e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(5); 1054-1060

Original Research Article

Risk Factors and Predictors of Mortality in Chronic Kidney Disease Patients in a Rural Tertiary Care Hospital

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Received: 25-02-2024 / Revised: 23-03-2024 / Accepted: 26-04-2024

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Conflict of interest: Nil

Abstract:

Background: An increase in the prevalence of Chronic Kidney Disease (CKD) was observed in the recent times. Regression analysis of risk factors and predictive factors of mortality in CKD patients in a community helps the physicians to be on the alert.

Aim of the Study: To study and evaluate the risk factors and predictive factors in the course of treating CKD patients for their accuracy using the area under the receiver operating characteristic (ROC) curve (AUC) analysis.

Methods: 47 non-transplant CKD patients at all stages of severity of both genders were included and the risk factors like. The Predictive factors for mortality were presented with AUC analysis and its associated 95% confidence interval (CI). AUC of 0.70-0.79 is considered acceptable, 0.80-0.89 is considered excellent, and more than 0.90 is considered outstanding.

Results & Conclusions: In view of the rapid increase in mortality of CKD patients due to development of Heart Failure worldwide an intense screening laboratory investigations such as BNPs, LAsR, E GFR, C reactive protein and UCPR are necessary which have a bearing on the mechanism of causing HF. These predictive factors are highly sensitive and caution the treating physician to take appropriate mode of treatment.

Keywords: Risk factors, Predictive factors, Chronic kidney disease, End stage kidney disease, Dialysis, Mortality, Death, Predictors.

Need for the Study: Though several clinical factors contributing to CKD and its mortality were mentioned, the accuracy of their role in resulting mortality was not clearly mentioned. The present study attempted to study the risk factors in depth and predictive factors of mortality in CKD patients using area under the receiver operating characteristic curve analysis. A total of 18 studies were identified. Eight hundred thirty two patients had non-dialysis CKD, and 13747 patients had end-stage kidney disease. Of 24 predictive factors, none were considered outstanding for mortality prediction. A total of seven predictive factors were identified as excellent. Our review summarizes the current accuracy of prognostic factors for CKD mortality.

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Introduction

Chronic Kidney Disease (CKD) is defined as a status of Kidney damage for more than 03 months, presenting with structural pathology and hematuria with a Glomerular Filtration rate (GFR) measuring less than 60mL/ min per 1.73 m^2 and/ or albuminuria more than 30mgin 24 hours. [1] The frequency with which CKD occurs in the community varies from geographical areas in India; it ranges from 08 to 16% of the populations. [3] CKD is recorded in lower and low middle income groups of populations. [4] (CKD) is less commonly observed in higher income groups. [5] As the age of the persons' increases from 30 years and above especially in those who have hypertension and Diabetes Mellitus the increased risk of CKD rose from 14.4% in 2020 to 16.7% in 2023. [6] In USA, among the general public the fall in GFR by 1 mL/min per 1.73 m^2 increased the risk of developing CKD by 50%. [7] As the CKD progresses, the adverse clinical outcomes also

increase and the likely such events are end-stage kidney disease (ESKD), dialysis dependent CKD, Associated CVS events, and all-cause increased mortality rate. [9] In a report by Tonelli et al [10] who undertook meta-analysis of nearly 38 studies, showed that the absolute risk for death increased exponentially with decreasing kidney function. [11]

Among various predictive factors of mortality in CKD patients, the most important factors requiring attention are age, diabetes, previous cardiovascular disease, adiponectin, and C-reactive protein. [12] In another study at Cleveland Clinic going through the CKD Registry by analysis the data showed that patients aged more than 65 years, had an increased risk of death with every one year increase in their age. Associated congestive heart failure, absent arteriovenous fistula, and deficient nephrology care before staring the dialysis played a significant role. [13] Bit the data on the mortality predictive factors for non-dialysis dependent CKD patients was found to be limited. [14]

As all these studies used regression analysis the accuracy of mortality Natriuretic peptides (NPs) are simple biomarkers in CKD patients to detect their risk of developing cardiovascular dysfunction. [15] The two commonly used NPs in clinical practice are B-type natriuretic peptide (BNP) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP). But their dependence on the predictability of mortality in CKD patients is debated. [16] In this context the present study attempted to study and evaluate the risk factors and predictive factors in the course of treating CKD patients for their accuracy using the area under the receiver operating characteristic (ROC) curve (AUC) analysis.

Materials

Type of Study: An observational prospective study.

Institution of study: Viswabharathi Medical College and Hospital, Kurnool.

Year of Study: March 2022 to February 2024.

Study populations involved 47 non- transplant CKD patients included from among the 136 CKD patients undergoing Dialysis unit of the Tertiary care Hospital situated in a rural area of Kurnool, District of Andhra Pradesh. An institution committee approval was obtained and an approved consent form and proforma was used to collect the data.

Inclusion Criteria: Patients aged above 30 years and below 65 years were included. Patients of both genders were included. Patients with non-transplant CKD of all CKD stage severity were included. Patients' Predictive factors for mortality were checked with AUC analysis and its associated 95% confidence interval (CI). Patients with long term follow up were included, (more than 4 years). All patients with stable stages III to V CKD with estimated GFR of 15 to 60 ml/min per 1.73 m^2 body surface area (BSA) were included. Patients willing to participate in the study were included.

Exclusion Criteria: Patients with transplant CKD were excluded. Patients aged below 30 years and above 65 years were excluded. Pediatric patients were excluded. Patients with history of coronary artery disease were excluded. Patients with LVEF less or equal to 50% or with regional wall motion deficit were excluded. Patients with congenital or organic valvular heart disease were excluded. Patients with cardiac arrhythmias including atrial fibrillation were excluded. Patients with CVA were excluded. Patients with peripheral vascular disease are excluded. Patients with hemoglobin less than 9 g/dl were excluded. Patients with liver dysfunction were excluded. Patients with acute systemic infections were excluded.

All the patients were encouraged to undergo an echocardiogram followed immediately by a blood sample draw. All the patients were examined clinically first and the following investigations were undertaken: Estimation of 1. BMI 2. N-terminal pro-brain natriuretic peptide (NT-proBNP). 3. Brain natruretic peptide (BNP). 4. Soluble urokinase plasminogen (SuPAR). 5. Left Atrial reservoir strain (LAsR). 6. C-reactive Protein (CRP), 7. Systolic BP; 8. Estimated Glomerular filtration rate (eGFR); 9. Urine protein creatinine ratio (UPCR) and; 10 Pulse pressure.

BNP: Also called a B-type natriuretic peptide test measured in picograms (pg) per milliliter (mL) or nanograms per liter. The range included was: Normal: Less than 100 pg/mL, High: More than 400 pg/mL, Between 100 to 400 pg/mL BNP less than 300 pg/mL was taken as normal, more than 450 pg/mL was considered that the patient is likely to have Heart Failure (HF); Values more than 9000pg/mL was considered as possible HF.

Similarly NT-proBNP values in patients with CKD not on dialysis were taken as 1850pg/mL with 95% sensitivity and 80% specificity to diagnose HF. For CKD patients on dialysis the values were 8000pg/mL with 87% sensitivity and 79% specificity. To diagnose HF in CKD patients the cut off value of NT–proBNP was taken as 4200pg/mL. The minimal detectable suPAR concentration was 33pg/ml. The intra-assay coefficients of variation for low (mean 836 pg/ml), medium (1593 pg/ml), and high (2412 pg/ml) suPAR levels were 2.1%, 4.1%, and 7.5%, respectively were considered as abnormal. For LAsR the median value of 35.5% was taken as significant in the subjects. The lower limit was

21.9%. GFR was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) formula and expressed in ml/min per 1.73 m^2 BSA. The normal urine protein/creatinine ratio is not more than 200 mg/g. The typical UPCR normal range is 0.15 to 0.50 mg/mg. Patients with CKD with 3.5/mg/mg (3500mg/g) were considered as risk of mortality. C-reactive protein values in serum above 50mg/L were considered as high risk for mortality in CKD patients. An AUC of 1.0 among the predictable factors for mortality was an ideal predictor with 100% sensitivity and 0% false positive rate. AUC values between 0.70 and 0.79 considered acceptable and finally 0.80-0.89 AUC values were considered excellent, and more than 0.90 considered outstanding. All the data was analysed using standard statistical methods.

Statistical Analysis:

Data analysis was performed using SPSS 15.0 software (SPSS Inc, Chicago, IL). Continuous data were checked for normality using the Kolmogorov-Smirnov test and expressed as mean ± SD or median (range) as appropriate, and categorical data as percentages.

Differences between groups were tested using one-way analysis of variance or a nonparametric alternative (Mann-Whitney test) as appropriate. Models were separately constructed for BNP and NT-proBNP. Statistical significance was set at $P < 0.05$.

Based on reported correlations (in the range of −0.2 to −0.3) between BNP and GFR for patients with and without HF, a sample size of 47 patients was considered sufficient to achieve statistical significance with 85% power and allowable 2-sided error of 0.05.

Results

Out of 47 non-transplants CKD patients 22 (46.80%) patients had non-dialysis CKD, and the remaining 25 (53.19%) patients had dialysis-dependent CKD. Among the 25 (53.19%) dialysis-dependent CKD patients, 13 (27.65%) required hemodialysis (HD) and 12 (25.53%) patient's required peritoneal dialysis (PD). The 22 (46.80%) non-transplant CKD patients were composed of non-differentiated mixed population of HD and PD patients.

There were 32 (68.08%) male patients and 15 female patients. The male to female ratio was 2.123: 1. 06 (12.76%) patients were aged between 08 and 15 years, 08 (17.02%) patients were aged between 16 and 25 years, 10 (21.27%) patients were aged between 26 and 35 years. 07 (14.89%) patients were aged between 36 and 45 years. 11 (23.40%) patients were aged between 46 and 55 years. 05 (10.63%) patients were aged between 56 and 65 years.

The mean age was 46.83±3.75 years. A total of 11 predictive factors for mortality were observed and analysed in the study. Based on their area under the receiver operating characteristic (ROC) curve (AUC) analysis the factors were divided into 03 categories. AUC values more than 0.90 was considered as outstanding for mortality of CKD patients.

AUC values between 0.70 and 0.79 were considered as acceptable range. AUC values between 0.80 and 0.89 were considered as excellent predictive factors of mortality. Age, clinical, Laboratory and other variables of the 47 non-transplant CKD patients were analysed and tabulated in the Table 1.

Table 1: Showing the mean values of clinical, laboratory test values and their ranges in the study (n-47)

Variable	Number	Percentage	P value
Age in Years			
08 to 15	06	12.76	
16 to 25	08	17.02	0.116
26 to 35	10	21.27	
36 to 45	07	14.89	
46 to 55	11	23.40	
56 to 65	05	10.63	
Gender			
Male	32	68.08	0.341
Female	15	31.91	
BMI (Mean ; SD)	24.85±3.11	--	0.103
Pulse pressure (Mean; SD)	48.24±2.54	--	**0.021**
Systolic BP, Mean; Range	151.36±6.11	--	**0.001**
N-terminal pro-brain natriuretic peptide (NT-proBNP in pg/mL). Mean; Range	2131 (1957- 6321)	--	**0.001**
Brain natruretic peptide (BNP). Mean; Range	457 (321- 1139)	--	**0.001**
Soluble urokinase plasminogen (SuPAR). Mean; Range	298 (254- 1012)	--	**0.001**
Left Atrial reservoir strain (LAsR). Mean; Range	37.5% (35% – 45%)	--	**0.001**
C-reactive Protein (CRP), Mean; Range	67 (56- 210)	--	**0.001**

Estimated Glomerular filtration rate (eGFR), Mean; Range	38 (26–54)	--	**0.001**
Urine protein creatinine ratio (UPCR), Mean; Range	4.1mg/mg(26-47mg/mg)	--	**0.001**
Follow up Duration	4.8 Yrss±1.10 Yrs		**0.001**
AUC values	Excellent (0.80-0.89)-26 Acceptable range (0.70-0.79)-21 Definite (more than 0.90)- 0		

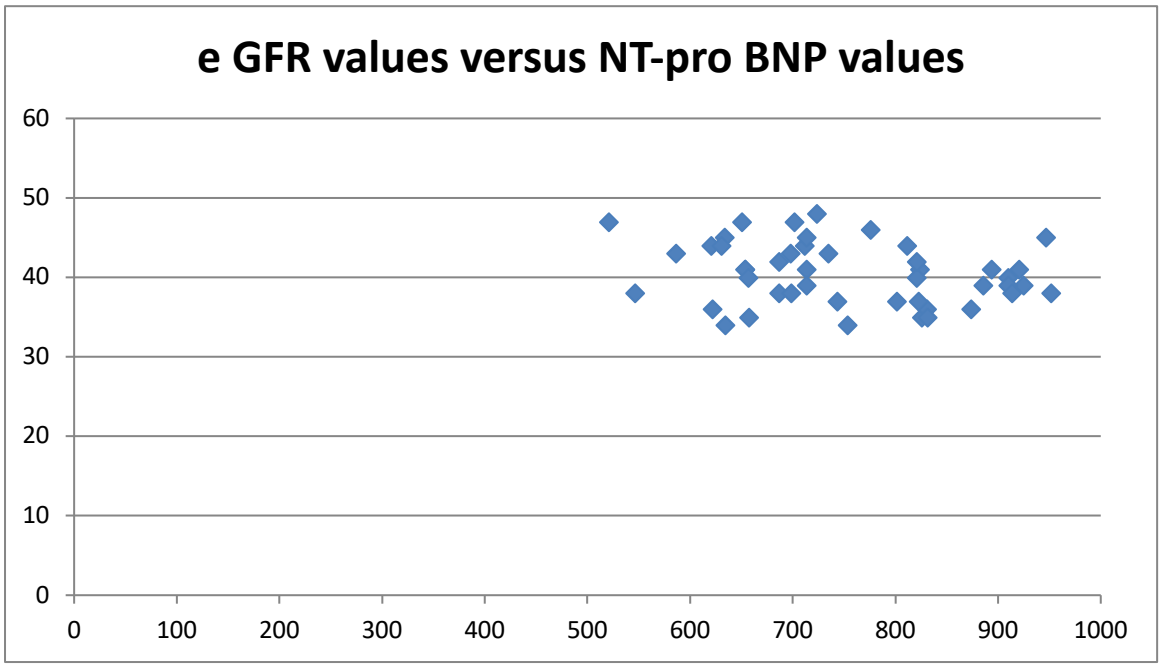

Figure 1: Showing the scatter plot of eGFR against NT-proBNP values in the study (n-47, (Y Axis: e GFR values and Y axis NT-proBNP values)

Discussion

Out of 47 non- transplant CKD patients 22 patients had non-dialysis CKD, and the remaining 25 patients had dialysis-dependent CKD. Among the 25 dialysis-dependent CKD patients, 13 required hemodialysis (HD) and 12 patients' required peritoneal dialysis (PD). The 22 non-transplant CKD patients were composed of non-differentiated mixed population of HD and PD patients. age, gender, AUC and its 95%CI, and follow-up duration. Full articles or conference abstracts that reported the AUC without 95%CI were excluded. An AUC of 1.0 represents the ideal predictor with 100% sensitivity and 0% false positive rate.

Thus, in this mortality model, factors with AUC closer to 1.0 represented a better predictor for mortality, with AUC of 0.70-0.79 considered acceptable, 0.80-0.89 considered excellent, and more than 0.90 considered outstanding. The risk factors and predictive factors which increase the chances of mortality were assessed in this study by using BMI, N-terminal pro-brain natriuretic peptide (NT-proBNP), Brain natruretic peptide (BNP), Soluble urokinase plasminogen (SuPAR), Left Atrial reservoir strain (LAsR), C-reactive Protein (CRP), Systolic BP, Estimated Glomerular filtration rate (eGFR), Urine protein creatinine ratio (UPCR) and Pulse pressure. All these laboratory investigations are commonly used in the clinical practice of treating the CKD patients who develop Heart Failure. [17] The NT-proBNP and BNP values showed a clear characterization of the dependence of these values on Kidney function as a common co-morbidity. [18] Among these the best NP value in predicting the cardiac dysfunction is yet not clear. [19]

The plasma BNP and its biological active fragment NT-proBNP are cleared through endocytosis and lysosomal degradation once they are bound to NP clearance receptor type C and secondarily through proteolysis by neutral endopeptidase [20] The renal clearance of NT-proBNP is not clear and their site of receptors also not known but it has action on heart muscle causing relaxation of coronary vessels, reduces the cardiac preload and sympathetic activity.

This results in inhibition of the secretion of catecholamines and the spread of sympathetic impulses, resulting in inhibition of vasoconstriction, thus relaxing arteries and veins. [23] Among the above two BNPs NT-proBNP is more prone than BNP to be influenced by renal dysfunction. [24] In the present study there was inverse correlation between GFR and NT-proBNP (Fig 1) but not with BNP in both asymptomatic stage III and IV CKD patients in whom cardiac risk stratification is of particular importance. [25] In another similar study by Multinational Study [5], showed a statistical correlation between GFR and BNP in patients with CKD and presenting with acute dyspnea. 35% of the patients also had history of HF and 25% had myocardial infarction. [26] In the study of Tsutamoto et al. [27], HF patients with e- GFR values less than 40 ml/min and with highest BNP levels were found to have high median LV end-diastolic pressure compared with those with better preserved GFR. [28]

Sometimes the low estimated GFR values may be recorded in CKD patients with poor renal perfusion or those on diuretics in acute HF, which might cause confusion over the actual relationship with NPs and HF. [5] Vickery et al. [9] from their study showed that 06% of the patients with increased BNPs concentrations associated with falling GFR, especially with NT-proBNP had HF even though the median LVEF was normal for all patients. [29] Luchner et al. [30], [10] also showed, that among the CKD patients who suffered from myocardial infarction had virtually two fold rise in the values of BNPs. [31]

In the present study a correlation between the BNP values and age, gender though reported to be positive in the western literature, was not observed on univariate analysis and also lacked independent predictive value. (Table 1), [32] A total of 10 predictive factors for mortality in CKD patients were identified. They were divided as three categories depending on their AUCs. None had an AUC greater than 0.90, which is considered outstanding for mortality prediction. The majority (n = 21) were in the acceptable range (AUCs 0.70-0.79). A total of seven predictive factors were identified as excellent (AUCs 0.80-0.89), (n-26). Table Table 1 shows the predictive factors for mortality based on the population studied.

Limitations

In this study there was a possibility of existing occult HF in CKD patients which was not taken care of while enlisting the patients by undertaking further ECHO Cardiography (2D ECHO). Other intensive screening test to rule out ischaemic heart disease in the CKD patients was not undertaken.

Conclusions

In view of the rapid increase in mortality of CKD patients due to development of Heart Failure worldwide an intense screening laboratory investigations such as BNPs, LAsR, E GFR, C reactive protein and UCPR are necessary which have a bearing on the mechanism of causing HF. These predictive factors are highly sensitive and caution the treating physician to take appropriate mode of treatment.

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