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Prevalence of left ventricular dysfunction in stage 3–5 chronic kidney disease among South Indian patients at a secondary health care center

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Abstract:

Left ventricular (LV) dysfunction is a major contributor to morbidity and mortality in chronic kidney disease (CKD). Therefore, it is of interest to determine the prevalence of LV Dysfunction among 195 patients with Stage 3A-5 CKD attending a secondary healthcare centre in South India using clinical evaluation and 2D echocardiography. The majority of patients were in CKD stages 4 and 5 and worsening renal function was significantly correlated with a decline in left ventricular ejection fraction, grades of diastolic dysfunction, E/A and E/e' ratios, deceleration time, haemoglobin levels and serum creatinine levels ($p < 0.05$). Serum sodium and hypertension were not significantly different across stages, whereas diabetes mellitus, oliguria and worsening NYHA functional class were significantly associated with advanced CKD. Thus, data shows the progressive relationship between renal dysfunction and cardiac impairment and underscore the importance of routine echocardiographic screening for early diagnosis and management of LV dysfunction in subjects with CKD.

Keywords: Chronic kidney disease (CKD), diastolic dysfunction, echocardiography, estimated glomerular filtration rate (eGFR), left ventricular dysfunction

Background:

The prevalence of chronic kidney disease (CKD) worldwide is generating a substantial healthcare challenge. Trends indicate a probable further increase in the upcoming years. The worldwide estimate of CKD indicates a prevalence of 850 million individuals [1]. The cardiovascular system is intricately linked to renal functions and it is established that renal impairment can adversely influence cardiac performance, resulting in heart failure, which in turn exacerbates renal function deterioration [2]. The prevalence of cardiovascular disease (CVD) is rising among patients with CKD. CKD may also be identified as an independent risk element for CVD. Therefore, it is imperative to make every effort to prevent the onset of CVD complications during the initial phases of CKD [3]. Left ventricular (LV) systolic dysfunction in chronic kidney disease (CKD) is less prevalent than LV diastolic dysfunction; however, approximately 15% of CKD patients initiating haemodialysis exhibit LV systolic dysfunction. Similar to diastolic dysfunction, left ventricular systolic dysfunction also poses a risk for heart failure in CKD [4]. A dearth of adequate data recording has resulted in a shortage of the prevalence rate associated with CKD in India. Prevalence rates of CKD range from 0.79% to 1.4% in community-based investigations. The research was conducted to identify the third stage of CKD and subsequent stages. In contrast to the reported prevalence, the precise prevalence is determined to be higher. The incidence of end-stage renal disease (ESRD) was estimated to be 160 to 232 per million populations, with an anticipated prevalence rate of 785 to 870 per million populations [5]. The Indian CKD registry was established in 2005 with the intention of acting as a comprehensive national data repository for researching the various facets of CKD. Approximately 63,538 patients were registered in the data house and 74% of them had stage 4 or stage 5 CKD [6]. Individuals with CKD stage 4 have the largest incidence of CVDs, according to the CKD registry (4). The majority of individuals expire before developing ESRD. Due to the mortality from CVD, the majority of people with early stages of CKD do not develop renal failure. CVD is recognised as a

significant competitive outcome or risk associated with kidney failure. Early-stage approaches to avert the onset and advancement of LV dysfunction will prove more efficacious. Early identification, constant monitoring and proper care in the first phases mitigate morbidity and mortality associated with CVD in CKD patients. CVD can be related to any stage of CKD, but individuals in Stage 1 and Stage 2 are typically asymptomatic [7]. The mortality rate is elevated in patients undergoing renal replacement therapy, approximately 30 times greater in individuals with ESRD. Echocardiography offers a straightforward and non-invasive technique for evaluating LV structure and function, facilitating the early identification of those at risk for severe CVD complications in CKD [8]. Therefore, it is of interest to report the prevalence of left ventricular (LV) diastolic and systolic dysfunction across different stages of chronic kidney disease (CKD). We also assessed various parameters, including E/A, E/e', E wave deceleration time, isovolumetric relaxation time (IVRT), left ventricular ejection fraction (LVEF) and percentage fractional shortening (%FS).

Materials and Methods:

This cross-sectional study was performed following approval from the institutional ethics committee among CKD patients receiving outpatient and inpatient care in the medicine and nephrology departments of Christian Fellowship Hospital, Oddanchatram, Dindigul, Tamil Nadu, and South India. The facility is a 299-bed secondary-level healthcare institution, serving low- and middle-socioeconomic populations in surrounding communities, with a daily outpatient volume averaging between 800 and 1000 patients. All participants in the study provided informed consent. The duration of the investigation was one year. This study covered all diagnosed cases of CKD as defined by the National Kidney Foundation. Cases were categorised into various phases of CKD according to the estimated glomerular filtration rate (eGFR). The eGFR was computed utilising the CKD-EPI equation. The inclusion criteria encompassed patients over 18 years of age, of either sex, with

confirmed CKD) characterised by one or more of the following: symptoms and signs of renal disease persisting for over 3 months, proteinuria exceeding 1g/dl, ultrasonographic evidence of renal impairment, diminished creatinine clearance (eGFR) indicative of CKD, individuals who have not undergone any renal replacement therapy and patients classified within CKD stages 3 to 5 according to the CKD-EPI equation. The exclusion criteria encompassed patients with pre-existing cardiac conditions, including rheumatic valvular heart disease, congenital heart disease, coronary heart disease and cardiomyopathy, as well as individuals undergoing dialysis or those who have received kidney transplants and patients with a recent history of circulatory collapse, such as shock or dehydration. The sample size was determined from a previous study [9] utilising the method $N = Zpq/L^2$, with a prevalence of $p=67.2\%$, $q=32.8\%$, margin of error $L=10\%$ and $Z=1.96$. The projected sample size was 195. A pre-established proforma was utilised to gather the demographic and clinical information of the patients. The evaluation of symptoms and activity levels was conducted using the NYHA classification. Blood tests were conducted and echocardiography was executed following established guidelines: patients with an ejection fraction (EF) below 55% were classified as having left ventricular (LV) systolic dysfunction, while diastolic dysfunction was assessed based on the ratio of early (E) to late (A) transmitral flow velocities (E/A ratio). The E/E' and E deceleration time (DT) were assessed and classified as grade 1 for an E/A ratio below 0.8, grade 2 for an E/A ratio between 0.8 and 1.5 and grade 3 for a value above 2.0.

Statistical analysis:

The SPSS software (Statistical Packages for Social Sciences Version 24.0) was utilised for statistical analysis. Means $\pm$ standard deviations (SD) of various parameters under study were calculated. The Chi-square or Fisher's exact test was used to evaluate the categorical variables and ANOVA was applied to analyse the quantitative variables at a 5% significance level.

Results:

The participants ($n=195$) ranged in age from 32 to 76 years. The average age of the sample population was 54.53 ± 9.63 years, indicating that the majority of the participants were middle-aged to older adults, which is in line with the typical age profile of those with CKD. The 61–70 years age group had the largest proportion of participants (62 participants, 31.8%), followed closely by the 51–60 years age group (61 participants, 31.3%) and the 41–50 years age group (57 participants, 29.2%). Only 13 participants (6.7%) were in the 31–40 year age group and 2 participants (1.0%) were between 71 to 80 years of age. The majority of participants were in Stage 5 CKD ($n=68$), followed by Stage 4 ($n=65$), Stage 3B ($n=52$) and Stage 3A ($n=10$). Stage 5 CKD was more common in the age group 61–70 years (25 participants), whereas Stage 4 CKD was more common in the age groups 51–60 and 61–70 years (24 and 23 participants, respectively). However, the association between age group and CKD stage was not statistically significant (Chi-square test, $p=0.069$), suggesting that CKD stages were not significantly

different across age categories in the study population. But with the increase in age, the stage of CKD increases, but it is not significant. The study included 195 participants, 129 (66.2%) males and 66 (33.8%) females, with male predominance in patients with CKD. Stage 5 had the highest proportion of females (30 participants) followed by Stage 4 (21 participants), Stage 3B (10 participants) and Stage 3A (5 participants). There were 44 Stage 4 and 3B males, 38 in Stage 5 and 5 in Stage 3A. Most of the CKD stages had a predominance of males, but the proportion of females increased in the advanced stages, particularly in Stage 5. Sex and CKD stage were statistically significantly associated (Chi-square test, $p = 0.024$), which means that the distribution of CKD stages was statistically significantly different between male and female participants. The highest proportion was stage 5 CKD (34.9%, $n=68$) followed closely by stage 4 (33.3%, $n=65$). Stage 3B had 52 participants (26.7%) and the least number of participants was in Stage 3A with only 10 participants (5.1%). In general, most of the study population (68.2%) were in the advanced stages of CKD (Stages 4 and 5). This finding indicates that most of the patients had severe renal impairment at the time of evaluation. The distribution of CKD stages in this study reveals that most of the study participants have advanced CKD. There was a significant association between the NYHA functional class and CKD stage ($p=0.003$). Subjects with Stage 4 and Stage 5 CKD had a higher proportion of NYHA Class II and III breathlessness, indicating worsening functional limitation with progression of stages of chronic kidney disease (**Table 1**). The clinical characteristics of patients with CKD show that only 4.6% reported chest pain, which was not significantly related to CKD stage ($p = 0.061$). Oliguria, observed in 5.6% of patients, was notably more prevalent in Stage 5 ($p=0.002$). Other symptoms were reported by 81.0% of patients without significant differences across stages ($p=0.101$). Diabetes mellitus occurred in 42.6% of patients and was significantly associated with advancing CKD ($p=0.004$), particularly in Stages 4 and 5. Though hypertension was common (67.7%), its distribution did not significantly vary with CKD stage ($p=0.174$) (**Table 2**). Thus, oliguria and diabetes mellitus are the key characteristics linked to worsening CKD stage. Laboratory and echocardiographic parameters reveal significant changes in CKD stages (**Table 3**). Haemoglobin levels decreased markedly with advancing stages ($p=0.0001$), while serum creatinine rose from 1.56 mg/dL in stage 3A to 7.04 mg/dL in stage 5 ($p=0.0001$). The eGFR also declined from 51.46 mL/min/1.73 m² in stage 3A to 9.28 mL/min/1.73 m² in stage 5 ($p=0.0001$). Serum potassium increased ($p=0.0001$), though serum sodium continued to be stable ($p=0.62$). Echocardiographic ally, left ventricular ejection fraction decreased from 57% in stage 3A to 43.51% in stage 5, along with significant changes in the E/A and E/e' ratios and DT ($p=0.0001$). Thus, CKD progression correlates with worsening renal function, anaemia, hyperkalaemia and left ventricular dysfunction. (**Table 4**) illustrates a significant correlation between the severity of LV diastolic dysfunction and the stage of CKD. Most subjects with normal diastolic function (Grade 0) were in Stage 3A, while mild dysfunction (Grade 1) was

common in Stages 3A and 3B. Diastolic dysfunction severity escalated with CKD progression; Grade 2 was more frequent in Stage 4 and Grades 3 and 4 were primarily found in Stages 4 and 5. Notably, 26 out of 30 patients with Grade 4 dysfunction were in Stage 5 CKD, highlighting the progressive effect of renal failure on cardiac function (p=0.0001). (Table 5) presents a comparison of laboratory and echocardiographic parameters against levels of LV dysfunction. As LV dysfunction grades rise, haemoglobin levels significantly decrease (p = 0.007), especially in severe cases. Renal function worsens, indicated by a rise in serum creatinine from 1.85 mg/dL in Grade 0 to 6.42 mg/dL in Grade 4 (p = 0.0001) and a reduction in eGFR from 41.55 to 10.26 mL/min/1.73 m² (p = 0.0001). There are no significant differences in serum sodium (p=0.858) and potassium (p=0.085) with LV dysfunction grades. Echocardiographic parameters deteriorate with advancing LV dysfunction: LVEF decreases from 55.82% to 41.80% (p = 0.0001) and both E/A and E/e' ratios increase significantly (p = 0.0001), indicating diastolic dysfunction and elevated filling pressures. Additionally, DT decreases significantly with worsening LV dysfunction (p=0.0001). In summary, echocardiographic changes, renal deterioration and decreased haemoglobin are significantly linked to worsening LV dysfunction, while serum electrolyte levels remain stable.

Table 1: NYHA grading of breathing difficulty in stages of CKD

Stage	Breathing difficulty-NYHA			Total	p-value
	1	2	3		
3A	5	5	0	10	0.003**
3B	25	24	3	52	
4	20	34	11	65	
5	18	38	12	68	
Total	68	101	26	195	

**highly significant (Fisher's exact test)

Table 2: Clinical characteristics of the sample population with different stages of CKD

		Stages				Total	p-value (Fisher's exact test)
		3A	3B	4	5		
Chest pain	No	9	51	62	64	186	0.0611
	Yes	1	1	3	4	9	
	Total	10	52	65	68	195	
Oliguria	No	9	51	65	59	184	0.002**
	Yes	1	1	0	9	11	
	Total	10	52	65	68	195	
Other symptoms	No	2	15	7	13	37	0.101
	Yes	8	37	58	55	158	
	Total	10	52	65	68	195	
Diabetes mellitus	No	3	38	29	42	112	0.004**
	Yes	7	14	36	26	83	
	Total	10	52	65	68	195	
Hypertension	No	5	13	26	19	63	0.174
	Yes	5	39	39	49	132	
	Total	10	52	65	132	195	

**highly significant

Table 3: Laboratory and echo parameters in stages of CKD

Variable	Stage	N	Mean	SD	p-value (ANOVA)
Haemoglobin	3A	10	9.790	2.3569	0.0001**
	3B	52	10.39	2.7138	
	4	65	9.925	2.0844	
	5	68	9.029	2.1430	
Serum creatinine	3A	10	1.56	0.8531	0.0001**

Sodium	3B	52	1.967	1.0836	0.62
	4	65	3.16	1.235	
	5	68	7.041	1.778	
	3A	10	136.2	4.876	
Potassium	3B	52	134.10	4.943	0.0001**
	4	65	134.37	5.235	
	5	68	134.22	5.510	
	3A	10	4.31	0.5231	
eGFR	3B	52	4.288	0.6327	0.0001**
	4	65	4.292	0.4744	
	5	68	4.722	0.5637	
	3A	10	51.46	5.2634	
LVEF	3B	52	38.17	7.7254	0.0001**
	4	65	21.06	8.9311	
	5	68	9.28	8.5026	
	3A	10	57.00	6.1124	
E/A ratio	3B	52	52.90	6.9833	0.0001**
	4	65	49.06	6.7780	
	5	68	43.51	6.3586	
	3A	10	1.009	0.224	
DT	3B	52	1.1092	0.5783	0.0001**
	4	65	1.7593	0.3675	
	5	68	2.1250	0.2947	
	3A	10	196.67	3.825	
E/e'	3B	52	196.05	4.157	0.0001**
	4	65	159.83	4.830	
	5	68	142.71	5.452	
	3A	10	7.525	1.416	
	3B	52	6.8963	1.547	0.0001**
	4	65	12.6768	1.496	
	5	68	14.4741	1.327	

**highly significant

Table 4: Diastolic dysfunction among stages of CKD

Grade of diastolic dysfunction	Stages of CKD				Total	p-value
	3A	3B	4	5		
0	1	10	0	0	11	0.0001**
1	6	27	2	1	36	
2	3	13	29	6	51	
3	0	2	30	35	67	
4	0	0	4	26	30	
Total	10	52	65	68	195	

**highly significant (Fisher's exact test)

Table 5: Laboratory parameters and echo parameters with grades of diastolic dysfunction

Variable	Grade	N	Mean	SD	p-value (ANOVA)
Haemoglobin	0	11	9.036	2.136	0.007**
	1	36	10.303	2.4173	
	2	51	10.384	2.3515	
	3	67	9.434	2.0879	
Serum creatinine	4	30	8.843	1.7324	0.0001**
	0	11	1.845	0.3078	
	1	36	2.103	0.8587	
	2	51	3.073	1.3458	
Sodium	3	67	5.324	3.4767	0.858
	4	30	6.423	2.9721	
	0	11	134.27	5.551	
	1	36	134.61	5.117	
Potassium	2	51	134.29	4.687	0.085
	3	67	134.61	4.499	
	4	30	133.50	4.167	
	0	11	4.427	0.6769	
eGFR	1	36	4.358	0.5823	0.0001**
	2	51	4.333	0.6677	
	3	67	4.433	0.6799	
	4	30	4.753	0.7619	
	0	11	41.55	5.492	0.0001**
	1	36	38.50	10.188	
	2	51	25.70	11.431	
	3	67	15.41	7.806	
	4	30	10.26	4.598	

LVEF	0	11	55.82	6.509	0.0001**
	1	36	53.11	7.273	
	2	51	51.31	8.123	
	3	67	45.85	7.102	
	4	30	41.80	8.219	
E/A ratio	0	11	1.7482	2.44149	0.0001**
	1	36	.7175	0.20110	
	2	51	1.2529	0.1490	
	3	67	2.2004	0.19012	
	4	30	2.3413	0.22730	
DT	0	11	199.47	2.4210	0.0001**
	1	36	207.31	3.838	
	2	51	178.76	9.262	
	3	67	139.87	6.939	
	4	30	138.20	8.083	
E/e'	0	11	3.4618	1.74067	0.0001**
	1	36	6.2136	1.92173	
	2	51	10.0427	1.63897	
	3	67	14.7364	1.37167	
	4	30	16.0267	.66011	

**highly significant

Discussion:

CKD is strongly associated with CVD, which remains the main cause of morbidity and mortality in patients with CKD. Progressive loss of renal function leads to structural and functional changes in the heart from hypertension, chronic volume overload, anaemia, activation of the renin-angiotensin-aldosterone pathway, sympathetic over activity, chronic inflammation, oxidative stress and myocardial fibrosis, resulting in the development of LV dysfunction [10, 11]. The current study evaluated the prevalence of LV dysfunction among patients with Stage 3A-5 CKD attending a secondary healthcare centre in South India and showed that the severity of cardiac dysfunction significantly upsurged with advancing CKD stage. The average age of the study sample was 54.53 ± 9.63 years and most of the patients in the 51-70-year age group. This finding agrees with recent epidemiological studies that showed CKD predominantly affects middle-aged and elderly people due to the rising prevalence of diabetes mellitus, hypertension and age-related nephron loss [10, 12]. Although age was insignificantly associated with CKD stage in the present study, advancing age is known as an independent risk element for myocardial remodelling, arterial stiffness and impaired ventricular relaxation and thus is associated with an increased likelihood of LV dysfunction [11]. The study sample consisted of 66.2% males, which is comparable to the findings reported in previous Indian hospital-based studies [13]. Male sex has been linked to faster CKD progression due to a higher burden of CVD risk components and lifestyle-related comorbidities. However, females were relatively more in number in the Stage 5 CKD patients in the present study and hence a statistically significant association of sex with CKD stage was found. Similar findings have been reported in recent cross-sectional studies, although gender-related differences in CKD progression remain controversial [13, 14]. The findings of this investigation suggested that the worse the CKD stage, the worse the NYHA functional class and that patient with Stage 4 and Stage 5 CKD were more likely to have NYHA Class II and III dyspnoea. This finding is consistent with recent evidence demonstrating that progressive renal dysfunction is associated with increasing

symptoms of heart failure and reduced functional capacity as a result of worsening LV systolic and diastolic dysfunction [11, 13 and 15]. The present study found that more than two-thirds (68.2%) of patients had Stage 4 or Stage 5 CKD, which is an important observation. This suggests late presentation of patients to healthcare facilities, which is a finding that has been widely reported in developing countries where routine CKD screening is limited [10, 16]. Late referral puts patients at risk for prolonged cardiovascular risk and the development of structural myocardial abnormalities before nephrology referral. Oliguria among the clinical features assessed had a significant association with the CKD stage, with the majority of the cases occurring in Stage 5 disease. Oliguria is a sign of severe nephron loss and progressive decline of glomerular filtration rate leading to fluid retention, ventricular volume overload and worsening of cardiac function [11]. As well, diabetes mellitus was also significantly associated with advanced CKD in this study. Diabetes is the most common cause of CKD globally and causes LV dysfunction through diabetic cardiomyopathy, endothelial dysfunction, myocardial fibrosis and accelerated atherosclerosis [10, 17]. Hypertension was present in nearly two-thirds of the patients, but its distribution was not significantly different across CKD stages, probably because hypertension occurs early in CKD and persists throughout the disease course. Laboratory studies showed a progressive decline in renal function with the progression of CKD. We observed statistically significant increases in serum creatinine from 1.56 mg/dL in stage 3A to 7.04 mg/dL in stage 5 and a statistically significant decline in eGFR from 51.46 to 9.28 mL/min/1.73 m². These results are expected and very similar to the progression of renal disease [10]. CKD stage progressed and haemoglobin levels decreased significantly, which was consistent with the progression of renal anaemia due to the impaired production of erythropoietin. Renal anaemia causes increased cardiac work, left ventricular hypertrophy, myocardial hypoxia and subsequent ventricular dysfunction [18]. Serum sodium levels were not significantly changed across CKD stages, but serum potassium levels increased significantly in Stage 5 disease, consistent with impaired renal potassium excretion in advanced renal failure [10]. This study showed progressive worsening of echocardiographic parameters as the CKD stage worsened. The LVEF decreased significantly from 57.0% in Stage 3A to 43.51% in Stage 5, consistent with the progressive development of systolic dysfunction. Significant increases in the E/A ratio and E/e' ratio and a significant decrease in DT at the same time suggested deterioration of diastolic function and increased LV filling pressures. Recently, echocardiographic studies have reported similar findings, showing a higher prevalence of systolic and diastolic dysfunction with worsening renal function [13, 14 and 19]. One of the important results of the present investigation was the significant association between the stage of CKD and the grade of diastolic dysfunction. Stage 3A CKD was mainly normal diastolic function and Stages 4 and 5 CKD were mainly Grade 3 and Grade 4 diastolic dysfunction. This is consistent with previous findings that diastolic dysfunction is frequently the first sign of uremic cardiomyopathy and precedes

overt systolic dysfunction [11, 14]. Declining renal function is associated with impaired myocardial relaxation due to progressive myocardial fibrosis, chronic pressure overload, vascular calcification and increased ventricular stiffness [11, 19]. In the current study, we found that higher grades of LV dysfunction were significantly associated with decreased haemoglobin levels, increased serum creatinine, decreased eGFR, decreased LVEF, increased E/A ratio and E/e' ratio and shortening of DT. The results suggest that progressive deterioration of both systolic and diastolic ventricular function may be strongly related to the progression of renal failure. Similar associations have been shown in recent observational studies and systematic reviews evaluating cardiovascular abnormalities across CKD stages [19-21]. The results of this study have important clinical implications. Because cardiac dysfunction develops slowly with deterioration of renal function and may be asymptomatic in early stages, screening with echocardiography should be routinely considered in patients with Stage 3 CKD or greater. If LV dysfunction is detected early, blood pressure control can be optimised early, anaemia can be corrected, glycemia can be managed and cardioprotective therapies can be instituted, thereby reducing cardiovascular morbidity and mortality [10, 11]. The present study offers valuable data from a secondary health care centre in South India, where evidence regarding cardiovascular manifestations of CKD is limited. However, the cross-sectional design limits the causal inference and the progression of subclinical myocardial dysfunction needs to be better characterised by longitudinal multicentre studies with advanced echocardiographic techniques such as speckle-tracking strain imaging. Overall, the present investigation demonstrated that progressive CKD is associated with a significant decline in renal function, worsening anaemia, progressive impairment of systolic and diastolic ventricular function and increasing severity of LV dysfunction. These results emphasise the necessity of incorporating routine echocardiographic evaluation in the standard workup of patients with Stage 3-5 CKD for early detection and prompt intervention.

Conclusion:

LV dysfunction was highly prevalent among subjects with Stage 3-5 CKD and increased significantly with advancing CKD stage. Lower haemoglobin levels and higher serum potassium concentrations were also significantly associated with advanced CKD and greater cardiac dysfunction. Diabetes mellitus and

oliguria showed significant associations with CKD progression, highlighting their role as important clinical indicators of advanced disease.

Advancement to knowledge:

The study findings suggest a progressive link between kidney disease and cardiac dysfunction, highlighting the need for routine echocardiographic screening to enable early detection and management of LV dysfunction in CKD patients.

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