Risk factors of the rebleeding according to the patterns of nonvariceal upper gastrointestinal bleeding

Ji Hyung Nam1, Tae Joo Jeon2, Jae Hee Cho3, Jae Hak Kim1

1Department of Internal Medicine, Dongguk University Ilsan Hospital, Dongguk University College of Medicine, Goyang, Korea
2Division of Gastroenterology, Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea
3Division of Gastroenterology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Korea

ABSTRACT

Background/Aims: Despite of successful endoscopic hemostasis of nonvariceal upper gastrointestinal bleeding (NGIB), rebleeding rate has not decreased. The aim of this study was to identify risk factors for rebleeding after endoscopic hemostasis in patients with NGIB according to bleeding patterns.

Materials and Methods: A retrospective analysis was performed on the consecutive patients with NGIB in whom successful primary endoscopic hemostasis had been achieved at three university hospitals in Korea. All patients underwent endoscopic treatment with hemoclips, epinephrine injection, argon-plasma coagulation, or its combinations within 12 h.

Results: A total of 198 patients were studied. The male-to-female ratio was 3:1. Mean age was 60.7±14.9 years. Rebleeding occurred in 41 cases (20.7%). Median day of rebleeding after endoscopic therapy was 2.0 days. Overall mortality rate was 5.1%. Risk factors for rebleeding were inpatients (odds ratio (OR) 2.61, 95% confidence interval (CI): 1.05-6.46, p=0.038) and Forrest Ib (OR=2.73, 95% CI: 1.15-6.47, p=0.023) by multivariate regression analysis.

Conclusion: Despite of successful emergent endoscopic therapy for NGIB, rebleeding occurred in 17.7% within a week. Endoscopic treatments should be more carefully performed for patients in hospitalization or patients with active oozing.

Keywords: Risk factors, gastrointestinal hemorrhages, therapeutics, endoscopy
confirmed to have active or recent bleeding from gastric or duodenal ulcer. We retrospectively reviewed medical records of the clinical factors including age, sex, comorbidities, history of anticoagulants or NSAID intake, admission status (outpatient or inpatient) and initial hemoglobin level. Endoscopic factors such as location and bleeding status, rebleeding, and mortality were also investigated. We excluded the patients with esophageal variceal bleeding, Mallory-Weiss syndrome, malignant ulcers, and peptic ulcers with clean base such as Forrest III. Written informed consent was obtained from all the patients before endoscopic procedures. This study was reviewed and approved by the Institutional review board of DUIH (No. 2009-63).

Endoscopic Hemostasis
All ulcer bleedings were treated by endoscopic procedure with hemoclipping, epinephrine (1:10,000) injection, argon-plasma coagulation or its combination within 12 h of presentation. We regarded spurting or oozing bleeding, visible blood vessels, and adherent blood clots needing endoscopic management (Forrest classification Ia, Ib, IIa, and IIb) as active bleeding and only included the patients with active bleeding ulcers to the study (15). All patients intravenously received standard dose of PPI for 48 h. Then, the patients were treated with a standard dose of oral PPI for 6-8 weeks.

Definitions
Rebleeding was defined as hematemesis, significant decreased in blood pressure (<80 mmHg or 25% decreased in baseline blood pressure), >20% increase in heart rate, >2 g/dL of hemoglobin decrease within 7 days after successful endoscopic therapy and had to be confirmed by second endoscopic examination. Old age was defined as age >65 years. Primary outcome was rebleeding rate within 7 days after successful endoscopic therapy.

Statistical Analysis
We analyzed whether there are differences in terms of patients’ baseline demographics, location of ulcer, ulcer bleeding pattern, endoscopic treatment modality and quality, underlying diseases, hemoglobin level, and history of medications between rebleeding group (case) and non-rebleeding group (control). A two-sample t-test was used for the comparison of mean age and the Pearson’s chi-square test or Fisher’s exact tests was used to compare differences for categorical variables. We estimated the odds ratio (OR) for risk of rebleeding in the different Forrest classification compared to Forrest IIb, in the ulcer located in the antrum or corpus compared to duodenal ulcer, in the different treatment modalities compared to hemoclip monotherapy, and in in-hospital bleeding compared to the outpatient bleeding by chi-square test. To evaluate the significant independent factors for rebleeding, independent variables which had a p value of <0.1 in the univariate tests were entered into a multivariate logistic regression model and adjusted by age, gender, and other variables which may be confounding factors of risks for rebleeding. ORs and 95% confidence intervals (CIs) were determined in the multivariate analysis. All p values are two-sided, and significance is indicated by a p value of <0.05. All statistical analyzes were performed using STATA software, version 10.1 (StataCorp, College Station, TX, USA).

RESULTS

Patient Characteristics
A total of 198 patients were evaluated. Male-to-female ratio was 3:1. Mean age was 60.7±14.9 years (range, 20-98). Baseline hemoglobin was 8.8±2.7 g/dL (range 2.6-17.4).

Cerebrovascular diseases were present in 20 cases (10.1%) and ischemic heart diseases were present in 14 cases (7.0%). Antiplatelet agents were administrated in 45 cases (22.6%).

Rebleeding occurred in 41 cases (20.7%). Median day of rebleeding after endoscopic management was 2.0 days (interquartile range 4 days, range 1-27 days). In-hospital mortality occurred in 10 patients (5.1%), and cause of death was ulcer bleeding in three patients (1.5%). The baseline patients’ demographics and endoscopic findings between rebleeding and control group are shown in Table 1. Gastric ulcers were in 135 cases (68.2%) and 76 cases (38.4%) were located in the corpus to fundus. There were no differences in terms of age and gender between the case and control groups.

Endoscopic Hemostasis
The distribution according to the Forrest classification was 16 (8.1%), 44 (22.2%), 98 (49.5%), and 40 (20.2%) cases in the Ia, Ib, Ila, and IIb, respectively. Ulcer with Forrest Ib was significantly associated with rebleeding (p=0.039), whereas the risk of rebleeding was not increased in Forrest Ia, Ila. The risk for rebleeding was not different according to ulcer location, treatment modality, underlying diseases, history of NSAIDs or anticoagulants, and hemoglobin level. Thirty-six patients (16.7%) experienced peptic ulcer bleeding during hospitalization; especially, eight of these (4.1%) occurred during ICU care. The risk for rebleeding was higher in in-hospital bleeding than in outpatient bleeding (p=0.012). In addition, it tended to be lower if the endoscopic managements were performed by attending staff rather than by training fellow (p=0.104).

Risk Factors for Rebleeding
In the multivariate analysis, the risk for rebleeding was significantly increased in patients with in-hospital bleeding (OR=2.61, 95% CI:1.05-6.46, p=0.038). Ulcer bleeding with Forrest Ib was significantly associated with rebleeding (OR=2.73, 95% CI:1.15-6.47, p=0.023) (Table 2).
DISCUSSION

Clinical implication of rebleeding is one of the most significant predictors relating to mortality (16). In this study, we confirmed that active oozing bleeding (Forrest Ib) and in-hospital bleeding were significantly associated with rebleeding in patients with active ulcer bleeding that needed urgent endoscopic management. The definition of active bleeding ulcer was heterogeneous from study to study, even though there have been several reports regarding the predictive risk factors of rebleeding in patients with active ulcer bleeding. Ulcers with spurting or oozing bleeding on endoscopy was one of the major predictors for rebleeding after initial endoscopic treatment (17). A previous study found that systolic blood pressure <100 mmHg, blood in the nasogastric tube, and visible vessel, which could suggest active bleeding, were independent predictors of rebleeding (18). Ulcers with signs of spurting or oozing bleeding and ulcers with a visible vessel are at high risk of recurrent bleeding, while the role of endoscopic therapy for ulcers with adherent blood clots remains uncertain (19). However, a randomized trial reported that combination endoscopic therapy of adherent clots significantly reduced the rebleeding rate compared with medical therapy alone (20). We performed endoscopic treatment in the majority of patients with adherent clots (Forrest IIb), and included these cases in the study.

Despite successful endoscopic therapy, overall rebleeding rate was 20.7%, which is similar to the result of the earlier study or somewhat higher than that of other studies (5,10,21). The exclusion of patients who experienced spontaneous hemostasis without endoscopic treatment and those who had inactive ulcers might cause increased rate of rebleeding in our study. Rebleeding was observed in 13 of the 36 patients (37.8%) in admission, and it was much higher than 14.6% of outpatient ulcer bleeding. A recent study showed that seven-day rebleeding rate was 34.6%, and thirty-day rebleeding rate was 51.1% in critically ill patients (22). Another study reported that in-hospital bleeding was one of significant risk factors for recurrent bleeding within 3 days and was the only independent risk factor for

### Table 1. Patients demographics and clinical characteristics: univariate analysis of the risk for rebleeding after endoscopic management

<table>
<thead>
<tr>
<th>Variables</th>
<th>Rebleeding (n=61)</th>
<th>Control (n=157)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age±SD, years</td>
<td>63.2±12.0</td>
<td>60.0±15.6</td>
<td>0.237</td>
</tr>
<tr>
<td>Old age, n (%)</td>
<td>21 (51.2)</td>
<td>72 (45.9)</td>
<td>0.540</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td>0.506</td>
</tr>
<tr>
<td>Male</td>
<td>29 (70.7)</td>
<td>119 (75.8)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12 (29.3)</td>
<td>38 (24.2)</td>
<td></td>
</tr>
<tr>
<td>Ulcer location, n (%)</td>
<td></td>
<td></td>
<td>0.251</td>
</tr>
<tr>
<td>Duodenum</td>
<td>10 (24.4)</td>
<td>53 (33.8)</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>31 (75.6)</td>
<td>104 (66.2)</td>
<td></td>
</tr>
<tr>
<td>Ulcer location, n (%)</td>
<td></td>
<td></td>
<td>0.162</td>
</tr>
<tr>
<td>Duodenum</td>
<td>10 (24.4)</td>
<td>52 (33.8)</td>
<td></td>
</tr>
<tr>
<td>Antrum, prepylorus</td>
<td>12 (29.3)</td>
<td>45 (29.2)</td>
<td>0.491</td>
</tr>
<tr>
<td>Corpus-fundus</td>
<td>19 (46.3)</td>
<td>57 (37.0)</td>
<td></td>
</tr>
<tr>
<td>Forrest classification, n (%)</td>
<td></td>
<td></td>
<td>0.486</td>
</tr>
<tr>
<td>Ia</td>
<td>3 (7.3)</td>
<td>13 (8.3)</td>
<td>0.840</td>
</tr>
<tr>
<td>Ib</td>
<td>14 (34.1)</td>
<td>30 (19.1)</td>
<td>0.039</td>
</tr>
<tr>
<td>Ila</td>
<td>20 (48.8)</td>
<td>78 (49.7)</td>
<td>0.918</td>
</tr>
<tr>
<td>IIb</td>
<td>4 (9.8)</td>
<td>36 (22.9)</td>
<td>0.080</td>
</tr>
<tr>
<td>Treatment modality, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoclip</td>
<td>14 (33.3)</td>
<td>49 (31.2)</td>
<td>0.719</td>
</tr>
<tr>
<td>Epinephrine injection</td>
<td>3 (7.3)</td>
<td>15 (9.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Coagulation</td>
<td>6 (14.6)</td>
<td>23 (14.6)</td>
<td>0.998</td>
</tr>
<tr>
<td>Combination</td>
<td>20 (48.8)</td>
<td>67 (42.7)</td>
<td></td>
</tr>
<tr>
<td>Underlying disease, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVA</td>
<td>4 (9.8)</td>
<td>16 (10.2)</td>
<td>0.934</td>
</tr>
<tr>
<td>CAD</td>
<td>3 (7.3)</td>
<td>11 (7.0)</td>
<td>0.945</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (14.6)</td>
<td>30 (19.1)</td>
<td>0.651</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (9.8)</td>
<td>18 (11.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>7 (17.1)</td>
<td>38 (24.2)</td>
<td>0.336</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>4 (9.8)</td>
<td>18 (11.5)</td>
<td>0.757</td>
</tr>
<tr>
<td>Place, n (%)</td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>Outpatient</td>
<td>28 (68.3)</td>
<td>134 (85.4)</td>
<td></td>
</tr>
<tr>
<td>In-hospital*</td>
<td>13 (31.7)</td>
<td>23 (14.6)</td>
<td></td>
</tr>
<tr>
<td>Initial hemoglobin, n (%)</td>
<td></td>
<td></td>
<td>0.460</td>
</tr>
<tr>
<td>&lt;8 g/dL</td>
<td>18 (43.9)</td>
<td>59 (37.6)</td>
<td></td>
</tr>
<tr>
<td>≥8 g/dL</td>
<td>23 (56.1)</td>
<td>98 (62.4)</td>
<td></td>
</tr>
<tr>
<td>Quality of procedure, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekend</td>
<td>7 (17.1)</td>
<td>23 (14.6)</td>
<td>0.807</td>
</tr>
<tr>
<td>Night</td>
<td>7 (17.1)</td>
<td>16 (10.2)</td>
<td>0.221</td>
</tr>
<tr>
<td>On call</td>
<td>9 (22.0)</td>
<td>34 (21.7)</td>
<td>0.967</td>
</tr>
<tr>
<td>By Staff</td>
<td>29 (70.7)</td>
<td>129 (82.2)</td>
<td>0.104</td>
</tr>
</tbody>
</table>

CAD: coronary artery disease; CI: confidence interval; CVA: cerebrovascular disease; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; SD: standard deviation

*Included bleeding developed during ICU care

### Table 2. ORs for the risk of rebleeding from a multivariate logistic regression model

<table>
<thead>
<tr>
<th>Variables</th>
<th>ORs*</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old age</td>
<td>1.14</td>
<td>0.50-2.57</td>
<td>0.758</td>
</tr>
<tr>
<td>Male</td>
<td>1.07</td>
<td>0.43-2.62</td>
<td>0.891</td>
</tr>
<tr>
<td>Location of ulcer†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forrest Ib</td>
<td>2.73</td>
<td>1.15-6.47</td>
<td>0.023</td>
</tr>
<tr>
<td>Treatment modality</td>
<td>1.72</td>
<td>0.80-3.67</td>
<td>0.181</td>
</tr>
<tr>
<td>In-hospital bleeding</td>
<td>2.61</td>
<td>1.05-6.46</td>
<td>0.038</td>
</tr>
<tr>
<td>Hemoglobin &lt; 8 g/dL</td>
<td>1.51</td>
<td>0.69-3.31</td>
<td>0.306</td>
</tr>
<tr>
<td>Endoscopist’s experience</td>
<td>0.47</td>
<td>0.20-1.15</td>
<td>0.100</td>
</tr>
</tbody>
</table>

CI: confidence interval; OR: odds ratio

*ORs for the risk of rebleeding occurred within a week
†We used three categories of duodenum, antrum to prepylorus, and corpus to fundus

---

Nam et al. Rebleeding risk according to the patterns of bleeding Turk J Gastroenterol 2017; 28: 266-71
Additional treatment after epinephrine injection reduced fur-
control (21). Several reports showed that hemoclip or combi-
nephrine monotherapy had higher in rebleeding group than in
studies (10,24,25). In addition, the number of patients with epi-
been reported relatively high, showing 13%-21% in previous
The rate of rebleeding after epinephrine monotherapy has
rest Ia to IIb), in-patient start of bleeding, and prior GI bleeding
followed population of 1,264 patients hospitalized with severe
peptic ulcer bleedings was conducted (6). The study demon-
strated that the ulcer size (≥10 mm), a high-risk stigmata (For-
rest la to IIb), in-patient start of bleeding, and prior GI bleeding
were the risk factors for worse outcome.

The rate of rebleeding after epinephrine monotherapy has
been reported relatively high, showing 13%-21% in previous
studies (10,24,25). In addition, the number of patients with epi-
epinephrine monotherapy had higher in rebleeding group than in
control (21). Several reports showed that hemoclip or combi-
nation therapy was superior to monotherapy with epinephrine
injection or heat probe in reduction of rebleeding rate (26,27).
Additional treatment after epinephrine injection reduced fur-
ther bleeding and mortality when compared to epinephrine
monotherapy regardless of which procedure was combined
(28). Barkun et al. (8) reported a meta-analysis that compared
various methods of endoscopic hemostasis for patients with
peptic ulcer bleeding that exhibited high-risk stigmata. They
concluded that optimal therapies included thermal therapy
or clips, either alone or in combination with other methods.
These previous studies are inconsistent with our result that did
not show different risk of rebleeding according to treatment
modalities. It may be because we preferred using hemoclip or
combination therapy for endoscopically more active bleeding
rather than adherent blood clots. While we performed hemo-
clipping alone or combination treatment for all patients with
Forrest Ia, epinephrine injection or coagulation monotherapy
was not done for those patients. In addition, the ORs for treat-
ment with hemoclips with or without combination therapy
were significantly lower in patients with Forrest IIa and IIb com-
pared with Forrest Ia.

Patients aged >65 years did not have increased risk of rebleed-
ing versus younger patients, and it is consistent with a recent
study on rebleeding risk of elderly patients (age ≥65 years)
compared to young patients (29). However, there have been
a few conflicting reports that evaluated whether the risk of re-
bleeding was increased with greater age (11,30). Because older
patients may have a possibility of having a more complicated
comorbidity and are vulnerable to recovery from initial hemo-
dynamic instability, they might have high risk for rebleeding
and high mortality rate. Thus, further studies are needed to
clarify this point. Several studies found that ulcers located on
the high gastric lesser curvatures or posterior duodenal bulb
had increased risks for rebleeding, which locations could be
related to difficulty of accurate focusing during endoscopic
management (9,17,31). In our cases, there was no significant
difference of rebleeding risk according to location of ulcer. It
may be caused by different distribution of treatment modaliti-
es among the locations of ulcers in our study and not dividing
in detail in terms of location of ulcer due to small sample size.

Forrest Ib was predictive risk factor of rebleeding after hemo-
stasis in present study. This finding was in contrast to the result
of other study, which showed that spurring bleeding (Forrest
la) is only a significant independent predictor of rebleeding in
multiple logistic regression (32). Our finding may be related
that direct focusing on bleeding site during endoscopic proced-
ure is harder in case of oozing (lb) bleeding than spurring (la).
Interestingly, a previous study reported that compared with
injection monotherapy, combination with hemoclipping was
more effective in treating ulcers with oozing bleeding, while
both were equivalent therapies in treating ulcers with spurring
bleeding (33). This report is similar to our result in that more ef-
fective endoscopic management could be needed for oozing
bleeding. In addition, even though there are some differences
in the studies, they are consistent in that endoscopically active
bleeding and disadvantage in endoscopic procedure increase
rebleeding risk.

There are several limitations to this study. First, this is a retrospec-
tive study and limited by the small sample size, particularly in
the analysis of independent variables divided by more than two cat-
egories. Thus, the findings of our study should be confirmed by
further large prospective studies. Second, as the part of informa-
tion relating to the use of NSAIDs or anticoagulants and underly-
ing diseases was obtained from history taking rather than from
objective data, these data were vulnerable to recall bias. Third,
we performed second-look endoscopy for some patients, espe-
cially those with clinical suspicion of rebleeding, rather than for
all patients. Even though routine second-look endoscopy with
thermal coagulation reduced recurrent ulcer bleeding in a re-
cent meta-analysis, there is no proven evidence of benefit from
second-look endoscopy for all patients with peptic ulcer bleed-
ing (34). However, we cannot exclude the possibility of underes-
timation of rebleeding rate. Fourth, we did not control for ulcer
size, initial hemodynamic status, and major comorbidity which
were important predictors for recurrent bleeding in other stud-
ies (17,23,35). Fifth, the subjects in our study were performed dif-
ferent endoscopic management. Because the rate of rebleeding
could be different according to treatment modalities, subgroup
studies according to this point were needed. Finally, most infor-
mmation relating to Helicobacter pylori infection status and eradi-
cation, which were closely associated with recurrence of peptic
ulcer bleeding, was not available; this is because the testing was
usually not performed at the time of urgent endoscopy, and
data relating to second endoscopy and the H. pylori testing were
insufficient for analysis (36,37).
In conclusion, it is important to exactly perform the endoscopic procedure on correct bleeding focus for prevention of rebleeding. Moreover, endoscopic treatments should be more carefully performed for patients with active oozing bleeding occurred during hospitalization.

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This work was supported by the Dongguk University Research Fund of 2014.

REFERENCES


prospective and randomized trial. Gastrointest Endosc 2001; 53: 147-51. [CrossRef]
35. Chiu PW, Joeng HK, Choi CL, Kwong KH, Ng EK, Lam SH. Predictors of peptic ulcer rebleeding after scheduled second endoscopy: clinical or endoscopic factors? Endoscopy 2006; 38: 726-9. [CrossRef]