The impact of glomerular filtration rate on short-term outcome in elderly patients with heart failure with preserved ejection fraction

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Abstract

Heart failure with preserved ejection fraction is a frequent condition among the elderly. The prevalence of chronic kidney disease is also very high, accounting for 5-10% of the population. The aim of this study was to investigate whether the decrease in renal function, assessed by estimated glomerular filtration rate (eGFR), was an independent predictor of adverse events such as death and new hospitalizations in elderly patients hospitalized with heart failure with preserved ejection fraction.

This study included hospitalized patients diagnosed with heart failure with preserved ejection fraction. Renal function was estimated by calculating glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula. Patients were stratified into two cohorts using the median eGFR value of 45.45 mL/min/1.73 m^2 as the cutoff. During a 3-month follow-up, a total of 30 events were recorded. Multivariate logistic analysis adjusted for confounding factors such as age, gender, anemia, and therapy revealed that eGFR was an independent predictive factor in various models: odds ratio (OR): 0.96, 95% confidence interval (CI) 0.93-0.99, p=0.016; OR: 0.95, 95% CI 0.93-0.98, p=0.003. GFR is an independent predictive factor of short-term events in a population of elderly patients with heart failure with preserved ejection fraction.

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Key words: heart failure, heart failure with preserved ejection fraction; chronic kidney disease.

Contributions: KK, conceptualization; GDC, CDB, investigation, data curation; GG, GT, methodology; GDC, CDB, KK, writing. All authors approved the final version of the manuscript.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: the study protocol was approved by the Institutional Review Board in accordance with the Helsinki Declaration (protocol number 21/06).

Informed consent: participants gave written consent for anonymous clinical data collection.

Patient consent for publication: not applicable.

Availability of data and materials: data will be available upon reasonable request to the corresponding author.

Funding: none.

Received: 28 December 2024.
Accepted: 12 May 2025.

Geriatric Care 2025; 11:13542
doi:10.4081/gc.2025.13542

Introduction

The overall prevalence of heart failure (HF) fluctuates between 0.2% up to 17.7% and the incidence in the population increases with age and doubles for each decade from 40 to 80 years of age, becoming the most frequent cause of hospitalization in people older than 65 years old.[1] The main classification of HF is based on the ejection fraction (EF), that reflects the contractile function of left ventricle, including HF with preserved ejection fraction (HFpEF) (EF≥50%), HF with mildly reduced ejection fraction (EF 40-49%) and HF with reduced ejection fraction (HFrEF) (EF≤40%).[1,2] The signs and symptoms of HF are attributable to venous congestion and peripheral tissue hypoperfusion, and they can combine in several ways in the individual patient to compose different clinical pictures variously determined by the underlying causes.[3] Chronic kidney disease (CKD) refers to the presence of a functional or structural alteration of the kidney, such as proteinuria, morphological alterations on renal biopsy, and alterations on imaging, even in the absence of a reduction in glomerular filtration, documented for at least three months. The prevalence of CKD is also extremely high, accounting for 5-10% of the population.[4,5] CKD is now a global health problem, and the treatment of chronic kidney failure in the dialysis phase has reached remarkably high social costs. The number of patients receiving renal replacement treatment is approximately 1.4 million, with an annual increase of 8%.

According to the National Kidney Foundation, there are 5 stages of CKD based on estimated glomerular filtrate rate (eGFR), from stage 1 with eGFR>90 mL/min to the end-stage renal disease (or stage 5) with eGFR<15 mL/min.[4] Due to the water and salt retention, most of the affected patients are hypertensive and show pleural effusion or pulmonary edema. The diagnosis of CKD is possible when morphological alterations of the kidneys are associated with an increase, even slight, in creatinine values for more than 3 months.

HF and CKD are two pathological conditions that are often connected, so that the term “cardiorenal syndrome” has been coined. There are five types of cardiorenal syndrome, according to whether the primary problem is in the heart (cardiorenal syndrome), the kidneys (reno-cardiac syndrome), or another organ (secondary cardiorenal syndrome), and whether the problem is acute or chronic. Type 1 is the most common and studied type in patients with the co-presence of HF and CKD.[6,7] The prognosis is generally poor, and multiple predictors of mortality and readmission are available to further assess individual patient prognosis, using several variables to predict in-hospital mortality and readmission rate, including urea nitrogen, systolic blood pressure, serum creatinine, brain natriuretic peptide, and response to diuretics.[8,9] Nevertheless, the role of eGFR in the prognosis of patients with acute HFpEF remains poorly understood. Our study aimed to verify whether eGFR was an independent predictor of adverse events such as death and new hospitalizations due to HF during short-term follow-up.

Materials and Methods

Study population

Patients aged 65 years and older, admitted at the Internal Medicine Unit of the Antonio Cardarelli Hospital (Campobasso, Italy) with a diagnosis of acute HFpEF, were screened for enrollment. The inclusion criteria were: i) diagnosis of acute HFpEF; ii) age ≥65 years. The study protocol was approved by the Institutional Review Board in accordance with the Helsinki Declaration, and the participants gave their written consent for anonymous clinical data collection.

Baseline data, including comorbidities such as hypertension, diabetes, atrial fibrillation (AF), dyslipidemia, coronary artery disease (CAD), stroke, chronic obstructive pulmonary disease (COPD), anemia, cancer, CKD, and dementia were recorded. Laboratory parameters based on blood tests were considered, such as hemoglobin (Hbg), white blood cells (WBC), platelets, fibrinogen and N-terminal pro B-type natriuretic peptide (NTproBNP). Regarding therapy, it was evaluated whether patients were taking diuretics (such as furosemide), aldosterone antagonists, β-blockers, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB), and calcium-channel blockers.

Diagnosis of acute heart failure with preserved ejection fraction

Diagnosis for every patient was based on clinical presentation, chest X-ray, echocardiography and NTproBNP elevation.

Renal function

Renal function was estimated through the eGFR obtained with the Chronic Kidney Disease Epidemiology Collaboration formula.

Follow-up

Within 3 months of hospitalization, patients were contacted by phone to determine survival or other hospitalizations for acute HFpEF.

Statistical analysis

Descriptive statistics were presented as numbers, proportions (%), or mean ± standard deviation. Continuous variables were compared using Student’s *t*-tests, while categorical variables were compared using chi-square ($\chi 2$) tests. The population was stratified into two groups based on the median value of eGFR. Logistic regression analysis was performed to identify whether eGFR is associated with events or death in HFpEF patients. Multivariable models adjusted for eGFR were performed to explore and find the association between eGFR and events. Parsimonious criteria were applied in the selection of variables.[10] In model 1, it was adjusted for basic demographics data, such as age and gender; in model 2, major comorbidities were included, such as diabetes and AF; in model 3 were further included such as Hbg and WBC; in model 4, the main therapies have been considered, that are ACEi/ARB and aldosterone antagonists. Odds ratios were analyzed and compared for the events with 95% confidence intervals (CI) in the two groups. Another model including all the above-mentioned variables was also tested. The p-value was considered significant when <0.05. The system used to perform statistical analysis was STATA 16.1.

Results

The population consisted of 102 patients with a mean age of 80.6±9.4 years, 53% of whom were male, and the mean body mass index (BMI) was 27.2±5.4. Regarding the comorbidities, 90 (88.24%) patients had hypertension, 33 (32.35%) were affected by diabetes, 55 (53.92%) had AF, 29 (28.43%) were dyslipidemic, 54 were suffering from COPD, 41 (40.20%) were anemic, 32 (31.37%) had cancer and 24 (23.53%) were affected by dementia. A total of 22 (21.57%) patients had CAD and 13 (12.75%) had a previous stroke. 67.65% (69) of the entire population were smokers. With regards to the New York Heart Association classification of HF, 36 (35.29%) patients belonged to class II, and 66 (64.71%) of them belonged to classes III and IV. Table 1 summarizes the population characteristics, anamnesis data, and comorbidities stratified by eGFR. In a univariate analysis, the population turned out homogeneous for the values of NTproBNP (p=0.76), and EF (p=0.82). Regarding comorbidities, the population was homogeneous for hypertension (p=1.00), diabetes (p=0.14), AF (p=0.16), dyslipidemia (p=0.50), CAD (p=0.63), stroke (p=0.77), COPD (p=0.24), cancer (p=0.40), and dementia (p=0.64). The population resulted homogeneous for smoking too (p=0.30). About therapies, the population was homogeneous for diuretics (p=0.56), aldosterone antagonists (p=0.40), β-blockers (p=0.23), and calcium channel blockers (p=0.30). Lastly, the population resulted homogeneous for BMI (p=0.66) and gender (male, p=0.84). On the other hand, the population resulted heterogeneous for some parameters like: age (p=0.06), Hbg value (p=0.01), anemia (p=0.03), and therapy with ACEi/ARB (p=0.05). Table 2*,* in the same way, contains the data about laboratory tests, clinical measurements and therapy.

Follow-up and multivariate analysis

During the short-term follow-up of 3 months, there were a total of 30 (29.41%) events, including 15 (14.71%) deaths and 15 (14.71%) hospitalizations with a diagnosis of acute HF. Both hospitalizations and deaths were subdivided into the two groups of patients in the same way: 5 (9.80%) patients belonged to the first cohort (eGFR>45.45), and 10 (19.6%) patients belonged to the second cohort (eGFR<45.45). A multivariate logistic regression analysis was conducted by structuring four models, which were all corrected for the eGFR.

Model 1 comprehended age, gender (male), and eGFR, and it showed: odds ratio (OR) 0.96; 95% CI 0.93-0.96; p=0.016. In model 2, comorbidities such as diabetes and AF were included with eGFR, and what came out was: OR 0.95; 95% CI 0.93-0.98; p=0.003.

Table 1. Characteristics of the population stratified by estimated glomerular filtration rate.

	All population n=102	GFR>45.45 (1) n_1=51	GFR≤45.45 (0) n_0=51	p
Age, mean±SD	80.6±9.4	78.8±8.7	82.3±9.8	0.06
BMI, mean±SD	27.2±5.4	27.4±5.5	26.9±5.4	0.66
Male, n (%)	53	26	27	0.84
Comorbidity, n (%)				
Hypertension	90 (88.24)	45 (88.24)	45 (88.24)	1.00
Diabetes	33 (32.35)	13 (25.49)	20 (39.22)	0.14
Atrial fibrillation	55 (53.92)	24 (47.06)	31 (60.78)	0.16
Dyslipidemia	29 (28.43)	13 (25.49)	16 (31.37)	0.50
CAD	22 (21.57)	12 (23.53)	10 (19.61)	0.63
Stroke	13(12.75)	7 (13.73)	6 (11.76)	0.77
COPD	54 (52.94)	30 (58.82)	24 (47.06)	0.24
Anemia	41 (40.20)	15 (29.41)	26 (50.98)	0.03
Cancer	32 (31.37)	18 (35.29)	14 (27.45)	0.40
Dementia	24 (23.53)	11 (21.57)	13 (25.49)	0.64
Events*	30 (29.41)	10 (19.61)	20 (39.22)	0.03
Deaths	15 (14.71)	5 (9.80)	10 (19.61)	0.80
Smoking	69 (67.65)	32 (62.75)	37 (72.55)	0.30
NYHA class, n (%)				
II	36 (35.29)	21 (41.18)	15 (29.41)	0.21
III/IV	66 (64.71)	30 (58.82)	36 (70.59)	

GFR, glomerular filtration rate; BMI, body mass index; SD, standard deviation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association. *As events were considered new hospitalizations within 3 months AND/OR deaths.

Table 2. Laboratory and drug therapy characteristics.

	All population n=102	GFR>45.45 (1) n_1=51	GFR≤45.45 (0) n_0=51	p
SBP, mean±SD	107.3±17.8	108.8±19.8	105.8±15.8	0.42
DBP, mean SD	61.8±13.1	63.3±12.1	60.4±13.8	0.25
HF, mean±SD	86.9±18.1	86.2±18.1	87.7±18.2	0.70
Hbg, mean±SD	11.7±2.1	12.2±2.0	11.2±2.1	0.01
WBC, mean±SD	10.6±4.1	9.9±3.4	11.3±4.6	0.08
PLT, mean±SD	229.3±78.1	231.4±76.8	227.3±80.0	0.78
Fibrinogen, mean±SD	440.3±147.9	443.2±161.1	437.3±134.8	0.84
NTproBNP, mean±SD	5042.9±4869.1	5188.3±5247.4	4897.6±4506.7	0.76
Ejection fraction, mean±SD	54.4±6.3	54.5±6.3	54.2±6.2	0.82
Diuretics (F), n (%)	99 (97.06)	50 (98.04)	49 (96.08)	0.56
Aldosterone antagonists, n (%)	68 (66.67)	36 (70.59)	32 (62.75)	0.40
β-blockers, n (%)	56 (54.90)	31 (60.78)	25 (49.02)	0.23
ACEi/ARB, n (%)	73 (71.57)	41 (80.39)	32 (62.75)	0.05
Calcium channel blockers, n (%)	18 (17.65)	11 (21.57)	7 (13.73)	0.30

Multivariate analysis

	Odds ratio	95% confidence interval	p
Model 1	1.07	1.01-1.14	0.012
Age	0.36	0.13-0.95	0.041
Gender (M)	0.96	0.93-0.99	0.016
eGFR	1.07	1.01-1.14	0.012
Model 2			
DM	0.50	0.18-1.41	0.19
AF	1.50	0.60-3.80	0.37
eGFR	0.95	0.93-0.98	0.003
Model 3			
Hbg	1.06	0.85-1.30	0.57
WBC	1.02	0.92-1.14	0.61
eGFR	0.96	0.93-0.98	0.06
Model 4			
ACEi/ARB	0.89	0.33-2.40	0.83
Aldosterone antagonists	1.90	0.70-5.30	0.20
eGFR	0.95	0.93-0.98	0.03

GFR, glomerular filtration rate; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hbg, hemoglobin; HF, heart failure; WBC, white blood cells; PLT, platelets; NTproBNP, N-terminal pro B-type natriuretic peptide; F, furosemide; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; AF, atrial fibrillation.

In model 3, laboratory parameters such as WBC and Hbg were considered with eGFR, and the results showed: OR 0.96; 94% CI 0.93-0.98; p=0.06.

In model 4, therapies such as ACEi/ARB and aldosterone antagonists with eGFR were considered and the results were: OR 0.95; 95% CI 0.93-0.98; p=0.03. Lastly, in a logistic regression analysis including all variables mentioned in the four models confirmed the independent role of eGFR (p=0.009) (*Supplementary Table 1*).

Discussion

The main finding of the current study is that renal function evaluated by eGFR is an independent predictor of short-term outcome in elderly patients admitted with acute HFpEF. This close correlation might be justified, as explained above, by the bond that exists between HF and kidney disease. A prospective study found a high prevalence of CKD among patients with HF,[11] and renal insufficiency has been suggested as a predictor in patients with HF.[12] Another study tested how the worsening of kidney function during hospitalization due to HF could predict adverse outcomes. The results indicated that renal impairment is common among HF patients and confers increased mortality.[8] The study by Okuno *et al*. aimed to demonstrate the impact of anemia on the prognosis of patients with preserved EF with mild CKD, prospectively examining 523 patients affected by both CKD and HFpEF.[13] The study by Mahone *et al*., instead, aimed to demonstrate the prognostic significance of estimated creatinine clearance (CrCl) related to 6-minute walking test results in patients affected by HF and stated that in outpatients with chronic congestive HF, CrCl predicts all-cause mortality regardless of established clinical, structural, and functional prognostic variables.[14] In addition, it has been reported that the presence of CKD or anemia increased the risk of death in hospitalized patients affected by HF. The association persisted after checking other factors associated with a higher risk of death in the same patients.[15] In line with our results, blood urea nitrogen and GFR were significant predictors of mortality in patients with HFpEF.[16-18] However, it should be mentioned that we focused on elderly patients hospitalized with acute HFpEF.

HFpEF and CKD are interconnected and can exacerbate each other. This analysis specifically examines how the deterioration of kidney function impacts the health of patients already suffering from HF, as well as their quality of life, which is already compromised to varying degrees. It has also been hypothesized that patients with kidney failure have an increased risk of drug toxicity and, therefore, do not get the same benefits from the same drugs that have been shown to be effective in healthier patients enrolled in the studies.[19] Since all the patients in our population are on polypharmacological therapy (as do most elderly patients), this hypothesis seems to be well-founded, even if only therapy with ACEi and/or ARBs showed statistical significance (p=0.05). Other parameters that have been shown to be influential, not surprisingly, were Hbg serum level and the prevalence among patients of anemia (p=0.01 and p=0.03, respectively). We can say that these data were expected because the correlation between Hbg serum levels and kidney function is widely known, as in the juxtaglomerular apparatus of the kidney, there is the production of erythropoietin, which acts as a stimulus to the production and survival of red blood cells. In addition, as reported above, anemia is commonly associated with a worse prognosis in patients with HF.[20,21] The prevalence of anemia is higher in patients with HFpEF.[22] In addition, Hbg levels are lower in HFpEF patients than in HFrEF patients, while eGFR is not significantly different between HFpEF and HFrEF patients.[23] Therefore, anemia has emerged as a crucial factor in patients suffering from concomitant CKD and HFpEF. A limitation of the study may be identified in the small size of sample, and conducted in a single center.

Conclusions

This study demonstrated that eGFR lower than 45.4 mL/min/1.73 m^2 was associated with all-cause death, and hospitalization for HF in elderly patients with HFpEF. Further studies are needed to explore the relationship between worsening renal function and adverse outcomes elderly patients admitted with acute HFpEF.

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Online supplementary material:

Supplementary Table 1. Logistic regression analysis.