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Risk factors for upper gastrointestinal bleeding among end-stage renal disease patients

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Risk factors for upper gastrointestinal bleeding among end-stage renal disease patients.

Background. The risk of upper gastrointestinal bleeding (UGIB) is increased among end-stage renal disease (ESRD) patients compared to the general population. However, correlates of UGIB among ESRD patients remain unknown. We conducted a cohort study of dialysis patients to ascertain risk factors for UGIB.

Methods. Data from the United States Renal Data System Dialysis Morbidity and Mortality Studies, Waves 2–4 were used to identify risk factors for incident UGIB among ESRD patients. First hospitalizations for UGIB were identified using hospital diagnosis codes between 12/31/93 and 12/31/99. Cox regression was used to estimate the association between predictors of interest and first diagnosis of UGIB.

Results. Cases of UGIB (698) were observed over 30,648 patient years of follow-up. Before adjustment for confounding factors, increasing age, diabetes, former and current smoking, cardiovascular disease (CVD), lower serum albumin, malnutrition, and inability to ambulate independently were associated with an increased risk of UGIB, while African Americans and transplant patients had a lower risk of UGIB. After adjustment, African American race was associated with a lower risk of UGIB (RR = 0.90; 0.82, 0.98), while current smoking (RR = 1.11; confidence interval 1.03, 1.19), history of CVD (RR = 1.32; 1.10, 1.59), and inability to ambulate independently (RR = 1.32; 1.07, 1.63) were associated with a higher risk of UGIB. Age, gender, diabetes, lower serum albumin, nourishment, treatment modality, aspirin use, nonsteroidal anti-inflammatory drug (NSAID) use, and antiplatelet or anticoagulant medication use were not found to be significantly related to the risk of UGIB after adjustment for potential confounding factors.

Conclusion. CVD, current smoking, and risk factors suggesting more disability are associated with a greater risk of UGIB among patients with ESRD.

Key words: end-stage renal disease, upper gastrointestinal bleeding, risk factors.

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Each year in the United States there are approximately 100 hospitalizations for upper gastrointestinal bleeding (UGIB) per 100,000 adults [1]. Furthermore, the occurrence of UGIB has been associated with a mortality rate of 5 to 15% [1–3]. The estimated annual cost of these hospitalizations exceeds $2.5 billion [4]. Reports suggest that the risk of UGIB may be greater among patients with acute renal failure, and among those with a serum creatinine >2.5 mg/dL [5–9]. Among end-stage renal disease (ESRD) patients, it has been estimated that UGIB accounts for 3 to 7% of all deaths [5]. The reasons for the high incidence of UGIB among those with ESRD are not known. In particular, it is not known what role factors known to increase the risk for UGIB in the general population may play in the dialysis population, including age, gender, alcohol use, smoking, ulcer disease, cardiovascular disease, immobilization, and anti-inflammatory medicine [6, 9–17]. Furthermore, it is not know if dialysis-specific factors such as heparin exposure during hemodialysis and platelet dysfunction resulting from uremia may also increase the risk of UGIB. We utilized data from the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality Studies, Waves 2–4 (USRDS DMMS, 2–4) to ascertain risk factors for UGIB among the ESRD patients.

METHODS

Subjects

Data for this study were obtained from the USRDS, a database containing demographic and clinical information on all United States ESRD patients surviving more than 90 days on renal replacement therapy and who qualify for Medicare. For the purposes of this study, we used data from the USRDS DMMS 2–4. Briefly, DMMS Wave 2 was a prospective study in which data were collected on a random sample of 4024 incident hemodial-

ysis and peritoneal dialysis patients initiating therapy in December of 1996. DMMS Waves 3 and 4 were historic prospective studies in which data were collected on a random sample of 11,142 prevalent ESRD patients receiving in-center hemodialysis on December 31, 1993. Although these special studies were conducted at different times and locations, data collection procedures and content were kept consistent across the studies, allowing them to be combined for analysis. Greater detail of the USRDS and these special studies is described elsewhere [18].

All ESRD patients with a valid USRDS identification number who participated in DMMS Wave 2, 3, or 4, survived more than 90 days on renal replacement therapy, and had treatment history records available, were considered eligible for the current study. In addition, only patients for whom Medicare was the primary payer of medical expenses at study start (81% of participants in DMMS Waves 2–4) were considered eligible for analysis. Since the current study sought to identify factors which may be associated with incident UGIB after initiation of dialysis, those patients who were reported as having experienced an UGIB between the date of initiation of care for ESRD and study start were excluded. In total, 10,842 patients met the inclusion criteria for the study (2479 from Wave 2; 4332 from Wave 3; and 4031 from Wave 4).

Risk factor identification

Covariates identified a priori as possible risk factors for UGIB were abstracted from the USRDS patient demographics file, the USRDS treatment history file, and the DMMS Waves 2–4 data files. Variables of interest included age at study start, gender, race (black, white, other), diabetes, treatment modality (hemodialysis, peritoneal dialysis, transplant), smoking status (never, former, current), cardiovascular disease (CVD), subjective assessment of undernourishment (yes, no), ability to ambulate independently (yes, no), KT/V, serum albumin, aspirin use (yes, no), non-steroidal medication use (yes, no), antiplatelet medication use (yes, no), and H2 blocker or proton pump inhibitor use (yes, no).

Outcome definition

Medicare billing data from December 31, 1993 to December 31, 1999 were linked to DMMS Wave 2–4 data via unique patient identification numbers. Patients were considered to have experienced a UGIB if a primary hospital discharge diagnosis indicating UGIB, as defined by any one of the International Classification of Diseases, 9th Revision (ICD9) diagnosis codes consistent with esophageal, gastric, duodenal, peptic, and gastrojejunal bleeds were reported (Table 1). Gastrointestinal bleed, unspecified, was not used to identify UGIB because it was felt to be too nonspecific with regard to location of bleeding. Primary billing codes, rather than secondary codes, were used to better capture hospitalizations for which UGIB was the primary reason for hospitalization. Secondary billing codes were felt more likely to reflect UGIBs that occurred after hospitalization.

Table 1. ICD-9 codes for upper GI bleeds

ICD-9 code	Description
530.4, 530.7, 530.82	Esophageal
578.0	Hematemesis
531.00, 531.10, 531.20, 531.40, 531.50, 531.60, 531.80	Gastric ulcer
532.00, 532.10, 532.20, 532.40, 532.50, 532.60, 532.80	Duodenal ulcer
533.00, 533.10, 533.20, 533.40, 533.50, 533.60, 533.80	Peptic ulcer
534.00, 534.10, 534.20, 534.40, 534.50, 534.60, 534.80	Gastrojejunal ulcer
535.X1	Gastritis/duodenitis with bleeding

Statistical analysis

Patient characteristics were summarized by the mean and corresponding standard deviation for continuous covariates and frequency for categorical covariates. In the event that Medicare billing data were not received over a continuous period of one year, patients were considered lost to follow-up. For all analyses, patients were considered at risk for UGIB from the maximum of 90 days following initiation of care for renal replacement therapy and the date of study start for their respective special study to the minimum date of UGIB, death, loss to follow-up, loss of Medicare coverage, or 12/31/1999. UGIB event rates were computed by dividing the total number of first primary diagnoses of UGIB by the total number of patient-years at risk.

To model the time from study start to the first report of UGIB, proportional hazards regression for censored survival data was used. Covariates were adjusted for multivariate models if a priori they were considered to be associated with the risk of UGIB. H2-blocking medications were not included in the multivariate analysis because of the potential for confounding by indication. Given the availability of data indicating ESRD treatment history over the course of the current study, treatment modality was modeled as a time-dependent variable, implying that patients were able to switch risk groups over the course of follow-up. All continuous variables considered for adjustment in the analysis were hypothesized to be linearly related to the outcome of interest, and forced into the model assuming this functional form. However, in secondary analyses, continuous variables were also categorized and diagnostic plots were used to verify that

the assumption of linearity was a reasonable one. Regression models were stratified by study participation (Waves 2, 3, and 4), implying that the association between each covariate of interest and the risk of UGIB was estimated within each special study, and estimates were then combined across the three strata. Point estimates associated with each covariate of interest did not differ appreciably across strata. Graphical diagnostics as well as formal hypothesis tests were used to determine the appropriateness of the assumption of proportional hazards for each adjustment covariate. All analyses were performed on a complete-case basis.

RESULTS

Cases of UGIB (698) were observed over 30,648 patient years of follow-up. Follow-up time on patients ranged between 1 day and 6 years, with a median of 2.7 years. Table 2 presents selected characteristics of the patients included in our analysis and the corresponding incidence densities for UGIB. At the time of study enrollment, the mean patient age was 61.0 years. Fifty-one percent of the patients in the current study were male, and 55% were Caucasian. Patients were more likely to be non-diabetic at the initiation of care for ESRD and non-smokers. The incidence of UGIB, regardless of study period, exceeded 21 bleeds per 1000 persons per year, and was highest among Caucasians, diabetics, current smokers, those with a history of CVD, those unable to ambulate independently, and those identified as undernourished. Figure 1 depicts incidence densities for those sources of bleeding considered in the study. Gastric ulcers were found to be the most common source of bleeding (7.0 per 1000 persons per year), while bleeding resulting from a gastrojejunal ulcer was least frequent (0.1 per 1000 persons per year). Duration of hospital stays for those patients diagnosed with a UGIB ranged between 1 and 87 days, with a median hospital stay of 5 days. For those hospital admissions resulting in a diagnosis of an UGIB, 73.2% of the surgical procedures performed during the hospital stay pertained to hemodialysis (ICD-9 surgical code 39.95; 12.6%), endoscopy (ICD-9 surgical codes 44.43, 45.13, and 45.16; 58.3%), and transfusion (ICD-9 surgical code 99.04; 2.3%).

Table 3 presents estimates of the unadjusted and adjusted relative risk for UGIB associated with each covariate of interest. Prior to adjustment, the incidence of UGIB was estimated to increase by 11% with each increasing decade of life [95% confidence interval (CI), 1.05 to 1.16, $P < 0.001$), and African Americans were estimated to experience a 12% lower risk of UGIB when compared to Caucasians (95% CI, 0.82 to 0.96, $P = 0.002$). The risk of UGIB did not differ significantly by gender. Diabetics were estimated to have a 13% higher risk of UGIB when compared to those without diabetes (95% CI, 1.05 to 1.22, $P < 0.001$), while former and current smokers had an 11% (95% CI, 1.01 to 1.21, $P = 0.027$) and 7% (95% CI, 1.00 to 1.15, $P = 0.036$) greater risk of UGIB, respectively. Patients with a history of CVD were estimated to experience a 1.6-fold increase in the risk of UGIB when compared to those without CVD (95% CI, 1.33 to 1.80, $P < 0.001$). Each 1 mg/dL decrease in albumin was associated with a 36% increased risk of UGIB (95% CI, 1.12 to 1.63, $P < 0.001$). Those patients who were subjectively considered undernourished or unable to ambulate independently experienced a 48% (95% CI, 1.19 to 1.84, $P = 0.001$), and 57% (95% CI, 1.32 to 1.87, $P < 0.001$) increased risk of UGIB respectively, when compared to patients without these factors. Renal transplant recipients experienced a 17% lower risk of UGIB when compared to patients treated with chronic hemodialysis (95% CI, 0.71 to 0.96, $P = 0.014$). In bivariate analyses, the use of antiplatelet or anticoagulant medications was not found to be significantly associated with the risk of UGIB. Kt/V was also not found to be associated with an increased risk of UGIB.

Following adjustment for potentially confounding factors, African Americans were estimated to have a 10% lower risk of UGIB when compared to Caucasians (95% CI, 0.82 to 0.98; $P = 0.021$) and current smokers were estimated to have experienced an 11% increase in the risk of UGIB compared to those who had never smoked (95% CI, 1.03 to 1.19, $P = 0.008$). Patients with CVD had a 32% higher risk of an UGIB (95% CI, 1.10 to 1.59, $P = 0.003$) when compared to those without. The risk of UGIB was estimated to increase by 32% for patients reportedly unable to ambulate independently (95% CI, 1.07 to 1.63, $P = 0.010$). Following adjustment for confounders, peritoneal dialysis and transplantation (relative to hemodialysis) were not significantly associated with the risk of UGIB. Other factors that were no longer statistically significant correlates of UGIB after adjustment included diabetes, malnourishment, serum albumin, and antiplatelet and anticoagulant medication use.

DISCUSSION

We conducted a cohort study to determine risk factors for incident UGIB among ESRD patients. The incidence of UGIB, regardless of study period, was greater than 21 bleeds per 1000 persons per year. In bivariate analyses, age, African American race, diabetes, former and current cigarette smoking, a history of CVD, lower serum albumin, undernourishment, and inability to ambulate independently were all associated with the risk of UGIB. Renal transplant recipients and peritoneal dialysis patients had a lower risk of UGIB compared to hemodialysis patients prior to adjustment for potential confounding factors. Following adjustment, African American race

Table 2. Patient characteristics

Characteristic	Mean (SD) or N (%)	Person years	Number of upper GI bleeds	Incidence density (per 1000 per year)
DMMS Wave				
Wave 2	2479 (22.9%)	5307	124	23.4
Wave 3	4332 (40.0%)	13,033	278	21.3
Wave 4	4031 (37.2%)	12,308	296	24.0
Age at study start *years*	61.01 (15.61)	30,648	698	22.8
Gender				
Male	5576 (51.4%)	15,817	367	23.2
Female	5266 (48.6%)	14,831	331	22.3
Race				
White	5976 (55.2%)	15,180	390	25.7
Black	4308 (39.8%)	13,771	273	19.8
Other	550 (5.1%)	1670	34	20.4
Diabetes as primary cause of ESRD				
No	5649 (55.7%)	17,612	364	20.7
Yes	4490 (44.3%)	11,206	301	26.9
Smoking status				
Never	4930 (52.9%)	14,779	302	20.4
Former	2928 (31.4%)	7656	193	25.2
Current	1463 (15.7%)	4300	120	27.9
History of CVD				
No	5096 (47%)	16,680	300	18.0
Yes	5746 (53%)	13,969	398	28.5
Serum albumin *g/dL*	3.67 (0.45)	30,648	698	22.8
Undernourished				
No	8257 (84%)	25,068	542	21.6
Yes	1568 (16%)	2939	96	32.7
Ability to ambulate				
No	2766 (27.3%)	5751	187	32.5
Yes	7362 (72.7%)	23,111	473	20.5
Aspirin use				
No	9315 (85.9%)	26,630	601	22.6
Yes	1527 (14.1%)	4019	97	24.1
NSAIDs use				
No	10,314 (95.1%)	29,153	657	22.5
Yes	528 (4.9%)	1495	41	27.4
Antiplatelet use				
No	10,562 (97.4%)	29,916	686	22.9
Yes	280 (2.6%)	732	12	16.4
H2 antogonists use				
No	8328 (76.8%)	24,053	529	22.0
Yes	2514 (23.2%)	6595	169	25.6
Proton pump inhibitors use				
No	8729 (80.5%)	25,088	544	21.7
Yes	2113 (19.5%)	5560	154	27.7
Other medication use[a]				
No	10,138 (93.5%)	28,890	660	22.8
Yes	704 (6.5%)	1758	38	21.6

[a] Includes warfarin, lepirudin, heparin, argatroban, aprotinin, enoxaparin, dalteparin, danaparoid, and lovenox

was associated with a decrease in the risk of UGIB, while current smoking, history of CVD, and inability to ambulate were all associated with an increased risk of UGIB. Factors not associated with UGIB in the adjusted analysis included age, gender, diabetes, Kt/V, treatment modality, aspirin, NSAIDs, and antiplatelet or anticoagulation medication use.

Our findings are comparable to those described among the general population, which report that CVD, current smoking, and co-morbidities such as inability to ambulate, place individuals at a greater risk of UGIB [6, 9, 19–21]. Kaplan et al [6] reported a 42% higher risk of UGIB associated with age ≥70, an almost 2-fold greater risk of UGIB associated with CVD, and a >2-fold greater risk associated with current smoking in the general population. Pahor et al [19, 20] describe several possible mechanisms for the increased risk of UGIB among inactive, elderly patients with CVD, including gut ischemia and reduced splanchnic circulation, which are both thought to worsen with inactivity. These vascular lesions may be particularly problematic among ESRD patients, who have pre-existing vascular disease, diabetes, and uremic factors, which accelerate microvascular pathology. In addition, several reports from the general

Table 3. Stratified[a] Cox regression estimates modeling the time to first upper GI bleed

Covariate	Unadjusted		Adjusted[b]	
	Relative risk (95% CI)	*P* value	Relative risk (95% CI)	*P* value
Age (per decade)	1.11 (1.05, 1.16)	<0.001	1.03 (0.97, 1.10)	0.290
Gender (female vs. male)	0.96 (0.83, 1.11)	0.578	0.96 (0.80, 1.14)	0.631
Race				
White	1.0			
Black	0.88 (0.82, 0.96)	0.002	0.90 (0.82, 0.98)	0.021
Other	0.97 (0.86, 1.09)	0.607	0.98 (0.86, 1.12)	0.753
Diabetes (yes vs. no)	1.13 (1.05, 1.22)	0.002	1.06 (0.97, 1.17)	0.179
Smoking status				
Never	1.0			
Former	1.11 (1.01, 1.21)	0.027	1.07 (0.97, 1.19)	0.158
Current	1.07 (1.00, 1.15)	0.036	1.11 (1.03, 1.19)	0.008
History of CVD (yes vs. no)	1.55 (1.33, 1.80)	<0.001	1.32 (1.10, 1.59)	0.003
Serum albumin (per 1 mg/dL decrease)	1.36 (1.12, 1.63)	0.001	1.18 (0.95, 1.46)	0.141
Undernourished (yes vs. no)	1.48 (1.19, 1.84)	<0.001	1.23 (0.96, 1.59)	0.105
Ability to ambulate (no vs. yes)	1.57 (1.32, 1.87)	<0.001	1.32 (1.07, 1.63)	0.010
Treatment modality				
HD	1.0			
PD	0.88 (0.75, 1.04)	0.132	0.88 (0.72, 1.07)	0.205
Transplant	0.83 (0.71, 0.96)	0.014	0.94 (0.80, 1.11)	0.485
Aspirin use (yes vs. no)	1.06 (0.85, 1.31)	0.612	0.95 (0.74, 1.21)	0.684
NSAIDs use (yes vs. no)	1.22 (0.89, 1.67)	0.220	1.20 (0.84, 1.71)	0.319
Antiplatelet use (yes vs. no)	0.72 (0.41, 1.27)	0.254	0.81 (0.45, 1.43)	0.461
Other medication use (yes vs. no)	0.94 (0.68, 1.30)	0.693	0.95 (0.67, 1.35)	0.794

Abbreviations are: CVD, cardiovascular disease; DMMS, Dialysis Morbidity and Mortality Studies; GI, gastrointestinal; HD, hemodialysis; NSAIDs, non-steroidal anti-inflammatory drugs; PD, peritoneal dialysis.

[a] Model is stratified by DMMS study participation

[b] Adjusted for all covariates listed

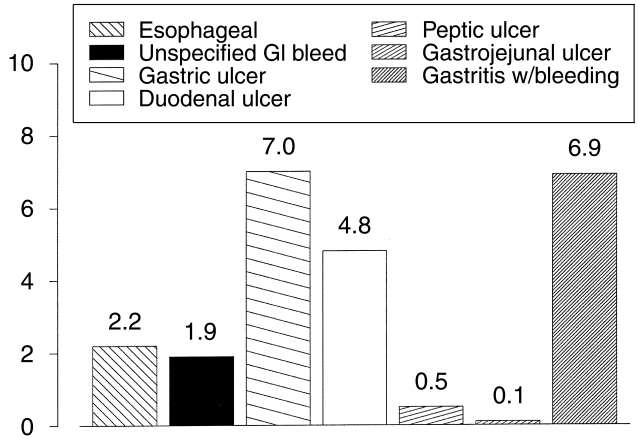

Fig. 1. Estimated incidence densities (per 1000 per year) for those categories of upper gastrointestinal bleeding (UGIB) displayed in Table 1. Incidence densities were calculated by dividing the total number of diagnoses occurring in the study sample by the total person years at risk and multiplying by 1000.

population cite an association between cigarette smoking and UGIB. Anderson et al [22] reported a strong association between current tobacco use and hospitalization for a perforated peptic ulcer (RR = 3.5, 95% CI, 1.7 to 7.1). In addition, Kaplan et al [6] reported that smokers greater than 65 years old had a higher risk of hospitalization for UGIB compared to non-smokers (HR = 2.14, 95% CI, 1.22 to 3.75). Although the exact mechanism has not been determined, it is proposed that smoking inhibits prostaglandins in the upper gastrointestinal tract, causing mucosal vasoconstriction and possible ischemia [22–24]. This effect may be especially pronounced among patients with ESRD who smoke and have microvascular disease, placing them at greater risk of UGIB compared to the general population.

Unlike many reports from the general population, we did not find an association between UGIB and use of aspirin, non-steroidal medications, or anticoagulants [1, 15, 25–29]. In our study, it is possible that medications such as aspirin or non-steroidals were under-reported, since these are non-prescription medications. In addition, medication use in our study was ascertained at only one time point, potentially leading to misclassification. Finally, patients at greatest risk of UGIB may avoid particular medications that could increase the risk of UGIB, such as anticoagulants or non-steroidals, or may be placed on prophylactic medications such as proton-pump inhibitors, thereby decreasing the risk of a UGIB.

Several dialysis specific factors have been postulated to increase the risk of UGIB, including poor platelet function resulting from uremia, mucosal abnormalities of the gastrointestinal tract, and hypergastrinemia [5, 30–32]. We were unable to find an association between Kt/V, a possible surrogate marker for uremia, and risk of UGIB.

However, Kt/V may not accurately reflect uremic factors that are important in the pathogenesis of UGIB among ESRD patients. Alternatively, our study may not have been able to detect such an association, since Kt/V was assessed at a single time point. This may have led to nondifferential misclassification, underestimating the association of Kt/V with UGIB. It has also been hypothesized that intermittent anticoagulation may place hemodialysis patients at greater risk for UGIB. If this were the case, one would anticipate that peritoneal dialysis and renal transplantation would be associated with a lower risk for UGIB compared to hemodialysis. In bivariate analyses, we found a lower risk of UGIB associated with renal transplant. However, following adjustment for potential confounding factors, the association between treatment modality and UGIB was no longer found to be statistically significant, although point estimates indicated that patients receiving peritoneal dialysis, or those with a renal transplant may be at a lower risk of UGIB when compared to hemodialysis patients. It is possible that factors such as chronic prednisone use and infection predispose these patients to peptic ulcer disease and increase the risk of UGIB [33–35].

Our study has several limitations. First, we have identified patients with UGIBs based on ICD-9 coding, which may result in some misclassification. However, this misclassification should be non-differential and result in an attenuation of estimated effects and less power to detect differences between groups. Second, we lack longitudinal information regarding medications, and nonprescription medications may be under-reported. Finally, we lack information regarding the presence of *Helicobacter pylori* among these patients, and are unable to assess this as a risk factor. Future prospective studies may be able to better estimate the association between medication use and UGIB. Despite these limitations, this study combines data on over 10,000 ESRD patients from around the country, and therefore the results should be generalizable to the entire ESRD population and not reflect specific dialysis unit practices.

CONCLUSION

Current cigarette smoking, the presence of CVD, and risk factors suggesting more disability are associated with a greater risk of UGIB among patients with ESRD. Further studies need to assess whether smoking cessation and the use of H2 blockers and proton pump inhibitors may reduce the risk of UGIB in these high-risk patients.

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