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Original Article



# Clinical Outcomes of Endoscopic Hemostasis for Bleeding in Patients with Unresectable Advanced Gastric Cancer

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## ABSTRACT

**Purpose:** Bleeding is one of the most serious complications of advanced gastric cancer (AGC) and is associated with a poor prognosis. This study aimed to evaluate the clinical outcomes of endoscopic hemostasis for bleeding in patients with unresectable AGC.
**Materials and Methods:** This study included 106 patients with bleeding associated with gastric cancer who had undergone endoscopic hemostasis between January 2010 and December 2013. Clinical characteristics, treatment outcomes, including rates of successful endoscopic hemostasis and rebleeding, risk factors for rebleeding, and overall survival (OS) were investigated.
**Results:** Successful initial hemostasis was achieved in 83% of patients. Rebleeding occurred in 28.3% of patients within 30 days. The median OS after initial hemostasis was lower in patients with rebleeding than in those without rebleeding (2.7 and 3.9 months, respectively, P=0.02). There were no significant differences in disease status and rebleeding rates among patients with partial response or stable disease (n=4), progressive disease (n=64), and first diagnosis of disease (n=38). Univariate and multivariate analyses (P=0.038 and 0.034, respectively) revealed that transfusion of ≥5 units of RBCs was a significant risk factor for rebleeding.
**Conclusions:** Despite favorable success rates of endoscopic hemostasis for bleeding associated with gastric cancer, the 30-day rebleeding rate was 28.3% and the median OS was significantly lower in patients with rebleeding than in those without rebleeding. Massive transfusion (≥5 units of RBCs) was the only significant risk factor for rebleeding. Patients with bleeding associated with AGC who have undergone massive transfusion should be observed closely following endoscopic hemostasis. Further research on approaches to reduce rebleeding rate and prevent death is needed.

**Keywords:** Endoscopic hemostasis; Hemorrhage; Stomach neoplasms

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**Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

## INTRODUCTION

Despite recent technical advances in therapeutic endoscopy, acute nonvariceal upper gastrointestinal bleeding (NVUGIB) remains an important medical issue that is strongly associated with morbidity and mortality [1,2]. Tumors are a common cause of NVUGIB, and bleeding associated with gastric cancer reportedly accounts for approximately 1%–5% of cases of acute upper gastrointestinal bleeding (UGIB) [3-5]. The 30-day mortality following endoscopic hemostatic therapy for gastrointestinal (GI) bleeding due to advanced gastric cancer (AGC) is much higher than that for GI bleeding due to other causes, and ranges from 15.9% to 43% [5,6].

However, availability of information about the effectiveness of endoscopic therapy for GI bleeding caused by AGC is limited [5,7]. The purpose of this study was to evaluate the clinical outcomes of endoscopic hemostasis and to assess the factors associated with rebleeding in patients with unresectable AGC.

## MATERIALS AND METHODS

### Patients

We reviewed the medical records of 187 patients with unresectable AGC who had undergone esophagogastroduodenoscopy (EGD) for suspected gastric-cancer-associated bleeding between January 2010 and December 2013 at Severance Hospital, Yonsei University, Seoul, Korea. Of these, 81 patients without stigmata of recent bleeding had received conservative treatment and did not undergo endoscopic hemostasis, and the remaining 106 patients who had undergone endoscopic hemostasis were included in this study (**Fig. 1**). Demographic data including sex and age, and data on coexisting disease were reviewed. The following factors were also evaluated: systolic blood pressure, diastolic blood pressure, pulse rate, hemoglobin level, platelet count, and number of transfused red blood cell (RBC) units. This retrospective study was approved by the Institutional Review Boards for Human Research of Yonsei University (IRB number: 4-2014-131).

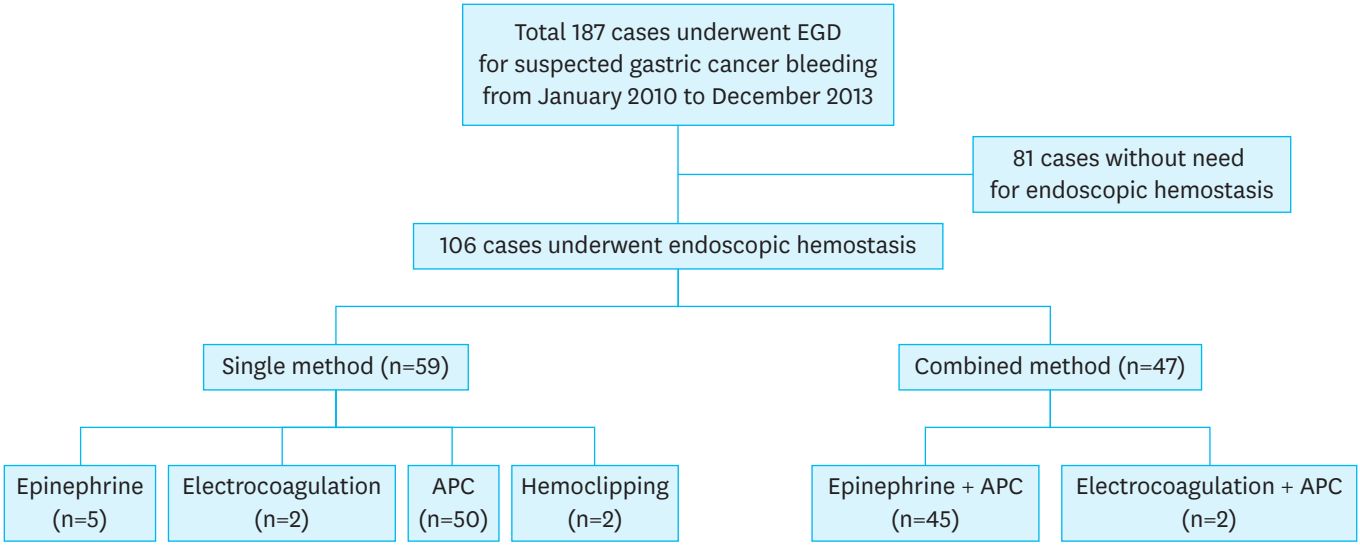


**Fig. 1.** Study flow diagram.
EGD = esophagogastroduodenoscopy; APC = argon plasma coagulation.


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### Endoscopic procedure

Endoscopic findings of bleeding were graded according to the Forrest classification. Spurting hemorrhage (Forrest Ia), oozing hemorrhage (Forrest Ib), non-bleeding visible vessels (Forrest IIa), and adherent clots (Forrest IIb) were identified via endoscopy. Endoscopic hemostasis was performed in patients with Forrest Ia, Ib, IIa, and IIb bleeding, and various endoscopic modalities including epinephrine injection (concentration 1:10,000), electrocoagulation, argon plasma coagulation (APC), and clipping were employed, alone or in combination, at the discretion of the endoscopist.

### Successful hemostasis and rebleeding

Successful hemostasis was defined as no evidence of bleeding from the treatment site after irrigation and 3 minutes of observation after treatment [8]. If the initial endoscopic hemostasis failed, angiographic embolization, surgery, or conservative treatment was performed according to the patient's condition.

Rebleeding was defined as clinical signs of UGIB or a decrease in the hemoglobin level (>2 g/dL), with stigmata of bleeding on endoscopic examination after initial hemostasis.

### Statistical analysis

Variables are presented as mean±standard deviation (SD). A P-value <0.05 was considered statistically significant. Univariate and multivariate analyses were performed to identify the factors associated with rebleeding by using the $\chi^2$ or Fisher's exact test. A multivariate logistic regression model was used to determine the independent factors associated with rebleeding. The Kaplan-Meier method was used to estimate the median time to rebleeding and overall survival (OS) after initial hemostasis. Analyses were performed using SPSS statistical software version 18.0 (SPSS, Chicago, IL, USA).

## RESULTS

### Patient characteristics

Patient characteristics are shown in **Table 1**. The mean age of the study group was 66.0±12.9 years and the majority of patients were male. Of the 106 patients, 105 had stage IV AGC (99.1%). Only 4 patients (3.8%) had partial response or stable disease and 64 (60.9%) had progressive disease at the time of bleeding. The remaining 38 patients (35.8%) were newly diagnosed with gastric cancer on the basis of the clinical manifestation of bleeding. Among the 68 patients who were diagnosed with AGC before bleeding occurred, 53 had received chemotherapy; 1, radiation therapy; 4, combined chemoradiation therapy; and 10, best supportive treatment before bleeding. Hematemesis occurred in 48 (45.3%) patients, and melena and hematochezia occurred in 37 (34.9%) and 12 (11.3%), respectively, at the initial presentation. The mean initial hemoglobin level was 8.6±2.4 g/dL.

### Endoscopic findings and hemostasis

The most common, gross AGC type was Borrmann type III (79 patients, 74.5%), and the mean size of the tumors was 3.6±1.2 cm. Active oozing hemorrhage (Forrest Ib) was the most common type of bleeding, followed by adherent clots (Forrest IIb). Various single or combined treatment modalities such as epinephrine injection (n=40), electrocoagulation (n=2), APC (n=82), and hemoclipping (n=27) were employed. Combination therapy was applied in 44.3% (47/106) of the patients.


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**Table 1.** Baseline patient characteristics

| Variables | Value (n=106) |
|---|---|
| Age (yr) | 66.0±12.9 |
| Sex | |
| Male | 72 (67.9) |
| Female | 43 (32.1) |
| Cancer stage | |
| Stage IIIB | 1 (0.9) |
| Stage IV | 105 (99.1) |
| Disease status of tumor at bleeding | |
| First diagnosis of disease | 38 (35.8) |
| Partial response or stable disease | 4 (3.8) |
| Progressive disease | 64 (60.9) |
| Coexisting illness | |
| Hypertension | 37 (34.9) |
| Cardiovascular disease | 12 (11.3) |
| Diabetes | 22 (20.8) |
| Chronic kidney disease | 2 (1.9) |
| Chronic liver disease | 11 (10.4) |
| Anticoagulation or antiplatelet treatment | 15 (14.2) |
| Initial presentation | |
| Melena | 37 (34.9) |
| Hematochezia | 12 (11.3) |
| Hematemesis | 48 (45.3) |
| Dizziness | 4 (3.8) |
| Hemoglobin decrease >3.0 g/dL | 9 (8.5) |
| Hemodynamic and laboratory findings | |
| Systolic blood pressure (mmHg) | 107±21 |
| Diastolic blood pressure (mmHg) | 62±13 |
| Pulse rate (beats per minute) | 93±18 |
| Hemoglobin (g/dL) | 8.6±2.4 |
| Platelet (×1,000 U/mL) | 244±135 |

Data are shown as mean±standard deviation or number (%).

A total of 106 patients underwent endoscopic treatment, and hemostasis was successfully achieved in 88 patients (83.0%). There was no statistical difference in initial success rates among various methods of hemostasis, as well as between single and combined hemostasis (79.7% [47/59] and 87.2% [41/46], respectively, P=0.435). In addition, there were no significant differences in rebleeding rates according to tumor gross type. In the case of treatment failure (n=18 patients), patients underwent additional treatment with transarterial embolization (n=3), surgery (n=3), repeated endoscopic therapy (n=3), and conservative treatment (n=9) at the physician's discretion (**Table 2**). Bleeding in all patients was controlled after treatment without 30-day mortality. However, 2 patients who underwent embolization and 1 who underwent surgery died of disease progression in 2 months. Median survival in the treatment failure group was 3.3 months (range 2–7 months).

## Outcomes of hemostasis

Transfusion with ≥5 units of RBCs was required in 49 patients, and rebleeding occurred in 30 patients (28.3%) within 30 days after initial hemostasis. The mean interval between initial hemostasis and recurrent bleeding was 5.9±4.3 days.

Of those with rebleeding, 3 received transarterial embolization, 1 underwent surgery, 18 received repeated endoscopic therapy, and 3 received radiation therapy.


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**Table 2.** Endoscopic findings and hemostasis

| Variables | Value (n=106) |
|---|---|
| Borrmann type | |
| I | 5 (4.7) |
| II | 9 (8.5) |
| III | 79 (74.5) |
| IV | 11 (10.4) |
| Size of tumor (cm) | 3.6±1.2 |
| Forrest classification | |
| Active spurting hemorrhage, Ia | 6 (5.7) |
| Active oozing hemorrhage, Ib | 59 (55.7) |
| Visible vessel, IIa | 14 (13.2) |
| Adherent clot, IIb | 27 (25.5) |
| Methods of hemostasis | |
| Epinephrine injection | 40 (37.7) |
| Electrocoagulation | 2 (1.8) |
| Argon plasma coagulation | 82 (77.3) |
| Hemoclipping | 27 (25.4) |
| Combined methods of hemostasis | 47 (44.3) |
| Outcome of initial hemostasis | |
| Success | 88 (83.0) |
| Failure | 18 (17.0) |
| Transarterial embolization | 3 (16.7) |
| Surgery | 3 (16.7) |
| Repeat endoscopic therapy | 3 (16.7) |
| Conservative treatment | 9 (50.0) |

Data are shown as mean±standard deviation or number (%).

Second-look endoscopy was performed in 18 patients (16.6%). The 30-day mortality rate after endoscopic therapy was 22.6% (**Table 3**). OS after initial hemostasis was lower in patients with rebleeding than in those without rebleeding (median months [interquartile range]; 2.7 [1–5.7] vs. 3.9 [0.9–7.8]; P=0.020 in **Fig. 2**).

## Predictive factors for rebleeding

Transfusion of ≥5 units of RBCs was a significant predictive factor for rebleeding after hemostasis in univariate analysis (P=0.038; **Table 4**), as well as in multivariate analysis (P=0.034; **Table 5**). Age <60 years, sex, disease status, anticoagulation treatment at the time of initial bleeding, shock, hemoglobin level, and active bleeding at endoscopy were not associated with rebleeding.

There were no significant differences in disease status and rebleeding rates among groups with partial response or stable disease (n=4), progressive disease (n=64), and first diagnosis

**Table 3.** Clinical outcomes of hemostasis

| Variables | Value (n=106) |
|---|---|
| Transfusion ≥5 units of RBCs | 49 (46.2) |
| 30-day rebleeding | 30 (28.3) |
| Rebleeding interval (day) | 5.9±4.3 |
| Treatment of rebleeding | |
| Transarterial embolization | 3 (10.0) |
| Surgery | 1 (3.3) |
| Repeat endoscopic therapy | 18 (60.0) |
| Radiation therapy | 3 (10.0) |
| Conservative treatment | 5 (16.7) |
| Second-look endoscopy | 18 (16.6) |
| 30-day mortality | 24 (22.6) |

Data are shown as mean±standard deviation or number (%).


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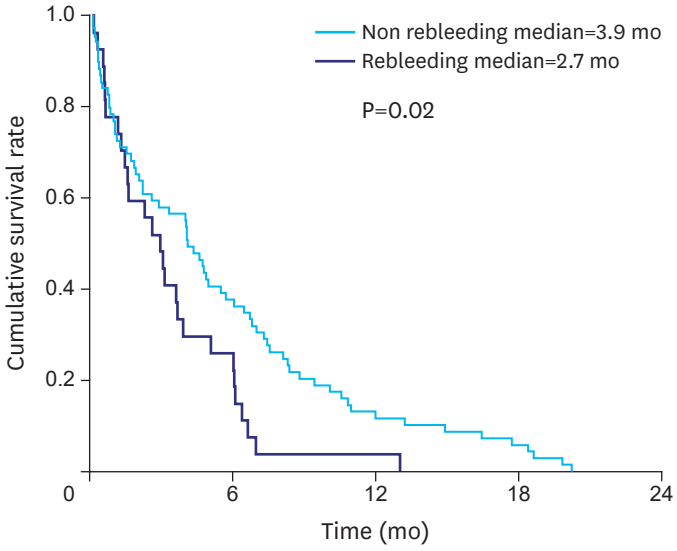


**Fig. 2.** Kaplan-Meier curves of OS according to the occurrence of rebleeding. In this model, OS after initial hemostasis was lower in patients with rebleeding than in those without rebleeding (median months [interquartile range], 2.7 [1–5.7] and 3.9 [0.9–7.8], respectively; P=0.020).
OS = overall survival.

**Table 4.** Predictive factors for rebleeding after initial hemostasis (univariate analysis)

| Variables | Non-rebleeding (n=76) | Rebleeding (n=30) | P |
|---|---|---|---|
| Age <60 yr | 23 (30.3) | 13 (43.3) | 0.201 |
| Male sex | 27 (35.5) | 7 (23.3) | 0.226 |
| Progression of disease at bleeding | 32 (42.1) | 16 (53.3) | 0.295 |
| Anticoagulation treatment at the time of initial bleeding | 12 (15.8) | 3 (10.0) | 0.548 |
| Shock | 12 (15.8) | 3 (10.0) | 0.548 |
| Hemoglobin <9 g/dL | 45 (59.2) | 19 (63.3) | 0.696 |
| Endoscopic active bleeding | 45 (59.2) | 20 (66.7) | 0.478 |
| Transfusion ≥5 units of RBCs | 31 (41.3) | 18 (64.3) | 0.038 |

Data are shown as number (%).

**Table 5.** Multivariate analysis for predictors of rebleeding

| Variables | Multivariate analysis | |
|---|---|---|
| | OR (95% CI) | P |
| Age <60 yr | 1.55 (0.60–3.98) | 0.201 |
| Male sex | 0.43 (0.15–1.25) | 0.122 |
| Transfusion ≥5 units of RBCs | 2.61 (1.04–6.52) | 0.034 |

OR = odds ratio; CI = confidence interval.

of the disease (n=38) (75.0% [3/4] vs. 25.0% [16/64] vs. 28.9% [11/38], P=0.09). Moreover, there were no significant differences in rebleeding rates between patients who received previous cancer treatment (n=58) and those who did not receive treatment (first diagnosis patients and conservative treatment, n=48) (32.8% [19/58] vs. 22.9% [11/48], P=0.263).

## DISCUSSION

According to the American Society for Gastrointestinal Endoscopy reports, benign or malignant GI tumors, whether primary or metastatic, are responsible for approximately 5% of UGIB cases, and endoscopic treatment has been considered effective for bleeding caused by AGC in previous studies [4,9,10]. However, few studies have assessed the outcomes of


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endoscopic therapy for cancer-associated bleeding. The optimal treatment modality has not yet been determined and depends on the goals of therapy [5].

Endoscopic treatment reportedly yields initial hemostasis rates similar to or lower than those seen in peptic ulcer disease [4,9,11,12]. In our study, the technical success rate (83.0%) of endoscopic hemostasis for cancer-associated bleeding in AGC patients was comparable to that reported in previous studies (86%–92.9%) [6,7]. However, the rate was significantly lower than the overall success rate of endoscopic hemostasis for NVUGIB in our institution (97%, data not shown). The reason for the low success rate of endoscopic hemostasis for cancer-associated bleeding compared with that in other NVUGIB cases seems to be the coagulopathy caused by thrombocytopenia due to bone marrow suppression from chemotherapy or multiple bone metastases, friability of cancer mucosa, and hypervascularity of gastric cancer [13,14]. Even though there was no statistical difference among the rates of initial success of various methods of hemostasis, or between single and combined hemostasis, use of combined hemostasis showed a trend of higher success rate than use of any single hemostatic method (87.2% vs. 79.7%). Kim et al. [7] reported that APC was used most often to achieve initial hemostasis in patients with unresectable gastric cancer (92% [104/113]). Akhtar et al. [15] showed that endoscopic APC may control bleeding caused by early esophageal and gastric cancer. In our study, APC was the most commonly performed treatment (77%), followed by epinephrine-saline injection and hemoclipping. Considering our results, APC, combined with epinephrine injection around a bleeding focus, may be the best option to achieve a higher rate of hemostasis in gastric-cancer-associated bleeding. APC is used to induce mostly superficial thermal effects on tissue in a non-contact manner and is considered useful in patients with diffuse or multiple bleeding sites. This technique has become one of the most commonly used endoscopic coagulation methods [16]. Kwan et al. [17] reported that APC was safe and effective for the treatment of GI vascular lesions.

The mean interval between initial hemostasis and recurrent bleeding was 5.9 days, which is similar to that reported in a previous study (6 days) [7]. The rebleeding rates after initial endoscopic hemostasis reportedly range between 16% and 80% [4,9,11,12]. In our study, the rebleeding rate (28%) was slightly lower than that reported in previous studies [5,7]. Sheibani et al. [6] reported that the rate of rebleeding caused by stomach cancer was 55%. There are several reasons for the lower rate of rebleeding in our study. First, almost all patients (n=105) received intravenous proton-pump inhibitor (PPI) treatment for bleeding. PPI therapy can reduce rebleeding and mortality in acute upper GI bleeding, and tumor bleeding events were significantly reduced during the first 4 months in patients with gastric cancer receiving chemotherapy. Second, in several cases in this study, 2 or more endoscopic modalities were used in combination to achieve complete hemostasis, and 44% of the patients underwent combination endoscopic therapy. Vergara et al. [18] showed that the risk of rebleeding was lower in patients receiving combination therapy than in those receiving epinephrine alone (relative risk, 0.53; 95% confidence interval [CI], 0.35–0.81).

In the present study, the 30-day mortality rate after endoscopic therapy was 22.9%, similar to that reported in a previous study (15.9%–43%) [5,6]. There were no deaths related to the endoscopic hemostasis procedures. Median survival after initial hemostasis was significantly lower in patients with rebleeding than in those without rebleeding (2.7 vs. 3.9 months, P=0.020).

In addition to endoscopic treatment, surgery, angiography, and radiation therapy can be considered to manage bleeding associated with gastric cancer [14]. Surgery is usually


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reserved for severe, uncontrolled bleeding; data on surgery are limited but patients requiring urgent surgery for cancer-associated bleeding have a poor prognosis. In one Japanese study, patients who had major bleeding tended to have larger tumor size and a poor prognosis; 30.7% surgery-related mortality and the median survival time of 3 months after emergency surgery [19]. Data on angiographic therapy in bleeding associated with gastric cancer are also limited, because angiography is usually considered second-line treatment for actively bleeding gastric tumors when endoscopic treatment fails. Similarly, few data are available on radiation therapy for treatment of bleeding associated with gastric cancer. In one study from the USA, bleeding was controlled in 14 of 20 patients treated with palliative radiation therapy. Side effects such as nausea, neutropenia, and dehydration were observed in 20% of patients and median survival was 5.2 months [14].

Bleeding submucosal tumors of the stomach can be resected laparoscopically in some cases. For example, in a small series of 9 patients with GI stromal tumors who presented acutely, 4 of the 9 underwent successful laparoscopic resection. Patients who underwent laparoscopic resection had less postoperative pain and shorter hospital stays[6, 7]. The choice of surgical approach depends on anatomic considerations and the surgeon's expertise.

Recently, some studies reported the risk factors associated with rebleeding. Sheibani et al. [6] demonstrated that age <60 years and hemodynamic instability were risk factors associated with rebleeding in multivariate analysis (odds ratio [OR], 2.49; 95% CI, 1.06–5.81; OR, 2.42; 95% CI, 1.08–5.46, respectively). This study suggested that hemodynamic instability and young age are associated with aggressive tumor biology. Kim et al. [7] reported that transfusion with ≥5 units of RBCs was associated with early rebleeding (3 days after initial hemostasis) (OR, 4.75; 95% CI, 1.45–15.57; P=0.010). Our results are consistent with those of previous studies, and transfusion of ≥5 units of RBCs was a significant predictive factor for rebleeding after hemostasis in univariate and multivariate analyses. Age <60 years, sex, anticoagulation treatment at the time of initial bleeding, shock, hemoglobin level, and active bleeding at endoscopy were not associated with rebleeding in our study.

In addition, we tried to determine whether disease status (first diagnosis of disease, partial response or stable disease, and progressive disease) and treatment history for AGC affect treatment outcomes, rebleeding rates, or survival rates, because reduction in vascularity may occur in response to treatment. There were no significant differences in the hemostatic success and rebleeding rates between the groups, but further research is needed to clarify this issue.

Our data suggested that endoscopic therapy was effective for controlling bleeding associated with gastric cancer. In particular, APC was the most common treatment modality for endoscopic hemostasis. Transfusion of ≥5 units of RBCs was the only significant risk factor for rebleeding. Considering the different survival rates of patients with and without rebleeding, further efforts should be made to reduce the rebleeding rates. This study has some limitations in that this was a single-center, retrospective study without randomization and therefore was subject to selection bias. To overcome these limitations, future randomized controlled trials are warranted.

In conclusion, despite favorable success rates for endoscopic hemostasis in bleeding associated with gastric cancer, the 30-day rebleeding rate was 28% and OS was significantly lower in patients with rebleeding than in those without rebleeding. Massive transfusion (≥5 units of RBCs) was the only significant risk factor for rebleeding. Patients with bleeding associated with AGC who have undergone massive transfusion should be observed closely


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following endoscopic hemostasis. Further research on approaches to reduce rebleeding rate and prevent death is needed.

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