Risk factors associated with mortality among chronic kidney disease patients on regular hemodialysis presenting in emergency services.

Authors: Dr. Tirtha Man Shrestha, MD [1]

Dr. Laxman Bhusal, MD, DMEM[1]

Dr. Ram Prasad Neupane, MD, DMEM[1]

Dr. Rajan Ghimire, MD[2]

Prof. Pratap Narayan Prasad, MD[3]

Affiliations of authors:[1]Department of General Practice and Emergency Medicine, Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal;

[2] Clinical Coordinator, District Hospital, Terhathum, Province 1, Nepal.

[3] Campus chief, Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal

Corresponding author: Tirtha Man Shrestha, Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University, Maharajgunj, Kathmandu, Nepal; email: tirtha_48@yahoo.com.au, Mobile number:+977-9851017345

ABSTRACT

Background

With the increasing number of chronic kidney disease (CKD), emergency visit of these patients is also increasing. This study tried to find some of the reasons for which patients with CKD visit the emergency room and the reasons for their mortality.

Method:

A cross-sectional study was done in the emergency room of Tribhuvan University Teaching Hospital, Kathmandu, Nepal. We conducted this study from 1 May 2018 to 31 October 2018 among the adult CKD patients under regular hemodialysis. We used a convenience sampling method. Three hundred patients were included. We studied the following variables: patients' age, sex, risk factors, laboratory parameter during the emergency visit (viz. hemoglobin, pH, serum bicarbonate level, and potassium level), emergency hemodialysis, blood transfusion, and clinical outcome during emergency room stay**.**

Result:

We enrolled 300 patients in the study. The mean age was 45.04 years in the mortality group and. 45.69years in the survival group. 152 (50.7%) of patients had hypertension. Mean hemoglobin was 6.52gm% (S. D=1.93). Mean hemoglobin in survivor and the non-survivor group was 6.59gm% and 5.58gm% respectively. Serum creatinine was 1220.87 mmol/L and 1064.01 mmol/L in mortality and survivor group respectively. Likewise, serum potassium was 6.13mEq/l and 5.74mEq/l among mortality and survivor groups respectively. Binary logistic regression showed significant association (p-value<0.05) of anemia, emergency dialysis. and presence of sepsis with the mortality. There was significant correlation of presence of comorbidities, anemia, serum creatinine, serum potassium level, and sepsis with mortality. Area under the Receiver

Operating Curve to predict mortality among CKD patients was 0.660 for potassium and 0.598 for serum creatinine.

CONCLUSION: Anemia, increased serum creatinine, and hyperkalemia was significantly correlated with mortality in chronic kidney disease and were causes of frequent visits in the emergency room. Therefore, we should address these factors during the management of CKD patients.

KEYWORDS: Chronic kidney disease, emergency presentation, mortality, risk factors.

INTRODUCTION

In Nepal, the cases of chronic kidney disease are increasing. In the same ratio complications related to CKD and hemodialysis are also increasing. The management of this disease is expensive. 10.6% of Nepalese had CKD during a community screen [1]. In contrast, 56.02% of outpatient and in-patient cases of a tertiary hospital in Nepal had chronic kidney disease[2]. Approximately 13.1% of United States adults had CKD and it led to ESRD, cardiovascular disease, and premature death.[3] The main reasons for frequent visits of CKD patients in emergency services were high blood pressure, anemia, high potassium, increased metabolic acidosis, pulmonary edema, hypoxia, hypocapnia, cardiac failure, and other cardiovascular problem[4]. Diabetes, hypertension, glomerulonephritis, and other disorder are major causes of CKD.[5–7]

Early detection and treatment can often prevent CKD from getting worse. The risk of death from cardiovascular disease is higher than requiring dialysis among CKD patients.[3] A study was done in Haryana, India in 2015 which showed chronic glomerulonephritis as the commonest

presentation (34.72%) followed by diabetic nephropathy (23.44%) as a cause of CKD.[5] Similar study in Nepal showed the presence of overweight, obesity, hypertension, diabetes, and proteinuria were 20%, 5.0%, 38.6%, 7.5%, and 5.1% respectively.[8] Cancer (31.9%) and cardiovascular disease (30.2%)[9] were the two most common causes of mortality. In patients with CKD having comorbidities like cardiovascular problems and malignancy, hyponatremia was associated with all-cause mortality. Hypernatremia was associated with all-cause and non-cardiovascular/non-malignancy related deaths.[10] Though metabolic acidosis is common among hemodialysis patients, respiratory acid-base disorders are also important to consider. Therefore, complete acid-base measurements should be done for a complete analysis of acid-base disorder in CKD patients [11] Patients with CKD have an increased risk of atrial fibrillation and stroke[12]. There are few centers for the diagnosis and management of kidney diseases in Nepal. CKD is one of the common causes of the Emergency visit. Therefore, the emergency physician should update their knowledge on this matter. Despite the maintenance hemodialysis, frequent emergency visits of patients point towards either inadequate hemodialysis or inadequate management of other medical conditions like hypertension, diabetes, anemia, hyperkalemia, etc. Therefore, this study aims to analyze the factors associated with the mortality of chronic kidney disease cases under regular maintenance hemodialysis during an emergency visit. This will help to improve the management of patients and decrease the emergency room visit of CKD patients.

METHODOLOGY

This was a prospective cross-sectional study. It was conducted in the emergency room of Tribhuvan University Teaching Hospital, Maharajgunj; Kathmandu; Nepal from 1 May 2018 to 31 October 2018.

Sample size

The sample size was calculated using the Daniel method.[8] Sample size was 300. We collected samples without randomization by purposive non-probability sampling method. The inclusion criteria for the study were: (a) Patients of age >16years. (b) Patients with chronic kidney disease under maintenance hemodialysis. (c) Patients visiting the emergency room. Pregnant women and patients with 'do not resuscitate' order were excluded from the study.

Data analysis

We studied variables in the following sectors:

Demographic data: Age, sex

Comorbid health conditions: diabetes, hypertension, glomerulonephritis, heart failure, liver failure, malignancy, chronic pulmonary disease,

Management in an emergency: emergency dialysis and blood transfusions

Laboratory values: hemoglobin, serum potassium, serum creatinine, serum bicarbonate.

Clinical outcome: Improved or died.

We collected data from the clinical record file of the patient after getting proper consent. Patients were followed until their stay in the emergency room. Clinical outcomes (survived and mortality) were studied during emergency stay only. These study variables were analyzed to search for any association with mortality among the patients using Pearson's Correlation. We did binary logistic regression to find the association of confounding factors. Receiver operating curve (ROC) analysis[13] and area under the ROC were used to calculate the efficacy of various laboratory tests to predict mortality in CKD patients. We used IBM SPSS 25.0 for all calculations. Institutional Review Board, Institute of Medicine, Tribhuvan University; Kathmandu; Nepal provided the

ethical clearance.

RESULTS

During the study period from 1 May 2018 to 31 October 2018, 300 patients met the criteria to participate in the study. Among them 190 (63.30%) were male and 110 (36.70%) were female. Among these patients, 152 (50.7%) had hypertension, 63 (21%) had diabetes, 63 (21%) had glomerulonephritis, and the remaining seven (2.33%) had other comorbidities like nephrolithiasis, benign enlargement of the prostate, renal tuberculosis, and polycystic kidney disease. 269 (89.7%) of these patients underwent emergency hemodialysis and 239 (79.7%) required blood transfusion. 20(6.7%) patients had sepsis. 23 (7.7%) participants died during the emergency stay.

The mean age of all patients was 45.64years (S.D=17.15). Mean hemoglobin was 6.52 gm% (S.D=1.93), pH was 7.17 (S.D=0.154), serum creatinine was 1076.3 mmol/l (S.D = 367.25), serum potassium was 5.77 mEq/l (S.D =0.76), pCO_2 was 22.48 (S.D=6.82), and serum bicarbonate was 10.81 mmol/L(S.D=4.36). Data for pH and serum potassium were negatively skewed (-0.192 and -0.271 respectively).

Out of 23(7.7%) mortality,16 (5.33%) were male and 7 (2.33%) were female. Among the non-survivors, 19(6.33%) had other comorbidities like hypertension, diabetes, and glomerulonephritis. 18 (6.0%) patients who had sepsis died and 2 (0.67%) survived(Table 1).

The mean age in the survivor and non-survivor groups were 45.04 (S.D= 18.96) and 45.96 (S.D=17.03) respectively. Patients who could not survive had lower hemoglobin (5.58 vs 6.59), pH (7.11 vs 7.18), serum bicarbonate (9.89 vs 10.89) than those who survived. Meanwhile, those

who could not survive had higher pCO_2 (24.04 vs 22.35), serum creatinine (1220 vs 1064), serum potassium (6.13 vs 5.74) than those who survived (*Table 2*).

Binary logistic regression analysis showed significant association of low hemoglobin (OR = 2.679, p value = 0.041), emergency dialysis (OR=0.016, p value =0.015) and presence of sepsis (OR=7649.521, p value < 0.001) to increase mortality rate in chronic kidney disease ( ). However, there was significant correlation of mortality with low hemoglobin (Pearson's correlation= 0.141, p value= 0.015); high serum creatinine (Pearson's correlation=-0.114, p value= 0.049); high serum potassium (Spearman's correlation= -0.148, p value=0.01); presence

	p-Value	Odds Ratio	95% C.I. for Odds Ratio		Pearson's correlation	p-value
			Lower	Upper		
Age in years	0.423	1.028	0.960	1.101	0.01	0.862
Sex	0.204	0.234	0.025	2.201	0.037	0.52
Hypertension	0.999	5093786.484	0.000		-0.016	0.778
Diabetes	0.999	5951714.182	0.000		-0.056	0.331
Glomerulonephritis	0.999	598326.416	0.000		0.005	0.928
Hemoglobin (gm%)	**0.041**	2.679	1.039	6.907	0.141	**0.015**
pH	0.415	92.508	0.002	4886427.644	0.111*	0.054
pCO2	0.747	1.025	0.883	1.190	-0.066	0.256
HCO3	0.342	0.813	0.531	1.246	0.061	0.295
Serum Creatinine	0.293	0.999	0.996	1.001	-0.114	**0.049**
Serum Potassium	0.144	0.456	0.159	1.307	-0.148*	**0.01**
Dialysis	**0.015**	0.016	0.001	0.450	-0.026	0.658
Blood Transfusion	0.291	0.137	0.003	5.487	0.052	0.368
Sepsis	**<0.001**	7649.521	137.294	426203.855	0.827	**<0.001**

of sepsis (Pearson's correlation= 0.827, p value<0.001). The value of serum potassium was negatively skewed so Spearman's correlation was used.

Receiver operating curve (ROC) and the area under the receiver operating curve (AUROC) for serum potassium and creatinine to predict mortality in CKD patients is shown in figure 1 and table 4. AUROC for both serum creatinine and potassium is <0.7 which means these tests are poor to predict mortality.

Youden index was maximum (0.33) at serum potassium 6.25mEq/L. So, using serum potassium level of 6.25mEq/L as a cutoff to predict mortality among CKD patients; sensitivity was 57% (positive likelihood ratio = 2.37) and specificity was 76% (negative likelihood ratio = 0.57). Similarly, the Youden index was maximum (0.30) at serum creatinine level 1195 mmol/L with a sensitivity of 61%(1.96) and specificity of 69% (0.57) (*Table 5*).Sensitivity decreases and specificity increases for an increase in the value of serum potassium and creatinine.

DISCUSSION

With the advancement in modern medicine, the incidence of communicable diseases is decreasing. Non-communicable diseases like hypertension and diabetes are rising as the prominent health problem[14]. With this, there is an increase in the incidence of CKD also[15]. The mean age of patients was similar to the study done by Sigdel MR and et .al in the same center [16]. The mean age in the mortality group was 45.04 years (S.D=18.96) and in the survivor group, it was 45.69 years (S.D=17.03). Similar results were found in studies from Saudi Arabia[17], Africa[18], India[19,20]. In a developed nation, the average age for CKD was 60years and above[21]. In our study, Hypertension(50.7%) was most common followed by diabetes (21%) and glomerulonephritis (21%). In another study, CKD was seen in newly diagnosed hypertensive patients (51.9%) and normotensive controls (23.6%) which were statistically significant (p-value

<0.001).[22] Chronic glomerulonephritis (42.3%) and diabetic nephropathy (21.1%) were the leading causes of CKD. Nephrotic syndrome accounted for 22.36%.[2]

We found that the mean serum bicarbonate level was 9.89mmol/L (S.D=5.06) in non-survivors and 10.89 mmol/L (S.D=4.30) in the survivor group. Patients with low eGFR had lower serum bicarbonate levels (<22mmol/L) which are associated with adverse renal outcome and mortality[10]. In our study, mean serum potassium in the mortality group was 6.13(S.D=0.89, range=4.2) and in survivor, it was 5.74(S.D= 0.78, range=6.20). The risk of hyperkalemia is increased with CKD, and its occurrence increases the odds of mortality[23–25] and need of dialysis[4]. Hypokalemia and hyperkalemia both increase the risk of mortality in CKD patients while hypokalemia is associated with faster CKD progression[25].

In our study, 89.7% of patients underwent emergency dialysis. A south Indian study showed that nearly 87.4% of patients with ESRD required emergency dialysis[26]. Scheduled dialysis decreased mortality (3%vs 17%, *P*=0.01; absolute risk reduction, 14%)[27] in comparison to emergency-only dialysis. In comparison to patients without hemodialysis, patients under maintenance hemodialysis had higher ED utilization and a significantly higher risk of resuscitation during ED visits[27].

Our study showed that overall mean hemoglobin was 6.52 gm% (S. D=1.93). Mean hemoglobin among the non-survivor group was 5.58 gm%(S.D=2.02) and in the survivor group, it was 6.59 gm%(S.D=1.9). The study done by Sigdel MR showed that mean hemoglobin was 9.98gm% in patients with CKD stage 3 and 8.23gm% in CKD stage 5[16]. 79.7% of our study population received blood transfusions. In another study, 20% of non-dialysis patients received at least one transfusion (mean of two units, range = 1-4). The mean hemoglobin before transfusion among these patients was 8.8g/dl (S.D=1.5)[28].

We found association of low hemoglobin (OR=2.679, p value=0.041), emergency dialysis (OR=0.016, p value=0.015) and presence of sepsis (OR=7649.521, p value < 0.001) to increase mortality rate in chronic kidney disease. There was significant correlation of mortality with low hemoglobin (Pearson's correlation= 0.141, p value= 0.015); high serum creatinine (Pearson's correlation=-0.114, p value= 0.049); high serum potassium (Spearman's correlation= -0.148, p value=0.01); presence of sepsis (Pearson's correlation= 0.827, p value <0.001).

Many studies had shown that hyperkalemia is associated with increased mortality in CKD patients[29]. Despite the normal range of hemoglobin, patients with CKD and low quintile hemoglobin (13.2g/dl, range 7.6 to 14.6 g/dl), had increased risk for CHD-related death[30]. In patients with CKD not under hemodialysis, erythropoiesis-stimulating agents (ESA), users had higher rates of death and cardiovascular events than non-users of ESA[31]. In contrast, a systemic review and meta-analysis involving ESA users showed an increased risk of mortality in the high Hb levels (RR 1.18; 95% CI 1.02 to 1.37). Overall, compared with low Hb levels(<10g/dl), high Hb levels(>13.0g/dl) are associated with increased risk of hypertension (RR = 1.40; 95% CI = 1.11 - 1.75), stroke (RR = 1.73; 95% CI = 1.31 - 2.29), and hospitalizations (RR = 1.07; 95% CI = 1.01 - 1.14)[31]. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend target hemoglobin levels in the range 11 to 12 g/dl, whereas hemoglobin >13 g/dl should be avoided[32]. In comparison to patients without CKD or with other chronic medical conditions, CKD patients had the highest 90-day mortality[33]. Mortality due to sepsis was about 50-fold higher in dialysis patients compared with the general population[34].

CKD increases the number of visits to emergency services and hence increases the resource use of emergency services. Certain factors like anemia, hyperkalemia, acid-base disorder, and the presence of other chronic health conditions like hypertension, diabetes, glomerulonephritis not

only leads to the poor outcome of these patients but also increases the emergency visits. The major limitation of this study is that it included laboratory parameters of CKD patients during an emergency visit. We studied mortality during the emergency room stay only. So we recommend to include clinical parameters, longer duration of follow up, and larger studies with randomization during further studies.

CONCLUSION

There were factors like anemia, hyperkalemia, increased serum creatinine, and sepsis which increased emergency visits and mortality of CKD patients. Therefore these factors need to be well controlled to decrease mortality and emergency visits of these patients.

DECLARATIONS:

Acknowledgments: Not applicable.

Authorship: Dr. TMS, Dr. PNP, and Dr. LB did paper conceptualization, ethical clearance, data collection, and submission to the journal**;** Dr. RPN and Dr. RG did data analysis and manuscript preparation**.** All authors consented to the publication of this article.

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INFORMED CONSENT: Verbal consent was taken from the patient and/or legal guardian if the patient was critically ill.

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TABLES

Table 1 Comparision of categorical variables among survivor and non-survivor group.

		Mortality			
		Yes (N=23)		No (N=277)	
		Number	%	Number	%
Sex	Male	16	5.33%	174	58.0%
	Female	7	2.33%	103	34.33%
Comorbidities	No	4	1.33%	11	3.67%
	Yes	19	6.33%	266	88.67%
Hypertension	Yes	11	3.67%	141	47.0%
	No	12	4.0%	136	45.33%
Diabetes	Yes	3	1.0%	60	20.0%
	No	20	6.67%	217	72.33%
Glomerulonephritis	Yes	5	1.67%	58	19.33%
	No	18	6.0%	219	73.0%
other comorbidities	Yes	0	0.0%	7	2.33%
	No	23	7.67%	270	90.0%
Emergency hemodialysis	Yes	20	6.67%	249	83.0%
	No	3	1.0%	28	9.33%
Blood Transfusion	Yes	20	6.67%	219	73.0%
	No	3	1%	58	19.33%
Sepsis	Yes	18	6.0%	2	0.67%
	No	5	1.67%	275	91.67%

Table 2 Comparision of discrete variables using measures of central tendencies among survivors and non-survivor groups.

	Mortality			
	Yes (N=23)		No (N=277)	
	Mean; S.D	Range	Mean; S.D	Range
Age in years	45.04; 18.96	62	45.69; 17.03	69.00
Hemoglobin (gm%)	5.58; 2.02	8	6.59; 1.9	10.00
pH	7.11; 0.21	0.82	7.18; 0.15	1.10
pCO2(mmHg)	24.04; 13.72	62	22.35; 5.94	39.00
Serum Bicarbonate (mmol/L)	9.89; 5.06	20.60	10.89; 4.30	23.00
Serum Creatinine (mmol/L)	1220.87; 481.58	1860	1064.01; 354.59	2210
Serum Potassium (mEq/L)	6.13; 0.89	4.20	5.74; 0.78	6.20

Table 3 Binary logistic regression and correlation analysis of variables in association with mortality in chronic kidney disease.

	p-Value	Odds Ratio	95% C.I. for Odds Ratio			
			Lower	Upper	Pearson's correlation	p-value
Age in years	0.423	1.028	0.960	1.101	0.01	0.862
Sex	0.204	0.234	0.025	2.201	0.037	0.52
Hypertension	0.999	5093786.484	0.000		-0.016	0.778
Diabetes	0.999	5951714.182	0.000		-0.056	0.331
Glomerulonephritis	0.999	598326.416	0.000		0.005	0.928
Hemoglobin (gm%)	**0.041**	2.679	1.039	6.907	0.141	**0.015**
pH	0.415	92.508	0.002	4886427.644	0.111*	0.054
pCO2	0.747	1.025	0.883	1.190	-0.066	0.256
HCO3	0.342	0.813	0.531	1.246	0.061	0.295
Serum Creatinine	0.293	0.999	0.996	1.001	-0.114	**0.049**
Serum Potassium	0.144	0.456	0.159	1.307	-0.148*	**0.01**
Dialysis	**0.015**	0.016	0.001	0.450	-0.026	0.658
Blood Transfusion	0.291	0.137	0.003	5.487	0.052	0.368
Sepsis	**<0.001**	7649.521	137.294	426203.855	0.827	**<0.001**

*Spearman's correlation is used as the data are negatively skewed. Bold values indicate statistically significant values with a p-value <0.05.

Table 4 Prediction of mortality among CKD patients using Area under the receiver operating curve.

Variables	Area	P-value	95% Confidence Interval	
			Lower Bound	Upper Bound
Serum potassium	0.660	0.011	0.530	0.791
Serum creatinine	0.598	0.119	0.457	0.739

Table 5 Sensitivity, specificity and Youden index of serum potassium and creatinine to predict mortality in chronic kidney disease

Potassium (mEq/L)	Sensitivity	Specificity	Youden Index	Creatinine (mmol/L)	Sensitivity	Specificity	Youden Index
5.95	0.65	0.67	0.32	1121	0.61	0.67	0.28
6.05	0.61	0.68	0.29	1185	0.61	0.69	0.29
6.25	0.57	0.76	0.33	1195	0.61	0.69	.30
6.35	0.52	0.79	0.32	1217	0.57	0.71	0.27
6.45	0.44	0.85	0.29	1228.50	0.48	0.72	0.20

FIGURES

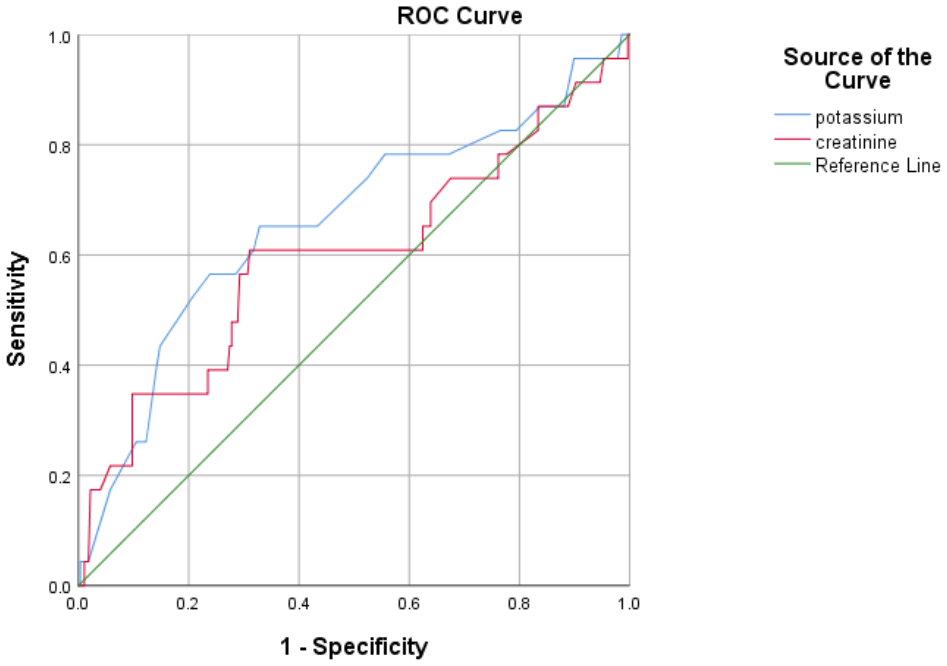

Figure 1 ROC curve to test the efficacy of serum Potassium and Creatinine to predict mortality in CKD patients under maintenance hemodialysis.