

Clinical and Biochemical Predictors of Rapid Decline in Chronic Kidney Disease: A Retrospective Cohort Study in a Tertiary Care Teaching Hospital

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Abstract:

Background: There is significant variability in the rate at which function is lost in the kidneys in chronic kidney disease (CKD), necessitating the recognition of rapid decliners for treatment purposes. Unfortunately, little empirical data exists on factors responsible for rapid progression of CKD among the South Asian population.

Methods: A retrospective analysis was conducted on adults suffering from stage G2–G4 chronic kidney disease who presented to a university hospital during the year 2025. The inclusion criteria included patients with baseline eGFR of 15-89 mL/min/1.73m² by the 2021 CKD-EPI equation with a minimum of two eGFR readings spaced at least 3 months apart for at least one year. The rapid decline was based on the KDIGO criteria of persistent decrease in eGFR of more than 5 mL/min/1.73m² annually. Comparison between clinical and biochemical parameters in different groups was done using appropriate parametric, non-parametric, and categorical tests.

Results: Of the 312 studied subjects, 107 (34.3%) fulfilled the criteria for rapid progression. Multiple logistic regression analysis revealed the following factors to be predictive of rapid progression: overt proteinuria, diabetes, poor control of blood pressure, hypoalbuminemia, and anemia at baseline. On the other hand, renin-angiotensin-aldosterone system (RAAS) blockade was negatively predictive. The final multivariate model had excellent discrimination (AUC = 0.79; 95% CI 0.74–0.84) and acceptable calibration.

Conclusion: High proteinuria, diabetes, poorly controlled high blood pressure, hypoalbuminemia, and anemia contribute to the rapid deterioration of kidney function independently, whereas blocking the renin-angiotensin-aldosterone system prevents such deterioration. Using these commonly available factors can improve the risk prediction process.

Keywords: Chronic kidney disease; Functional decline; Estimated eGFR slope; Proteinuria.

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Introduction

An alarming increase in the prevalence of chronic kidney disease (CKD) has been seen amongst the public health issues across the globe. The estimated prevalence of CKD is about 9-10%. It has also caused serious heart problems and mortality rates.[1,2] The country faces great impact on it. The studies carried out through the ICMR-INDIAB survey and International Society of Nephrology's Kidney Disease Data Center have revealed that the prevalence rate of CKD in the area is 6-17% due to the epidemic of diabetes and hypertension, along with CKD of unknown cause.[3,4] These impacts have been worsened because of the facts that there

is delay in diagnosis, no treatments for the kidney disorders, and costly consequences.

CKD natural history is diverse. Whereas in some patients kidney function deteriorates slowly with aging, a significant proportion of patients progress rapidly to kidney failure.[6] Rapid progressors according to KDIGO criteria are those who show sustained annual decline of eGFR by more than 5 mL/min/1.73 m², and these patients have an increased likelihood of poor outcomes of both kidneys and cardiovascular disease. Early detection of such patients is essential from a clinical point of view, as there are many factors contributing to their fast deterioration of renal function, namely

proteinuria, inadequate glycaemic control and hypertension, and anaemia, which are all modifiable, and RAAS blockade and sodium-glucose cotransporter-2 inhibitors have been found to be efficient.[7,8]

There is considerable data on predictors of a faster rate of progression, such as more severe proteinuria, diabetes, poorly controlled blood pressure, hypoalbuminemia, hyperuricemia, and anemia.[10-13] However, most of the data is derived from western populations or from registries and the importance of these variables may vary among Indian patients based on the differences in aetiology, referral bias, nutritional issues, and presentation for nephrology care.[14] Various risk-prediction models, such as Kidney Failure Risk Equation, have been validated primarily in North America and Europe, and their relevance to the everyday practice at Indian tertiary care hospitals is not well understood.[15] Information about predictors of rapid, as opposed to any, progression from Indian teaching hospitals is relatively scarce.

Thus, a retrospective observational cohort study was conducted at a teaching hospital providing tertiary care in order to assess the prevalence of rapid progression of the disease among patients with CKD, and to identify the clinical and biochemical factors which independently contribute to the rapid progression of the disease. The hypothesis of the study is that the tests which can be applied to cheaply stratify risk are independent predictors of CKD.

Materials and Methods

Study design and setting: This was a retrospective cohort study conducted in the Department of Nephrology in an academic hospital in India. The records of all patients who had visited the outpatient and in-patient departments of nephrology between 1st January 2025 and 31st December 2025 were analyzed. This study was conducted using the guidelines provided by STROBE statement. [16] Ethical approval for this study was obtained from the Institutional Ethics Committee ([reference no.], [date]). Since this study involved analysis of patient records, there was no need for consent.

Participants: Those who were above the age of 18 years and had CKD stages G2-G4 (basal eGFR of 15-89 mL/min/1.73 m²) were deemed as eligible. Participants must have had at least two measures of their serum creatinine levels within an outpatient setting where each measure was taken apart from each other for at least three months and follow-up period of at least 12 months.

The exclusion criteria included CKD stages G5 (eGFR <15 mL/min/1.73 m²) at baseline, patients on maintenance dialysis or with functioning kidney transplantation, those who had developed acute

kidney injury on top of CKD and not recovered back to a baseline condition, patients whose serum creatinine curve could be due to reversible causes (obstructive uropathy, contrast nephropathy or nephrotoxin use within last one month), pregnant women, with active malignancy or lacking complete baseline data regarding the variables of interest. Using these criteria, 156 out of 468 screened individuals were excluded, giving us 312 patients for further analysis.

Definitions and outcome: The eGFR was calculated from the serum creatinine based on the CKD-EPI creatinine equation for 2021 without the use of a race coefficient.[17] The value of serum creatinine was measured with the use of a kinetic Jaffe assay traceable to isotope dilution mass spectrometry using the same automated system throughout the study period.

The rapid progression of CKD served as the primary end point in the study based on the definition by KDIGO as a sustained fall in eGFR exceeding 5 mL/min/1.73 m² per year.[7] The slope of the annual rate of eGFR was estimated for each subject with the use of a least squares regression of all eGFR data obtained in the follow-up period, where a negative slope exceeding -5 mL/min/1.73 m² per year was a rapid progressor, while others were not.

Variables and data collection: Date of the initial nephrology appointment was considered as the baseline. Demographic, clinical and biochemical information was abstracted using a pre-tested data abstraction form by two independent investigators, and a random 10% of the subjects was re-abstracted independently as a quality control measure.

Baseline assessment encompassed demographic and clinical factors like age, sex, BMI, diabetes, hypertension, cardiovascular disease, and smoking status. Diabetes was classified by the presence of a history of the same, use of glucose lowering therapy, and HbA1c level of $\geq 6.5\%$ or more, while a patient was classified as hypertensive based on a history of the condition and antihypertensive therapy. Hypertension was deemed uncontrolled if the mean baseline blood pressure was $\geq 140/90$ mmHg despite the ongoing therapy.

The laboratory measurements included serum creatinine, eGFR, blood urea, albumin, haemoglobin, uric acid, calcium, phosphate, and glucose (fasting/random). The proteinuria was assessed using the UPCR either as a continuous measurement or with ≥ 1 g/g cutoff level. Hypoalbuminaemia was defined as albumin levels <3.5 g/dL, while anaemia was defined as haemoglobin <10 g/dL. The baseline use of RAAS inhibitors, including ACE inhibitors and ARBs, was also noted.

Sample size: All eligible subjects were included in the study in the specified period, as opposed to targeting a specific number. Since there were 107 events (rapid progressors), and six potential predictors were included in the final regression, the analysis met the traditional criteria of having at least ten events per predictor.[18]

Statistical analysis: Continuous variables were described as mean $\pm$ SD or median (IQR) depending on whether they had normal distribution, which was determined by the Shapiro-Wilk test. Categorical variables were described as frequency and percentages. Comparison of characteristics between rapid and non-rapid progressors was done using the Chi-square or Fisher's exact test for categorical variables and the independent Student's t-test or Mann-Whitney U-test for continuous variables, as appropriate.

Variables with a p-value < 0.10 from the univariate analysis, along with clinically significant variables, were included in the multivariable logistic regression analysis. Results were presented as OR or aOR with 95% CI. The presence of multicollinearity was tested using variance inflation factor. The discriminatory ability and goodness of fit of the model were analyzed using area under the curve of the receiver operating characteristic (ROC) curve and the Hosmer-Lemeshow test, respectively. Statistical significance was set at p-value < 0.05 . Analyses were done using SPSS version 26.0.

Results

Cohort characteristics: After performing patient selection and exclusions, the end result was the inclusion of adult patients diagnosed with CKD in the analysis. In the entire study population, the prevalence of males was higher than females, and most of the patients included were hypertensive. More than half of the cohort had diabetes mellitus, and many of the patients were on RAAS inhibition.

Based on the serial eGFR profiles during the course of follow-up period, the patients were divided into two categories based on their status of progression i.e. rapid progressors and non-rapid progressors. Generally speaking, more than a third of the subjects met the criteria of faster progression of deterioration in kidney function. The characteristics of the two categories are shown in Table 1 below.

Comparison of rapid and non-rapid progressors: Comparing the two groups, differences emerged in terms of their baseline

characteristics. Individuals who experienced a fast drop in their kidney function were older and exhibited a greater prevalence of metabolic and vascular diseases including diabetes mellitus and uncontrolled systemic hypertension. There was a high degree of proteinuria in the rapidly progressing group, regardless of the assessment of continuous proteinuria (urine protein/creatinine ratio) or high-grade proteinuria criteria. Also, patients with rapid progression had a lower serum albumin level, low hemoglobin, higher levels of uric acid and phosphate in serum compared to those who maintained stability. However, the use of RAAS inhibitor therapy was significantly common in non-rapidly progressing patients. Sex composition, body mass index, tobacco smoking history, and glucose control did not differ significantly between the two groups.

Univariable analysis: As seen from the results of univariate logistic regression, all of the above conditions such as presence of significant proteinuria, diabetes mellitus, low albumin levels, poorly controlled high blood pressure and anemia showed strong association with increased risk of faster progression of disease. In addition, hyperuricemia and advanced age were positively associated. On the other hand, higher levels of baseline eGFR and previous use of RAAS inhibitors were found to be negative correlated with faster progression. Preexisting cardiovascular disease had a weak trend but was not statistically significant.

Multivariable analysis & Model Performance:

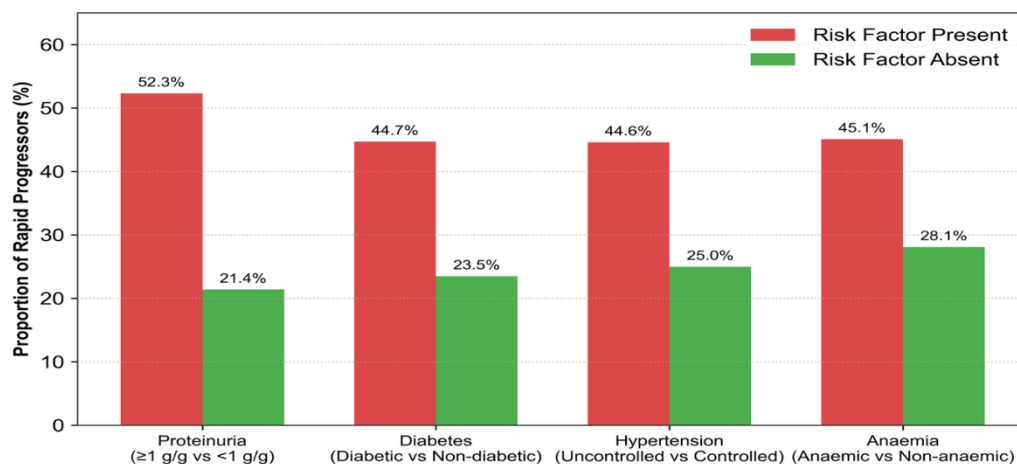
The candidate variables from crude screening along with clinical covariates were incorporated into the multivariable logistic regression analysis model. Diagnostics for collinearity were run and results showed no variance inflation in the predictors included. After adjustments, five clinical and laboratory risk factors were found to be independently significant with rapid decline: presence of heavy proteinuria (this was the biggest single contributor to the risk), presence of diabetes mellitus, uncontrolled blood pressure, hypoalbuminemia, and baseline anemia. On the other hand, RAAS inhibitor treatment was found to be independently significant in reducing the risk of rapid progression. The variables such as age, serum uric acid, baseline eGFR, and cardiac disease history became insignificant after multivariable adjustment. Adjustment effect estimates are shown in Table 3.

Table 1: Baseline characteristics of rapid and non-rapid progressors (N = 312)

Characteristic	Rapid progressors (n = 107)	Non-rapid progressors (n = 205)	P value
Age, years (mean $\pm$ SD)	56.8 $\pm$ 12.1	52.8 $\pm$ 13.0	0.009
Male sex, n (%)	68 (63.6)	124 (60.5)	0.59
Body mass index, kg/m ² (mean $\pm$ SD)	24.1 $\pm$ 3.8	24.6 $\pm$ 4.0	0.29
Current smoking, n (%)	28 (26.2)	44 (21.5)	0.35
Diabetes mellitus, n (%)	71 (66.4)	88 (42.9)	<0.001
Hypertension, n (%)	98 (91.6)	179 (87.3)	0.25
Uncontrolled hypertension, n (%)	66 (61.7)	82 (40.0)	<0.001
Cardiovascular disease, n (%)	31 (29.0)	40 (19.5)	0.061
RAAS inhibitor use, n (%)	52 (48.6)	138 (67.3)	0.002
Baseline eGFR, mL/min/1.73 m ² (median [IQR])	38 (28–49)	42 (31–55)	0.041
Serum creatinine, mg/dL (median [IQR])	1.9 (1.4–2.6)	1.7 (1.3–2.3)	0.047
UPCR, g/g (median [IQR])	1.6 (0.8–2.9)	0.7 (0.3–1.4)	<0.001
Proteinuria $\geq$ 1 g/g, n (%)	68 (63.6)	62 (30.2)	<0.001
Serum albumin, g/dL (mean $\pm$ SD)	3.6 $\pm$ 0.6	3.9 $\pm$ 0.5	<0.001
Hypoalbuminaemia (<3.5 g/dL), n (%)	42 (39.3)	40 (19.5)	<0.001
Haemoglobin, g/dL (mean $\pm$ SD)	10.4 $\pm$ 2.0	11.3 $\pm$ 1.9	<0.001
Anaemia (<10 g/dL), n (%)	51 (47.7)	62 (30.2)	0.002
Serum uric acid, mg/dL (mean $\pm$ SD)	7.2 $\pm$ 1.8	6.6 $\pm$ 1.7	0.004
Serum calcium, mg/dL (mean $\pm$ SD)	8.8 $\pm$ 0.7	9.0 $\pm$ 0.6	0.011
Serum phosphate, mg/dL (mean $\pm$ SD)	4.4 $\pm$ 0.9	4.1 $\pm$ 0.8	0.003

SD, standard deviation; IQR, interquartile range; eGFR, estimated glomerular filtration rate; UPCR,

urine protein-to-creatinine ratio; RAAS, renin–angiotensin–aldosterone system.

**Figure 1: Grouped bar chart comparing the proportion of rapid progressors across key baseline risk factor strata.****Table 2: Univariable logistic regression for predictors of rapid CKD progression**

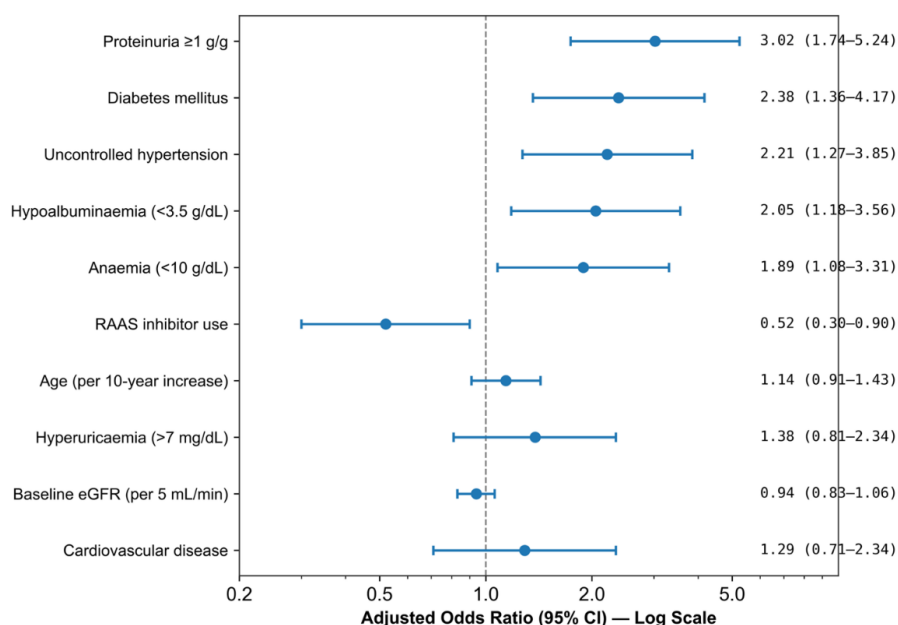
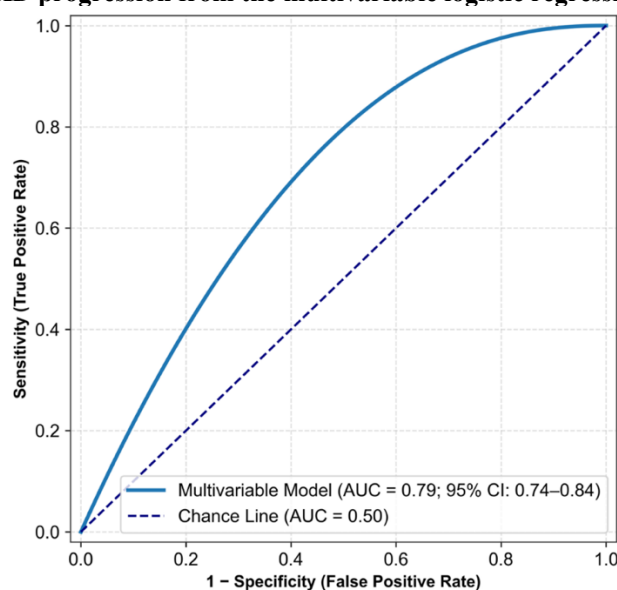
Variable	OR (95% CI)	P value
Age (per 10-year increase)	1.28 (1.05–1.56)	0.014
Male sex	1.14 (0.71–1.83)	0.59
Diabetes mellitus	2.62 (1.61–4.28)	<0.001
Uncontrolled hypertension	2.41 (1.49–3.90)	<0.001
Cardiovascular disease	1.68 (0.98–2.88)	0.061
Proteinuria $\geq$ 1 g/g	4.02 (2.46–6.57)	<0.001
Hypoalbuminaemia (<3.5 g/dL)	2.67 (1.60–4.44)	<0.001
Anaemia (<10 g/dL)	2.10 (1.30–3.40)	0.002
Hyperuricaemia (>7 mg/dL)	1.71 (1.06–2.76)	0.028
Baseline eGFR (per 5 mL/min/1.73 m ² higher)	0.88 (0.79–0.98)	0.020
RAAS inhibitor use	0.46 (0.28–0.75)	0.002

OR, odds ratio; CI, confidence interval.

Table 3: Multivariable logistic regression for independent predictors of rapid CKD progression

Variable	Adjusted OR (95% CI)	P value
Proteinuria ≥ 1 g/g	3.02 (1.74–5.24)	<0.001
Diabetes mellitus	2.38 (1.36–4.17)	0.002
Uncontrolled hypertension	2.21 (1.27–3.85)	0.005
Hypoalbuminaemia (<3.5 g/dL)	2.05 (1.18–3.56)	0.011
Anaemia (<10 g/dL)	1.89 (1.08–3.31)	0.026
RAAS inhibitor use	0.52 (0.30–0.90)	0.019
Age (per 10-year increase)	1.14 (0.91–1.43)	0.26
Hyperuricaemia (>7 mg/dL)	1.38 (0.81–2.34)	0.23
Baseline eGFR (per 5 mL/min/1.73 m ² higher)	0.94 (0.83–1.06)	0.31
Cardiovascular disease	1.29 (0.71–2.34)	0.40

Model discrimination: area under the ROC curve 0.79 (95% CI 0.74–0.84). Calibration: Hosmer–Lemeshow $\chi^2 = 6.94$, df = 8, P = 0.54.

**Figure 2: Forest plot of adjusted odds ratios (95% CI) on a log scale displaying independent predictors of rapid CKD progression from the multivariable logistic regression model.****Figure 3: Receiver operating characteristic curve of the multivariable model for predicting rapid CKD progression (AUC 0.79; 95% CI 0.74–0.84).**

Discussion

Among 312 patients with chronic kidney disease (CKD) stages G2-G4 enrolled in this retrospective cohort study at a tertiary care teaching hospital, almost one-third (34.3%) experienced rapid decline, with a loss of more than 5 mL/min/1.73 m² in their estimated glomerular filtration rate (eGFR) per year. Proteinuria ≥ 1 g/g, diabetes mellitus, uncontrolled hypertension, hypoalbuminaemia, and anaemia were significantly related to rapid decline, while use of RAAS inhibitor was significantly associated with reduced risk. The multivariable model, incorporating these routinely obtained parameters, predicted rapid versus non-rapid progressors rather well and was well-calibrated. Given that all of these parameters are obtained during routine nephrology care, this information is easily implementable in clinical practice.

The frequency of rapid progressors that we have identified is similar to those previously documented where the percentage of patients that satisfied the KDIGO criteria has varied between one-fourth to one-third based on the patient population and period of follow-up.[6,10] The concentration of rapid progression within a specific subpopulation, instead of an overall decrease among the patients, further justifies the need for early stratification of patients and the notion that CKD is not a single entity.

The association with proteinuria was the most significant independent factor, an observation which is in line with a considerable number of studies which have highlighted albuminuria and more severe degrees of proteinuria as key factors determining renal outcomes and the most important target for treatment modification.[7,10,19] The robustness of this relationship along with the inclusion of proteinuria in risk assessment tools such as the Kidney Failure Risk Equation further reinforces the validity of our finding.[15] The strength of the observed relationship—the odds being approximately tripled suggests that measuring and monitoring of proteinuria should be performed at initial contact with the nephrologist and not based only on eGFR.

The independent significance of diabetes and hypertension appears in line with the acknowledged fact that both conditions are responsible for CKD development not only in India but also worldwide.[3,4,20] The findings of the study imply that poor regulation of blood pressure is significant for the patient's outcome while being hypertensive itself does not matter much, in accordance with evidence that the intensive management of blood pressure and its environment slows down the process of renal function loss.[21] Hypoalbuminaemia and rapid CKD progression may be due to the presence of such factors as heavier

proteinuria, inflammatory process, and malnutrition, and serum albumin may act as a good cheap predictor of adverse outcomes.[12,22]

The association between anaemia and rapid progression was independent, consistent with observational evidence linking anaemia and accelerated decline in kidney function, possibly via hypoxic injury to tubular interstitium and the subsequent process of fibrosis.[13,23] It is still unclear whether anaemia correction would affect the rate of kidney function deterioration, and such conclusion cannot be drawn based on our observational approach. Hyperuricaemia correlated with rapid progression in the univariable analysis, but not after adjustment, in contrast to the mixed findings in randomised trials on the effect of lowering uric acid levels.[24]

The reduced risk of rapid progression in patients treated with RAAS inhibitors is well in line with the known nephroprotective effect of this class of medications, especially in the setting of proteinuria.[8,9] The link must be cautiously interpreted in a non-randomized study due to potential systematic differences between treated and untreated patients, including their indication and tolerance for medication. We consider the finding to be hypothesis-confirming rather than hypothesis-proving, but we do appreciate its consistency with randomized trials.

There are several strengths to our study. We have used a relatively large and well-defined cohort from the real-life setting of a tertiary care center in India, the latest version (2021) of CKD-EPI formula for estimating eGFR, and a slope from a regression line of multiple eGFR estimates instead of only two to avoid the problem of misclassification due to fluctuations. Events-per-variable ratio was sufficient, and the model underwent discrimination and calibration analyses.

There are several caveats to these results. First, the retrospective single-centre study design reduces its applicability to other settings and increases its susceptibility to unmeasured confounding, as well as under-reporting or lack of standardization in documentation, even though we employed a pre-tested proforma and double abstraction. Secondly, individuals attending a tertiary care nephrology clinic probably represent a more advanced/selected sample than those receiving primary care, and thus the apparent prevalence of rapid progression may be overstated. Lastly, we used the eGFR calculated from creatinine level as well as the UPCR and not the albumin-creatinine ratio, and we were not able to obtain cystatin C levels, ambulatory BP or glycated haemoglobin trends, or medication changes during follow-up. Fourth, the root cause of CKD was not investigated as a predictor, while CKD of unknown etiology, which is pertinent to

the Indian population, was not studied separately. Fifth, as mentioned, the study is an observational one, and thus associations were reported without causation inferences; especially the association with RAAS inhibitors is vulnerable to confounding by indication. Lastly, the model has not been validated externally and further needs validation in other populations.

The following points out obvious future directions for this research topic. Prospective, multicenter studies that involve standardized albuminuria measurements, etiological classifications, and external validation of the predictive model, including the use of novel medications like sodium-glucose cotransporter-2 inhibitors, could enhance the current observations. Until then, this study gives a basis for using a small set of inexpensive and readily available markers to screen for patients who are at risk of experiencing rapid progression, thereby allowing them to be treated with proteinuria reduction, blood pressure and glycemia management, RAAS inhibition if needed, and close monitoring.

Conclusion

Rapid progression was common in this study carried out in a tertiary teaching hospital on patients with CKD stages G2-G4, and it was present in about one third of patients. Risk factors associated with rapid progression of kidney disease include high-grade proteinuria, diabetes mellitus, uncontrolled hypertension, hypo-albuminaemia, and anaemia, while the use of RAAS inhibitors was associated with less rapid progression of kidney disease. Since these risk factors are easy and cheap to obtain even during the first appointment with a nephrologist, they provide an excellent foundation for risk stratification and intensification of the management of proteinuria, hypertension, and hyperglycemia in these patients. Large multicentre prospective studies with standard measurements of albuminuria are needed to confirm these results and broaden their scope.

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