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Original Article

Study to Determine the Average Time Taken to Reach End Stage Renal Disease from Mild or Moderate Stages with Different Risk Factors in Chronic Kidney Disease Patients

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ABSTRACT

Background: Chronic Kidney Disease (CKD) is a growing global burden that presents a myriad of complications and is a leading cause of mortality. There are limited studies from India on prognosis of CKD. Our aim was to identify the risk factors associated with CKD prognosis and to determine the average time taken for progression to End Stage Renal Disease or Renal Replacement Therapy from mild or moderate stages with different risk factors. **Materials and Methods:** It was a retrospective study based on patient data over a period of six years (2015-2020). Patients diagnosed with CKD admitted under Nephrology department were included while those with cancer or autoimmune disorders were excluded. **Results:** Among 103 patients' data analysed comprising of adult population 71%, there was a male preponderance of 69%, and 62.14% of patients were in CKD stages 4 and 5. A comparison of the first and latest visit showed a significant association for BMI, hemoglobin, uric acid, urine albumin, and serum creatinine. The average time taken for progression from stage 2 to 5 of CKD was 49.5 months, stage 3 to 5 was 33.95 months and stage 4 to 5 were 24.54 months. Hypertension was the most common comorbidity. **Conclusion:** With the prognosis of CKD being definitive and the time taken for ESRD shortens as the patient reaches higher stages, paramount efforts to delay progression and a need for patient-centred care in the early stages are undeniable.

Keywords: Chronic Kidney Disease, Risk Factors, Average Time for Progression.

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INTRODUCTION

In 2017, The Lancet stated that the global prevalence of CKD was 679.5 million and in India alone 115.1 million cases.[1] Over the past few years, there has been an increase in these numbers and is still counting. Most CKD patients eventually develop End Stage Renal Disease (ESRD) or will die from related complications. Patients with ESRD eventually depend on RRT (on-going dialysis or kidney transplantation) for survival.[2]

The number of cases of chronic kidney disease is increasing, especially in a developing country like India.[3] Many complications arise in relation to CKD. Beyond a level of decline in renal function, the rate of progression from early stages of CKD to ESRD is accelerated. The irreversible loss of kidney function is a debilitating health condition, and the cost of treatment adds to the economic burden as well.[4] CKD is a topic of prime importance that must be adequately addressed.

The need for therapies to slow down the progression is critical. The development of more novel and effective diagnostic and therapeutic approaches is essential to improve the quality of life and prognosis of CKD patients in India.[5]

An international group of patients with advanced CKD, were studied to propose a surrogate endpoint which could be suitable for assessing CKD progression in diverse clinical settings. They found that different subgroups had varying results for surrogate endpoints. The study provides evidence supporting the potential use of combined surrogate endpoints in CKD that can be useful for evaluating new treatments in clinical practise.[6]

A time-centred approach to understanding risk factor for the progression of CKD to estimate person-specific trajectories of function, and used these trajectories to estimate time spent in each CKD stages.[7] A heterogeneous interplay of risk factors associated with rapid linear CKD progression and mortality in patients with CKD. Rapid progressors had an annual rate of mortality or ESRD of 47 per 100 patients compared with 6 per 100 stable patients.[8]

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This study focuses on the average time taken to progress to the end stage so as to understand risk factors and implement screening of at-risk populations for early detection and initiate treatment of modifiable risk factors for ESRD. Intervening in the early stages of renal disease aids in addressing the problem at the earliest and will provide a clinical chance of reducing the progression.

MATERIALS AND METHODS

Study design

A Retrospective observational study was carried out from data over a period of six years (2015-2020) in a tertiary care hospital. The Data collection was carried out from December 2021 to May 2022.

Table 1: Baseline and latest characteristics of sample according to CKD stage.

	CKD STAGE						
	Stage 1	**Stage 2**	**Stage 3a**	**Stage 3b**	**Stage 4**	**Stage 5**	***p***
First visit							
Total Participants	3	8	10	18	30	34	
Age (years)	48.00±3.46	57.38±14.39	55.60±19.27	53.89±13.12	55.77±13.20	54.82±15.36	0.952
BMI (kg/m^2)	24.13±3.38	25.64±3.73	23.19±3.99	23.54±2.56	24.35±3.36	28.23±18.31	0.629
Length of stay (days)	7.33±5.86	3.88±2.64	5.40±2.95	3.44±1.54	6.20±5.77	4.26±3.66	0.183
Neutrophil (%)	61.67±9.50	69.63±12.22	75.00±15.73	69.22±12.85	71.73±11.61	75.44±15.81	0.401
ESR (mm/hr)	21.00±11.53	56.75±20.20	41.70±36.39	32.83±28.48	47.77±38.94	63.03±38.51	< 0.05
Hb (g/dl)	14.03±1.67	11.94±1.28	10.99±3.02	12.10±1.73	10.70±1.69	9.11±1.94	< 0.001
Uric acid (mg/dl)	3.50±.87	3.64±0.59	4.15±2.06	5.53±2.32	6.90±3.30	6.72±2.00	< 0.001
Urine Albumin (mg/dl)	0.38±0.54	0.50±0.53	0.97±1.41	0.48±0.63	0.91±0.99	0.55±1.06	0.493
Creatinine (mg/dl)	0.67±0.06	0.95±0.21	1.47±0.11	1.84±0.31	2.99±0.73	6.56±3.36	< 0.001
Latest visit							
Total Participants	0	4	2	4	13	80	
Age (years)		62.25±12.84	63.00±5.66	38±13.11	64.33±9.32	56.90±14.58	0.053
BMI (kg/m^2)		25.17±4.29	26.6±0.71	5.33±2.08	8.00±6.95	3.72±2.76	0.054
Length of stay (days)		9.50±9.47	6.50±0.71	5.33±2.08	8.00±6.95	3.72±2.76	< 0.001
Neutrophil (%)		67.25±17.6	66.00±12.73	72.00±20.66	82.17±12.66	76.46±13.11	0.239
ESR (mm/hr)		41.00±49.20	27.00±9.90	31.00±25.00	52.83±36.42	54.19±37.42	0.651
Hb (g/dl)		11.88±2.72	11.35±1.77	10.53±1.75	10.00±1.89	9.08±21.6	< 0.05
Uric acid (mg/dl)		6.90±2.68	10.70±1.56	6.53±0.38	6.71±2.19	6.75±1.67	< 0.05
Urine Albumin (mg/dl)		25.25±49.17	49.50±70	33.67±56.58	25.50±44.33	26.39±42.88	0.959
Creatinine (mg/dl)		1.24±0.31	1.42±0.04	1.84±0.25	2.77±0.77	7.13±3.20	< 0.001

Data Collection Procedure

Data pertinent to the study including demographic details, stages of CKD, risk factors, complications and time taken for progression to ESRD or RRT, were collected from patient records and electronic records from Mediware and recorded using a pre-designed data collection form. The data was compiled in Microsoft excel.

Sampling Method

The sample size was calculated using Cochran's formula. The required sample size was calculated to be 94. A total of 103 patients' data were analysed.

Study population

Patients diagnosed with CKD admitted under Nephrology department were included while those with cancer or autoimmune disorders were excluded.

Statistical Analysis

IBM SPSS 25 was used for statistical analysis. ANOVA tests for continuous variables were used. For comparison Wilcoxson Signed Rank Test and McNemar Test were used. Analyses at 5% level of statistical significance ($p < 0.05$) were considered significant.

RESULTS

A total of 103 patients were included in the study. About 71% of study population comprised of adults. There was a male preponderance 71 (69%). Out of 71 male patients, 42 (59.1%) were in later stages of CKD (Stage4 and Stage 5) and among the 32 female patients 22 (68.7%) were in Stages 4 and 5. Mean age of the population was 55.01± 14.28 years with a range of 22-79 years.

Baseline and latest visit characteristics of sample population (n=103) were analysed using One-Way ANOVA in first visit and latest visit (Table 1) Haemoglobin, ESR, uric acid and serum creatinine levels were significantly associated to stage of CKD, and as the stages progressed, in latest visit, haemoglobin, uric acid, and serum creatinine levels were significant. Then Wilcoxon signed rank test was used to compare first visit and latest visit which showed a significant association for Stages of CKD with BMI, platelet count, Neutrophil count, Haemoglobin, uric acid, urine albumin and serum creatinine (Table 2).

Average time taken for progression

Among the study population, 61 patients showed progression in stage of CKD. Twenty-six patients showed progression from stage 4 to 5. Nineteen patients showed progression from stage 3 to 5. Only 2 patients progressed from stage 2 to 5 and 1

Table 2: Comparison of baseline and latest characteristics of sample.

Characteristics (Latest visit – First visit) (n=103)	Negative Ranks	Positive Ranks	Ties	p
Stage of CKD	6	61	36	< 0.001
Length of stay (days)	48	39	16	0.458
Age (years)	0	98	5	< 0.001
BMI (kg/m^2)	29	62	12	< 0.001
Total count (4000-11000/mm)	56	47	0	0.940
Platelet count (1.4-4 lakh/m)	61	36	6	< 0.05
Neutrophil (%)	37	61	5	< 0.05
ESR (mm/hr)	44	54	5	0.424
Hb (g/dl)	66	36	1	< 0.001
Uric acid (mg/dl)	36	63	4	< 0.001
Urine Albumin (mg/dl)	15	68	20	< 0.001
Serum Creatinine (mg/dl)	21	81	1	< 0.001

patient progressed from stage 1 to 5. The average time taken for progression from each stage is given in Table 3.

Risk factors

Diabetes mellitus, Hypertension, CAD, Dyslipidemia and Thyroid disorders were the main comorbidities found in study population. Association of comorbidities by comparing first and latest visit in patients with progression (n=61) (Table 4). Significantly larger proportion of patients was found to have diabetes mellitus, hypertension, dyslipidemia, and CAD (p <0.05) The common comorbidities observed in latest visit were hypertension and diabetes mellitus.

The risk factors associated with progression of stages of CKD were found to be increased age, BMI, neutrophil count, uric acid, urine albumin and decreased haemoglobin levels and platelet counts. Comorbidities like hypertension, diabetes mellitus, CAD and dyslipidemia were also found to be risk factors for progression of CKD.

Table 3: Average time taken for progression.

Progression of stages	Average time taken(months)
1 to 5	43
2 to 5	49.5
3 to 5	33.95
4 to 5	24.54

DISCUSSION

A total number of 103 CKD patients were included in the present study, out of which 71 (69%) were male patients This is similar to the observations made by other researchers Bajait C *et al.* at Maharashtra, India and Bharani K *et al.* at Madhya Pradesh, India.[9,10]

Demographic analysis shown a mean age of 55.01± 14.28 years. A study at Mangalore, India by Al-Jabri MM *et al.* showed that the mean age was 54.5±13.4 years.[11]

Among the study population, 61 patients progressed to higher stages of CKD. More number of patients were in CKD stage 5. Among the 61 progression cases, nineteen patients progressed from stage 3 to 5 and the average time taken was 33.95 months. Twenty-six patients progressed from stage 4 to 5 and the average time taken was found to be 24.54 months. This shows the time taken for progression from severe to end stage (4 to 5) was shorter than time taken for progression from moderate to end stage (3 to 5). Similar results were shown in a study conducted by Ku E *et al.* in the United States, that the median time spent in each CKD stages became shorter with later stages of CKD.[7]

In our study patients were first diagnosed in an advanced stage of CKD. Probably, the lack of awareness regarding kidney disease among patients and ignorance may lead to delay in diagnosis. The renal function decline of 18 patients out of 61 progression cases were not identified in other departments during their visit. They were in stages 3a, 3b and 4 of CKD. They visited the nephrology department at later stages only. Renal decline was identified for rest of the patients at the earlier stages from nephrology

Table 4: Comparison of comorbidities in first and latest visit.

Comorbidities	First Visit	Latest Visit		Total	McNemar χ2	p
		No	Yes			
Diabetes Mellitus	No	47	6	53	5.04	< 0.05
	Yes	0	50	50		
	Total	47	56			
Hypertension	No	11	12	23	11.02	< 0.001
	Yes	0	80	80		
	Total	14	89			
Dyslipidemia	No	70	10	80	9.02	< 0.05
	Yes	0	23	23		
	Total	70	33			
CAD	No	62	9	71	8.03	< 0.05
	Yes	0	32	32		
	Total	62	41			
Thyroid Disorder	No	86	4	90	3.06	0.125
	Yes	0	13	13		
	Total	86	17			

department. Importance of early documentation was emphasised in a study conducted at Georgia, United states by Guessous I *et al.*[12]

The patients had hypertension (88.35%) and diabetes mellitus (53.39%) followed by CAD (39.81%) as comorbid conditions. Significantly larger proportion of patients was found to have diabetes mellitus (*p=0.031*), hypertension (*p=0.001*), dyslipidemia (*p=0.002*), and CAD (*p=0.004*). The data obtained is found to be analogous with studies conducted at Mangalore, India by Al-Jabri MM *et al.* and Suthar J *et al.* at Ahmedabad, India which showed hypertension and diabetes mellitus as the most common comorbidities.[11,13]

Progression of CKD is inevitable. Availability and affordability of therapeutic approaches are important issues to be addressed. One of the main hurdles in managing CKD is identification of CKD at earlier stages. Also, it is known that CKD cannot be cured only managed appropriately. Many patients are hesitant to seek treatment at the initial stages and only reach the doctor when it has progressed towards the end stages of kidney disease where the management is quite aggressive and costly.

Novel therapies that can delay the progression are the future of CKD management. The FDA approval of Dapagliflozin for use in CKD even without diabetes was one such breakthrough.

It shows reduced risk of CKD progression. In our study 39.81% patients had CAD and it was significantly associated with progression of CKD. Cardiovascular events are significantly associated with CKD. DAPA-HF trials found that a person aged 65 years has an extrapolated average event-free survival time of 8.3 years. In a multi-centred study conducted by McMurray J J *et al.* dapagliflozin showed reduced risk of kidney failure in CKD patients with or without diabetes, also independent of history of HF.[14] A multi-centred study by Rossing P et al. found that Finerenone significantly reduced progression of kidney failure and secondary cardiovascular outcomes with or without use of SGLT2 inhibitors.[15]

Such novel therapies that can delay progression of CKD should be further investigated and medical managements that can actually help in delaying the progression of the disease must be given importance.

CONCLUSION

Validating CKD prognosis in a population might help clinicians make better decisions. Increased BMI, neutrophil count, uric acid, urine albumin and decreased haemoglobin levels and platelet counts were the risk factors identified with progression. The time taken for progression becomes shorter in later stages eventually leading to RRT. Affordability of RRT is an economic burden; hence assessing prognosis has the added benefit of enhancing socioeconomic outcomes.

Despite the swarm of CKD-related problems, understanding risk factors and implementing screening of populations at risk will increase early detection, initiate treatment of modifiable risk factors for ESRD, along with appropriate use of novel therapeutic strategies for mitigating CKD progression. Broadening the choice of medications that retards progression becomes a pressing need. Intervening in the early stages of renal disease aids in addressing the problem at the earliest and may provide a clinical chance of reducing the progression. With the outcome of CKD being definitive, paramount efforts on prevention strategies and a need for patient centred care is undeniable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

CKD: Chronic Kidney Disease; **ESRD:** End Stage Renal Disease; **RRT:** Renal Replacement Therapy; **BMI:** Body Mass Index; **Hb:** Hemoglobin; **ESR:** Erythrocyte Sedimentation Rate; **CAD:** Coronary Artery Disease; **FDA:** Food and Drug Administration; **SGLT2:** Sodium-glucose cotransporter-2.

SUMMARY

- Chronic Kidney Disease is a growing global burden that presents a myriad of complications and is a leading cause of mortality. There are limited studies from India on prognosis of CKD. This study focuses on the average time taken to progress to the end stage so as to understand risk factors and implement screening of at-risk populations for early detection and initiate treatment of modifiable risk factors for ESRD.
- A total of 103 patients were included in the study.
- ANOVA tests for continuous variables were used. For comparison Wilcoxson Signed Rank Test and McNemar Test were used.
- The risk factors associated with progression of stages of CKD were found to be increased age, BMI, neutrophil count, uric acid, urine albumin and decreased haemoglobin levels and platelet counts. Comorbidities like hypertension, diabetes mellitus, CAD and dyslipidemia were also found to be risk factors for progression of CKD.
- Among the study population, 61 patients progressed to higher stages of CKD. More number of patients were in CKD stage 5. Among the 61 progression cases, nineteen patients progressed from stage 3 to 5 and the average time taken was 33.95 months. Twenty-six patients progressed from stage 4 to 5 and the average time taken was found to be 24.54 months. This shows the time taken for progression from

severe to end stage (4 to 5) was shorter. Intervening in the early stages of renal disease aids in addressing the problem at the earliest and will provide a clinical chance of reducing the progression.

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