Recurrence and Mortality Among Patients Hospitalized for Acute Lower Gastrointestinal Bleeding

Tomonori Aoki,* Naoyoshi Nagata,* Ryota Niikura,* Takuro Shimbo,‡ Shohei Tanaka,* Katsunori Sekine,* Yoshihiro Kishida,* Kazuhiro Watanabe,* Toshiyuki Sakurai,* Chizu Yokoi,* Junichi Akiyama,* Mikio Yanase,* Masashi Mizokami,§ and Naomi Uemura‖

*Department of Gastroenterology and Hepatology, ‡Department of Clinical Research and Informatics, National Center for Global Health and Medicine, Tokyo; and §The Research Center for Hepatitis and Immunology, ‖Department of Gastroenterology and Hepatology, Kohnodai Hospital, National Center for Global Health and Medicine, Kohnodai, Chiba, Japan

BACKGROUND & AIMS: **The long-term recurrence of lower gastrointestinal bleeding (LGIB) and associated mortality have not been studied extensively. We investigated rates of recurrence of LGIB, mortality, and associated risk factors.**

METHODS: **In a retrospective study, we analyzed data from 342 patients hospitalized for overt LGIB at the National Center for Global Health and Medicine in Japan from December 2004 through June 2013. All patients underwent colonoscopy. We assessed Charlson comorbidity index scores and the use of nonsteroidal anti-inflammatory drugs, low-dose aspirin, other antiplatelet drugs, or warfarin. Rebleeding, the total number of rebleeding episodes, and mortality were measured. The Cox proportional hazards model was used to estimate hazard ratios (HRs).**

RESULTS: **Rebleeding occurred in 84 patients, at a mean follow-up time of 19 months. The cumulative percentages of patients with rebleeding at 1 and 5 years were 19% and 46%, respectively. During the follow-up period, 29 patients (39%) had secondary rebleeding and 18 patients (62%) had subsequent rebleeding. Multivariate analysis showed age 65 years and older (HR, 1.7; $P = .04$) and the use of nonsteroidal anti-inflammatory drugs (HR, 2.0; $P < .01$) and nonaspirin antiplatelet drugs (HR, 1.8; $P < .05$) as independent risk factors for rebleeding. Dual therapy had a higher risk than single therapy (adjusted HR, 1.8; $P < .05$). During the mean follow-up period of 28 months, 21 patients died (2 from bleeding). Cumulative mortality rates at 1 and 5 years were 4.2% and 13%, respectively. Mortality was associated significantly with age ≥65 years ($P < .05$), Charlson comorbidity index score, and warfarin use.**

CONCLUSIONS: **Based on a retrospective analysis of patients with LGIB, 46% of all patients have rebleeding, and the overall mortality rate is 13% within 5 years after hospitalization. Besides age ≥65 years, use of antithrombotic drugs increases the risk of bleeding recurrence and mortality among patients with LGIB.**

Keywords: Antithrombotic Agents; Anticoagulants; Poor Clinical Outcomes; Lower Gastrointestinal Hemorrhage; LGIB; Recurrence; Mortality.

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The estimated annual incidence of acute lower gastrointestinal bleeding (LGIB) is 33 patients per 100,000 population,[1] and LGIB is a common indication for hospital admission.[2–4] Although rebleeding is known to occur after initial management of LGIB,[5–7] its natural history remains unclear. The in-hospital mortality rate of LGIB patients is less than 5%,[2,4,5] but the long-term mortality rate is unknown. Patients with rebleeding typically undergo frequent examinations, hospitalizations, and repeated blood transfusions, and consequently experience a decreased quality of life. Thus, it is important to provide patients hospitalized for LGIB with sufficient information on the natural history of the disease and to identify the risk factors for recurrence.

Abbreviations used in this paper: **CI, confidence interval; LGIB, lower gastrointestinal bleeding; NCGM, National Center for Global Health and Medicine; NSAID, nonsteroidal anti-inflammatory drug; HR, hazard ratio; SHR, subdistribution hazard ratio; UGIB, upper gastrointestinal bleeding.**

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Unlike upper gastrointestinal bleeding (UGIB), which can be treated by anti-acid therapy,[8] there are no effective therapies for preventing LGIB, and the risk factors for overt LGIB have not been studied to the same degree as those for UGIB. Various comorbidities and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin have been reported as risk factors for LGIB,[9–12] but the associations of these factors with recurrence and mortality remains unknown.[7] Therefore, in this long-term follow-up study of patients hospitalized for acute LGIB diagnosed by colonoscopy and several imaging modalities, we aimed to elucidate the rates of recurrence and mortality, and the associated risk factors.

Methods

Patients

We identified 369 patients admitted for acute overt LGIB at the National Center for Global Health and Medicine (NCGM) (Japan), from December 2004 to June 2013. The NCGM is one of the largest tertiary emergency hospitals (900 beds) in the Tokyo metropolitan area. Patients with UGIB and those who did not undergo colonoscopy were excluded. This study was approved by the ethics committee of the NCGM.

Parameters

We evaluated comorbidity with the Charlson comorbidity index (Charlson index),[13,14] a validated and commonly used predictive index of mortality. The use of NSAIDs, low-dose aspirin (81 mg buffered aspirin or 100 mg enteric-coated aspirin), nonaspirin antiplatelet drugs (clopidogrel, ticlopidine, cilostazol, and dipyridamole), or warfarin (defined as oral administration within 1 month before admission) also was assessed at the initial hospitalization.

Acute Lower Gastrointestinal Bleeding and Outcome Measures

A high-resolution electronic video endoscope (CFH260; Olympus Optical, Tokyo, Japan) was used to diagnose colorectal disease after sufficient bowel preparation. LGIB was defined as follows: endoscopy-proven lower GI events; frank melena or rectal bleeding with no evidence of source on upper endoscopy or nasogastric aspirate or on capsule endoscopy or double-balloon endoscopy; and lesions considered responsible for bleeding on colonoscopy. Multidetector computed tomography additionally was performed for patients with persistent or massive LGIB at the emergency outpatient unit or with recent hemorrhage.

Rebleeding was defined as significant amounts of fresh bloody or wine-colored stools ($>$200 mL) during the follow-up period, and was evaluated by both anoscopy and multidetector computed tomography within 12 hours of onset. Clinically suspected rebleeding should prompt further colonoscopy when possible, but no routine second-look colonoscopy was performed when rebleeding occurred during hospitalization or within 1 month of discharge. Colonoscopy was used to confirm rebleeding and to determine the need for intervention when frequent or massive bleeding occurred along with unstable vital signs, a systolic blood pressure of $\leq$90 mm Hg or pulse of $\geq$110 beats/min, and a nonresponse to 2 or more units of transfused blood during a 24-hour period. We distinguished between rebleeding and remaining blood from the index bleeding episode according to the earlier-described criteria.

Patients were re-examined if they experienced secondary or subsequent rebleeding during the follow-up period. The total number of rebleeding episodes per patient, death, and cause of death during this period were calculated. Data were collected from the medical records and death certificates of the study hospital. Cause of death was classified as bleeding-related or non–bleeding-related.[15] Causes of non–bleeding-related death were defined as the diseases diagnosed by laboratory tests, multiple imaging modalities, or autopsy.

Statistics

In the rebleeding analysis, the end point was rebleeding and data were censored at the time of the last visit. The Kaplan–Meier method was used to estimate the cumulative recurrence of LGIB at 1, 12, 24, 36, 48, 60, 72, 84, and 96 months. Risk factors for rebleeding were evaluated by univariate analysis using the log-rank test. Cox proportional hazards modeling was used to estimate unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). The use of different antiplatelet drugs was compared between patients receiving no, single-, and dual-antiplatelet therapy. Antiplatelet drugs included aspirin, nonaspirin antiplatelets, and NSAIDs according to the American Society for Gastrointestinal Endoscopy guideline.[16] To analyze the adjusted HR of dual therapy, factors were adjusted according to age $\geq$65 years, sex, Charlson index, and warfarin use. Next, using Fine and Gray's test[17] in the competing risk analysis, we calculated the subdistribution hazard ratio (SHR) with the 95% CI, treating death without rebleeding as a competing risk. The relationships between the factors and the number of recurrences per patient during the follow-up period were analyzed using the Wilcoxon rank-sum test.

In the survival analysis, the end point was death and data were censored at the time of the last visit. The Kaplan–Meier method was used to estimate the cumulative mortality at 1, 12, 24, 36, 48, 60, 72, 84, and 96 months. Risk factors for mortality were evaluated by univariate analysis using the log-rank test.

P values less than .05 were considered significant. All statistical analyses were performed using STATA version 13 software (StataCorp, College Station, TX).