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Cardiogenic Shock in Idiopathic Dilated Cardiomyopathy Patients: Red Flag for Myocardial Decline

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Idiopathic dilated cardiomyopathy (IDCM) is one of the most common forms of nonischemic cardiomyopathy worldwide, possibly leading to cardiogenic shock (CS). Despite this heavy burden, the outcomes of CS in IDCM are poorly reported. Based on a large registry of unselected CS, our aim was to shed light on the 1-year outcomes after CS in patients with and without IDCM. FRENCHOCK was a prospective registry including 772 patients with CS from 49 centers. The 1-year outcomes (re-hospitalizations, mortality, heart transplantation [HTx], ventricular assist devices [VAD]) were analyzed and adjusted on independent predictive factors. Within 772 CS included, 78 occurred in IDCM (10.1%). Patients with IDCM had more frequent history of chronic kidney failure and implantable cardioverter-defibrillator implantation. No difference was found in 1-month all-cause mortality between groups (28.2 vs 25.8% for IDCM and others, respectively; adjusted hazard ratio 1.14 [0.73 to 1.77], $p=0.57$). Patients without IDCM were more frequently treated with non-invasive ventilation and intra-aortic balloon pump. At 1 year, IDCM led to higher rates of death or cardiovascular re-hospitalizations (adjusted odds ratio 4.77 [95% confidence interval 1.13 to 20.1], $p=0.03$) and higher rates of HTx or VAD for patients aged <65 years (adjusted odds ratio 2.68 [1.2 to 5.91], $p=0.02$). In conclusion, CS in IDCM is a very common scenario and is associated with a higher rate of 1-year death or cardiovascular re-hospitalizations and a more frequent recourse to HTx or VAD for patients aged <65 years, encouraging the consideration of it as a red flag for myocardial decline and urging for a closer follow-up and earlier evaluation for advanced heart failure therapies.

Idiopathic dilated cardiomyopathy (IDCM), currently defined by left or biventricular dilatation and systolic dysfunction in the absence of significant abnormal loading conditions or coronary artery disease,¹ is 1 of the most common forms of nonischemic cardiomyopathy (NICM) and 1 of the main indications for heart transplantation (HTx) worldwide.² Notwithstanding recent improvements in its prognosis thanks to a better understanding of its mechanisms, it remains a challenging heart failure (HF) condition, with a 5-year survival rate as low as 50%,³ leading to acute HF and cardiogenic shock (CS).⁴ Several studies have already investigated the short- and long-term outcomes in NICM versus ischemic cardiomyopathy (ICM), whether in chronic HF, showing no major difference between them,^{5,6} or in CS, resulting in conflicting results.^{7,8} However, NICM mixes various HF etiologies with divergent prognoses, whose characteristics remain to be specified.⁵ Despite its heavy burden, few data have been reported about short- and long-term outcomes of CS in the specific case of IDCM, underrepresented by current or past surveys,⁹ resulting in a crucial need for more data to standardize customized guidelines. Hence, this study aimed to shed light on the 1-year outcomes of CS between patients with and without IDCM based on the multicenter prospective FRENCHOCK registry.

METHODS

As previously described,^{4,10} FRENSHOCK is a prospective, observational, and multicenter survey, conducted between April and October 2016, including 772 patients admitted for CS in intensive care units and intensive cardiac care units in France, coming from various types of institutions (primary to tertiary centers, university and nonuniversity, and public and private hospitals).

All adult patients (aged ≥ 18 years) with CS were prospectively included in this registry if they met at least 1 criterion of each of the following 3 components: (1) low cardiac output: low systolic blood pressure < 90 mm Hg and/or the need for maintenance with vasopressors/inotropes and/or a low cardiac index < 2.2 l/min/m²; (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, or mottled skin) and/or biologic (lactate > 2 mmol/l, metabolic acidosis, renal failure, or liver insufficiency).

For each patient, at inclusion, the investigators were invited to identify the history of preexisting HF, distinguishing several etiologies of cardiomyopathy (ischemic, dilated, hypertrophic, valvular, toxic, or hypertensive) based on the consensual definitions and available recommendations. In the IDCM group, we considered only patients with an isolated diagnosis of dilated cardiomyopathy reported by local investigators. Patients with IDCM

were compared with others. The secondary causes of left ventricular dilatation (toxic, metabolic, obstructive valvulopathy, inflammatory, hypertensive, or iatrogenic) were not included in the IDCM group.

The data collection protocol has already been detailed.^{4,10} Briefly, data recording included past medical history, previous treatments, in-hospital CS management (especially inotropes/vasopressors, mechanical ventilation, renal replacement therapy, and short-term mechanical circulatory support [MCS]), clinical, biologic, and echocardiographic parameters (at admission and at 24 hours). For each patient, investigators had to specify 1 to 3 triggers among the following: ischemic (type 1 or 2 acute myocardial infarction), mechanical complications (valvular injury, ventricular septal defect), ventricular and supraventricular arrhythmia, severe bradycardia, iatrogenesis (medication induced), infections, and/or nonobservance of previous medication.

All-cause mortality, heart transplantation, and ventricular assist devices (VAD) were assessed at 1 month and 1 year. The primary end point was 1-year all-cause mortality. The secondary end points included 1-month all-cause mortality; 1-year need for HTx or VAD; 1-year rate of cardiovascular rehospitalizations; and composites of 1-year mortality or cardiovascular rehospitalizations and 1-year mortality, HTx, or VAD, with censoring after the first event occurrence.

The study was conducted in accordance with the Declaration of Helsinki and French law. Written informed consent was obtained for all patients. Recorded data and their storage were approved by the French Health Research Data Processing Advisory Committee (No. 15.897) and the French Data Protection Agency (No. DR-2016-109).

Continuous variables are reported as means and SD or medians and interquartile ranges, when appropriate. Categorical variables are described as frequencies and percentages. Comparisons were made using the Mann–Whitney nonparametric test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Paired data were analyzed with Wilcoxon signed-rank test. To find the independent predictors for each outcome of interest, a multivariate stepwise logistic regression analysis was performed. First, the association of all baseline characteristics and each primary and secondary outcome was assessed using univariable logistic regression analyses. Then, all significant independent predictors were integrated in multivariable analyses for each outcome and backward reduced to only significant characteristics ($p \leq 0.05$). Finally, these significant characteristics were incorporated in multivariable models as fixed covariates for each adjusted outcome analysis. The variance inflation factor was used to rule out multicollinearity among the variables. The primary outcome of all-cause mortality was assessed using the Kaplan–Meier time-to-event analysis, and Cox proportional hazards models were used to determine the

adjusted hazard ratio (HR), 95% confidence interval (CI), and p values. The secondary outcomes (HTx, VAD, and further composites) are reported as their adjusted odds ratio (OR) and 95% CI.

The main analysis was a comparison between the IDCM and non-IDCM CS group. To consider the commonly recognized selection constraints relating to age in the management of advanced HF, we conducted 2 sensitivity analyses examining the previously mentioned primary and secondary outcomes, including only patients aged <65 and 70 years, representing the group of the most suitable candidates for HTx or VAD, according to most recent advanced HF guidelines.¹¹ Furthermore, another sensitivity analysis was performed excluding participants from the IDCM group with ischemic CS trigger. The analyses were performed using R software (version 4.1.2 [2021/11/1]). All tests were 2-tailed. A value of $p \leq 0.05$ was accepted as statistically significant.

RESULTS

As reported in [Figure 1](#), 772 patients with CS were included in 49 centers, whose baseline characteristics are listed in [Table 1](#). Patients were predominantly men (71.5%), with mean age of 65.7 ± 14.9 years and frequent occurrence of common cardiovascular risk factors, with 47.2%, 35.9%, 28.2%, and 27.8% for hypertension, dyslipidemia, diabetes mellitus, and current smoking, respectively. Chronic kidney failure (21.3%) and peripheral artery disease (11.8%) were the most frequently associated conditions. [Table 2](#) lists the initial clinical, biologic, and echocardiographic data. The mean blood pressure was 74.9 ± 18.3 mm Hg, with initial cardiac arrest for 79 patients (10.2%). The mean left ventricular ejection fraction (LVEF) was $26.3 \pm 13.4\%$, with a median tricuspid annular plane systolic excursion of 13 mm (10 to 16) and a median

peak systolic velocity tissue Doppler imaging of 8 cm/s (6 to 11).

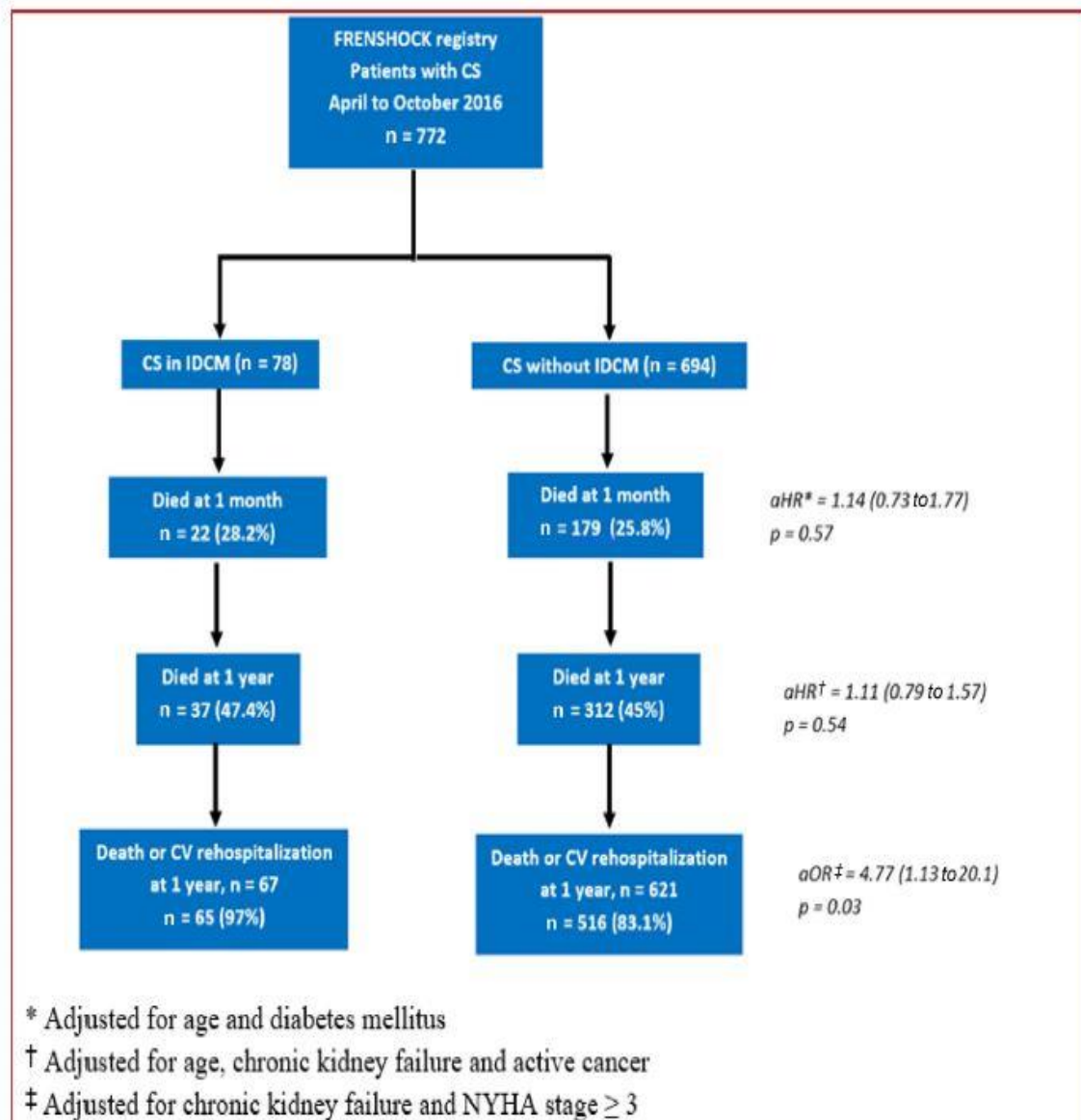


Figure 1. Flow chart of the study. Each adjusted outcome analysis included significant characteristics found as independent predictive factors in multivariable analyses and used as fixed covariates. aHR = adjusted hazard ratio; aOR = adjusted odds ratio; CV = cardiovascular.

Table 1
Clinical characteristics at admission according to cardiomyopathy (IDCM vs non-IDCM)*

	Overall population (n = 772)	IDCM group (n = 78)	Non-IDCM group (n = 694)	p value
Age, mean ± SD, years	65.7 ± 14.9	63.9 ± 13.9	65.9 ± 15	0.2
Male, n (%)	552 (71.5)	61 (78.2)	491 (70.7)	0.21
Body mass index, mean ± SD, kg/m ²	25.8 ± 5.6	25.8 ± 6.3	25.8 ± 5.5	0.49
Risk factors, n (%)				
Diabetes mellitus	217 (28.2)	20 (25.6)	197 (28.5)	0.69
Hypertension	364 (47.2)	31 (39.7)	333 (48.1)	0.2
Dyslipidaemia	277 (35.9)	26 (33.3)	251 (36.2)	0.7
Current smoker	206 (27.8)	11 (14.3)	195 (29.4)	< 0.01
Medical history, n (%)				
Peripheral artery disease	91 (11.8)	8 (10.3)	83 (12)	0.79
Chronic kidney failure	164 (21.3)	27 (34.6)	137 (19.8)	< 0.01
ICD	127 (18.3)	37 (47.4)	90 (13)	< 0.01
COPD	50 (6.5)	4 (5.1)	46 (6.6)	0.79
Active cancer	51 (6.6)	3 (3.8)	48 (6.9)	0.43
NYHA functional status, n (%)				
I	263 (34.9)	10 (13.2)	253 (37.4)	
II	195 (25.9)	13 (17.1)	182 (26.9)	< 0.01
III	201 (26.7)	40 (52.6)	161 (23.8)	
IV	94 (12.5)	13 (17.1)	81 (12)	
Previous medications, n (%)				
Aspirin	288 (37.4)	19 (24.4)	269 (38.9)	0.02
Vitamin K antagonist	165 (21.4)	32 (41)	133 (19.2)	< 0.01
Direct oral anticoagulant	56 (7.3)	15 (19.2)	41 (5.9)	< 0.01
ACE inhibitors	292 (37.9)	50 (6.4)	242 (35)	< 0.01
Sacubitril/valsartan	18 (2.5)	9 (11.8)	9 (1.4)	< 0.01
Beta blockers	316 (41)	48 (61.5)	268 (38.7)	< 0.01
Loop diuretics	376 (48.8)	65 (83.3)	311 (44.9)	< 0.01
Aldosterone antagonist	108 (14)	27 (34.6)	81 (11.7)	< 0.01
Amilorone	132 (17.6)	26 (34.2)	106 (15.7)	< 0.01

*The total number of participants may vary for certain variables owing to missing data.

ACE = angiotensin-converting enzyme; COPD = chronic obstructive pulmonary disease; CS = cardiogenic shock; ICD = implantable cardioverter-defibrillator; IDCM = dilated cardiomyopathy; NYHA = New York Heart Association; SD = standard deviation

Table 2
Clinical, echocardiographic, and biologic initial presentation according to cardiomyopathy (IDCM vs non-IDCM)*

	Overall population (n = 772)	IDCM group (n = 78)	Non-IDCM group (n = 694)	p value
Clinical presentation at admission				
Heart rate, mean ± SD, bpm	95.6 ± 29.6	86.3 ± 24.6	96.7 ± 29.9	< 0.01
SBP, mean ± SD, mmHg	101.2 ± 25.2	99.3 ± 18.7	101.4 ± 25.8	0.7
DBP, mean ± SD, mmHg	63.2 ± 17.4	62.6 ± 16.3	63.2 ± 17.5	0.85
MBP, mean ± SD, mmHg	74.9 ± 18.3	73.9 ± 15.4	75 ± 18.6	0.81
Sinus rhythm, n (%)	399 (52)	39 (50)	360 (52.2)	0.81
Cardiac arrest, n (%)	79 (10.2)	5 (6.4)	74 (10.7)	0.33
Blood tests at admission, median (IQR)				
Sodium, mmol/L	135 (132 – 139)	134 (130 – 137.8)	136 (132 – 139)	0.01
Creatinin, μmol/L	133 (96 – 190)	143 (113.3 – 217.8)	133 (94 – 183.5)	0.03
Bilirubin, mg/L	16 (9 – 29)	26 (14.3 – 42)	16 (9 – 27.4)	< 0.01
Arterial blood lactates, mmol/L	3 (2 – 4.7)	2 (1.3 – 3.1)	3 (2 – 5)	< 0.01
PT, %	59 (37 – 77)	43 (23 – 63.3)	61 (39 – 78)	< 0.01
BNP, pg/mL	1,150 (476.8 – 2,757.3)	2,813.5 (1,062.8 – 4,262.5)	1,099.5 (457.8 – 2,518.5)	< 0.01
Nt-proBNP, pg/mL	9,276.5 (4,057.8 – 22,702.5)	9,700 (5,006 – 26,000)	9,037 (3,897 – 21,802)	0.73
Baseline echocardiography				
LVEF, mean ± SD, %	26.3 ± 13.4	20.2 ± 7.7	27 ± 13.7	< 0.01
TAPSE, median (IQR), mm	13 (10 – 16)	12 (10 – 16)	13 (10 – 17)	0.98
PSVtdi, median (IQR), cm/s	8 (6 – 11)	7 (6 – 8)	8 (6 – 11)	0.04
Severe mitral regurgitation, n (%)	107 (14.6)	20 (26)	87 (13.2)	< 0.01

*The total number of participants may vary for certain variables because of missing data.

BNP = brain natriuretic peptide; DBP = diastolic blood pressure; IDCM = dilated cardiomyopathy; IQR = interquartile range; LVEF = left ventricular ejection fraction; MBP = mean blood pressure; PSVtdi = peak systolic velocity tissue Doppler imaging; PT = prothrombin time; SBP = systolic blood pressure; SD = standard deviation; TAPSE = tricuspid annular plane systolic excursion

Among the 772 CS cases, 78 occurred in preexisting IDCM (10.1%). The main CS triggers reported in the non-IDCM group were ischemia (39.2%), supraventricular tachycardia (12.5%), infectious disease (12.4), and ventricular arrhythmia (12.1%) (Supplementary Table 1). By contrast, in the IDCM group, the main triggers were supraventricular tachycardia (20.5%), ventricular arrhythmia (16.7%), ischemia (10.3%), and infectious disease (7.7%). Of note, within the 8 participants of the IDCM group with ischemic CS trigger, coronary angiography data were available for 5, revealing type 2 AMI for 4 of them and type 1 AMI for the last 1.

As listed in Table 1, patients with IDCM presented with higher rates of chronic kidney failure (34.6% vs 19.8%, $p < 0.01$) and past implantable cardioverter-defibrillator implantation (47.4% vs 13%, $p < 0.01$). Previous treatments with loop diuretics, β blockers, sacubitril/valsartan, aldosterone antagonist, amiodarone, vitamin K antagonists, and direct oral anticoagulants were significantly more spreadly used in the IDCM group.

At admission, IDCM presented with lower LVEF (20.2% vs 27%, $p < 0.01$) and peak systolic velocity tissue Doppler imaging (7 vs 8 cm/s, $p = 0.04$). The median blood lactates level was superior in the non-IDCM group (2 vs 3 mmol/l, $p < 0.01$), whereas patients with IDCM showed higher levels of creatinine (143 vs 133 $\mu\text{mol/l}$, $p = 0.03$) and bilirubin (26 vs 16 mg/l, $p < 0.01$) associated with lower prothrombin time (43% vs 61%, $p < 0.01$) (Table 2), with slight improvement after 24 hours of management (Supplementary Table 2).

As listed in Table 3, inotropes (e.g., dobutamine, norepinephrine, adrenaline, and levosimendan) were used in 91.1% of the overall population, with no difference between groups, except for levosimendan, which was more frequently used in the IDCM group (20.5% vs 5.9%, $p < 0.01$). Noninvasive ventilation was more often required in the non-IDCM group (27% vs 15.4%, $p = 0.04$). Although there was no difference in the overall use of acute MCS (13% vs 18.1%, $p = 0.34$), intra-aortic balloon pump (IABP) was

exclusively implemented in the non-IDCM group (6.9%). No difference was found for renal replacement therapy.

Figure 2 shows the absence of difference in all-cause mortality at 1-month and 1-year between patients with and without IDCM, with respective adjusted HRs of 1.14, 95% CI 0.73 to 1.77, $p = 0.57$, and 1.11, 95% CI 0.79 to 1.57, $p = 0.54$. Nevertheless, IDCM led to a significantly higher rate of mortality or cardiovascular rehospitalizations at 1 year than the non-IDCM group, with an adjusted OR of 4.77, 95% CI 1.13 to 20.1, $p = 0.03$. No difference was found for HTx and VAD need in the overall population.

Including only patients aged <65 years, IDCM showed a trend toward poorer long-term outcomes, culminating in a significantly higher rate of 1-year HTx or VAD (adjusted OR 2.68, 1.21 to 5.91, $p = 0.02$), as reported in Figure 3. The 1-month and 1-year mortality rates were similar between groups, with respective adjusted HRs of 0.69, 0.3 to 1.58, $p = 0.28$ and 1.1, 0.65 to 1.89, $p = 0.7$. The second sensitivity analysis, restricted to participants <70 years, yielded consistent results with the main analysis, illustrated by a higher rate of 1-year mortality or rehospitalizations in the IDCM group (Supplementary Figure 1), without reaching significance for HTx and VAD.

Eventually, the last sensitivity analysis, excluding 8 patients from the IDCM group with ischemic CS trigger, also led to similar results as the main analysis (Supplementary Figure 2).

DISCUSSION

In this study of a French nationwide representative sample of 772 patients with CS, 10.1% of them were previously known to have IDCM, leading to a higher rate of 1-year death or cardiovascular rehospitalizations and increased recourse to HTx or VAD for patients <65 years.

To the best of our knowledge, FRENSHOCK is the largest prospective, multicenter CS registry in Europe, reflecting a real-world population of unselected CS, including a relevant number of IDCM. Although extensive research has been conducted on ischemic heart disease-related CS,¹² our understanding of NICM remains limited despite constituting

up to 60% of patients with CS.⁴ Nonischemic related CS are underrepresented in the present and previous trials,⁹ highlighting the urgent need for more research focusing on these CS subpopulations. Given the broad range of underlying causes and prognosis variances within NICM,⁵ our study narrows its focus to IDCM for a more thorough analysis.

Table 3
In-hospital management according to cardiomyopathy*

	Overall population (n = 772)	CS in IDCM (n = 78)	CS without IDCM (n = 694)	p value
Medications used, n (%)				
Dobutamine	632 (82.3)	69 (87.2)	563 (81.6)	0.18
Norepinephrine	410 (53.4)	35 (44.9)	375 (54.3)	0.14
Epinephrine	95 (12.4)	6 (7.7)	89 (12.9)	0.25
Levosimendan	57 (7.4)	16 (20.5)	41 (5.9)	< 0.01
Respiratory support, n (%)				
Non-invasive	198 (25.8)	12 (15.4)	186 (27)	0.04
Invasive	291 (37.9)	22 (28.2)	269 (39)	0.08
Short-term mechanical circulatory support, n (%)				
Overall	135 (17.6)	10 (13)	125 (18.1)	0.34
IABP	48 (6.3)	0 (0)	48 (6.9)	0.03
Impella	26 (33.9)	1 (1.3)	25 (3.6)	0.46
ECLS	85 (11.1)	10 (13)	75 (10.8)	0.7
Renal replacement therapy, n (%)	122 (15.8)	9 (11.5)	113 (16.3)	0.35

*The total number of participants may vary for certain variables because of missing data.

CS = cardiogenic shock; ECLS = extracorporeal life support; IABP = intra-aortic balloon pump; IDCM = idiopathic dilated cardiomyopathy

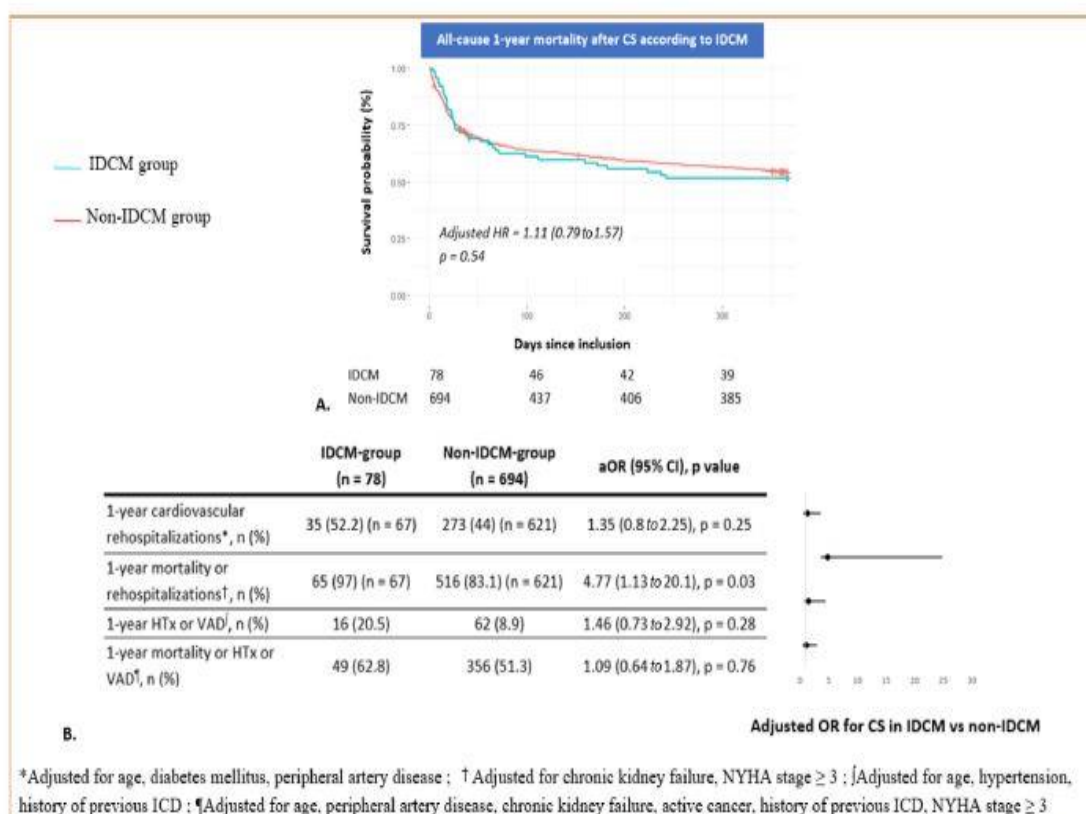


Figure 2. Primary and secondary outcomes for CS according to an idiopathic dilated cardiomyopathy. Panel A represents 1-year overall mortality. The cumulative incidences of 1-year and 1-month mortality were estimated with the use of the Kaplan–Meier method; hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models. Panel B focuses on secondary outcomes including rehospitalizations, heart transplantation and ventricular assist devices. According to significant characteristics found as independent predictive factors in multivariable analyses, 1-year mortality was adjusted for age, chronic kidney failure and active cancer. aOR = adjusted odds ratio.

In this study, we found that CS in IDCM differs from other cardiomyopathies in several ways. Despite the absence of a difference in the 1-month all-cause mortality, patients with IDCM exhibited numerous indicators of heightened preexisting HF and concurrent co-morbidities, as evidenced by higher levels of creatinine, brain natriuretic peptide, and bilirubin, along with decreased LVEF. Conversely, participants without IDCM demonstrated higher lactate levels, suggestive of a more severe organ malperfusion.

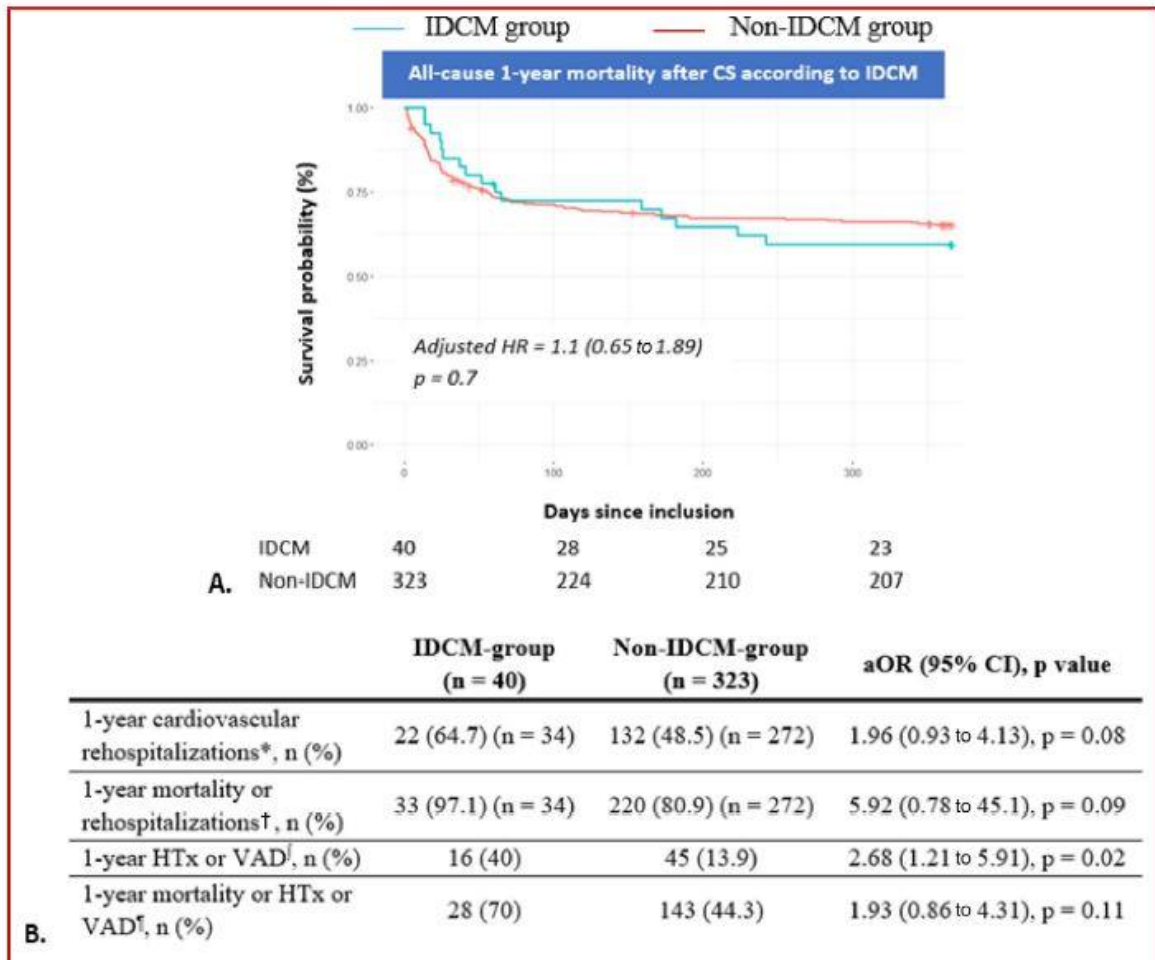
Beyond these clinical differences, our investigation highlights the therapeutic discrepancies between ischemic and nonischemic CS. Indeed, all the advancements in revascularization procedures and enhanced use of antiatheromatous therapies have propelled progress in managing ischemic CS,¹² but the handling of nonischemic CS is still matter of debate, emphasizing the necessity for tailored therapeutic strategies. Our findings offer several leads for exploration and improvement in this area.

First, in our study, IDCM presented with more frequent severe mitral regurgitation, of mainly secondary mechanism, perhaps highlighting a privileged therapeutic target,

especially when the mitral regurgitation is anatomically accessible to edge-to-edge valve repair, which is achievable in most patients with CS and associated with significantly lower mortality and HF hospitalization at 1 year.¹³

In addition, the management of inotropic agents in CS is also a subject of ongoing debate, suffering from lack of randomized data, raising concern about their strategic use and their safety profile.¹¹ A recent study¹⁴ emphasized an enhanced responsiveness to levosimendan in NICM, leading to lower 1-month CS mortality. Even though levosimendan was more commonly administered within our IDCM group, its overall use was the lowest among all amines (7.4% in total and 20.5% in the IDCM group), possibly masking any discernible outcome differences. The upcoming LEVOHEARTSHOCK study (NCT04020263) intends to include 610 patients in a comparison of early levosimendan initiation versus placebo and could provide valuable insights for clinicians.

The role of short-term MCS in treatment remains controversial owing to a paucity of data. Current findings suggest that the results of MCS in CS, whether through extracorporeal life support¹⁵ or Impella,¹⁶ are no worse in NICM than ICM. Although the use of IABP is waning in ICM after the IABP-SHOCK II trial,¹⁷ its role in NICM cases still invites discussion. IABP may lead to clinical stabilization and enhanced tissue perfusion in NICM, potentially serving as a beneficial bridging tool to VAD or HTx.¹⁸ However, our cohort, which is not purposed for this evaluation, does not



*Adjusted for age, diabetes mellitus, peripheral artery disease ; †Adjusted for chronic kidney failure, NYHA stage ≥ 3 ; ‡Adjusted for age, hypertension, history of previous ICD ; §Adjusted for age, peripheral artery disease, chronic kidney failure, active cancer, history of previous ICD, NYHA stage ≥ 3

Figure 3. Primary and secondary outcomes for CS according to an idiopathic dilated cardiomyopathy for patients under 65 years old. Panel A represents 1-year overall mortality. The cumulative incidences of 1-year and 1-month mortality were estimated with the use of the Kaplan–Meier method; hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models. Panel B focuses on secondary outcomes including rehospitalizations, heart transplantation and ventricular assist devices. According to significant characteristics found as independent predictive factors in multivariable analyses, 1-year mortality was adjusted for age, chronic kidney failure and active cancer. aOR = adjusted odds ratio.

clarify this point, particularly because IABP was not used in our patients with IDCM. A recent extensive retrospective study disclosed a correlation between MCS use (Impella or extracorporeal life support) in NICM and reduced 30-day mortality compared with medical therapy alone, albeit with increased complications.¹⁹ More randomized trials are required to establish standardized short-term MCS use in NICM and evaluate its outcomes.

After 1-year follow-up, patients with IDCM experienced a 4.77-fold increased risk of all-cause death or cardiovascular rehospitalizations relative to patients without IDCM after controlling for potential confounders. Notably, IDCM

precipitated a 2.68-fold enhanced risk of 1-year HTx or VAD in patients aged <65 years, representing the group of the most suitable candidates for HTx or VAD.¹¹ Conversely, outside of CS contexts, multiple studies concur that the ischemic nature of HF is an adverse prognostic factor, leading to increased mortality and rehospitalization rates.^{20,21} A range of factors, including superior responses to standard HF treatments such as resynchronization therapy²² and well-implemented medical treatments enabling substantial left ventricular reverse remodeling,²³ likely contribute to this trend. Yet, in our research, the elevated rate of all-cause death or cardiovascular rehospitalizations 1-

year after the CS episode in patients with IDCM implies quicker myocardial deterioration than other HF etiologies. Our findings align with previous research that places IDCM as the primary indication for HTx worldwide.^{2,24} New findings suggest that post-HTx follow-up incurs lower mortality for NICM than ICM,²⁵ whereas long-term outcomes post-LVAD implantation seem to be parallel between NICM and ICM,²⁶ with the potential advantage of serving as a bridge-to-transplant therapy. The synthesis of the higher 1-year mortality and/or rehospitalization rates after IDCM, coupled with the improved long-term post-HTx outcomes for NICM, leads our data to propose the onset of CS in IDCM as a critical juncture in the natural progression of HF, signifying an accelerated impending myocardial decline. This necessitates a more intensive follow-up and earlier evaluation for advanced HF treatments, with HTx as the optimal long-term strategy, possibly with VAD as a bridge-to-transplant option.

Importantly, the diagnosis of IDCM was determined by local investigators, thereby potentially introducing diagnostic errors. We selected only patients with a single diagnosis of IDCM, whereas toxic dilated cardiomyopathy was considered separately. At the time of the study, the understanding of IDCM, particularly in relation to genetic causes and research, was less developed and therefore unavailable.

Strong evidence exists for already known poor prognostic factors in IDCM related to clinical or echocardiographic data, IDCM family history, late gadolinium enhancement in cardiac magnetic resonance imaging, or the presence of an underlying mutation could not be integrated.^{27–29} Furthermore, our study focused exclusively on IDCM, although there are many secondary causes of IDCM (e.g., peripartum and so on), for which data on prognosis are missing.

Although the burden of IDCM is also considerable in children, representing their leading indication for HTx worldwide, our study included only adult patients (age ≥ 18 years). Even though this separation remains clinically relevant, because there is mounting evidence that pediatric and adult IDCM represent distinct pathological entities, further studies could investigate the same issue specifically in children, especially because we have no guarantee about the effectiveness of HF standard treatments usually given to adults in children.³⁰

As previously described,¹⁰ the FRENDSHOCK registry also involves risks of selection bias related to nonconsecutive inclusions or exclusion of the most severe cases. We did not use the SCAI SHOCK stage classification because it was not yet available at the time of our study.

In conclusion, CS in IDCM is a very common scenario, which is underrepresented in past and current CS surveys, leading to a higher rate of death or cardiovascular rehospitalizations at 1 year and a more frequent recourse to HTx or VAD for patients aged < 65 years than other cardiomyopathies. These results encourage to consider CS in IDCM as a red flag for myocardial decline in the natural course of HF, urging a closer follow-up and earlier evaluation for advanced HF therapies.

Declaration of Competing Interest

The authors have no competing interests to declare.

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