 ^{b,c}
BNP, pg/ml	455 [97–1213]	737 [261–1908]	1089 [514–1904]	352 [61.50–768.50]	<0.001 ^{b,c}
BNP 24 h, pg/ml	426 [204–873]	557 [325.50–1136]	620 [420.75–1150]	384 [176–633.50]	0.013 ^b
Blood gas analysis					
pH	7.37 [7.28–7.44]	7.42 [7.36–7.46]	7.40 [7.34–7.46]	7.33 [7.22–7.41]	<0.001 ^{b,c}
pH 24 h	7.45 [7.40–7.49]	7.47 [7.43–7.50]	7.46 [7.41–7.50]	7.44 [7.39–7.48]	0.001 ^b
pCO ₂ , mmHg	35 [30–42]	31 [27–37]	32.50 [28–38]	37 [32–45.50]	<0.001 ^{b,c}
pCO ₂ 24 h, mmHg	35.00 [31.00–40.00]	34.00 [30.00–38.00]	34.00 [30.00–38.00]	36.00 [33.00–41.00]	<0.001 ^{b,c}
pO ₂ , mmHg	98 [78–141.50]	91 [77–116.50]	94 [75.50–123]	105 [79.75–154.25]	0.001 ^{b,c}
pO ₂ 24 h, mmHg	101 [83–136]	95 [80–112]	102 [85–129]	107.50 [85–152]	<0.001 ^{a,b}
pO ₂ /FiO ₂ ratio	250 [159.25–362.50]	310 [210–389]	278.50 [203–353]	215 [131–325]	<0.001 ^{b,c}
pO ₂ /FiO ₂ ratio 24 h	280.5 [207–360]	314 [235.5–400]	303 [240–359.5]	250 [193.5–330]	<0.001 ^{b,c}
Lactates, mmol/L	2.70 [1.60–5.80]	2.30 [1.60–4.25]	1.80 [1.30–2.90]	3.40 [1.90–7.12]	<0.001 ^{a,b,c}
Lactates 24 h, mmol/L	1.50 [1.10–2.40]	1.40 [1.10–1.90]	1.50 [1.00–1.90]	1.75 [1.17–2.70]	<0.001 ^{b,c}
SvO ₂ , %	62 [51–71]	57.90 [45–66.90]	57.80 [46–66]	66.40 [55.90–73]	<0.001 ^{b,c}
SvO ₂ 24 h, %	65.95 [58.25–73]	61.40 [56–69]	63 [57.22–69.43]	69.15 [60.40–74.05]	<0.001 ^{b,c}
SCAI class, n (%)					<0.001 ^{b,c}
A	20 (3.3)	4 (2.3)	7 (7.8)	9 (2.6)	
B	64 (10.5)	30 (17.1)	14 (15.6)	20 (5.8)	
C	318 (52.3)	114 (65.1)	58 (64.4)	146 (42.6)	
D	138 (22.7)	21 (12.0)	11 (12.2)	106 (30.9)	
E	68 (11.2)	6 (3.4)	0 (0.0)	62 (18.1)	
SCAI class 24 h, n (%)					<0.001 ^{b,c}
A	42 (7.3)	23 (13.9)	6 (6.8)	13 (4.1)	
B	100 (17.5)	39 (23.5)	27 (30.7)	34 (10.7)	
C	295 (51.6)	88 (53.0)	43 (48.9)	164 (51.6)	
D	100 (17.5)	12 (7.2)	12 (13.6)	76 (23.9)	
E	35 (6.1)	4 (2.4)	0	31 (9.7)	
Mortality, n (%)					
24-h mortality	20 (3.0)	5 (2.5)	1 (1.0)	14 (3.9)	0.317
60-day all-cause mortality, n (%)	229 (34.9)	58 (29.3)	25 (26.0)	146 (40.2)	0.005 ^{b,c}

Data are presented as median (interquartile range), unless indicated otherwise.

ADHF, acute decompensated heart failure; ALT, alanine transaminase; AMI, acute myocardial infarction; BNP, B-type natriuretic peptide; CS, cardiogenic shock; FiO₂, fractional inspired oxygen concentration; iMV, invasive mechanical ventilation; LVEF, left ventricular ejection fraction; NIV, non-invasive ventilation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OT, oxygen therapy; pCO₂, partial pressure of carbon dioxide; PE, pulmonary embolism; pO₂, partial pressure of oxygen; RAP, right atrial pressure; SBP, systolic blood pressure; SCAI, Society for Cardiovascular Angiography and Interventions; SpO₂, saturation of peripheral oxygen; SvO₂, venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion.

*P-values are calculated with the Kruskal-Wallis test for continuous variables and the Chi-square test for categorical variables. Pairwise comparisons are performed using the Mann-Whitney test for continuous variables and the Chi-square test for categorical variables, in both cases p-values are adjusted by Holm correction: adjusted p < 0.05 for the difference between (°) OT vs. NIV, (°) OT vs. iMV, (°) NIV vs. iMV.

Table 2 Pharmacological, mechanical circulatory support and ventilatory support

Characteristics	Overall (n = 657)	OT (n = 198)	NIV (n = 96)	iMV (n = 363)	p-value*
Pharmacological treatment, n (%)					
Dobutamine	253 (38.5)	112 (56.6)	35 (36.5)	106 (29.2)	<0.001 ^{a,b}
Dopamine	78 (11.9)	26 (13.1)	14 (14.6)	38 (10.5)	0.436
Vasopressin	16 (2.4)	0 (0.0)	0 (0.0)	16 (4.4)	0.001 ^b
Sodium nitroprusside	204 (31.1)	65 (32.8)	51 (53.1)	88 (24.2)	<0.001 ^{a,b,c}
Enoximone	14 (2.1)	3 (1.5)	2 (2.1)	9 (2.5)	0.751
Milrinone	29 (4.4)	7 (3.5)	4 (4.2)	18 (5.0)	0.729
Epinephrine	352 (53.6)	56 (28.3)	55 (57.3)	241 (66.4)	<0.001 ^{a,b}
Norepinephrine	372 (56.6)	85 (42.9)	35 (36.5)	252 (69.4)	<0.001 ^{b,c}
Levosimendan	224 (34.1)	60 (30.3)	41 (42.7)	123 (33.9)	0.108
Inhaled nitric oxide	39 (5.9)	0 (0.0)	0 (0.0)	39 (10.7)	<0.001 ^{b,c}
Mechanical circulatory support, n (%)					
Any support	428 (65.3)	98 (50.0)	54 (56.2)	276 (76.0)	<0.001 ^{b,c}
IABP	342 (79.9)	89 (92.7)	48 (88.9)	205 (73.7)	<0.001 ^b
Impella	95 (22.2)	9 (9.3)	6 (11.1)	80 (28.9)	<0.001 ^{b,c}
ECMO	128 (29.8)	6 (6.2)	0 (0.0)	122 (43.7)	<0.001 ^{b,c}
Ventilatory support					
Duration of ventilation, h	72 [36–212]		48 [24–96]	96 [39–240]	<0.001
PEEP, cmH ₂ O	7 [5–10]		7 [6–8]	7 [5–10]	0.293

Data are presented as median (interquartile range), unless indicated otherwise.

ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; iMV, invasive mechanical ventilation; NIV, non-invasive ventilation; OT, oxygen therapy; PEEP, positive end-expiratory pressure.

*P-values are calculated with the Kruskal–Wallis test for continuous variables and the Chi-square test for categorical variables. Pairwise comparisons are performed using the Mann–Whitney test for continuous variables and the Chi-square test for categorical variables, in both cases p-values are adjusted by Holm correction: adjusted p < 0.05 for the difference between (^a) OT vs. NIV, (^b) OT vs. iMV, (^c) NIV vs. iMV.

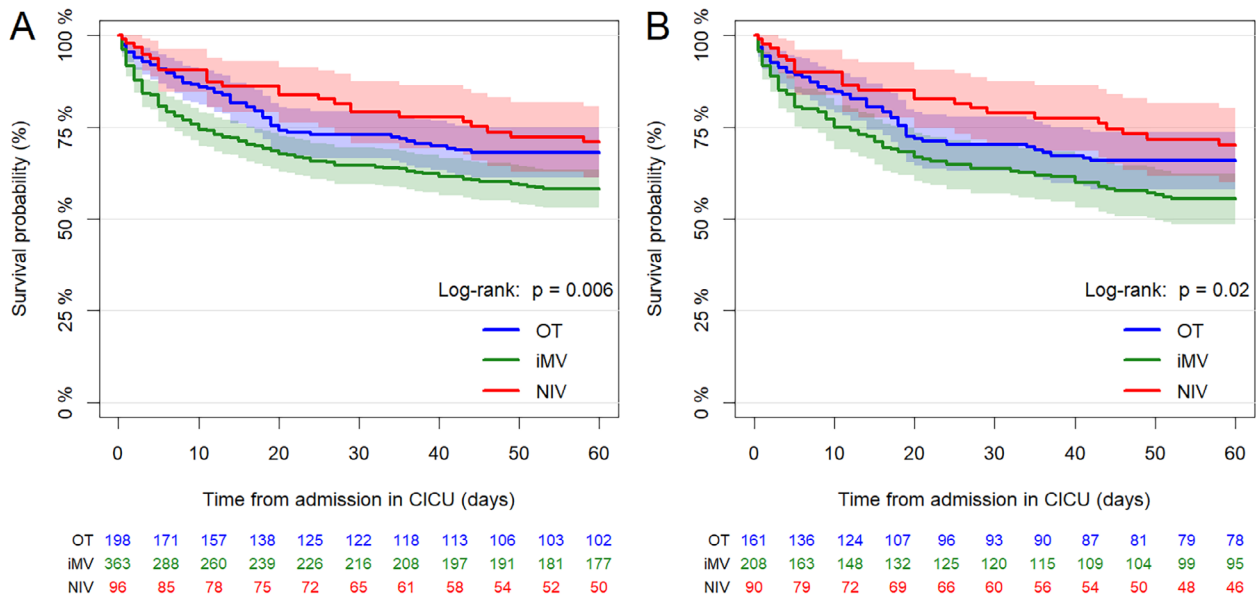


Figure 1 Mid-term survival by respiratory support (A) and mid-term survival by respiratory support, after excluding patients with cardiac arrest at presentation (B). (A) Pairwise comparisons with p-values adjusted by Holm correction: oxygen therapy (OT) vs. non-invasive ventilation (NIV) p = 0.439, OT vs. invasive mechanical ventilation (iMV) p = 0.032, NIV vs. iMV p = 0.032. (B) Pairwise comparisons with p-values adjusted by Holm correction: OT vs. NIV p = 0.343, OT vs. iMV p = 0.103, NIV vs. iMV p = 0.034. CICU, cardiac intensive care unit.

No difference was found between OT, NIV and iMV groups with respect to heart replacement therapy, either left ventricular assist device (3%, 4.2% and 4.4%, $p = 0.722$) or orthotopic heart transplantation (4.5%, 4.2% and 4.7%, $p = 0.977$).

Mortality

All-cause mortality at 24 h was similar in the three groups (Table 1), whereas 60-day mortality was significantly higher in the iMV group compared with the OT and NIV groups (40.2% vs. 29.3% and 26%, respectively, $p = 0.005$) (Table 1 and Figure 1A).

Furthermore, after exclusion of 156 patients with cardiac arrest at presentation, iMV was still associated with lower survival compared to the NIV group (Figure 1B). After adjustment for age, lactates, and tMCS, iMV was associated with a higher risk of 60-day mortality (iMV vs. NIV: HR 2.24, 95% CI 1.36–3.68) (Table 3).

Table 3 Multivariate Cox regression analysis for 60-day mortality on patients with no cardiac arrest ($n = 459$)

Variable	HR (95% CI)	p-value
Age, per year	1.05 (1.03–1.06)	<0.001
NIV vs. OT	0.84 (0.50–1.40)	0.502
iMV vs. OT	1.63 (1.10–2.39)	0.014
Lactates, per unit	1.06 (1.02–1.10)	0.006
MCS yes vs. no	0.79 (0.54–1.16)	0.231
Inotropic score, per unit	1.02 (1.01–1.03)	<0.001

CI confidence interval; HR, hazard ratio; iMV, invasive mechanical ventilation; MCS, mechanical circulatory support; NIV, non-invasive ventilation; OT, oxygen therapy.

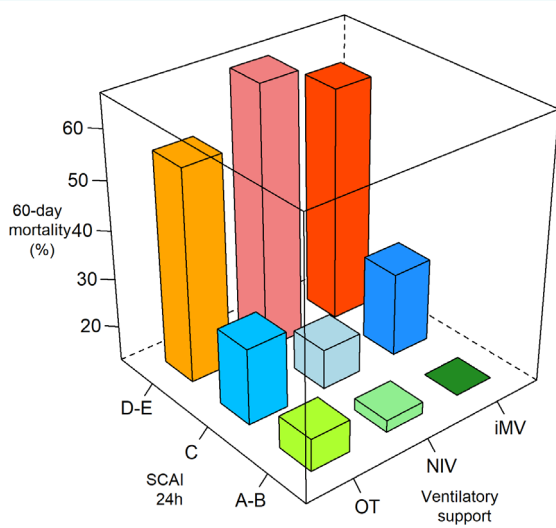


Figure 2 Sixty-day mortality of the oxygen therapy (OT), non-invasive ventilation (NIV) and invasive mechanical ventilation (iMV) groups stratified by SCAI at 24 h.

Table 4 Multivariate Cox regression analysis for 60-day mortality on subgroups of SCAI at 24 h and adjusted for age and mechanical circulatory support

Variable	HR (95% CI)	p-value
SCAI/24 h A-B ($n = 142$)		
Age, per year	1.07 (1.02–1.11)	0.002
NIV vs. OT	1.06 (0.35–3.21)	0.919
iMV vs. OT	1.13 (0.39–3.27)	0.820
MCS yes vs. MCS no	0.68 (0.25–1.82)	0.439
Inotropic score, per unit	1.02 (1.01–1.04)	0.004
SCAI/24 h C ($n = 295$)		
Age, per year	1.04 (1.02–1.06)	<0.001
NIV vs. OT	0.65 (0.30–1.39)	0.264
iMV vs. OT	0.92 (0.55–1.54)	0.745
MCS yes vs. MCS no	0.80 (0.50–1.28)	0.357
Inotropic score, per unit	1.02 (1.01–1.03)	<0.001
SCAI/24 h D ($n = 135$)		
Age, per year	1.03 (1.00–1.05)	0.034
NIV vs. OT	1.17 (0.38–3.60)	0.791
iMV vs. OT	2.14 (0.81–5.66)	0.125
MCS yes vs. MCS no	0.38 (0.19–0.76)	0.007
Inotropic score, per unit	1.01 (0.99–1.02)	0.244

CI, confidence interval; HR, hazard ratio; iMV, invasive mechanical ventilation; MCS, mechanical circulatory support; NIV, non-invasive ventilation; OT, oxygen therapy; SCAI, Society for Cardiovascular Angiography and Interventions.

Figure 2 illustrates the 60-day mortality rates among the OT, NIV and iMV groups, categorized by SCAI at 24 h. In the multivariate analysis conducted across the entire population, stratified by SCAI stage, NIV was found to be associated with a non-significant trend towards a reduced risk of 60-day mortality. Notably, this trend persisted even in more severe SCAI stages, including stage D (iMV vs. NIV: HR 1.97, 95% CI 0.85–4.56) (Table 4).

Discussion

This study compares the use of ventilatory support in a real-world, multicentre, prospective, contemporary cohort of patients with CS. The main findings of our study are as follows: (i) compared with previous data, there is a growing trend in NIV utilization among CS patients, including those in higher SCAI stages (C–D), with a low rate of escalation to iMV; (ii) iMV patients have a higher risk of 60-day mortality even after adjustment for lactates, MCS use and SCAI stage (Graphical Abstract).

In the AHEAD, CCCTN, and CardShock registries,^{7,8,19} only 8%, 5%, and 12% of patients, respectively, were treated with NIV. Notably, compared to the CardShock results, we were able to describe the maximum intensity of ventilatory support during the index event throughout the entire hospital stay and not just during the first 24 h.

In our study, 16.4% of patients received initial treatment with NIV, a markedly higher percentage than in previous studies, accompanied by a low rate of escalation to iMV, mostly within the first 24 h. The rate of patients treated with OT was 30%, similar to

the CardShock study.⁸ This cohort did not differ significantly from the NIV group in terms of baseline characteristics. Compared to the iMV group, OT patients were more often hospitalized with ADHF-CS and had better baseline oxygenation. Moreover, these patients had lower SCAI stages at baseline compared to the iMV group, confirming that CS treatment should be tailored to patient risk.

While PPV is typically used to manage respiratory failure, it also exerts a favourable haemodynamic impact by reducing the respiratory workload. This facilitates the redistribution of oxygen delivery from respiratory muscles to vital organs, optimizing myocardial oxygen consumption.¹⁰ In addition, PPV improves left ventricular afterload by modulating transmural pressure, reduces left ventricular preload,¹⁰ and promotes hydrostatic displacement of alveolar oedema.²⁰

In a randomized trial, PPV was shown to be superior to OT in improving respiratory, haemodynamic, and metabolic outcomes without a clear effect on mortality.²¹ Within the spectrum of PPV, both iMV and NIV are used in CS patients, depending on patient's respiratory status, haemodynamic stability, and the need for short-term intra-procedural sedation or anaesthesia. IMV allows the control of respiratory mechanics, while NIV can serve as an alternative for awake cooperative patients with intact respiratory drive. All these modalities, in contrast to OT, offer higher flows to support the greater minute ventilation request (up to 60 L/min), which is the key factor to reduce the work of breathing.²²

Invasive mechanical ventilation setting strategies, such as lung protective ventilation, have been imported from studies in acute respiratory failure of different aetiologies than cardiogenic pulmonary oedema.²³ However, recent clinical experiences shed light on the potential limitations of traditional approaches in this specific patient population.¹¹ As a result, a shift towards personalized ventilation strategies that consider both pulmonary and cardiac pathophysiology has gained momentum. Unfortunately, data on the use of PPV in CS are scarce, despite the increasing incidence of respiratory failure in CICUs. According to available studies,^{19,24,25} most patients with CS, especially AMI-CS, requiring ventilatory support are ventilated invasively.

Based on this limited evidence, the European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure recommend correcting hypoxaemia when $SpO_2 < 90\%$ or $PaO_2 < 60$ mmHg by starting PPV as soon as available in patients with respiratory distress to improve gas exchange, without providing further recommendations on the type of support (NIV or iMV) in patients with CS.²⁶ In addition, the 2017 European Respiratory Society/American Thoracic Society clinical practice guidelines on the use of NIV in acute respiratory failure do not provide recommendations for patients with CS, given the complexity of the disease interaction and the lack of evidence specifically in these patients.²⁷

Our results suggest that the iMV group included a more severe CS SCAI stage, defined by a higher incidence of cardiac arrest, metabolic acidosis, higher lactate levels. Worse respiratory alveolar exchanges were also evident in the iMV group, despite the more intensive respiratory support, as indicated by the higher degree of hypoxaemia and hypercarbia. Conversely, the NIV group included

more patients with a higher degree of congestion, probably due to the higher prevalence of ADHF aetiology, but less hypoperfusion compared to the iMV group.

According to the aetiology, patients with AMI-CS were more frequently classified as SCAI E likely due to a higher incidence of cardiac arrest in this group. The IABP was the most used device across both groups, whereas the Impella device was more frequently utilized in AMI-CS patients.

Our study presents an analysis of ventilation modalities alongside the incorporation of SCAI stage classification, effectively filling a notable void observed in previous research.^{7,8,19,24}

The lack of phenotyping has posed a significant limitation in discerning which patients might derive benefits from different ventilation modalities, particularly in critical clinical scenarios where prompt intervention is essential.

Knowing that reclassification of SCAI stage at 24 h improves outcome prediction,¹⁶ we observed that patients identified as SCAI D at 24 h and treated with NIV did not have worse outcomes compared to iMV.

A limited number of patients progressed to higher SCAI stages. Among the 33 patients in the OT group with SCAI A or B at admission, 10 (30.3%) progressed to SCAI C ($n = 8$) or D ($n = 2$) at 24 h. In the NIV group, of the 21 patients with SCAI A or B at admission, 2 (9.5%) progressed to SCAI C ($n = 1$) or D ($n = 1$) at 24 h. For the iMV group, among 28 patients with SCAI A or B at admission, 8 (28.6%) progressed to SCAI C ($n = 6$) or D ($n = 2$) at 24 h.

Regarding the NIV group, the potential reasons for the limited progression to higher SCAI stages, although speculative due to the intrinsic selection bias of an observational prospective study, may include: (i) close monitoring of the NIV group given the high risk of acuity progression; and (ii) prompt allocation of PPV and its beneficial haemodynamic and respiratory effects, allowing stabilization of clinical conditions.

Furthermore, the stages delineated in the SCAI pyramid²⁸ exhibit a nuanced gradation of severity which does not take into account the role of respiratory failure and its severity, nor the type of ventilatory support required. Insights on respiratory failure and the choice of ventilatory modality might provide clinicians with valuable insights for refined risk stratification, facilitating tailored therapeutic interventions.

Although the number of SCAI D patients receiving NIV in our registry is limited, our data underscore the potential of non-invasive modalities as a first-line approach even in advanced SCAI. It has been demonstrated that each hour delay to iMV in patients with respiratory failure leads to a steep increase in mortality.²⁹ Hence, it is conceivable that patients with elevated SCAI stages could be effectively treated with non-invasive modalities, and that a strict monitoring to evaluate the need for rapid step up in case of worsening cardiovascular/respiratory conditions, allows a right allocation of resources without detrimental effect on short-term outcome (Table 4).

The differences in pharmacologic settings between the NIV and iMV groups are consistent with the level of medical support required by the specific populations. IMV typically requires more vasoactive medications, either because of greater acuity or to

counteract the circulatory effects of sedative medications. Conversely, the higher use of vasodilator drugs applies to non-sedated patients where haemodynamics are permissive (no severe hypotension).

Of note, our population included a high proportion of ADHF-CS patients, for whom there is little evidence to guide the optimal mechanical ventilation settings, since this population has been excluded or poorly represented in critical care studies.

In the cohort of patients treated with tMCS, a high rate of ADHF-CS patients were supported with IABP. Few studies have evaluated the combination of mechanical ventilation and tMCS: Liu and colleagues reported that the combination of IABP with PPV was associated with improvement in left ventricular function compared with IABP alone in a small retrospective study.³⁰

The potential benefit of PPV in CS patients receiving IABP is most likely due to the concomitant effect of the afterload optimization secondary to PEEP application, the direct IABP effect on arterial elastance,³¹ as well as the alveolar recruitment and oedema reabsorption, leading to improved oxygenation and oxygen delivery.

After the exclusion of patients with cardiac arrest, Kaplan–Meier curves (Figure 1B) confirmed a higher mortality in iMV patients at 60 days.

Ultimately, these data confirm the detrimental effect of iMV on mortality in patients with CS and calls for a renewed interest on lung function and pulmonary oedema as therapeutic targets of the haemodynamic platform to tackle CS, including decongestion of the pulmonary circulation via reduction of pulmonary capillary wedge pressure.

Moreover, iMV patients had more often respiratory complications in terms of pneumonia and consequently they had a longer CICU stay.

Invasive mechanical ventilation is a life-saving therapeutic strategy for patients who meet the criteria for its use. Notably, two sub-studies of the TRIUMPH and CULPRIT-SHOCK trials^{29,32} reported worse outcomes in patients where iMV initiation was delayed after the onset of CS. Many studies have found a correlation between iMV and increased mortality, which may be attributed to the higher acuity of patients needing iMV. Our results suggest that short-term iMV was not associated with increased mortality, but longer durations were. The justification for these findings, along with the use of NIV in advanced SCAI stages, may be speculative. Factors include the appropriate and timely selection and allocation of patients to different ventilation strategies.³³ Thus, iMV should not be seen as an intervention to avoid but rather one to be used judiciously based on patient needs.

This study should be interpreted in view of some limitations. First, due to its observational nature, possible unmeasured confounders prevent the establishment of causal relationships. Second, the limited sample size does not allow for a complete evaluation of the ischaemic versus non-ischaemic subgroups, with their peculiar clinical characteristics and adaptation mechanisms: different ventilation modalities likely have a different impact on pathophysiology. Third, the approach taken by the investigators was not standardized, as it relied on institutional protocols and best practices, which may differ across different medical centres. Furthermore, details

such as pressure support levels, variations in PEEP and types of NIV interfaces were not provided, potentially impacting the outcomes of the study.

Finally, in fragile or elderly patients limitations on treatment intensity could have influenced the choice between NIV and iMV. However, a previous survey conducted by our group and focused on a cohort of ADHF-CS patients, showed that therapy-limiting practice are not routine in the Italian centres participating in the AltShock registry.³⁴

Conclusion

Our analysis of the AltShock-2 registry indicates that NIV could be a safe first-line ventilation option for patients with CS, including those with advanced SCAI classes. Further studies are needed to explore personalized ventilation approaches based on underlying aetiologies, considering factors such as interface selection, ventilation modalities, settings, standardized reporting criteria, sedation protocols, and optimal weaning strategies for CS patients.

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