Long-Term Risk of Upper Gastrointestinal Hemorrhage after Advanced AKI

Pei-Chen Wu,*‡ Chih-Jen Wu,*†‡§ Cheng-Jui Lin,†‡ Vin-Cent Wu,* for the National Taiwan University Study Group on Acute Renal Failure Group

Abstract

Background and objectives There are few reports on temporary dialysis-requiring AKI as a risk factor for future upper gastrointestinal bleeding (UGIB). This study sought to explore the long-term association between dialysis-requiring AKI and UGIB.

Design, setting, participants, & measurements This nationwide cohort study used data from the Taiwan National Health Insurance Research Database. Patients who recovered from dialysis-requiring AKI and matched controls were selected from hospitalized patients age ≥18 years between 1998 and 2006. The cumulative incidences of long-term de novo UGIB were calculated, and the risk factors of UGIB and mortality were identified using time-varying Cox proportional hazard models adjusted for subsequent CKD and ESRD after AKI.

Results A total of 4565 AKI-recovery patients and the same number of matched patients without AKI were analyzed. After a median follow-up time of 2.33 years (interquartile range, 0.97–4.81 years), the incidence rates of UGIB were 50 (by stringent criterion) and 69 (by lenient criterion) per 1000 patient-years in the AKI-recovery group and 31 (by stringent criterion) and 48 (by lenient criterion) per 1000 patient-years in the non-AKI group (both P<0.001). When compared with patients in the non-AKI group, the multivariate hazard ratio (HR) for UGIB was 1.30 (95% confidence interval [95% CI], 1.14 to 1.48) for dialysis-requiring AKI, 1.83 (95% CI, 1.53 to 2.20) for time-varying CKD, and 2.31 (95% CI, 1.92 to 2.79) for time-varying ESRD (all P<0.001). Finally, the risk for long-term mortality increased after UGIB (HR, 1.24; 95% CI, 1.12 to 1.38) and dialysis-requiring AKI (HR, 1.66; 95% CI, 1.54 to 1.78).

Conclusions Recovery from dialysis-requiring AKI was associated with future UGIB and mortality.


Introduction

The risk of upper gastrointestinal bleeding (UGIB) in patients with CKD (1) or ESRD is reportedly greater than that observed in the general population (1,2). Additionally, patients with ESRD who developed UGIB have higher mortality than those without ESRD who developed UGIB (3–6). While several uremia-specific factors, including platelet dysfunction and impaired platelet-vessel wall interaction (7,8), have been postulated to increase the risk of UGIB and mucosal abnormalities of the gastrointestinal tract, some studies suggest that repeated anticoagulant exposure (8) and the frequent use of ulcerogenic agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs) (1,9) and antiplatelets (10), also have important roles.

Because of the advances in critical care medicine and dialysis technologies, an increasing number of hospitalized patients could be discharged alive after AKI (11–17). Acute gastrointestinal hemorrhage, especially in the upper gastrointestinal tract, is the most frequent cause of bleeding after AKI (18). The incidence of short-term acute gastrointestinal bleeding in hospital stay varies widely in patients with AKI, ranging from 13.4% to 26% (18,19). However, few reports have addressed the effect of AKI, especially temporary dialysis-requiring AKI, on the long-term risk of gastrointestinal hemorrhage. We hypothesized that dialysis-requiring AKI is an independent risk factor for UGIB. Specifically, we sought to determine the incidence and risk factors of UGIB after AKI using a nationwide inpatient cohort.

Materials and Methods

Data Source

This population-based cohort study was based on medical information from Taiwan’s National Health Insurance (NHI), a nationwide compulsory healthcare program that covers outpatient visits, hospital admissions, prescriptions, interventional procedures, disease profiles, and vital status. The study cohort consisted of 2.6 million patients hospitalized between 1998 and 2006, representing nearly 10% of all NHI enrollees.

Because all personal information was de-identified in the database to protect privacy, no informed consent was required and the study was exempt from a full ethical
review by the institutional review board of the National Taiwan University Hospital (201212021RINC).

**Study Population**

This study included patients age ≥18 years who developed *de novo* dialysis-requiring AKI during their index admissions (identified by the procedure codes for acute dialysis) and subsequently recovered from dialysis for 30 days after discharge (Figure 1). Comorbidities were identified from at least three outpatient visits or one inpatient claim within 1 year preceding the index admission. All diagnoses were obtained from International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), codes. We excluded patients who had AKI or ESRD within 1 year before admission and patients with UGIB or peptic ulcers before or during admission. Also excluded were patients who underwent renal transplantation, vascular access creation for long-term dialysis, or peritoneal-dialysis catheter implantation; those who were hospitalized for >180 days; and those who did not survive for ≥30 days after discharge (Figure 2). UGIB and peptic ulcers were excluded by ICD-9 codes (Supplemental Table 1). AKI was defined by ICD-9 codes for AKI (584.3, 634.3, 635.3, 636.3, 637.3, 638.3, 639.3, 693, 598.5), as well as by procedure codes for acute dialysis. ESRD was identified under the NHI Scheme by “catastrophic illness certificates” for ESRD on which the commencement dates of long-term dialysis for at least 3 months were recorded.

For comparison, we constructed a control group (non-AKI group), which was selected from the remaining hospitalized patients who did not have a history of AKI, dialysis, and UGIB before and during the index admission and were matched with the study group (AKI-recovery group) on a 1:1 ratio basis according to age, sex, calendar year of index admission, and propensity scores before and during the index hospitalization.

**Outcome Measures**

Our primary outcome was postdischarge nonvariceal UGIB, which was identified using two modified criteria: a stringent criterion and a lenient criterion as previously reported (Table 1) (20,21). By the stringent criterion, UGIB was defined using ICD-9-CM codes that specified the lesions responsible for the hemorrhage (e.g., Mallory–Weiss syndrome, gastric ulcer with hemorrhage). UGIB defined by the lenient criterion encompassed that defined by the stringent criterion and ICD-9-CM codes that did not specify the cause of the bleeding (e.g., hematemesis plus chronic gastric ulcer without mention of hemorrhage, gastrointestinal hemorrhage plus upper gastrointestinal endoscopy performed). Each patient was followed from the date of discharge to the first documented UGIB event and was censored at death or the end of the study (December 31, 2008), whichever occurred first.

**Research Variables**

The Charlson comorbidity index (22) was calculated using preadmission comorbidities. The following were recorded during index hospitalization: intensive care unit admission, categories of major surgeries and acute organ dysfunction, and specific acute comorbidities that might be associated with AKI (e.g., severe sepsis, shock, myocardial infarction, hepatorenal syndrome, obstructive uropathy, and exposure to contrast material).

After recovery from acute dialysis, the renal function status was evaluated in mutually exclusive subgroups of non-CKD, CKD, advanced CKD, and ESRD. Because GFR could not be obtained from our insurance database, CKD was defined by ICD-9 codes (23) and advanced CKD was defined by codes for CKD plus simultaneous erythropoiesis-stimulating agent (ESA) treatment. On the basis of the regulation of NHI, ESA can be prescribed only in anemic patients with CKD who have a hematocrit level of ≥28% and a serum creatinine level of ≥6 mg/dl (i.e., advanced CKD). Renal status was assessed in two overlapping periods: within 0–90 days of discharge and long term after discharge (at some time from the day of discharge to the day of UGIB, death, or the end of the study). Patients were labeled as having advanced CKD or ESRD in certain periods according to the timing of the commencement of ESA or long-term dialysis.

![Figure 1. Schematic diagram of study design.](image-url)

**Figure 1.** Schematic diagram of study design. H2RA, histamine-2 receptor antagonist; LMWH, low-molecular-weight heparin; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitor; UGIB, upper gastrointestinal bleeding.
Taking into account the potential confounders of UGIB, we also obtained information on pertinent disorders (e.g., myocardial infarction, atrial fibrillation) and medications from the day of discharge to the day of UGIB, death, or the end of the study. The select medications were proton-pump inhibitors, histamine-2 receptor antagonists, systemic corticosteroids, NSAIDs, aspirin, clopidogrel, warfarin, heparin, and low-molecular-weight heparin (LMWH) (Supplemental Table 2). The prevalence of Helicobacter pylori infection was assessed according to treatment with triple or quadruple eradication therapy (24), defined as a proton-pump inhibitor or histamine-2 receptor antagonist, plus clarithromycin or metronidazole, plus amoxicillin or tetracycline, with or without bismuth.

**Statistical Analyses**

To reduce the bias in assessing the detrimental effects of AKI, we constructed a comparable non-AKI group using the propensity score method in an attempt to make an unbiased estimate of all the confounders predicting dialysis. Continuous variables are described as mean±SD or median (interquartile range) as appropriate; discrete variables are presented as counts and percentages. We used independent t tests or Mann–Whitney U tests to compare continuous variables and chi-squared tests for categorical ones.

For simplicity and specificity, the following analyses were made under the condition of UGIB defined by the stringent criterion; the outcome defined by the lenient criterion was used only in the sensitivity analysis. Taking into consideration the higher risk of developing CKD or ESRD after AKI and the strong correlations of CKD/ESRD with UGIB and mortality, we used a Cox proportional hazards model with CKD/ESRD as time-dependent covariates (15,25,26), denoted by time-varying CKD/ESRD, to account for the effects of CKD/ESRD developing at some time during follow-up on the risks of UGIB and mortality. Comorbidities and postdischarge medications (use versus nonuse) were also incorporated into the analysis. Variable selection was performed by using stepwise multiple regression, with a p-to-enter and p-to-leave both equal to 0.15. Final results of multivariate analyses were summarized by hazard ratios (HRs) and 95% confidence intervals (CIs).

After obtaining the Cox regression equation, we estimated the hazard function along with the time for a reference patient who did not have AKI during the index hospitalization;
did not have AKI, CKD, or ESRD for 10 years after discharge; and had the mean values of all the other covariates for our study patients. On the basis of this hazard function, we further simulated and depicted 10-year survival curves of the probability of freedom from UGIB events under different scenarios of kidney conditions in regard to AKI, CKD, advanced CKD, and ESRD. Specifically, we stratified patients by the status of AKI during index admission and by the renal status after discharge.

All analyses were performed using R software, version 2.15.2 (Free Software Foundation, Inc., Boston, MA). A two-sided \( P \) value <0.05 was considered to represent statistically significant difference.

**Results**

**Patient Characteristics**

Among the 4898 patients with *de novo* transient dialysis-requiring AKI, 4565 were matched with the same number of controls without AKI (Figure 2). The average age was 63.6±16.5 years, 56.9% of participants were male, and the median preadmission Charlson comorbidity index score

<table>
<thead>
<tr>
<th>Table 1. Nonvariceal upper gastrointestinal bleeding defined by modified stringent and lenient criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Stringent criteria: diagnosis in group A</td>
</tr>
<tr>
<td>2. Lenient criteria: one of the following:</td>
</tr>
<tr>
<td>Any diagnosis in group A</td>
</tr>
<tr>
<td>Any diagnosis in group B (hematemesis/GI bleeding) plus at least one in group C (upper GI illness)</td>
</tr>
<tr>
<td>Any diagnosis in group B (hematemesis/GI bleeding) plus upper gastrointestinal endoscopy performed (Taiwan procedure codes: 28015C, 28016C, 28010B)</td>
</tr>
<tr>
<td>3. Exclude diagnosis in group D and associated endoscopic procedure (47025B, 47067B, 47078B)</td>
</tr>
</tbody>
</table>

**Group A: Specific diagnosis for nonvariceal UGIB, according to ICD-9 code**

- 530.21: Ulcer of esophagus with bleeding
- 530.7: Gastroesophageal laceration-hemorrhage syndrome (Mallory–Weiss syndrome)
- 530.82: Esophageal hemorrhage
- 531.0: Gastric ulcer, acute with hemorrhage
- 531.2: Gastric ulcer, acute with hemorrhage and perforation
- 531.4: Gastric ulcer, chronic or unspecified with hemorrhage
- 531.6: Gastric ulcer, chronic or unspecified with hemorrhage and perforation
- 532.0: Duodenal ulcer, acute with hemorrhage
- 532.2: Duodenal ulcer, acute with hemorrhage and perforation
- 532.4: Duodenal ulcer, chronic or unspecified with hemorrhage
- 532.6: Duodenal ulcer, chronic or unspecified with hemorrhage and perforation
- 533.0: Peptic ulcer, acute with hemorrhage
- 533.2: Peptic ulcer, acute with hemorrhage and perforation
- 533.4: Peptic ulcer, chronic or unspecified with hemorrhage
- 533.6: Peptic ulcer, chronic or unspecified with hemorrhage and perforation
- 534.0: Gastrojejunal ulcer, acute with hemorrhage
- 534.2: Gastrojejunal ulcer, acute with hemorrhage and perforation
- 534.4: Gastrojejunal ulcer, chronic or unspecified with hemorrhage
- 534.6: Gastrojejunal ulcer, chronic or unspecified with hemorrhage and perforation
- 535. × 1: Gastritis and duodenitis with hemorrhage
- 537.83: Angiodysplasia of stomach and duodenum with hemorrhage
- 537.84: Dieulafoy lesion (hemorrhagic) of stomach and duodenum

**Group B: Diagnosis for gastrointestinal bleeding but not specific for location, according to ICD-9 code**

- 578.0: Hematemesis
- 578. ×: Gastrointestinal hemorrhage

**Group C: Diagnosis for upper gastrointestinal disease but not specific for bleeding, according to ICD-9 code**

- 530–538: Disease of esophagus, stomach, and duodenum

**Group D: Diagnosis specific for esophageal variceal bleeding**

- 456.0: Esophageal varices with bleeding
- 456.2: Esophageal varices in diseases classified elsewhere with bleeding

**Taiwan procedure codes**

- 28010B: Enteroscopy
- 28015C: Esophagoscopy
- 28016C: Upper gastrointestinal endoscopy, exam
- 47025B: Esophageal injection of sclerosing therapy
- 47043B: Endoscopic control of gastric or duodenal bleeding
- 47067B: Endoscopic esophageal variceal ligation
- 47078B: Gastric variceal sclerosing therapy

GI, gastrointestinal; UGIB, upper gastrointestinal bleeding; ICD-9, International Classification of Diseases, Ninth Revision.
was 2 (interquartile range, 0–3) (Table 2). The baseline co-morbidities and the proportions of patients undergoing operations were similar in both groups. In the AKI-recovery group, more patients had severe sepsis, hepatorenal syndrome, obstructive uropathy, and exposure to contrast material during hospitalization.

**Outcomes**

As shown in Table 3, more AKI-recovery patients received corticosteroids, warfarin, heparin, and LMWH and had CKD, advanced CKD, and ESRD within 0–90 days of discharge and during long-term follow-up. After a median follow-up period of 2.33 years (interquartile range, 0.97–4.81 years), the AKI-recovery group had a higher incidence of UGIB and higher mortality. The incidence rates of UGIB were 50 (by stringent criterion) and 69 (by lenient criterion) per 1000 patient-years in the AKI-recovery group and 31 (by stringent criterion) and 48 (by lenient criterion) per 1000 patient-years in the non-AKI group (both $P<0.001$). The median time from discharge to the first episode of UGIB according to the stringent criterion was 1.37 years in the AKI-recovery group, which was not statistically different from the 1.22 years in the non-AKI group ($P=0.41$). Peptic ulcer disease with hemorrhage accounted for 66.2% and 51.7% of the UGIB events in the AKI-recovery and non-AKI groups, respectively ($P<0.001$). Of note, the number of patients receiving triple or quadruple therapy for *H. pylori* infection was small.

Table 4 shows the clinical predictors of UGIB after we applied the time-varying Cox regression hazards model. In contrast to the non-AKI group, the AKI-recovery group had a higher long-term risk for UGIB (HR, 1.30; 95% CI, 1.14 to 1.48), independent of the effects from other covariates of age, hepatic dysfunction, severe sepsis, corticosteroids, NSAIDs, aspirin, time-varying CKD, advanced CKD, and ESRD. The model exhibited modest

### Table 2. Clinical characteristics in the propensity score–matched AKI-recovery and non-AKI cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AKI-Recovery Group (n=4565)</th>
<th>Non-AKI Group (n=4565)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>2598 (56.9)</td>
<td>2598 (56.9)</td>
<td>0.99</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>63.63±16.53</td>
<td>63.63±16.51</td>
<td>0.97</td>
</tr>
<tr>
<td>Preadmission comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson comorbidity index score*</td>
<td>2 (0–3)</td>
<td>2 (0–3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>174 (3.8)</td>
<td>191 (4.2)</td>
<td>0.39</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>553 (12.1)</td>
<td>531 (11.6)</td>
<td>0.50</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>70 (1.5)</td>
<td>87 (1.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>476 (10.4)</td>
<td>510 (11.2)</td>
<td>0.27</td>
</tr>
<tr>
<td>Dementia</td>
<td>116 (2.5)</td>
<td>121 (2.7)</td>
<td>0.79</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>524 (11.5)</td>
<td>488 (10.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>Rheumatologic disease</td>
<td>55 (1.2)</td>
<td>70 (1.5)</td>
<td>0.21</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>62 (1.4)</td>
<td>71 (1.6)</td>
<td>0.49</td>
</tr>
<tr>
<td>Malignancy</td>
<td>310 (6.8)</td>
<td>293 (6.4)</td>
<td>0.50</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1511 (33.1)</td>
<td>1587 (34.8)</td>
<td>0.10</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>274 (6)</td>
<td>251 (5.5)</td>
<td>0.32</td>
</tr>
<tr>
<td>CKD</td>
<td>533 (11.7)</td>
<td>540 (11.8)</td>
<td>0.85</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2059 (45.1)</td>
<td>2010 (44)</td>
<td>0.31</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>436 (9.6)</td>
<td>429 (9.4)</td>
<td>0.83</td>
</tr>
<tr>
<td>In-hospital acute comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>2972 (65.1)</td>
<td>2995 (65.6)</td>
<td>0.63</td>
</tr>
<tr>
<td>Operation categories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiothoracic</td>
<td>191 (4.2)</td>
<td>171 (3.7)</td>
<td>0.31</td>
</tr>
<tr>
<td>Upper gastrointestinal</td>
<td>28 (0.6)</td>
<td>29 (0.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>Lower gastrointestinal</td>
<td>96 (2.1)</td>
<td>81 (1.8)</td>
<td>0.29</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>58 (1.3)</td>
<td>54 (1.2)</td>
<td>0.78</td>
</tr>
<tr>
<td>Acute organ dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>326 (7.1)</td>
<td>307 (6.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Respiratory</td>
<td>855 (18.7)</td>
<td>843 (18.5)</td>
<td>0.77</td>
</tr>
<tr>
<td>Hepatic</td>
<td>86 (1.9)</td>
<td>84 (1.8)</td>
<td>0.94</td>
</tr>
<tr>
<td>Neurologic</td>
<td>80 (1.8)</td>
<td>94 (2.1)</td>
<td>0.32</td>
</tr>
<tr>
<td>Hematologic</td>
<td>70 (1.5)</td>
<td>82 (1.8)</td>
<td>0.37</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>835 (18.3)</td>
<td>527 (11.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shock</td>
<td>335 (7.3)</td>
<td>286 (6.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>271 (5.9)</td>
<td>372 (8.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>9 (0.2)</td>
<td>0 (0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>110 (2.4)</td>
<td>5 (0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exposure to contrast material</td>
<td>1082 (23.7)</td>
<td>922 (20.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Unless otherwise noted, values are the number (percentage) of participants. ICU, intensive care unit.

*Median (25th–75th percentile).
discrimination with a $c$ statistic of 0.70 and an adjusted $R^2$ value of 0.08. Furthermore, the strength of the association between AKI recovery and long-term UGIB was stronger when time-varying CKD/ESRD was not incorporated into the analysis (HR, 1.71; 95% CI, 1.52 to 1.93; $P_{<0.001}$). Warfarin, heparin, and LMWH were not predictive of UGIB.

For sensitivity analysis, we replaced UGIB defined by the stringent criterion with UGIB defined by the lenient criterion and conducted the time-varying Cox regression model again. The analysis showed that AKI recovery was significantly associated with long-term UGIB as well (HR, 1.23; 95% CI, 1.10 to 1.36; $P_{<0.001}$), with a $c$ statistic of 0.69 and an adjusted $R^2$ value of 0.09.

We also analyzed the risk factors for mortality by applying the Cox regression model with time-varying covariates. AKI recovery (HR, 1.66; 95% CI, 1.54 to 1.78) and UGIB (HR, 1.24; 95% CI, 1.12 to 1.38) were significantly associated with long-term mortality. The model’s prediction ability was good ($c$ statistic=0.77; adjusted $R^2=0.35$).

### Discussion

To our knowledge, our study is the first to identify that hospitalized patients surviving temporary acute dialysis have
higher long-term risk for UGIB and mortality than those without a history of dialysis-requiring AKI. After adjustment for age, comorbidities, and postdischarge drugs, hospitalization for dialysis-requiring AKI remains a significant risk factor for future UGIB, even though the AKI event is momentary. In our statistical models, both CKD and ESRD were handled as time-dependent covariates so that the association between AKI and subsequent UGIB was independent of the development or progression of CKD/ESRD. Moreover, the strength of the association between AKI and UGIB was stronger when CKD/ESRD was not considered, and there was a trend that the risks for UGIB were higher among patients with worse renal status during follow-up. These findings are consistent with the hypothesis that part of the connection between AKI and subsequent UGIB is mediated through the development of CKD/ESRD after AKI.

The crude incidence rates of UGIB in our patients with dialysis-requiring AKI were 50 and 69 per 1000 patient-years according to the stringent and lenient criteria, respectively. To our knowledge, this is the only study estimating the long-term incidence of UGIB in patients with AKI based on both inpatient and outpatient claims. In comparison, the incidence of UGIB requiring hospitalization in patients with ESRD was reported to be 23–42 per 1000 patient-years (2.9). However, these reports retrieved data only from more severe UGIB that required hospitalization. It is important to stress that approximately 40% of UGIB events reported in the United States Medicare records were managed in an outpatient setting (27). By also incorporating outpatient claims, a recent population-based study of nearly 1 million patients with ESRD reported an incidence rate of 57 and 328 UGIB episodes per 1000 patient-years, according to the stringent and lenient definitions, respectively (21). Despite the lack of a head-to-head comparison, the incidence of UGIB in patients recovering from advanced AKI is seemingly lower than that observed in patients with ESRD, but it is still much greater than the occurrence in the general population, for which an overall incidence of 89–112 UGIB events per 100,000 patient-years was reported (28). Patients with ESRD receiving hemodialysis are frequently exposed to anticoagulants, which undoubtedly augment the bleeding risk. In our study, heparin and LMWH were not predictive of UGIB. Because the number of patients receiving heparin and LMWH was similar to that of ESRD patients, the presence of ESRD might mask the salient effects of heparin and LMWH.

Consistent with the results from our cohorts suggesting that peptic ulcer disease with hemorrhage was the most prominent cause of UGIB in AKI-recovery patients (66.2%), one other study reported that gastroduodenal ulcers accounted for around 60% of UGIB cases viewed with endoscopy in patients with CKD (29). In another recent population-based study, peptic ulcer disease (35.2%) and gastroduodenitis with hemorrhage (29.1%) were the leading causes of UGIB in patients with ESRD (21,30). In brief, the role of peptic ulcer disease with hemorrhage might be more prominent in patients recovering from advanced AKI. Although AKI involves some degree of inflammation (31–33), an “immunoparalysis” state, similar to that ensuing from sepsis and critical illness (34,35), may coexist and make the effects of 

### Table 4. Independent predictors of upper gastrointestinal bleeding (defined by stringent criterion) after dialysis-requiring AKI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per decade)</td>
<td>1.20 (1.15 to 1.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AKI-recovery group*</td>
<td>1.30 (1.14 to 1.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Premorbid moderate/severe liver disease</td>
<td>1.57 (1.25 to 1.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute hepatic dysfunction</td>
<td>1.59 (1.10 to 2.29)</td>
<td>0.01</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>1.29 (1.08 to 1.54)</td>
<td>0.01</td>
</tr>
<tr>
<td>Long-term use of corticosteroids</td>
<td>1.28 (1.01 to 1.62)</td>
<td>0.04</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1.58 (1.32 to 1.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1.71 (1.36 to 2.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time-varying CKD</td>
<td>1.85 (1.53 to 2.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time-varying advanced CKD</td>
<td>2.10 (1.31 to 3.36)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time-varying ESRD</td>
<td>2.31 (1.92 to 2.79)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*In contrast to non-AKI group.

**a**Time-varying” denotes some time during follow-up.
Figure 3. Future 10-year probability of freedom from upper gastrointestinal bleeding was lower among patients with worse renal status during follow up. The simulation curves (A) were depicted based on different scenarios of morbid conditions with regard to AKI, CKD, advanced CKD, and ESRD (B).
that UGIB was a significant risk factor for peptic ulcer rebleeding in patients with ESRD, a dose-dependent response pattern was not found (6). The effect of the dose and frequency of ulcerogenic agents on UGIB after advanced AKI remains unsolved.

Another limitation is that our database does not contain data regarding smoking, which is a risk factor for UGIB in patients with ESRD (9). In light of the idea from the joint modeling of multiple diseases (41), we captured the effect of smoking through investigating its proxies, namely chronic obstructive pulmonary disease, lung cancer, myocardial infarction, and diabetes mellitus, which are highly related to smoking (42,43). We found that AKI was associated with UGIB independent of the effects of these proxies, suggesting smoking might not have a significant role in UGIB after AKI.

In conclusion, the current study found that dialysis-requiring AKI was associated with a higher risk of long-term UGIB, and that UGIB was a significant predictor of long-term mortality after AKI. The high accumulation rates of NSAIDs and anti-platelets use after AKI augmented the possibility of UGIB. These findings are of clinical importance for physicians who care for patients surviving advanced AKI.

Acknowledgments

We would like to thank Dr. Ju-Yeh Yang for her experience in using the US Renal Data System to evaluate UGIB in patients with ESRD; Professor Likwang Chen for her offering of the database and statistical support; and Drs. Chi-Feng Pan, Tao-Min Huang, Che-Hsiung Wu, and Tai-Shuan Lai for their dedication to data interpretation and revision of the statistical models.

This study was supported by the following grants: National Science Council (NSC)-102-2314-B-002-140-MY2, National Taiwan University Hospital Clinical Trials (NTUH)-103-082, NTUH-103-S-2467, NTUH-102-CGN03, NTUH-102-2314-B-002-147-MY3; National Taiwan University Hospital Clinical Trials (NTUH)-103-082, NTUH-103-S-2467, NTUH-102-CGN03, NTUH-102-52097, NTUH-101-M1953, and NTUH-100-N1776; and National Health Research Institute (NHRI)-PH1-101-SP-09 and NHRI-PH1-102-SP-09.

Disclosures

None.

References


**Received:** February 3, 2014 **Accepted:** November 11, 2014

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjASN.asnjournals.org/lookup/suppl/doi:10.2215/CJN.01240214/-/DCSupplemental.