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Long-Term Prognostic Impact of Estimated Glomerular Filtration Rate on Admission in Patients Hospitalized for Acute Heart Failure

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Keywords
Acute heart failure · Glomerular filtration rate · Mortality · Prognosis · Readmissions

Abstract

Introduction: Although small-sample size studies have shown that basal alterations of estimated glomerular filtration rate (eGFR) are related to short- and mid-term higher mortality in acute heart failure (AHF), there is scarce information on the influence of an altered eGFR on long-term mortality and readmissions. Therefore, this multicenter study sought to investigate the relationship between eGFR on admission for AHF and both long-term mortality and readmissions in a large sample of patients. ***Methods:*** We retrospectively evaluated 4,595 patients consecutively discharged after admission for AHF at three tertiary-care hospitals from January 1, 2008, to January 1, 2020. To investigate the effect of eGFR on admission with long-term morbimortality, we stratified the patients according to four eGFR categories: <30 mL·min^{-1}·1.73 m^{-2} (G4 and G5 patients, n = 534), 30–44 mL·min^{-1}·1.73 m^{-2} (G3b patients, n = 882), 45–59 mL·min^{-1}·1.73 m^{-2} (G3a patients, n = 1,080), and ≥60 mL·min^{-1}·1.73 m^{-2} (G1 and G2 patients, n = 2,099). eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation within the first 24 h following admission. ***Results:*** At a median follow-up of 2.20 years, multivariate analyses revealed that compared to G1 and G2 patients, G4 and G5 patients exhibited a higher risk of all-cause (HR = 1.15, 95% CI: 01.02–1.30, p = 0.020) and cardiovascular (CV) (HR = 1.20, 95% CI: 1.04–1.39, p = 0.013) mortality. Similarly, multivariate analyses also showed that the lower the eGFR, the higher the risk of readmissions. In fact, compared to G1 and G2 patients, G4 and G5 patients displayed signifi-

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cantly increased incident rate ratios of total all-cause (28%), CV (26%), and HF-related (30%) readmissions. ***Conclusion:*** Data from this large study provide evidence that an eGFR below 30 mL·min^{-1}·1.73 m^{-2} on admission could be an independent predictor for long-term mortality and readmissions in patients with AHF.

Introduction

Acute heart failure (AHF) is often accompanied by multiple comorbidities, which adversely affect outcomes and may complicate management [1]. Among them, chronic kidney disease (CKD) is one of the most relevant comorbidities, affecting up to 50% of AHF patients with either a preserved or reduced ejection fraction [2, 3]. In addition to impaired baseline kidney function, the estimated glomerular filtration rate (eGFR) is highly dynamic during worsening heart failure (HF) episodes, with substantial individual heterogeneity in eGFR trajectories during hospitalization [4]. Nonetheless, such heterogeneity in eGFR does not appear to provide additional prognostic information to baseline eGFR [4]. Furthermore, there is scarce information on the influence of reduced eGFR on admission and long-term prognosis in patients with AHF, with few small retrospective studies focused on short-term mortality [5]. Thus, this multicenter study sought to investigate the relationship between eGFR on admission for AHF and both long-term mortality and readmissions in a large sample of patients.

Methods

We retrospectively evaluated a consecutive cohort of 4,812 patients admitted with AHF at three tertiary-care hospitals in Valencia, Spain, from January 1, 2009, to January 1, 2020. All patients with a final diagnosis of AHF (either new-onset or decompensated chronic HF) as the principal diagnosis were eligible. After the exclusion of 217 in-hospital deaths during the index admission, the final study sample included 4,595 patients. Data were collected on patient demographics, medical history, vital signs, and physical examination at presentation, laboratory tests, 12-lead electrocardiogram, echocardiographic parameters, and treatments at discharge, using pre-established registry questionnaires. This study complied with the Declaration of Helsinki and was approved by the local institutional review committees.

Biomarkers were assessed together within the first 24 h after admission and analyzed in the local laboratory at each center. eGFR was calculated based on the creatinine levels using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [6].

Patients who died during index admission were excluded from this analysis. For the remaining cohort, patient follow-up continued until death through January 1, 2020. After discharge, a multidisciplinary HF team followed patients in close collaboration with primary care physicians. Based on the first evaluation and treatment upon discharge, therapeutic strategies and monitoring were individualized according to clinical guidelines.

After discharge, all-cause deaths, cardiovascular (CV) deaths, and the total burden of rehospitalizations (all-cause, CV-, and HF-related admissions) were registered. Deaths of CV etiology included sudden death, HF death, and deaths attributable to other cardiovascular causes (such as myocardial infarction, stroke, etc.) [7]. Unknown causes of death were those that could not be classified as CV or non-CV due to limited information (the only available information was "patient died") and were also considered CV deaths [7]. Only unplanned readmissions were included. HF-related readmissions were those in which worsening HF or AHF was the primary diagnosis at discharge. CV related were those admissions due to worsening HF, acute myocardial infarction, unstable angina, stroke or transient ischemic attack, cardiac arrhythmias, or peripheral artery disease. Information regarding patients' survival status was ascertained at each hospitalization, during office visits, or through a review of electronic medical records. The person in charge of endpoint adjudications was blinded to the exposure variable and patients' clinical data.

Patients were stratified according to eGFR categories into four clinical strata: <30 mL·min^{-1}·1.73 m^{-2} (G4 and G5 categories); 30–44 mL·min^{-1}·1.73 m^{-2} (G3b category); 45–59 mL·min^{-1}·1.73 m^{-2} (G3a category); and ≥60 mL·min^{-1}·1.73 m^{-2} (G1 and G2 categories) [8]. Continuous variables are presented as mean (± standard deviation) or median (interquartile range), as appropriate. Categorical variables are expressed as percentages. Comparisons across eGFR categories were performed by χ^2 test for categorical variables. For continuous variables, one-way analysis of variance and Kruskal-Wallis test were used for those variables with a parametric and nonparametric distribution, respectively.

The association of variables with time to all-cause mortality (AC mortality) was assessed using multivariate Cox proportional-hazard regression models. For estimating the multivariate risk of CV death, we used a Fine and Gray regression model by accounting for other causes of death as competing events. Risk estimates for the Cox and the Fine and Gray analyses were expressed as hazard or sub-distribution hazard ratios, respectively, with their 95% confidence intervals (95% CIs). A descriptive analysis of recurrent events was performed by counting the number of hospitalizations during follow-up. Crude incidence rates (expressed as the number of readmissions per 100 person-years) were calculated for every readmission endpoint. For recurrent events, we used bivariate negative binomial regression models that simultaneously model the number of readmissions (as counts) and mortality (as a terminal event). Regression estimates for both outcomes are mutually adjusted utilizing shared frailty (accounting for the positive correlation between the two outcomes) [9]. Estimates of risk were expressed as incidence rate ratios. For the multivariate regression models, candidate covariates were chosen based on prior medical knowledge/biological plausibility independent of their p value. The linearity assumption for all continuous variables was simultaneously tested, and the variable transformed, if appropriate, with fractional polynomials. Then, reduced and parsimonious models were derived by using backward stepwise selection. Discriminative

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Table 1. Baseline characteristics across eGFR categories

Variable	G1 and G2 (eGFR ≥60 mL·min^{-1}·1.73 m^{-2}) *N* = 2,099	G3a (eGFR 45–59 mL·min^{-1}·1.73 m^{-2}) *N* = 1,080	G3b (eGFR 30–44 mL·min^{-1}·1.73 m^{-2}) *N* = 882	G4 and G5 (eGFR <30 mL·min^{-1}·1.73 m^{-2}) *N* = 534	*p* value
Demographics and medical history					
Age, years	70.1 (12.3)	76.4 (9.2)	77.9 (8.5)	77.9 (8.5)	<0.001
Male	1,174 (55.9)	583 (54.0)	433 (49.1)	258 (48.3)	<0.001
First HF admission	1,581 (75.3)	708 (65.6)	537 (60.9)	322 (60.3)	<0.001
NYHA III-IV	264 (12.6)	169 (15.6)	192 (21.8)	142 (26.6)	<0.001
DM	841 (40.1)	480 (44.4)	407 (46.1)	281 (52.6)	<0.001
Hypertension	1,516 (72.2)	901 (83.4)	748 (84.8)	478 (89.5)	<0.001
Ischemic heart disease	583 (27.9)	399 (37.1)	329 (37.3)	218 (41.0)	<0.001
Charlson's index*	1.0 (0.0, 2.0)	2.0 (1.0, 3.0)	3.0 (1.0, 4.0)	4.0 (3.0, 5.0)	<0.001
Vital signs, electrocardiogram, echocardiogram					
Heart rate, bpm	99.6 (27.3)	96.8 (28.5)	91.5 (27.6)	88.6 (25.4)	<0.001
SBP, mm Hg	145.7 (29.9)	143.9 (32.0)	141.9 (31.7)	141.3 (31.1)	<0.001
DBP, mm Hg	83.2 (18.5)	79.7 (19.4)	76.5 (18.4)	74.1 (16.6)	<0.001
Atrial fibrillation	952 (45.4)	522 (48.3)	399 (45.2)	239 (44.8)	0.354
LVEF*	49.1 (15.6)	50.0 (14.7)	50.8 (15.0)	50.8 (14.8)	0.011
HF phenotype					
HFrEF	718 (34.2)	328 (30.4)	252 (28.6)	140 (26.2)	0.002
HFmrEF	277 (13.2)	156 (14.4)	132 (15.0)	95 (17.8)	
HFpEF	1,104 (52.6)	596 (55.2)	498 (56.5)	299 (56.0)	
Blood tests					
Creatinine, mg/dL	0.9 (0.2)	1.2 (0.2)	1.5 (0.3)	2.5 (1.0)	<0.001
BUN, mg/dL	24.9 (9.3)	31.6 (10.3)	38.4 (13.6)	52.9 (18.6)	<0.001
Serum sodium, mEq/L	138.4 (4.3)	138.6 (4.4)	138.6 (4.5)	138.1 (4.6)	0.038
Serum potassium, mEq/L	4.2 (0.5)	4.3 (0.5)	4.5 (0.7)	4.6 (0.7)	<0.001
Hemoglobin, g/dL	12.9 (1.9)	12.5 (1.9)	12.1 (2.0)	11.4 (1.8)	<0.001
CA125,* U/mL	49.0 (21.4, 115.0)	50.5 (21.8, 115.0)	48.8 (22.4, 104.0)	50.6 (25.0, 102.0)	0.818
NT-proBNP*, pg/mL	2,514.0 (1,368.0, 4,713.6)	3,580.6 (2,117.2, 6,649.4)	4,888.9 (2,625.0, 8,830.0)	8,337.0 (4,702.2, 15,779.7)	<0.001
Treatment at discharge					
RASi	1,547 (73.7)	774 (71.7)	549 (62.2)	254 (47.6)	<0.001
Beta-blockers	1,505 (72.3)	761 (70.7)	582 (66.4)	359 (68.4)	0.011
MRA	975 (46.5)	469 (43.4)	340 (38.5)	143 (26.8)	<0.001
Diuretics	1,982 (95.2)	1,042 (96.8)	863 (98.3)	506 (95.5)	<0.001
FED, mg	60.0 (40.0, 80.0)	80.0 (40.0, 80.0)	80.0 (40.0, 80.0)	80.0 (40.0, 120.0)	<0.001

Data given as *n* (%), mean (SD), or median (IQR)*. eGFR, estimated glomerular filtration rate; HF, heart failure; NYHA, New York Heart Association; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; CA125, carbohydrate antigen 125; NT-proBNP, amino-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; RASi, renin-angiotensin system inhibitors; MRA, mineralocorticoid receptor antagonist; FED, furosemide-equivalent doses.

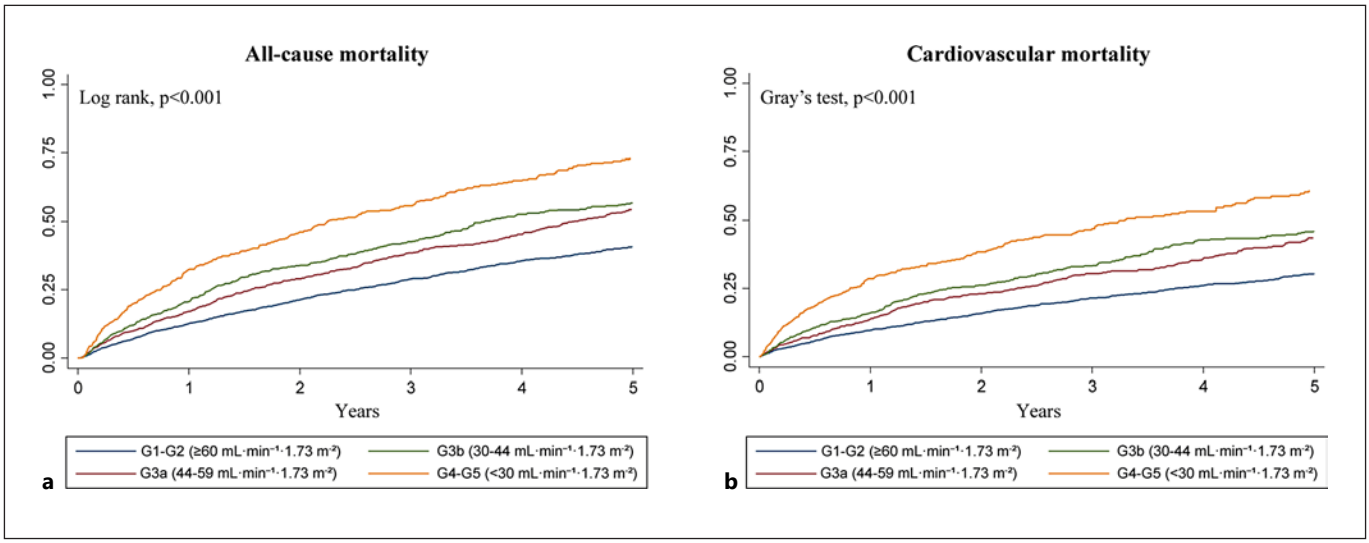

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Fig. 1. a Kaplan-Meier estimates and cumulative incidence plots for AC mortality according to estimated glomerular filtration rate (eGFR) categories (as defined in the text). **b** Kaplan-Meier estimates and cumulative incidence plots for cardiovascular mortality according to eGFR categories (as defined in the text).

abilities of the multivariate models were evaluated with Harrell's c-statistics. The final multivariate model for AC mortality included the following covariates: age, gender, prior HF admission, type 2 diabetes, heart rate, systolic blood pressure, left ventricular ejection fraction (LVEF), hemoglobin, amino-terminal pro-brain natriuretic peptide (NT-proBNP), antigen carbohydrate 125, and treatment at discharge (furosemide-equivalent doses, beta-blockers, mineralocorticoid receptor antagonists, and renin-angiotensin system inhibitors). The same set of covariates was used to estimate the multivariate risk of CV death, number of hospitalizations for all causes, CV-related causes, and HF-related causes.

We set a two-sided p value of <0.05 as the threshold for statistical significance. Stata 15.1 (Stata Statistical Software, Release 15 [2017]; StataCorp LP, College Station, TX, USA) was used for this analysis.

Results

The total cohort's mean age was 74 ± 11.2 years, 46.7% were female, and 54.3% had HFpEF. The mean of blood urea nitrogen, creatinine, and eGFR was 32.3 ± 14.9 mg/dL, 1.3 ± 0.7 mg/dL, and 58.3 ± 22.9 mL·min^{-1}·1.73 m^{-2}, respectively.

The distribution of the sample across eGFR categories was 2,149 (45.7%) G1 and G2 categories, 1,080 (23.5%) G3a category, 882 (19.2%) G3b category, and 534 (11.6%) G4 and G5 categories. As shown in Table 1, patients with eGFR categories G4 and G5 had a worse baseline risk profile. The majority of these patients were women, with a higher prevalence of T2DM and hypertension. Furthermore, 56% had preserved LVEF, presented worst New York Heart Association (NYHA) functional class, showed higher NT-proBNP values, and lower Hb levels. Likewise, these patients were less likely to be treated with renin-angiotensin system inhibitors and mineralocorticoid receptor antagonist.

At a median follow-up of 2.20 years (p25:0.74–p75:4.71), 2,257 (15.2 per 100 person-years) and 1,611 (10.9 per 100 person-years) all-cause and CV deaths were registered in those discharged alive from the hospitalization index (n = 4,595), respectively. Kaplan-Meier and cumulative incidence function plots showed higher risk in eGFR categories G4 and G5 (Fig. 1a, b). Compared to those with eGFR categories G1 and G2, multivariate analyses showed that, after adjusting for established prognosticators and total rehospitalizations, the subset of patients with eGFR categories G4 and G5 remained associated with the higher risk of all-cause (hazard ratio [HR] = 1.15, 95% CI: 1.02–1.30, p = 0.020) and CV mortality (HR = 1.20, 95% CI: 1.04–1.39, p = 0.013) (Fig. 2). Patients with eGFR categories G3b and G3a did not show an adjusted increase of risk of all-cause (HR = 0.98, 95% CI: 0.89–1.08, and HR = 1.00, 95% CI: 0.91–1–10, respectively) and CV mortality (HR = 1.02, 95% CI: 0.90–1.15, and HR = 1.02, 95% CI: 0.90–0.17), respectively (Fig. 2).

We registered 9,281, 5,387, and 4,139 total all-cause, CV-related, and HF-related readmissions in 3,145, 2,346, and 1,880 patients during the follow-up, respectively. There was a stepwise increase in the risk of recurrent total

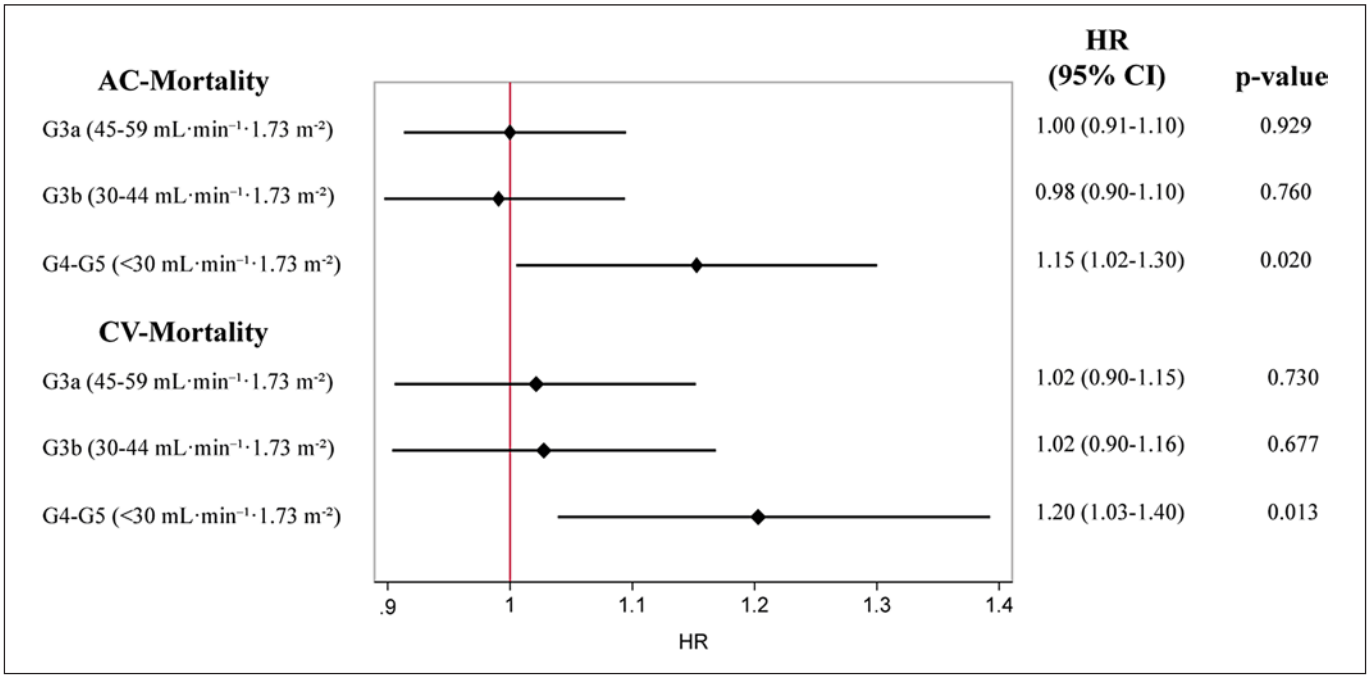

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Fig. 2. Adjusted estimate risk of AC mortality and CV mortality across estimated glomerular filtration rate (eGFR) categories (as defined in the text). AC mortality, all-cause mortality; CV mortality, cardiovascular-related mortality; HR, hazard ratio.

all-cause, CV-related, and HF-related hospitalizations when moving from lower to higher GFR categories (Table 2). Multivariate analyses adjusting for established CV risk factors and controlling for death as a competing event confirmed that the higher the eGFR category, the higher the risk of total all-cause, CV-related, and HF-related readmissions (Fig. 3). Specifically, compared to patients with eGFR categories G1 and G2, those with eGFR categories G4 and G5 displayed a significantly increased risk up to 28%, 26%, and 30% of total all-cause, CV-related, and HF-related readmissions, respectively.

Table 2. Rates of all-cause and the specific cause of readmission across eGFR categories

All-cause readmissions	
G1-G2 (eGFR ≥60 mL·min^{-1}·1.73 m^{-2})	67.5 × 100 person-year
G3a (eGFR 45–59 mL·min^{-1}·1.73 m^{-2})	94.5 × 100 person-year
G3b (eGFR 30–44 mL·min^{-1}·1.73 m^{-2})	113 × 100 person-year
G4-5 (eGFR <30 mL·min^{-1}·1.73 m^{-2})	147 × 100 person-year
CV readmissions	
G1-G2 (eGFR ≥60 mL·min^{-1}·1.73 m^{-2})	38.8 × 100 person-year
G3a (eGFR 45–59 mL·min^{-1}·1.73 m^{-2})	58,2 × person-year
G3b (eGFR 30–44 mL·min^{-1}·1.73 m^{-2})	71,5 × person-year
G4-5 (eGFR <30 mL·min^{-1}·1.73 m^{-2})	92,5 × person-year
HF readmissions	
G1-G2 (eGFR ≥60 mL·min^{-1}·1.73 m^{-2})	29.4 × 100 person-year
G3a (eGFR 45–59 mL·min^{-1}·1.73 m^{-2})	47.1 × 100 person-year
G3b (eGFR 30–44 mL·min^{-1}·1.73 m^{-2})	60.4 × 100 person-year
G4-5 (eGFR <30 mL·min^{-1}·1.73 m^{-2})	78.7 × 100 person-year

eGFR, estimated glomerular filtration rate.

Discussion

In this large contemporary cohort of patients hospitalized for AHF, we identify three major findings: (1) Approximately 12% of patients had eGFR categories G4 and G5 at admission. (2) Patients with eGFR categories G4 and G5 were significantly and independently associated with higher long-term mortality. (3) Despite this increased risk of death, patients with lower eGFR categories on admission (particularly G4 and G5) also had an increased risk of total all-cause, CV-related, and HF-related readmissions.

HF and CKD frequently coexist as a consequence of overlapping pathophysiology (i.e., CRS) [10, 11] or as a result of shared cardiometabolic risk factors that drive both disease states in parallel [12, 13]. In the current study, eGFR categories G4 and G5 at admission were pre-

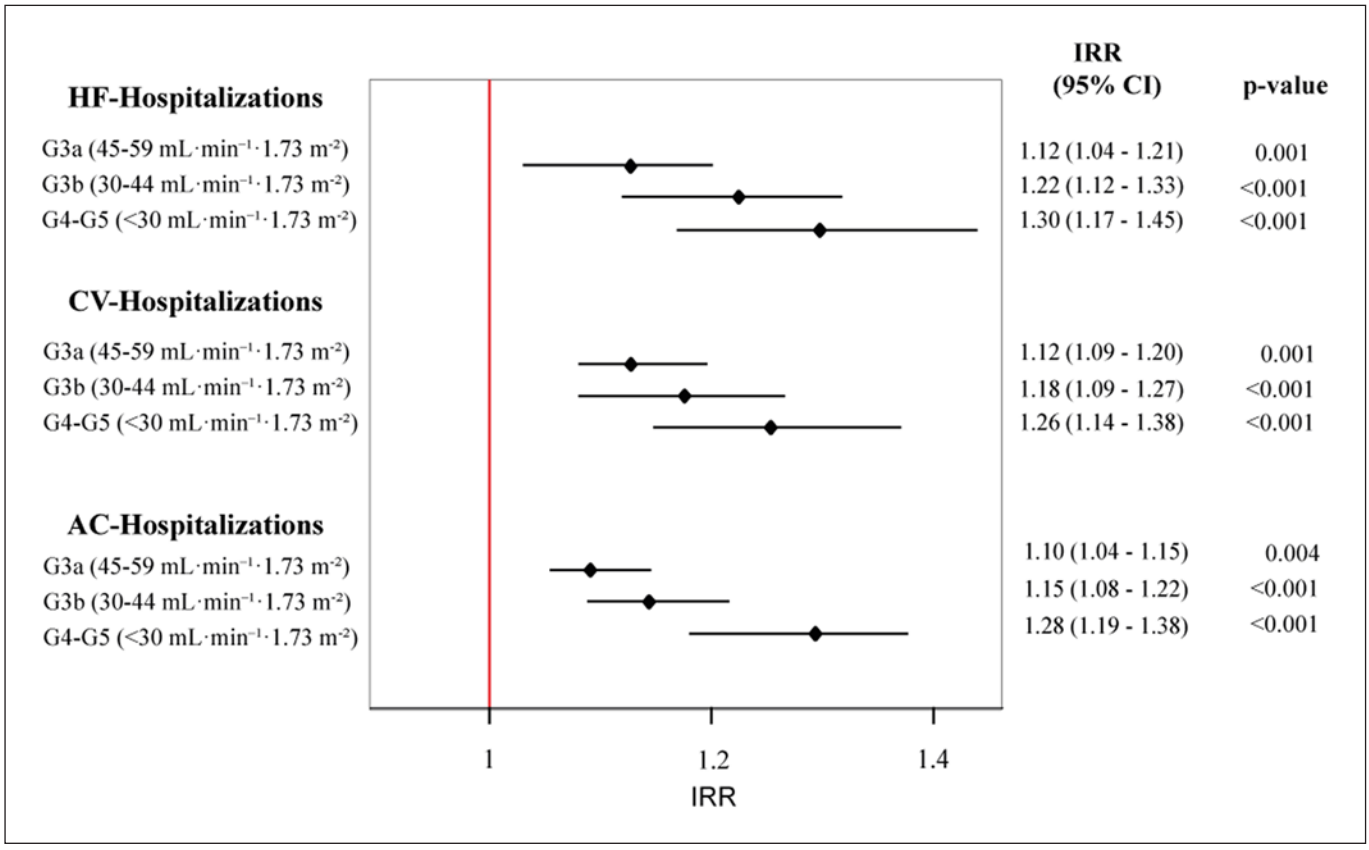

Fig. 3. Adjusted estimate risk of recurrent admissions across estimated glomerular filtration rate (eGFR) categories (as defined in the text). AC hospitalizations, total all-cause readmissions; CV readmissions, cardiovascular-related readmissions; HF readmissions, heart failure-related readmissions; IRR, incidence rate ratio.

dominantly observed in patients with a worst NYHA functional class and higher NT-proBNP values. Although these findings cannot reveal the exact pathophysiological mechanisms behind them, we speculate that some of the connection is related to the inability of the more diseased kidneys to handle the myriad of hemodynamic and non-hemodynamic stressors commonly present in AHF, together with the negative impact of increased left- and right-sided filling pressures on intrarenal hemodynamics. Moreover, patients with eGFR categories G4 and G5 at admission were predominantly female exhibiting a high prevalence of traditional CV risk factors (including T2DM and hypertension) and preserved LVEF. This patient population commonly have a higher prevalence of oxidative stress [14], inflammation [15], and endothelial dysfunction [16], which are well-known risk factors for kidney disease progression [17, 18]. When taken together, our results are consistent with the emerging "cardiorenal phenotype", characterized by CKD, congestion, and preserved LVEF [19].

Some studies have demonstrated that eGFR on admission independently predicts future adverse events in patients hospitalized for AHF [20–22]. Nonetheless, most of the evidence in this field has evaluated the risk using time-to-first-event methods, with AC mortality as the main terminal event [23]. However, patients with AHF and impaired eGFR commonly represent a highly comorbid population with an increased risk of recurrent admissions and in whom non-CV deaths account for a substantial proportion of deaths [24]. In these scenarios, recent initiatives advocate for a more comprehensive approach evaluating disease-specific causes of death and accounting for all hospitalizations during follow-up to provide a more "realistic" picture of the disease burden [25]. To the best of our knowledge, this is the first study evaluating the total morbimortality risk profile of eGFR categories on admission in patients hospitalized for AHF through recurrent events methodology.

Consistent with previous data [23], we also found an increased risk of all-cause and CV-related mortality among

patients with AHF and impaired eGFR. Interestingly, and despite this increased risk of death, patients with AHF and eGFR categories G4 and G5 also showed a higher burden of total all cause (28%), CV related (26%), and HF related (30%) compared to patients with eGFR categories G1 and G2.

There are likely multiple and interdependent mechanisms that may explain this increased morbimortality risk burden. First, patients with the lower eGFR categories showed clinical and biochemical data of a more advanced disease, which may explain the observed increased risk. Second, the management of fluid overload in patients with AHF and eGFR categories G4 and G5 is often challenging because of the higher prevalence of diuretic resistance [26] and the common misinterpretation of creatinine changes during decongestion [5]. For instance, a moderate increase in plasma creatinine during decongestive therapy in a patient with severely impaired eGFR often prompts physicians to reduce diuretic doses, based on the false assumption that further decongestion might accelerate kidney disease or damage [27, 28]. As a result of this "nephroprotective approach," patients with eGFR categories G4 and G5 are prone to be discharged with residual congestion, which is a well-known risk factor for adverse outcomes [29]. Third, in the present cohort, the use of disease-modifying therapies was markedly lower among those with eGFR categories G4 and G5. Even though the often fluctuating and somewhat uncertain trajectory of kidney function after discharge may partially explain the low prescription rates due to concerns for side effects, the lack of solid evidence of benefit from randomized clinical trials in subjects with eGFR categories G4 and G5 is a significant barrier to its use [30]. Furthermore, the perception of limited life expectancy and competing geriatric syndromes commonly present in this patient population may also drive the underutilization of life-saving therapies. Fourth, clinical cardiologists and HF specialists often ignore additional kidney-specific risk factors, such as iron deficiency, disturbances of calcium-phosphate metabolism, and acid-base disorders, which are well-known drivers of CV and kidney disease progression [31–33].

Overall, there is a risk-treatment paradox in the management of patients with AHF and advanced CKD or kidney failure, such that patients with the highest morbimortality burden are treated with lesser disease-modifying medical therapies [34]. Therefore, patients with eGFR categories G4 and G5 suffering from an episode of AHF represent one of the most important subgroups that could benefit from cardiorenal-specific programs aimed to personalize care and reduce readmission and mortality risk burden [35].

Limitations

Our study has several limitations that need to be highlighted: (1) The present study is observational in nature and, consequently, exposed to different types of bias and residual confounding; (2) we included only patients with AHF, so our conclusions do not apply to patients with stable CHF; (3) the adjudication of the specific cause of death and readmissions was mainly done using the patient's chart review of electronic medical records, which may introduce some error in the competing risk estimates; (4) we used only the eGFR as a marker of kidney function, which could limit the study's precision; (5) eGFR at discharge was not available in a substantial proportion of study participants. Accordingly, we could not formally evaluate the differential prognostic value of eGFR categories between the two time-points; and (6) although the results were obtained from a large population at three different tertiary hospitals, further studies are necessary to quantify the morbimortality burden attributable to impaired kidney function in other healthcare scenarios.

Conclusions

In summary, eGFR categories G4 and G5 (representing advanced CKD and kidney failure, respectively) are frequent at admission in patients hospitalized for AHF and are associated with higher long-term mortality and morbidity burdens.

Acknowledgments

The authors thank nurses of the three hospitals.

Statement of Ethics

The study protocol was approved by the Institutional Review Board of the Ethical Committee (approval number: 283) and was conducted in accordance with the principles of the Declaration of Helsinki. All subjects have given their written informed consent.

Conflict of Interest Statement

Rafael de la Espriella, Pau Llàcer, and Julio Núñez received board speaker fees and travel expenses from Novartis, Rovi, Pfizer, Daiichi Sankyo, AstraZeneca, NovoNordisk, Boehringer Ingelheim, and Lilly. Antoni Bayés-Genís reports honoraria for lectures and/or consulting from Abbott, AstraZeneca, Boehringer Ingelheim, Critical Diagnostics, Novartis, Roche Diagnostics, and Vifor. Patricia Palau received board membership fees, speaker fees, and

consulting fees from Boehringer Ingelheim, Menarini, and Novartis. Gema Miñana received speaker fees and travel expenses from Abbott. Enrique Santas received board speaker fees and travel expenses from Novartis, Rovi, Pfizer, Daiichi Sankyo, AstraZeneca, NovoNordisk, and Boehringer Ingelheim. Jose Luís Gorriz received board membership fees, speaker fees, and consulting fees from AstraZeneca, Boehringer-Inglenheim, Lilly, Janssen, Mundipharma, Menarini, and Novonordisk. Javier Díez received board membership fees, speaker fees, and consulting fees from AstraZeneca, Bayer, and Vifor. All other authors declare no competing interests.

Author Contributions

Rafael de la Espriella, Jorge Navarro, and Julio Núlez: conception and design of the study. Julio Núñez and Rafael de la Espriella: analysis and interpretation of data and drafting the article. Anna Mollar, Luis D'Marco, Patricia Palau, Gema Miñana, Pau Llácer, Enrique Santas, Raquel Heredia, and Miguel González: acquisition of data. Antoni Bayés-Genís, José Luis Górriz, Pau Codina, and Javier Díez: revising the article critically for important intellectual content. All authors: final approval of the version to be submitted.

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Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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