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Renal function trajectories in 'De Novo' heart failure with reduced ejection fraction: impact on outcomes

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ABSTRACT

Aims Heart failure (HF) often coexists with chronic kidney disease (CKD), impacting prognosis. This study aims to evaluate renal function trajectories and their impact on major clinical outcomes in a cohort of patients hospitalised for 'de novo' HF with reduced ejection fraction (HFrEF).

Methods This is a prospective cohort study that included patients hospitalised for 'de novo' HFrEF at two university hospitals. Renal function was assessed using the CKD-Epidemiology Collaboration formula. Total mortality and the combined total mortality and HF readmissions were evaluated during follow-up.

Results Of 370 patients, 306 were eligible. At discharge, 24.6% had estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2. Higher eGFR at discharge was associated with better outcomes. During follow-up, 79.1% showed eGFR ≥45 mL/min/1.73 m^2. Patients with stable or improved eGFR had lower total mortality and HF readmission rates. Factors associated with renal function improvement or stabilisation included less prior CKD, hypertension and younger age, higher eGFR values at discharge and more use of quadruple therapy at the end of uptitration period.

Conclusions In patients with 'de novo' HFrEF, renal function deterioration at discharge correlated with poorer outcomes. However, stabilisation or improvement during follow-up was linked to better prognosis. Routine renal function assessment is crucial in HFrEF management, guiding personalised treatment strategies to mitigate renal function decline and improve patient care.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Renal dysfunction is frequent in patients with heart failure (HF) with reduced ejection fraction (HFrEF) and worsens prognosis.
⇒ Prior studies have not focused on renal function trajectories in 'de novo' HFrEF after first hospitalisation.
⇒ Understanding these trajectories is needed to optimise management and outcomes.

WHAT THIS STUDY ADDS

⇒ Deterioration of renal function at discharge predicts higher mortality and HF readmissions.
⇒ Stabilisation or improvement of renal function during follow-up is linked to better prognosis.
⇒ Younger age, less prior chronic kidney disease and quadruple therapy are associated with stabilisation or improvement of renal function.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Routine monitoring of renal function can guide individualised treatment in HFrEF.
⇒ Preservation of renal function may improve survival and reduce hospitalisations.
⇒ These findings support multidisciplinary care and wider use of guideline-directed therapies in patients with HFrEF and renal dysfunction.

INTRODUCTION

Heart failure (HF) and acute and chronic kidney disease (CKD) often coexist and share common risk factors in their development. The cardiorenal syndrome describes the close inter-relationships between the heart and the kidney, and both heart and kidney disease can worsen each other's prognosis.[1]

The HF syndrome is characterised by haemodynamic, disease-related and treatment-induced alterations in kidney function which need to be monitored across the HF trajectory. These changes may be associated with an adequate therapy response to disease-modifying HF therapies as well as disease progression.[2]

In the context of hospital admissions for worsening HF, the presence of kidney dysfunction is relatively common and was associated with a worse prognosis. Furthermore, it was described that patients with worsened kidney function were associated with a lower use of therapies with a recognised prognostic benefit.[3] On the other hand, several therapeutic interventions in patients with HF have shown an association with kidney protection related to a reduction in the progressive

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decline in kidney function, facts associated with a better kidney and cardiovascular outcomes.[4]

To date, a very limited number of publications assess the kidney function trajectory during the follow-up of patients with HF, as well as its influence on the prognosis of the patients, particularly in patients with kidney dysfunction at hospital discharge and especially in patients with the 'de novo' HF with reduced left ventricular ejection fraction (LVEF) after a first hospitalisation for worsening HF.[5] Such information could help to establish the best approach for kidney function recovery and preservation in these patients and prevent the progression of cardiorenal syndrome.[6]

The primary objective of this study was to establish the prognostic value of the changes in kidney function in a population with 'de novo' HF with reduced LVEF with a first hospitalisation for worsening HF, as well as the factors associated with the absence of impairment during the follow-up.

METHODS

Study population

A prospective observational cohort study was conducted, enrolling 370 patients admitted for 'de novo' HF with reduced ejection fraction (HFrEF), characterised by LVEF of less than 40%, between March 2021 and October 2023, from two university hospitals. Initially, 16 patients were excluded in the first analysis due to insufficient data on kidney function at discharge, and an additional 48 patients were excluded in the second analysis due to inadequate data on kidney function at follow-up. Thus, the final cohort comprised 306 patients.

Demographic, clinical, echocardiographic and laboratory characteristics on admission were prospectively collected in an electronic database named 'IANUS'.

Renal function laboratory parameters during follow-up were retrospectively collected by reviewing electronic clinical histories under cardiologist supervision.

This study adhered to the principles outlined in the Declaration of Helsinki, and approval was obtained from the Santiago de Compostela (Galicia, Spain) and La Fe (Valencia, Spain) Research Ethics Committee.

Definitions

'De novo' HFrEF was diagnosed according to current clinical practice guidelines, involving a comprehensive clinical assessment and echocardiographic evidence of left ventricular dysfunction (LVEF <40%),[7] calculated using the Simpson's biplane method.

Kidney function was assessed using the CKD-Epidemiology Collaboration formula. Patients were classified according to the Kidney Disease: Improving Global Outcomes criteria: G1≥90 mL/min/1.73 m^2; G2=60–89 mL/min/1.73 m^2, G3a=45–59 mL/min/1.73 m^2, G3b=30–44 mL/min/1.73 m^2, G4=15–29 mL/min/1.73 m^2 and G5<15 mL/min/1.73 m^2.[8]

Kidney function improvement or stabilisation was defined as maintaining an estimated glomerular filtration rate (eGFR) above 45 mL/min/1.73 m^2 during follow-up if it was already above 45 mL/min/1.73 m^2 at discharge or increasing to above 45 mL/min/1.73 m^2 if it was below 45 mL/min/1.73 m^2 at discharge, and vice versa for deterioration.

Kidney function parameters at discharge were obtained from blood samples taken within the last 24 hours prior to hospital discharge. Kidney function during follow-up was assessed after the completion of guideline-directed medical therapy titration.

Total mortality and the combined total mortality and HF readmissions were evaluated during follow-up to assess prognosis.

Follow-up

Follow-up involved actively reviewing electronic clinical histories available in our autonomous region, along with reviewing all available medical visits and hospital records. The median follow-up period was 15 months (IQR): 7–22 months).

Statistical analysis

Univariate analysis of categorical variables used the χ^2 test, expressed as absolute frequencies (percentages). Continuous variables were analysed using analysis of variance, with results expressed as mean±SD.

Receiver operating characteristic (ROC) curve analysis was employed to determine an eGFR cut-off beyond which prognosis significantly worsened.

Survival curves were constructed based on time-to-event outcomes (total mortality and the combined total of total mortality and HF readmissions) using Kaplan-Meier estimates. The log-rank test compared survival curves. Cox proportional hazards models were constructed for univariate and multivariate analyses to determine the influence of clinical variables, including kidney function improvement or stabilisation.

Coefficients of the regression model estimated HRs and corresponding 95% CI.

Multivariate Cox models incorporated adjustments for all baseline covariates statistically significant (<0.05), as well as variables known to be associated with mortality.

Statistical analysis was conducted using SPSS, V.28.0 (IBM, Armonk, New York, USA).

RESULTS

Relative prognosis based on eGFR at discharge

Over a period of 31 months (March 2021 to October 2023), 370 patients with 'de novo' HFrEF were admitted. Kidney function data at discharge were available for 354 patients, following the exclusion of 16 patients for whom this data could not be obtained. Of these, 87 (24.6%) had an eGFR <45 mL/min/1.73 m^2, while 267 (75.4%) had an eGFR ≥45 mL/min/1.73 m^2. Subsequently, ROC curve analysis identified an eGFR cut-off of 45 mL/min/1.73 m^2, beyond which prognosis significantly worsened.

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Baseline characteristics

At discharge, baseline characteristics were compared between patients with eGFR <45 mL/min/1.73 m^2 and those with eGFR ≥45 mL/min/1.73 m^2. The results are summarised in table 1. Patients with eGFR <45 mL/min/1.73 m^2 were older (76±11 vs 67±14 years, p<0.001) and had a higher prevalence of hypertension (86.2% vs 59.6%, p<0.001), type 2 diabetes mellitus (59.8% vs 27.3%, p<0.001) and dyslipidaemia (67.8% vs 48.3%, p=0.002) compared with those with eGFR ≥45 mL/min/1.73 m^2. While differences in HF aetiology were not statistically significant, patients with eGFR <45 mL/min/1.73 m^2 tended to have a higher prevalence of ischaemic heart disease (35.6% vs 26.6%, p=0.107) and hypertensive heart disease (10.3% vs 4.5%, p=0.051). Additionally, patients with eGFR <45 mL/min/1.73 m^2 exhibited lower haemoglobin levels (12.9±2.3 vs 14.4±2.2 g/dL, p<0.001), higher serum creatinine levels (2.1±0.8 vs 1.0±0.2 mg/dL, p<0.001) and higher levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) both at admission (12 600 vs 4400, p<0.001) and discharge (5078 vs 1480, p<0.001). Furthermore, patients with eGFR <45 mL/min/1.73 m^2 were less likely to receive certain HF medications at discharge, including angiotensin receptor-neprilysin inhibitors (ARNI) (41.4% vs 69.3%, p<0.001), mineralocorticoid receptor antagonists (MRA) (46.0% vs 88.0%, p<0.001) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) (64.4% vs 87.6%, p<0.001), compared with those with eGFR ≥45 mL/min/1.73 m^2. In terms of cardiac function and post-uptitration treatment, patients with eGFR <45 mL/min/1.73 m^2 exhibited a trend towards less improvement in LVEF (52.8% vs 66.8%, p=0.063) and a lower LVEF at follow-up (41.8±10.9 vs 46.0±11.3, p=0.023) compared with those with eGFR ≥45 mL/min/1.73 m^2. Additionally, after uptitration, patients with eGFR <45 mL/min/1.73 m^2 were less likely to receive quadruple therapy (28.7% vs 72.8%, p<0.001) and certain HF medications, including ARNI (54.9% vs 69.8%, p=0.014), MRA (50.0% vs 89.1%, p<0.001) and SGLT2i (69.9% vs 94.2%, p<0.001).

Total mortality and heart failure readmissions

During the follow-up of the 354 patients with available renal function data at discharge, 46 deaths (13.0%) and a total of 105 events of combined total mortality and HF readmissions (29.6%) occurred. Of the total deaths, 22 (25.3%) occurred in the eGFR <45 mL/min/1.73 m^2 group and 24 (1.0%) in the eGFR ≥45 mL/min/1.73 m^2 group. Regarding the combined endpoint of death and HF readmissions: 42 events (48.3%) occurred in the eGFR <45 mL/min/1.73 m^2 group and 63 events (23.6%) in the eGFR ≥45 mL/min/1.73 m^2 group. In the univariate analysis, patients with eGFR ≥45 mL/min/1.73 m^2 exhibited a lower overall mortality (HR: 0.29, p<0.001), and total mortality and HF readmissions (HR: 0.32, p<0.001). After adjusting for age, body mass index (BMI), alcohol use, hypertension, LVEF and beta-blockers at discharge, eGFR ≥45 continued to be a significant factor for protection from overall mortality (HR: 0.43, p=0.028), and total mortality and HF readmissions (HR: 0.53, p=0.038) (table 2 and figure 1).

Relative prognosis based on change in eGFR (stabilisation or improvement vs deterioration) at follow-up (end of uptitration medications)

Of the 354 patients with eGFR values at discharge, data on kidney function at follow-up (end of uptitration) was available for 306 patients (86.4%), excluding 48 patients for whom these data could not be obtained. Among these patients, 242 (79.1%) had an eGFR ≥45 mL/min/1.73 m^2 (stabilisation or improvement) and 64 (20.9%) had eGFR <45 mL/min/1.73 m^2 (deterioration or previously <45 mL/min/1.73 m^2).

Baseline characteristics

Table 3 reflects baseline characteristics of patients with 'de novo' HFrEF according to change in renal function at the end of the titration period. Patients with eGFR <45 mL/min/1.73 m^2 were older (mean age 77±11 years) compared with those with eGFR ≥45 mL/min/1.73 m^2 (mean age 66±14 years, p<0.001). Additionally, patients with eGFR <45 mL/min/1.73 m^2 had lower mean BMI (25±3.9 vs 28.3±5.8, p<0.001), and higher prevalence of hypertension, type 2 diabetes mellitus, dyslipidaemia, CKD and peripheral artery disease (p<0.01 for all). No significant differences were observed between the two groups in terms of HF aetiology. Regarding laboratory parameters, patients with eGFR <45 mL/min/1.73 m^2 had lower haemoglobin levels and higher creatinine levels at admission compared with those with eGFR ≥45 mL/min/1.73 m^2 (p<0.001 for both). Additionally, NTproBNP levels (both at admission and discharge) were significantly higher in patients with eGFR <45 mL/min/1.73 m^2 compared with those with eGFR ≥45 mL/min/1.73 m^2 (p<0.001 for both). Regarding HF treatment at discharge, patients with eGFR <45 mL/min/1.73 m^2 were less likely to receive angiotensin receptor blockers, ARNI, MRA and SGLT2i to those with eGFR ≥45 mL/min/1.73 m^2 (p<0.05 for all). At follow-up, patients with eGFR <45 mL/min/1.73 m^2 exhibited a lower mean LVEF (40.1% vs 45.6%, p=0.009) and were significantly less likely to receive quadruple therapy (26.6% vs 76.9%, p<0.001) compared with those with eGFR ≥45 mL/min/1.73 m^2. Furthermore, they showed a decreased likelihood of receiving certain crucial HF medications, including ARNI (53.2% vs 73.6%, p=0.003), MRA (48.4% vs 89.6%, p<0.001) and SGLT2i (72.6% vs 93.8%, p<0.001), as well as more use of loop diuretics (81.0% vs 50.8%, p<0.001).

Total mortality and heart failure readmissions

During the follow-up of the 306 patients with available renal function data, 31 deaths (10.1%) and a total of 87 events of combined death and readmission

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Table 1 Baseline characteristics of patients with 'de novo' HFrEF according to renal function at discharge (eGFR <45 mL/min or ≥45 mL/min)

	Total (N=354, 100)	eGFR <45 mL/min (n=87, 24.6)	eGFR ≥45 mL/min (n=267, 75.4)	P value
Personal background				
Age (years)	69±14	76±11	67±14	<0.001
Sex (female)	96 (27.1)	21 (24.1)	75 (28.1)	0.472
Tobacco use	120 (33.9)	19 (21.8)	101 (37.8)	0.007
Alcohol	93 (26.3)	16 (18.4)	77 (28.8)	0.057
BMI (kg/m^2)	27.6±5.7	26.3±5.1	28±5.8	0.020
Hypertension	234 (66.1)	75 (86.2)	159 (59.6)	<0.001
T2DM	125 (35.3)	52 (59.8)	73 (27.3)	<0.001
Dyslipidaemia	188 (53.1)	59 (67.8)	129 (48.3)	0.002
AF or flutter (prior)	114 (32.2)	29 (33.3)	85 (31.8)	0.795
CKD (prior)	87 (24.6)	61 (60.1)	26 (9.7)	<0.001
COPD/OSAHS	48 (13.6)	11 (12.6)	37 (13.9)	0.774
PAD	37 (10.5)	15 (17.4)	22 (8.2)	0.018
HF aetiology				
Ischaemic	102 (28.8)	31 (35.6)	71 (26.6)	0.107
Hypertensive	21 (5.9)	9 (10.3)	12 (4.5)	0.051
Tachycardiomyopathy	77 (21.8)	13 (14.9)	64 (24.0)	0.079
Infiltrative	6 (1.7)	3 (3.4)	3 (1.1)	0.166
Idiopathic	70 (19.8)	15 (17.2)	55 (20.6)	0.495
Valvular	21 (5.9)	8 (9.2)	13 (4.9)	0.144
Others	57 (16.1)	8 (9.2)	49 (18.4)	0.048
Echo/ECG/laboratory (admission)				
LVEDD (mm)	61±10	60±14	61±9	0.615
Severe MR	45 (12.7)	9 (10.5)	36 (13.5)	0.467
Severe TR	17 (4.8)	4 (4.7)	13 (4.9)	0.935
SPAP	38±13	42±17	37±11	0.053
TAPSE	17±4	16±4	17±4	0.251
QRS (ms)	126±29	121±31	114±28	0.052
LBBB	84 (24.0)	26 (30.2)	58 (22.0)	0.242
LVEF at discharge	28.7±6.9	28.9±7.0	28.6±6.8	0.711
Rhythm at discharge				0.797
Sinus rhythm	244 (68.9)	59 (67.8)	185 (69.3)	
Atrial fibrillation/flutter	110 (31.1)	28 (32.2)	82 (30.7)	
Haemoglobin (g/dL)	14±2.3	12.9±2.3	14.4±2.2	<0.001
Creatinine (mg/dL)	1.3±0.7	2.1±0.8	1.0±0.2	<0.001
eGFR (ml/min)	63±24	31±9	73±17	<0.001
Potassium	4.3±0.6	4.5±0.8	4.2±0.5	<0.001
NTproBNP, pg/mL (admission)	5278 (2400–11 200)	12 600 (5900–25 800)	4400 (2200–8000)	<0.001
NTproBNP, pg/mL (discharge)	1874 (766–4900)	5078 (1700–12 900)	1480 (670–3200)	<0.001
HF treatment (discharge)				
ACEI	44 (12.4)	9 (10.3)	35 (13.1)	0.498
ARB	35 (9.9)	11 (12.6)	24 (9.0)	0.324
ARNI	221 (62.4)	36 (41.4)	185 (69.3)	<0.001

Continued

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Table 1 Continued

	Total (N=354, 100)	eGFR <45 mL/min (n=87, 24.6)	eGFR ≥45 mL/min (n=267, 75.4)	P value
MRA	275 (77.1)	40 (46.0)	235 (88.0)	<0.001
Beta-blockers	321 (90.9)	75 (87.2)	246 (92.1)	0.170
SGLT2i	290 (81.9)	56 (64.4)	234 (87.6)	<0.001
Loop diuretics	258 (72.9)	66 (75.9)	192 (71.9)	0.472
Admission duration (days)	9.0±6.7	10.0±8.0	8.8±6.2	0.158
Follow-up				
Uptitration (days)	118±108	100±106	124±109	0.111
NYHA class (1st visit)				<0.001
NYHA ≤II	312 (93.1)	70 (86.4)	242 (95.2)	
NYHA >II	23 (6.9)	11 (13.6)	12 (4.7)	
NTproBNP (pg/mL)	810 (307–1700)	1700 (570–5100)	674 (260–1300)	<0.001
eGFR (ml/min)	66±25	40.2±18.9	73.8±21.2	<0.001
Potassium	4.6±0.5	4.7±0.5	4.5±0.5	0.010
Haemoglobin (g/dL)	14.2±2.2	13±2.2	14.6±2.1	<0.001
Rhythm				0.247
Sinus rhythm	237 (75.7)	59 (80.8)	178 (74.2)	
Atrial fibrillation/flutter	76 (24.3)	14 (19.2)	62 (25.8)	
QRS (ms)	115±28	123±32	112±26	0.006
LBBB	57 (19.5)	19 (26.8)	38 (17.2)	0.183
Improved LVEF	151 (63.7)	28 (52.8)	123 (66.8)	0.063
LVEF (%)	45±11	41.8±10.9	46.0±11.3	0.023
HF treatment (uptitration)				
Quadruple therapy	218 (61.9)	25 (28.7)	193 (72.8)	<0.001
ACEI	42 (12.4)	8 (9.6)	34 (13.3)	0.383
ARB	20 (5.9)	6 (7.1)	14 (5.5)	0.573
ARNI	225 (66.2)	45 (54.9)	180 (69.8)	0.014
Beta-blockers	317 (93.0)	75 (90.4)	242 (93.8)	0.291
MRA	271 (79.7)	41 (50.0)	230 (89.1)	<0.001
SGLT2i	301 (88.3)	58.8 (69.9)	243 (94.2)	<0.001
Loop diuretics	199 (58.2)	59 (70.2)	140 (54.3)	0.011

Data are presented as mean±SD, n (%) or median (IQR), as appropriate.
ACEI, ACE inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitors; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonists; NTproBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSAHS, obstructive sleep apnoea-hypopnoea syndrome; PAD, peripheral artery disease; SGLT2i, sodium-glucose cotransporter 2 inhibitors; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; T2DM, type 2 diabetes mellitus; TR, tricuspid regurgitation.

due to HF (28.4%) occurred. In the univariate analysis, patients with eGFR ≥45 mL/min/1.73 m^2 exhibited a lower overall mortality (HR: 0.27, p<0.001), and total mortality and HF readmissions (HR: 0.30, p<0.001). After adjusting for age, BMI, alcohol use, hypertension, LVEF at discharge and beta-blockers at discharge, eGFR ≥45 continued to be a significant factor for protection from overall mortality (HR: 0.43, p=0.048), and total mortality and HF readmissions (HR: 46, p=0.014) (figure 1).

Determining factors for kidney function improvement at the end of the titration period

Table 4 and figure 2 show the results of the multivariate analysis of the variables that may influence the eGFR value at the end of the titration period. A higher prevalence

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Table 2 Univariate and multivariate analysis of total mortality and HF readmissions in patients with 'de novo' HFrEF according to renal function at discharge (eGFR <45 mL/min or ≥45 mL/min)

	Total mortality				Total mortality and HF readmissions			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
eGFR ≥45 mL/min, discharge	0.29 (0.15 to 0.55)	<0.001	0.43 (0.20 to 0.91)	0.028	0.32 (0.20 to 0.54)	<0.001	0.53 (0.30 to 0.97)	0.038
Age, years	1.08 (1.05 to 1.12)	<0.001	1.05 (1.01 to 1.08)	0.009	1.04 (1.02 to 1.06)	<0.001	1.03 (1.01 to 1.05)	0.023
BMI (kg/m2)	0.92 (0.86 to 0.98)	0.011	0.95 (0.088 to 1.02)	0.202	0.94 (0.90 to 0.98)	0.007	0.97 (0.92 to 1.02)	0.195
Alcohol	0.38 (0.16 to 0.92)	0.033	0.69 (0.26 to 1.82)	0.455	0.43 (0.25 to 0.76)	0.005	0.60 (0.32 to 1.15)	0.125
Hypertension	2.13 (1.02 to 4.44)	0.044	1.23 (0.48 to 3.2)	0.666	1.96 (1.19 to 3.22)	0.008	1.46 (0.77 to 2.77)	0.241
LVEF, discharge (%)	1.07 (1.02 to 1.12)	0.005	1.06 (1.01 to 1.23)	0.026	1.01 (0.98 to 1.05)	0.467	0.99 (0.96 to 1.03)	0.734
Beta-blockers, discharge	0.19 (0.08 to 0.42)	<0.001	0.26 (0.10 to 0.66)	0.005	0.19 (0.09 to 0.42)	<0.001	0.19 (0.08 to 0.44)	<0.001

BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.

of CKD and elevated eGFR values on hospital discharge correlated with increased eGFR values at the conclusion of the up-titration period. Conversely, advanced age and the presence of hypertension were associated with less improvement in renal function. Additionally, increased utilisation of quadruple therapy at the end of the uptitration period was linked to higher eGFR values. Other variables found significant in the univariate analysis, such as tobacco use, BMI or diabetes, did not appear to exert influence on eGFR values at the conclusion of the titration period.

DISCUSSION

In our study, we present novel insights into the renal function trajectories of patients hospitalised for 'de novo' HFrEF and their impact on patient outcomes. We observed that deterioration in renal function at discharge,

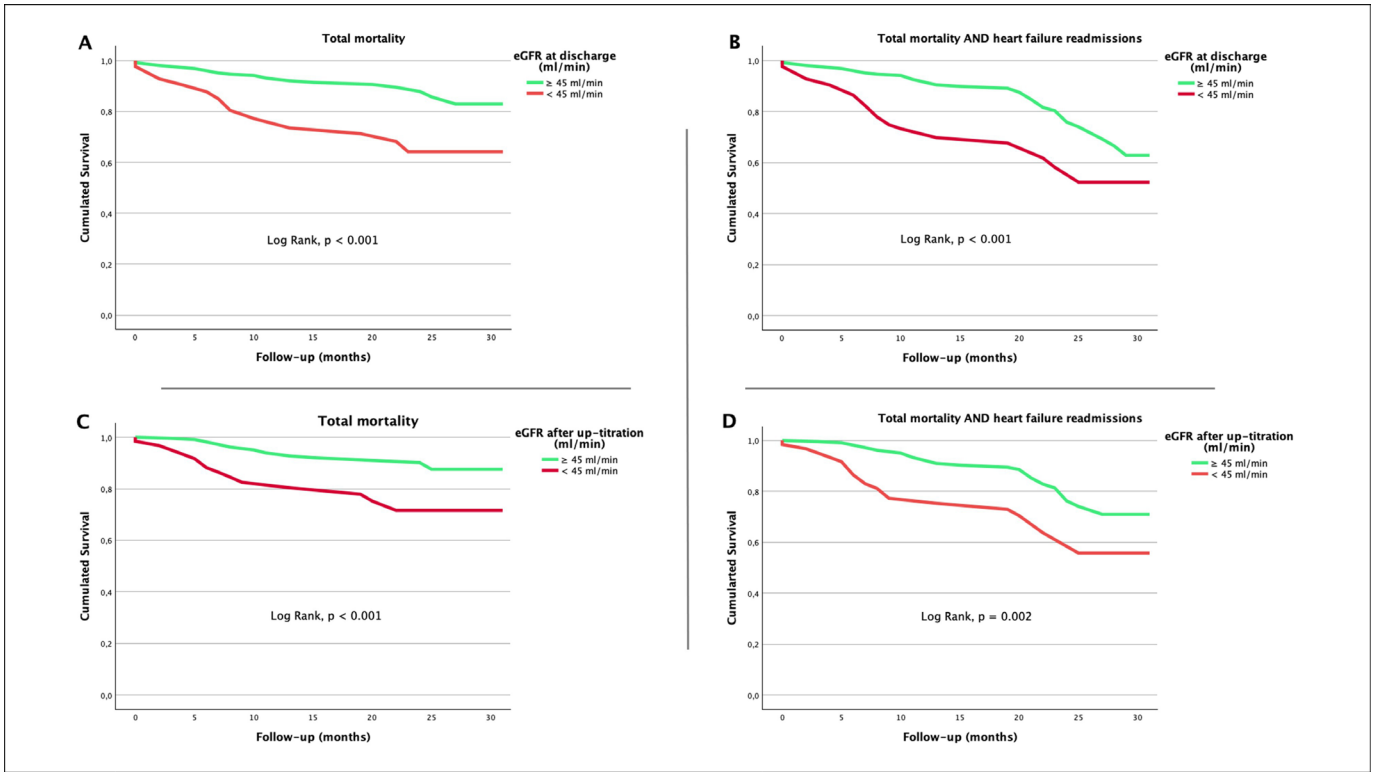


Figure 1 Kaplan-Meier survival curves illustrating the impact of renal function at discharge and changes in renal function post uptitration period on clinical outcomes. (A) Total mortality based on renal function at discharge; (B) Total mortality and HF readmissions based on renal function at discharge; (C) Total mortality based on improvement/stabilisation versus deterioration of renal function after the uptitration period; (D) Total mortality and HF readmissions based on improvement/stabilisation versus deterioration of renal function after the uptitration period. eGFR, estimated glomerular filtration rate; HF, heart failure.

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Table 3 Baseline characteristics of patients with 'de novo' HFrEF according to change in renal function at the end of titration period (eGFR <45 mL/min or ≥45 mL/min)

	Total (N=306, 100)	eGFR <45 mL/min (n=64, 20.9)	eGFR ≥45 mL/min (n=242, 79.1)	P value
Personal background				
Age (years)	68±14	77±11	66±14	<0.001
Sex (female)	82 (26.8)	22 (34.4)	60 (24.8)	0.135
Tobacco use	100 (32.7)	12 (18.8)	88 (36.4)	0.008
Alcohol	83 (27.1)	10 (15.6)	73 (30.2)	0.021
BMI (kg/m^2)	27.6±5.6	25±3.9	28.3±5.8	<0.001
Hypertension	195 (63.7)	52 (81.3)	143 (59.1)	0.001
T2DM	106 (34.6)	37 (57.8)	69 (28.5)	<0.001
Dyslipidaemia	160 (52.3)	43 (67.2)	117 (48.3)	0.008
AF or flutter (prior)	100 (32.7)	20 (31.3)	80 (33.1)	0.753
CKD (prior)	75 (24.5)	44 (68.8)	31 (12.8)	<0.001
COPD/OSAHS	45 (14.7)	12 (18.8)	33 (13.6)	0.276
PAD	34 (11.1)	13 (20.6)	21 (8.8)	0.010
HF aetiology				
Ischaemic	86 (28.1)	22 (34.4)	64 (26.4)	0.200
Hypertensive	16 (5.2)	4 (6.3)	12 (5.0)	0.691
Tachycardiomyopathy	65 (21.2)	8 (12.5)	57 (23.6)	0.064
Infiltrative	5 (1.6)	1 (1.6)	4 (1.7)	0.954
Idiopathic	63 (20.6)	15 (23.4)	48 (19.8)	0.547
Valvular	17 (5.6)	6 (9.4)	11 (4.5)	0.147
Others	54 (17.6)	8 (12.5)	46 (19.0)	0.219
Echo/ECG/laboratory (admission)				
LVEDD (mm)	60±8	59±8	60±8	0.427
Severe MR	36 (11.8)	8 (12.5)	28 (11.6)	0.855
Severe TR	15 (4.9)	5 (7.8)	10 (4.1)	0.239
SPAP	38±13	44±17	36±12	0.013
TAPSE	17±4	15±4	17±4	0.037
QRS (ms)	115±29	119±30	114±28	0.153
LBBB	70 (23.2)	20 (31.7)	50 (20.9)	0.041
LVEF at discharge	28.6±6.8	29.8±6.1	28.2±6.9	0.107
Rhythm at discharge				0.722
Sinus rhythm	214 (69.9)	46 (71.9)	168 (69.4)	
Atrial fibrillation/flutter	92 (30.1)	18 (28.1)	734 (30.6)	
Haemoglobin (g/dL)	14.1±2.3	12.7±2.2	14.5±2.2	<0.001
Creatinine (mg/dL)	1.3±0.6	1.9±0.9	1.1±0.3	<0.001
eGFR (ml/min)	63±23	38±17	70±20	<0.001
Potassium	4.3±0.6	4.5±0.8	4.2±0.6	0.004
NTproBNP, pg/mL (admission)	5200 (2400–11 200)	9460 (5900–25 800)	3700 (1980–7450)	<0.001
NTproBNP, pg/mL (discharge)	1800 (760–4900)	4530 (2100–12 000)	1180 (525–2630)	<0.001
HF treatment (discharge)				
ACEI	35 (11.4)	7 (10.9)	28 (11.6)	0.871
ARB	29 (9.5)	11 (17.2)	18 (7.4)	0.023
ARNI	206 (67.3)	33 (51.6)	173 (71.5)	0.003

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Table 3 Continued

	Total (N=306, 100)	eGFR <45 mL/min (n=64, 20.9)	eGFR ≥45 mL/min (n=242, 79.1)	P value
MRA	243 (79.4)	33 (51.6)	210 (86.8)	<0.001
Beta-blockers	282 (92.5)	58 (90.6)	224 (92.9)	0.545
SGLT2i	257 (84.0)	41 (64.1)	216 (89.3)	<0.001
Loop diuretics	216 (70.6)	51 (79.7)	165 (68.2)	0.079
Admission duration (days)	9.0±6.9	7.8±4.1	9.3±7.4	0.130
Follow-up				
Uptitration (days)	119±108	109±94	124±110	0.337
NYHA class (first visit)				<0.001
NYHA ≤II	286 (93.8)	54 (85.7)	232 (95.9)	
NYHA >II	19 (6.2%)	9 (14.3%)	10 (4.1%)	
NTproBNP (pg/mL)	800 (300–1700)	2660 (1170–6700)	670 (265–1300)	<0.001
eGFR (mL/min)	66±25	30.6±9.1	75.8±18.5	<0.001
Potassium	4.6±0.5	4.7±0.5	4.6±0.5	0.007
Haemoglobin (g/dL)	14.2±2.2	12.9±2.4	14.6±2.0	<0.001
Rhythm				0.813
Sinus rhythm	219 (76.3)	46 (74.2)	173 (76.5)	
Atrial fibrillation/flutter	68 (23.7)	16 (25.8)	53 (23.5)	
QRS (ms)	114±27	121±34	113±26	0.074
LBBB	50 (18.5)	15 (25.4)	35 (16.5)	0.126
Improved LVEF	142 (63.6)	20 (48.8)	122 (65.6)	0.052
LVEF (%)	45±11	40.1±10.6	45.6±11.2	0.009
HF treatment (uptitration)				
Quadruple therapy	203 (66.3)	17 (26.6)	186 (76.9)	<0.001
ACEI	37 (12.3)	5 (8.1)	32 (13.3)	0.257
ARB	16 (5.3)	5 (8.1)	11 (4.6)	0.285
ARNI	211 (69.4)	33 (53.2)	178 (73.6)	0.003
Beta-blocker	285 (93.8)	54 (87.1)	231 (95.5)	0.021
MRA	246 (81.2)	30 (48.4)	216 (89.6)	<0.001
SGLT2i	272 (89.5)	45 (72.6)	227 (93.8)	<0.001
Loop diuretics	174 (57.0)	51 (81.0)	123 (50.8)	<0.001

Data are presented as mean±SD, n (%) or median (IQR), as appropriate.
ACEI, ACE inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitors; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonists; NTproBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSAHS, obstructive sleep apnoea-hypopnoea syndrome; PAD, peripheral artery disease; SGLT2i, sodium-glucose cotransporter 2 inhibitors; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; T2DM, type 2 diabetes mellitus; TR, tricuspid regurgitation.

identified by an eGFR cut-off of 45 mL/min/1.73 m^2, affected nearly a quarter of our cohort (24.6%) and was associated with worse outcomes in terms of survival and HF readmissions. Patients with eGFR <45 mL/min/1.73 m^2 at discharge displayed unfavourable baseline characteristics, including older age (76±11 years), a higher prevalence of classic cardiovascular risk factors and were less likely to receive essential cardiac treatments, such as ARNI, MRA and SGLT2i. This subgroup also exhibited a lower mean LVEF at follow-up compared with those with eGFR ≥45 mL/min/1.73 m^2 (41.8 vs 46.0%, p=0.023). Additionally, our analysis revealed that improvement or stabilisation of renal function during follow-up (eGFR ≥45 mL/min/1.73 m^2), observed in over three-quarters of our patients (79.1%), was linked with factors including lower prevalence of prior CKD and hypertension, younger age, higher eGFR values at discharge and increased utilisation of quadruple therapy at the conclusion of the

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Table 4 Multivariate analysis of predictors of eGFR improvement at the end of the uptitration period in patients with 'de novo' HFrEF

Variables	Coefficient	SE	P value
Intercept	65.316	10.090	<0.001
Age, years	−0.408	0.086	<0.001
Tobacco use	−0.353	2.139	0.869
BMI (kg/m^2)	−0.038	0.180	0.833
Hypertension	−4.556	2.205	0.040
T2DM	1.831	2.122	0.389
CKD (prior)	−10.024	2.859	<0.001
eGFR (mL/m2), discharge	0.495	0.058	<0.001
Quadruple therapy, uptitration	4.586	2.264	0.044

BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; T2DM, type 2 diabetes mellitus.

uptitration period. These findings resonate with the emerging understanding of the cardiorenal syndrome, highlighting the critical interplay between heart and kidney dysfunction in patient prognosis.[9]

Our study has several clinical implications. First, it underscores the prevalence of kidney dysfunction in patients with HFrEF, with over 40% of our cohort exhibiting reduced eGFR (<60 mL/min/1.73 m^2). This emphasises the substantial burden of renal impairment within this population and aligns with existing literature demonstrating the frequent coexistence of HF and CKD, which share common risk factors and pathophysiological mechanisms.[10 11] Second, routine assessment of renal function, both at baseline and during follow-up, should be integrated into the management of patients with HFrEF. Early identification of renal dysfunction allows for timely intervention and optimisation of medical therapy, potentially improving patient outcomes. Moreover, efforts to preserve or improve renal function should be prioritised, including optimisation of guideline-directed medical therapy, management of comorbidities such as hypertension and diabetes, and avoidance of nephrotoxic agents. Lastly, personalised approaches to risk stratification and treatment decision-making, considering renal function trajectories and associated prognostic implications, are warranted in patients with HFrEF.

The impact of renal function on patient outcomes remained consistent throughout our study. Patients with eGFR <45 mL/min/1.73 m^2 at discharge had significantly higher mortality rates and rates of combined total mortality and HF readmissions during follow-up compared with those with eGFR ≥45 mL/min/1.73 m^2. This association remained significant even after adjusting for potential confounders, underscoring the independent prognostic value of renal function in patients with HFrEF.

Furthermore, changes in renal function during follow-up, particularly stabilisation or improvement versus deterioration, were strongly associated with outcomes. Patients experiencing stabilisation or

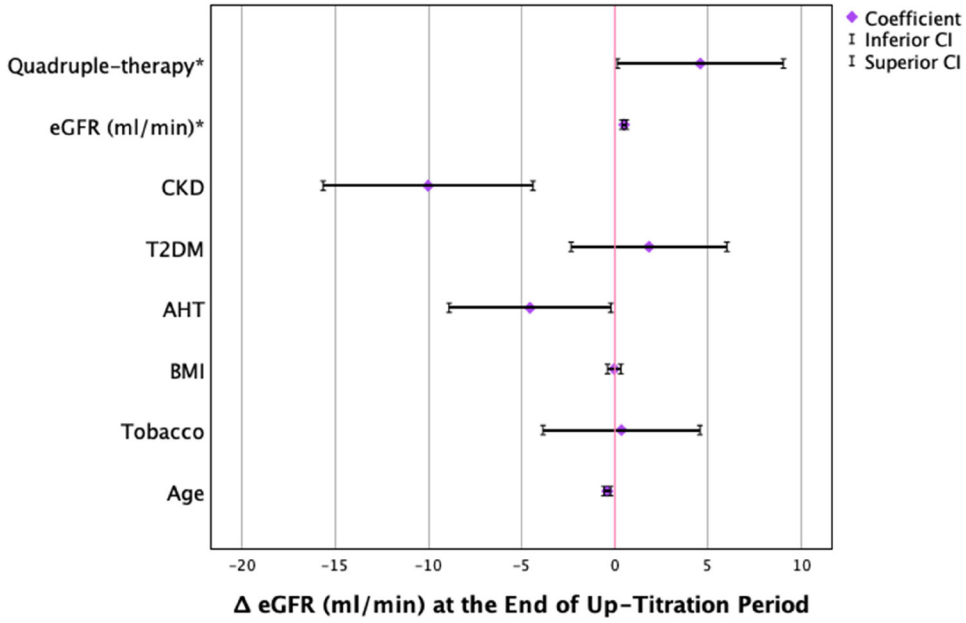


Figure 2 Multivariate analysis of predictors of eGFR improvement at the end of uptitration period in patients with 'de novo' HFrEF. The X-axis shows the change in eGFR at the end of the uptitration period. Positive values indicate an increase in eGFR, while negative values indicate a decrease. On the Y-axis, the predictor variables are displayed. If a line crosses the central line at 0, there is no significant effect. Lines above 0 indicate a positive relationship between eGFR and the predictor variable, and vice versa. *Quadruple therapy refers to quadruple therapy at the end of the uptitration period. *eGFR refers to eGFR at hospital discharge. AHT, arterial hypertension; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; T2DM, type 2 diabetes mellitus.

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improvement in renal function had significantly lower mortality rates and rates of combined death and HF readmissions compared with those with deteriorating renal function. These findings underscore the importance of monitoring renal function over time and implementing strategies to preserve or enhance renal function in patients with HFrEF.[12]

Our study also identified several factors associated with renal function improvement at the end of the titration period. Lower prevalence of prior CKD and hypertension, younger age, higher eGFR values at discharge and increased utilisation of quadruple therapy at the conclusion of the uptitration period emerged as independent predictors of renal function improvement. These findings offer insights into potential targets for intervention to mitigate renal function decline in patients with HFrEF.

Our study contributes significantly to the existing body of literature by elucidating the clinical implications of renal function trajectories in patients with HFrEF. While previous research has investigated the association between renal dysfunction and outcomes in patients with HF, few studies have specifically addressed the trajectory of renal function over time. Notably, our study stands out as the first to analyse the trajectory of renal function in patients with 'de novo' HFrEF following their initial hospitalisation for HF and its influence on major clinical outcomes.

A recent study published in the Journal of the American College of Cardiology provided valuable insights into the trajectory of renal function in patients with HF. However, this study predominantly focused on the general HF population and did not specifically examine the trajectory of renal function in patients with 'de novo' HFrEF following their initial hospitalisation for HF. This study highlights a concerning trend of progressive renal function decline among patients with HF, reporting an average eGFR slope of −1.70 mL/min/1.73 m^2 per year, notably exceeding the expected age-related decline (1 mL/min/1.73 m^2). Furthermore, their findings revealed a significant association between this deterioration in renal function and adverse prognostic outcomes, including increased total and cardiovascular mortality.[13]

Our study has several strengths, including its prospective design and comprehensive assessment of baseline characteristics and renal function parameters. Additionally, it is the first study to analyse the trajectory of renal function in patients with 'de novo' HFrEF following their initial hospitalisation for HF. However, certain limitations should be acknowledged. First, our study was conducted at two university hospitals, potentially limiting its generalisability to other settings or populations. Second, the observational nature of our study precludes causal inference, and residual confounding may be present despite adjustment for potential confounders. Additionally, the relatively small sample size may limit the statistical power and robustness of our findings.

CONCLUSIONS

In summary, our study highlights the prevalence of renal dysfunction in a cohort of patients with 'de novo' HFrEF after their initial hospitalisation for HF and its influence on major clinical outcomes. Deterioration in renal function at discharge was associated with worse survival and increased HF readmissions, while improvement or stabilisation during follow-up was linked to better outcomes. These findings underscore the importance of routine assessment and monitoring of renal function in HFrEF management, with implications for personalised treatment approaches to mitigate renal function decline and improve patient care. Further research is needed to validate these findings in larger cohorts and explore targeted interventions for preserving renal function in patients with HFrEF.

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