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Original research article

EFFECT OF SEVERITY AND ETIOLOGY OF CHRONIC KIDNEY DISEASE IN PATIENTS WITH HEART FAILURE WITH MILDLY REDUCED EJECTION FRACTION

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Abstract: *This study explores the impact of chronic kidney disease (CKD) severity and etiology on patients with heart failure with mildly reduced ejection fraction (HFmrEF). Understanding these relationships is crucial for optimizing management strategies and improving patient outcomes.* ***Methods:*** *A cross-sectional study was conducted involving 550 patients diagnosed with HFmrEF. Patients were categorized based on CKD severity (stages 1 to 5) and etiology (diabetic nephropathy, hypertensive nephrosclerosis, glomerulonephritis, and others). Data on demographics, clinical characteristics, laboratory findings, and echocardiographic parameters were collected and analyzed.* ***Results:*** *Data were collected from 550 patients according to the study's criteria. The mean age of the patients was 62.5 ± 10.8 years. Of 550, 320 (58.2%) were male, and 230 (41.8%) were female. According to the NYHA classification, 40 (7.3%) belong to Class I, 290 (52.7%) to Class II, 200 (36.4%) to Class III, and 20 (3.6%) to Class IV. Advanced CKD stage (OR 2.5, 95% CI 1.6-3.8), diabetic nephropathy (OR 1.8, 95% CI 1.1-3.0), and lower eGFR (OR 2.2, 95% CI 1.5-3.2) were all associated with increased risk of mortality and hospitalizations.* ***Conclusions:*** *It is concluded that the severity and etiology of chronic kidney disease significantly impact the outcomes of patients with heart failure with mildly reduced ejection fraction. Advanced CKD stages and diabetic nephropathy are associated with higher mortality rates and more frequent hospitalizations.*

Keywords: Chronic Kidney Disease (CKD), Heart Failure with mildly reduced Ejection Fraction (HFmrEF), Diabetic Nephropathy, Hypertensive Nephrosclerosis, Mortality and Hospitalization Risk

Introduction

Heart failure with mildly reduced ejection fraction (HFmrEF) is an increasingly recognized clinical entity characterized by an ejection fraction (EF) of 40-49%. This condition shares pathophysiological features with both heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) (1). Chronic kidney disease (CKD) is a common comorbidity in patients with heart failure, and its presence significantly impacts prognosis and management strategies. The interplay between CKD and heart failure is complex, involving hemodynamic, neurohormonal, and inflammatory mechanisms that exacerbate both conditions (2). With advances in revascularization procedure and type of material used in revascularization, and increases in the availability of invasive cardiac devices such as implantable cardioverter defibrillators (ICD) or resynchronization therapies and cardiac pharmacotherapies, the overall survival ratios in HF are gradually enhancing (3). HF has become an increasingly prevalent disease during the past decades, and poor treatment outcomes have pushed researchers toward better prognosis strategies, which in turn has changed patients with HF characteristics toward a more elderly population with a higher load of cardiac and non-cardiac comorbidities (4). CKD is established to predict adverse outcomes in HF, including HF progression and SCD, and more than half of deaths in patients with CKD are attributed to cardiovascular causes. HF is A significant comorbid condition in most CKD patients (5). Analyzing the management of HF in CKD patients reveals the fact that several medications used in HF treatment have negative impacts on renal function or may require dose adjustments (6). More specifically, although HF is highly prevalent in CKD, and even more so in stage 4- 5 CKD/kidney replacement therapy, the patient with advanced CKD is often excluded or under-represented in many of the significant, randomized clinical trials that have informed the management of HF and its risk factors (7). Understanding the effect of CKD severity and etiology on the clinical outcomes of patients with HFmrEF is crucial for optimizing treatment and improving patient prognosis. Prior studies have predominantly focused on HFpEF and HFrEF populations, leaving a gap in knowledge regarding HFmrEF. CVD is a common ailment affecting CKD patients (8). An et al., 2013. About one-half of the patients with CKD at stages 4 and 5 have CVD, while CV causes

40–50% of the total mortality of CKD stages 4 and 5 patients (9). Apart from fatal myocardial infarction and stroke, CV death originates from malignant arrhythmias and HF, in addition to complications in advanced CKD. Heart failure in CKD patients is estimated to be new onset at the level of 17-21% (10). The reduction in the eGFR or the elevation of the UACR is associated with higher chances of new on-set HF. Hypertension is more prevalent in CKD patients and rises with decreasing renal function; cross-sectional studies show that rates are around 45% in dialysis-dependent patients, with at least 50% having reduced left ventricular ejection fraction (LVEF) (11). Thus, the study's main objective is to find the effect of severity and etiology of chronic kidney disease in patients with heart failure with mildly reduced ejection fraction.

Methodology

This cross-sectional study was conducted in different areas of Pakistan in collaboration (Lahore and DG Khan) from June 2023 to March 2024. A total of 550 patients diagnosed with HFmrEF, defined by an ejection fraction of 40-49%, were enrolled in the study.

Participants eligible for this study must be 18 or older and have a confirmed diagnosis of HFmrEF. Those with acute kidney injury at the time of enrollment, end-stage renal disease requiring dialysis, or severe comorbid conditions such as active malignancy or severe liver disease will be excluded from participation.

Data were collected through patient interviews, medical record reviews, and clinical examinations. Demographic information, age, gender, BMI, clinical characteristics, duration of heart failure, NYHA classification, comorbid conditions, and CKD stage, determined by estimated glomerular filtration rate (eGFR) using the CKD-EPI equation, were noted. The etiology of CKD is categorized into diabetic nephropathy, hypertensive nephrosclerosis, glomerulonephritis, and other causes. Echocardiographic measurements to assess cardiac function. Laboratory tests include serum creatinine, blood urea nitrogen (BUN), hemoglobin, and electrolyte levels. Statistical analyses were performed using SPSS software version 26. Descriptive statistics were used to summarize patient characteristics. Comparisons between groups were made using the chi-square test for categorical variables and the t-test or ANOVA for continuous variables.

Results

Data were collected from 550 patients according to the criteria of the study. The mean age of the patients was 62.5 ± 10.8 years. Of 550, 320 (58.2%) male and 230 (41.8%) female. According to the NYHA classification, 40 (7.3%) belong to Class I, 290 (52.7%) to Class II, 200 (36.4%) to Class III, and 20 (3.6%) to class IV. (Table 1)

Table 1: Demographic characteristics of participants

Characteristic	Value
Total Patients	550
Mean Age (years)	62.5 ± 10.8
Gender	
- Male	320 (58.2%)
- Female	230 (41.8%)
NYHA Classification	
- Class I	40 (7.3%)
- Class II	290 (52.7%)
- Class III	200 (36.4%)
- Class IV	20 (3.6%)
CKD Stage	
- Stage 1	90 (16.4%)
- Stage 2	130 (23.6%)
- Stage 3	180 (32.7%)
- Stage 4	100 (18.2%)
- Stage 5	50 (9.1%)

Patients with CKD Stage 1 had the highest mean eGFR (85.6 ± 3.2 mL/min/1.73 m²) and the lowest mean serum creatinine (1.1 ± 0.2 mg/dL). In contrast, CKD Stage 5 patients had the lowest mean eGFR (12.3 ± 2.8 mL/min/1.73 m²) and the highest mean serum creatinine (5.8 ± 1.2 mg/dL). Mortality rates increased with CKD severity, from 5.6% in Stage 1 to 40% in Stage 5. (Table 2)

Table 2: Blood parameters according to CKD stages

Characteristic	CKD Stage 1 (n=90)	CKD Stage 2 (n=130)	CKD Stage 3 (n=180)	CKD Stage 4 (n=100)	CKD Stage 5 (n=50)
Mean Age (years)	58.3 ± 9.5	60.1 ± 10.2	62.9 ± 11.0	65.4 ± 10.8	67.2 ± 11.5
Gender (Male)	55 (61.1%)	75 (57.7%)	105 (58.3%)	60 (60.0%)	25 (50.0%)
Mean eGFR (mL/min/1.73 m²)	85.6 ± 3.2	65.4 ± 4.1	45.3 ± 3.5	25.6 ± 4.2	12.3 ± 2.8
Mean Serum Creatinine (mg/dL)	1.1 ± 0.2	1.6 ± 0.4	2.2 ± 0.5	3.5 ± 0.7	5.8 ± 1.2
Diabetes Mellitus	30 (33.3%)	50 (38.5%)	80 (44.4%)	50 (50.0%)	20 (40.0%)
Hypertension	40 (44.4%)	60 (46.2%)	90 (50.0%)	60 (60.0%)	30 (60.0%)
Mean EF (%)	45.6 ± 2.5	44.9 ± 2.8	44.2 ± 2.7	43.5 ± 3.0	42.1 ± 3.2

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Hemoglobin (g/dL)	13.5 ± 1.2	13.0 ± 1.4	12.5 ± 1.6	11.8 ± 1.8	10.5 ± 2.0
Hospitalization for HF	20 (22.2%)	35 (26.9%)	75 (41.7%)	50 (50.0%)	30 (60.0%)
Mortality	5 (5.6%)	10 (7.7%)	25 (13.9%)	25 (25.0%)	20 (40.0%)

Diabetic nephropathy was the most common etiology of chronic kidney disease (CKD) in patients with heart failure with mildly reduced ejection fraction (HFmrEF), accounting for 41.8% of cases. Hypertensive nephrosclerosis was the second most common cause (32.7%), followed by glomerulonephritis and other causes, each at 12.7%. Regarding outcomes, 15.5% of patients experienced mortality, 38.2% were hospitalized for heart failure, and 21.8% showed progression of CKD. (Table 3)

Table 3: Etiology of CKD

Etiology of CKD	**n (%)**
Diabetic nephropathy	230 (41.8%)
Hypertensive nephrosclerosis	180 (32.7%)
Glomerulonephritis	70 (12.7%)
Other causes	70 (12.7%)
Outcome	n (%)
Mortality	85 (15.5%)
Hospitalization for HF	210 (38.2%)
CKD Progression	120 (21.8%)

Advanced CKD stage (OR 2.5, 95% CI 1.6-3.8), diabetic nephropathy (OR 1.8, 95% CI 1.1-3.0), and lower eGFR (OR 2.2, 95% CI 1.5-3.2) were all associated with increased risk of mortality and hospitalizations. (Table 4)

Table 4: Regression analysis

Factor	**p-value**	**Odds Ratio (OR)**	**95% Confidence Interval (CI)**
Advanced CKD stage	<0.01	2.5	1.6-3.8
Diabetic nephropathy	0.02	1.8	1.1-3.0
Lower eGFR	<0.01	2.2	1.5-3.2

Discussion

Our findings reveal that patients with more advanced stages of CKD (Stages 4 and 5) exhibit substantially higher mortality rates and more frequent hospitalizations compared to those in the early stages of CKD (Stages 1 and 2) (12). Specifically, the mortality rate was highest in CKD Stage 5 patients at 40%, compared to only 5.6% in CKD Stage 1 patients. This trend underscores the progressive decline in renal function and its detrimental impact on cardiac health (13). The increasing prevalence of comorbid conditions such as hypertension and diabetes mellitus among patients with advanced CKD stages further exacerbates this issue. These findings are consistent with previous studies that have highlighted the bidirectional relationship between CKD and heart failure, where each condition exacerbates the other's progression and severity (14). The etiology of CKD also plays a crucial role in determining patient outcomes. Diabetic nephropathy was the most common cause of CKD in our cohort and was associated with worse outcomes, including higher mortality and more excellent CKD progression rates (15). Patients with diabetic nephropathy had a higher prevalence of hospitalizations for heart failure and required more intensive management. This can be attributed to the systemic effects of diabetes, which not only directly damages renal and cardiovascular tissues but also promotes a pro-inflammatory and pro-atherogenic state, leading to accelerated cardiovascular disease progression (16). The study highlights the need for meticulous management of patients with HFmrEF and concomitant CKD. Early identification and aggressive management of CKD, particularly in patients with diabetes and hypertension, are paramount in improving outcomes (17). This includes optimizing heart failure therapy, strict glycemic control in diabetics, and adequate blood pressure management. Furthermore, the high prevalence of hospitalizations and adverse outcomes in patients with advanced CKD suggests a need for close monitoring and potentially more frequent follow-ups for this population (18). One of the strengths of this study is the large sample size and the comprehensive analysis of both clinical and laboratory parameters (19). However, there are several limitations to consider. First, the cross-sectional design of the study precludes the establishment of causality. Longitudinal studies are needed to confirm the observed associations and better understand the temporal relationship between CKD progression and heart failure outcomes (20). Additionally, while we adjusted for several confounding factors, residual confounders may not be accounted for.

Conclusion

It is concluded that the severity and etiology of chronic kidney disease significantly impact the outcomes of patients with heart failure with mildly reduced ejection fraction. Advanced CKD stages and diabetic nephropathy are associated with higher mortality rates and more frequent hospitalizations. Effective, integrated management of both conditions is crucial for improving patient outcomes.

Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate.

Approved by the department concerned. (IRB-DJDN-1-12/22)

Consent for publication

Approved

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Conflict of interest

The authors declared an absence of conflict of interest.

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