Cardiogenic shock and chronic kidney disease: Dangerous liaisons

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Abstract

Background:

Chronic kidney disease (CKD) is one of the leading causes of death worldwide, closely interrelated with cardiovascular diseases, ultimately leading to the failure of both organs - the so-called "cardiorenal syndrome". Despite this burden, data related to cardiogenic shock outcomes in CKD patients are scarce.

Methods:

FRENSHOCK (NCT02703038) was a prospective registry involving 772 patients with cardiogenic shock from 49 centres. One-year outcomes (rehospitalization, death, heart transplantation, ventricular assist device) were analysed according to history of CKD at admission and were adjusted on independent predictive factors.

Results:

CKD was present in 164 of 771 patients (21.3%) with cardiogenic shock; these patients were older (72.7 vs. 63.9years) and had more comorbidities than those without CKD. CKD was associated with a higher rate of all-cause mortality at 1month (36.6% vs. 23.2%; hazard ratio 1.39, 95% confidence interval 1.01-1.9; P=0.04) and 1year (62.8% vs. 40.5%, hazard ratio 1.39, 95% confidence interval 1.09-1.77; P<0.01). Patients with CKD were less likely to be treated with norepinephrine/epinephrine or undergo invasive ventilation or receive mechanical circulatory support, but were more likely to receive renal replacement therapy (RRT). RRT was associated with a higher risk of all-cause death at 1month and 1year regardless of baseline CKD status.

Conclusions:

Cardiogenic shock and CKD are frequent "cross-talking" conditions with limited therapeutic options, resulting in higher rates of death at 1month and 1year. RRT is a strong predictor of death, regardless of preexisting CKD. Multidisciplinary teams involving cardiac and kidney physicians are required to provide integrated care for patients with failure of both organs.

Abbreviations

ACE angiotensin-converting enzymeCI confidence intervalCKD chronic kidney diseaseCS cardiogenic shockHR hazard ratioRRT renal replacement therapySD standard deviation

1. Introduction

Chronic kidney disease (CKD) is one of the most prominent causes of death in the 21st century, making it a major public health issue [1]. Besides, cardiovascular diseases represent the leading cause of death in patients with advanced CKD, and the incidence of these conditions starts to increase during the early stages of CKD [1, 2]. Indeed, cardiac and renal diseases interact in a complex bidirectional and interdependent manner in both acute and chronic settings, described as cardiorenal syndrome [3].

Cardiogenic shock is a life-threatening haemodynamic condition caused by severe impairment of myocardial performance that results in diminished cardiac output and end-organ hypoperfusion, still associated with a high mortality rate, approaching 50–60% at1 year [4]. Although the occurrence of an acute kidney injury in the early phase of cardiogenic shock is commonly considered a poor prognosis factor, worsening short- and long-term mortality [5, 6], less is known about the impact of preexisting CKD, and the few available data mainly concern cardiogenic shock complicating acute myocardial infarction [7]. Yet, cardiogenic shock with CKD remains a common scenario, with challenging considerations including fluid balance and haemodynamic support, all the trickier in the context of CKD.

This study aimed to compare short- and long-term outcomes inpatients admitted for cardiogenic shock with or without a history of CKD at admission.

2. Materials and methods

2.1. Patient population

FRENSHOCK (NCT02703038) was a prospective, observational, multicentre survey conducted in France between April and October2016 [4, 8]. The study involved 772 patients admitted for cardiogenic shock to intensive care or intensive cardiac care units from a range of different institutions (primary to tertiary centres, university and non-university, public and private hospitals).

All adults (≥ 18 years of age) with cardiogenic shock were prospectively included in the registry if they met at least one criterion from each of the following three components: (1) low cardiac output: systolic blood pressure < 90 mmHg and/or the need for maintenance with vasopressors/inotropes and/or a cardiac index < 2.2 L/min/m2; (2) elevation of left and/or right heart filling pressure, defined by clinical signs, radiology, blood tests, echocardiography or signs of invasive haemodynamic overload; and (3) signs of organ malperfusion, which could be clinical (oliguria, confusion, pale and/or cold extremities, mottle signs) or biological(lactate > 2 mmol/L, metabolic acidosis, renal failure, liver insufficiency).

Investigators had to specify one to three triggers of cardiogenic shock for each patient from among the following: ischaemic event (type 1 or 2 acute myocardial infarction), mechanical com-plications (valvular injury, ventricular septal defect), ventricular and supraventricular arrhythmia, severe bradycardia, iatrogenesis (medication induced), infections, non-observance of previous medication. Investigators were invited to identify history of CKD at inclusion and previous chronic dialysis.

2.2. Data collection

The data collection protocol has been published elsewhere [4, 8]. In brief, data recording included medical history, previous treatments, in-hospital management of cardiogenic shock (inotropes/vasopressors, mechanical ventilation and acute mechanical circulatory support), clinical, biological and echocardiographic parameters (at admission and at 24 h). Data relating to renal-dedicated therapies involved the use of diuretics (loop, thiazide, aldosterone antagonists) and the need for renal replacement therapy (RRT).

2.3. Follow-up

Occurrence of all-cause death, heart transplantation and use of ventricular assist devices was assessed at 1 month and 1 year. The primary outcome was 1-year all-cause death. Secondary outcomes included 1-month all-cause death and composites of 1-year death or cardiovascular rehospitalizations as well as 1-year death, heart transplantation or ventricular assist device, with **censoring after occurrence of the first event.**

2.4. Ethics

The study was conducted in accordance with the Declaration of Helsinki and French law. Written consent was obtained from all patients. Data recording and storage were approved by the French Health Research Data Processing Advisory Committee (Comité consultatif pour le traitement de l'information en matière de recherche dans le domaine de la santé; no15.897) and the French data protection agency (Commission Nationale de l'Informatique et des Libertés; noDR-2016-109).

2.5. Statistical analysis

Continuous variables are reported as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Categorical variables are described as frequencies and percentages. The Shapiro–Wilk test was used to analyse the normal distributions of continuous variables. Comparisons were made using Mann–Whitney non-parametric test for continuous variables and X^2 test or Fisher's exact test for categorical variables. Paired data were analysed using the Wilcoxon signed-rank test. To identify in dependent predictors for each outcome, a multivariable stepwise logistic regression approach was employed. Initially, univariate logistic regression analyses assessed the association of all baseline characteristics with each primary and secondary outcome. Subsequently, based on their statistical significance in univariate analyses and clinical relevance, a backward reduction process was applied to include only characteristics with $P \leq 0.05$ in the multivariable models in the adjusted outcome analyses. The variance inflation factor was used to ensure the absence of multicollinearity among variables. The primary outcome of all-cause death was assessed using Kaplan–Meier time-to-event analysis, and Cox proportional hazards models were used to determine adjusted hazard ratios (HR) with 95% confidence intervals (CI) and P-values. Secondary out-comes (heart transplantation, ventricular assist device and further composites) are reported as their adjusted odds ratio (OR) and 95%CI. The primary analysis was a comparison between cardiogenic shock patients with versus without a history of CKD at admission. To investigate the impact of need for RRT independently of preexisting CKD, a second comparison was made in patients requiring RRT, between CKD and non-CKD patients. Vice versa, to assess the impact of prior CKD before cardiogenic shock regardless of need for RRT, we compared CKD and non-CKD patients without need for RRT.

All tests were two-tailed. $P \leq 0.05$ was accepted statistically significant. Analyses were performed using R software [version4.1.2 (2021-11-01)].

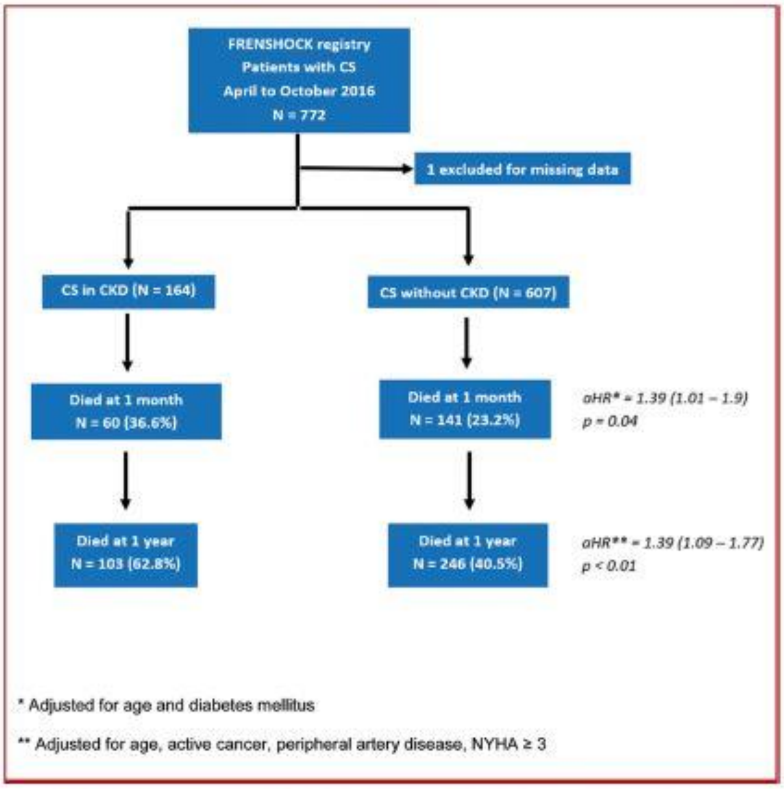

Fig. 1. Study flow chart. Each adjusted outcome analysis included significant characteristics found to be independent predictive factors in multivariable analyses and used as fixed covariates. aHR: adjusted hazard ratio; CKD: chronic kidney disease; CS: cardiogenic shock.

3. Results

3.1. Baseline characteristics

A total of 772 patients with cardiogenic shock were enrolled in the FRENSHOCK study. Previous CKD status was unknown in one patient, who was excluded from the analysis (Fig. 1). The study population therefore comprised 771 patients from 49 centres. Patient baseline characteristics are described in Table 1. Preexisting CKD was present in 21.3% of patients, with 11 (1.4%) already under-going long-term dialysis. Cardiovascular risk factors, peripheral artery disease and history of stroke were more prevalent in the CKD group. History of cardiac disease was also more common in CKD patients, with a predominance of ischaemic (47.6% vs. 25.1%), dilated and valvular cardiomyopathies, and appeared more severe, with a higher rate of cardioverter-defibrillator implantations and heart failure (New York Heart Association class III or IV). Baseline treatment with loop diuretics, thiazide diuretics, beta-blockers and statins was more common in the CKD group (all $P < 0.01$).

Compared with the non-CKD group, triggers in the CKD group were more frequently supraventricular tachycardia (20.1% vs.11.5%) and less frequently ischaemia (24.4% vs. 39.5%). Other triggers were infectious disease (14.0%) and ventricular arrhythmias (6.7%) (Table A.1).

Table 1
Clinical characteristics at admission, overall and according to CKD status.

Variable	Overall population (n = 771)	CKD group (n = 164)	No-CKD group (n = 607)	P[a]
Age, years	66 (58–77)	73.5 (64–82)	65 (56–75)	<0.01
Male sex	551 (71.5)	123 (75.0)	428 (70.5)	0.3
Body mass index, kg/m²	24.8 (22.4–28.4) (n = 743)	25.1 (22.2–29.3) (n = 158)	24.7 (22.4–28.1) (n = 585)	0.33
Risk factors				
Diabetes mellitus	217 (28.2) (n = 769)	63 (38.7) (n = 163)	154 (25.4) (n = 606)	<0.01
Hypertension	364 (47.3) (n = 770)	102 (62.2)	262 (43.2) (n = 606)	<0.01
Dyslipidaemia	277 (35.9) (n = 771)	84 (51.2)	193 (31.8) (n = 606)	<0.01
Current smoker	205 (27.7) (n = 739)	18 (11.4) (n = 158)	187 (32.2) (n = 581)	<0.01
Medical history				
Peripheral artery disease	91 (11.8)	29 (17.7)	62 (10.2)	0.01
Implantable cardioverter-defibrillator	127 (18.3)	55 (33.5)	72 (11.9)	<0.01
Active cancer	51 (6.6)	13 (7.9)	38 (6.3)	0.56
Stroke	62 (8.0)	27 (16.5)	35 (5.8)	<0.01
NYHA functional status III or IV	295 (39.2) (n = 752)	90 (55.6) (n = 162)	205 (34.7) (n = 590)	<0.01
History of cardiac disease	n = 770		n = 606	
All cause	433 (56.2)	140 (85.4)	293 (48.3)	<0.01
Ischaemic	230 (29.9)	78 (47.6)	152 (25.1)	<0.01
Hypertrophic	11 (1.4)	4 (2.4)	7 (1.2)	0.39
Toxic	34 (4.4)	6 (3.7)	28 (4.6)	0.75
Dilated	78 (10.1)	27 (16.5)	51 (8.4)	<0.01
Valvular	65 (8.4)	23 (14)	42 (6.9)	<0.01
Hypertensive	24 (3.1)	9 (5.5)	15 (2.5)	0.09
Previous medications	n = 769			
Aspirin	288 (37.5)	72 (43.9)	216 (35.7) (n = 605)	0.07
Vitamin K antagonist	165 (21.5)	80 (48.8)	85 (14) (n = 605)	<0.01
Direct oral anticoagulant	56 (7.3)	15 (9.1)	41 (6.8) (n = 605)	0.39
ACE inhibitor	292 (38)	76 (46.3)	216 (35.7) (n = 605)	0.02
Sacubitril/valsartan	18 (2.5)	5 (3.2) (n = 154)	13 (2.3) (n = 572)	0.69
Statin	286 (37.2)	83 (50.6)	203 (33.6) (n = 605)	<0.01
Beta-blocker	316 (41.1)	96 (58.5)	220 (36.4) (n = 605)	<0.01
Loop diuretic	376 (48.9)	129 (78.7)	247 (40.8) (n = 605)	<0.01
Aldosterone antagonist	108 (14)	31 (18.9)	77 (12.7) (n = 605)	0.058
Thiazide diuretic	45 (6) (n = 753)	17 (10.6) (n = 160)	28 (4.7) (n = 593)	<0.01
Amiodarone	132 (17.6) (n = 751)	49 (31.4) (n = 156)	83 (13.9) (n = 595)	<0.01

Data are expressed as mean ± standard deviation, number (%) or median (interquartile range). ACE: angiotensin-converting enzyme; CKD: chronic kidney disease; CS: cardiogenic shock; NYHA: New York Heart Association; SD: standard deviation.
[a] CKD group vs. no-CKD group.

3.2. Cardiogenic shock presentation and evolution at 24 h according to CKD status

Table 2 reports the clinical, biological and echocardiographic parameters at initial presentation. The CKD group was characterized by a higher rate of clinical signs of right heart failure ($P < 0.01$),consistent with echographic parameters including lower tricuspid annular plane systolic excursion and peak systolic velocity tissue Doppler imaging, and with biological evidence of chronic congestion, indicated by higher levels of bilirubin and NT-pro-B-type natriuretic peptide (both $P < 0.01$). Whereas non-CKD patients showed a higher median concentration of blood lactates, the reduction of prothrombin time was more pronounced in the CKD group, which was also associated with more common signs of chronic kidney failure, through higher levels of potassium and creatinine and lower haemoglobin (all $P < 0.01$). After 24 h of in-hospital management, the biological and echocardiographic recovery was similar int e CKD and non-CKD groups (Table A.2).

3.3. In-hospital management according to CKD status

Most patients (91.1%) were taking inotropes (e.g. dobutamine, norepinephrine, epinephrine, levosimendan) (Table 3). Norepinephrine and epinephrine were less frequently used in the CKD group (respectively, $P = 0.03$ and $P = 0.04$), which was also characterized by lower rates of invasive ventilation ($P < 0.01$) and acute mechanical circulatory support ($P < 0.01$), regardless of type (intra-aortic balloon pump, Impella®, extracorporeal life support). Coronary angiography was less frequent in the CKD group ($P < 0.01$), with fewer culprit lesions found ($P = 0.01$) and they had a lower rate of percutaneous coronary interventions ($P = 0.01$).

3.4. Renal-dedicated therapies according to CKD status

Loop diuretics were more widely used for CKD patients, whether it was during initial management or at discharge (Table 3). In contrast, a higher proportion of the non-CKD group were prescribed a mineralocorticoid receptor antagonist at discharge. Although the use of thiazide diuretics was higher for CKD patients during the acute management, this difference subsided at discharge and1 year. The need for acute RRT was more prevalent in the CKD group ($P < 0.01$), with an estimated relative risk of 1.96 (95% CI:1. 24–3.1). Indications for initiation of acute RRT were balanced bet-ween groups, whether for anuria, fluid overload, hydroelectrolytic disorders or acidosis (Table 3).

Table 2
Clinical, echocardiographic and biological characteristics according to CKD status.

Variable	Overall population (n = 771)	CKD group (n = 164)	No-CKD group (n = 607)	P[a]
Clinical presentation at admission				
Systolic blood pressure, mmHg	98 (85–114) (n = 769)	95 (85–113.3)	99 (84–116) (n = 605)	0.61
Diastolic blood pressure, mmHg	61 (51–74) (n = 768)	59 (51.8–70)	62 (50–75) (n = 604)	0.08
Mean blood pressure, mmHg	73 (63–86) (n = 766)	70 (63.5–82.5) (n = 163)	75 (62.5–87) (n = 603)	0.08
Mottling	256 (38.8) (n = 660)	51 (36.7) (n = 139)	205 (39.3) (n = 521)	0.64
Left heart failure	553 (71.9) (n = 769)	123 (75)	430 (71.1) (n = 605)	0.37
Right heart failure	377 (49.2) (n = 767)	112 (68.3)	265 (43.9) (n = 603)	<0.01
Cardiac arrest	79 (10.3) (n = 770)	9 (5.5)	70 (11.6) (n = 606)	0.03
Blood tests at admission				
Potassium, mmol/L	4 (4–5) (n = 637)	4.6 (4–5) (n = 137)	4 (4–5) (n = 500)	<0.01
Creatinine, µmol/L	133.5 (95.8–190) (n = 760)	207 (156–283.5) (n = 163)	120 (89–153) (n = 597)	<0.01
Bilirubin, mg/L	16 (9–29) (n = 544)	19 (13–32.3) (n = 109)	16 (9–28) (n = 435)	<0.01
Haemoglobin, g/dL	12.6 (11–14) (n = 753)	11.8 (10–13) (n = 160)	13 (11–14.1) (n = 593)	<0.01
Arterial blood lactates, mmol/L	3 (2–4.7) (n = 683)	2.2 (1.5–3.5) (n = 146)	3 (2–5) (n = 537)	<0.01
Prothrombin time, %	59 (37–77) (n = 730)	41 (23–61) (n = 155)	63 (42–80) (n = 575)	<0.01
NT-proBNP, pg/mL	9276.5 (4057–22,702) (n = 224)	20,520 (11,040–35,000) (n = 63)	6627 (3142–14,000) (n = 161)	<0.01
BNP, pg/mL	1150 (476–2757) (n = 264)	2551 (1444–4007) (n = 48)	1008.5 (428–2328) (n = 216)	<0.01
Baseline echocardiography				
Left ventricular ejection fraction, %	23 (15–35) (n = 762)	20 (15–30) (n = 163)	25 (15–35) (n = 599)	0.57
Tricuspid annular plane systolic excursion, mm	13 (10–16) (n = 259)	12 (9–14) (n = 57)	14 (10–17) (n = 202)	0.03
PSVtdi, cm/s	8 (6–11) (n = 206)	7 (5–8) (n = 45)	9 (7–11) (n = 161)	<0.01
Severe mitral regurgitation	107 (14.6) (n = 732)	34 (21.5) (n = 158)	73 (12.7) (n = 574)	<0.01

Data are expressed as mean ± standard deviation, number (%) or median (interquartile range). BNP: B-type natriuretic peptide; CKD: chronic kidney disease; NT-proBNP: N-terminal-pro hormone B-type natriuretic peptide; PSVtdi: peak systolic velocity tissue Doppler imaging.
[a] CKD group vs. no-CKD group.

3.5. Short- and long-term outcomes

As presented in Fig. 2, after adjusting on potential confounders(age and diabetes mellitus for 1-month death; age, active cancer, peripheral artery disease and previous NYHA status III or IV for1-year death), history of CKD at admission for cardiogenic shock led to a higher all-cause mortality rate at 1 month (36.6% vs. 23.2%;HR: 1.39, 95% CI: 1.01–1.90; $P = 0.04$) and 1 year (62.8% vs. 40.5%;HR: 1.39, 95% CI: 1.09–1.77; $P < 0.01$), as well as a higher rate of1-year rehospitalizations and/or death (94.2% vs. 81.6%, adjusted odds ratio: 2.93, 95% CI: 1.42–6.03; $P < 0.01$) (Table 4). Upon hospital discharge, CKD patients exhibited a higher rate of use of loop diuretic therapy (76.8% vs. 60.4%; $P < 0.01$), contrasting with a lower rate of aldosterone antagonist initiation (21.2% vs. 33.3%; $P = 0.03$) and no significant difference in use of beta-blockers (52.5%vs. 56.6%; $P = 0.53$) or angiotensin-converting enzyme inhibitors (54.5% vs. 63.5%; $P = 0.12$). After 1 year, the prevalence of loop diuretic treatment continued to be higher in the CKD group (73%vs. 44.6%; $P < 0.01$), with fewer beta-blockers (47.6% vs. 68.8%;$P < 0.01$) and angiotensin-converting enzyme inhibitors (52.4%vs. 72.7%; $P < 0.01$) and no difference for aldosterone antagonists(30.2% vs. 39.1%; $P = 0.24$) (Table A.3). The mean overall length of hospital stay was not statistically different between groups (26.2vs. 21.1 days; $P = 0.1$).

Table 3
In-hospital and long-term management according to CKD status.

Variable	Overall population ($n = 771$)	CKD group ($n = 164$)	No-CKD group ($n = 607$)	P[a]
Medications	$n = 767$	$n = 163$	$n = 604$	
Dobutamine	631 (82.3)	136 (83.4)	495 (82)	0.75
Norepinephrine	409 (53.3)	74 (45.4)	335 (55.5)	0.03
Epinephrine	95 (12.4)	12 (7.4)	83 (13.7)	0.04
Levosimendan	57 (7.4)	18 (11)	39 (6.5)	0.07
Respiratory support				
Non-invasive	198 (25.8) ($n = 767$)	40 (24.5) ($n = 163$)	158 (26.2) ($n = 604$)	0.75
Invasive	291 (37.9) ($n = 767$)	41 (25.2) ($n = 163$)	250 (41.4) ($n = 604$)	< 0.01
Coronary angiography performed	399 (51.8)	58 (35.4)	341 (56.2)	< 0.01
≥ 1 culprit lesion	256 (80.5) ($n = 318$)	34 (66.7) ($n = 51$)	222 (83.1) ($n = 267$)	0.01
Any PCI performed	224 (70.4) ($n = 318$)	28 (54.9) ($n = 51$)	196 (73.4) ($n = 267$)	0.01
Coronary artery bypass graft surgery	9 (1.2)	1 (0.6)	8 (1.3)	0.69
Acute mechanical circulatory support		$n = 162$		
Overall	124 (16.1) ($n = 768$)	11 (6.8)	124 (20.5) ($n = 606$)	< 0.01
Intra-aortic balloon pump	48 (6.3) ($n = 767$)	3 (1.9)	45 (7.4) ($n = 605$)	< 0.01
Impella	26 (3.4) ($n = 767$)	1 (0.6)	25 (3.3) ($n = 605$)	0.03
Extracorporeal life support	85 (11.1) ($n = 768$)	8 (4.9)	77 (12.7) ($n = 606$)	< 0.01
Loop diuretic				
24 h	467 (67.5) ($n = 692$)	128 (84.8) ($n = 151$)	339 (62.7) ($n = 541$)	< 0.01
Discharge	346 (63.4) ($n = 546$)	76 (76.8) ($n = 99$)	270 (60.4) ($n = 447$)	< 0.01
1 year	235 (65.1) ($n = 361$)	30 (47.6) ($n = 63$)	205 (68.8) ($n = 298$)	< 0.01
Thiazide diuretic				
24 h	27 (4) ($n = 681$)	14 (9.5) ($n = 147$)	13 (2.4) ($n = 534$)	< 0.01
Discharge	14 (2.6) ($n = 532$)	4 (4.2) ($n = 96$)	10 (2.3) ($n = 436$)	0.29
1 year	8 (2.4) ($n = 330$)	2 (3.5) ($n = 57$)	6 (2.2) ($n = 273$)	0.63
Aldosterone antagonist				
24 h	91 (13.2) ($n = 692$)	27 (17.9) ($n = 151$)	64 (11.8) ($n = 541$)	0.057
Discharge	170 (31.1) ($n = 546$)	21 (21.2) ($n = 99$)	149 (33.3) ($n = 447$)	0.02
1 year	135 (37.5) ($n = 360$)	19 (30.2) ($n = 63$)	116 (39.1) ($n = 297$)	0.2
Acute RRT				
Overall	122 (15.8) ($n = 770$)	39 (23.8)	83 (13.7) ($n = 606$)	< 0.01
CVVHDF/CVVHF	89 (11.6) ($n = 767$)	29 (17.8) ($n = 163$)	60 (10) ($n = 604$)	< 0.01
Intermittent haemodialysis	27 (3.5) ($n = 767$)	7 (4.3) ($n = 163$)	20 (3.3) ($n = 604$)	0.63
Indications for acute RRT	$n = 110$	$n = 30$	$n = 80$	
Anuria	81 (73.6)	22 (73.3)	59 (73.8)	1
Fluid overload	50 (45.5)	13 (43.3)	37 (46.3)	0.83
Hydroelectrolytic disorders	16 (14.5)	5 (16.7)	11 (13.8)	0.76
Acidosis	19 (17.3)	3 (10)	16 (20)	0.27

Data are expressed as mean ± standard deviation or number (%). CKD: chronic kidney disease; CVVHDF: continuous venovenous hemodiafiltration; CVVHF: continuous venovenous haemofiltration; PCI: percutaneous coronary intervention; RRT: renal replacement therapy.
[a] CKD group vs. no-CKD group.

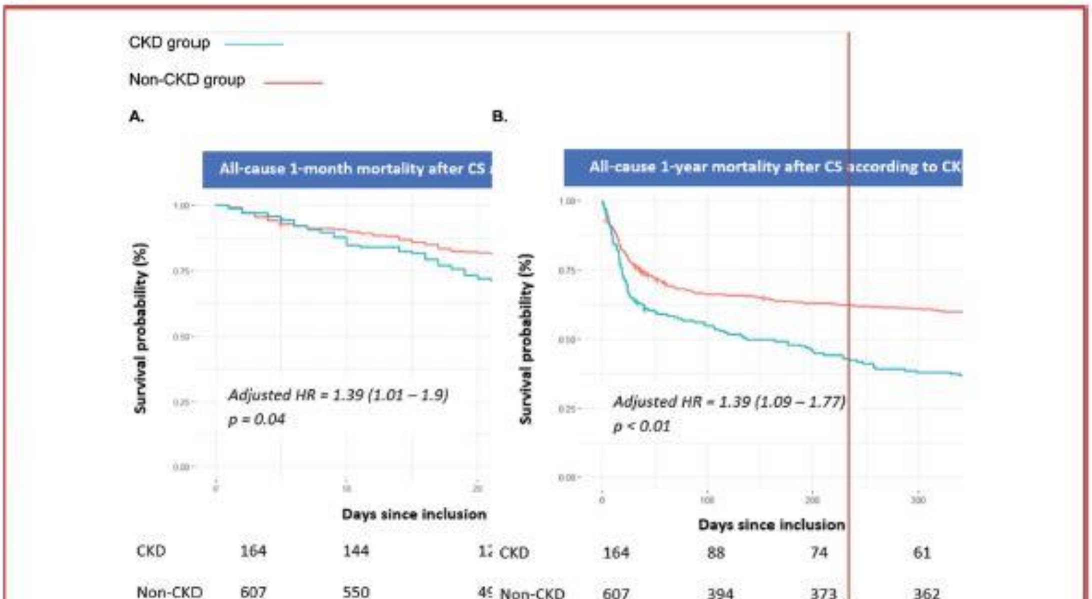

Fig. 2. Short- and long-term mortality outcomes after cardiogenic shock according to CKD status. Panel A represents 1-month all-cause mortality. Panel B focuses on 1-year mortality. The cumulative incidences of 1-year and 1-month mortality were estimated using the Kaplan–Meier method; hazard ratios and 95% confidence intervals were estimated using Cox regression models. According to significant characteristics found as independent predictive factors in multivariable analyses, 1-year mortality was adjusted for age, active cancer, peripheral artery disease, NYHA III or IV. One-month mortality was adjusted for age and diabetes mellitus. CKD: chronic kidney disease; CS: cardiogenic shock; HR: hazard ratio.

3.6. Acute RRT and CKD

The baseline characteristics of patients in the CKD group according to the need for RRT showed no significant differences except for age (Table A.4).

Fig. 3 shows that CKD remains a strong independent predictor of1-month and 1-year death regardless of the use of acute RRT. Nevertheless, requiring RRT was independently associated with worse short- and long-term prognoses, regardless of whether it is preceded by a CKD (Figs. 3 and 4 and Fig. A.1). After excluding patients who died during hospitalization, CKD remained an independent risk factor for 1-year death, increasing the risk by a factor of 1.5(95% CI 1.01 − 2.2; P = 0.046) (Fig. A. 2).

4. Discussion

To date, the FRENSHOCK registry is the largest European cohort of unselected patients with cardiogenic shock, managed in routine clinical practice in primary, secondary and tertiary care centres. In this large, prospective multicentre registry, 21.3% of patients had a history of CKD, and were older and more comorbid conditions, with a higher rate of previous cardiac disease, resulting in a higher all-cause death rate at 1 month and 1 year. Acute need for RRT was required for 15.8% of the cardiogenic shock population and was strongly associated with increased short- and long-term death, independently of previous renal function.

Published data relating to outcomes of CKD patients with cardiogenic shock are scarce. A retrospective cohort of exclusively patients with acute myocardial infarction–cardiogenic shock revealed that end-stage kidney disease was an independent predictor of higher in-hospital death, with limited data on long-term outcomes [6]. Another smaller cohort of 248 patients highlighted that presence of CKD before admission is a strong, independent predictor of in-hospital and long-term death in cardiogenic shock, particularly in acute myocardial infarction–cardiogenic shock [9].

In our study, cardiogenic shock in CKD patients differed from other patients in several ways. First, despite a higher prevalence of previous ischaemic heart disease and cardiovascular risk factors, CKD patients were mainly affected by non-ischaemic cardiogenic shock triggers, with acute ischemia rising to only 24.4%, significantly less common than non-CKD patients (39.5%). Of note, supra ventricular tachycardia and conduction disorders were more frequent in the CKD group. Yet, most previous studies focused on acute myocardial infarction–cardiogenic shock, whereas non-ischaemic cardiogenic shock implies major concerns due to their frequency and severity, with mounting evidence of their under-representation in previous and current cardiogenic shock surveys [10]. Our study included 771 patients with cardiogenic shock, mostly non-ischaemic cardiogenic shock, contrasting with previous surveys, and accounting for more than 60% of all cases [8].These findings provide prospective unexplored data to help stratify patients in cardiogenic shock based on their baseline characteristics.

Secondly, CKD patients were more frequently affected by severe congestive heart failure, illustrated through a higher rate of right heart failure, leading to a more common use of loop and thiazide diuretics, culminating in a more frequent recourse to acute continuous RRT. Acute right-sided heart failure often drives cardiorenal syndrome type 1, sometimes on a preexisting cardiorenal syndrome type 2. It produces venous congestion and reduces renal perfusion pressure, given that persistent or new congestive phenotypes within the first 24 hours of cardiogenic shock are associated with worse outcomes [11]. Reciprocally, preexisting CKD in cardiogenic shock (type 4 cardiorenal syndrome) makes cardiogenic shock management even harder because of reduced natriuresis, which ultimately leads to fluid overload, and is reported to be an important factor associated with increased short-term death in both acute cardiac [12] and renal [13] failure.

Table 4
Secondary outcomes for patients with cardiogenic shock according to CKD status.

Outcome	CKD group (n= 164)	No-CKD group (n= 607)	Adjusted odds ratio (95% CI)	P
1-year mortality or rehospitalizations[a]	145 (94.2) (n= 154)	436 (81.6) (n=534)	2.93 (1.42–6.03)	<0.01
1-year mortality or heart transplantation or ventricular assist device[b]	113 (68.9)	292 (48.1)	1.72 (1.15–2.58)	<0.01

Data are expressed as number (%). CI: confidence interval; CKD: chronic kidney disease.
[a] Adjusted for active cancer, history of ischaemic heart disease and history of dilated cardiomyopathy.
[b] Adjusted for age, peripheral artery disease, active cancer, history of previous implantable cardioverter-defibrillator and NYHA stage III or IV.

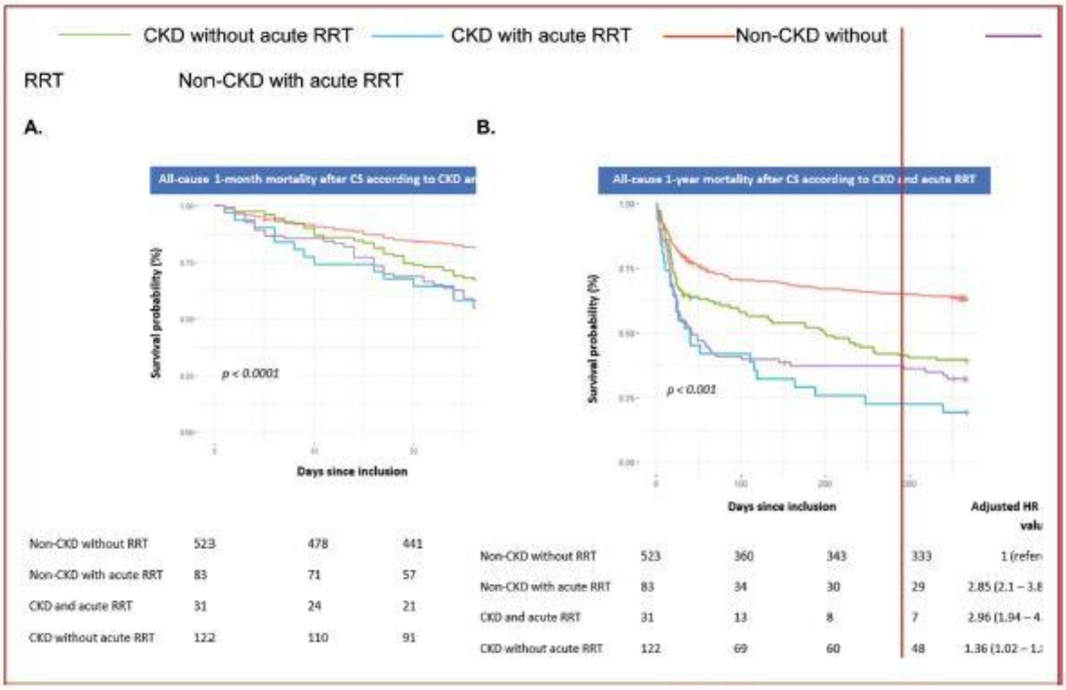

Fig. 3. Short- and long-term mortality outcomes after cardiogenic shock according to CKD status and acute RRT. Panel A represents 1-month overall mortality. Panel B focuses on 1-year mortality. The cumulative incidences of 1-year and 1-month mortality were estimated using the Kaplan–Meier method; hazard ratios and 95% confidence intervals were estimated using Cox regression models. Chronic dialysis patients (n= 11) were excluded to avoid confounding bias. According to significant characteristics found as independent predictive factors in multivariable analyses, 1-year mortality was adjusted for age, active cancer, peripheral artery disease and NYHA III or IV. One-month mortality was adjusted for age and diabetes mellitus. CKD: chronic kidney disease; HR: hazard ratio; RRT: renal replacement therapy.

Third, even if non-CKD patients initially presented with a higher arterial blood lactate concentration, which is well documented as an important predictor of short-term death in cardiogenic shock [8], 1-month all-cause death remained higher in the CKD group, emphasizing its strong impact in worsening prognosis, even after adjusting for the main clinical parameters of severity and comorbidity. Besides, though initial hemodynamical and clinical parameters were not significantly different between groups, consensual cardiogenic shock therapies such as norepinephrine, invasive ventilation and acute mechanical circulatory support were provided less frequently for CKD patients. This could be explained at least partly by older age and a higher rate of comorbidities, which may sometimes have led to limitations of aggressive therapies. Even in case of invasive management, survival is poorer in case of CKD, whether it is for Impella [14], extracorporeal life support [15] or intra-aortic balloon pump [16]. This urges for a more accurate selection of most suitable candidates on which further studies should focus.

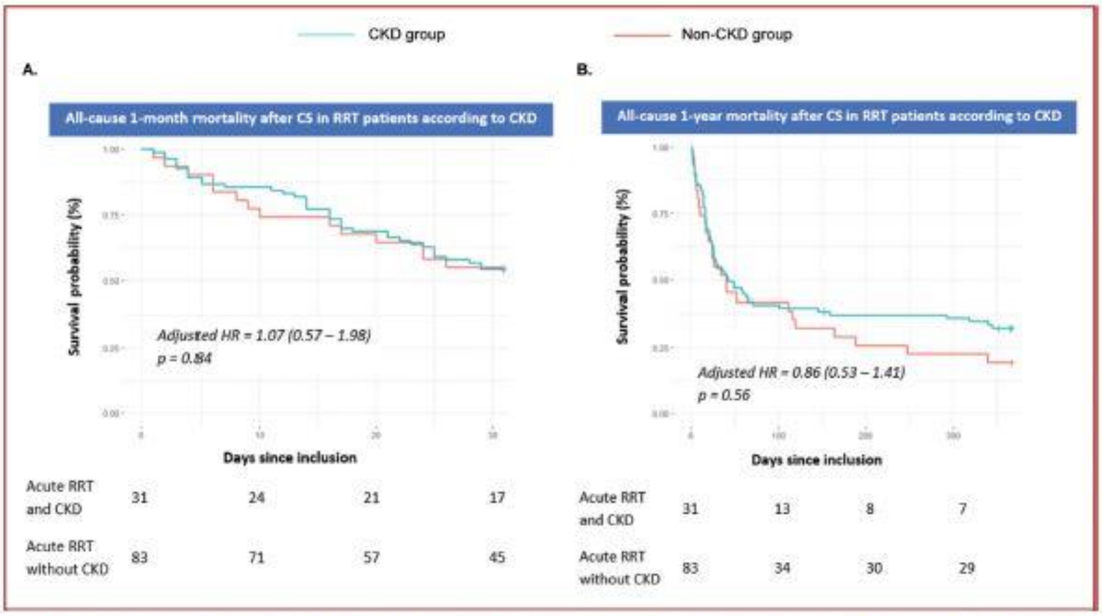

Fig. 4. Comparison of short- and long-term mortality outcomes in patients requiring acute RRT according to CKD status. Panel A represents 1-month overall mortality. Panel B focuses on 1-year mortality. The cumulative incidences of 1-year and 1-month mortality were estimated using the Kaplan–Meier method; hazard ratios and 95% confidence intervals were using Cox regression models. Chronic dialysis patients ($n = 11$) were excluded to avoid confounding bias. According to significant characteristics found as independent predictive factors in multivariable analyses, 1-year mortality was adjusted for age, active cancer, peripheral artery disease and NYHA III or IV. One-month mortality was adjusted for age and diabetes mellitus. CKD: chronic kidney disease; HR: hazard ratio; RRT: renal replacement therapy.

The common co-occurrence of chronic heart failure and CKD represents a well-established vicious circle [2], since the presence of one condition promotes the other. Consistently, our main result reveals increased 1-month and 1-year death after cardiogenic shock in CKD, regardless of the occurrence of severe acute kidney injury. In fact, most medical treatments that improve survival and are strongly recommended in chronic heart failure are often under-prescribed in patients with CKD, especially sacubitril/valsartan, angiotensin-converting enzyme inhibitors and mineralocorticoid receptor antagonists, owing to concerns about hyperkalemia and worsening renal function [17]; this limitation may explain in part the higher rate of 1-year all-cause death of our study.

Consistent with our findings, acute kidney injury and need for RRT is well-established as a strong predictor of short- and long-term death in cardiogenic shock [3, 5, 18]. They have even been included in various mortality risk scores, whether for general intensive care (Sequential Organ Failure Assessment, Simplified Acute Physiology Score II) or specifically for cardiogenic shock (intra-aortic balloon pump-SHOCK2, Cardiogenic Shock Score, Card Shock score). The Survival After Veno-Arterial ECMO (SAVE) score, which predicts survival in adults after extracorporeal life support for refractory cardiogenic shock, incorporates both previous CKD and acute kidney injury. In our study, we did not observe a difference in short- or long-term prognosis in patients who received acute RRT between CKD and non-CKD, corroborating it as a powerful independent predictor of death, regardless of renal function before cardiogenic shock. However, it is essential to acknowledge that we did not have the necessary data to stratify the severity of acute kidney injury according to the usual KDIGO definitions. Therefore, our focus was on acute RRT, which represents the most severe form of acute kidney injury, although a more nuanced analysis considering degrees of acute kidney injury severity based on standard definitions would provide a more comprehensive understanding of the association with death.

In this respect, several suggestions for improved management can be put forward. First, the preventive approach reminds us that, despite conflicting initial results [19], telemonitoring could reduce all-cause death and unplanned cardiovascular hospital admissions when performed in selected patients by a trained cardiology team[20]. Similarly, mounting evidence suggests that remote pulmonary artery haemodynamic monitoring (CardioMEMS®) is a promising technology, effective in reducing heart failure admissions inpatients across the spectrum of CKD [21]. Given their predisposition to fluid overload, CKD patients appear to be a preferred target for such remote monitoring or telemonitoring. Second, for phenotypes without severe cardiac output impairment with pre-dominantly refractory congestion due to diuretic resistance and repeated hospitalizations, initiation of long-term dialysis is appealing for selected candidates, reducing hospital days and improving heart function without deteriorating kidney function [22,23]. Third, patients with type 2 cardiorenal syndrome (primarily the consequence of chronic low cardiac output without severe intrinsic renal disease) may benefit from repeat infusion of inotropes such as levosimendan; this approach allows the titration of guideline-directed medical therapies and is associated with improvement in quality of life and a possible decrease in short-term death, even if the benefit for long-term mortality remains a matter of debate 24]. Several ongoing trials (e.g. the LEIA-HF trial, NCT04705337) may help to determine the efficacy of repeat infusions of levosimendan in advanced heart failure. For these patients, isolated heart-replacement therapy such as heart transplantation or ventricular assist device, may lead to spectacular improvements in renal function and extended survival due to restoration of renal perfusion. In this context, heart-replacement therapy could represent a rescue therapy for both cardiac and renal functions avoiding the need for double heart–kidney transplantation [25]. However, it is worth noting that the benefit and safety of RRT are strongly affected by the presence of previous CKD. Indeed, there is clear evidence that irrespective of post-ventricular assist device implantation or post-heart transplantation, short- and long-term survival decrease with a pre–heart-replacement therapy estimated glomerular filtration rate of < 60 mL/min/1.73 m2[25,26]. Hence, for suitable patients, the next step could lead to simultaneous heart and kidney transplantation, whose superiority in improving survival compared with heart transplantation alone was reinforced in a recent study [27] for dialysis-dependent and non–dialysis-dependent recipients up to an estimated glomerular filtration rate of approximately 40 mL/min/1.73 m2. The association between CKD and heart-replacement therapy may also be influenced by the fact that patients with CKD tend to be older and burdened with more comorbidities, rendering them more fragile and potentially less amenable to heart-replacement therapy. Future studies should focus on investigating the reasons for non-referral or criteria for non-eligibility for heart transplantation and/or ventricular assist device in cases of advanced heart failure.

Overall, whether through refractory congestion, challenges in initiating optimal heart failure treatment due to its nephrotoxic effects, or the unfavourable long-term outcomes of heart transplantation or ventricular assist device in the presence of preexisting CKD, the management of cardiogenic shock with CKD is particularly challenging, with severe short- and long-term prognoses. As a result, to provide the most thorough and individualized care, the management of these patients should be extensively discussed within multidisciplinary teams involving nephrologists, cardiologists, cardiothoracic surgeons and anaesthesiologists. This collaboration is essential to cover the spectrum of therapeutic possibilities ranging from congestion management, RRT indication and close monitoring of renal function when implementing guideline-directed medical therapies, to potential indications for single or double transplant.

Finally, in our study, CKD was associated with more frequent severe mitral regurgitation, mainly a secondary mechanism, known to carry an almost threefold increase in death [28]. Targeting mitral regurgitation may be discussed for selected patients with suitable ventricular and mitral anatomy, based on a recent large study that showed a reduction in mitral regurgitation by edge-to-edge valve repair in most cardiogenic shock patients and its association with significantly lower rates of death and heart failure hospitalization at1 year [29]. However, only 27.5% of the participants had secondary mitral regurgitation, and the study was not specifically designed for CKD, in which fluid overload hampers optimal patient selection.

4.1. Limitations

The main limitation is the declarative nature of CKD history reported by the investigators at admission without a prespecified definition, but this reflects the real-life acute management of critically ill patients. Moreover, from available data, we were not able to distinguish the five stages of CKD severity, preventing us from correlating progression of kidney failure with decrease in survival. Baseline creatinine levels, indicative of kidney function before cardiogenic shock and their evolution during its management, were probably sought for most patients, but these data were not captured in the case report form, limiting further comparisons stratified according to degree of acute kidney failure. Similarly, we had no information on the exact distribution of cardiorenal syndrome subtypes, which limits considerations on the recovery of renal function after acute management, heart transplantation or ventricular assist device. Data on duration of acute RRT and its long-term continuation were not available. Finally, the FRENSHOCK survey was conducted in 2016, before large-scale distribution of sodium–glucose cotransporter 2 inhibitors, revolutionizing the management of chronic heart failure and CKD, with strong evidence of reduced mortality and rehospitalizations whether for chronic heart failure [18] or after acute decompensated heart failure [30],which are likely to improve short- and long-term outcomes. As previously described [8], the FRENSHOCK registry also involves risks of selection bias related to non-consecutive inclusions or exclusion of the most severe cases. We were unable to use the SCAI SHOCK Stage classification given that it was not available at the time of our study.

5. Conclusion

Cardiogenic shock and CKD are frequent cross-talking conditions, leading to a vicious circle with limited therapeutic options and resulting in higher rates of 1-month and 1-year death. Acute need for RRT was associated with worse outcomes regard-less of baseline CKD status. Multidisciplinary collaborative teams involving cardiac and kidney physicians are required to provide integrated care for patients with failure of both organs (Central Illustration).

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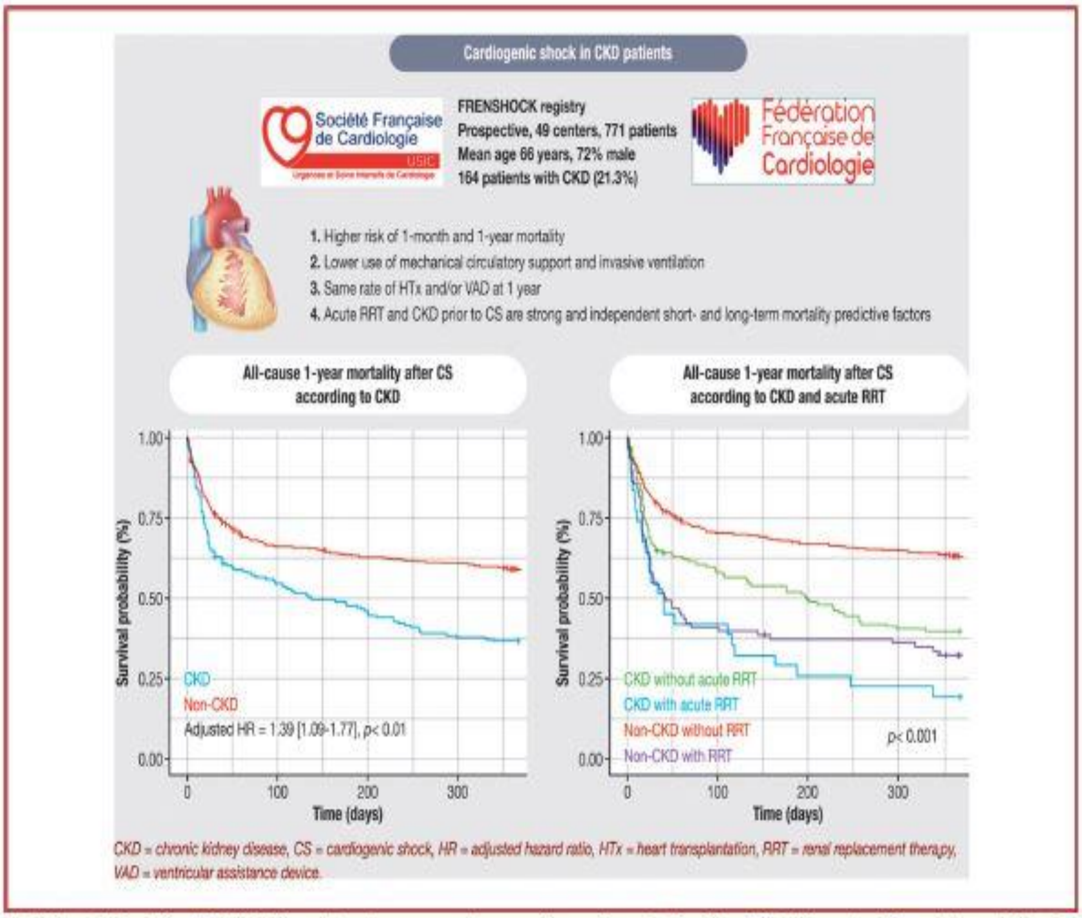
Disclosure of interest

The authors declare that they have no competing interest.



Central Illustration. The FRENSHOCK registry. One-year outcomes after cardiogenic shock in CKD. AKI: acute kidney injury; CKD: chronic kidney disease; HR: adjusted hazard ratio; HTx: heart transplantation; RRT: renal replacement therapy; VAD: ventricular assistance device.

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