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A Multistate Model for the Analyzing of Chronic Kidney Disease Progression with Detecting Risk Factors Effect

By

Ahsan Abdalkhaliq Taha
Department of Statistics and Informatics College of Administration and Economics
Sulaimani University, Kurdistan
E,mail: ahsan.taha@univsul.edu.iq

Monem Aziz Mohammad
Department of Statistics and Informatics College of Administration and Economics
Sulaimani University, Kurdistan
E,mail: monem.mohammed@univsul.edu.iq

Abstract

Background

The evolution of kidney disease can be well modeled using a multistate model. In health economics, where the specification of health policies may be based on projections of long-term costs, it can play a pivotal role in medical decision making for kidney disease, where the prediction of outcomes is necessary under different treatment strategies and the multi-state model is an adequate tool to model the effects of covariates that influence the onset, progression of kidney function.

Objective

The primary purpose of this research is to create a stochastic model for the progression of Chronic Kidney Disease (CKD) into various stages.

Methodology

The kidney dysfunction progression data from 153 patients was analyzed using a continuous time homogeneous multistate model based on Markov processes. Kidney disease was classified into four phases using the Kidney Disease Improving Global Outcome (KDIGO) scale. The model incorporates four transitional states and a renal failure in an absorbing condition. Each patient's gender, age, BMI, diabetes, hypertension, Corona virus status, urea, serum creatinine, albumin, and disease duration were noted as predictive markers.

Results

The average time spent in states 1, 2, 3, and 4 prior to kidney failure was 7.23, 4.24, 4.59, and 1.68 years respectively. Covid-19 has a fivefold increased risk of progressing from stage 3 and 4 to absorbing condition. Also Age, hypertension, diabetes, urea, and serum creatinine all play a significant role in the progression of chronic kidney disease (CKD) into later stages

Conclusion

The findings of the study will be helpful to public health officials, who can utilize them to establish treatment programs and policies that will increase patients' chances of surviving their conditions. In addition, modeling the evolution of the disease assists in gaining an idea of the anticipated severity of the condition.

Keywords: Multi-State Model, Chronic Kidney Disease (CKD), Transition Intensity, Markov Models, Covid-19

Introduction

Chronic kidney disease has become a major issue in the health of the general people. However, kidney issues can be permanently avoided with early care. Medication and behavioral modification are effective means of preventing and slowing the progression of chronic diseases like kidney disease. Hospitalization is a common consequence of renal disease, so physicians are naturally curious about what they may learn from modeling outcomes like length of stay, survival, and the development of the disease. A large percentage of the adult population in industrialized nations suffers from chronic kidney disease (CKD) [1][2]. According to recent estimates, chronic kidney disease affects over 850 million people around the world [21]. Deterioration of renal function over a period of months or years is a hallmark of this condition. Increased risk of CKD is seen in those who also suffer from hypertension, diabetes, or cardiovascular disease. [1][2][3][4]. Patients with chronic kidney disease (CKD) have been found to be at a higher risk of contracting COVID-19 than the general population [20]. Research shows that those with CKD have a higher chance of contracting and dying from the new COVID-19 virus [22] [23]. Renal problems, such as severe proteinuria and hematuria, as well as increased serum creatinine and blood urea nitrogen, have been linked to COVID-19 infection [24]. Patients in stages 3,4 and 5 of chronic kidney disease were more severely affected by COVID-19 in terms of illness, everyday life, and psychiatric problem than those in stages 1-2. Anxiety levels among patients with CKD stages 3,4 and 5 spiked during the COVID-19 epidemic [25]. Serum creatinine levels are typically measured to diagnose CKD. A lower glomerular filtration rate (GFR), which is a measure of the kidneys' ability to eliminate waste materials in the urine, is associated with a higher serum creatinine level. GFR values can be determined using a variety of different formulas. The multi-state model is frequently utilized in cancer research, because there are various stages of cancer, which each indicate the course of the disease. [5,6] In a similar vein, research is being done to determine which aspects in HIV patients' lives are most likely to hasten the course of AIDS [7][8][9]. A multi-state model, as opposed to a straightforward survival model, can be utilized to effectively manage conditions such as diabetes, chronic renal disease, and other similar conditions [10] [11]. Kidney Disease Outcomes Quality Initiative (KDOQI) phases of CKD, which are irreversible and describe the degree to which kidney function has deteriorated in nature, are as follows [12]:

Table (1) *Chronic Kidney Disease Staging*.

Stage	Description	eGFR(ml/min/1.73 m^2)
1	Kidney damage with normal ↓ in GFR	> 90
2	Kidney damage with mild ↓ in GFR	60-89
3	Moderate ↓ in GFR	30-59
4	Severe ↓ in GFR	15-29
5	Kidney failure	< 15 (or dialysis)

GRF: Glomerular Filtration Rate

In order to describe the transitions that an individual makes between several states in continuous time, a multi-state Markov model has become a standard tool. The probability of changing from state i to state j can be calculated using this tool. Because chronic kidney illness is permanent, we have utilized this model to estimate the chances of passing from one

state to another. We have also calculated the average length of time spent in each state. The chronic kidney disease stage represents the kidney's overall health. Stages 1,2,3,4 and 5 of chronic kidney disease (CKD) are defined by the severity of the disease. Multistate Markov modeling for the development of CKD has not been performed in Iraq, as far as we are aware.

Materials and Methods

Data Description

In order to access CKD patient records, researchers contacted various accredited laboratories and hospitals from Shar Hospital at Sulemani governorate. Over two hundred and sixty-seven patients gave a favorable response, meaning they were willing to give their information. All of them gave their informed consent. Only 153 patients' records were determined to be consistent with the findings of this investigation. This study is a retrospective study of 153 CKD patients seen between February 2015 and May 2022.

Each patient's vital statistics, including their gender, age, and body mass index, were recorded. Each patient's medical history was documented, along with their diabetes, blood pressure, corona virus status, and creatinine, albumin, and urea levels. There was a doctor looking over the patients. Sex, hypertension, diabetes, and covid-19 status are taken as categorical variables, with the World Health Organization's or internationally acknowledged norms as the reference value for each. Hypertension (HTN) is diagnosed when systolic blood pressure (SBP) is greater than 130 mm Hg and diastolic blood pressure (DBP) is greater than 90 mm Hg, Age, BMI, serum creatinine, urea, and albumin are the continuous variables (Alb). Blood albumin should be between 4 and 5 grams per deciliter (g/dl), urea should range from 42 to 131 milligrams per deciliter (mg/dl), and serum creatinine should be less than 1.4 mg/dl for nephropathy to be diagnosed.

Multi-state model fitting relies heavily on properly organizing the data. Individual subjects are easily categorized according to the assigned identification numbers. Therefore, when capturing the data, care should be taken to ensure that all information pertaining to a single patient is included under the same unique ID. Table (2) provides the data format for the example data set.

Table (2) *Example of a Data Structure for a Model with Multiple States.*

Patient ID	age	years	gender	state	HTN	Diabetes	Covid-19
24	44.14520548	4.038356	1	2	1	0	0
24	46.14246575	6.035616	1	2	1	0	0
24	47.15616438	7.049315	1	3	1	0	0
85	60.63561644	6.975342	0	3	1	1	0
85	61.64931507	7.989041	0	3	1	1	1
85	62.61369863	8.953425	0	5	1	1	1
139	42.79726027	4.032877	0	1	0	1	0
139	43.83013699	5.065753	0	1	0	1	0
139	44.7890411	6.024658	0	1	0	1	0
139	45.80273973	7.038356	0	2	0	1	0

HTN: Hypertension.

In the context of a study, a transition is a change in state, and the probability of a transition is the rate at which that change occurs. There are five stages of chronic kidney

disease, numbered 1 through 5. The first four phases are all temporary, while phase five is deeply engrossing. Only forward transitions between distinct temporary states are permitted for a patient continuously.

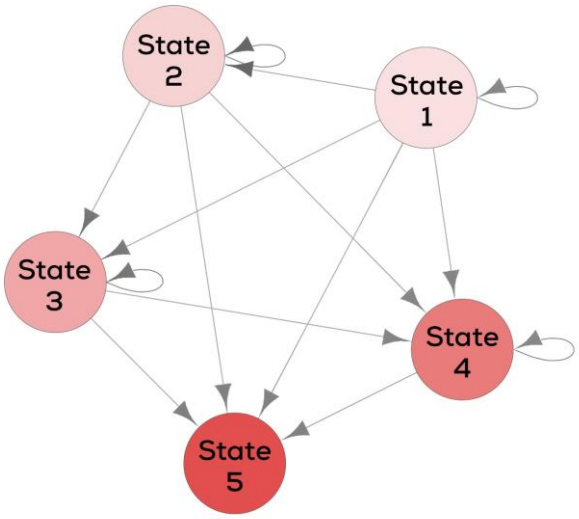

Figure (1) *State Transition Diagram*

Multi-State Model

It is common practice to employ Markov process-based multi-state models to simulate the development of a disease over continuous time, since such a process typically involves multiple transitions between states. [13]

For the renal disease progression data, we suggested a five-state continuous time homogeneous multi-state Markov model. A process is Markovian if the future is solely dependent on the present. Figure 1 depicts the model. The stages of CKD are continuous in time, but the state spaces are discontinuous. Due to the fact that disease progression is a continuous function of time and that the transition probability between states is time-dependent and thus independent of the time at which the transition actually occurs, we have considered a Markov process-based continuous time homogeneous multistate model [14].

If we define the patient's current state as $S(t) = k$, then the transition intensity is the rate at which the patient changes states during the time interval $(t + \delta\, t)$ is given by:

$$\lambda_{ij}(t) = \lim_{\Delta t \to 0} \frac{P(X_{t+\Delta t} = j | X_t = i)}{\Delta t}$$

Where λ_{ij} represents the immediate peril of transitioning from state i to state j. The matrix of transition intensities is given by:

$$Q(t) = \begin{bmatrix} -(\lambda_{12}+\lambda_{13}+\lambda_{14}+\lambda_{15}) & \lambda_{12} & \lambda_{13} & \lambda_{14} & \lambda_{15} \\ 0 & -(\lambda_{23}+\lambda_{24}+\lambda_{25}) & \lambda_{23} & \lambda_{24} & \lambda_{25} \\ 0 & 0 & -(\lambda_{34}+\lambda_{35}) & \lambda_{34} & \lambda_{35} \\ 0 & 0 & 0 & -\lambda_{45} & \lambda_{45} \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

For a process with an arbitrary number of states, denoted by n, Q is the transition intensity matrix (n rows by n columns). The pace at which a system changes from one state to another can be calculated instantly using the transition intensity. When there is no way for i to change to j, the entry (ij) is zero. List of diagonal entries:

$$\lambda_{ii}(t) = \lambda_{i.} = -\sum_{i \neq j} \lambda_{ij}(t)$$

When$i \in S$. Since state 5 is an absorbing state, there is no chance of leaving it. Each row of the transition matrix has a total value of zero. Finding the unknown transition intensities that optimize the likelihood of a multi-state model is called "fitting" the model [15].

The average amount of time a patient spends in a transitory condition during a single stay is estimated by the multi-state model. The average length of stay is determined by the formula$\frac{-1}{\lambda_{jj}}$, where jj is the j^{th} diagonal element of $Q(t)$.

$P(t) = exp\ [Q(t)]$ is a formula used to calculate the probability of a transition given its intensity at time t. The matrix of transition probabilities is defined as:

$$P(t) = \begin{bmatrix} P_{11}P_{12}P_{13}P_{14}P_{15} \\ P_{21}P_{22}P_{23}P_{24}P_{25} \\ P_{31}P_{32}P_{33}P_{34}P_{35} \\ P_{41}P_{42}P_{43}P_{44}P_{45} \\ P_{51}P_{52}P_{53}P_{54}P_{55} \end{bmatrix}$$

InP, adding up the rows gives you a total of one. $P_{jj}(s,t) = 1$ For the absorption state j. It is the transition probabilities that are used to construct the likelihood function. This L(Q)likelihood function is defined as follows:

$$L(Q) = \prod_{i} L_i = \prod_{i,j} L_{i,j} = \prod_{i,j} P_{S(t_{ij})S(t_{i,j+1})}(t_{i,j+1} - t_{ij})$$

This is the transition probability matrix, where the element $L_{i,j}$ is the $S(t_{ij})^{th}$ row and $S(t_{i,j+1})^{th}$ column entry.

Bidirectional transition rates were computed after accounting for covariate effects (such as gender, hypertension, diabetes, and corona virus status). Covariate effects on transition severities were accounted for using a proportional hazards regression model. Assuming we have a covariance matrix Z,

$$\lambda_{ij}[t|Z(t)] = \lambda_{ij0} \exp\ [B_{ij}^{T} Z(t)]$$

The regression coefficients, denoted by the vectorB_{ij}.

To conduct the multistate analysis, we used the msm package in R version 4.2.2.[16]

The likelihood ratio test was used to determine which model to use. The Akaike Information Criterion (AIC) value has been used to make comparisons between the various stochastic models for CKD stage development. The Akaike Information Criterion (AIC) is a measure of how well one statistical model compares to others. It is calculated using the formula$AIC = 2K - 2\ln(\hat{L})$, where Kthe total is number of free parameters in the model and $\hat{L}$ is the highest value of the likelihood function. Reduced AIC model is favored over other models. The likelihood ratio test provides a second criterion for model selection. It's a way to see how well two different models match the data, with the null model serving as an example of an alternative model. It relies on the likelihood ratio, which shows how much more likely

one model is to explain the data than another. The LR statistic, or log likelihood ratio statistic, is used in hypothesis testing. To calculate the LR statistic:

$$\text{LR Statistic} = -2(\ln \text{reduced model}) - (-2(\ln \text{current model}))$$

A higher LR value in general, the existing model performs better as $(-2\ln L)$ increases. A larger value suggests that the present model is preferable to the reduced model, as indicated by the smaller p-value. If there are many observations, the LR statistic will have the form of a chi-square test with K degrees of freedom, where K is the total number of predictors [11].

Results and Discussion

Exploratory data analysis

The purpose of this historical analysis was to simulate patients' renal disease development through time. From table (3) there were 153 patients, 90 of whom were male and 63 of them were female. Patients' mean (SD) ages were 47.53. (12.83%). There were 64 patients with hypertension (41.83%), 75 patients with diabetes (49.02%), 49 patients get Covid-19 (32.03%), and the means (SDs) for body mass index 25.84(5.83), creatinine 2.7(1.36), urea 98.08(3.36), and albumin 3.45(0.64).

Table (3) *Demographic and Clinical Characteristics.*

Variables	n (%) or mean (SD)
age in year(SD)	47.53(12.83)
gender-male(%)	90(58.82)
diabetic-yes(%)	75(49.02)
HTN-yes(%)	64(41.83)
Covid-19-yes(%)	49(32.03)
BMI(SD)	25.84(5.83)
Urea(SD)	98.08(33.4)
Cr(SD)	2.7(1.36)
Alb(SD)	3.45(0.64)

Categorical data are provided as frequency (%) and continuous values as mean (SD).

Table (4) *Summary of the Transitions.*

from	to				
	1	2	3	4	5
1	346	82	37	12	2
2	0	121	47	30	4
3	0	0	74	35	10
4	0	0	0	31	18

Multi-State Analysis

The first state had 67 patients, the second had 21, the third had 26, and the fourth had 39. The subsequent visit state shift of CKD patients is displayed in Table (4). The frequency of a CKD patient's regular checkups is directly linked to the severity of their condition. Regular checkups are expected from patients with CKD Stage 3, more so than those with CKD Stages 1,2 and 4. Stage 1 patients who returned for follow-up visits 346 times remained in that stage. A number of transition to stage 5 from stage 1,2 3 and 4 are (2,4,10 and 18) respectively. Due to the rapid decline in kidney function that characterizes CKD stage 4, a disproportionately large number of patient progress from this stage to stage 5. The numbers

on the diagonal represent the proportion of times when patients maintained their initial condition across many time points. Table (5) provides the average projected length of stay, and The fitted survival probability Plot is shown in Figure. 2.

Table (5) *Estimates of Mean Sojourn Time.*

stage	estimate	SE	C.I
1	7.23	0.45	(5.413397-8.205257)
2	4.24	0.37	(3.580825- 5.047805)
3	4.59	0.59	(3.598595-5.984023)
4	1.68	0.86	(0.2617, 3.7265)

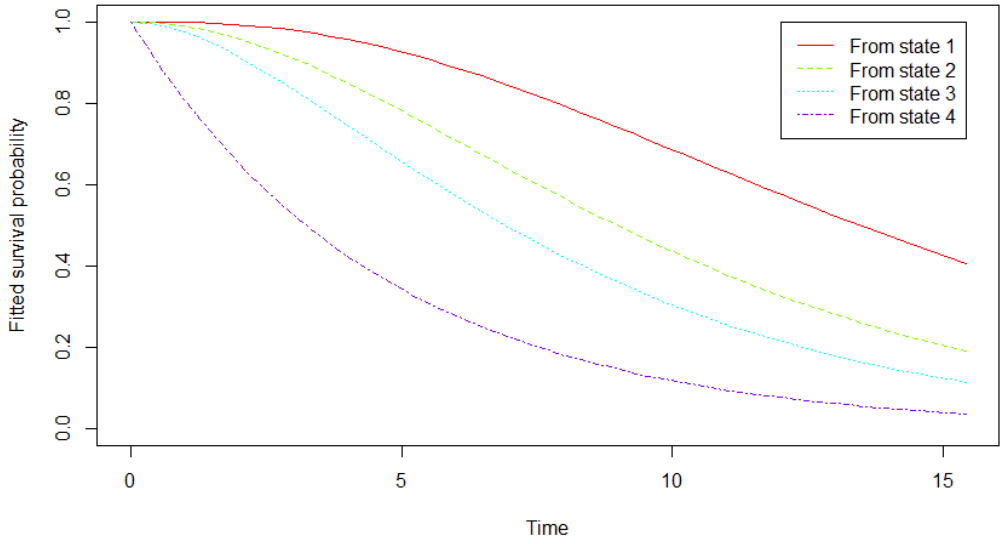

Figure (2) *Plot of Fitted Survival Probability*

This demonstrates that the 10-year survival probability for those with severe CKD is roughly 0.1, compared to 0.4 for those with moderate CKD, 0.5 for those with mild CAV, and 0.7 for those with normal CKD. If you have severe CKD, your chances of surviving past the first five years of the disease drop precipitously, to roughly 0.3.

Table (6) *Likelihood Ratio Test Statistics and P-Values of the Selected Models*

Covariate	-2 * log-likelihood	LR	df	p-value
no covariate	1664.15			
age	1626.902	37.248	10	0.0000512
gender	1643.34	20.81	10	0.022458106
BMI	1648.87	15.28	10	0.122182123
HTN	1641.9	22.25	10	0.013880449
diabetes	1637.45	26.7	10	0.002904481
Covid-19	1634.78	29.37	10	0.00108522
Urea	1632.23	31.92	10	0.000412916
Cr	1630.29	33.86	10	0.000195058
Alb	1636.54	27.61	10	0.002083701

HTN: Hypertension.

The likelihood ratio test statistics, p value, and -2 Log Likelihood values of the model with several covariates are displayed in Table (6). Model with covariate Age fits much better

than the base model with no covariates, as seen by the likelihood ratio test statistic of 37.248 (corresponding to Age) compared to a chi-square distribution with 10 degrees of freedom. However, although the model including the covariate BMI has a lower AIC value than the base model without covariates, the likelihood ratio test statistic of 15.28 does not indicate statistical significance when compared to a chi square distribution with 10 degrees of freedom ($p > 0.05$). It's possible to apply the same meaning to the other models. We started by fitting the model with a single covariate, and then we expanded our search to include many covariates. The models based on these covariates show that age, gender, hypertension, diabetes, urea, serum creatinine, and albumin are significant determinants for the progression of CKD into distinct stages, with a p value of less than 0.05. However, our data shows that BMI is not a significant covariate. Multi-state analysis was carried out using the msm package in order to learn how different factors influenced the strengths of the transitions. Clinically relevant factors were incorporated into univariate multistate models. In the final models, we included only the covariates that were statistically significant in the univariate analysis (p-value 0.5). Table (7) displays the hazard ratio and 95% confidence interval for each state change.

Table (7) *Hazard Ratio and 95% Confidence Interval.*

Transitions	Gender	HTN	diabetics	Covid-19
1-2	**2.39(1.17-3.82)**	1.29(0.491-3.39)	1.0141(0.171-1.86)	2.73 (1.25-9.92)
1-3	0.66(0.333-0.952)	1.13(0.626-2.035)	1.0141 0.171 1.86	0.05 (0.02-7.35)
1-4	0.97(0.626-2.035)	1.096(0.135-6.93)	1.0141 0.171 1.86	1.73 (1.06-8.72)
1-5	0.85(0.25-1.65)	1.07 (0.24,4.72)	1.0003(0.157-1.84)	1.23 (0.51-2.97)
2-3	1.68 (0.684–2.00)	**2.76(1.519-3.23)**	**3.7412(1.90-3.58)**	1.89 (0.73-4.85)
2-4	0.88 (0.31,1.51)	1.29(0.391-3.288)	2.0126(1.17-2.86)	**2.72 (1.73-5.90)**
2-5	1.097(0.134-8.93)	1.23 (0.51,2.97)	2.08 (0.76-5.58)	1.02 (0.44-2.31)
3-4	**0.28 (0.06–1.56)**	**2.34(1.19-3.95)**	1.211(0.14-3.77)	1.71 (0.89-25.06)
3-5	**2.01(1.35-4.95)**	2.26 (0.76,3.51)	**2.8624(2.02-3.71)**	**4.71 (0.89-25.06)**
4-5	0.13(0.07-0.89)	**4.72 (1.53,6.90)**	**3.9706(3.13-4.81)**	**5.23 (2.09-9.86)**

Bold values are significant. HTN: Hypertension.

Improvement rates among males were significantly higher than those among women. When compared to female patients in the same state, male patients in state 1 have a higher risk of illness progression [HR: 2.39; 95% CI (1.17-3.82)]. Males in state 3 have 72% reduced risk of experiencing state 4 compared to females but male patients in state 3 have a higher risk of illness progression to state 5 [HR: 2.01; 95% CI (1.35-4.95)]. Patients without diabetes fared better in terms of rates of improvement compared to those with diabetes, and those with diabetes in states 2,3 and 4 were at increased risk of complications [hazard ratio [HR] = 3.74 [95% confidence interval (CI] = 1.9–3.58], 2.8624 [95% CI = 2.02–3.71], and 3.9706 [95% CI = 3.13–4.81]]. Patients in states 2, 3, and 4 of hypertension are at greater risk for the development of the condition. The covid-19 was a risk factor and its effect on the progression from state 2 to state 4 was considerable [2.72 (1.25,5.9)]. The Covid-19 was a risk factor that had a noticeable impact on the shift from states 3 and 4, to ultimately the absorbing state. This shows that there is a significant mortality risk for patients with covid-19.

Men are more likely to develop CKD than women are. Significant factors in the development of CKD include diabetes and hypertension. The progression of CKD is frequently modeled and analyzed using multi-state models based on Markov processes [17]. The model's ability to shed light on the treatment's efficacy by illuminating the underlying

causes of adverse events makes it a powerful research tool. Studies of cancer are making use of the multi-state model since the disease progresses through distinct stages that correspond to qualitatively distinct transitions [18]. Chronic renal disease, and other disorders can also be controlled more effectively with a multi-state model rather than a basic survival model [19]. Multi-state model fitting was performed using the msm package in R 4.2.2 [16].

The CKD population is complex, hence we suggested a five-state multi-state model to describe the course of renal disease. There are some of the most fundamental requirements for implementing the multi-state model: As illustrated in Figure. 1 and Table 1, many states and transitions can be used to characterize the process. Make sure you're recording the information correctly as Table 2. Modify the model with the right program or suite and analyze and understand the findings. Study limitation are some participants did not reply favorably or were against giving their data, so they were left out of the current study. Considering that the study's original participants skew heavily White, our results may not be transferable to other groups.

Conclusion

Understanding how chronic diseases develop is crucial for appraising the future disease burden and determining the efficacy and cost-effectiveness of intervention strategies. Many studies of chronic disease use Markov chain models because of their ability to describe the time evolution of an individual across multiple states. Modeling is helpful in quantifying the rate at which diseases develop and the factors that influence this rate.

Important prognostic factors include age, gender, hypertension, diabetes, urea, and serum creatinine levels. According to the results of the likelihood test, the model including diabetes, HTN and covid-19 as a single covariate is the most plausible explanation for CKD development. CKD progresses slowly at first but quickly in later stages. Our finding the present study Covid-19 makes a significant chance about five times more of progressing from stage 3 and 4 to absorbing stage, also high blood pressure and diabetes status were significant predictors of CKD development and progression. Severe COVID-19 infection appears to be linked to CKD. Therefore, it is recommended that patients with CKD take additional measures to protect themselves against the infection. Patients with CKD who are suspected of having COVID-19 should be monitored closely by their doctors to catch any early warning signs of the disease.

Resources and information readily available

All relevant data used and/or analyzed during this investigation can be obtained from the corresponding author.

Author Contributions

The author designed the study, gathered the data, conducted the statistical analysis, and drafted the report. The work was subject to a critical review. Finally, Authors read and approved the final manuscript version.

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