JACC: HEART FAILURE VOL. ■, NO. ■, 2024

PUBLISHED BY ELSEVIER

Trajectories of Kidney Function in Heart Failure Over a 15-Year Follow-Up

Clinical Profiling and Mortality

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ABSTRACT

BACKGROUND Limited data are available on the long-term trajectory of estimated glomerular filtration rate (eGFR) in patients with chronic heart failure.

OBJECTIVES The authors evaluated eGFR dynamics using the 2009 Chronic Kidney Disease Epidemiology Collaboration equation and its prognostic significance in a real-world cohort over a 15-year follow-up.

METHODS A prospective observational registry of ambulatory heart failure outpatients was conducted, with regular eGFR assessments at baseline and on a 3-month schedule for ≤15 years. Urgent kidney function assessments were excluded. Locally weighted error sum of squares curves were plotted for predefined subgroups. Multivariable longitudinal Cox regression analyses were conducted to assess associations with all-cause and cardiovascular death.

RESULTS A total of 2,672 patients were enrolled consecutively between August 2001 and December 2021. The average age was 66.8 ± 12.6 years, and 69.8% were men. Among 40,970 creatinine measurements, 28,634 were used for eGFR analysis, averaging 10.7 ± 8.5 per patient. Over the study period, a significant decline in eGFR was observed in the entire cohort, with a slope of −1.70 mL/min/1.73 m^2 per year (95% CI: −1.75 to −1.66 mL/min/1.73 m^2 per year). Older patients, those with diabetes, a preserved ejection fraction, a higher baseline eGFR, elevated hospitalization rates, and those who died during follow-up experienced more pronounced decreases in the eGFR. Moreover, the decrease in kidney function correlated independently with all-cause mortality and cardiovascular death.

CONCLUSIONS These findings highlight the sustained decline in eGFR over 15 years in patients with heart failure, with variations based on clinical characteristics, and emphasize the importance of regular eGFR monitoring in this population. (J Am Coll Cardiol HF 2024;■:■-■) © 2024 by the American College of Cardiology Foundation.

Renal impairment is prevalent in nearly one-half of all patients with heart failure (HF), and it is anticipated that the incidence of individuals with both HF and chronic kidney disease (CKD) will continue to rise as survival rates improve for both conditions.[1,2] HF can affect kidney function in a number of ways, including a decrease in renal blood flow, venous congestion, impaired renal hemodynamics, and activation of the renin-angiotensin-aldosterone system (RAAS). The overlap between HF and CKD can also be explained by shared etiological factors, including hypertension and diabetes, which

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received October 2, 2023; revised manuscript received December 20, 2023, accepted January 4, 2024.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2024.01.004

ABBREVIATIONS AND ACRONYMS

ARNI = angiotensin receptor neprilysin inhibitor

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

LME = linear mixed effect

LVEF = left ventricular ejection fraction

RAAS = renin-angiotensin-aldosterone system

SGLT2i = sodium glucose co-transporter 2 inhibitor

may have a detrimental impact on kidney function.[3] In turn, CKD contributes to progressive left ventricular remodeling, fibrosis, and cardiac dysfunction by inducing fluid overload, anemia, uremia, and sustained activation of the RAAS and sympathetic nervous system.[1] Given the intricate relationship between the heart and the kidneys, it is highly recommended to monitor kidney function in individuals with HF[4] regularly.

Worsening kidney function, as assessed by estimated glomerular filtration rate (eGFR), frequently occurs in patients with HF.[5] However, the available information on this topic is predominantly limited to follow-up periods of 2 to 3 years. Consequently, there is a lack of comprehensive understanding regarding the longitudinal trajectories of kidney function in outpatient HF settings, which is crucial for optimizing guideline-directed medical therapy. Misinterpreting the dynamics of eGFR could lead to the premature discontinuation of decongestive or neurohormonal blocker therapies in clinical practice. There is a need to better delineate the long-term trajectories of kidney function in patients with HF to ensure appropriate treatment decisions and avoid potential therapeutic disruptions.[4]

The objective of this study was to examine the dynamics of eGFR, as determined by the Chronic Kidney Disease Epidemiology Collaboration equation, and its prognostic significance in a real-world cohort of ambulatory patients with HF over a 15-year follow-up period. The study aimed to investigate the long-term trajectory of kidney function outside of HF decompensations, evaluate its correlation with clinical variables and HF phenotypes, and assess its association with both all-cause and cardiovascular mortality.

METHODS

STUDY POPULATION. We examined all consecutive ambulatory patients referred to a structured multidisciplinary HF clinic of a university hospital between August 2001 and December 2021, regardless of HF etiology. HF was diagnosed according to current European Society of Cardiology Guidelines at the time of enrolment. The collection of blood samples including renal function for subsequent analysis was prospectively designed and scheduled from the start. Follow-up visits were performed after 1 month and then every 3 months, as previously described in detail.[6,7] During the first visit, patients provided written informed consent to the use of their clinical data for research purposes. The study was performed in compliance with the law protecting personal data in accordance with the international guidelines on clinical investigation of the World Medical Association's Declaration of Helsinki. Fatal events were identified from electronic health records or by contacting patient relatives. Data were verified by accessing data from the Catalan and Spanish Health Systems and the Spanish Death Registry databases. Events were adjudicated by staff of the HF clinic, and an ad hoc committee of 3 to 4 members chaired by J.L., which resolved all discrepancies.

KIDNEY FUNCTION ASSESSMENT. This study focused on serum creatinine values obtained from outpatient clinic visits, including the baseline visit and scheduled follow-up visits. Creatinine measurements from urgent visits, outlier values (creatinine >10 mg/dL and <0.1 mg/dL), as well as measurements taken after initiating dialysis treatment or undergoing a renal transplant, were excluded from the analysis.

Creatinine levels were analyzed using the Siemens CREA method (ref FD33A) on a Dimension RxL Clinical Chemistry System (Siemens), and since 2016 by enzymatic reaction on an AU5800 analyzer (Bekman Coulter). Creatinine values measured before 2011 were standardized according to IDMS reference method: standardized creatinine values (mg/dL) = 1.00 × Dimension RxL creatinine values (mg/dL) − [0.168] (Technical Bulletin: Correlation factors for correlating Jaffe creatinine methods to the IDMS creatinine reference procedure, D-01674 Siemens Healthcare Diagnostics, Inc, March 2011, rev1.0). The eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.[8]

STATISTICAL ANALYSIS. Categorical variables were expressed as absolute numbers and percentages. Continuous variables were expressed as the mean ± SD or median (IQR) according to normal or non-normal distributions. Normal distribution was assessed with normal quantile-to-quantile plots. Locally weighted error sum of squares curves adjusted by follow-up time were plotted for the whole cohort and prespecified subgroups (sex, ischemic etiology, diabetes, HF classification based on left ventricular ejection fraction [LVEF], age quartiles, HF hospitalizations, and vital status at the end of follow-up). Linear mixed effects (LME) models were used to evaluate and compare the effect of time over the eGFR change for the total cohort and the prespecified subgroups. Random intercepts LME models were fitted based on the assumption that there are important individual-level effects and patients have similar rates of change over time. Missing values during follow-up

TABLE 1 Baseline Clinical Characteristics and Treatments at Baseline and During Follow-Up (N = 2,672)

Age, y	66.8 ± 12.6
Male	1,864 (69.8)
Caucasian	2,603 (97.4)
Etiology	
Ischemic heart disease	1,206 (45.1)
Dilated cardiomyopathy	460 (17.2)
Hypertensive	205 (7.7)
Alcohol	127 (4.8)
Drugs	78 (2.9)
Valvular	238 (8.9)
Other	358 (13.4)
HF duration, mo	7 (2-45)
LVEF, %	35.9 ± 14.4
HFrEF	1,935 (72.4)
HFmrEF	292 (10.9)
HFpEF	445 (16.7)
NYHA functional class (N = 2,668)	
I	208 (7.8)
II	1,809 (67.8)
III	635 (23.8)
IV	16 (0.6)
Diabetes	1,114 (41.7)
Hypertension	1,693 (63.4)
COPD	431 (16.1)
Peripheral vasculopathy	327 (12.2)
Anemia[a] (N = 2,647)	772 (29.2)
Renal insufficiency[b]	1,107 (41.4)
AF/AFL	607 (22.7)
BMI, kg/m^2 (N = 2,648)	27.9 (24.3-30.5)
Creatinine	1.18 (0.85-1.38)
eGFR, mL/min/1.73 m^2	67.4 ± 25.9
Urea, mg/dL (N = 2,603)	54 (40.3-75.7)
Sodium, mmol/L (N = 2,641)	138 (136-140)
Hemoglobin, g/dL (N = 2,647)	13.0 ± 1.8
NT-proBNP, ng/L (N = 2,057)	1,511 (658-3,366)
Treatments baseline	
ACE inhibitor or ARB	1,865 (69.8)
Beta-blocker	2,000 (74.9)
MRA	1,169 (43.8)
ARNI	142 (5.3)
Loop diuretic	2,035 (76.2)
Digoxin	527 (19.7)
Ivabradine	262 (9.8)
SGLT2i	31 (1.2)
CRT	112 (4.2)
ICD	217 (8.1)
Treatments during follow-up	
ACE inhibitor or ARB	2,226 (83.3)
Beta-blocker	2,432 (91.0)
MRA	1,775 (66.4)
ARNI	654 (24.5)
Loop diuretic	2,410 (90.2)
Digoxin	904 (33.8)
Ivabradine	630 (23.6)
SGLT2i	594 (22.3)
CRT	328 (12.3)
ICD	434 (16.2)

Values are mean ± SD, median (IQR), or n (%). [a]According to World Health Organization criteria (<13 g/dL in men and <12 g/dL in women). [b]eGFR <60 mL/min/1.73 m^2.

ACE = angiotensin-converting enzyme; AF/AFL = atrial fibrillation/flutter; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; HF = heart failure; HFmrHF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardiac defibrillator; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SGLT2i = sodium glucose co-transporter 2 inhibitor.

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were assumed to be distributed randomly. We treated the primary outcome, eGFR, as a continuous dependent variable in our LME model. The variable time was included as a fixed effect, to model the average trajectory of eGFR across the entire cohort over the study period. The *P* values for the slopes were obtained from the LME model using conventional statistical tests (cftest and anova commands).

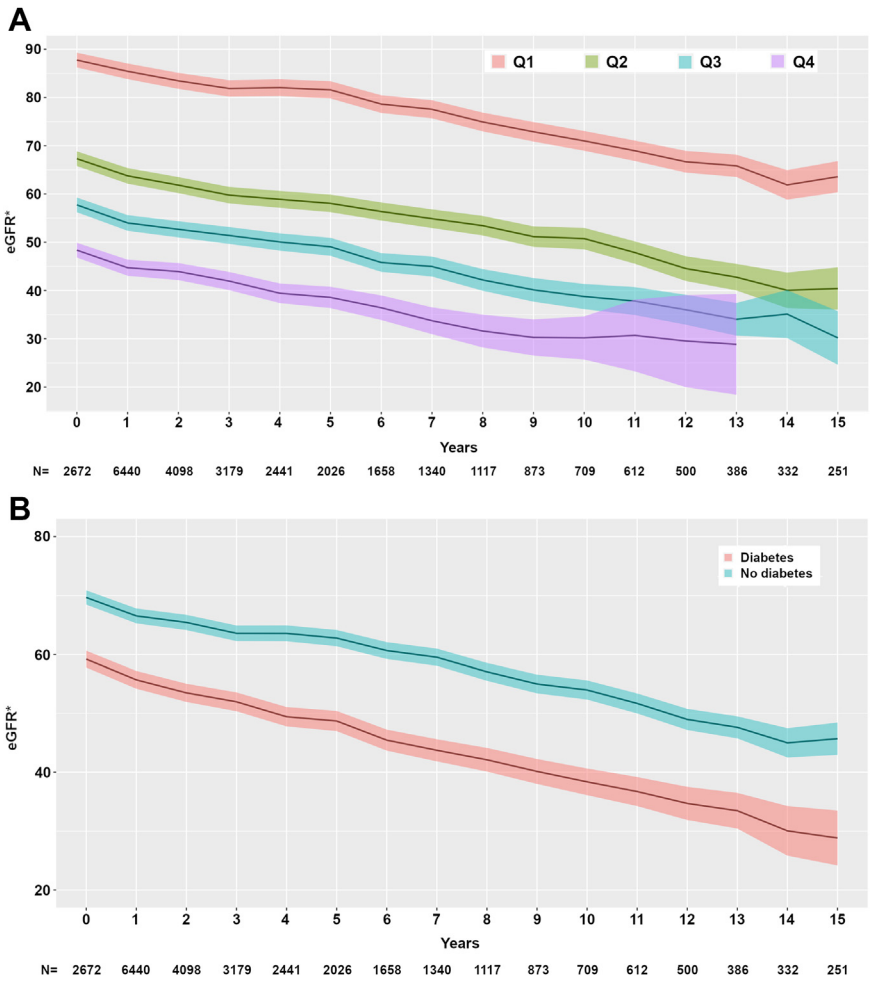
Multivariable longitudinal Cox regression analyses adjusted by baseline eGFR were performed for assessing the prognostic role of eGFR trajectories on all-cause death and on cardiovascular death, using in the later the Fine and Gray method for competing risks, taking into account noncardiovascular death as the competing event. The variable eGFR, representing the repeated measurements of eGFR, was included as a time-varying covariate. This method allows us to analyze how changes in eGFR over time were related to the risk of survival events. To address the nonlinear trend in eGFR, our model included both the baseline eGFR and the time-varying eGFR. This dual inclusion enables us to capture the initial renal function and its progression, providing a comprehensive view of how eGFR influences survival.

Statistical analyses were performed using SPSS 24 (SPSS Inc), and R (A Language and Environment for Statistical Computing) by R Core Team (R Foundation for Statistical Computing). For generalized LME models, we used the nlme R package, version 3.1-131 by Pinheiro, Bates, DebRoy, Sarkar, and R Core Team (2017). A 2-sided value of $P < 0.05$ was considered significant.

RESULTS

A total of 3,117 consecutive patients were visited for the first time from August 2001 to December 2021. Among them, 2,672 patients (86%) met the criteria of not having undergone a renal transplant, not being on

FIGURE 1 LOESS Spline Curves of Long-Term eGFR Trajectories Based on Predetermined Subgroups



(A) Long-term eGFR trajectories based on quartiles of age; Q1 <58.33 years (red); Q2 58.33-68.59 years (green); Q3 >68.59-76.32 years; (blue); and Q4 >76.32 years (purple). Comparisons among quartiles for baseline eGFR all $P < 0.001$. Decline in eGFR (slopes): Q1 vs Q2; $P = 0.176$; Q1 vs Q3; $P = 0.036$; Q1 vs Q4; $P = 0.003$; Q2 vs Q3; $P = 0.835$; Q2 vs Q4; $P = 0.116$; Q3 vs Q4; $P = 0.391$. (B) Patients with diabetes (red) vs patients without diabetes (blue). $P < 0.001$ for differences in baseline eGFR and in trajectory changes between groups. (C) Trajectories based on the HF universal classification according to LVEF: HFrEF (red), HFmrEF (green), and HFpEF (blue). The baseline eGFR was significantly higher in HFrEF than in HFpEF ($P = 0.002$). There were no differences in other group comparisons (HFrEF vs HFmrEF; $P = 0.769$; HFmrEF vs HFpEF; $P = 0.186$. P values for differences in trajectory changes between groups: HFrEF vs HFpEF; $P = 0.042$; HFrEF vs HFmrEF; $P = 0.039$; HFmrEF vs HFpEF; $P = 0.952$. Shaded regions displayed around curves represent the CI at level = 0.95. *mL/min/1.73 m^2. eGFR = estimated glomerular filtration rate; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LOESS = locally weighted error sum of squares; LVEF = left ventricular ejection fraction; N = number of eGFR measurements at baseline and along the year.

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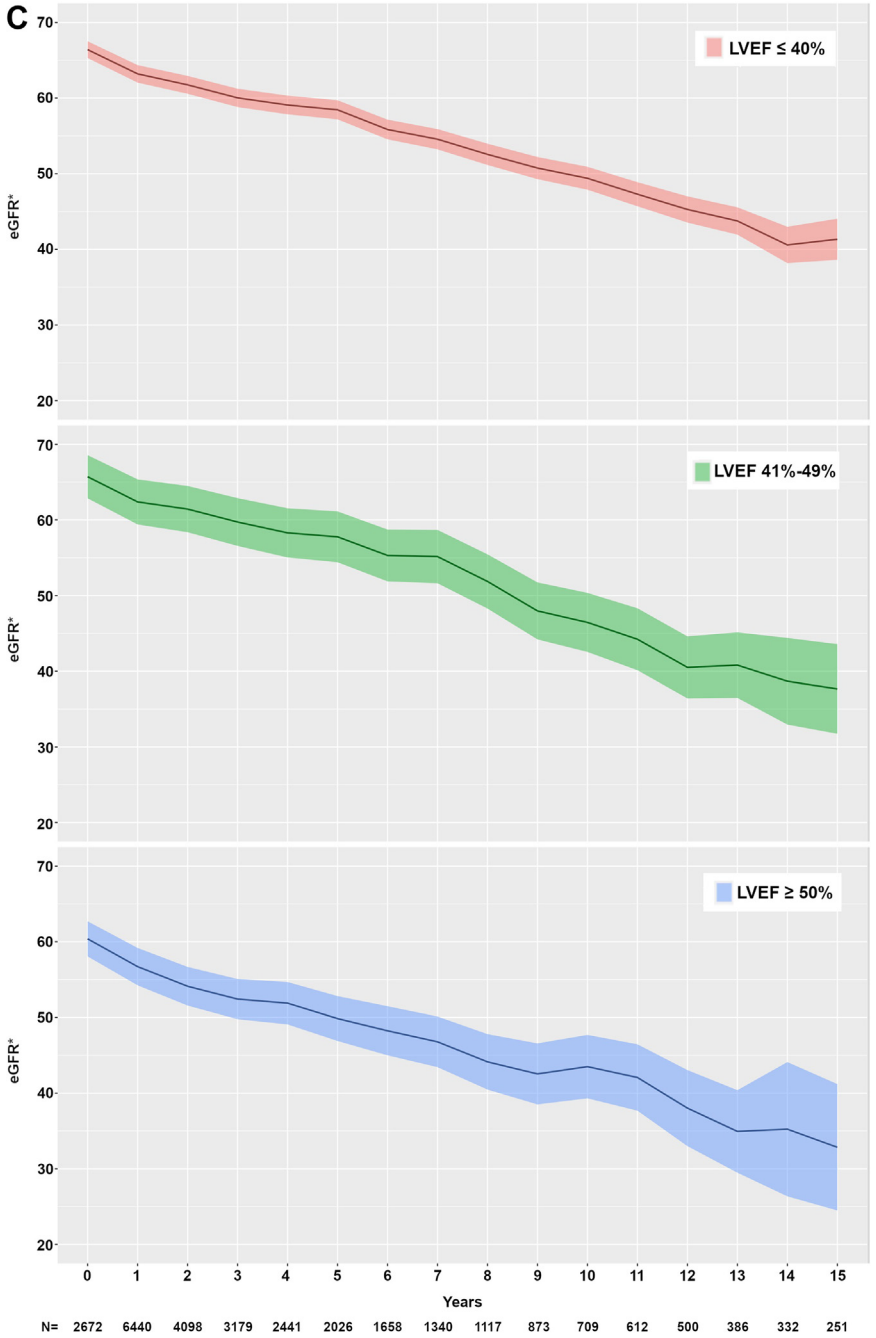
dialysis, and having multiple (a minimum of 2) scheduled creatinine measurements (Supplemental Figure 1). Their baseline characteristics are depicted in **Table 1**. The mean age was 66.8 ± 12.6 years, 69.8% were men, 72.4% had HF with reduced ejection fraction (HFrEF), and the most common etiology was ischemic heart disease (45.1%). Baseline eGFR was 67.4 ± 25.9 mL/min/1.73 m^2, 41.4% had an eGFR or <60 mL/min/1.73 m^2; 18.2%, 45.0 to 59.9 mL/min/1.73 m^2; 15.8%, 30.0 to 44.9 mL/min/1.73 m^2; and 7.5% <30 mL/min/1.73 m^2). Treatments at baseline and during follow-up are shown in **Table 1**.

Of 40,970 creatinine measurements, 28,634 were obtained in scheduled visits and considered for the study (71% of the total) (Supplemental Figure 1), with

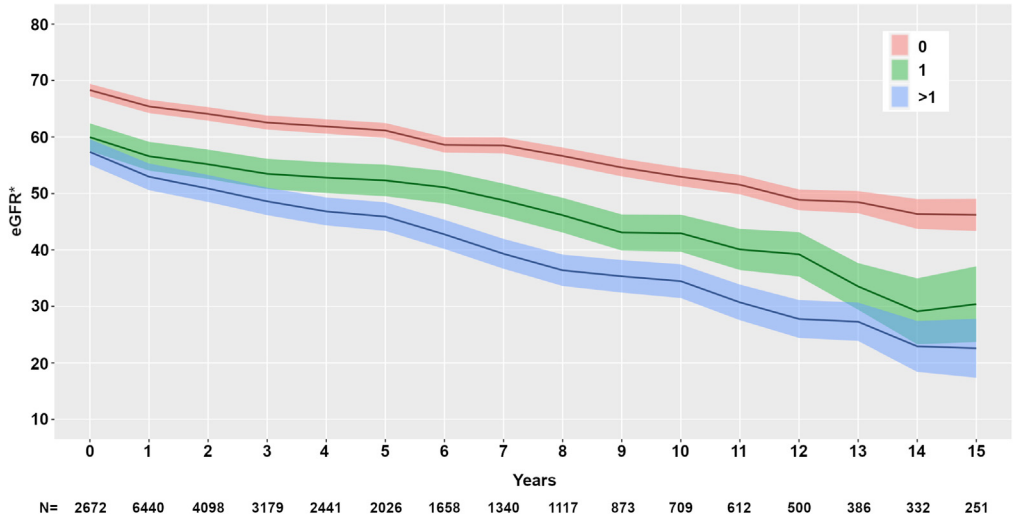
FIGURE 1 Continued



a mean of 10.7 ± 8.5 values per patient. The last creatinine measurement was obtained on December 30, 2022. Follow-up extended from 0.1 to 15.0 years (mean: 5.8 ± 4.3 years; median: 4.6 years; IQR: 2.2-8.5 years). Supplemental Figure 2 shows the number of patients and visits during the whole study. Over the 15-year follow-up, eGFR showed a progressive decrease with a slope of −1.70 mL/min/1.73 m^2 per year (95% CI: −1.75 to −1.66 mL/min/1.73 m^2 per year). This decrease in the eGFR was influenced by various factors.

When dividing the patients into quartiles (Q) based on age, we observed a significant decrease in baseline eGFR with advancing age ($P < 0.001$ for all

FIGURE 2 LOESS Spline Curves of Long-Term eGFR Trajectories Based on HF Hospitalizations During Follow-Up



None (red), 1 (green), and >1 (blue). $P < 0.001$ for slope differences among all groups. Shaded regions displayed around curves represent the CI at level = 0.95. *mL/min/1.73 m^2. Abbreviations as in Figure 1.

comparisons). Furthermore, there was a trend of increasing decline in eGFR with age (P for trend < 0.001): Q1 (−1.61; 95% CI: −1.69 to −1.54), Q2 (−1.73; 95% CI: −1.81 to −1.64), Q3 (−1.78; 95% CI: −1.88 to −1.68), and Q4 (−1.94; 95% CI: −2.11 to −1.77). However, the differences in eGFR decline were statistically significant only between Q1 vs Q3 and Q1 vs Q4 (Figure 1A).

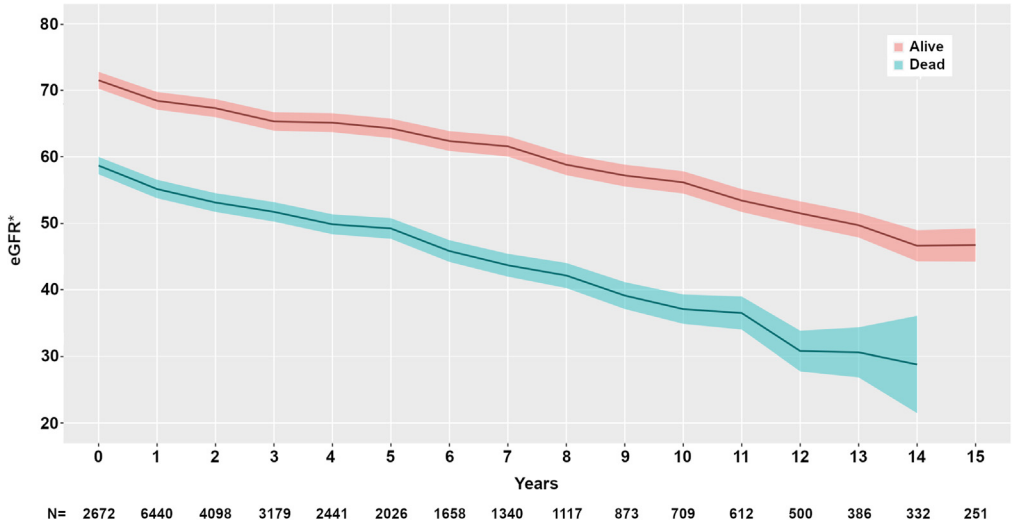
Women had a lower baseline eGFR than men (62.8 ± 26.2 mL/min/1.73 m^2 vs 69.4 ± 25.6 mL/min/1.73 m^2; $P < 0.001$). Although women showed a slightly greater decrease in the eGFR during the follow-up period (−1.76; 95% CI: −1.85 to −1.67) compared with men (−1.68; 95% CI: −1.73 to −1.63), this difference did not reach statistical significance ($P = 0.141$) (Supplemental Figure 3).

Patients with diabetes had a significantly lower eGFR compared with patients without diabetes (61.0 ± 25.1 mL/min/1.73 m^2 vs 72.0 ± 25.6 mL/min/1.73 m^2, respectively; $P < 0.001$). Moreover, patients with diabetes exhibited a significantly greater decline in eGFR during the follow-up period (slope: −2.04; 95% CI: −2.12 to −1.95) compared with patients without diabetes patients (slope: −1.56; 95% CI: −1.61 to −1.50) ($P < 0.001$) (Figure 1B). Furthermore, it was observed that patients with ischemic HF had a significantly lower baseline eGFR compared with those without ischemic HF (65.1 ± 24.7 mL/min/1.73 m^2 vs 69.3 ± 26.8 mL/min/1.73 m^2; $P < 0.001$), without significant differences in the rates of decline of kidney function (slope: −1.73; 95% CI: −1.79 to −1.66 vs slope: −1.67; 95% CI: −1.74 to −1.61, respectively; $P = 0.237$) (Supplemental Figure 4). Baseline eGFR was notably worse in patients with HF with preserved ejection fraction (HFpEF) compared with those with HFrEF, and the decrease in the eGFR was more significant in patients with HFpEF as well (slope: −1.87; 95% CI: −2.03 to −1.71 vs slope: −1.66; 95% CI: −1.72 to −1.61, respectively; $P = 0.042$). The decrease in the eGFR in patients with HF with mildly reduced ejection fraction (HFmrEF) was similar to that of patients with HFpEF (slope: −1.84; 95% CI: −1.97 to −1.71; $P = 0.952$) (Figure 1C).

Supplemental Figure 5 illustrates the relationship between eGFR trajectories and baseline eGFR strata. The findings indicate that the higher the baseline eGFR, the more pronounced the decline in eGFR. Specifically, for different baseline eGFR strata, the following slopes were observed: <30 mL/min/1.73 m^2 (slope: −0.64; 95% CI: −0.97 to −0.32); 30 to 59 mL/min/1.73 m^2 (slope: −1.22; 95% CI: −1.32 to −1.12); 60 to 89 mL/min/1.73 m^2 (slope: −1.77; 95% CI: −1.84 to −1.70); and ≥90 mL/min/1.73 m^2 (slope: −1.93; 95% CI: −2.00 to −1.85). Notably, there were significant differences in the decline rates of eGFR among all the groups ($P < 0.001$).

Patients were categorized based on their HF hospitalizations during the follow-up period: none, 1, or >1. Among the study participants, 1,850 patients did not experience any HF hospitalization, 382 required 1

FIGURE 3 LOESS Spline Curves of Long-Term eGFR Trajectories Based on Vital Status at the End of Follow-Up



Alive (orange) vs dead (blue). $P < 0.001$ for differences in baseline eGFR and in trajectory changes between groups. Shaded regions displayed around curves represent the CI at level = 0.95. *mL/min/1.73 m^2. Abbreviations as in Figure 1.

HF hospitalization, and 440 had multiple HF hospital admissions. The analysis revealed that the decrease in eGFR was significantly lower in patients without HF hospitalizations (slope: −1.47; 95% CI: −1.53 to −1.41) compared with those with 1 HF hospitalization (slope: −1.72; 95% CI: −1.84 to −1.60) and those with >1 HF hospital admissions (slope: −2.34; 95% CI: −2.43 to −2.24). The observed differences in eGFR decline were statistically significant in all group comparisons ($P < 0.001$) (Figure 2).

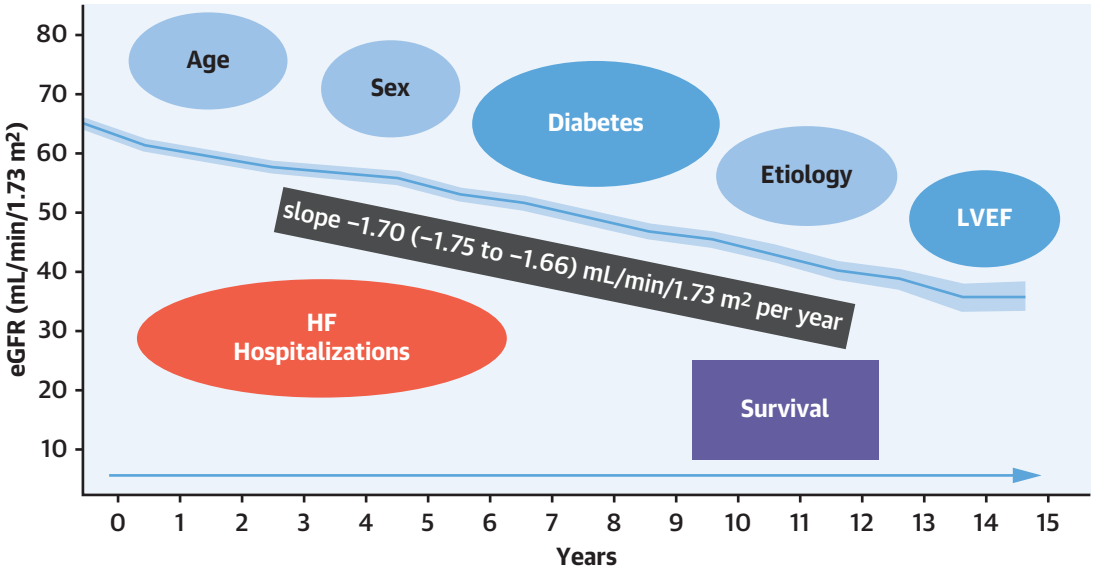
A total of 1,291 deaths were recorded during the complete follow-up. Comparisons between patients who died during the follow-up period and those who remained alive revealed significantly worse baseline eGFR values in the deceased group (61.1 ± 24.6 mL/min/1.73 m^2) compared with the alive group (73.4 ± 25.8 mL/min/1.73 m^2; $P < 0.001$). Furthermore, the trajectory slope of eGFR decline was significantly steeper in patients who died (slope: −2.05; 95% CI: −2.13 to −1.96) compared with those who remained alive (slope: −1.56; 95% CI: −1.61 to −1.50; $P < 0.001$) (Figure 3).

In the multivariable longitudinal Cox regression analyses adjusted for baseline eGFR, age, sex, ischemic etiology, hypertension, LVEF, and treatments such as angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, angiotensin receptor neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonist, and beta-blockers, the decrease in eGFR during follow-up was statistically significantly associated with both all-cause death (HR: 1.02; 95% CI: 1.01-1.02; $P < 0.001$) (Supplemental Table 1) and cardiovascular death (HR: 1.01; 95% CI: 1.01-1.02; $P < 0.001$) (Supplemental Table 2).

DISCUSSION

To address the lack of available data on the long-term trajectory of kidney function in patients with chronic HF, this study undertook a comprehensive analysis spanning ≤15 years. Among the scheduled visits of patients with HF, nearly 30,000 creatinine measurements were collected, with an average of 10.7 ± 8.5 values per patient. Our analysis revealed a progressive decline in eGFR over time, with a slope of −1.70 mL/min/1.73 m^2 per year (95% CI: −1.75 to −1.66 mL/min/1.73 m^2 per year), which was influenced by clinical factors and had prognostic impact (**Central Illustration**). Notably, this decline rate is considerably higher than the expected physiological decline of kidney function, which is approximately 1 mL/min/1.73 m^2 per year.[9] In a substudy of the GISSI-HF trial, in which the effect of rosuvastatin in patients with chronic heart failure was studied, a decrease in the eGFR of 3.7 ± 18.0 mL/min/1.73 m^2 was reported at 36 months of follow-up, corresponding with a median decrease of 2.57 mL/min/1.73 m^2 per year.[10] It is important to note that the GISSI-HF trial excluded patients with creatinine levels of >2.5 mg/dL. This information highlights

CENTRAL ILLUSTRATION **LOESS Spline Curves of Long-Term (15 Years) eGFR Trajectories for the Total Cohort of Patients With HF**



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An average decrease of −1.70 mL/min/1.73 m^2 was observed. Several clinical factors, such age, presence of diabetes, left ventricular ejection fraction, baseline eGFR and hospitalizations in the follow-up influenced the degree of such decline. Decline in eGFR had a significant impact on survival. eGFR = estimated glomerular filtration rate; HF = heart failure; LOESS = locally weighted error sum of squares; LVEF = left ventricular ejection fraction.

the variability in eGFR decline and underscores the need for further research to understand the underlying mechanisms and implications for patients with HF.

The rate of decline in kidney function varied among different patient subgroups. Factors such as age, presence of diabetes, HF phenotype, and higher baseline eGFR, as well as prior hospitalization, were associated with a more pronounced decline in kidney function over time. These observations indicate that these specific patient characteristics may play a role in accelerating the decline of kidney function in individuals with HF.

The decline in GFR with age is a topic of debate, with some studies suggesting a physiological process of aging and others proposing underlying kidney disease as the cause.[9] In our study, we observed that older patients seemed to experience a greater decline in estimated eGFR during follow-up period (P for trend <0.001). However, when we divided the patients into quartiles based on their age, the differences in eGFR decline were statistically significant only between Q1 and Q3, as well as between Q1 and Q4.

Studies have reported differences in GFR between men and women, with women generally having lower filtration rates. However, the decline in kidney function with aging seems to be less pronounced in women.[11] In our study, we observed that women with HF had a lower baseline eGFR than men, which is consistent with findings from the GISSI-HF trial.[10] Additionally, women showed a numerically more prominent decrease in eGFR during follow-up, although this difference did not reach statistical significance. It is possible that the presence of HF and other cardiovascular risk factors, which are more prevalent in this group of patients, could have influenced the normal relationship between eGFR and sex observed in the general population.

In our study, patients with diabetes with HF exhibited a lower baseline eGFR and a significantly greater decline in kidney function during follow-up. This finding is in contrast to the findings of the GISSI-HF trial, which did not identify an interaction between time and the association of eGFR slope in patients with diabetes.[10] It is important to note that the GISSI-HF analysis on renal impairment and CKD had a shorter duration of 36 months compared with

the 15-year follow-up reported in our study. Previous research has shown that risk factors such as diabetes are associated with a faster decline in the eGFR slope.[12] Additionally, a more pronounced decrease in the eGFR has been linked to a higher risk of adverse events. Unfortunately, we have no data on the presence of albuminuria, which could explain the differences between baseline eGFR and greater decline in patients with diabetes vs patients without diabetes.

Sodium glucose co-transporter 2 inhibitors (SGLT2is) have demonstrated their ability to reduce renal dysfunction in patients with HF.[13] However, because of the recent incorporation of SGLT2is into our therapeutic options, we did not have sufficient data to analyze the potential beneficial effects of SGLT2is on eGFR evolution in our cohort.

Forty-eight percent of our patient cohort had HF of ischemic etiology, and these patients had a significantly lower baseline eGFR compared with other etiologies. However, there were no significant differences in the rate of decline of kidney function between the ischemic and nonischemic groups. It is worth noting that several risk factors, such as hypertension, diabetes, obesity, albuminuria, and diuretic use have been associated with a faster decrease in the GFR slope.[12] Renal damage in the context of cardiovascular disease can be attributed to various pathogenic factors, including hemodynamic changes, oxidative stress, inflammation, exposure to radiocontrast agents, and certain pharmacological treatments. Although these factors can contribute to the development of kidney failure, it remains uncertain whether an ischemic etiology itself plays an additional role in kidney function decline.

We found that patients with HFpEF had a worse baseline eGFR compared with those with HFrEF, and they also experienced a more prominent decline in kidney function over time. Interestingly, patients with HFmrEF had a similar decline in eGFR to those with HFpEF. Although in our experience HFmrEF might be a transition phenotype in many patients,[14] we cannot discard that some degree of overlap between HFmrEF and HFpEF phenotypes exists. The HFpEF patient population is known to have distinct characteristics, including older age and a higher burden of comorbidities, which could potentially explain these findings. A study by Huang et al[15] observed that impaired kidney function, defined as an eGFR of ≤60 mL/min/1.73 m^2, was associated with a higher 5-year mortality rate across different HF phenotypes, regardless of whether patients had HFpEF, HFrEF, or HFmrEF. This finding highlights the prognostic significance of impaired kidney function in patients with HF, regardless of the specific phenotype. Furthermore, the use of SGLT2is has shown promising effects in improving kidney function deterioration in patients with HF.[16,17] Considering the potential benefits of SGLT2is in preserving kidney function, their use may be particularly beneficial in patients with HFpEF, who are more prone to renal dysfunction.

In contrast with previous studies that reported a greater decline in eGFR among patients with a lower baseline eGFR,[18] we found that the higher the baseline eGFR, the greater the decline in kidney function. This finding is consistent with the observations made in the GISSI-HF trial.[10] The phenomenon of a less pronounced decline in eGFR among patients with poorer initial kidney function has been previously described. It has been suggested that this result could be attributed to the fact that patients with more severe renal impairment face a higher risk of mortality. Consequently, their renal disease may progress to end stage before significant declines in eGFR become evident.[19,20] In other words, the competing risk of death may restrict the extent of kidney function decline among these patients. The long-term effects of pharmacological treatments used in HF, such as RAAS inhibitors, ARNI, or SGLT2is, on the worsening of kidney function are not well-established in long-term studies. In our study, because of the relatively recent introduction of ARNI and SGLT2i therapies, we could not analyze the potential beneficial effects of these treatments on the evolution of eGFR over time. During extended follow-up, alterations in treatment regimens, including changes in drug doses, as well as temporary or permanent discontinuations and reinitiations of these medications, are common. Analyzing the impact of all these changes on the evolution of eGFR was not feasible.

The impact of HF hospitalization on kidney function is a complex and dynamic process. In our study, we acknowledge that we relied on ambulatory and scheduled creatinine values to assess kidney function, which may not fully capture the changes that occur during hospitalization. It is important to note that the worsening of kidney function during HF admission may not necessarily reflect a true decline in kidney function, as transient renal deterioration can be a result of hemodynamic changes and effective decongestion, which can actually be associated with a better prognosis.[2] When we compared patients based on the number of HF hospitalizations during follow-up (none vs 1 vs >1), we observed that the decline in eGFR was significantly lower in patients without HF hospitalizations, followed by those with one HF hospitalization, while patients with more than one HF

hospital admission showed the highest decline in kidney function. This finding suggests that HF admissions may reflect a more advanced or uncontrolled disease state, which can contribute to the worsening of kidney function. The study by Ishigami et al[20] analyzed the decline in kidney function after hospitalization in a large cohort of patients with cardiovascular disease, including HF.[2] They found that the HF group had the fastest decline in kidney function compared with patients with coronary heart disease and stroke. The decline was more pronounced in patients with lower initial eGFR. These findings further support the notion that HF hospitalization have a significant impact on kidney function and lead to a faster decline in patients with pre-existing renal impairment.

Future studies should investigate whether the faster deterioration of kidney function observed in certain patient subgroups has an impact on patient outcomes. It would be valuable to examine whether medications such as ARNI and SGLT2is can effectively slow down the decline in kidney function over the long term in real-world clinical settings, as has been demonstrated in clinical trials. In the meantime, the identification of patient subgroups that are particularly susceptible to a decline in eGFR has important implications for clinical practice. Clinicians can use this information to guide their management approach, such as implementing closer follow-up and more cautious up-titration of medications targeting the RAAS. Additionally, the prompt introduction of medications such as sacubitril/valsartan and SGLT2is, known to have renal protective effects, may be beneficial in mitigating the decline in kidney function in these susceptible patients. The finding of a greater decline in kidney function in HFpEF compared with HFrEF further supports the importance of using renal protective medications in HFpEF as well.

This study is not without limitations inherent to prospective observational registries. We lack a control group without HF for comparative purposes. The assessment of kidney function should ideally involve a comprehensive evaluation of various parameters, such as proteinuria or serum cystatin C levels, which was not included in this study. The focus on eGFR alone may not provide a complete picture of kidney function. The study cohort consisted of patients from a specific multidisciplinary HF clinic in a tertiary care hospital, predominantly referred from the cardiology department. We only have genetic information in a limited number of patients with a nonischemic etiology. We analyzed the relationship of eGFR trajectories and LVEF only at baseline, although we are aware that LVEF is dynamic in patients with HF.[21] It is important to consider potential differences in patient demographics, comorbidities, and health care settings when extrapolating the results. However, it is worth noting that the application of a common treatment protocol to all patients in the study helps to minimize the bias arising from different management strategies or treatment protocols. Nevertheless, the changes in medication doses, discontinuation, and reintroduction that often occur during follow-up were not analyzed in relation to their influence on eGFR evolution, which could be a potential limitation. Certainly, the therapeutic landscape for HFrEF and HFpEF has undergone significant changes in recent years. Studying how these treatments will impact the long-term trajectories of eGFR will require further research in the future.

CONCLUSIONS

The longitudinal assessment of eGFR spanning ≤15 years in patients with HF revealed a progressive decline that surpassed the normal age-related decline observed in the general population. Several clinical characteristics were found to significantly influence this decline, including age, diabetes, LVEF categories, baseline eGFR, and hospitalizations during follow-up. The decline in kidney function demonstrated independent associations with both all-cause mortality and cardiovascular mortality. Future research should prioritize the identification of interventions or therapeutic approaches that can attenuate the decline in kidney function in patients with HF, ultimately leading to improve outcomes within this patient population.

ACKNOWLEDGMENTS The authors thank the nurses in the HF unit (Beatriz González, Carmen Rivas, Ana Pulido, Patricia Velayos, Eva Crespo, Dakota Barés and Violeta Díaz) for data collection and for their invaluable work in the unit.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Bayes-Genis has lectured or participated in advisory boards for Abbott, AstraZeneca, Boehringer-Ingelheim, Bayer, Novartis, Roche Diagnostics, and Vifor. Dr Nuñez has received personal fees or advisory boards from Alleviant, AstraZeneca, Boehringer Ingelheim, Bayer, Novartis, NovoNordisk, Rovi, and Vifor CSL. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The long-term trajectory of kidney function in individuals with HF remains unknown.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with HF, we observed a sustained decline in the eGFR rate over time, exceeding the expected physiological decline. This decline was influenced by patient characteristics and associated with various outcomes.

TRANSLATIONAL OUTLOOK: Regular monitoring of kidney function and implementation of interventions aimed at slowing down the decline in kidney function are needed in the management of HF.

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KEY WORDS cardiorenal, estimated glomerular filtration rate, heart failure, kidney function, prognosis

APPENDIX For supplemental tables and figures, please see the online version of this paper.