Long term peptic ulcer rebleeding risk estimation in patients undergoing hemodialysis: a 10-year nationwide cohort study

Short title: Peptic ulcer rebleeding in renal failure

Chun-Ying Wu,[1-4] Ming-Shiang Wu,[5] Ken N. Kuo,[6] Chang-Bi Wang,[2]
Yi-Ju Chen[1] and Jaw-Town Lin[5,7]

[1]Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan;
[2]Division of Gastroenterology, Taichung Veterans General Hospital, Taichung, Taiwan;
[3]Department of Public Health, College of Public Health, China Medical University, Taichung, Taiwan;
[4]Department of Life Sciences, National Chung-Hsing University, Taichung, Taiwan;
[5]Division of Gastroenterology, National Taiwan University Hospital, Taipei, Taiwan;
[6]Center for Health Policy Research and Development, National Health Research Institutes; Miaoli, Taiwan;
[7]Department of Internal Medicine, E-Da Hospital and I-Shou University, Kaohsiung County, Taiwan

* Correspondence:

Chun-Ying Wu, MD, MPH, PhD
Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan
155, Sec. 2, Linong Street, Taipei 112, Taiwan
E-mail: chun@vghtc.gov.tw
Tel: +886-4-23592525 # 3304; Fax: +886-4-23741331

Jaw-Town Lin, MD, PhD
Department of Internal Medicine, E-Da Hospital and I-Shou University
No.1, E-Da Rd., Jiau-Shu Tsuen,Yan-Chau Shiang, Kaohsiung County 824, Taiwan;
Division of Gastroenterology, National Taiwan University Hospital, Taipei, Taiwan;
E-mail: jawtown@ntu.edu.tw
Tel: +886-2-23562246; Fax: +886-2-23947899

Wu CY and Lin JT contributed equally to this work as corresponding authors.

Keywords: peptic ulcer, bleeding, end-stage renal disease (ESRD), cirrhosis, *H. pylori*, non-steroidal anti-inflammatory drugs (NSAIDs)

Word count: 3386 words

ABSTRACT

Objective: We aim to study 1-, 5-, and 10-year risks of peptic ulcer rebleeding among end-stage renal disease (ESRD) patients with regular hemodialysis, to identify high risk subpopulation, and to estimate the number needed to harm (NNH) to increase a peptic ulcer rebleeding in different periods.

Design: A nationwide cohort study

Setting: Data from the Taiwan National Health Insurance Research Database (NHIRD)

Patients: Uremic cohort and matched controls were selected from among hospitalized patients with a primary diagnosis of peptic ulcer bleeding. Totally, 6,447 uremic patients and 25,788 age-, gender-, and gastroprotective agent use-matched controls were selected.

Intervention: no

Main outcome measures: Cumulative incidences and hazard ratios (HRs)

Results: The cumulative incidences of ESRD patients were significantly higher than the cumulative incidences of matched controls (1 year: 18.8% vs. 14.2%; 5 years: 38.5% vs. 31.4%; and 10 years: 46.3% vs. 39.4%; all $p<0.001$). The NNH to increase a peptic ulcer rebleeding by ESRD at 1, 5, and 10 years were 22, 15 and 15, respectively. On multivariate analysis, ESRD (HR=1.38, $P<0.0001$) was an independent risk factor for rebleeding. Compared with matched controls, ESRD was associated with higher risk of rebleeding especially in patients using ulcerogenic agents (HR=1.33-1.45), indication to prescribe gastroprotective agents (HR=1.44) and with liver cirrhosis (HR=1.45).

Conclusions: ESRD patients had higher long-term risk of peptic ulcer rebleeding, especially in certain populations. The enhanced risk gradually decreased after the first year and stabilized after the 5^{th} year.

Summary:

What is already known about his subject?

- Although the incidences of peptic ulcer diseases decreased in past decades, peptic ulcer bleeding remains a common medical emergency, especially in patients with co-morbidities.
- ESRD are one of the highest risk populations for short-term risk of peptic ulcer rebleeding.
- Liver cirrhosis, *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs (NSAIDs) use also enhance the risk of peptic ulcer rebleeding.
- Gastroprotective agents were underutilized in high risk populations.

What are the new findings?

- ESRD patients had higher 1-, 5- and 10-year risks of peptic ulcer rebleeding. The NNH to increase a peptic ulcer rebleeding by ESRD at 1, 5, and 10 years were 22, 15 and 15, respectively.
- On multivariate analysis, ESRD was an independent risk factor for peptic ulcer rebleeding.
- Compared with matched controls, ESRD was associated with higher risk of rebleeding especially in patients using ulcerogenic agents, indication to receive gastroprotective agents and with liver cirrhosis.

How might it impact on clinical practice in the foreseeable future?

- For ERSR patients with high risk of peptic ulcer rebleeding, long-term PPI or other gastroprotective agents should not be underutilized.

INTRODUCTION

Although there have been significant decreases in the incidences of peptic ulcer disease in past decades, peptic ulcer bleeding remains a common medical emergency worldwide. In the United States, peptic ulcer bleeding leads to more than 250,000 admissions annually and costs more than $2.5 billion per year.[1] The annual incidence increases with age.[1] In Scotland, admission rates for peptic ulcer decreased between 1982 and 2002. However, admission rates for bleeding peptic ulcer increased for subjects aged above 74 years.[2] In a Danish study, the incidences decreased 29-33% for uncomplicated peptic ulcers between 1993 and 2002, while the incidence of bleeding ulcer remained stable.[3] In Taiwan, we found the incidences of gastric and duodenal ulcer diseases decreased 42%-48% and 41%-71%, respectively, between 1997 and 2006 in a nationwide cohort study.[4] The decreases in incidences were not only observed in uncomplicated peptic ulcer, but also in bleeding peptic ulcers. However, the decreases in incidences among patients older than 80 years were significantly smaller than for the other age groups.[4] The increasing proportion of elderly persons in the general population and the associated increases in comorbidities, especially chronic renal failure, liver cirrhosis, and *Helicobacter pylori* infection, as well as more frequent use of ulcerogenic agents, such as aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), all enhance the risk of peptic ulcer bleeding.[3-5]

Patients with end-stage renal disease (ESRD) are one of the highest risk populations for peptic ulcer bleeding.[6] Several factors contribute to the pathogenesis of higher risk of peptic ulcer bleeding, including platelet dysfunction, platelet-vessel wall interaction, and blood coagulation abnormalities.[7,8] Dialysis and the use of erythropoietin to correct anemia reduce the incidence of peptic ulcer bleeding, but do

not completely eliminate the risk.[9] Although the role of renal failure in increased risk of peptic ulcer rebleeding briefly after admission has been identified,[10,11] long-term risk estimation of rebleeding in patients with ESRD and the number needed to harm (NNH) to increase a case of peptic ulcer rebleeding has not been carried out. The influences of age, gender, comorbidities, *H. pylori* infection, and use of ulcerogenic agents on the long term risk of peptic ulcer rebleeding also remain unclear.

PATIENTS AND METHODS

Study design:

In this population-based cohort study, we recruited patients with ESRD receiving regular hemodialysis admitted due to peptic ulcer bleeding based on data from Taiwan's National Health Insurance Research Database (NHIRD). The NHIRD consists of health care data from nearly the entire Taiwan population of 23.74 million and comprises comprehensive health care information, which has been described in detail in our previous studies.[5,11,12] This study has been approved by the National Health Research Institutes.

Study population and subjects:

Hospitalized patients admitted for the first time between January 1, 1997 and December 31, 2006 with a primary diagnosis of peptic ulcer bleeding (PUB) (ICD-9 codes: 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, and 533.6) were screened. If patients were re-admitted to the same hospital or transferred to another hospital within 3 days of the index hospitalization, the subsequent admissions were included in the same course of index hospitalization. Patients less than 20 years of age and patients who underwent gastric resection or vagotomy before index hospitalization discharge were excluded. We also excluded patients who developed gastric cancer within the first two years of the index hospitalization as it is difficult to differentiate peptic ulcer from gastric cancer mimicking gastric ulcer.

Uremic cohort and matched controls:

Among the PUB patients, uremic cohort was defined as patients with renal failure diagnosed on previous admission (ICD-9 codes 585 and 586) and receiving regular

hemodialysis (more than 9 months) before the index PUB hospitalization. Patients receiving renal transplantation were excluded. Each uremic patient was matched with four controls from the PUB population by age (± 2 years), gender and frequency of gastroprotective agent use (0.02% percentage of use of proton pump inhibitors or H_2 receptor antagonists). All study subjects were followed up from the index hospitalization to rehospitalization for another episode of PUB, death, or until the end of 2006.

Outcomes:

We analyzed the risk of peptic ulcer rebleeding and mortality for the ESRD patients and their matched controls. Rehospitalization was defined if the study subjects were admitted with a primary diagnosis of PUB following the index hospital discharge for PUB. Cumulative incidences of rebleeding over 1-, 5-, and 10-year periods and hazard ratios (HRs) for these two cohorts were calculated. All-cause mortality within 3 months of rehospitalization due to peptic ulcer bleeding was analyzed.

To investigate whether the risk associated with the severity of renal failure, we further analyzed the cumulative incidences of peptic ulcer rebleeding among patients with different frequency of hemodialysis.

Exposure to ulcerogenic medications and co-morbidities:

For all subjects of the two cohorts, ulcerogenic drugs during the whole period of follow-up after the index hospitalization were analyzed, including low-dose and high-dose aspirin, NSAIDs, COX-2 specific inhibitors, and other anti-coagulants (clopidogrel, dipyridamole, warfarin, ticlopidine, cilostazol and cerenin). All information on ulcerogenic drug use by individual patients was obtained from the NHIRD, as this database contains details of every prescription for nearly the entire population of

Taiwan, including dose, frequency, starting and ending dates, and administration routes, etc. The frequency of ulcerogenic drug use was defined as average number of days taking these drugs per 30 days within the whole follow-up years. Occasional, frequent and regular users were defined if the study subjects received 1-10 days, 10-19 days, and 20-30 days per month, respectively.

Co-morbidities, including previous ischemic heart disease, cerebral infarction, hypertension, diabetes, chronic obstructive lung disease, liver cirrhosis, and hyperlipidemia, were defined as diseases diagnosed on admissions before the index hospitalization and during the period of follow-up.

***Helicobacter pylori* associated peptic ulcer:**

Helicobacter pylori associated peptic ulcer was defined as the receiving of *H. pylori* eradication therapy during or after the index hospitalization. *H. pylori* eradication therapy was defined as proton pump inhibitors or H_2 receptor antagonists, plus clarithromycin or metronidazole, plus amoxicillin or tetracycline, with or without bismuth, et al. (details of all eligible *H. pylori* eradication regimens are described in our previous studies).[11,12]

Statistical analysis:

Cumulative incidence analyses were conducted using Kaplan-Meier method, and the differences between the curves were calculated with the two-tailed log-rank test. NNH was calculated as the inverse of the attributable risk (the absolute difference between two cohorts compared). Cox proportional hazards model was used to determine whether ESRD is an important risk factor for peptic ulcer rebleeding. We included frequency of ulcerogenic drug use, frequency of gastroprotective agent use, dialysis, *H. pylori*-associated ulcer, and all comorbidities listed in Table 1 in the model analysis. Assessment of goodness-of-fit of the models with step-down method was

used to analyze the independent prognostic factors. All data management and SIR analyses were performed using SAS 9.1 software (SAS Institute, Cary, NC, USA). Cumulative incidences and HRs were analyzed via the SPSS program for Windows 11.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Demographic data:

Among the 271,030 subjects who were admitted for the first time with a primary diagnosis of peptic ulcer bleeding between 1997 and 2006, 6,447 were diagnosed with ESRD and 25,788 were selected as controls by matching age, gender, and frequency of gastroprotective agent use. Twenty-four male patients with ESRD who could not be matched to male controls due to insufficient numbers were matched to male controls. Other demographic data, including *H. pylori* associated peptic ulcer, mean follow-up time, frequency of ulcerogenic drug use, frequency of gastroprotective agent use, and co-morbidities, are shown in Table 1. Among the uremic cohorts, only 47 subjects received peritoneal hemodialysis. The median, 25% and 75% quartiles of frequency of dialysis for the uremic cohort was 2.98, 0.94 and 3.28 times per week, respectively.

Table 1. Baseline characteristics of uremic cohort and matched controls

Characteristic	Uremic cohort (N=6,447)		Matched controls[+] (N=25,788)	
	Number	%	Number	%
Age (mean ± SE)	65.58 ± 0.16		65.46 ± 0.08	
20-39 years of age	206	3.20	886	3.44
40-49 years of age	606	9.40	2,416	9.37
50-59 years of age	1,203	18.66	4,798	18.61
60-69 years of age	1,840	28.54	7,373	28.59
≥ 70 years of age	2,592	40.20	10,315	40.00
Gender				
Male	3,488	54.10	13,858	53.74
Female	2,959	45.90	11,930	46.26
H. pylori-associated peptic ulcer	558	8.66	5,743	22.27
Gastroprotective agents (per 30 days)[#]	3.54 ± 0.09		3.55 ± 0.04	

Follow-up year (mean ± SE)	1.88 ± 0.03		3.08 ± 0.02	
Ulcerogenic drugs (per 30 days)[#]				
Aspirin	1.85 ± 0.07		1.88 ± 0.03	
NSAIDs	2.69 ± 0.07		3.12 ± 0.04	
Other ulcerogenic agents*	3.27 ± 0.09		2.74 ± 0.04	
Co-morbidity				
Ischemic heart disease	896	13.90	1,468	5.69
Cerebral vascular disease	1,011	15.68	2,707	10.50
Hypertension	4,848	75.20	11,268	43.69
Diabetes	3,141	48.72	7,224	28.01
Chronic obstructive lung disease	1,464	22.71	5,406	20.96
Liver cirrhosis	1,718	26.65	6,290	24.39
Hyperlipidemia	377	5.85	1,100	4.27

[+]Matched by age (± 2 years), gender and the frequency of gastroprotective agent use (0.02% percentage of use of proton pump inhibitors or H_2 receptor antagonists).
[#]Average number of days taking the drugs per 30 days within the follow-up years after the index hospitalization, expressed as mean ± SE; calculated for whole cohort
*Clopidogrel, dipyridamole, warfarin, ticlopidine, cilostazol, cerenin

Cumulative incidences of peptic ulcer rebleeding and mortality:

The 1-year cumulative incidence of peptic ulcer rebleeding in ESRD patients was significantly higher than the 1-year cumulative incidence of controls (18.8% vs. 14.2%, $p<0.001$). The 5-year and 10-year cumulative incidences of peptic ulcer rebleeding in ESRD patients were also significantly higher than the 5-year and 10-year cumulative incidences of matched controls (5 years: 38.5% vs. 31.4%, $p<0.0001$; 10 years: 46.3% vs. 39.4%, $p<0.001$) (Figure 1). The numbers needed to increase a case of peptic ulcer rebleeding by ESRD (number needed to harm, NNH) for 1, 5, and 10 years were 22, 15 and 15, respectively. Patients receiving hemodialysis less than three times per week had a slightly, but not significantly lower risk of peptic ulcer

rebleeding compared with those receiving hemodialysis equal or more than 3 times per week (p=0.9068) (Supplemental Figure 1).

The cumulative incidences of rebleeding within 7 days were 1.7% and 1.0% for ERSD patients and matched controls, respectively (P<0.001) (Supplemental Figure 2A). The cumulative incidences of rebleeding in the first 30 days after discharge were 5.0% and 2.7% for uremic patients and controls, respectively (Supplemental Figure 2B).

The 1, 5, and 10-year cumulative incidences of mortality in ESRD patients were significantly higher than the 1, 5, and 10-year cumulative mortality incidences of controls (1 year: 3.5% vs. 1.4%, p<0.0001; 5 year: 7.0% vs. 2.8%, p<0.0001; 10 years: 9.0% vs. 3.9%, p<0.0001) (Figure 2).

The 10-year cumulative incidences of rebleeding according to *H. pylori* and NSAIDs status for both cohorts were as follows: *H. pylori* associated (ESRD vs. controls: 53.8% vs. 44.8%, p<0.0002), non-*H. pylori* associated (ESRD vs. controls: 45.0% vs. 37.4%, p<0.0001), NSAIDs associated (ESRD vs. controls: 48.0% vs. 36.1%, p<0.0001) and non-NSAIDs associated (ESRD vs. controls: 41.2% vs. 45.5%, p=0.4416).

For cirrhotic patients, the 10-year cumulative incidences of peptic ulcer rebleeding were 55.1% and 47.8% for ESRD patients and controls, respectively (p<0.0001). The 10-year cumulative incidences of variceal bleeding were 24.1% and 22.3% for uremic patients and the matched controls, respectively.

Relative risk of peptic ulcer rebleeding:

On Cox multivariate proportional hazards analysis, ESRD (HR=1.38, P<0.0001), ulcerogenic drugs (HR=1.03 for each 10% incremental use in frequency, p<0.0001), *H.*

pylori- associated peptic ulcer (HR=1.19, p<0.0001), and comorbidities with past history of liver cirrhosis (HR=1.44, p<0.0001) were independent risk factors for peptic ulcer rebleeding (Table 2).

Table 2. Multivariate Cox proportional hazards model analysis for prediction of peptic ulcer rebleeding

	Hazard Ratios	95%CI	P value
End stage renal disease	1.38	1.30 – 1.46	<0.0001
Ulcerogenic drugs [+]	1.03	1.02 – 1.03	<0.0001
Helicobacter pylori	1.19	1.13 – 1.25	<0.0001
Ischemic heart disease	0.83	0.76 – 0.91	<0.0001
Diabetes	1.02	0.97 – 1.07	0.4352
Liver cirrhosis	1.44	1.37 – 1.51	<0.0001

[+]: each 10% incremental use in frequency

We further analyzed the data to examine the immediate effect of ulcerogenic drugs use within 14 days before the end time of observation period. We found each one incremental day use of ulcerogenic agent increased 6% risk of peptic ulcer rebleeding (Table 3).

Table 3. Multivariate Cox proportional hazards model analysis for prediction of peptic ulcer rebleeding (ulcerogenic drugs within 14 days before the end time)

	Hazard Ratios	95%CI	P value
End stage renal disease	1.39	1.31 – 1.47	<0.0001
Ulcerogenic drugs [+]	1.06	1.06 – 1.06	<0.0001
Helicobacter pylori	1.17	1.11 – 1.23	<0.0001

Ischemic heart disease	0.86	0.78 – 0.94	<0.0001
Diabetes	1.05	1.00 – 1.10	0.0563
Liver cirrhosis	1.40	1.34 – 1.47	<0.0001

[+]: each one incremental day use within 14 days before the end time

Multivariate stratified analysis:

Figure 3 shows the results of multivariate stratified analysis. In each stratum, the hazards ratios were compared between uremic patients and the matched cohort subjects. For the 20-49, 50-59, 60-69, and ≥70 age groups, ESRD was associated with significantly higher risks of peptic ulcer rebleeding compared with the matched controls (HR=1.71, 1.37, 1.55, and 1.24, respectively). For male and female, ESRD was associated with similar risks of rebleeding. For patients with indications to receive gastroprotective agents, ESRD had higher risk of rebleeding than controls (HR=1.44). For patients not receiving ulcerogenic agents, ESRD was not associated with higher risk of rebleeding. For those receiving occasional, frequent, or regular ulcerogenic agents, higher risks of rebleeding were found in the ESRD patients (HR=1.45, 1.33, and 1.38, respectively). For patients with liver cirrhosis, ESRD was associated with higher risk of rebleeding (HR=1.45).

DISCUSSION

Although the role of ESRD in short-term peptic ulcer rebleeding risk has been investigated, our study is the first to analyze the role of ESRD in the 10-year risk of peptic ulcer rebleeding and mortality. ESRD is found to be associated with significantly higher risk of peptic ulcer rebleeding and mortality starting from the beginning of discharge from the index hospitalization and persisting for 10 years. The enhanced risk gradually decreases from the first year and stabilizes after 5 years. NNH remains stable between 5 years and 10 years.

ESRD and liver cirrhosis were found to be the most significant risk factors for peptic ulcer rebleeding. The impact of these comorbidities was even higher than the influences of age, gender, status of *H. pylori* infection, and use of ulcerogenic agents. Our observations are compatible with previous reports regarding short-term risk of peptic ulcer rebleeding. Rockall et al reported that renal failure and liver failure were the highest predictors of peptic ulcer mortality and rebleeding.[10] Blatchford et al found liver disease predicted higher risk of rebleeding.[13] In a recent study, liver cirrhosis was found to be one of the major risk factors related to peptic ulcer rebleeding.[14] On stratified analysis, we found ESRD had significantly higher risk of peptic ulcer rebleeding in cirrhotic patients.

Meta-analysis has approved that *H. pylori* eradication is effective to prevent peptic ulcer rebleeding;[15] however, a recent study by Wong et al. found peptic ulcer rebleeding and mortality rates were higher in patients with neither *H. pylori* nor NSAIDs bleeding ulcers.[16] These observations were actually consistent in considering the different etiologies of peptic ulcer bleeding. For those with *H. pylori*-negative idiopathic bleeding ulcers, comorbidities may be the major reason of bleeding and contribute to the following rebleeding and mortality. For *H. pylori*-infected

patients, eradication therapy eliminates the pathogen and reduces the risk of rebleeding. In the present study, we defined *H. pylori* associated peptic ulcer as the receiving of *H. pylori* eradication therapy during or after the index hospitalization. Since the time of *H. pylori* eradication was likely to be close to the first episode of bleeding, rebleeding events 5- 10 years after *H. pylori* eradication should not be considered to be *H. pylori*-associated. However, rebleeding events shortly after the index hospitalization may still be increased by *H. pylori* infection. Compared with the *H. pylori* and NSAID-negative patients reported by Wong et al., the rebleeding rates in both ESRD patients and controls in the present study were similar.[16] However, the overall mortalities in the present study were much lower because we only analyzed morality within 3 months of rehospitalization due to peptic ulcer bleeding, in contrast to mortality at any time point reported by Wong et al.

Use of ulcerogenic agents was found to be and independent risk factor for rebleeding. In addition, we did not find a dose-dependent response pattern. Instead, the change in the impact of ESRD on peptic ulcer rebleeding was more dramatic. Once patients used ulcerogenic agents, the risk of peptic ulcer rebleeding increased no matter whether the use of these ulcerogenic agents was occasional, frequent or regular. Despite most guidelines recommended gastroprotection in high risk patients, underutilization of gastroprotective agents have been reported in many studies.[17-19] In the United States, more than 80% patients receiving aspirin after percutaneous coronary intervention missed their PPI co-therapy initiation.[17] In Canada, 44% of aspirin users with a prior history of peptic ulcer complications did not receive concomitant PPI therapy.[18] In France, only half of NSAIDs users above 65 years received gastroprotective agents.[19] Our observations provided important evidences to avoid underutilization of gastroprotective agents in high risk patients receiving NSAIDs.

In the present study, it was not sure whether the higher risk of rebleeding was bleeding from the same ulcer or recurrent but a new ulcer. It was also unclear whether the increase in rebleeding rate was related to the increased use of heparin or anti-coagulant for dialysis or it was related to the ESRD. We could only hypothesize that if it was related to the anti-coagulants used; the recurrent bleeding was more likely to arise from the same ulcer and rebled earlier. In supplemental figure 2, we found 7-day and 30-day cumulative incidences of rebleeding for uremic cohorts were 1.7% and 5.0%, respectively. If recurrent bleeding occurred one month thereafter could be defined as new ulcers, most rebleeding events in the present study were related to ESRD instead of anticoagulants use. Using long-term PPI or gastroprotective agents as secondary prevention could be substantiated.

In Taiwan, the prescription of PPIs or H2RAs is strictly limited to patients who have had active or healing peptic ulcers confirmed by gastroendoscopy in the past four months. Once peptic ulcer has healed, gastroprotective agents were not paid by national health insurance and the prescription orders cannot be found in the NHIRD. Therefore, the use of PPIs or H2RAs was actually an indicator of prescription of gastroprotective agents to treat active or healing ulcer. To prevent the use of gastroprotective agent as a significant confounder, we matched controls not only by age and gender, but also by the frequency of use of gastroprotective agents.

There are several limitations to the present study. First, we did not have endoscopic findings which are widely used to predict peptic ulcer rebleeding, including active bleeding, visible vessels, and adherent clots.[20,21] However, most of these parameters play important roles briefly after peptic ulcer bleeding, but not in the long term. Second, our results were based on a retrospective cohort study. Although we matched the controls to balance the demographic characteristics of the study cohorts

and conducted multivariate analysis, as well as stratified analysis, to confirm the robustness of our results, unmeasured confounders that affect both groups may exist. In addition, the multiple comparisons conducted may lead to some unexpected results hard to explain, such as ischemic heart disease as an independent protective factor. Third, *H. pylori* associated peptic ulcer was defined as the receiving of *H. pylori* eradication therapy in the present study. Based on the insurance database, it is impossible to confirm whether a patient was still infected and whether the rebleeding was due to *H. pylori* associated peptic ulcer. For those not receiving *H. pylori*, the status of *H. pylori* infection was unknown. It contributed to the large percentages of non-*H. pylori* ulcers in both cohorts. Fourth, self-paid ulcerogenic agents could not be identified in the NHIRD, which tended to underestimate the prevalence of ulcerogenic users. However, the underestimation may only weaken the association, but not bias the results. Finally, we cannot confirm the underlying diseases causing the ESRD in the NHIRD to investigate whether rebleeding risks were altered by different etiologies of ESRD.

In conclusion, ESRD patients had significantly higher long-term risk of peptic ulcer rebleeding. The increased risk was observed on subgroup analysis regardless of patient age, gender, use of gastroprotective agents or ulcerogenic drugs, *H. pylori* status, or comorbidities.

Acknowledgments:

This work was supported by the National Health Research Institutes of Taiwan (Grant numbers: PH-099-PP-26 and PH-099-PP-16).

Competing interest: No competing interest for all authors

FIGURE LEGENDS:

Figure 1: Cumulative incidences of peptic ulcer rebleeding for uremic cohort and age-, gender-, and gastroprotective agent-matched controls.

Figure 2: Cumulative incidences of all-cause mortality within 3 months of rehospitalization due to peptic ulcer bleeding

Figure 3: Multivariate stratified analysis: hazard ratios for end-stage renal disease (ESRD) in subgroups of patients after adjusting for all other factors. In each stratum, the hazards ratios were compared between ESRD patients and the matched cohort subjects.

Supplemental Figure 1: Cumulative incidences of peptic ulcer rebleeding for uremic cohort according to frequency of dialysis.

Supplemental Figure 2: Cumulative incidences of peptic ulcer rebleeding for uremic cohort and matched controls in the first 7-days and 30-days after index hospitalization.

References

1 Longstreth GF. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: a population-based study. Am J Gastroenterol 1995; 90:206-10.

2 Kang JY, Elders A, Majeed A, et al. Recent trends in hospital admissions and mortality rates for peptic ulcer in Scotland 1982-2002. Aliment Pharmacol Ther 2006; 24:65-79.

3 Lassen A, Hallas J, Schaffalitzky de Muckadell OB. Complicated and uncomplicated peptic ulcers in a Danish county 1993-2002: a population-based cohort study. Am J Gastroenterol 2006; 101:945-53.

4 Chan FK, Leung WK. Peptic-ulcer disease. Lancet 2002; 360:933-41.

5 Wu CY, Wu CH, Wu MS et al. A nationwide population-based cohort study shows reduced hospitalization for peptic ulcer disease associated with H pylori eradication and proton pump inhibitor use. Clin Gastroenterol Hepatol 2009; 7:427-31.

6 Toke AB. GI bleeding risk in patients undergoing dialysis. Gastrointest Endosc 2010; 71:50-2.

7 Boccardo P, Remuzzi G, Galbusera M. Platelet dysfunction in renal failure. Semin Thromb Hemost 2004; 30:579-89.

8 Kaw D, Malhotra D. Platelet dysfunction and end-stage renal disease. Semin Dial 2006; 19:317-22.

9 Galbusera M, Remuzzi G, Boccardo P. Treatment of bleeding in dialysis patients. Semin Dial 2009; 22:279-86.

10 Rockall TA, Logan RF, Devlin HB, et al. Risk assessment after acute upper gastrointestinal haemorrhage. Gut 1996; 38:316-21.

11 Wu CY, Kuo KN, Wu MS, et al. Early Helicobacter pylori eradication decreases risk of gastric cancer in patients with peptic ulcer disease. Gastroenterology 2009; 137:1641-8.

12 Wu CY, Wu MS, Kuo KN, et al. Effective Reduction of Gastric Cancer Risk With Regular Use of Nonsteroidal Anti-Inflammatory Drugs in Helicobacter Pylori-Infected Patients. J Clin Oncol 2010; 28: 2952-7

13 Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. Lancet 2000; 356:1318-21.

14 Travis AC, Wasan SK, Saltzman JR. Model to predict rebleeding following endoscopic therapy for non-variceal upper gastrointestinal hemorrhage. J Gastroenterol Hepatol 2008; 23:1505-10.

15 Gisbert JP, Khorrami S, Carballo F, et al. *H. pylori* eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer. Cochrane Database Syst Rev 2004; CD004062.15

16 Wong GL, Wong VW, Chan Y, et al. High incidence of mortality and recurrent bleeding in patients with *Helicobacter pylori*-negative idiopathic bleeding ulcers. Gastroenterology 2009; 137:525-31.

17 Casado-Arroyo R, Scheiman JM, Polo-Tomas M, et al. Underutilization of gastroprotection for at-risk patients undergoing percutaneous coronary intervention: Spain compared with the United States. Aliment Pharmacol Ther 2010; 32:689-95.

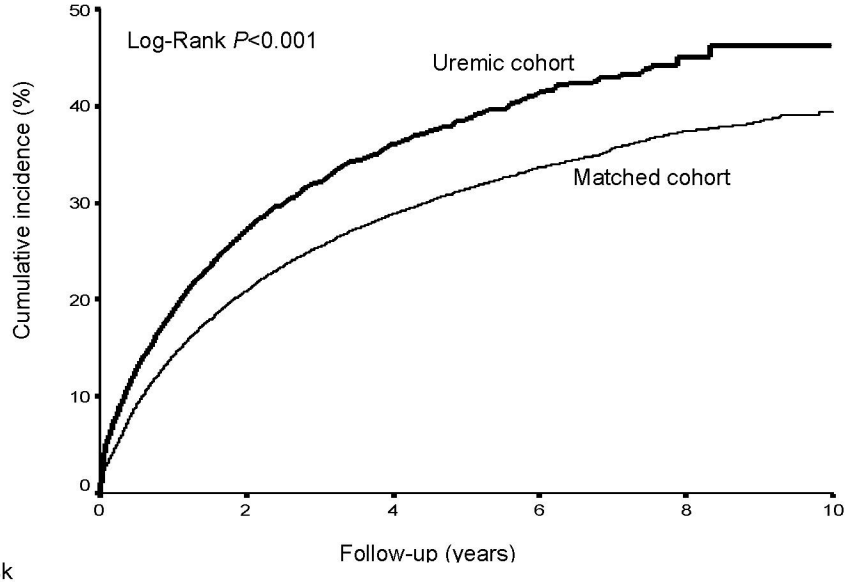
18 Targownik LE, Metge CJ, Leung S. Underutilization of gastroprotective strategies in aspirin users at increased risk of upper gastrointestinal complications. Aliment Pharmacol Ther 2008; 28:88-96.

19 Thiefin G, Schwalm MS. Underutilization of gastroprotective drugs in patients receiving non-steroidal anti-inflammatory drugs. Dig Liver Dis 2010 Nov 2. [Epub ahead of print].

20 Laine L, Peterson WL. Bleeding peptic ulcer. N Engl J Med 1994; 331:717-27.

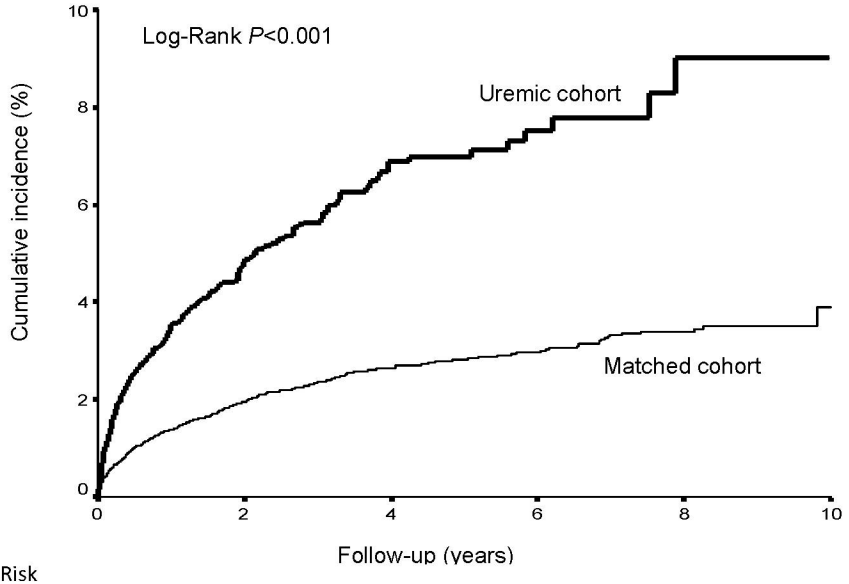
21 Forrest JA, Finlayson ND, Shearman DJ. Endoscopy in gastrointestinal bleeding. Lancet 1974; 2:394-7.

Figure 1

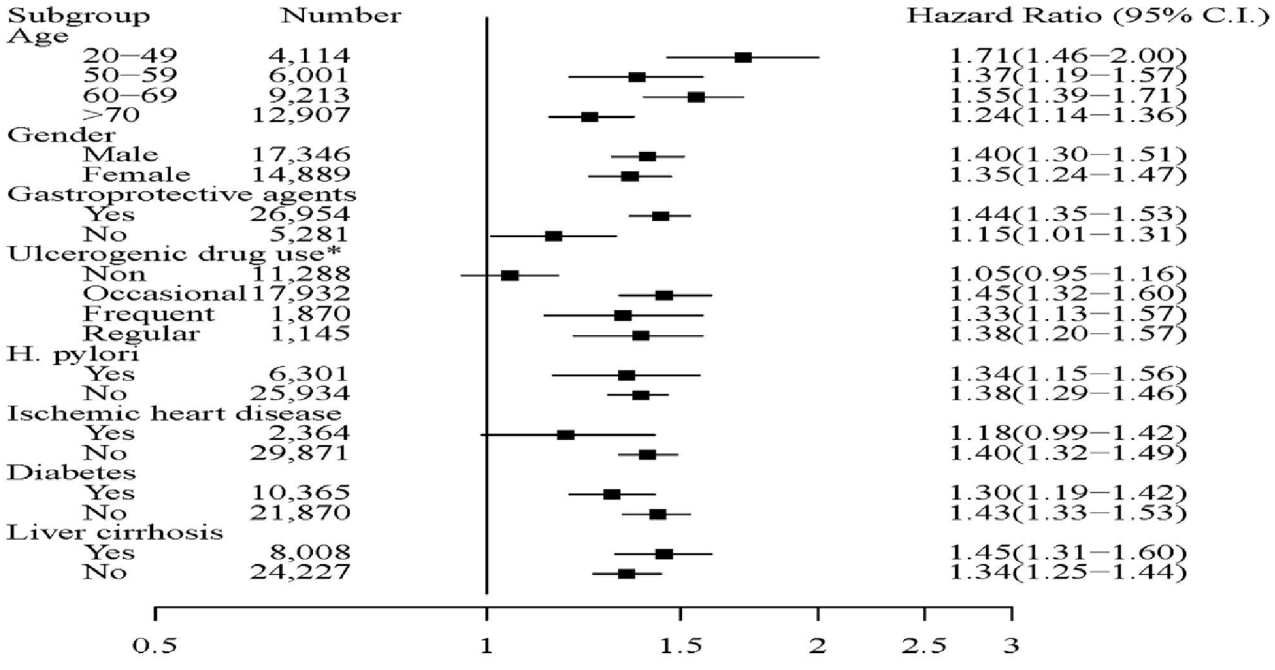


No. at Risk					
Uremic cohort	6,447	2,175	977	403	116
Matched cohort	25,788	13,477	8,203	4,732	2,158

Figure 2



No. at Risk					
Uremic cohort	6,447	2,175	977	403	116
Matched cohort	25,788	13,477	8,203	4,732	2,158


Subgroup
Number
Hazard Ratio (95% C.I.)
Age
20–49 4,114 1.71(1.46–2.00)
50–59 6,001 1.37(1.19–1.57)
60–69 9,213 1.55(1.39–1.71)
>70 12,907 1.24(1.14–1.36)
Gender
Male 17,346 1.40(1.30–1.51)
Female 14,889 1.35(1.24–1.47)
Gastroprotective agents
Yes 26,954 1.44(1.35–1.53)
No 5,281 1.15(1.01–1.31)
Ulcerogenic drug use*
Non 11,288 1.05(0.95–1.16)
Occasional 17,932 1.45(1.32–1.60)
Frequent 1,870 1.33(1.13–1.57)
Regular 1,145 1.38(1.20–1.57)
H. pylori
Yes 6,301 1.34(1.15–1.56)
No 25,934 1.38(1.29–1.46)
Ischemic heart disease
Yes 2,364 1.18(0.99–1.42)
No 29,871 1.40(1.32–1.49)
Diabetes
Yes 10,365 1.30(1.19–1.42)
No 21,870 1.43(1.33–1.53)
Liver cirrhosis
Yes 8,008 1.45(1.31–1.60)
No 24,227 1.34(1.25–1.44)
0.5
1
1.5
2
2.5
3