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Exploring Risk Factors Involved in The Progression of Chronic Kidney Disease: A Prospective Study in A Quaternary Care Hospital - Chennai.

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ABSTRACT

Purpose: The study investigates the rising prevalence of chronic kidney disease (CKD) and its associated challenges, including co-morbidities and uncertain prognosis. Patients often face disease progression without clear identification of those at high risk for rapid advancement to end-stage renal disease. Conducted in a hospital setting, the research examines a cohort of adults with CKD to determine the rate of progression from early to advanced stages and identify predictors of rapid advancement.

Methods: Patients meeting inclusion/exclusion criteria provided written consent before screening. The Modification of Diet in Renal Disease (MDRD-4) equation determined eGFR, and staging was based on admission results. Data were categorized into early and advanced stages according to eGFR values. Demographic details, clinical features, risk factors, comorbidities, laboratory results, and other supportive care information were extracted from hospital records. The collected data were analyzed to identify risk factors influencing CKD progression.

Results: A comparative analysis of baseline characteristics revealed that age, gender, and BMI significantly contributed to the development of end-stage kidney disease. Key factors such as serum creatinine, serum uric acid, eGFR, random blood sugar, and fluid intake showed statistical significance in the progression of kidney disease. The risk of end-stage CKD was notably elevated with smoking, alcohol consumption, and increased fluid intake.

Conclusion: The study demonstrated a significant association between CKD progression and parameters such as age, BMI, habits like alcohol intake and smoking, as well as clinical factors including serum creatinine, serum uric acid, eGFR, and random blood sugar. Patients with diabetes, coronary artery disease (CAD), and anemia exhibited a more accelerated decline in renal function. These factors can be modified through appropriate treatment.

KEYWORDS: Chronic kidney disease, estimated glomerular filtration rate, end-stage renal disease, Modification of Diet in Renal Disease, CKD progression, Risk factors.

INTRODUCTION

Chronic Kidney Disease (CKD) poses a substantial global public health challenge, entailing considerable medical and financial burdens. The estimated global prevalence of CKD stands at 13.4%, with projections indicating that 4.902 to 7.083 million individuals may require renal replacement therapy for End-Stage Kidney Disease (ESKD) [1]. Between 1990 and 2017, CKD prevalence increased by 29.3%, accompanied by a corresponding 41.5% rise in the death rate. In 2020, CKD accounted for 1.2 million deaths worldwide, ranking as the 10th leading cause of death. In India, kidney failure-related mortality increased by 38% from 2001–2003 to 2010–2013 [2]. Chronic kidney disease is a multifaceted condition [3], with its progression influenced by diverse and individual-specific risk factors. The pace of advancement is also shaped by the presence of underlying CKD risk factors and the cause of renal failure. Recent research has identified certain factors contributing to CKD progression, leading to morbidity and

mortality across different ethnic and racial groups. These factors fall into two categories: initiating and perpetuating. Nephron loss initiation is prompted by factors like diabetes, old age, or male sex, while disease progression is fueled by factors such as proteinuria, hypertension, or hyperuricemia [4]. This study aims to explore the prevalence of chronic kidney disease (CKD) in a diverse population within a hospital setting. The focus is on determining the prevalence of risk factors that contribute to CKD progression and identifying key elements that lead to rapid progression in patients initially diagnosed with CKD at a multispecialty hospital. The study's findings will highlight the crucial risk factors that should be addressed to either prevent or slow down CKD progression in patients.

METHODOLOGY

Study subjects' recruitment:

The study utilized a prospective cohort design and took place at Hindu Mission Hospital in West Tambaram, Chennai, spanning a duration of 6 months. The study cohort comprised 147 hospitalized individuals diagnosed with chronic kidney disease. Participants, ranging in age from 18 to 80, were included regardless of gender, and they were admitted to the hospital. The study received ethical approval from the Institutional Ethics Committee of the hospital in May 2022 (HMH/IEC/2022/STEA23). All procedures carried out during the study strictly adhered to the guidelines set forth in the declaration of Helsinki. Before participating, each patient provided written informed consent. This consent was obtained after a thorough explanation of the study's objectives and procedures, ensuring that participants had a comprehensive understanding before agreeing to take part.

Data collection:

The study conducted an extensive data collection process, encompassing various datasets that included socio-demographic details, anthropometric measurements, blood pressure readings, medical histories, lifestyle patterns, and dietary habits. Biochemical parameters, such as hemoglobin, blood urea, serum creatinine, sodium, potassium, chloride, bicarbonate, serum uric acid, calcium, phosphorus, random blood sugar, SGOT, and SGPT, were meticulously recorded both at the beginning and conclusion of the study period. Furthermore, the study thoroughly evaluated treatment regimens, prescribed medications, and the presence of comorbidities for all participants throughout the entire study duration. This comprehensive approach to data collection aimed to capture a holistic understanding of the patients' health profiles, allowing for the tracking of any changes or developments over the course of the study period.

Staging of CKD:

The staging of chronic kidney disease (CKD) was determined using the modification of diet in renal disease (MDRD-4) equation to calculate the estimated glomerular filtration rate (eGFR) and categorize individuals into different stages:

- Stage 1 CKD: eGFR of 90 ml/min/1.73m² or more
- Stage 2 CKD: eGFR between 60 ml/min/1.73m² to 89 ml/min/1.73m²
- Stage 3a and 3b CKD: eGFR between 30 ml/min/1.73m² to 59 ml/min/1.73m²
- Stage 4 CKD: eGFR between 15 ml/min/1.73m² to 29 ml/min/1.73m²
- Stage 5 CKD: eGFR greater than 15 ml/min/1.73m²

For the study's analysis, stages 1 to 4 were collectively grouped as the early stage of CKD, while patients in stage 5 were categorized as having advanced CKD. Comparisons and analyses were conducted between these two groups to investigate differences and potential associations between the early and advanced stages of CKD.

Statistical analysis:

The data were presented as Mean ± SD, median with inter-quartile range, or frequency with percentage, depending on their distribution. Normality of the data was evaluated using a Q-Q plot. To determine significant differences in means or medians, an independent t-test or Mann-Whitney test was employed. The Chi-square test was utilized to assess significant differences between groups. All calculations were executed using a statistical software program (SPSS v.16.0, Chicago, IL).

RESULTS

As per the findings in Table 1, several baseline characteristics, including age, gender, BMI, and pulse rate, have been identified as significant factors contributing to the development of end-stage kidney disease. The study also reveals that alcohol consumption and chronic smoking emerged as significant risk factors for the progression of chronic kidney disease. However, the association of non-steroidal anti-inflammatory drugs (NSAIDs) and herbal supplement intake with CKD progression did not reach statistical significance.

Table 2 provides an overview of the differences in various laboratory parameters between patients in the early and advanced stages of chronic kidney disease. Noteworthy factors contributing to the progression of kidney disease, such as serum creatinine (p 0.01), serum uric acid (p< 0.04), estimated glomerular filtration rate (eGFR) (p<0.01), random blood sugar (p<0.01), and fluid intake (p=0.01), were found to be statistically significant. Table 3 outlines the co-morbidities observed among subjects with chronic kidney disease (CKD). There was a notable increase in co-morbidity rates in CKD patients. In our study population, the prevalence of diabetes and hypertension appeared higher in the advanced CKD stage, with diabetes being statistically significant. Anemia was more frequent in the advanced stage (81.2%), demonstrating a significant p-value of 0.001. Surprisingly, only 1% of individuals in the advanced CKD stage had cardiovascular disease (CVD) compared to the early stage. In contrast, the frequency of coronary artery disease (CAD) was higher in the early stage, and this difference was statistically significant. These findings shed light on the varying prevalence of co-morbidities across different stages of CKD.

Table 4 details the utilization of anti-hypertensive drugs among different groups, with no statistically significant differences observed. The predominant class of drugs prescribed throughout the study sample was related to Calcium Channel Blockers (CCB), with Statins following closely behind. This indicates that there was a uniformity in the usage of anti-hypertensive medications across the groups, and the prevalent classes were Calcium Channel Blockers and Statins. The lack of statistical significance suggests similar patterns of drug utilization in the context of hypertension management among the study participants.

Table 5 summaries the precipitating causes of chronic kidney disease (CKD) across different groups. In our study population, diabetes and hypertension emerged as the most prevalent causes, with a relatively equal distribution among the groups. Notably, the advanced stage group exhibited a statistically significant increase in the frequency of unknown factors and a family history of CKD. This finding underscores the importance of recognizing these factors, as their significance was more pronounced in the advanced CKD stage.

DISCUSSION

CKD has emerged as a significant global health concern, marked by its increasing occurrence, link to cardiovascular disease (CVD) mortality, unfavorable outcomes, and serious complications. These factors contribute substantially to healthcare expenses and pose a considerable burden on healthcare systems. In 2016, CKD accounted for 1.2 million deaths worldwide, ranking as the 12th leading cause of death and the 14th risk factor for disability-adjusted life years (DALYs) among 79 identified risk factors in 2013. By 2019, the prevalence of CKD globally had reached 13.4%. Over the past decade, there has been considerable focus on identifying predictive factors for the progression of CKD due to its escalating prevalence on a global scale.

The frequency of declining renal function tends to be higher among older individuals. Age plays a significant role in CKD outcomes, primarily by showcasing a continuous decline in the glomerular filtration rate (GFR) as people grow older [7]. While older age appears to trigger this decline, it may not actively sustain the process, as renal function gradually diminishes with age. Several studies have delved into this association between age and reduced renal function, elucidating how aging correlates with a decline in estimated GFR (eGFR) [23-29]. In a subpopulation analysis encompassing 15,625 individuals from the third National Health and Nutrition Examination Survey (NHANES III), age emerged as a pivotal predictor of CKD prevalence. Our study echoes these findings, showing statistically significant evidence linking age to the progressive decline of eGFR.

Gender-based differences in CKD are well-documented, showcasing distinct disparities. Although men exhibit a higher prevalence of CKD, data from the United States Renal Data System highlights that they are more prone to developing kidney failure compared to women [17]. This observation might suggest that women either experience a slower loss of kidney function or are more likely to pass away before reaching kidney failure. Despite extensive adjustments for socio-demographic, clinical, and laboratory factors, regression analysis demonstrated that women had a 28% lower incidence of kidney failure than men [18]. One proposed explanation for these distinctions revolves around the potential protective role of endogenous estrogens [19]. Gender emerged as a statistically significant factor in our own sample study, further emphasizing its relevance in understanding CKD patterns.

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There's a notable contrast in the prevalence of diabetes mellitus (DM) between the early and advanced stages of CKD. Alan S. et al. conducted a study investigating the correlation between DM presence and CKD progression. Their findings indicated that 23.0% of patients with diabetes experienced rapid CKD progression compared to 15.3% of those without diabetes. Factors such as proteinuria, age exceeding 80 years, heart failure, anemia, and higher systolic blood pressure were identified as multivariable predictors for fast CKD progression, with consistency across both diabetic and non-diabetic groups [6]. Additionally, elevated systemic blood pressure has long been acknowledged as a significant contributor to CKD progression [9].

In the MDRD study, the primary analysis did not show a significant disparity in CKD progression rates over a 2.2-year follow-up period between patients with low target blood pressure and those receiving standard treatment. However, a secondary analysis indicated a noteworthy reduction in the risk of progressing to end-stage renal disease (ESRD) specifically in patients with high proteinuria and low target blood pressure. This suggests that proteinuria, rather than hypertension, may be the more crucial risk factor [10].

The correlation between elevated systemic blood pressure and the advancement of CKD has long been acknowledged [9]. In a study by Anderson et al., the connection between time-updated systolic blood pressure and CKD progression was examined through marginal structural analysis [20]. The findings indicated an increased risk of kidney failure with a systolic blood pressure of 130 mmHg, aligning with the AHA's suggestion that individuals with CKD should strive for a blood pressure goal of 130/80 mmHg [30]. However, our study did not yield similar results, as there was no statistically significant difference in systolic blood pressure between the two groups.

The breakdown of smoking habits in our study is intriguing, revealing that 74.1% of participants were non-smokers, 25.2% were former smokers, and only 0.7% were current smokers. A notable statistical difference in smoking behavior emerges when comparing individuals in the early and advanced stages of chronic kidney disease (CKD). This observation aligns with Yacoub, R., Habib, H., Lahdo, A., et al.'s investigation, which also indicates a link between heavy cigarette smoking and an elevated risk of CKD. Moreover, our study supports Bundy et al.'s findings, emphasizing an increased risk of CKD progression in individuals using both tobacco and alcohol compared to non-users [16]. Notably, our study reveals a statistically significant difference in alcohol consumption between the two groups, despite previous research suggesting a lower risk of all-cause mortality among CKD patients who consume alcohol. These observations add depth to the understanding of the complex relationship between smoking, alcohol use, and their impact on the progression of CKD.

Chang, Wen-Xiu, et al. conducted a study to investigate the time-dependent risk factors associated with the decline of estimated GFR. Proteinuria, blood pressure, and anaemia are the three major risk factors of CKD. Uric acid and phosphorus are emerging risk factors in the clinical course of CKD, indicating that the appropriate intervention may retard the progression of CKD. In our study, uric acid is statistically significant between the two groups ($p = 0.043$), and phosphorus does not show any statistical significance ($p = 0.090$). Srivastava et al. conducted a study to find the association between the increased uric acid level and the increased risk of kidney failure, and it shows that uric acid is an independent risk factor for kidney failure in earlier stages of CKD [15].

Due to the increased risk for CKD, increased risk for a progressive decline in renal function, and related mortality, there is an urgent need to improve public awareness of the identification of risk factors for CKD. This knowledge about risk factors may provide important evidence-based information for policymakers and healthcare professionals regarding strategies for risk factor modification, CKD prevention, and healthcare planning.

LIMITATIONS

The study has limitations, including a relatively short duration and a limited number of subjects, potentially affecting the generalizability of findings. To address CKD progression variability, patients were categorized into early and advanced stages, recognizing potential nuances within each stage. The 6-month follow-up period may be insufficient for a comprehensive assessment. Additionally, self-reported tobacco and alcohol data may be influenced by social desirability bias, introducing uncertainty. While the study provides valuable insights, these limitations should be considered, and future research with extended follow-up and a larger, diverse sample is recommended for a more comprehensive understanding of CKD progression and associated risk factors.

CONCLUSION

This hospital-based study has been instrumental in uncovering pivotal risk factors associated with the progression of chronic kidney disease. The research highlights a robust association between CKD progression and a spectrum of parameters, including

demographic aspects like age, physiological indicators such as BMI, and lifestyle habits like alcohol intake and smoking. Furthermore, clinical factors like serum creatinine, serum uric acid, eGFR, and random blood sugar were identified as significant contributors to CKD progression. Notably, patients with concurrent conditions such as diabetes, coronary artery disease (CAD), and anemia exhibited a more pronounced decline in renal function. This underscores the urgency of early detection and tailored management of these risk factors.

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Table 1: Comparison of Baseline and Sociodemographic Characteristics between Early Stage and Advanced Stage CKD Patients

Parameters		**Early Stage *(n=51)***	**Advanced Stage *(n=96)***	***p value***
Age		66.55±10.271	56.30±14.48	***0.032***
Gender	***Male***	39(76.5)	57(59.4)	***0.038***
	Female	12(23.5)	39(40.6)	
BMI *(kg/m 2)*		23.29±3.25	22.413±4.46	***0.021***
Systolic BP *(mmhg)*		137.04±23.24	145.02±27.54	0.122
Diastolic BP (*mmhg)*		80±15.23	80.10±12.52	0.852
Pulse rate (*bpm)*		87.06±15.12	82.78±10	***0.001***
Alcohol	***Never***	33(64.7)	77(80.2)	***0.039***
	Former	18(35.3)	19(19.8)	
Smoking	***Never***	32(62.7)	77(80.2)	***0.040***
	Former	19(37.3)	19(19.8)	
NSAIDS	***Never***	45(88.2)	69(71.9)	0.074
	Often	0	5(5.2)	
	Once a week	6(11.8)	18(18.8)	
	Once a month	0	4(4.2)	
Herbal	***Never***	49(96.1)	83(86.5)	0.086
	Often	0	7(7.3)	
	Once a week	0	4(4.2)	
	Once a month	2(3.9)	2(2.1)	
Salt Intake		3.56±1.19	2.75±1.34	0.670

Table 2: Comparison of Laboratory Parameters between Early Stage and Advanced Stage Chronic Kidney Disease (CKD) Patients

Parameters	**Early Stage *(n=51)***	**Advanced Stage*(n=96)***	***p value***
Haemoglobin *(g/dl)*	9.94±1.63	10.98±14.35	0.304
Serum creatinine (*mg/dl)*	2.51±1.06	7.69±2.87	***0.001***
Sodium (*mEq/L)*	135.76±3.28	136.48±3.23	0.913
Potassium (*mmol/L)*	4.47±0.65	4.97±0.59	0.168
Chloride (*mEq/L)*	100.11±1.86	100.30±4.25	0.406
Bicarbonate (*mmol/L)*	22.12±1.32	21.87±1.45	0.876
Serum uric acid *(mg/dL)*	5.32±2.79	5.61±2.10	***0.043***
Calcium *(mg/dl)*	7.44±2.90	8.78±4.01	0.429
Phosphorus *(mg/dl)*	4.09±2.11	4.86±1.63	0.090
Random blood sugar *(mg/dl)*	195.94±101.19	159.12±75.64	***0.017***
AST (*unit/litre*)	22.97±20.39	20.11±8.86	0.088
ALT *(unit/litre)*	20.23±11.26	19.11±7.85	0.137
eGFR (*ml/min)*	34.04±12.53	9.92±7.80	***0.001***

Table 3: **Status of Co-morbidity in the Progression of Chronic Kidney Disease**

Parameters	**Early Stage (n=51)**	**Advanced Stage (n=96)**	***p value***
T2DM	37(72.5)	36(37.5)	***0.001***
Hypertension	40(78.4)	71(74)	0.548
CAD	19(37.3)	5(5.2)	***0.001***
CVD	0	1(1)	0.465
Anemia	30(58.8)	78(81.2)	***0.003***

Note: CAD-Coronary Artery disease, CVD- Cardio Vascular Disease

Table 4: Distribution of Anti-Hypertensive Drugs Between Groups

Medications	**Early Stage *(n=51)***	**Advanced Stage *(n=96)***	***p value***
Diuretics	15(29.4)	35(36.5)	0.475
Alpha-blockers	13(25.5)	21(21.9)	0.423
Beta-blockers	14(27.5)	31(32.3)	0.462
CCB	21(41.2)	61(63.5)	0.498
ARB	0	2(2.1)	0.116
Statin	25(49)	40(41.7)	0.498

Note: CCB-Calcium Channel Blockers, ARB- Angiotensin Receptor 2 Blocker

Table 5: **The Precipitating Causes of Chronic Kidney Disease between Groups**

Parameters	**Early stage(n=51)**	**Advanced stage(n=96)**	***p value***
Unknown	16(31.4)	61(63.5)	***0.001***
HTN	23(45.1)	23(24)	***0.001***
DM	12(23.5)	12(12.5)	***0.001***
Family history of CKD	1(2)	11(11.5)	***0.045***

Note: HTN-Hypertension, DM-Diabetes mellitus, CKD- chronic kidney disease