In-Hospital Mortality Risk Estimation in Single Episodic Upper Gastrointestinal Bleeding Patients Undergoing Hemodialysis: A Retrospective Cohort Study

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Abstract

BACKGROUND: Upper gastrointestinal bleeding (UGIB) is a major cause of clinical bleeding among patients with end-stage renal disease (ESRD). The purpose of this study was to investigate the association of mortality in uremic patients with single UGIB.

METHODS: From 2004 to 2010, a tertiary hospital-based retrospective cohort comprising 244 patients undergoing hemodialysis was investigated. All patients were diagnosed with UGIB according to ICD-9 codes which included peptic ulcer bleeding, duodenal ulcer bleeding, among other symptoms. UGIB was required to be one of the first three discharge diagnoses. Rehospitalization within 3 days after discharge was regarded as the same course. Exclusion criteria were UGI re-bleeding, patients younger than 20 y/o, previous gastric resection or vagotomy, or gastric cancer within the first 2 years of the index hospitalization.

RESULTS: The mean age in the group with single UGIB was 71.3 ± 14.7 years. The all-cause mortality was 31.1% (76/244). Using Cox regression models, we found the higher mortality of the single UGIB group was significantly correlated with older age (adjusted hazard ratio [HR] = 1.02, 95% confidence interval [CI] = 1.00-1.04), hepatitis (adjusted HR = 1.96, 95% CI = 1.03-3.71) and albumin < 3 g/dL (adjusted HR = 2.61, 95% CI = 1.44-4.72). Patients with a greater number of infection events during hospitalization were more likely to have poor outcome (crude HR = 1.70, 95% CI = 1.07-2.71). However, after adjustment for covariates, the number of infection episodes was not significantly related to poor outcome.

CONCLUSION: In conclusion, single episodic UGIB was correlated with significantly higher mortality in uremic patients during the follow-up. Older age, hepatitis, and albumin < 3 g/dL appeared to worsen all-cause mortality in patients with single UGIB.

KEY WORDS: albumin, gastrointestinal, older age, uremic
Introduction

Upper gastrointestinal bleeding (UGIB) encompasses a broad array of clinical scenarios in uremic patients. In patients with renal failure, UGIB can vary from occult to massive hemorrhage and lead to a higher morbidity and mortality than in the general population (1). Helicobacter pylori (H. pylori) infection, cigarette smoking, non-steroid anti-inflammatory drug (NSAID) usage, and older persons are well-established traditional risk factors in UGIB (1, 2). However, a recent study by Wong et al. found peptic ulcer re-bleeding and mortality rates were higher in patients with neither H. pylori nor NSAIDs (3). Another retrospective study showed that ESRD patients with peptic ulcer bleeding have greater re-bleeding and mortality than patients not on dialysis (4). A greater level of co-morbidity was found to be the only significant predictor of mortality in a multivariate analysis (OR = 6.0, 95% CI = 2.9-12.3; \( P = 0.001 \)) (4).

The diminishing incidences of gastric ulcer and duodenal ulcer disease of 42-48% and 41-71%, respectively, between 1997 and 2006 in Taiwan may be attributed to early diagnosis and effective usage of acid suppressive drugs (5). However, data from the US Renal Data System showed the rate of nonvariceal UGIB among patients undergoing dialysis has not decreased in the past 10 years (6). The pathogenesis of UGIB in ESRD may be due to impaired hemostasis caused by intrinsic platelet abnormalities, impaired platelet-vessel wall interaction, anemia, dialysis, and medications (7).

However, the long-term risk of first-time UGIB mortality in uremic patients themselves remains unclear. Therefore, the aim of this study was to investigate the causal relationships of mortality in uremic patients with single UGIB.

Materials and Methods

Study Design

In this hospital-based retrospective cohort study, we reviewed the medical records of all patients who had ESRD on maintenance hemodialysis and simultaneously suffered from acute UGIB. We retrieved data, including the admission diagnosis, discharge diagnosis and laboratory data from multiple hospitalizations (emergency room and out-patient department) from our hospital’s Clinical Informatics Research and Development Center between 31 December, 2004 and 24 August, 2010 and these patients were followed until 31 December, 2010. This study was approved by the Institutional Review Board of Taichung Veterans General Hospitals (no. CE11183-1). Informed consent was waived because there was no breach of privacy and the study did not interfere with clinical decisions related to patient care. A total of 675 hospitalizations due to UGIB and ESRD on maintenance hemodialysis were collected, which included 322 patients who were recruited at Taichung Veterans General Hospital. The exclusion criteria were UGI re-bleeding, which was defined as two or more bleeding episodes, patients younger than 20 y/o, previous gastric resection or vagotomy, and gastric cancer within the first 2 years of the index hospitalization. We found that the risk for mortality was high in single episodic UGIB patients undergoing hemodialysis at certain time points. Therefore, if we included the recurrent bleeding cases, the severity of the disease would be less pronounced. Finally, single episodic UGIB occurred in 244 uremic patients. As the primary endpoint of this study was all-cause mortality, the uremic cohort with single episodic UGIB was categorized into survival and mortality subgroups (Fig. 1).

Study Population and Subjects

All hospitalized UGIB patients had one of following diagnosis codes among the first three discharge diagnoses, as defined by the International Classification of Diseases, 9th Revision (ICD-9): esophageal, gastric, duodenal, peptic, and gastrojejunal bleeds (Esophageal 530.4, 530.7, 530.82; Hematemesis 578.0; Gastric ulcer 531.00, 531.10, 531.20, 531.40, 531.50, 531.60, 531.80; Duodenal ulcer 532.00, 532.10, 532.20, 532.40, 532.50, 532.60, 532.80; Peptic ulcer 533.00, 533.10, 533.20, 533.40, 533.50, 533.60, 533.80; Gastrojejunal ulcer 534.00, 534.10, 534.20, 534.40, 534.50, 534.60, 534.80; Gastritis/duodenitis with bleeding 535.X1). Hypertension (HTN), cardio-

![Study flow of the uremic cohort with single episodic UGIB bleeding.](image-url)
vascular (CV) disease and numbers of chronic diseases within 19 evaluated chronic diseases were defined based on the admission diagnosis and discharge diagnosis as well as a review of the patient’s medication, such as anti-hypertensive agents, anti-platelets or anticoagulants. If patients were re-admitted due to GI bleeding or transferred to another hospital within 3 days, they were included in the same course. Patients with rehospitalization due 2 or more episodes of UGIB were assigned to the UGI re-bleeding group and were excluded from the analysis.

**Outcomes**

Our primary endpoint was to investigate the single UGIB patients undergoing hemodialysis. We applied the Cox proportional hazards model analysis to predict the outcomes of single UGIB in patients undergoing hemodialysis.

**Data Analysis**

All data analyses were performed using SPSS 17.0. Chi-square analysis was used to compare demographic data between the survival and mortality groups at the end of the follow-up study. Independent samples t-test was used to analyze the continuous variables. Cox proportional hazards model analysis was used to identify predictive factors of outcomes in uremic patients with single UGIB. A *P* value of less than 0.05 was considered significant.

**Results**

The mean age of the patients at enrollment was 71.3 ± 14.7 years. Fig. 1 shows the all-cause mortality was 31.1% (76/244). Table 1 shows the baseline characteristics of the single UGIB patients in the uremic cohort. The number of hospitalization days was higher in the mortality group compared with that in the survival group (31.9 ± 27.7 vs. 25.4 ± 24.8 days, *P* = 0.071). The number of infection events during hospitalization was higher in the mortality group than in the survival group in the single UGIB patients (61.8% vs. 42.3%, *P* = 0.006). The percentage of patients with hypertension and type 2 DM in the survival group was high (59.5% vs. 35.5%, *P* = 0.001; 83.3% vs. 6.6%, *P* = 0.042). The percentage of patients with hepatitis in the mortality group was high (15.8% vs. 6.5%, *P* = 0.040). The mean duration of follow-up in the mortality group was significantly shorter than that
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in the survival group (0.9 vs. 3.8 months, \( P < 0.001 \)). However, there were no significant differences in any of the other variables between the survival and mortality groups for single UGIB patients. Table 2 shows the laboratory data of the uremic patients based on survival and mortality. Serum albumin was relatively lower in the mortality group of the single UGIB patients (values of the continuous variable: mortality 2.3 ± 0.8 vs. survival 2.8 ± 0.7 g/dL, \( P = 0.000 \); values of the category variable: albumin < 3 g/dL, mortality 80.3% vs. survival 47.6%, \( P = 0.000 \)). Blood leukocytosis and high serum CRP level were found in the mortality group for single UGIB patients. The continuous variant of the serum C-reactive protein was relatively higher in the mortality subgroup for single UGIB patients compared with the corresponding values in the survival group (13.0 ± 9.3 vs. 8.3 ± 8.1 mg/L, \( P = 0.000 \)). There was no significant difference in use of acid suppressive drugs, except for pantoprazole, which was associated with a higher percentage of mortality in the single UGIB patients (Table 3). Using Cox regression models, we found the higher mortality of the single UGIB group was significantly correlated with older age (adjusted HR = 1.02, 95% CI = 1.00-1.04), hepatitis (adjusted HR = 1.96, 95% CI = 1.03-3.71) and albumin < 3 g/dL (adjusted HR = 2.61, 95% CI = 1.44-4.72). Patients who had a higher number of infection episodes during hospitalization were more likely to have a poor outcome (crude HR = 1.70, 95% CI = 1.07-2.71). However, after adjustment for covariates, including age, hypertension, type 2 DM, hepatitis, and albumin < 3 g/dL, the number of infection episodes was not significantly related to poor outcome (Table 4).

**Discussion**

The incidence of acute nonvariceal UGIB among dialysis patients is generally thought to be higher than that in the general population (7). We conducted a retrospective cohort study to determine risk factors for single episodic UGIB mortality among ESRD patients. Although Haimanot reported that the incidence density of UGIB among ESRD patients was 21.3-24.0 per 1000 per year and accounted for 3-7% of the occurrence of all deaths regardless of study period (8), our study showed the all-cause mortality of the single UGIB group was higher than that in the UGI re-bleeding group (1st-month mortality-single UGIB vs. UGI re-bleeding: 16.4% vs. 5.1%, \( P = 0.007 \); 6th-month mortality-single UGIB vs. UGI re-bleeding: 30.3% vs. 15.4%, \( P = 0.001 \); 1st-year mortality-single UGIB vs. UGI re-bleeding: 30.7% vs. 15.4%, \( P = 0.001 \) (Data not shown)). This result was similar to a finding in a study by Yang that revealed an overall 30-day mortality of 11.8% (7). In a multivariate analysis

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**Table 2. Laboratory data of the single UGI bleeding patients in the uremic cohort**

<table>
<thead>
<tr>
<th></th>
<th>Survival (n = 168)</th>
<th>Mortality (n = 76)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (/cumm)</td>
<td>9765.6 ± 5135.5</td>
<td>11286.0 ± 8223.6</td>
<td>0.354*</td>
</tr>
<tr>
<td>HgB (mg/dL)</td>
<td>9.8 ± 2.5</td>
<td>9.7 ± 2.2</td>
<td>0.849*</td>
</tr>
<tr>
<td>LDH (u/L)</td>
<td>472.2 ± 1074.3</td>
<td>428.6 ± 412.7</td>
<td>0.224*</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.8 ± 0.7</td>
<td>2.3 ± 0.8</td>
<td>0.000*</td>
</tr>
<tr>
<td>Albumin &lt; 3 (g/dL)</td>
<td>80 (47.6)</td>
<td>61 (80.3)</td>
<td>0.000†</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>88.1 ± 76.0</td>
<td>87.3 ± 59.7</td>
<td>0.360*</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>8.3 ± 8.1</td>
<td>13.0 ± 9.3</td>
<td>0.000*</td>
</tr>
<tr>
<td>Blood Gas pH</td>
<td>7.4 ± 0.1</td>
<td>7.4 ± 0.1</td>
<td>0.611*</td>
</tr>
<tr>
<td>Blood Gas HCO₃⁻ (mmol/L)</td>
<td>21.1 ± 5.4</td>
<td>20.7 ± 5.9</td>
<td>0.295*</td>
</tr>
</tbody>
</table>

\*\( P \) values were calculated by independent-samples t-test.

†\( P \) values were calculated by Chi-square test.

**Table 3. Gastroprotective agents used by uremic patients in single UGI bleeding based on survival and mortality**

<table>
<thead>
<tr>
<th></th>
<th>Survival (n = 168)</th>
<th>Mortality (n = 76)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantoprazole</td>
<td>126 (75.0)</td>
<td>69 (90.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>35 (20.8)</td>
<td>16 (21.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>84 (50.0)</td>
<td>35 (46.1)</td>
<td>0.583</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>17 (10.1)</td>
<td>8 (10.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>38 (22.6)</td>
<td>10 (13.2)</td>
<td>0.117</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>4 (2.4)</td>
<td>1 (1.3)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

\( P \) values were calculated by Chi-square test.

In the survival group (0.9 vs. 3.8 months, \( P < 0.001 \)). However, there were no significant differences in any of the other variables between the survival and mortality groups for single UGIB patients. Table 2 shows the laboratory data of the uremic patients based on survival and mortality. Serum albumin was relatively lower in the mortality group of the single UGIB patients (values of the continuous variable: mortality 2.3 ± 0.8 vs. survival 2.8 ± 0.7 g/dL, \( P = 0.000 \); values of the category variable: albumin < 3 g/dL, mortality 80.3% vs. survival 47.6%, \( P = 0.000 \)). Blood leukocytosis and high serum CRP level were found in the mortality group for single UGIB patients. The continuous variant of the serum C-reactive protein was relatively higher in the mortality subgroup for single UGIB patients compared with the corresponding values in the survival group (13.0 ± 9.3 vs. 8.3 ± 8.1 mg/L, \( P = 0.000 \)). There was no significant difference in use of acid suppressive drugs, except for pantoprazole, which was associated with a higher percentage of mortality in the single UGIB patients (Table 3). Using Cox regression models, we found the higher mortality of the single UGIB group was significantly correlated with older age (adjusted HR = 1.02, 95% CI = 1.00-1.04), hepatitis (adjusted HR = 1.96, 95% CI = 1.03-3.71) and albumin < 3 g/dL (adjusted HR = 2.61, 95% CI = 1.44-4.72). Patients who had a higher number of infection episodes during hospitalization were more likely to have a poor outcome (crude HR = 1.70, 95% CI = 1.07-2.71). However, after adjustment for covariates, including age, hypertension, type 2 DM, hepatitis, and albumin < 3 g/dL, the number of infection episodes was not significantly related to poor outcome (Table 4).

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conducted by Cheung, it was found that ESRD was an independent predictor of peptic ulcer re-bleeding along with high-risk ulcer stigmata (4). The number of patients undergoing *H. pylori* examination was less than 15%. The inclusion of these patients may have confounded the results to some extent because adequate endoscopic diagnosis and therapy are not routinely performed during UGIB, and *H. pylori*-negative idiopathic bleeding tends to be related to the patient’s co-morbid condition (3, 4).

Our findings were also comparable to the results of a study which investigated UGIB risk prediction in ESRD patients, which reported age and undernourishment (serum albumin per 1 mg/dL decrease) as risk factors (8). Our data revealed that UGIB patients with uremia were older, had longer hospital stays in the mortality group, had a high infection rate during hospitalization, and had blood leukocytosis, general anemia, poor nutrition, and elevated serum CRP level. More than half of our ESRD patients were admitted due to UGIB and ≥ 3 concomitant chronic diseases. We postulate that the bleeding mechanism in ESRD patients may be different from that in individuals with several co-morbidities in the general population. Our univariate analysis revealed that older age, infection during hospitalization, hepatitis, and malnutrition independently contributed to the all-cause mortality. After adjustment, older age, hepatitis, and malnutrition were found to increase the risk of single UGIB mortality. The bleeding diathesis of patients with uremia is a significant clinical concern, especially when surgery and other invasive procedures are required (9). Several factors may contribute to uremic bleeding, namely, complex platelet dysfunction with abnormal platelet-vessel wall interaction, abnormal production of nitric oxide, uremic toxin, anemia, and drug treatment (6, 9).

Finally, the aim of the present study was to identify factors associated with the high mortality rate in the single UGIB group. One of the strengths of this study was the use of a hospital-based cohort design in a well-defined population which allowed for identification of mortality risk and long-term monitoring. Thus, in patients with single UGIB, older age, hepatitis, and poor nutritional status were found to significantly affect mortality. The increased morbidity and mortality may be associated with the high incidence of a pre-existing co-morbid condition.

There were several limitations in this longitudinal study. First, we identified patients with UGIBs based on ICD-9 coding, which may have resulted in some misclassification. However, such misclassification was probably non-differential and would likely have resulted in less statistical power to detect estimated effects. Second, we could not definitively ascertain whether these patients experienced an episode of UGIB before or after the index episode. Third, not all patients had endoscopic findings, which are used to make a definite diagnosis, including active bleeding, visible vessels, and adherent clots. Fourth, the results were based on a retrospective cohort study. There were several unmeasured confounders that could have affected both groups, including antiplatelet and anticoagulant drugs that were associated with more bleeding risk. Fifth, we did not identify ulcerogenic drugs which tend to worsen the overall effect of UGIB. Sixth, proton-pump inhibitors and H2-blocking medication were not included in the multivariate analysis because of the potential for confounding by indication.

**Conclusion**

In conclusion, single episodic UGIB had a significantly higher mortality rate in uremic patients during follow-up. Older age, hepatitis, and albumin < 3 g/dL worsened all-cause mortality in patients with single UGIB.

**Acknowledgments**

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References