

Original Research Article

A clinical study of plasma homocysteine levels in chronic kidney disease at a tertiary care center

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Received: 18 July 2025

Revised: 06 September 2025

Accepted: 10 September 2025

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ABSTRACT

Background: Chronic kidney disease (CKD) is associated with progressive loss of renal function and elevated plasma homocysteine levels, which may increase cardiovascular risk. This study aimed to assess the association between renal function decline and homocysteine levels in CKD patients.

Methods: A single-center, prospective observational study was conducted over 18 months involving 50 CKD patients. Demographic, clinical, and biochemical data including plasma homocysteine, serum creatinine, blood urea nitrogen (BUN), urea, glomerular filtration rate (GFR), and albumin levels were collected. Patients were stratified by homocysteine levels (normal $<15 \mu\text{mol/l}$, elevated $>15 \mu\text{mol/l}$), and associations with renal parameters were analyzed.

Results: Elevated homocysteine was observed in 38 (76%) patients. Patients with elevated homocysteine had significantly higher plasma homocysteine levels ($21.98 \pm 7.52 \mu\text{mol/l}$) compared to the normal group ($12.22 \pm 1.83 \mu\text{mol/l}$, $p=0.001$). Serum creatinine was higher in the elevated group ($8.30 \pm 4.68 \text{ mg/dl}$) versus normal ($4.68 \pm 2.17 \text{ mg/dl}$, $p=0.001$). Similarly, BUN ($57.89 \pm 15.41 \text{ mg/dl}$ versus $42.18 \pm 6.22 \text{ mg/dl}$, $p=0.001$) and urea ($121.58 \pm 32.37 \text{ mg/dl}$ versus $88.58 \pm 13.06 \text{ mg/dl}$, $p=0.001$) were elevated. The mean GFR was significantly lower in the elevated homocysteine group ($11.68 \pm 6.30 \text{ ml/minute}$) compared to the normal group ($16.44 \pm 7.93 \text{ ml/minute}$, $p=0.03$). Significant correlations were found between homocysteine and serum creatinine ($r=0.305$, $p=0.03$), BUN ($r=0.335$, $p=0.01$), urea ($r=0.345$, $p=0.01$), and GFR ($r=-0.412$, $p=0.01$).

Conclusions: Elevated homocysteine levels may serve as a useful biomarker and potential therapeutic target to mitigate cardiovascular risk and disease progression in CKD.

Keywords: Cardiovascular risk, Chronic kidney disease, Glomerular filtration rate, Homocysteine, Renal function

INTRODUCTION

Chronic kidney disease (CKD) is a significant global public health concern characterized by a gradual loss of renal function over time, culminating in end-stage renal disease (ESRD) if left untreated. CKD prevalence is steadily increasing, driven primarily by rising rates of diabetes mellitus, hypertension, and an aging population.¹ The progression of CKD is marked by multiple biochemical and metabolic alterations, one of which is elevated plasma homocysteine levels, also known as hyperhomocysteinemia.²

Homocysteine is a sulfur-containing amino acid formed during the metabolism of methionine, an essential amino acid derived primarily from dietary protein. Under normal physiological conditions, homocysteine is metabolized either by remethylation to methionine or by transsulfuration to cysteine.³ However, impaired renal function disrupts these metabolic pathways, resulting in elevated plasma homocysteine concentrations. Elevated homocysteine levels are clinically significant due to their association with increased risks of cardiovascular disease, thrombosis, and endothelial dysfunction.⁴

Previous studies have demonstrated a direct correlation between declining glomerular filtration rate (GFR), a primary indicator of kidney function, and elevated homocysteine levels.⁵ This inverse relationship suggests a potential pathophysiological link wherein declining renal function leads to decreased clearance and impaired metabolism of homocysteine, thereby resulting in its accumulation. However, the precise mechanisms underlying this association remain incompletely understood. Factors such as decreased renal clearance, altered enzymatic activity, deficiencies in folate, vitamin B₁₂, and vitamin B₆, and inflammatory processes within renal tissue may all contribute to hyperhomocysteinemia in CKD patients.

Hyperhomocysteinemia in CKD patients is increasingly recognized as a potentially modifiable cardiovascular risk factor.⁶ Given that cardiovascular diseases represent the leading cause of morbidity and mortality among CKD patients, understanding the relationship between homocysteine and renal impairment is crucial. Studies have also indicated that elevated homocysteine levels can contribute to the progression of kidney disease itself, suggesting a bidirectional relationship between hyperhomocysteinemia and CKD progression.⁷ Therefore, effective management of homocysteine levels could potentially mitigate cardiovascular complications and slow the progression of renal disease.

Despite growing awareness of hyperhomocysteinemia in CKD, clinical guidelines for routine screening and management are yet to be universally established. The heterogeneity of findings across various studies highlights the need for further comprehensive research to elucidate the exact nature of the association between declining renal function and elevated homocysteine levels. This knowledge gap underscores the importance of clearly delineating the correlation between GFR reduction and homocysteine elevation, which may inform targeted therapeutic strategies aimed at reducing cardiovascular risks and preserving kidney function in CKD patients.

The present study aimed to systematically investigate and quantify the association and correlation between declining renal function and elevated homocysteine levels in CKD patients.

METHODS

This was a single-centered, prospective, observational investigation conducted over a period of 18 months from April 2023 to September 2024. A total of 50 cases were selected using a simple random sampling method. Patients diagnosed with chronic kidney disease (CKD) and admitted to the department of general medicine, Al Ameen Medical College, either for symptoms specifically related to CKD or for other medical reasons, were enrolled. Upon enrolment, detailed demographic information including age, sex, weight, height, and residential address was recorded. Additionally, comprehensive patient histories

were collected, including information on family history of CKD, current dialysis status, and presence or absence of coexisting conditions such as diabetes mellitus, systemic hypertension, chronic liver disease, and lifestyle habits like smoking and alcohol consumption. Each participant underwent thorough general and systemic clinical examinations as a part of the study protocol to ensure accurate and consistent data collection.

Patients with chronic kidney disease who are admitted to Al Ameen medical college for symptoms related to chronic kidney disease or other reasons are selected for this study. Personal characteristics like age, sex, weight height, address will be noted. Patients will be enquired for presence of family history of chronic kidney disease or whether patient is undergoing dialysis for the chronic kidney disease, presence or absence of diabetes mellitus, systemic hypertension, chronic liver disease, smoking habits or alcohol consumption. General and systemic examinations were done.

The study was approved by institutional ethical committee, department of general medicine, Al Ameen Medical College, Vijayapura, Karnataka, India.

Inclusion criteria

Adults above 18 years of age, CKD stage 1 to stage 5 as per KDIGO guidelines, written informed consent provided, elevated blood urea and serum creatinine, eGFR<60 ml/minute/1.73 m², ultrasound of abdomen showing features of chronic kidney disease.

Exclusion criteria

Patients not willing for consent, acute kidney injury patients, patients who were current smokers, patients who were current alcoholics, patients with diabetes mellitus, chronic liver disease patients.

All patients underwent comprehensive general and systemic examinations to assess their clinical status. Renal function was evaluated primarily by measuring the estimated glomerular filtration rate (eGFR) using serum creatinine values, following the CKD-EPI equation. Blood samples were collected in the fasting state to measure plasma homocysteine levels using a validated enzymatic assay. Additional routine laboratory parameters were also recorded, including blood glucose, lipid profile, and hemoglobin levels.

Data analysis

Data were entered in Microsoft Excel Spreadsheet and analyzed using SPSS software. Categorical variables were expressed in frequency and percentages. Continuous variables were expressed in mean and standard deviation. Student 't' test was applied as the test of significance. 'p' value less than 0.05 was considered statistically significant.

RESULTS

This study evaluates the relationship between decreased renal function and increased homocysteine levels in chronic kidney disease patients. The demographics and clinical characteristics of the patients was shown in Table 1.

Table 1: Demographics, clinical characteristics and biochemical parameters of the CKD patients.

Parameters	Values (n=50)
Age in years (mean±SD)	56.08±10.01
Gender (%)	
Male	36 (72)
Female	14 (28)
Weight in kgs (mean±SD)	57.82±11.54
Family history of kidney disease (%)	29 (58)
CKD stage (%)	
Stage3	3 (6)
Stage4	12 (24)
Stage5	35 (70)
Dialysis (%)	17 (34)
Biochemical parameters (mean±SD)	
Plasma homocysteine (μmol/l)	19.64±7.83
Serum creatinine (mg/dl)	7.43±4.47
Blood urea nitrogen (mg/dl)	54.12±15.29
Urea (mg/dl)	113.66±32.12
Glomerular filtration rate (ml/minute)	12.82±6.95
Albumin (mg/dl)	3.03±0.74

The study included 50 chronic kidney disease patients with a mean age of 56.08±10.01 years, and a majority were male (72%). Most patients were in advanced CKD stages, with 70% in stage 5 and 24% in stage 4. Additionally, 58% had a family history of kidney disease, and 34% were undergoing dialysis at the time of the study. The mean plasma Homocysteine level among the CKD patients was

19.67±7.83 μmol/l. The mean serum creatinine level was 7.43±4.47 mg/dl, blood urea nitrogen (BUN) was 54.12±15.29 mg/dl and urea was 113.66±32.128 mg/dl. The mean glomerular filtration rate was 12.82±6.95 ml/minute and the mean albumin level was 3.03 ±0.74 mg/dl.

Table 2: Status of homocysteine levels among the CKD patients.

Homocysteine level	Frequency (%)
Elevated (>15 μmol/l)	38 (76)
Normal (<15 μmol/l)	12 (24)

In this study elevated homocysteine levels (hyperhomocysteinemia) were observed in 38 (76%) of the patients. The results are shown in Table 2.

The association between homocysteine level categories and renal biochemical parameters was shown in Table 3. The study found a significant association between CKD stage and elevated homocysteine levels, with none of the stage 3 patients showing elevated levels, while 78.9% of stage 5 patients had elevated homocysteine (p=0.003). Patients with elevated homocysteine had significantly higher plasma homocysteine concentrations (21.98±7.52 μmol/l) compared to those with normal levels (12.22±1.83 μmol/l, p=0.001). Additionally, elevated homocysteine levels correlated with significantly increased serum creatinine (8.30±4.68 mg/dl), BUN (57.89±15.41 mg/dl), and urea (121.58±32.37 mg/dl) compared to normal homocysteine groups (p=0.001 for all). A significant reduction in GFR (11.68±6.30 ml/minute) and serum albumin (2.84±0.62 gm/dl) was observed in patients with elevated homocysteine versus those with normal levels (p=0.03 and p=0.002, respectively). These findings indicate a strong correlation between worsening renal function and increased homocysteine concentrations in CKD patients.

Table 3: Association between homocysteine level categories and renal biochemical parameters.

Variables	Homocysteine levels		P value
	Normal (<15 μmol/l)	Elevated (>15 μmol/l)	
CKD stage (%)			
Stage 3	3 (25)	0 (0)	0.003**
Stage 4	4 (33.3)	8 (21.1)	
Stage 5	4 (41.7)	30 (78.9)	
Plasma homocysteine (μmol/l)	12.22±1.83	21.98±7.52	0.001 ^{b*}
Creatinine (mg/dl)	4.68±2.17	8.30±4.68	0.001 ^{b*}
BUN (mg/dl)	42.18±6.22	57.89±15.41	0.001 ^{b*}
Urea (mg/dl)	88.58±13.06	121.58±32.37	0.001 ^{b*}
GFR (ml/minute)	16.44±7.93	11.68±6.30	0.03 ^{b*}
Albumin	3.59±0.81	2.84±0.62	0.002 ^{b*}

*indicates significant (p<0.05); a- Chi square test; b- unpaired students t-test.

In the present study there was a significant positive correlation between homocysteine level and serum creatinine ($r=0.305$; $p=0.03$), serum BUN ($r=0.335$; $p=0.01$), urea ($r=0.345$; $p=0.01$) and negative correlation between GFR ($r=-0.412$). Meanwhile, there was no significant correlation between homocysteine level and serum albumin ($r=0.145$; $p=0.54$). The results were shown in Table 4.

Table 4: Correlation between homocysteine level and renal parameters.

Parameters	Pearson's correlation (r)	P value
Homocysteine level versus serum creatinine levels	0.305	0.03*
Homocysteine level versus serum BUN levels	0.335	0.01*
Homocysteine level versus serum urea levels	0.345	0.01*
Homocysteine level versus GFR	- 0.412	0.01 *
Homocysteine level versus serum albumin	0.143	0.54NS

*Statistically significant.

DISCUSSION

Chronic kidney disease (CKD) remains a major global health concern, with its progressive nature leading to end-stage renal disease and significant cardiovascular morbidity. This study highlights the close relationship between declining renal function and elevated plasma homocysteine levels in CKD patients, reaffirming the importance of homocysteine as both a marker and a potential contributor to disease progression.

In our cohort of 50 patients, the mean age was 56.08 ± 10.01 years, with a predominance of males (72%). Most patients presented in advanced CKD stages, with 70% in stage 5 and 24% in stage 4, reflecting the typical demographic of a tertiary care center. In a study done by Yaqub et al the mean age of the CKD patients was The mean age of the patients was 50.62 ± 16.29 years.⁸ The male preponderance (72%) seen in this study mirrors global data showing a higher incidence of CKD in men, which might be related to factors such as lifestyle, higher prevalence of hypertension, or delayed diagnosis in women. Likewise, in a study done by Yadav et al 68% were males.⁹ The association between Stage 5 CKD and higher levels of homocysteine, as demonstrated in the statistical analysis, points to the cumulative burden of kidney dysfunction and elevated homocysteine on cardiovascular and renal health. Likewise, in a study done by Patel et al 50% of the patients were in CKD stage 5.¹⁰

The mean plasma homocysteine concentration was notably elevated at 19.64 ± 7.83 $\mu\text{mol/l}$, and

hyperhomocysteinemia was observed in 76% of patients, confirming the high prevalence of this metabolic disturbance in advanced CKD. In this study, we observed a significant association between homocysteine levels and the stage of chronic kidney disease (CKD), particularly noting a higher frequency of hyperhomocysteinemia in patients with stage 5 CKD compared to those in Stage 4 and stage 3 CKD. The findings revealed that 78.9% of stage 5 CKD patients had elevated homocysteine levels, whereas only 21.1% of stage 4 and 0% of stage 3 CKD patients exhibited hyperhomocysteinemia, with a p value of 0.003. Likewise, in a study done by Song et al there was an increasing trend in homocysteine level with an increasing CKD stage. In CKD stage 5 the homocysteine level was $19 \mu\text{mol/l}$.¹¹

The study demonstrated a significant difference in homocysteine levels between hyperhomocysteinemia cases and those with normal homocysteine levels, with values of $21.89 \mu\text{mol/l}$ and $12.22 \mu\text{mol/l}$, respectively ($p=0.001$). This significant elevation in homocysteine levels in the hyperhomocysteinemia group highlights the association between elevated homocysteine and renal dysfunction, particularly in CKD patients. Elevated homocysteine has been shown to contribute to oxidative stress, vascular damage, and endothelial dysfunction, which are key factors in kidney damage and cardiovascular risk.¹²

The present study found that creatinine levels were significantly higher in hyperhomocysteinemia cases (8.30 mg/dl) compared to cases with normal homocysteine levels (4.68 mg/dl , $p=0.01$). Likewise, in a study done by Shih et al the creatinine level was higher in hyperhomocysteinemia when compared to normal levels (0.98 versus 0.72 mg/dl ; $p=0.00$).⁶

The present study revealed that BUN levels were significantly higher in hyperhomocysteinemia cases (57.89 mg/dl) compared to those with normal homocysteine levels (42.18 mg/dl , $p=0.001$). Elevated BUN is a marker of renal dysfunction, particularly reflecting the kidney's impaired ability to excrete nitrogenous waste. The significant difference in BUN levels supports the hypothesis that hyperhomocysteinemia contributes to worsening kidney function, potentially through mechanisms like oxidative stress and vascular injury.¹³

The study found that urea levels were significantly higher in hyperhomocysteinemia cases (121.58 mg/dl) compared to those with normal homocysteine levels (88.58 mg/dl , $p=0.001$). In a study done by Yang et al the homocysteine level showed significant correlation with urea levels ($p<0.05$).¹⁴

The present study highlights a novel association between elevated homocysteine levels and diminished renal function, as indicated by the significant reduction in GFR in hyperhomocysteinemia cases. The lower GFR observed

in these patients (11.68 ml/minute) compared to those with normal homocysteine levels (16.44 ml/minute) underscores the potential role of homocysteine in accelerating kidney damage beyond traditional risk factors. Likewise in a study done by Levi et al the GFR was lower in hyperhomocysteinemia cases as compared to normal homocysteine levels (95.2 ± 13.8 versus 98.8 ± 13 ; ml/minute/ 1.732 m^2 ; $p < 0.001$).⁵ Recent studies have reinforced the role of homocysteine as a critical contributor to renal dysfunction in CKD.¹⁵

The present study found that albumin levels were significantly lower in hyperhomocysteinemia cases (2.84 mg/dl) compared to those with normal homocysteine levels (3.59 mg/dl, $p = 0.03$). In a study done by Yadav et al there was significant correlation between albumin level and homocysteine levels ($p = 0.003$).⁹ Low albumin levels are indicative of malnutrition, proteinuria, and increased kidney damage in CKD patients.¹⁶

The present study found significant correlations between homocysteine levels and various renal parameters, shedding light on the potential role of homocysteine in the progression of chronic kidney disease (CKD). Specifically, a positive correlation was observed between homocysteine and serum creatinine ($r = 0.305$; $p = 0.03$), serum BUN ($r = 0.335$; $p = 0.01$), and urea ($r = 0.345$; $p = 0.01$), suggesting that as homocysteine levels rise, renal function declines. Likewise, in a study done by Xie et al there was a significant correlation between hyperhomocysteinemia and renal function decline.¹⁷

In addition, the negative correlation between homocysteine levels and glomerular filtration rate (GFR) ($r = -0.412$) further underscores the impact of hyperhomocysteinemia on kidney function. In a study done by Kumar et al there was a significant negative correlation between GFR levels and homocysteine level ($r = -0.267$; $p = 0.0008$).¹⁸ In another study done by Dohat et al there was a significant correlation between GFR and homocysteine levels ($r = -0.305$; $p = 0.031$).¹⁹

This study's single-center design and relatively small sample size limit the generalizability of the findings. Exclusion of patients with diabetes and liver disease may restrict applicability to the broader CKD population.

CONCLUSION

This study establishes a significant association between declining renal function and elevated plasma homocysteine levels in patients with chronic kidney disease. Elevated homocysteine correlates positively with markers of renal impairment such as serum creatinine, blood urea nitrogen, and urea, and inversely with glomerular filtration rate. These findings underscore the potential of homocysteine as a valuable biomarker for disease severity and a modifiable risk factor to reduce cardiovascular complications in CKD. Integrating homocysteine monitoring into routine clinical practice

may improve risk stratification and guide therapeutic interventions aimed at slowing CKD progression and improving patient outcomes.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Kumar MV, Rao V, Hussaini SMM, Baig ATT. A clinical study of plasma homocysteine levels in chronic kidney disease at a tertiary care center. *Int J Res Med Sci* 2025;13:4243-8.