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Original Article

Risk factors of the peptic ulcer bleeding in aging uremia patients under regular hemodialysis

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Abstract

Background: Previous studies have shown that uremia patients under hemodialysis (HD) have a significantly higher occurrence of peptic ulcer bleeding (PUB) than healthy controls and that elderly patients remain at high risk of peptic ulcer disease (PUD) and PUB. Here we aimed to identify the risk factors for PUB in aging (≥65-years-old) uremic patients under regular HD.

Methods: Using data from the National Health Insurance Research Database of Taiwan, we compared 18,252 aging regular HD patients and 17,883 age-, gender-, and medication-matched patients without kidney disease (control group). The log-rank test was performed to analyze the differences in accumulated hazard of PUB between the two groups. Cox proportional hazard regressions were performed to evaluate independent risk factors for PUB between the two groups and identify risk factors of PUB in aging HD patients.

Results: In a 7-year follow-up, aging HD patients had significantly higher incidences of PUB than the matched controls ($p < 0.001$ by the log-rank test). By Cox proportional hazard regression analysis, HD (hazard ratio [HR] = 4.61; 95% confidence intervals [CI] 4.03−5.27) was independently associated with increased risk of PUB. Age, diabetes mellitus (DM), history of uncomplicated PUD, cirrhosis, and use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids were risk factors for PUB in aging HD patients.

Conclusion: Aging HD patients are associated with higher risk of PUB. The use of NSAIDs and corticosteroids and co-morbidities including DM, history of uncomplicated PUD, and cirrhosis were identified as risk factors for PUB in these patients.

Keywords: Aging; Co-morbidity; Hemodialysis; Peptic ulcer bleeding; Uremia

1. Introduction

Peptic ulcer disease (PUD) is the most common cause of upper gastrointestinal bleeding (UGIB), including in elderly people.[1] Although the incidence of uncomplicated PUD has decreased in the general population in recent years, elderly patients remain at higher risk for PUD.[2] Previous studies have shown that the rates of hemorrhage and hospital admissions have increased among elderly people with PUD.[3,4] In the elderly, not only does the wide use of nonsteroidal anti-inflammatory drugs (NSAIDs) play a key role in the patho-physiology of PUB, but also the presence co-morbidities (e.g., cardiovascular disease, cerebral vascular disease, diabetes mellitus [DM], chronic kidney disease, orthopedic disease) and multidrug therapy, especially antiplatelet drugs and

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anticoagulants, have been identified as significant risk factors for PUD and PUB.[5–7]

The incidence of end-stage renal disease (ESRD) is increasing globally. Taiwan has the highest incidence and prevalence rate of ESRD in the world[8] and 90% of ESRD patients have received regular HD, which was covered by the National Health Insurance (NHI) program.[9] In recent decades, emerging evidence suggests that ESRD patients have a higher prevalence of PUD.[10] Previous studies have also shown that uremic patients under HD have a significantly higher occurrence of PUB.[10,11] Considering the elderly and ESRD patients together, the literature about the risk factors of PUB in aging uremic patients is limited. The aim of this nationwide population-based cohort study was to clarify the risk factors of PUB in aging uremic patients under regular HD in Taiwan.

2. Methods

2.1. Database

The National Health Insurance (NHI) program in Taiwan was established in 1995 to provide comprehensive medical care for the population of Taiwan, and currently covers over 99% of the population of 23 million. The NHI research database (NHIRD), established in cooperation with the Bureau of National Health Insurance (BNHI) and the National Health Research Institute (NHRI), is one of the largest administrative healthcare databases in the world and is available to scientists for research purposes.[12,13] The NHRI released a cohort dataset of 1,000,000 randomly sampled individuals and a special dataset of patients with some catastrophic illnesses (e.g., ESRD and cancer) who were alive in 2000, and collected all records on these individuals from 1995 to 2006.[11] There were no statistically significant differences in the age, sex, and healthcare costs between the sample group and all of the health insurers. Comprehensive healthcare data included the enrollment files, claims data, catastrophic illness files, and registry for drug prescription.

2.2. Study group

After excluding patients with alcohol-related diseases (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 291.xx, 303.xx, 305.xx), malignancy of the GI tract (150.xx, 151.xx, 152.xx, 153.xx, 154.xx), inflammatory bowel disease (556.x, 555.x), coagulopathy (286.xx), vascular insufficiency of the intestine (557.xx), and gastroenteritis or colitis due to radiation (558.1) as the primary hospitalization claims before and after January 1st 2000 and patients with PUB (ICD-9-CM codes 531.0, 531.00, 531.01, 531.2x, 531.4x, 531.6x, 532.0, 532.00, 532.01, 532.2x, 532.4x, 532.6x, 533.0, 533.00, 533.01, 533.2x, 533.4x, 533.6x, 534.0, 534.00, 534.01, 534.2x, 534.4x, and 534.6x.) as the primary hospitalization claims before January 1st 2000, aging patients with ESRD in need of long-term (more than 3 months) renal replacement therapy with catastrophic illness registration cards from the Bureau of NHI were considered for enrollment. The study identified 18,252 ESRD aging patients who were ≥65-years-old and had been diagnosed with chronic renal failure with (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]) codes 585 and under regular HD for more than 3 months after January 1st 2000. Patients receiving PD or renal transplantation before and after enrollment were excluded.

2.3. Control group

Using the same exclusion criteria as the study group, a control group with aging subjects (≥65 year-old) without kidney disease (ICD-9-CM codes: 580.X-588.X, 250.4x, 274.1x, 283.11, 403.x1, 404.x2, 404.x3, 440.1, 442.1, 447.3, 572.4, 642.1x, and 646.2x) before and after enrollment were selected from the database in a 1:1 ratio. They were matched with the HD patients in terms of age, gender, time of enrollment, and some ulcerogenic medications (e.g., non-steroidal anti-inflammatory drugs [NSAIDs], aspirin, corticosteroid, thienopyridine [clopidogrel and ticlopidine], and warfarin). Medication were identified and classified by the National Drug Code and the Anatomic Therapeutic Chemical Code, which is an internationally accepted classification system of drugs coordinated by the WHO Collaborating Center for Drug Statistics Methodology.[14] The use of the above-mentioned medications (e.g., NSAIDs and aspirin) were defined as prescription of these medications for more than 4 weeks within 8 weeks before the index date or censoring.[14]

Other recorded pre-existing co-morbidities included hypertension (ICD-9-CM codes 401.xx-405.xx), coronary artery disease (ICD-9-CM codes 411.xx-414.xx), heart failure (ICD-9-CM codes: 428.00–428.9), diabetes mellitus (DM) (ICD-9-CM codes 250.xx), liver cirrhosis (ICD-9-CM codes 571.2, 571.5, and 571.6), and uncomplicated PUD (ICD-9-CM codes 531.30, 531.70, 531.90, 532.30, 532.70, 532.90, 533.30, 533.70, and 533.90). Co-morbidity was defined as a corresponding ICD-9-CM code in primary hospitalization claims data once or three times in outpatient claims before enrollment.[15]

2.4. Clinical endpoints

The study endpoint was the occurrence of administrative claims of PUB as the main diagnosis during hospitalization. PUB was proven by endoscopic examination and therapy, as well as prescription of proton pump inhibitor (PPI) with corresponding ICD-9-CM codes (531.0, 531.00, 531.01, 531.2x, 531.4x, 531.6x, 532.0, 532.00, 532.01, 532.2x, 532.4x, 532.6x, 533.0, 533.00, 533.01, 533.2x, 533.4x, 533.6x, 534.0, 534.00, 534.01, 534.2x, 534.4x, and 534.6x).

2.5. Ethics

In the cohort dataset, each patient's original identification number was encrypted for privacy. This study was approved by the Institutional Review Committee of Taipei Veterans General Hospital (IRB: 2012-10-010AC).

2.6. Statistical analysis

All data were expressed as frequency (percentage) or mean ± standard deviation (SD). Parametric continuous data between the case and control groups were compared by Student's *t*-test while categorical data were compared by Chi-square test and Yates' correction or Fisher's exact test, as appropriate. The cumulated incidence of UGIB was assessed using the Kaplan−Meier analysis with significance based on the log-rank test. Multiple regression analysis was carried out using Cox proportional hazard regression analysis. *p*-values < 0.05 were considered statistically significant. Microsoft SQL Server 2005 was used for data management and computing, and all statistical analysis was performed using the SPSS software (version 18.0, SPSS Inc., Chicago, Illinois, USA).

3. Results

The demographic data of the aging HD patients (study group) and aging patients without kidney disease (control group) are shown in Table 1. Except for thienopyridine, concurrent medications (e.g., NSAIDs, aspirin, corticosteroids, and warfarin) between the HD and control groups were comparable ($p > 0.05$) (Table 1). However, co-morbidities, including hypertension, coronary heart disease, heart failure, DM, cirrhosis, and uncomplicated PUD were not matched between the two groups (Table 1).

During the 7-year follow-up period, 1773 (4.9%) of 36,135 patients developed PUB. Among them, 1413 were from the HD group (7.7% of ESRD patients with HD) and 360 from the control group (2.0% of the controls) (Table 1). The log-rank test and Kaplan−Meier survival analysis showed that the HD group had a significantly higher rate of PUB than the control group ($p < 0.001$) (Fig. 1).

After adjusting for age, gender, presence of hypertension, coronary artery disease, heart failure, DM, cirrhosis, uncomplicated PUD, and use of aspirin, NSAIDs, corticosteroids, thienopyridine, and warfarin, the hazard ratio (HR) of PUB was 4.61-times greater (95%CI, 4.03−5.27) in the HD group compared to the control group. Other risk factors of PUB in aging patients included age (HR, 1.02; 95%CI, 1.02−1.03), male gender (HR, 1.15; 95%CI, 1.05−1.26), DM (HR, 1.24; 95%CI, 1.12−1.38), heart failure (HR, 1.17; 95%CI, 1.04−1.31), cirrhosis (HR, 1.63; 95%CI, 1.30−2.03), history of uncomplicated PUD (HR, 1.21; 95%CI, 1.03−1.40), and use of NSAIDs (HR, 1.90; 95%CI, 1.69−2.15) and corticosteroids (HR, 1.34; 95%CI, 1.05−1.63).

Among all the aging HD patients, Cox multivariate regression analysis showed that aging, DM, history of uncomplicated PUD, cirrhosis, and use of NSAIDs and corticosteroids were risk factors for PUB in aging ESRD patients under regular HD (Table 2).

In the subgroup analysis of aging HD patients with DM, Cox multivariate regression analysis showed that hypertension, history of uncomplicated PUD, cirrhosis, and use of NSAIDs were risk factors for PUB in aging DM patients under regular HD (Table 3).

In the subgroup analysis of aging HD patients without DM, Cox multivariate regression analysis showed that aging, history of uncomplicated PUD, cirrhosis, and use of NSAIDs and corticosteroids were risk factors for PUB in aging non-DM patients under regular HD (Table 4).

4. Discussion

We conducted a nationwide population-based cohort study to determine risk factors for aging uremic patients under regular HD. In our study, HD is independently associated with higher risk of PUB in aging patients. The use of NSAIDs and corticosteroids and co-morbidities, including DM, history of uncomplicated PUD, and cirrhosis, were important risk factors for PUB in these aging HD patients.

For all the aging patients enrolled in this study, the risk factors associated with PUB after Cox proportional hazard

Table 1
Comparison of demographic data and peptic ulcer bleeding between aging HD patients and matched controls.

	Aging patients with HD (n = 18,252)	Aging patients without kidney disease (n = 17,883)	*p*
Age, years	74.5 ± 6.6	74.5 ± 6.6	0.754
Male, n (%)	8233 (45.1)	8126 (45.4)	0.526
Hypertension, n (%)	16,267 (89.1)	7887 (44.1)	<.001
Diabetes, n (%)	10,385 (56.9)	2466 (13.8)	<.001
Coronary artery disease, n (%)	8183 (44.8)	3687 (20.6)	<.001
Heart failure, n (%)	5632 (30.9)	852 (4.8)	<.001
Cirrhosis, n (%)	743 (4.1)	171 (1.0)	<.001
Uncomplicated PUD, n (%)	3302 (18.1)	1501 (8.4)	<.001
Medication			
Aspirin, n (%)	3412 (18.7)	3311 (18.5)	0.665
NSAIDs, n (%)	1901 (10.4)	1830 (10.2)	0.580
Corticosteroids, n (%)	560 (3.1)	534 (3.0)	0.667
Thienopyridine, n (%)	1150 (6.3)	924 (5.2)	<.001
Warfarin, n (%)	124 (0.7)	104 (0.6)	0.259
Peptic ulcer bleeding	1413 (7.7)	360 (2.0)	<.001

Abbreviations: HD = hemodialysis; NSAIDS = non-steroidal anti-inflammatory drugs, PUD = peptic ulcer disease.
Data are mean ± SD; T test and chi-square test were used for continuous variables and categorical variables, respectively.

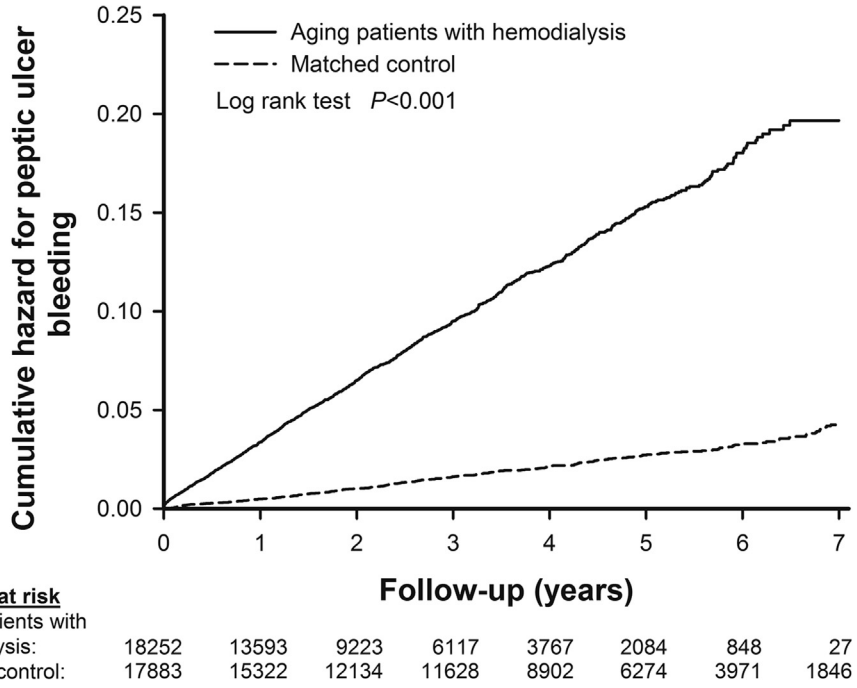

Fig. 1. Kaplan−Meier estimates of cumulative hazard of peptic ulcer bleeding in aging patients (≥65-year-old) categorized by hemodialysis (HD) and control. ($p < 0.001$ between the two groups by the log-rank test).

Table 2
Significant risk factors for peptic ulcer bleeding in aging uremic patients under regular hemodialysis, by multivariate Cox regression analysis.

Risk factors	Hazard ratio (95% CI)	*p*
Age	1.02 (1.01−1.03)	<.001
Diabetes	1.26 (1.30−1.42)	<.001
Uncomplicated PUD	1.65 (1.48−1.81)	<.001
Cirrhosis	1.59 (1.26−2.00)	<.001
NSAIDs usage	1.81 (1.58−2.08)	<0.001
Corticosteroids usage	1.36 (1.04−1.78)	0.025

NSAIDS = non-steroidal anti-inflammatory drugs; PUD = peptic ulcer disease.
Each variable was adjusted for every other variable listed.

Table 3
Significant risk factors for peptic ulcer bleeding in aging uremic patients with diabetes under regular hemodialysis, by multivariate Cox regression analysis.

Risk factors	Hazard ratio (95% CI)	*p*
Hypertension	1.46 (1.30−1.62)	<.001
Uncomplicated PUD	1.55 (1.28−1.81)	<.001
Cirrhosis	1.69 (1.36−2.02)	<.001
NSAIDs usage	1.68 (1.48−1.89)	<.001

NSAIDS = non-steroidal anti-inflammatory drugs; PUD = peptic ulcer disease.
Each variable was adjusted for every other variable listed.

regression analysis included age, male gender, DM, cirrhosis, HD, heart failure, history of uncomplicated PUD, and use of NSAIDs and corticosteroids. Our findings were comparable to Higuchi's study, which showed that risk factors related to PUB in elderly patients have shifted from *Helicobacter pylori* infection to co-morbidities.[7] However, the individual risk factor-co-morbidity was not further evaluated in Higuchi's study. In our study, we found that the impact of HD was higher (HR = 4.61) than for the other co-morbidities, including DM, heart failure, cirrhosis, and history of uncomplicated PUD for PUB among the elderly.

Table 4
Significant risk factors for peptic ulcer bleeding in aging uremic patients without diabetes under regular hemodialysis, by multivariate Cox regression analysis.

Risk factors	Hazard ratio (95% CI)	*p*
Age	1.03 (1.02−1.04)	<.001
Uncomplicated PUD	1.74 (1.49−1.99)	<.001
Cirrhosis	1.51 (1.26−1.75)	<.001
NSAIDs usage	1.99 (1.61−2.37)	<.001
Corticosteroids usage	1.49 (1.11−1.87)	0.009

NSAIDS = non-steroidal anti-inflammatory drugs; PUD = peptic ulcer disease.
Each variable was adjusted for every other variable listed.

Despite an increasing proportion of elderly people in the general population[16] and increasing prevalence co-morbidities in aging people, especially ESRD, few studies have addressed the possible risk factors for PUB in aging uremic patients. The present study is the first population-based cohort study to evaluate the risk factors of PUB for aging uremic patients under regular HD. The pathogenesis of PUB in aging HD patients might be related to several factors: (1) the vulnerable gastroduodenal mucosa in the elderly[17]; (2) platelet dysfunction in the form of impaired platelet adhesiveness and altered platelet vessel−wall interaction in HD patients[18]; and (3) exposure to more inflammation and oxidative stress, which

might damage or worsen gastric or small intestinal mucosa in HD patients.[19,20] In our study, age, the use of NSAIDs and corticosteroids and co-morbidities, including DM, history of uncomplicated PUD, and cirrhosis, were associated with an increased risk of PUB among aging uremic patients under regular HD after adjustment for possible confounding factors. Our results are consistent with previous studies reporting that DM, cirrhosis, and the use of NSAIDs place uremic patients at a greater risk of PUB.[9,11,22]

In our study, unexpectedly, we did not find the use of antiplatelet agents, including aspirin and thienopyridine, to be associated with an increased risk for PUB among aging HD patients. Aspirin is frequently used in uremic patients due to its safety and effectiveness for ischemic stroke and cardiovascular disease prevention.[23] Ethier's and Liang's report shows that the use of aspirin does not increase the risk of PUD among HD patients and patients with chronic kidney disease respectively.[24,25] Further studies are needed to clarify the reasons for this finding. Similar to previous findings,[11,25,26] use of warfarin was not associated with an increased risk of PUB in the current study.

The literature on corticosteroids as an independent risk factor for upper gastrointestinal bleeding (UGIB) or PUB in uremia patients is limited.[27] Contrary to the findings from two large population-based cohort studies focused on the risk for PUB among ESRD patients under regular HD,[9,11] we found the use of corticosteroids to be associated with an increased risk for PUB among aging uremic patients under regular HD. Higuchi et al. reported that corticosteroids are exacerbating factors for PUB in elderly patients compared with nonelderly patients.[7] This could be explained by the use of corticosteroids, one of the delayed mucosal healing factors, which act on an already compromised gastroduodenal mucosa in elderly patients.[28,29]

Due to DM becoming the leading cause of ESRD since 2000,[30] after adjustment for possible confounding factors, our subgroup analysis identified hypertension, history of uncomplicated PUD, cirrhosis, and use of NSAIDs as risk factors for PUB in aging diabetic ESRD patients under regular HD. Our findings are consistent with Peng's study, which found that chronic renal disease, peptic ulcer history, and NSAIDs use, but not low-dose aspirin use, are important risk factors for PUB in type II diabetic patients.[15]

This study has several limitations that are worth noting. First, observations are retrospective and based on hospitalized patients with PUB. Certain selection biases might exist, such that caution must be taken in extrapolating the results. Yang et al. reported that approximately 10% of UGIB episodes in the dialysis population are managed in the ambulatory care department.[31] However, we propose that most aging people in our study (HD or without kidney disease) received hospitalization care for PUB, due to aging and the accessibility and affordability of care.[32] Second, NSAIDs consumption is likely to be partly underestimated in the elderly, since some aging people use these medications as over-the-counter therapy.[33] However, such underestimations can occur in both the HD group and control group. Third, the NHRI database does not include *Helicobacter pylori* infection status, a well-known important risk factor for PUB. However, previous studies have shown that *H. pylori* infection is not a risk factor for ulcer or recurrent ulcer in uremic patients.[21,34] Fourth, smoking and alcohol consumption are independent risk factors for PUD, but this information was not available in the NHRI database. Finally, we did not evaluate the protective factors of PUD, such as PPI usage. In Taiwan's National Health Insurance, the use of PPI is strictly limited to treating patients with endoscopic erosive esophagitis or PUD for 4 months.[11] Gastro-protective agents are not paid for by the NHI for prophylaxis against ulcer or ulcer bleeding, and self-paid prophylactic prescriptions are not found in the NHIRD.[11]

As uremic HD patients have a high risk of PUB, these patients with PUD history, DM, or cirrhosis should be managed as a high-risk group who might benefit from PPI prophylaxis.[18] Taking the elderly who carry a high prevalence of PUB risk factors and a vulnerable gastroduodenal mucosa together, the development of strategies including avoidance of NSAIDs and corticosteroids usage to decrease the risk of PUB for aging uremic patients under regular HD is important in clinical practice.

In conclusion, we found that aging HD patients are independently associated with higher risk of PUB. The use of NSAIDs and corticosteroids and co-morbidities, including DM, history of uncomplicated PUD, and cirrhosis, were identified as risk factors for PUB in these aging HD patients.

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