

Effects of chronic renal insufficiency on risk factors and results of endoscopy in patients with upper gastrointestinal system bleeding

Üst gastrointestinal sistem kanamalı hastalarda kronik böbrek yetmezliğinin risk faktörleri ve endoskopi sonuçlarına etkisinin değerlendirilmesi

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Abstract

Aim: Acute upper gastrointestinal system (GIS) bleeding is one of the leading causes of mortality and morbidity. Presence of concomitant disease in upper GIS bleeding is a mortality-associated risk factor, and chronic renal insufficiency (CRI) is one of these concomitant diseases. In the present study, patients with CRI, who had upper GIS bleeding and been treated as inpatient between January 2016 and January 2017 at Tepecik Training and Research Hospital Clinic of Gastroenterology, and the patients that had upper GIS bleeding without renal insufficiency were comparatively investigated in terms of demographic characteristics, presence of concomitant disease, drug usage, endoscopic results, Forrest classification, and need for endoscopic intervention and mortality.

Materials and Methods: A total of 194 patients were retrospectively evaluated. The CRI group with a glomerular filtration rate (GFR) lower than 60 mL/min/1.73 m² comprised 90 patients, whereas the control group with a GFR of 60 mL/min/1.73 m² and higher comprised 104 patients.

Results: As the result of the study, it was determined that CRI group was older and 96% of the patients had a concomitant disease. Drug usage rate was higher than the control group with aspirin used most frequently. Endoscopy was performed on day 1 in more than 70% of the cases.

Conclusion: Hospital mortality rate was higher in CRI group (5.66% vs 2.88%, p=0.475) with lower total mortality rate found in the present study as compared to the literature.

Keywords: Chronic renal insufficiency, gastrointestinal bleeding, mortality.

Öz

Amaç: Akut üst gastrointestinal sistem (GİS) kanamaları sık karşılaşılan mortalite ve morbidite nedenlerindedir. Üst GİS kanamalarında ek hastalık varlığı mortalite ile ilişkili bir risk faktörü olup kronik böbrek yetmezliği de (KBY) bunlardan biridir. Bu çalışmamızda, Tepecik Eğitim Araştırma Hastanesi Gastroenteroloji Kliniği'nde Ocak 2016-Ocak 2017 tarihleri arasında yatırılarak tedavi altına alınan üst GİS kanaması geçiren KBY'li hastalar ile üst GİS kanaması geçiren renal yetmezliği olmayan hastalar demografik özellikler, ek hastalık varlığı, ilaç kullanımı, endoskopik sonuçlar, Forrest sınıflaması ve endoskopik girişim gereksinimi ve mortalite açısından karşılaştırmalı olarak incelendi.

Gereç ve Yöntem: Toplam 194 hasta retrospektif olarak değerlendirilmeye alındı. Glomerüler filtrasyon hızı (GFR) 60 mL/dk/1,73 m²'nin altı olan kronik böbrek yetmezliği grubunda 90 hasta, GFR 60 mL/dk/1,73 m²'nin ve üzerinde olan kontrol grubunda ise 104 hasta çalışmaya dahil edildi.

Bulgular: Çalışma sonucunda KBY grubunun daha yaşlı olduğu ve bu grupta hastaların %96'sında eşlik eden ek hastalık varlığı saptandı. İlaç kullanımı kontrol grubundan daha yüksekti ve en sık kullanılan ilaç olarak aspirin tespit edildi. Olguların % 70'inden fazlasına ilk gün endoskopi uygulandı.

Sonuç: KBY grubunda hastane mortalite oranı kontrol grubuna göre yüksekti (%5,66'ye %2,88; p=0,475) ve total mortalite oranlarımız literatüre göre daha düşük tespit edildi.

Anahtar Sözcükler: Kronik böbrek yetmezliği, gastrointestinal kanama, mortalite.

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Introduction

GIS bleeding is encountered in 1-2 out of 1000 subjects in the population and disease-related mortality changes between 6% and 10% (1). Mortality-related factors include advance age, rebleeding, presence of concomitant disease, peptic ulcer or surgical intervention in the past, presenting with hematemesis, development of hypotension, and esophageal variceal bleeding (2). Need for surgery has notably decreased along with increased use of endoscopy in the diagnosis and treatment, and thereby, mortality and morbidity rates have also decreased (3).

It is known that incidence of upper GIS bleeding is higher in the patients with chronic renal insufficiency. Various mechanisms have been suggested to explain this situation. Peptic ulcer, which is one of the most common causes of GIS bleeding, is prevalent in uremic patients (4). Increase in the incidence of peptic ulcer is associated with hypersecretion of gastrin and increase in *Helicobacter pylori* (H.pylori) colonization. Other mechanisms include uremia-induced thrombocyte dysfunction, adverse events due to multiple medications received in CRI, erosive gastritis, and increase in the incidence of esophagitis (4). Again, decreased mucosal blood flow as well is one of the important etiological factors of gastrointestinal bleeding. Factors such as prolonged bleeding time, decreased activity of thrombocyte factor III, abnormal thrombocyte aggregation and adhesion, and impaired prothrombin consumption contribute to coagulation defects and make the patients with renal insufficiency prone to GIS bleeding (5).

The present study aimed to evaluate effect of CRI on risk factors, endoscopy results, and prognosis and mortality in the patients with upper GIS bleeding.

Materials and Methods

In the present study, 194 patients, who had been hospitalized between January 2016 and January 2017 at the Ministry of Health İzmir Tepecik Training and Research Hospital Gastroenterology Clinic for upper GIS bleeding, were retrospectively evaluated. Patients were divided into two groups. Chronic renal insufficiency group comprised patients, GFR of whom was lower than 60 mL/min/1.73 m² in the last 3 months according to MDRD formula, whereas the control group comprised the patients with GFR of 60 mL/min/1.73 m² and over. There were 90 patients in the CRI group and 104 patients in the control group. The groups were comparatively evaluated in terms of demographic characteristics, presence of concomitant diseases, drug usage, need for transfusion, results of endoscopy, mortality rate, rebleeding, and need for surgery.

“Statistical Package for Social Sciences (SPSS) for Windows 22.0” program was used for statistical analyses.

Level of significance was analyzed using Mann Whitney U test, Pearson chi-square test and independent sample t-test. A *p* value less than 0.05 was considered statistically significant.

Results

Of the patients with CRI, 53.3% was male and 46.7% was female, whereas 68.3% of the control group was male and 31.7% was female. CRI group was older with 78.9% of the patients determined to be at the age of 65 years and over. Whilst 96% of the patients in the CRI group had concomitant chronic diseases, this rate was 58.7% in the control group (Table-1). Hypertension, coronary artery disease and heart failure were statistically significantly more common in CRI group versus the control group (Table-2).

Table-1. Demographic Characteristics.

		CRI (%)	Control (%)	<i>p</i>
Gender	Male	53.3	68.3	
	Female	46.7	31.7	0.033
Age	<65 years	21.1	61.5	
	≥65 years	78.9	38.5	<0.001
Concomitant disease	No	3.3	41.3	
	Yes	96.7	58.7	<0.001

CRI: Chronic renal insufficiency.

Table-2. Concomitant Diseases.

Concomitant disease	CRI (n)	Control (n)	<i>p</i>
Hypertension	62	30	<0.001
Diabetes mellitus	15	21	0.529
Coronary artery disease	32	16	0.001
Malignancy	6	4	0.518
Heart failure	12	5	0.038

CRI: Chronic renal insufficiency.

Prevalence of receiving at least one medication was 94.4% in the CRI group and 77.9% in the control group (*p*=0.001). Aspirin was the most frequently used drug in both groups followed by nonsteroidal anti-inflammatory drugs (NSAID). The use of aspirin and clopidogrel was statistically higher in the CRI group (Table-3).

The mean hematocrit value at the time of hospital admission was 25.5±7.2% in the CRI group and 29.6±7.5% in the control group. Hemoglobin and albumin concentrations were significantly lower in the CRI group (Table-4). No statistical difference was determined between the groups in terms of amount of transfusion (Table-5).

Table-3. Drugs Being Received at the Time of Admission.

	CRI (n, %)	Control (n, %)	p
Drug	85 (94.4)	81(77.9)	0.001
ASA	46 (51.1)	29 (27.9)	0.001
NSAID	15 (16.9)	22 (21.2)	0.449
Clopidogrel	9 (10)	3 (2.9)	0.04
Warfarin	6 (6.7)	5 (4.8)	0.577
Gastroprotective	17 (18.9)	22 (21.2)	0.695

CRI: Chronic renal insufficiency. NSAID: Nonsteroidal anti-inflammatory drugs.

The mean hematocrit value at the time of hospital admission was 25.5±7.2% in the CRI group and 29.6±7.5% in the control group. Hemoglobin and albumin concentrations were significantly lower in the CRI group (Table-4). No statistical difference was determined between the groups in terms of amount of transfusion (Table-5).

Table-4. Laboratory Parameters.

Laboratory	CRI	Control	p
Hematocrit	25.5±7.2	29.6±7.5	0.001
Hemoglobin	8.6±2.5	10.13±2.6	<0.001
Albumin	3.23±0.6	3.51±0.6	0.003
Calcium	8.88±0.6	8.92±0.6	0.643

CRI: Chronic renal insufficiency.

Endoscopy was performed within 24 hours in 72.2% (n=65) of the patients in the CRI group and in 82.7% (n=86) of the patients in the control group (p= 0.08).

Endoscopy revealed that the most prevalent lesion (25.6%) was gastric ulcer in the CRI group and duodenal ulcer (27.9%) in the control group. Lesions consistent with malignancy were more common in the CRI group (4 gastric + 1 esophagus cancer) as compared to the control group (1 gastric cancer) (5.6% vs. 1%) (p<0.05) (Figure-1). Forrest classification of the patients with peptic ulcer revealed that Forrest 2a was most prevalent in the CRI group, whereas Forrest 3 was most prevalent in the control group (Figure-2). Endoscopic intervention was performed in 49% of the cases in CRI group and in 53% of the cases in the control group. Sclerotherapy was the most frequently performed procedure followed by band ligation and sclerotherapy+hemoclips. Need for endoscopic therapy was not different between the groups (p>0.05).

The mean duration of hospital stay was 4.65 days (range, 1-6). Duration of hospital stay was longer in the CRI group (p>0.321).

Rebleeding was determined in 12 patients in each group (13.3% in the CRI group and 11.5% in the control group). Surgical procedure was performed in a total of 12 patients, but no statistical difference was determined between the groups (p>0.05). Upper GIS bleeding was mortal in 5

(5.56%) patients in the CRI group and in 3 (2.88%) patients in the control group (Table-6).

Table-5. Amount of Transfusion.

Amount of transfusion	CRI	Control	p
Erythrocyte suspension	3.49±3.04	2.7±2.573	0.052
Fresh Frozen Plasma (FFP)	1.49±2.314	1.24±2.529	0.479

CRI: Chronic renal insufficiency.

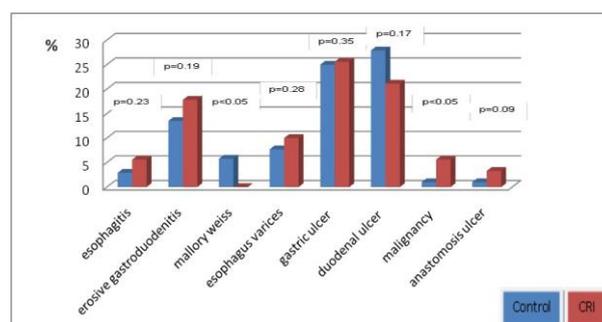


Figure-1. Bleeding reasons in the CRI and control groups.

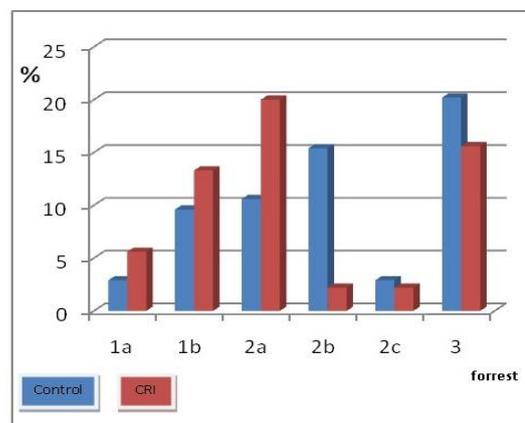


Figure-2. Forrest classification in the patients with peptic ulcer.

Table-6. Rebleeding, Control Endoscopy, Surgical Intervention and Mortality Rates.

	CRI	Control	p
Rebleeding	13.3% (n=12)	11.5% (n=12)	0.705
Control endoscopy	28.9% (n=26)	35.6% (n=37)	0.321
Surgical intervention	5.6% (n=5)	6.7% (n=7)	0.735
Mortality	5.66% (n=5)	2.88% (n=3)	0.475

CRI: Chronic renal insufficiency.

It was found that calcium and albumin concentrations were lower in the patients with mortality versus without mortality in the CRI group. Again, prevalence of

rebleeding was statistically significantly higher in the group with mortality; however, no relation was determined between mortality and duration of hospital stay and gender.

Discussion

It is known that prevalence of upper gastrointestinal bleeding is higher in the patients with chronic renal insufficiency, and in these patients, upper gastrointestinal bleeding is deemed responsible for 3-7% of overall deaths (6).

In the present study, male/female ratio was 1.1/1 in the CRI group and 2.1/1 in the control group. Male/female ratio in the CRI group was similar to that in the study conducted by Wasse et al. (7). Higher prevalence of GIS bleeding in males has been tried to be explained by higher prevalence of underlying disease and alcohol consumption in males (8). However, the reason for increasing prevalence in females is unclear.

It was observed that the patients in the CRI group were older than the patients in the control group. Higher prevalence of gastrointestinal system bleeding in elderly can be explained by increased prevalence of concomitant disease and drug use, increase in the prevalence of H.pylori with age, and increased prevalence of ischemic mucosal injury (9). Wasse et al. determined that the risk of upper GIS bleeding in CRI patients increases by 11% with each decade (7).

In the present study, prevalence of chronic disease was higher in the CRI group with hypertension, coronary artery disease and heart failure being the most prevalent. In the literature, Theoscharis et al. (9) found cardiovascular disease to be the leading followed by hypertension and diabetes mellitus. Wasse (7) determined that presence of cardiovascular disease and diabetes enhance the risk of upper GIS bleeding by 1.6 and 1.13, respectively.

Prevalence of drug usage was significantly higher in the CRI patients with aspirin used most frequently. Oliveira et al. (10) determined peptic ulcer and erosive gastritis/duodenitis to be the leading causes of upper GIS bleeding in 301 patients with CRI, and bleeding was attributed to NSAID in the majority of these patients. In another study conducted in 190 hemodialysis patients, it was found that the use of antiaggregant agent in hemodialysis patients 3 times enhanced the risk of bleeding.

Hemoglobin and hematocrit values at the time of admission is important for monitoring, prognosis, and manipulating treatment in the patients present with upper GIS bleeding. In the present study, low hemoglobin values in the CRI group was considered to be

associated with chronic disease anemia. Mean amount of erythrocyte transfusion over the course of hospital stay was 3.4 units in the CRI group and 2.7 units in the control group. In the literature, Gado et al. (11) found the mean amount of erythrocyte transfusion to be 3 units.

The rate of endoscopy performed in 24 hours was higher in the present study as compared to many studies. More than 70% of the patients in each group underwent endoscopy within 24 hours. Whilst Zaltman et al. (8) found the prevalence of endoscopy performed in 24 hours as 52.8%, Hearnshaw et al. (12) found it to be 50%.

On endoscopic examination, gastric ulcer was the most common lesion (25.6%) in the CRI group, whereas duodenal ulcer was most common (27.9%) in the control group. In the study conducted by Chalasani et al., the most frequent endoscopic lesions were gastric ulcer (37%) and duodenal ulcer (23%) followed by angiodysplasia, and it was stated that angiodysplasia is more prevalent in CRI patients as compared to the patients with normal renal functions (13). Prevalence of variceal bleeding was 10% in the CRI group and 7.7% in the control group. Golánová et al. (14) found the prevalence of variceal bleeding as 10%.

In the CRI group, upper GIS malignancy was seen in 5 patients (5.6%) whereas in 1 patient (1%) in the control group. We had not seen a study about upper GI malignancies at CRI patients in literature. In these patients, the high rate of malignant neoplasm of the stomach to be age-related and also may be associated with gastrin hypersecretion, increase H. pylori colonization. New studies for GIS malignancies are needed in CRI patients with more patients.

With regard to Forrest classification, the majority of patients in the CRI group was Forrest 2a and the majority of patients in the control group was Forrest 3 indicating that severity of ulcer was more common in peptic ulcer-related bleeding in the CRI group. This was considered to be associated with increased drug use with age, which is a risk factor for ischemic mucosa. In the present study, endoscopic intervention was performed in averagely 51% of patients. This was higher than that found by Kapsoritakis et al. (2), which was 32.7%. Also we found that the rate of control endoscopy applied to the patients were higher in the control group. We thought that the reason for this is due to the higher rates of gastric and duodenal ulcer seen in the control group (control: 53%, CRI: 46.7%).

Zuckerman et al. (15) conducted a study in CRI patients with upper GIS bleeding and observed that CRI patients had more frequent rebleeding; they found the prevalence of rebleeding to be 25% in the patients with renal

insufficiency and 11% in the patients without renal insufficiency. Also Lee et al. (16) shows that predictive factors for rebleeding in non-variceal upper gastrointestinal bleeding are; CRI, hemodynamic instability, and endoscopic high-risk appearance. In the present study, however, rebleeding occurred in 13.3% of CRI patients and in 11.5% of the control group with no significant difference determined between CRI group and the control group different from the literature. In the recent years, favorable advances both in medical and surgical treatments have caused surgical treatment to take the backseat. Actually, Theocharis (9) found the prevalence of surgical treatment in the patients with upper GIS bleeding to be 5.9% in 1995 and 3.1% in 2005. In the present study, prevalence of surgical treatment was higher than the literature with 5.6% found in the CRI group and 6.7% in the control group.

Parasa et al. (17) conducted a study in 2013 and determined mortality rate to be significantly higher in CRI patients with peptic ulcer bleeding as compared to the control group (4.8%-1.9%). Again, it was determined that these patients lead to higher tendency to surgery, longer duration of hospital stay and higher hospital cost. In the present study, hospital mortality rate was higher in the CRI group, but no statistical difference was determined between the groups. Duration of hospital stay was similar in both groups; however, need for transfusion and the rate of hospital-acquired complications were higher in the CRI group with higher hospital cost determined in this group. Weng et al. (18) evaluated cases with renal insufficiency and upper GIS bleeding and found mortality rate to be 13.7% in the first month and 27% in the first year; they determined that mortality is associated with advance age, female gender, hospital-acquired infections, and low albumin and white blood cell concentrations. Lower hospital mortality rate in the present study as compared to that study was considered to be associated with exclusion of long-term mortality

from the study. Similar with the literature, the present study found that hospital mortality rate is correlated with low albumin (exitus patients: 2.68 g/dL, non-exitus: 3.27 g/dL; $p=0.028$) and calcium (exitus patients: 8.24 mg/dL, non-exitus: 8.92 mg/dL; ($p=0.04$) concentrations and rebleeding (exitus patients: 25%, non-exitus: %2.5; $p=0.016$), but not with gender ($p=0.367$) and duration of hospital stay ($p=0.143$).

Conclusion

In summary, the CRI patients have an increased risk for upper GIS bleeding due to several mechanisms such as gastrin hypersecretion, increase *H. pylori* colonization, uremia-induced thrombocyte dysfunction etc. In addition, patients with CRI are more likely to be older, disabled, tobacco smoker, and have concomitant cardiovascular disease, all of which are additional risk factors for GI bleeding. It was determined that concomitant chronic diseases and history of drug use (clopidogrel, aspirin, and other nonsteroidal anti-inflammatory agents) are higher in CRI patients with gastrointestinal bleeding, and therefore, bleeding is severe in these patients.

Since most of these cases have chronic anemia, it should not be forgotten that they may also experience with cardiovascular problems in acute GIS bleeding. Especially in patients with hypoalbuminemia or hypocalcemia at the time of admission to the hospital, should be monitored in the intensive care unit until bleeding stabilization is achieved. We also believe that proton pump inhibitors would be appropriate for prophylaxis of GIS bleeding in these patients because the vast majority of patients are older, have multiple drug use and have a history of cardiovascular disease.

In our study, malignant neoplasm of the stomach was seen at high rates in CRI patients. GIS screening is crucial in these patients because anemia in these patients may not be related to the anemia of chronic disease.

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