CREATININE CLEARANCE AS EFFECTIVE NON-INVASIVE MARKER IN DETERMINING GASTROINTESTINAL LESIONS AND HELICOBACTER PYLORI INFECTION

Zubia Jamil, Saima Ambreen*, Omar Ahsan

Foundation University Medical College Islamabad Pakistan, *Holy Family Hospital Rawalpindi Pakistan

ABSTRACT

Objective: The objective of this study focuses to unfold the importance of creatinine clearance in determining the gastrointestinal mani-festations and Helicobacter Pylori infection.

Study Design: Cross-sectional comparative study.

Place and Duration of Study: Medicine department of Fauji Foundation Hospital Rawalpindi, from Jun 2015 to Dec 2016.

Material and Methods: Creatinine clearance of 73 CKD patients was calculated. UGI endoscopy was performed to detect gastro-intestinal lesions. *H.pylori* was detected by histopathology of gastric mucosal biopsy. The diagnostic accuracy of CCl in determining the presence of gastrointestinal (GI) lesions was determined by receiver operating characteristic (ROC) curve (AUC). Cut-off value, sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios were obtained by Youden index.

Results: Mean CCl was 27.09 ± 12.16 ml/min. Diabetes mellitus was the top most cause of CKD (45.2%). Upper GI endoscopic lesions were present in 68.5% patients (p-value<0.05). The most common abnormality was erythematous gastritis. *H. pylori* infection was lower in disease group compared to controls, but statistically insignificant (p>0.05). The AUC for CCl in determining the gastrointestinal lesions was 0.8 (p-value≤0.0001), cutoff value was <35ml/min (Sensitivity 81.82%, Specificity 72.4%). The AUC for CCl in determining the presence of *H. Pylori* infection was 0.7 (p-value=0.0004), cutoff value was <27 ml/min (Sensitivity 83.33%, Specificity 58.18%).

Conclusion: CCl was found, noninvasive marker in predicting the GI abnormalities. It can be used to identify the high risk patients. Such patients then can undergo endoscopy for further management. *H.pylori* eradication therapy should be offered to those patients in whom its presence is proven by other tests as well.

Keywords: Chronic kidney disease, Creatinine, Endoscopy, Gastritis, Helicobacter pylori, Peptic ulcer.

INTRODUCTION

Gastrointestinal (GI) manifestations are common among patients of chronic kidney diseases (CKD)[1]. On one hand these gastrointestinal events impairs the quality of life by disturbing social, physical and mental health of these patients[2,3] and on the other hand, can affect the mortality by GI bleeding[4]. Delayed gastric emptying due to reduced gut motility[5-7], intestinal mucosal inflammation[8], amyloid deposition[9], calciphylaxis[10], hypergastrinemia leading to hyper secretion of acids[11], colonization with Helicobacter pylori (*H.pylori*) are all well understood mechanisms resulting in GI disorders in these patients[12,13]. They result in various GI symptoms in uremic patients including epigastric burning sensation, abdominal pain, diarrhea, constipation, postprandial fullness, early satiety, bloating and belching, etc[1,14]. Just like GI symptoms the upper GI endoscopic findings are also showing a wide range of abnormalities ranging from simple inflammatory lesions to complex lesions resulting in complications with chronic blood loss or massive GI bleeding. Pangastritis, esophagitis, duodenitis, gastric erosions, peptic ulcers, gastric lymphomas and gastric polyps are all known GI lesions found in these patients[15-18]. Some patients develop life threatening upper GI bleeding as a result of these GI lesions[4]. Association of *H.pylori* infection with GI diseases has put strong emphasis on early diagnosis and eradi-

Correspondence: Dr Zubia Jamil, Department of Medicine, Foundation University Medical College, Islamabad Pakistan
Email: zubiajamil321@gmail.com
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cation therapy of this organism. Early eradication therapy should be given to all patients with end organ damage, as it may complicate the natural history of the disease process[12,19].

Proper evaluation of CKD patients with routine upper GI endoscopy may be needed so that these GI lesions are diagnosed and managed in time to prevent complications[4]. Upper GI endoscopy cannot be performed in every patient of CKD because it is invasive and costly diagnostic tool and the burden of disease is becoming high day by day. The relationship of serum creatinine and effects of creatinine clearance (CCl) on GI manifestations is not a well studied spectrum of disease process. The rationale of this study was to determine the importance of CCl as a non-invasive indicator for the presence of upper gastrointestinal lesions and *H. pylori* infection in these patients with CKD.

MATERIAL AND METHODS

This cross sectional comparative study was carried out in the Medicine department of Fauji Foundation Hospital, Rawalpindi from June 2015 to December 2016. Sampling method was consecutive non-probability sampling. With the help of WHO sample size calculator, sample size of 73 patients was calculated (Confidence level 95%, Anticipated population proportion 25%, Absolute percentage required 10%. Patients having CKD due to any cause were included in this study. The diagnosis of CKD was made by

1. Patients on regular hemodialysis for CKD.
2. Patient's medical records relating to their disease were present.
3. New cases having positive risk factors leading to the development of CKD (Diabetes mellitus, hypertension, renal stones, glomerulone-phritis, etc.) and biochemical abnormalities and ultrasonographic findings were suggestive of CKD. The features suggesting chronic kidney disease were
   a) Small sized kidneys with size less than 8 cm or kidneys with asymmetrical size or polycystic kidneys or grade 3 or 4 renal parenchymal changes on ultrasound
   b) Elevated serum creatinine for more than 3 months,
   c) Presence of symptoms suggestive of uremia and other biochemical abnormalities suggestive of CKD (anaemia, hyperparathyroidism, hypocalcaemia, hyperphospatemia, etc.) for more than 3 months.

Patients were excluded from the study if

1. They were having associated liver disease,
2. Case of GI malignancy,
3. They have taken therapy for *H. pylori* eradication previously,
4. Patients who were on medications which can alter the findings of endoscopy such as proton pump inhibitors, H2 receptor antagonists, other antacids, antibiotics and NSAIDs within last 2 weeks.

Seventy three patients with these criteria were selected. Ethical approval was taken and informed written consent was taken from patients. The complete history of these patients was taken, including the demographic profile, cause of CKD, GI symptoms. Serum creatinine was obtained by taking 3ml of clotted sample (serum) and was analysed by chemical analyzer. (Dimensions RxL max chemistry analyzer; siemens healthineers labortaroies, USA) CCL of each patient was calculated by using Cockcroft-Gault GFR formula[20].

Creatinine Clearance (CCl) = (140-age x weight in kg)/(serum Creatinine x 72) x (0.82 for females)

Staging of CKD was done using Kidney Disease Outcomes Quality Initiative (KDOQI) classification. (Stage 1: Creatinine Clearance (CCl) >90ml/min; Stage 2: CCl 60-90ml/min; Stage 3: CCl 30-60ml/min; Stage 4: CCl 15-30ml/min; Stage 5: CCl<15ml/min or on hemodialysis).

The upper GI endoscopy was considered as a standard modality for detecting upper GI lesions. All the patients underwent upper GI endoscopy

by using Video scope. (Exera 160 series; olympus endoscopy system, Japan) All endoscopies were performed by single trained physician. Multiple biopsies were taken from the antrum of stomach of all patients and sent for histopathological evidence of presence of *H.pylori* infection. Detection of *H.pylori* in biopsy specimen was done by two kinds of staining method. First hematoxylin and eosin staining was used and then giemsa staining was used

Seventy three patients who were age and sex matched with study group were taken as control group. Control group was not having any renal disease and all individuals of control group underwent upper GI endoscopy for the presence of GI lesions and *H. pylori* infection after informed consent. Total sample size was 146.

Statistical Analysis

Quantitative data was statistically analyzed using the terms mean, standard deviation and ranges. Frequencies and percentages were used for qualitative data. A *p*-value was calculated by using contingency coefficient. The area under the receiver operating characteristic (ROC) curve was used to determine the accuracy of CCI in determining the upper GI lesions and *H pylori* infection. The cutoff value of CCl and sensitivity, specificity, positive, negative predictive values and positive, negative likelihood ratios of this cutoff value was calculated by Younden index. SPSS-20 was used for analysis. A *p*-value less

Table-I: Baseline characteristics of the study group in terms of number of patient and percentage.

Eitiology of CKD	N=Number of patients	Percentage (%)
Diabetes mellitus	33	45.2
Hypertension	10	13.6
Diabetes mellitus and hypertension	23	31.5
Glomerulonephritis	5	6.8
Renal stones	2	2.7
KDOQI Stages of CKD		
Stage 3	32	43.8
Stage 4	24	32.9
Stage 5	17	23.3
Clinical Features		
Asymptomatic	6	8.2
Heartburn	48	65
Nausea	44	60.3
Vomiting	20	27.4
Anorexia	19	26
Constipation	13	17.8
Diarrhea	6	8.2
Borbrygmi	8	11
Upper GI bleed	4	5.5

CKD: Chronic Kidney Disease, KDOQI: Kidney Disease Outcomes Quality Initiative, GI: Gastrointestinal.

Table-II: Comparison of variables between patients with chronic kidney disease and control group.

Variables	CKD patients		Control group		Contingency Coefficient	*p*-value
	Positive	Negative	Positive	Negative		
Outcome of upper GI endoscopy	44 (60.3%)	29 (39.7%)	25 (34.2%)	48 (65.8%)	0.226	0.002
Presence of H. pylori associated gastritis	18 (24.7%)	55 (75.3%)	43 (58.9%)	30 (41.1%)	0.103	<0.001

CKD: Chronic kidney disease, H pylori: Helicobacter pylori, GI: Gastrointestinal

than or equal to 0.05 was considered as a significant value.

RESULTS

The average age of 73 patients was 48.84 ± 14.29 years (mean ± SD) ranging from 15-85 years. Among them, 49 (67.1%) were males and 24 (32.9%) were females. The main cause of CKD was diabetes mellitus. The CCl was 27.09 ± 12.16 ml/min (mean ± SD) ranging from 6.60-47.00 ml/min. Among 73 patients 91.8% patients were having GI symptoms. The baseline characteristics of the study group is shown in table-I.

In 73 patients, upper GI endoscopy was performed which showed normal study in 23 (31.5%) patients. The most common endoscopic finding was erythematous gastritis found in 19 (26%) patients. Other endoscopic abnormalities found were erythematous duodenitis 9 (12.3%), pangastritis 7 (9.6%), erosive gastritis 6 (8.2%), erythematous esophagitis 4 (5.5%), hiatal hernia 2 (2.7%), peptic ulcers 1 (1.4%), GAVE disease 1 (1.4%) and gastric polyp in 1(1.4%) patients. Among the causes of bleeding, 3 patients were bleeding from erosions and one was found to have watermelon stomach (GAVE disease). Three patients out of 6 asymptomatic patients were having gastrointestinal lesions on endoscopy. Two patients were having erythematous gastritis and one was having hiatal hernia. Age and sex matched control group also underwent upper GI endoscopy and it was found that GI lesions were found in only 34.2% patients (p=0.002). Histopathology of gastric specimens of 73 patients with CKD showed *H. pylori* was present in 18 (24.7%) patients. Nonspecific antral gastritis was found in 44 (60%) patients and 11 (15.1%) were having normal gastric mucosa. In the control group, *H. pylori* associated antral gastritis was present in 58.9% patients. Although the higher frequency of individuals were infected with *H. Pylori* infection in the control group than the disease group, but statistically this difference was significant (p<0.001). Comparison between patients with CKD and control group in terms of contingency coefficient and p-value is shown in table-II. The area under the ROC curve for CCl in determining the presence of GI lesion was 0.8 (AUC=0.78, 95% Confidence interval=0.67 to 0.87, Standard Error=0.05, p-value≤0.0001). The cutoff value calculated by Younden Index was found <35 ml/min (fig-1). The area under the ROC curve for CCl in determining the presence of *H. Pylori* infection in patients with CKD was 0.7 (AUC=0.71, 95% Confidence interval=0.59 to 0.81, Standard Error=0.06, p-value <0.001). The cutoff value of creatinine clearance calculated by Younden Index was found <27 ml/min (fig-2).

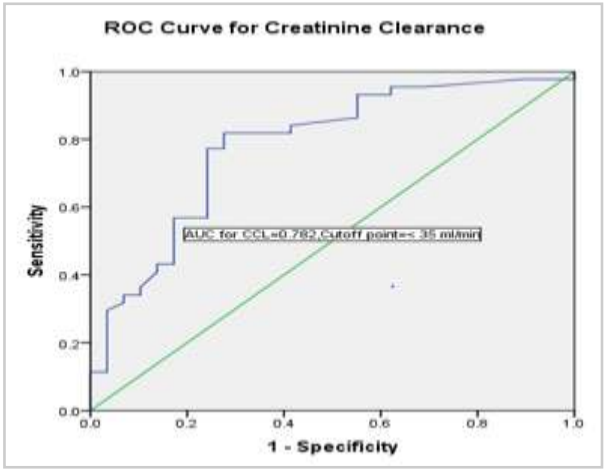

Figure-1: Receiver operating characteristic (ROC) curve for creatinine clearance in determining the presence of upper gastrointetinal leisons in patients with chronic kidney disease.

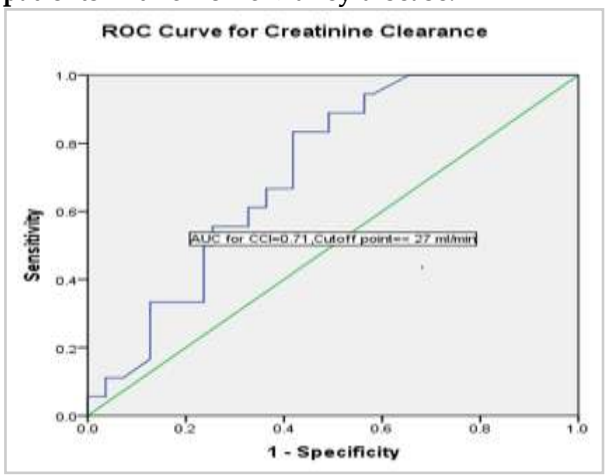

Figure-II: Receiver operating characteristic (ROC) curve for creatinine clearance in determining the presence of H. Plylori infection in patients with chronic kidney disease.

The cutoff value of CCl with its sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values in determining the presence of upper GI lesions and *H. pylori* infection in patients with CKD is shown in table-III.

DISCUSSION

Patients with CKD suffer from many GI diseases which complicate the natural course of disease[1]. We primarily focused on the importance of CCl in determining the GI lesions and *H.pylori* infection in CKD patients in this study. We found diabetes mellitus as the foremost cause of CKD. Many meta-analyses have favored the similar results showing diabetes mellitus is the chief cause of CKD[21-23]. We found that GI symptoms are common among these patients. GI symptoms were present in 92% (67) of our study group. This shows a majority of uremic patients are symptomatic. Many studies have also shown that GI symptoms are common in uremic patients. Sales Junior *et al*[6] showed that about 70% of patients present with GI symptoms. The upper GI symptoms which we found in our study are similar to those found in other studies[13,16]. The upper GI endoscopy was carried out in all patients with chronic kidney disease in our study. It was found that 68% of patients were having endoscopic abnormalities (p=0.002). Tamadon *et al*[24] also showed that 72% of patients were having abnormal gastric mucosa during endoscopic examination. Among endoscopic abnormalities the most common abnormality was erythematous gastritis. Gastric erosions and inflammation affecting esophagus, gastric and duodenal mucosa are common, as found in our study and studies conducted by Ala-Kaila *et al*[17] and Ahmed *et al*[18]. Four patients in our study presented with GI bleeding. But none of them was suffering from massive GI bleeding, which can lead to shock or death. Three out of four patients had gastric erosions as cause of GI bleeding. Many studies have shown that gastric erosions are the common cause of GI bleeding in these patients[16]. Peptic ulcers, angiodysplasias and Dieulafoy's lesions also result in gastrointestinal bleeding[4,25]. Endoscopic lesions were present in 50% asymptomatic patients. Bunchorntavakul *et al*[26] conducted their study on asymptomatic patients with CKD and found that nearly 45% asymptomatic patients were having GI lesions. It shows that GI lesions are common in these patients regardless of the presence or absence of GI symptoms. *H.pylori* infection was found in 24.7% patients (p<0.05). Our study showed that CKD patients have lower frequency of *H. pylori* infection as compared to the control group (24.7% vs 58.9%). Many studies have also suggested the low prevalence of *H. pylori* infection in these patients[12]. Bunchorntavakul *et al*[26] found that *H. pylori* infection was found in 27.1% of uremic patients. Alterations in gastric pH due to hyper-gastrenemia, achlorhydria, inflammatory cyto-kines, inhibition of *H. pylori* growth due to high urea and nitrogen levels, repeated use of anti-biotics in these patients are all known to be causing low prevalence of *H. pylori* in CKD patients[12,27]. *H. pylori* infection was determined by histopathological examination of gastric mucosa and double

Table-III: The accuracy of creatinine clearance in determining the presence of upper gastrointestinal lesions and H-pylori infection in patients with CKD. Its cutoff value, sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values.

Parameter	AUC	Cutoff point	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	-PV
CCl for upper GI lesions	0.78	≤35	81.82%	67.3-91.8	72.4%	52.8-87.3	2.97	1.6-5.4	0.25	0.1-0.5	24.8	97.3
CCl for H pylori infection	0.71	≤27	83.33%	58.6-96.4	58.18%	44.1-71.3	1.99	1.4-2.9	0.29	0.1-0.8	18.1	96.9

H pylori: Helicobacter pylori, CCl: Creatinine Clearance, GI: Gastrointestinal, AUC: Area under curve,+PV: Positive predictive value,-PV: Negative predictive value, +LR: Positive likelihood ratio, -LR: Negative likelihood ratio, CI: Confidence interval

staining method. The other methods like *H pylori* antigens from patient's stools, anti *H pylori* antibodies and urea breath tests are also available for detection of *H.pylori* infection. These tests have debatable sensitivity and specificity[24,28,29]. Therefore, Calvet *et al* and López *et al*[28,29] carried out multiple tests for detection of *H.pylori* infection in their study group. The results suggestive of low prevalence of *H.pylori* infection should be further elaborated by using different diagnostic tests on this disease group. The relationship between rising urea levels in the body and gastrointestinal manifestations are well established and well understood. Limiting studies are available showing any association of creatinine clearance to presence of GI diseases. Seyyedmajidi *et al*[30] showed the effect of CCl on eradication of *H. pylori* infection. But still, this study does not show any direct relationship between GI lesions and CCl. In our study, we proposed that CCl calculated at the bedside of patients by Cockcroft-Gault GFR formula, is a useful non-invasive marker in patients with CKD in determining the presence of GI lesions (AUC=0.8, *p*-value ≤0.001) and the presence of *H pylori* infection in these patients. (AUC=0.71, *p*-value<0.001). The cutoff value of <35 ml/min showed sensitivity of 81.82% and specificity 72.4% in determining GI lesions and the cutoff value of <27 ml/min showed sensitivity of 83.33% and Specificity 58.18% in determining *H pylori* infection. The notable results are likelihood ratios. The positive likelihood ratios are >1 and negative likelihood ratios are <1 indicating that CCl at these cutoff value can be used as a predictive marker.

CONCLUSION

CCl was identified as bedside and a useful noninvasive marker in patients with chronic kidney disease for determining the presence of GI lesions. (AUC=0.8, *p*-value<0.001). CCl can be used to identify the high risk patients who are more likely to develop GI lesions and subsequent complications. Patients with complications can undergo upper GI endoscopy for further advanced management. *H pylori* eradication therapy should be offered to those patients in whom tests with better sensitivity and specificity have proven its presence.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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