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ORIGINAL ARTICLE

Clinical profile, short and long-term outcomes of non-ischaemic cardiogenic shock: A FRENSHOCK sub-analysis

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Abstract

Aims Although predominant in routine practice, non-ischaemic cardiogenic shock (NICS) remains underrepresented in past studies, mainly focused on ischaemic cardiogenic shock (CS). This study aims to describe the current NICS picture and define its independent correlates of short- and long-term outcomes.

Methods and results FRENSHOCK is a prospective registry including 772 CS patients from 49 centers. One-year mortality was the primary outcome. One-month mortality and the composite of 1-year mortality, heart transplantation (HTx), or ventricular assistance device (VAD) were secondary outcomes. Within 772 patients included, 492 (63.7%) were NICS. One-month and 1-year mortality rates were 25.6% and 45.7%, with a combined endpoint of 1-year mortality, HTx, or VAD of 53.9%. Multivariate analysis showed five independent factors for 1-year mortality: age (per year: aHR 1.03 [1.01–1.05], $P < 0.01$), chronic kidney disease (CKD) (aHR 1.87 [1.25–2.80], $P < 0.01$), norepinephrine use (aHR 1.52 [1.02–2.26], $P = 0.04$), active cancer (aHR 1.91 [1.07–3.42], $P = 0.03$) and acute renal replacement therapy (aHR 1.57 [1.01–2.46], $P = 0.049$). Age, CKD and norepinephrine were also predictive of 1-month mortality and 1-year mortality and/or HTx and/or VAD. Additionally, 1-month mortality was associated with septic triggers, and 1-year mortality and/or HTx and/or VAD with acute mechanical circulatory support, NYHA stage ≥ 3 and fluid administration.

Conclusions In this large study, NICS accounted for almost two-thirds of all CS cases, with substantial rates of short- and long-term mortality. Future studies should evaluate interventions to improve early stratification and management.
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Keywords Cardiogenic shock; Epidemiology; Mortality; Prognosis

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Introduction

Cardiogenic shock (CS) is a syndrome due to primary cardiac dysfunction resulting in an inadequate cardiac output, comprising a life-threatening state of tissue hypoperfusion, which can result in multi-organ failure and death.[1] Despite improved pharmacologic and device-based therapies, CS remains a complex challenge to the medical community, without any clear consensus regarding the best practices in evaluation and management,[2] resulting in a poor prognosis as illustrated by a mortality rate approaching 25–30%[3] at 1 month and 45–60% at 1 year.[4] Even though several clinical scenarios can cause CS, the most frequently reported and extensively studied CS aetiology is acute myocardial infarction (AMI),[5,6] with substantial data enabling the development of various predictive factors and prognostic scores.[7,8] Hence, the only evidence-based treatment for CS is early revascularization of the culprit lesion in case of AMI-CS,[1,6] whereas there is no evidence-based treatment for non-ischaemic cardiogenic shock (NICS).

Yet, there is growing evidence that, although NICS may constitute the majority of cases managed in routine practice,[3,9] it remains underrepresented in most parts of past and ongoing randomized trials in this field, including mainly or exclusively AMI-CS patients.[10,11] However, it seems clear that each CS aetiology requires specific diagnostic, therapeutic and prognostic considerations,[2,3] with marked differences between AMI-CS and NICS, urging individualized management. For instance, in a retrospective, multicentre, international, propensity score-matched study exclusively including NICS patients, acute mechanical circulatory support (aMCS) was associated with a 24% relative risk reduction in 30-day mortality.[12] Despite being retrospective observational data, these results for NICS appear to contrast with those for AMI-CS included in the IABP-SHOCK II trial[13] and the ECLS-SHOCK trial,[11] in which aMCS has still not provided real evidence of efficacy. The scarcity of data on the management of NICS highlights a crucial knowledge deficit in this domain, emphasizing the need for dedicated investigations[14] to refine NICS prognostic stratifications, as the majority of known scores in the context of CS have been developed based on cohorts predominantly composed of AMI-CS. Addressing this gap is essential for a comprehensive understanding of CS aetiology and prognosis, paving the way for more nuanced and tailored clinical interventions.

Therefore, this study aimed to investigate the short- and long-term outcomes of NICS, based on the FRENSHOCK registry, a multicentric prospective cohort.

Methods

Patient population

As previously reported,[3,15] FRENSHOCK is a prospective, observational and multicentre survey, conducted between April and October 2016, including 772 patients admitted for CS in ICU/ICCU in France, coming from various types of institutions (primary to tertiary centres, universities, and non-university, public and private hospitals).

All adult patients (≥18 years old) with CS were prospectively included in this registry if they met at least one criterion of each of the following three components: (1) low cardiac output: low SBP $<$ 90 mmHg and/or the need for maintenance with vasopressors/inotropes and/or a low cardiac index $<$2.2 L/min/m^2; (2) left and/or right heart filling pressure elevation, defined by clinical signs, radiology, blood tests, echocardiography, or signs of invasive hemodynamic overload and (3) signs of organ malperfusion, which could be clinical (oliguria, confusion, pale and/or cold extremities, mottled skin) and/or biological (lactate $>$2 mmol/L, metabolic acidosis, renal failure and liver insufficiency).

Each patient had up to three identified triggers for CS determined by the local investigator, classified as ischaemic (Type 1 or Type 2 AMI following European guidelines), ventricular and supraventricular arrhythmia, conduction disorder, infectious disease, non-compliance (inadequate adherence to medical treatment or hygiene and diet rules, such as stopping or skipping an angiotensin-converting enzyme inhibitor or beta-blocker treatment, deviation from a low sodium diet etc.), or iatrogenesis. NICS was defined by the absence of ischaemic triggers, thus excluding all patients with Type 1 or Type 2 AMI.

Data collection

Baseline characteristics data, encompassing demographics [age, sex and body mass index (BMI)], risk factors (hypertension, diabetes, current smoking and hypercholesterolaemia), and medical history [including cardiomyopathy, stroke, peripheral artery disease (PAD), chronic kidney disease (CKD), active cancer and chronic obstructive lung disease], were gathered as previously explained.[3,15] Investigators could additionally note other existing factors or aetiologies, denoted as 'other'. The presence of signs of left (dyspnoea, rales and crepitations) and right (ascites, hepatojugular reflux, hepatomegaly, lower limb oedema and pleural effusion) heart failure was collected at admission. Details about the need for medications (inotropes, vasopressors and diuretics); and

organ replacement therapies such as mechanical ventilation (invasive or non-invasive); aMCS [intra-aortic balloon pump (IABP); extracorporeal membrane oxygenation or Impella® (Abiomed, Danvers, MA, USA)]; and renal replacement therapy (RRT) were also documented. Management was carried out according to the usual practices of local Heart Teams.

Unfortunately, the SCAI SHOCK Stage Classification[16] was not yet available at the time of our study, which is why this data could not be prospectively collected. However, by relying on the method previously described by Thayer et al.,[17] we were able to retrospectively determine the maximum SCAI classification stage reached during hospitalization based on the total use of vasopressors, inotropes and aMCS devices. Briefly, Stage A represents patients at risk for CS, which was not applicable to our study population. Stage B encompasses patients with early symptoms not involving hypoperfusion and thus do not require pharmacological or mechanical support. Stage C includes patients with hypoperfusion requiring initial intervention with either one drug or one MCS device. Stage D refers to patients whose condition worsens despite initial intervention, necessitating additional drugs or MCS treatment. Lastly, Stage E identifies patients who deteriorate further and require maximal support, defined as needing at least two MCS devices and two drugs during hospitalization.

Outcomes

The primary outcome was 1-year all-cause mortality. Secondary outcomes included 1-month all-cause mortality and the overall composite criteria of 1-year mortality or heart transplantation (HTx) or ventricular assistance device (VAD) among the entire cohort (mutually alternative outcomes).

Ethics

The study was conducted per the Helsinki declaration and French law. Written consent was obtained for all patients. Recorded data and their storage were approved by the CCTIRS (French Health Research Data Processing Advisory Committee) (no. 15.897) and the CNIL (French Data Protection Agency) (no. DR-2016-109).

Statistical analysis

Continuous variables are reported as means and standard deviation (SD) or medians and interquartile ranges (IQR) when appropriate. Categorical variables are described as frequencies and percentages. Comparisons were made using Mann–Whitney non-parametric test for continuous variables and chi-square test or Fisher's exact test for categorical variables. Primary outcome of all-cause mortality was assessed using Kaplan–Meier survival curves. To identify factors associated with 1-year and 1-month mortality, we used a Cox proportional hazards regression model and reported adjusted hazard ratios (aHRs) with corresponding 95% confidence intervals (CIs). Multivariable logistic regression was performed to identify factors associated with the composite outcome of death, HTx or VAD at 1 year, and it was reported using adjusted odds ratios (aORs) with 95% CIs. Covariates included in predictive models were selected with binary logistic regression (threshold < 0.2 for variable elimination) and their physiological relevance and potential to be associated with outcomes, according to the Prognosis Research Strategy guidelines,[18] which advocate for a clinically hypothesis-driven approach for a priori selection of model variables. Sensitivity analysis was conducted by excluding patients with active cancer[19] to account for confounding biases and assess the robustness of the results.

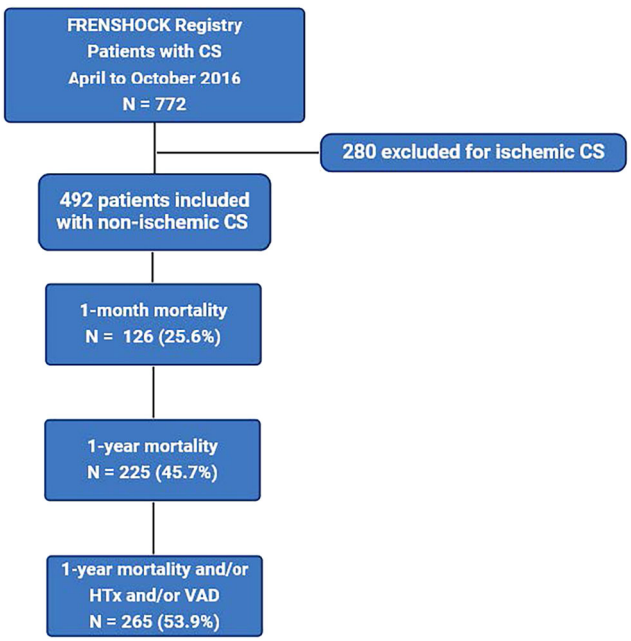
All tests were two-tailed. A value of $P \leq 0.05$ was accepted as statistically significant. Analyses were performed using R software [version 4.1.2 (2021-11-01)].

Results

Baseline characteristics

From a cohort of 772 CS patients, 492 patients (63.7%) with NICS were ultimately selected (280 excluded for ischaemic CS, *Figure 1*), 21.3% of whom were transferred from another

Figure 1 Flow chart of the study. CS, cardiogenic shock, HTx, heart transplantation, VAD, ventricular assistance device.



centre (emergency or other department). Based on our adapted classification, 46 patients (9.4%) were categorized as SCAI shock stage B, 182 (37.1%) as SCAI stage C, 258 (52.5%) as SCAI stage D, and 5 (1.0%) as SCAI stage E (with 1 unknown). The NICS cohort had an average age of 64.8 years (±15.3), predominantly consisting of males (70.9%) (*Table 1*). A substantial portion (65.4%) had a documented history of cardiac disease, with 30.1% attributed to ischaemic cardiomyopathy (ICM) and 14.2% to dilated cardiomyopathy. In the overall cohort, 45.7% of patients were classified as having a New York Heart Association (NYHA) stage ≥ 3, and the prevalence of implantable cardioverter defibrillator use was 21.8%. Furthermore, there were elevated prevalence rates for hypertension (42.3%), dyslipidaemia (35%), diabetes mellitus (25%) and current smoking (35.2%). Associated co-morbidities included stroke (7.7%), PAD (11.2%) and CKD (25.3%).

Upon admission, the average systolic blood pressure (SBP) was 99.9 mmHg (±25.4), while the mean heart rate was 96 b. p.m. (±31.1) (*Table 2*). Mottling was present in 37.5% of instances, and prior cardiac arrest was reported in 7.1%. Clinical signs of both left and right heart failure were observed in 71.7% and 57.7% of cases, respectively. Most patients exhibited multiple organ failure, as indicated by renal dysfunction, hepatic cytolysis and cholestasis, and elevated lactate levels, consistent with a left ventricular ejection

Table 1 Comparison of baseline characteristics of non-ischaemic cardiogenic shock patients between 1-year survivors and non-survivors.

	Overall population (n = 492)	1-year survivors (n = 267)	1-year non-survivors (n = 225)	P value
Age, mean ± SD, years	64.8 ± 15.3	60.9 ± 15.1	69.4 ± 14.3	<0.01
Male, n (%)	349 (70.9)	188 (70.4)	161 (71.6)	0.86
Body mass index, mean ± SD, kg/m^2	25.7 ± 5.8 (n = 466)	26 ± 6.4 (n = 252)	25.5 ± 5.1 (n = 214)	0.75
Risk factors, n (%)				
Diabetes mellitus	133 (27.1) (n = 491)	60 (22.6) (n = 266)	73 (32.4)	0.02
Hypertension	208 (42.3)	101 (37.8)	107 (47.6)	0.04
Dyslipidaemia	172 (35.0)	76 (28.5)	96 (42.7)	<0.01
Current smoker	119 (25.0) (n = 476)	75 (28.8) (n = 260)	44 (20.4) (n = 216)	0.04
Medical history, n (%)				
Peripheral artery disease	55 (11.2) (n = 491)	25 (9.4) (n = 266)	30 (13.3)	0.22
Chronic kidney disease	124 (25.3) (n = 491)	39 (14.7) (n = 266)	85 (37.8)	<0.01
COPD	39 (7.9) (n = 491)	16 (6.0) (n = 266)	23 (10.2)	0.12
ICD	107 (21.8) (n = 491)	50 (18.8) (n = 266)	57 (25.3)	0.1
Active cancer	36 (7.3) (n = 491)	9 (3.4) (n = 266)	27 (12.0)	<0.01
Stroke	38 (7.7) (n = 491)	13 (4.9) (n = 266)	25 (11.1)	0.02
NYHA functional status, n (%)				
≥3	220 (45.8) (n = 480)	102 (39.5) (n = 258)	118 (53.2) (n = 222)	<0.01
History of cardiac disease, n (%)				
All causes	322 (65.4)	149 (55.8)	173 (76.9)	<0.01
Ischaemic	148 (30.1)	68 (25.5)	80 (35.6)	0.02
Hypertrophic	9 (1.8)	6 (2.2)	3 (1.3)	0.52
Toxic	30 (6.1)	17 (6.4)	13 (5.8)	0.93
Dilated	70 (14.2)	35 (13.1)	35 (15.6)	0.52
Valvular	51 (10.4)	17 (6.4)	34 (15.1)	<0.01
Hypertensive	15 (3)	4 (1.5)	11 (4.9)	0.06
Previous medications, n (%)				
Aspirin	152 (31) (n = 491)	79 (29.7) (n = 266)	73 (32.4)	0.58
P2Y12 inhibitors	50 (10.2) (n = 491)	25 (9.4) (n = 266)	25 (11.1)	0.63
Vitamin K antagonist	131 (26.7) (n = 491)	48 (18) (n = 266)	83 (36.9)	<0.01
Direct oral anticoagulant	45 (9.2) (n = 491)	29 (10.9) (n = 266)	16 (7.1)	0.2
Beta-blocker	219 (44.6) (n = 491)	111 (41.7) (n = 266)	108 (48.0)	0.19
ACE inhibitors	193 (39.3) (n = 491)	100 (37.6) (n = 266)	93 (41.3)	0.45
Sacubitril/valsartan	15 (3.3) (n = 461)	6 (2.4) (n = 247)	9 (4.2) (n = 214)	0.42
Statins	172 (35.0) (n = 491)	82 (30.8) (n = 266)	90 (40.0)	0.04
Loop diuretics	277 (56.4) (n = 491)	122 (45.9) (n = 266)	155 (68.9)	<0.01
Aldosterone antagonist	95 (19.3) (n = 491)	47 (17.7) (n = 266)	48 (21.3)	0.36
Thiazide diuretics	32 (6.6) (n = 483)	13 (4.9) (n = 264)	19 (8.8) (n = 219)	0.14
Amiodarone	102 (21.3) (n = 480)	48 (18.4) (n = 261)	54 (24.7) (n = 219)	0.12
Other anti-arrhythmic	23 (4.8) (n = 477)	12 (4.6) (n = 260)	11 (5.1) (n = 217)	0.99
Maximal SCAI stage, n (%)				0.01
B	46 (9.4) (n = 491)	30 (11.2)	16 (7.1) (n = 224)	
C	182 (37.1) (n = 491)	110 (41.2)	72 (32.1) (n = 224)	
D	258 (52.5) (n = 491)	126 (47.2)	132 (58.9) (n = 224)	
E	5 (1.0) (n = 491)	1 (0.4)	4 (1.8) (n = 224)	

ACE, angiotensin-converting enzyme; BB, beta-blockers; COPD, chronic obstructive pulmonary disease; CS, cardiogenic shock; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; SD, standard deviation.

Table 2 Comparison of index admission characteristics among patients with non-ischaemic cardiogenic shock between 1-year survivors and non-survivors.

	Overall population (n = 492)	1-year survivors (n = 267)	1-year non-survivors (n = 225)	P value
Clinical presentation at admission				
Heart rate, mean ± SD, b.p.m.	96 ± 31.1 (n = 490)	97.5 ± 32 (n = 266)	94.2 ± 30 (n = 224)	0.24
SBP, mean ± SD, mmHg	99.9 ± 25.4 (n = 491)	103.6 ± 25.2 (n = 266)	95.6 ± 25 (n = 225)	<0.01
DBP, mean ± SD, mmHg	62.9 ± 18 (n = 490)	66.5 ± 18.6 (n = 266)	58.7 ± 16.3 (n = 224)	<0.01
MBP, mean ± SD, mmHg	74.1 ± 19.1 (n = 488)	78.2 ± 19.6 (n = 265)	69.3 ± 17.2 (n = 223)	<0.01
Sinus rhythm, n (%)	232 (47.4) (n = 489)	136 (51.5) (n = 264)	96 (42.7)	0.06
Mottling, n (%)	154 (37.5) (n = 411)	74 (34.3) (n = 216)	80 (41.0) (n = 195)	0.19
Clinical signs of left heart failure[a], n (%)	352 (71.7) (n = 491)	187 (70.3) (n = 266)	165 (73.3)	0.52
Clinical signs of right heart failure[b], n (%)	282 (57.7) (n = 489)	138 (52.1) (n = 265)	144 (64.3) (n = 224)	<0.01
Prior cardiac arrest, n (%)	35 (7.1)	22 (8.2)	13 (5.8)	0.38
Blood tests at admission, median (IQR)				
Sodium, mmol/L	135.0 (131.0–138.0) (n = 482)	136.0 (132.0–138.0) (n = 260)	133.5 (130.0–138.0) (n = 222)	<0.01
Potassium, mmol/L	4.1 (4.0–5.0) (n = 415)	4.1 (4.0–5.0) (n = 229)	4.1 (4.0–5.0) (n = 186)	0.39
Creatinin, μmol/L	139.0 (103.0–204.0) (n = 483)	125.0 (91.0–164.0) (n = 261)	162.0 (124.8–239.0) (n = 222)	<0.01
eGFR ≤ 30 mL/min	150 (31.4) (n = 477)	49 (19.1) (n = 257)	101 (45.9) (n = 220)	<0.01
Bilirubin, mg/L	19.0 (11.0–33.0) (n = 353)	18.0 (10.0–30.8) (n = 194)	21.4 (12.4–38.0) (n = 159)	0.04
Haemoglobin, g/dL	12.3 (11.0–14.0) (n = 476)	13.0 (11.4–14.5) (n = 258)	11.9 (10.1–13.2) (n = 218)	<0.01
Arterial blood lactates, mmol/L				
<2 mmol/L	169 (39.7) (n = 426)	94 (41.4) (n = 227)	75 (37.7) (n = 199)	
2–4 mmol/L	121 (28.4) (n = 426)	65 (28.6) (n = 227)	56 (28.1) (n = 199)	0.62
>4 mmol/L	136 (31.9) (n = 426)	68 (30.0) (n = 227)	68 (34.2) (n = 199)	
ASAT, UI/L	64.0 (34.8–186.5) (n = 356)	60.0 (33.0–178.8) (n = 200)	71.5 (35.8–208.5) (n = 156)	0.15
ALAT, UI/L	49.5 (24.0–173.5) (n = 360)	55.5 (25.3–181.0) (n = 202)	46.0 (23.0–164.0) (n = 158)	0.61
PT, %	52.0 (32.0–71.0) (n = 458)	58.0 (36.0–76.0) (n = 248)	47.0 (28.0–66.8) (n = 210)	<0.01
Nt-proBNP, pg/mL	9700.0 (4817.0–24 937.0) (n = 149)	6410.0 (3480.0–14 420.0) (n = 81)	12 840.5 (7301.5–33 424.3) (n = 68)	<0.01
BNP, pg/mL	1437.0 (560.5–2839.0) (n = 175)	957.0 (453.5–2467.5) (n = 99)	1937.5 (911.8–3221.5) (n = 76)	<0.01
CRP, mg/L	28.5 (11.3–63.8) (n = 266)	28.0 (12.0–65.0) (n = 135)	40.0 (15.5–100.5) (n = 131)	<0.01
Baseline echocardiography				
LVEF ≤ 30%, n (%)	371 (76.2) (n = 487)	198 (75.0) (n = 264)	173 (77.6) (n = 223)	0.58
TAPSE, median (IQR), mm	12.0 (10.0–16.0) (n = 170)	13.0 (10.0–16.0) (n = 96)	11.0 (9.0–15.8) (n = 74)	<0.01
PSVtdi, median (IQR), cm/s	7.0 (6.0–10.0) (n = 141)	8.0 (6.0–10.0) (n = 75)	7.0 (6.0–8.8) (n = 66)	0.1
Severe mitral regurgitation, n (%)	86 (18.4) (n = 468)	44 (17.2) (n = 256)	42 (19.8) (n = 212)	0.54
Severe aortic stenosis, n (%)	24 (4.9) (n = 485)	8 (3.0) (n = 264)	16 (7.2) (n = 221)	0.055
Severe aortic regurgitation, n (%)	7 (1.5) (n = 480)	5 (1.9) (n = 263)	2 (0.9) (n = 217)	0.46

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BB, beta-blockers; BNP, brain natriuretic peptide; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; MBP, mean blood pressure; NT-proBNP, N-terminal-pro hormone BNP; PSVtdi, peak systolic velocity tissue Doppler imaging; PT, prothrombin time; SBP, systolic blood pressure; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion.

[a]Dyspnoea, rales and crepitations.

[b]Ascites, hepatojugular reflux, hepatomegaly, lower limb oedema and pleural effusion.

fraction (LVEF) ≤ 30% in 76.2% (86.9% had an LVEF ≤ 40%, 5.1% had an LVEF between 40% and 50%, 8.0% had an LVEF ≥ 50%), and median TAPSE and PSVDtdi at 12 mm and 7 cm/s, respectively.

Main identified CS triggers (not mutually exclusive) were supraventricular tachycardia (18.7%), infectious diseases (15.7%) and ventricular arrhythmias (13%) (*Figure 2*).

In-hospital management

Dobutamine was the predominant inotrope administered, with a utilization rate of 82.2% (*Table 3*). Norepinephrine was employed in 50.8% of patients, while epinephrine and levosimendan were used in 10.6% and 8%. Ventilatory support, whether invasive or non-invasive, was implemented in 22.7% and 33.3% of cases, respectively. Acute mechanical circulatory support was initiated in 13.6% of instances, with a median duration of 5.0 days (3.8–8.0) and extracorporeal life support (ECLS) being the most prevalent type at 9.3%. Additional circulatory support included IABP in 2.4% of cases and Impella in 1.4%. Of note, only 5 patients underwent a combination of ECLS and Impella or IABP (4 ECLS/Impella and 1 ECLS/IABP): 4 were treated sequentially as part of an aMCS escalation strategy, all included within the non-survivors group (the remaining patient underwent a simultaneous double implantation of ECLS and Impella). Lastly, RRT was instituted in 17.5% of cases.

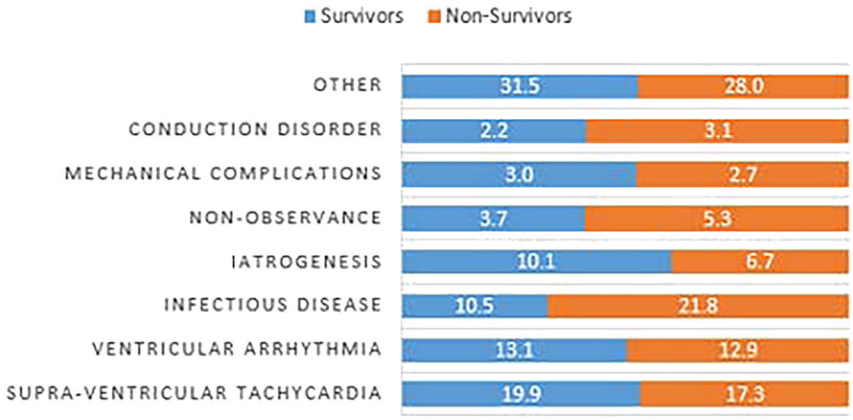
Short and long-term outcomes

The overall mortality rates at 1 month and 1 year were 25.6% and 45.7%, respectively. Additionally, 55 patients (11.2%) underwent HTx or VAD implantation at 1 year, resulting in a combined endpoint of 1-year mortality, HTx or VAD of 53.9%. Of note, out of the 35 transplanted patients, 30 underwent in-hospital HTx, while out of the 24 implanted VADs, 9 were implanted in-hospital (6 left VADs and 3 biventricular VADs).

Comparison between 1-year survivors and non-survivors

Baseline characteristics according to vital status at 1 year are outlined in *Table 1*. In general, non-survivors were older (69.4 ± 14.3 vs. 60.9 ± 15.1 years) with similar sex ratios. Comparison of the distribution of SCAI Shock stages revealed a significant trend towards a higher proportion of stages D (58.9% vs. 47.2%) and E (1.8% vs. 0.4%) (P = 0.01) among

Figure 2 Distribution of CS triggers. CS, cardiogenic shock.



	Overall population (n = 492)	1-year survivors (n = 267)	1-year non-survivors (n = 225)	p value
Supraventricular tachycardia, n (%)	92 (18.7)	53 (19.9)	39 (17.3)	0.55
Ventricular arrhythmia, n (%)	64 (13)	35 (13.1)	29 (12.9)	1
Infectious disease, n (%)	77 (15.7)	28 (10.5)	49 (21.8)	< 0.01
Iatrogenesis, n (%)	42 (8.5)	27 (10.1)	15 (6.7)	0.23
Non-observance, n (%)	22 (4.5)	10 (3.7)	12 (5.3)	0.53
Mechanical complications, n (%)	14 (2.8)	8 (3)	6 (2.7)	1
Conduction disorder, n (%)	13 (2.6)	6 (2.2)	7 (3.1)	0.75
Other, n (%)	147 (29.9)	84 (31.5)	63 (28)	0.46

Table 3 In-hospital management among patients with non-ischaemic cardiogenic shock.

	Overall population (n = 492)	1-year survivors (n = 267)	1-year non-survivors (n = 225)	P value
Medications used, *n* (%)				
Dobutamine	403 (82.2) (n = 490)	214 (80.5) (n = 266)	189 (84.4) (n = 224)	0.31
Norepinephrine	249 (50.8) (n = 490)	118 (44.4) (n = 266)	131 (58.5) (n = 224)	<0.01
Epinephrine	52 (10.6) (n = 490)	25 (9.4) (n = 266)	27 (12.1) (n = 224)	0.42
Levosimendan	39 (8.0) (n = 490)	18 (6.8) (n = 266)	21 (9.4) (n = 224)	0.37
Loop diuretics	309 (70.4) (n = 439)	171 (70.4) (n = 243)	138 (70.4) (n = 196)	1
Thiazide diuretics	23 (5.3) (n = 431)	8 (3.3) (n = 239)	15 (7.8) (n = 192)	0.07
Aldosterone antagonist	70 (15.9) (n = 439)	45 (18.5) (n = 243)	25 (12.8) (n = 196)	0.13
Fluid administration	179 (36.6) (n = 489)	88 (33.1) (n = 266)	91 (40.8) (n = 223)	0.09
Respiratory support, *n* (%)				
Non-invasive	111 (22.7) (n = 490)	64 (24.1) (n = 266)	47 (21) (n = 224)	0.48
Invasive	163 (33.3) (n = 490)	79 (29.7) (n = 266)	84 (37.5) (n = 224)	0.08
Acute mechanical circulatory support, *n* (%)				
Overall	67 (13.6)	33 (12.4)	34 (15.1)	0.45
IABP	12 (2.4)	7 (2.6)	5 (2.2)	1
Impella	7 (1.4)	3 (1.1)	4 (1.8)	0.71
ECLS	46 (9.3)	21 (7.9)	25 (11.1)	0.29
Duration of aMCS, median (IQR), days	5.0 (3.8–8.0) (n = 52)	5.5 (4.0–8.0) (n = 28)	5.0 (2.0–10.0) (n = 24)	0.68
Renal replacement therapy, *n* (%)	77 (17.5)	22 (8.2)	55 (24.4)	<0.01

aMCS, acute mechanical circulatory support; ECLS, extracorporeal life support; IABP, intra-aortic balloon pump.

Table 4 Independent variables associated with primary and secondary outcomes in all patients with non-ischaemic cardiogenic shock.

	1-month mortality		1-year mortality		1-year mortality and/or VAD and/or HTx	
	aHR (95% CI)	P value	aHR (95% CI)	P value	aOR (95% CI)	P value
Age (per year)	1.03 (1.01–1.05)	P = 0.01	1.03 (1.01–1.05)	P < 0.01	1.04 (1.01–1.06)	P = 0.01
Chronic kidney disease	2.20 (1.25–3.89)	P < 0.01	1.87 (1.25–2.80)	P < 0.01	4.96 (2.41–10.59)	P < 0.01
Septic trigger	1.93 (1.09–3.39)	P = 0.02	1.44 (0.94–2.21)	P = 0.09	1.03 (0.47–2.25)	P = 0.95
Use of norepinephrine	1.93 (1.12–3.33)	P = 0.02	1.52 (1.02–2.26)	P = 0.04	1.96 (1.04–3.74)	P = 0.04
Active cancer	1.46 (0.61–3.50)	P = 0.40	1.91 (1.07–3.42)	P = 0.03	3.08 (0.94–11.47)	P = 0.08
Acute renal replacement therapy	1.63 (0.90–2.97)	P = 0.11	1.57 (1.01–2.46)	P = 0. 049	1.46 (0.63–3.50)	P = 0.39
NYHA ≥ 3	1.42 (0.86–2.33)	P = 0.17	1.37 (0.95–1.97)	P = 0.09	2.30 (1.25–4.26)	P = 0.01
Fluid administration	0.79 (0.45–1.36)	P = 0.39	1.10 (0.76–1.61)	P = 0.61	2.64 (1.36–5.27)	P < 0.01
Acute mechanical circulatory support	1.33 (0.61–2.92)	P = 0.47	1.53 (0.87–2.66)	P = 0.14	5.63 (2.03–17.01)	P < 0.01
Transfer from another center	1.20 (0.66–2.20)	P = 0.55	0.99 (0.64–1.53)	P = 0.96	2.03 (0.96–4.39)	P = 0.07

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CI, confidence interval; HTx, heart transplantation; NYHA, New York Heart Association; VAD, ventricular assistance device.

the 1-year non-survivors. They also exhibited a higher prevalence of diabetes history (32.4 vs. 22.6%, $P < 0.01$), hypertension (47.6 vs. 37.8%, $P = 0.04$) and dyslipidaemia (42.7 vs. 28.5%, $P < 0.01$). Analysis of co-morbidities further highlighted a predominance of CKD (37.8 vs. 14.7%, $P < 0.01$), active cancer (12 vs. 3.4%, $P < 0.01$) and stroke (11.1 vs. 4.9%, $P = 0.02$). A history of cardiomyopathy was also more prevalent among non-survivors (76.9 vs. 55.8%, $P < 0.01$), as was NYHA status ≥ 3 (53.2 vs. 39.5%, $P < 0.01$).

Regarding CS triggers, infectious disease was more prevalent in non-survivors (21.8 vs. 10.5%, $P < 0.01$). Other triggers for CS were similarly distributed between survivors and non-survivors (*Figure 2*).

Upon admission, non-survivors had lower systolic, diastolic and mean blood pressure, with a higher prevalence of right heart failure (64.3 vs. 52.1%, $P < 0.01$) (*Table 2*). They also showed higher levels of natriuretic peptides and inflammatory markers (C-reactive protein), and more frequent kidney and hepatic injuries, along with lower haemoglobin levels. Eventually, non-survivors yielded a higher use of norepinephrine (58.5% vs. 44.4%, $P < 0.01$) and renal replacement therapy (24.4% vs. 8.2%, $P < 0.01$).

Independent correlates of mortality, heart transplantation, and ventricular assist device

At admission, age (per year: aHR 1.03, 95% CI: 1.01–1.05, $P < 0.01$), CKD (aHR 1.87, 95% CI: 1.25–2.80, $P < 0.01$), use of norepinephrine (aHR 1.52, 95% CI: 1.02–2.26, $P = 0.04$), active cancer (aHR 1.91, 95% CI: 1.07–3.42, $P = 0.03$) and acute RRT (aHR 1.57, 95% CI: 1.01–2.46, $P = 0.049$) were independently associated with higher mortality at 1 year. As indicated in *Table 4*, increased age, CKD and the use of norepinephrine

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were associated with both 1-month mortality and 1-year mortality and/or HTx and/or VAD. Moreover, the presence of a septic trigger was identified as a specific factor influencing 1-month mortality. On the other hand, NYHA stage ≥ 3, fluid administration, and aMCS were identified as specific factors associated with the composite outcome of 1-year mortality and/or HTx and/or VAD.

Tables S1, *S2* and *S3* describe all aHRs/aORs with 95% CIs of all variables tested for each outcome of interest.

Comparison between non-ischaemic and ischaemic cardiogenic shock

NICS patients exhibited lower rates of hypertension (42.3% vs. 55.9%, $P < 0.01$) and active smoking (25.0% vs. 33.0%, $P = 0.03$), as opposed with a higher prevalence of CKD (25.3% vs. 14.3%, $P < 0.01$) and COPD (7.9% vs. 3.9%, $P = 0.04$) (*Table S4*). Furthermore, they were characterized by a greater history of chronic cardiomyopathy (65.4% vs. 39.8%, $P < 0.01$), particularly idiopathic (14.2% vs. 2.9%, $P < 0.01$) and toxic (6.1% vs. 1.4%, $P < 0.01$) dilated cardiomyopathies, in line with a higher prevalence of ICD (21.8% vs. 7.1%, $P < 0.01$) and NYHA stage ≥ 3 (45.8% vs. 27.5%, $P < 0.01$). At admission, they also exhibited lower median values of diastolic (99.9 vs. 103.4 mmHg, $P = 0.02$) and mean (74.1 vs. 76.2 mmHg, $P = 0.02$) blood pressure, along with a higher incidence of clinical signs of right heart failure (57.7% vs. 34.1%, $P < 0.01$) and more severe median levels of creatinine, bilirubin, ASAT, ALAT, prothrombin time and natriuretic peptide (*Table S5*). Besides, 76.2% of NICS patients presented with an LVEF $\leq 30\%$, against 64.9% for AMI-CS patients ($P < 0.01$), consistent with lower median values of TAPSE (12 vs. 14 mm, $P < 0.01$) and PSVtdi (7 vs. 10 cm/s, $P < 0.01$). Lastly, NICS patients required less ventilatory support, both non-invasive (22.7% vs. 31.7%, $P < 0.01$) and invasive (33.3% vs. 46%, $P < 0.01$) (*Table S6*), and fewer use of aMCS (13.6% vs. 27.3%, $P < 0.01$). As depicted in *Figure 3*, no difference was observed in all-cause mortality, either at 1 month (HR 0.92 [0.69–1.22], $P = 0.55$) or at 1 year (HR 1.01 [0.81–1.26], $P = 0.9$).

Sensitivity analysis after exclusion of patients with active cancer

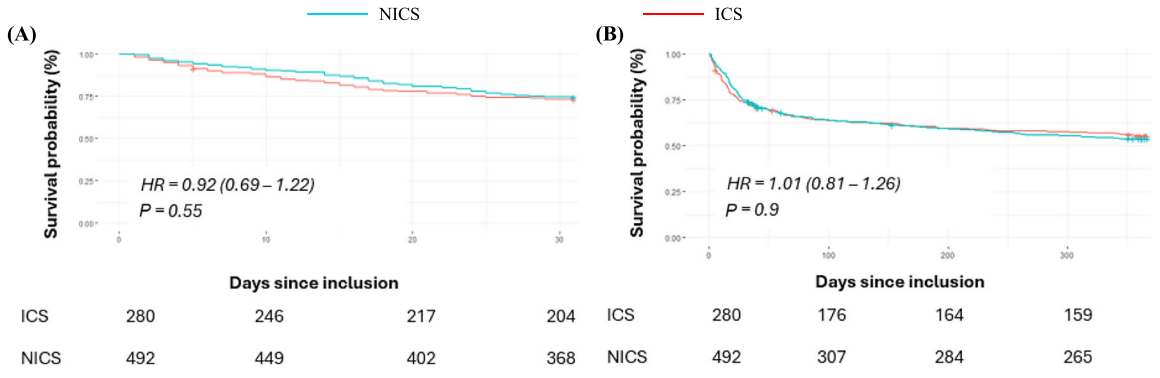
Similarly, non-survivors exhibited an older age, a higher proportion of vascular risk factors (diabetes mellitus and dyslipidaemia), co-morbidities (CKD and stroke) and a history of cardiac disease, consistent with a higher prevalence of NYHA status > 3. Sensitivity analysis also yielded consistent results with those of the main analyses regarding a higher prevalence of hypotension and clinical signs of right heart failure, reflected biologically by higher median levels of creatinine, bilirubin, natriuretic peptides and prothrombin time, resulting in more frequent use of norepinephrine and acute RRT. Predictors of 1-year mortality were also similar, characterized by age (aHR 1.04 [1.02–1.05], $P < 0.01$), CKD (aHR 1.84 [1.21–2.79], $P < 0.01$) and a history of cardiac disease (aHR 1.69 [1.02–2.78], $P = 0.04$). Despite a trend, the use of norepinephrine did not reach significance (aHR 1.48 [0.97–2.23], $P = 0.07$).

All data comparing 1-year survivors and non-survivors after excluding the 36 patients with active cancer are reported in *Tables S6*, *S7*, *S8*, *S9* and *S10*.

Discussion

To the best of our knowledge, The FRENSHOCK registry currently stands as the largest European prospective, observational multicentre study focusing on CS. It portrays a contemporary cohort comprising unselected CS patients with a broad range of aetiologies. The noteworthy aspects of this

Figure 3 Short- and long-term mortality outcomes between ischaemic and non-ischaemic CS. CS, cardiogenic shock, HR, hazard ratio.



investigation arise from the diverse profiles of patients, attributable to the inclusion of patients across different departments (ICU, ICCU, etc.). Another distinctive feature of this registry is the evident majority of NICS, accounting for 63.7% of the patient cohort. Furthermore, NICS mortality rates at 1 month and 1 year were 25.6% and 45.7%, respectively, which is slightly lower than reported in previous studies,[5,7,14] while the overall rate of 1-year mortality and/or HTx and/or VAD was 53.9%. Notably, age, CKD and the use of norepinephrine were each independently associated with a significant increase in mortality at both 1 month and 1 year, as well as in the composite outcome of 1-year mortality/HTx/VAD. Additionally, 1-month mortality was exacerbated by septic triggers, while at 1 year, it was influenced by the presence of active cancer and the initiation of acute RRT. Eventually, an initial NYHA stage $\geq$ 3, the utilization of temporary aMCS, and fluid administration were all linked to the composite outcome of 1-year mortality and/or HTx and/or VAD.

While much of the research on CS has focused on patients with ischaemic CS,[5–7,20] recent studies indicate that only a minority of CS cases can be attributed to AMI.[2] Instead, the majority of CS managed in routine practice involve NICS, mainly associated with acute-on-chronic heart failure.[10] The potential discrepancy between the practical realities of CS and the existing literature raises concerns, given the mounting evidence that CS is a polymorphic disease, potentially resulting from a wide range of possible aetiologies, each with specific implications in terms of assessment, prognosis and treatment.[3] In our study, we did not observe a significant difference in mortality at either 1 month or 1 year between AMI-CS and NICS. However, NICS patients appeared to be affected by a greater burden of co-morbidities (CKD and COPD) and more severe chronic HF (higher prevalence of cardiomyopathy of all causes and ICD), resulting in significantly worse initial severity markers (acute kidney and liver injuries, natriuretic peptides) in the NICS group. Surprisingly, this absence of increased mortality despite more unfavourable baseline prognostic factors suggests a slightly better overall prognosis in NICS. However, these results should be interpreted with caution, particularly given the highly heterogeneous nature of the NICS and AMI-CS groups, which included not only type 1 AMI but also type 2, without distinction between STEMI and NSTEMI. Besides, the limited existing data to date are contradictory,[7,14,21,22] reinforcing the need to study its characteristics and enhance the level of evidence for specific treatments.

Risk stratification is the cornerstone of CS management, determining which patients to treat in the earliest and optimal manner possible, and has already been widely discussed in several publications, primarily addressing in-hospital or 1-month mortality in settings of AMI-CS. Factors such as age, impaired renal function, and the use of catecholamines are frequently implicated as adverse prognostic factors,[7,8,23,24] partly aligning with our data. Yet many limitations should be acknowledged regarding the existing CS-specific risk scores. For instance, the SHOCK score,[23] designed to identify clinical predictors of short-term outcomes, is commonly recognized for its complexity, making it impractical for routine use, and was built using data from a cohort with widespread adoption of primary percutaneous coronary intervention. Contemporary risk-stratification tools like the CardShock[7] and IABP-SHOCK II[25] scores, exclusively derived from AMI-CS, were found to be suboptimal when applied to patients without AMI in a recent external validation study.[26] Thereafter, the Cardiogenic Shock Score[8] (CSS, which includes nine variables: age, sex, acute myocardial infarction, systolic blood pressure, heart rate, pH, lactate, glucose and cardiac arrest) demonstrated better performance for CS stratification in both AMI-CS and NICS patients compared with the CardShock and IABP-SHOCK-II scores. Nevertheless, its discriminatory capacity is limited by the retrospective nature of its data collection, and the restriction to data available only at admission, omitting crucial information such as biomarker or hemodynamic data. Unfortunately, we were unable to assess the performance of these pre-existing scores in our cohort of unselected NICS due to missing key data required for their calculation. Future studies could focus on this objective. Lastly, the SCAI Shock classification is emerging as a reference standard for CS phenotyping.[16,17] However, most studies validating the association between the SCAI Shock stage and mortality suffer from significant heterogeneity in the definitions used for staging (lactates and hypoperfusion), and were mainly based on cohorts of AMI-CS. Through a higher prevalence of stages D and E in the group of 1-year non-survivors, our study suggests the possibility to apply the SCAI classification in NICS. Nevertheless, larger studies focusing on NICS with real-time prospective assignment of the SCAI Shock stage are warranted to draw formal conclusions.

On the other hand, there is a noticeable scarcity of data regarding the long-term prognosis post-CS, with the focus once again primarily revolving around AMI-CS. In a recent study including 9789 AMI-CS patients,[5] Sterling *et al*. identified age, Charlson co-morbidity index, residency in long-term care before the index admission, duration of vasoactive medication use and acute RRT as factors predicting 1-year mortality. Our results partially align with these findings for NICS, because age, CKD, the utilization of norepinephrine, active cancer and acute RRT were linked to an increased risk of 1-year mortality. Consequently, certain factors are indeed common to both AMI-CS and NICS and more generally, to the entire cohort of patients managed in critical care settings.[27]

The linkage between HTx and VAD with mortality as an overall composite criterion offers an alternative lens through which to consider myocardial decline, distinct from mortality alone. Indeed, the selection of patients undergoing HTx or VAD introduces various constraints related to overall health, age and co-morbidities, while also representing a common

scenario of advanced heart failure, in which there is a lack of data pertaining to the selection of patients to include in this trajectory.[1] However, very little data exist on this topic, leaving out NICS. Yet this endpoint warrants careful consideration, as non-ischaemic cardiomyopathies not only predominate among indications for HTx[28] globally but also exhibit a growing body of evidence pointing to lower post-HTx mortality rates when compared with ICM,[29] with similar outcomes after VAD implantation.[30] In our study, baseline NYHA status and the use of aMCS were strongly associated with the composite outcome of 1-year mortality/HTx/VAD, in addition to age, CKD and the use of norepinephrine, which were also predictive of mortality alone. This illustrates that the prognosis assessment of CS combines, on the one hand, baseline factors reflecting physiological reserve capacities (age, CKD and NYHA stage), and, on the other hand, factors reflecting the severity of CS in the acute phase (use of norepinephrine, aMCS).

Lastly, we also observed a lower utilization of aMCS in NICS patients compared with AMI-CS, predominantly represented by ECLS. This can be contextualized by the presence of more co-morbidities such as CKD or COPD in the NICS group, which may have influenced the management towards medical treatment alone, or by a lack of high evidence level regarding the place of aMCS in NICS patients despite encouraging results found in observational studies.[12]

Limitations

Even though this is one of the largest studies available on NICS, the total number of subjects remains relatively low compared with past studies on AMI-CS. We were unable to enhance the multivariate analysis model with additional data related to detailed early management and severity markers (acute kidney and hepatic injuries) or to stratify the degree of CKD (a frequently implicated prognostic factor), as the necessary data were not available. Moreover, we did not have data on long-term functional outcomes, which nevertheless represent an important aspect of management in the context of heart failure.

As previously described,[3] the FRENSHOCK registry also involves risks of selection bias related to non-consecutive inclusions or exclusion of the most severe cases.

Furthermore, this cohort focused on the broad analysis of all-cause mortality, aiming for a realistic representation of the daily evolution of HF patients. However, it may be worth considering conducting similar analyses focusing on cardiovascular-specific mortality. Lastly, we acknowledge that the term 'non-ischaemic' encompasses a wide array of different triggers (arrhythmias, pulmonary embolism, valvular disease, heart failure progression and myocarditis), among which it would be desirable to delve deeper into distinctions to elucidate the peculiarities of each subgroup, which was not feasible within the scope of this study due to lack of available data. Future studies would benefit from exploring this aspect further.

Conclusion

In this large cohort of unselected CS cases, non-ischaemic causes were largely predominant, accounting for almost two-thirds of all cases. NICS is still associated with a high mortality rate, similar to that of AMI-CS, influenced by numerous factors related to patient history (age, CKD, cancer) or management modalities (use of norepinephrine, RRT). Future studies should not only focus on AMI-CS but also evaluate treatment strategies for patients with NICS, for which prospective data are lacking in all areas.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Supporting information

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

Table S1. Description of all odds ratios and 95% confidence intervals of all variables tested in multivariate analysis models for 1-month all-cause mortality.
Table S2. Description of all odds ratios and 95% confidence intervals of all variables tested in multivariate analysis models for 1-year all-cause mortality.

Table S3. Description of all odds ratios and 95% confidence intervals of all variables tested in multivariate analysis models for 1-year all-cause mortality and/or HTx and/or VAD.

Table S4. Baseline Characteristics of Patients With Non-Ischemic and Ischemic Cardiogenic Shock.

Table S5. Index Admission Characteristics Among Patients With Non-Ischemic and Ischemic Cardiogenic Shock.

Table S6. In-Hospital Management Among Patients With Non-Ischemic and Ischemic Cardiogenic Shock.

Table S7. Comparison of baseline characteristics of non-ischemic cardiogenic shock patients between 1-year survivors and non-survivors after exclusion of patients with active cancer.

Table S8. Comparison of Index Admission Characteristics Among Patients With Non-Ischemic Cardiogenic Shock between 1-year Survivors and Non-survivors after Exclusion of Patients with Active Cancer.

Table S9. In-Hospital Management Among Patients With Non-Ischemic Cardiogenic Shock after Exclusion of Patients with Active Cancer.

Table S10. Independent variables associated with primary and secondary outcomes in non-ischemic cardiogenic shock after exclusion of patients with active cancer.

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