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ORIGINAL ARTICLE

Clinical Trials Study

# Systematic treatment in gastric cancer patients with overt bleeding: A propensity score matching analysis

Yan-Hong Yao, Hua Zhang, Yu Xiao, Zhen-Tao Liu, Yan-Yan Shi, Jin-Yu Yu, Qian Li, Bao-Shan Cao

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## Abstract

***BACKGROUND***

Hemorrhage, which is not a rare complication in patients with gastric cancer (GC)/gastroesophageal junction cancer (GEJC), can lead to a poor prognosis. However, no study has examined the effectiveness and safety of chemotherapy as an initial therapy for GC/GEJC patients with overt bleeding (OB).

***AIM***

To investigate the impact of OB on the survival and treatment-related adverse events (TRAEs) of GC/GEJC patients.

***METHODS***

Patients with advanced or metastatic GC/GEJC who received systematic treatment at Peking University Third Hospital were enrolled in this study. Propensity score matching (PSM) analysis was performed.

***RESULTS***

After 1:2 PSM analysis, 93 patients were assessed, including 32 patients with OB before treatment (OBBT) and 61 patients without OBBT. The disease control rate was 90.6% in the group with OBBT and 88.5% in the group without OBBT, and this difference was not statistically significant. There was no difference in the incidence of TRAEs between the group with OBBT and the group without OBBT. The median overall survival (mOS) was 15.2 months for patients with OBBT and 23.7 months for those without OBBT [hazard ratio (HR) = 1.101, 95% confidence interval (CI): 0.672-1.804, log rank $P$ = 0.701]. The mOS was worse for patients

with OB after treatment (OBAT) than for those without OBAT (11.4 months *vs* 23.7 months, HR = 1.787, 95%CI: 1.006-3.175, log rank *P* = 0.044).

***CONCLUSION***

The mOS for GC/GEJC patients with OBBT was similar to that for those without OBBT, but the mOS for patients with OBAT was worse than that for those without OBAT.

**Key Words:** Gastric cancer/gastroesophageal junction cancer; Overt bleeding; Risk factors; Systematic treatment; Overall survival



**Core Tip:** Overt bleeding (OB) is a dangerous condition in patients with advanced or metastatic gastric cancer (GC)/gastroesophageal junction cancer (GEJC). Are these patients at significant risk for systematic treatment? This study retrospectively assessed the survival and treatment-related adverse events (TRAEs) of GC/GEJC patients with OB. The median overall survival (mOS) of patients with OB before treatment (OBBT) was similar to that of patients without OBBT. Nevertheless, the mOS was worse for patients with OB after treatment (OBAT) than for those without OBAT. The incidence of grade 3-4 TRAEs between the groups with OBBT and without OBBT was similar.

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## INTRODUCTION

Gastric cancer (GC) was the fifth most common cancer and ranked fourth in terms of cancer mortality worldwide in 2020 [1]. Hemorrhage, which is not a rare complication of GC/gastroesophageal junction cancer (GEJC), affects approximately 15% of patients with GC/GEJC[2]. Bleeding not only reduces the quality of life of GC/GEJC patients but also leads to a poor prognosis, and such bleeding can affect anticancer treatment and may even be life-threatening if it fails to stop in a timely manner[3,4].

The risk factors for bleeding in patients with GC/GEJC vary and include age, smoking history, chronic disease and so on[2,5,6]. Radical gastrectomy is ideal for early-stage GC/GEJC with overt bleeding (OB)[7], but there is rarely a curable chance for patients with advanced or metastatic GC/GEJC[8]. Successful hemostasis *via* endoscopic therapy strategies is achieved in 67%-100% of GC patients with OB. However, the rebleeding rate is high, ranging from 16% to 80%, and the median overall survival (mOS) is poor, ranging from 1.0 to 6.5 months[3,9,10]. Endoscopic hemostasis is prone to failure for bleeding lesions larger than 2 cm[11]. The success rate of hemostasis by transcatheter embolotherapy in GC patients with bleeding is 40%-100%. The rebleeding rate is 16%-41%, and the mOS is no more than three months for unresectable disease[10,11]. Prior studies have reported that the rate of successful hemostasis by palliative radiotherapy ranges from 50% to 80%. The response duration and the mOS are 0.9-3.7 months and 2.1-5.3 months, respectively, for unresectable GC [10,12,13]. Above all, the rebleeding rate is high, and survival is poor after local hemostasis therapy for unresectable GC with bleeding. Systematic therapy is the preferred treatment strategy for advanced or metastatic GC/GEJC. However, there are no reports about the efficacy and safety of chemotherapy as an initial therapy for GC/GEJC patients with OB.

This retrospective study aimed to investigate the impact of OB on treatment-related adverse events (TRAEs) in GC/GEJC patients receiving systematic anticancer treatment, evaluate the risk factors for OB after treatment (OBAT), and assess the influence of OB before treatment (OBBT) and OBAT on OS.

## MATERIALS AND METHODS

### *Data sources and study patients*

We retrospectively enrolled patients who were diagnosed with advanced or metastatic GC/GEJC from January 1, 2013 to December 31, 2021, at the Department of Medical Oncology and Radiation Sickness of Peking University Third Hospital. The patient eligibility criteria were as follows: (1) Were older than 18 years; (2) Had a histologically confirmed diagnosis of advanced or metastatic GC/GEJC; (3) Received systematic therapy as initial anticancer treatment, including chemotherapy, targeted therapy or immune checkpoint inhibitor (ICI); and (4) Had no history of gastrectomy before systematic therapy. The exclusion criteria were as follows: (1) Had incomplete clinical data; and (2) Diagnosed as Siewert type I esophageal cancer.

The patients' information collected from the database was as follows: Age, sex, height, weight, Eastern Corporative Oncology Group Performance Status (ECOG-PS), chronic disease status, drinking history, smoking history, primary tumor location, clinical stage according to the 8th edition of the American Joint Committee on Cancer (AJCC) cancer staging manual, OB status, therapeutic strategy, best response to treatment, TRAEs and so on.

### Assessments and outcomes

The diagnosis of OB was that the following conditions occurred within one month before the first dose of systematic treatment: (1) Melena, he-matemesis or hematochezia caused by a gastric lesion; or (2) Gastric hemorrhage confirmed by endoscopy. This study only analyzed the impact of gastric OB (not including occult bleeding) on patients. The radiographic best response to treatment was assessed by clinicians as complete response (CR), partial response (PR), stable disease (SD), no CR or no progressive disease (PD), or PD on the basis of response evaluation criteria in solid tumors 1.1. The objective response rate (ORR) was defined as the proportion of patients with the best response CR or PR. The disease control rate (DCR) was defined as the proportion of patients whose best response was CR, PR, no CR or no PD, or SD. Patients were followed up at regular intervals. The criterion for terminating follow-up was death for any reason. OS was defined as the time from the first cycle of systematic therapy to death from any cause. TRAEs were evaluated according to the National Cancer Institute Common Toxicity Criteria version 4.0.

Age, sex, smoking history, comorbidities, nutritional status, and lesion status are reported to be risk factors for gastric bleeding in patients with gastrointestinal cancer. Therefore, we analyzed the relationships between rebleeding and several of these factors, including age, sex, personal history, such as smoking history and drinking history, common chronic diseases, such as hypertension, coronary heart disease, cerebral infarction, diabetes, chronic renal failure, and chronic liver disease, indications of nutritional status such as weight loss, body mass index (BMI), and cancer stage. We had found that the ECOG-PS score was a significant predictor of therapy tolerance and efficacy in our daily work, so we analyzed the associations between the ECOG-PS score and OBAT. BMI was calculated by dividing the body weight in kilograms by the square of the height in meters and was divided into three levels according to the criteria of the Chinese obesity scale[14]: Less than 18.5, 18.5 to 23.9, and greater than 23.9. The proportion of weight loss was calculated by dividing the weight lost by the patient's base body weight before weight loss. Weight loss was classified into two levels according to the cutoff point for the diagnostic criterion of cachexia[15]: Less than 5% and greater than 5%.

### Statistical analysis

We used SPSS version 25.0 (International Business Machines, New York, NY, United States) to analyze the data and considered that differences to be statistically significant if the two-sided *P* values were less than 0.05. The classified variables were assessed by the $\chi^2$ test or Fisher's exact test. A binary logistic regression model (entry method) was used to identify items independently associated with OBAT. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Survival curves were estimated *via* the Kaplan-Meier method with the log-rank test. Hazard ratios (HRs) and 95%CIs were calculated *via* the Cox proportional hazards model, and a check on the assumption of proportional risk was evaluated.

### Propensity score matching analysis

Propensity score matching (PSM) analysis was performed between the group with OBBT and the group without OBBT to reduce the impact of bias. The propensity score model was estimated *via* a logistic regression model that adjusted for variables including sex, age, BMI, weight loss, smoking history, drinking history, chronic disease status, ECOG-PS score, primary tumor location, and cancer stage. PSM was performed *via* a 1:2 matching method and nearest-neighbour matching without replacement with a caliper width of 0.02. A standard mean difference of less than 0.2 after matching was set to indicate good balance.

## RESULTS

### Enrolled patients

From 560 patients with GC/GEJC from January 1, 2013 to December 31, 2021, 171 patients were enrolled in the study (Figure 1). The most common reason for exclusion was radical gastrectomy at an early stage. The characteristics of the included patients are listed in Table 1. Approximately three-quarters (129/171) of the patients were at stage IV, and the others were at stage III. Forty-one (24.0%) of the 171 included patients had OBBT. The patient characteristics in the group with OBBT and the group without OBBT were not balanced (Table 1). After a 1:2 PSM analysis, there were 32 patients in the group with OBBT and 61 patients without OBBT, for which the patient characteristics were well balanced (Table 2). The median follow-up period was 17.1 months in the group with OBBT and 25.2 months in the group without OBBT.

### Response to systematic anticancer treatment and TRAEs

All the patients received systematic anticancer treatment, including a chemotriplet regimen (fluorouracil, platinum and taxane), a chemodoublet-based regimen (chemodoublet regimen plus/minus targeted therapy or ICI), and fluorouracil or ICI monotherapy. Among patients with OBBT, 75.0% (24/32) received a chemodoublet-based regimen, 18.8% (6/32) received a triplet regimen, and 6.3% (2/32) received fluorouracil or ICI monotherapy. In the group without OBBT, a chemotriplet regimen and a chemodoublet-based regimen were used in 49.2% (30/61) and 49.2% (30/61) of the patients, respectively (Table 3).

**Table 1 Baseline characteristics of patients before propensity score matching, *n* (%)**

| Variables | Patients with OBBT (*n* = 41) | Patients without OBBT (*n* = 130) | *P* value | SMD |
|---|---|---|---|---|
| Gender | | | | |
| Male | 30 (73.2) | 94 (72.3) | 0.914 | 0.019 |
| Female | 11 (26.8) | 36 (27.7) | | |
| Age (range, years) | 65 (47-85) | 64 (29-83) | 0.003 | 0.486 |
| BMI (range, kg/m$^2$) | 21.0 (15.2-27.2) | 22.0 (16.0-33.6) | 0.153 | 0.259 |
| Weight loss (range, %) | 8.3 (0-37.4) | 5.7 (0-26.0) | 0.044 | 0.399 |
| Smoking history | | | | |
| Yes | 15 (36.6) | 60 (46.2) | 0.282 | 0.195 |
| No | 26 (63.4) | 70 (53.8) | | |
| Drinking history | | | | |
| Yes | 7 (17.1) | 17 (13.1) | 0.521 | 0.112 |
| No | 34 (82.9) | 113 (86.9) | | |
| [1]Chronic disease | | | | |
| Yes | 16 (39.0) | 42 (32.3) | 0.428 | 0.141 |
| No | 25 (61.0) | 88 (67.7) | | |
| ECOG-PS | | | | |
| 0 | 1 (2.5) | 5 (3.8) | 0.010 | 0.473 |
| 1 | 32 (78.0) | 119 (91.5) | | |
| 2 | 8 (19.5) | 6 (4.6) | | |
| Primary tumor location | | | | |
| Body | 15 (36.6) | 74 (56.9) | 0.061 | 0.429 |
| Pylorus | 13 (31.7) | 24 (18.5) | | |
| Cardia | 13 (31.7) | 32 (24.6) | | |
| Cancer stage (AJCC 8$^{th}$) | | | | |
| Stage III | 9 (22.0) | 33 (25.4) | 0.656 | 0.081 |
| Stage IV | 32 (78.0) | 97 (74.6) | | |

[1]Consisting of hypertension, coronary heart disease, cerebral infarction, diabetes, chronic renal failure, and chronic liver disease.
OBBT: Overt bleeding before treatment; SMD: Standard mean difference; BMI: Body mass index; ECOG-PS: Eastern Corporative Oncology Group Performance Status; AJCC: American Joint Committee on Cancer.

In this study, the ORR in the group with OBBT was greater than that in the group without OBBT [34.4% (11/32) *vs* 16.4% (10/61), $P = 0.049$]. The DCR was 90.6% in the group with OBBT and 88.5% in the group without OBBT, and this difference was not statistically significant. The rates of radical surgery after systematic therapy were 15.6% in the group with OBBT and 14.8% in the group without OBBT (Table 3).

The most common TRAEs were gastrointestinal disorders (nausea, vomiting, decreased appetite, constipation, and diarrhea) and hematological toxicity (leukopenia/neutropenia and thrombocytopenia). The incidence of all-grade and grade ≥ 3 TRAEs did not differ between the two groups (Table 4).

### *Analysis of OBAT in GC/GEJC patients*

In the matched population, 17.2% (16/93) of patients experienced OBAT, including ten patients with OBBT and six without OBBT. $\chi^2$ tests (Table 5) revealed that OBBT [62.5% (10/16) *vs* 28.6% (22/77), $P = 0.009$] was a risk factor for OBAT. After adjusting for factors whose *P* value was less than 0.25, including drinking history, chronic disease, primary tumor location, OBBT status, and radiographic best response to systematic therapy, logistic regression analysis revealed that drinking history ($P = 0.027$), tumors located in the body ($P = 0.028$), presence of OBBT ($P = 0.006$) and radiographic best response PD ($P = 0.038$) were independent, positive influencing factors for OBAT (Table 5).

**Table 2 Baseline characteristics of patients after propensity score matching, *n* (%)**

| Variables | Patients with OBBT (*n* = 32) | Patients without OBBT (*n* = 61) | *P* value | SMD |
|---|---|---|---|---|
| Gender | | | | |
| Male | 23 (71.9) | 39 (63.9) | 0.440 | 0.171 |
| Female | 9 (28.1) | 22 (36.1) | | |
| Age (range, years) | 64.5 (47-80) | 67 (29-81) | 0.629 | 0.100 |
| BMI (range, kg/m$^2$) | 22.8 (15.9-27.2) | 21.8 (16.0-28.1) | 0.757 | 0.066 |
| Weight loss (range, %) | 7.5 (0-33.3) | 6.5 (0-23.80) | 0.671 | 0.092 |
| Smoking history | | | | |
| Yes | 12 (37.5) | 22 (36.1) | 0.891 | 0.030 |
| No | 20 (62.5) | 39 (63.9) | | |
| Drinking history | | | | |
| Yes | 5 (15.6) | 8 (13.1) | 0.986 | 0.072 |
| No | 27 (84.4) | 53 (86.9) | | |
| [1]Chronic disease | | | | |
| Yes | 13 (40.6) | 25 (41.0) | 0.973 | 0.007 |
| No | 19 (59.4) | 36 (59.0) | | |
| ECOG-PS | | | | |
| 0 | 1 (3.1) | 2 (3.3) | 0.943 | 0.076 |
| 1 | 29 (90.6) | 54 (88.5) | | |
| 2 | 2 (6.3) | 5 (8.2) | | |
| Primary tumor location | | | | |
| Body | 12 (37.5) | 26 (42.6) | 0.891 | 0.105 |
| Pylorus | 9 (28.1) | 16 (26.2) | | |
| Cardia | 11 (34.4) | 19 (31.1) | | |
| Cancer stage (AJCC 8$^{th}$) | | | | |
| Stage III | 6 (18.8) | 13 (21.3) | 0.771 | 0.064 |
| Stage IV | 26 (81.2) | 48 (78.7) | | |

[1]Consisting of hypertension, coronary heart disease, cerebral infarction, diabetes, chronic renal failure, and chronic liver disease.
OBBT: Overt bleeding before treatment; SMD: Standard mean difference; BMI: Body mass index; ECOG-PS: Eastern Corporative Oncology Group Performance Status; AJCC: American Joint Committee on Cancer.

### *Survival analysis*

As of June 20, 2024, 71 (76.3%) deaths had occurred, and four patients were lost to follow-up. The mOS was 15.2 months for patients with OBBT and 23.7 months for those without OBBT (HR = 1.101, 95%CI: 0.672-1.804, *P* = 0.701) (Figure 2A). The mOS was worse for the GC/GEJC patients with OBAT than for those without OBAT (11.4 months *vs* 23.7 months, *P* = 0.044) (Figure 2B), and the HR for death in the group with OBAT, as compared with the group without OBAT, was 1.787 (95%CI: 1.006-3.175).

## DISCUSSION

OB in patients with advanced or metastatic GC/GEJC patients is a severe and potentially dangerous event that may affect anticancer treatment. Although many studies have reported several treatment modalities for GC/GEJC with OB, the analysis of chemotherapy efficacy and long-term survival for the patients still needs to be met. Our study showed that the safety of chemotherapy for hemostatic GC/GEJC patients was similar to that of patients without OB. Controlled bleeding after chemotherapy did not affect survival in patients with OBBT, but bleeding or rebleeding after treatment decreased the survival.

**Table 3 Therapeutic regimen and best response in patients after propensity score matching, *n* (%)**

| Characteristics | Total (*n* = 93) | Patients with OBBT (*n* = 32) | Patients without OBBT (*n* = 61) | *P* value |
|---|---|---|---|---|
| Therapeutic regimen | | | | |
| Chemotriplet regimen | 36 (38.7) | 6 (18.8) | 30 (49.2) | 0.006 |
| [1]Chemodoublet-based regimen | 54 (58.1) | 24 (75.0) | 30 (49.2) | |
| [2]Monotherapy | 3 (3.2) | 2 (6.3) | 1 (1.6) | |
| Radiographic best response | | | | |
| CR or PR | 21 (22.6) | 11 (34.4) | 10 (16.4) | 0.157 |
| SD/no CR or no PR | 62 (66.7) | 18 (56.2) | 44 (72.1) | |
| PD | 7 (7.5) | 3 (9.4) | 4 (6.6) | |
| NA | 3 (3.2) | 0 | 3 (4.9) | |
| Radical surgery after systematic treatment | | | | |
| Yes | 14 (15.1) | 5 (15.6) | 9 (14.8) | 0.911 |
| No | 79 (84.9) | 27 (84.4) | 52 (85.2) | |

[1]Regimen included a chemodoublet regimen, a chemodoublet plus targeted therapy regimen, and a chemodoublet plus immune checkpoints inhibitor regimen.
[2]Fluorouracil monotherapy or immune check points inhibitor monotherapy.
OBBT: Overt bleeding before treatment; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; NA: Not available.

**Table 4 Treatment-related adverse events (≥ 5%) in patients after propensity score matching, *n* (%)**

| | Patients with OBBT (*n* = 32) | | Patients without OBBT (*n* = 61) | |
|---|---|---|---|---|
| | Any grade | Grade ≥ 3 | Any grade | Grade ≥ 3 |
| Any TRAEs | 32 (100) | 13 (40.6) | 55 (90.2) | 23 (37.7) |
| Leukopenia/Neutropenia | 23 (71.9) | 5 (15.6) | 39 (64.0) | 13 (21.3) |
| Constipation | 18 (56.3) | 0 | 33 (54.1) | 0 |
| Peripheral sensory neuropathy | 17 (53.1) | 1 (3.1) | 30 (49.2) | 3 (4.9) |
| Fatigue | 16 (50.0) | 0 | 30 (49.2) | 0 |
| Decreased appetite | 14 (43.8) | 1 (3.1) | 29 (47.5) | 0 |
| Thrombocytopenia | 13 (40.6) | 6 (18.8) | 16 (26.2) | 2 (3.3) |
| Nausea | 12 (37.5) | 1 (3.1) | 27 (44.3) | 4 (6.5) |
| Vomiting | 4 (12.5) | 2 (6.3) | 13 (21.3) | 4 (6.5) |
| Diarrhea | 4 (12.5) | 2 (6.3) | 14 (23.0) | 5 (8.2) |
| Infection | 3 (9.4) | 0 | 5 (8.2) | 0 |
| Oral mucosal ulcer | 2 (6.3) | 0 | 6 (9.8) | 2 (3.3) |
| Febrile neutropenia | 1 (3.1) | 1 (3.1) | 6 (9.8) | 6 (9.8) |
| Liver injury | 1 (3.1) | 0 | 4 (6.5) | 1 (1.6) |

OBBT: Overt bleeding before treatment; TRAEs: Treatment-related adverse events.

Our research revealed that the occurrence of TRAEs was similar to that reported in previous studies[16,17], and the incidence of all grade and grade 3-4 TRAEs in the group with OBBT was not greater than that in the group without OBBT, which was better than expected. Most patients with OBBT received intravenous injection treatment with a chemodoublet regimen. For the chemodoublet regimen strategy, the incidence of Grade3-4 TRAEs was lower than that for the chemotriplet regimen strategy[18,19], and gastrointestinal TRAEs were milder for the injection regimen strategy than for the oral regimen[20]. Another reason may be that the dose of the regimen for some patients with OBBT was appropriately reduced by 10%-25%. The ORR in this study was poorer than that reported in previous clinical trials[16-19], because, in

**Table 5 Analysis of factors related to overt bleeding after treatment, *n* (%)**

| Characteristics | $\chi^2$ test | | | Binary logistic analysis | |
|---|---|---|---|---|---|
| | Patients with OBAT (*n* = 16) | Patients without OBAT (*n* = 77) | *P* value | OR (95%CI) | *P* value |
| Gender | | | | | |
| Male | 12 (75.0) | 50 (64.9) | 0.565 | | |
| Female | 4 (25.0) | 27 (35.1) | | | |
| Age (year) | | | | | |
| < 65 | 7 (43.8) | 35 (45.5) | 0.901 | | |
| ≥ 65 | 9 (56.3) | 42 (54.5) | | | |
| Smoking history | | | | | |
| No | 12 (75.0) | 47 (61.0) | 0.396 | | |
| Yes | 4 (25.0) | 30 (39.0) | | | |
| Drinking history | | | | | |
| No | 12 (75.0) | 68 (88.3) | 0.228 | Reference | |
| Yes | 4 (25.0) | 9 (11.7) | | 8.512 (1.279-56.655) | 0.027 |
| [1]Chronic disease | | | | | |
| No | 7 (43.8) | 48 (62.3) | 0.169 | Reference | |
| Yes | 9 (56.3) | 29 (37.7) | | 3.929 (0.974-15.855) | 0.055 |
| ECOG-PS | | | | | |
| 0 or 1 | 14 (87.5) | 72 (93.5) | 0.346 | | |
| 2 | 2 (12.5) | 5 (6.5) | | | |
| BMI (kg/m$^2$) | | | | | |
| ≤ 18.4 | 2 (12.5) | 9 (11.7) | 0.668 | | |
| 18.5-23.9 | 8 (50.0) | 47 (61.0) | | | |
| ≥ 24.0 | 6 (37.5) | 21 (27.3) | | | |
| Weight loss | | | | | |
| < 5% | 8 (50.0) | 31 (40.3) | 0.472 | | |
| ≥ 5% | 8 (50.0) | 46 (59.7) | | | |
| Primary tumor location | | | | | |
| Pylorus | 2 (12.5) | 23 (29.9) | 0.168 | Reference | |
| Body | 10 (62.5) | 28 (36.4) | | 10.104 (1.287-79.302) | 0.028 |
| Cardia | 4 (25.0) | 26 (33.8) | | 1.773 (0.209-15.072) | 0.600 |
| Cancer stage (AJCC 8$^{th}$) | | | | | |
| Stage III | 4 (25.0) | 15 (19.5) | 0.734 | | |
| Stage IV | 12 (75.0) | 62 (80.5) | | | |
| OBBT status | | | | | |
| No | 6 (37.5) | 55 (71.4) | 0.009 | Reference | |
| Yes | 10 (62.5) | 22 (28.6) | | 7.015 (1.726-28.505) | 0.006 |
| Therapeutic regimen | | | | | |
| Chemotriplet regimen | 5 (31.3) | 31 (40.3) | 0.761 | | |
| [2]Chemodouble- based regimen | 11 (68.8) | 43 (55.8) | | | |
| [3]Monotherapy | 0 | 3 (3.9) | | | |

| | | | | | |
|---|---|---|---|---|---|
| Grade 3/4 TRAEs | | | | | |
| No | 10 (62.5) | 47 (61.0) | 0.913 | | |
| Yes | 6 (37.5) | 30 (39.0) | | | |
| Radiographic best response | | | | | |
| CR or PR | 2 (12.5) | 19 (24.7) | 0.149 | Reference | |
| SD/no CR or no PR | 10 (62.5) | 52 (67.5) | | 2.763 (0.462-16.504) | 0.265 |
| PD | 3 (18.8) | 4 (5.2) | | 14.039 (1.158-170.260) | 0.038 |
| NA | 1 (6.3) | 2 (2.6) | | 32.043 (1.248-822.685) | 0.038 |

[1]Consisting of hypertension, coronary heart disease, cerebral infarction, diabetes, chronic renal failure, and chronic liver disease.
[2]Regimen included a chemo-doublet regimen, a chemo-doublet plus targeted therapy regimen, and a chemo-doublet plus immune checkpoints inhibitor regimen.
[3]Fluorouracil monotherapy or immune checkpoints inhibitor monotherapy.
OBAT: Overt bleeding after treatment; OR: Odds ratio; CI: Confidence interval; ECOG-PS: Eastern Corporative Oncology Group Performance Status; BMI: Body mass index; OBBT: Overt bleeding before treatment; TRAEs: Treatment-related adverse events; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; NA: Not available.

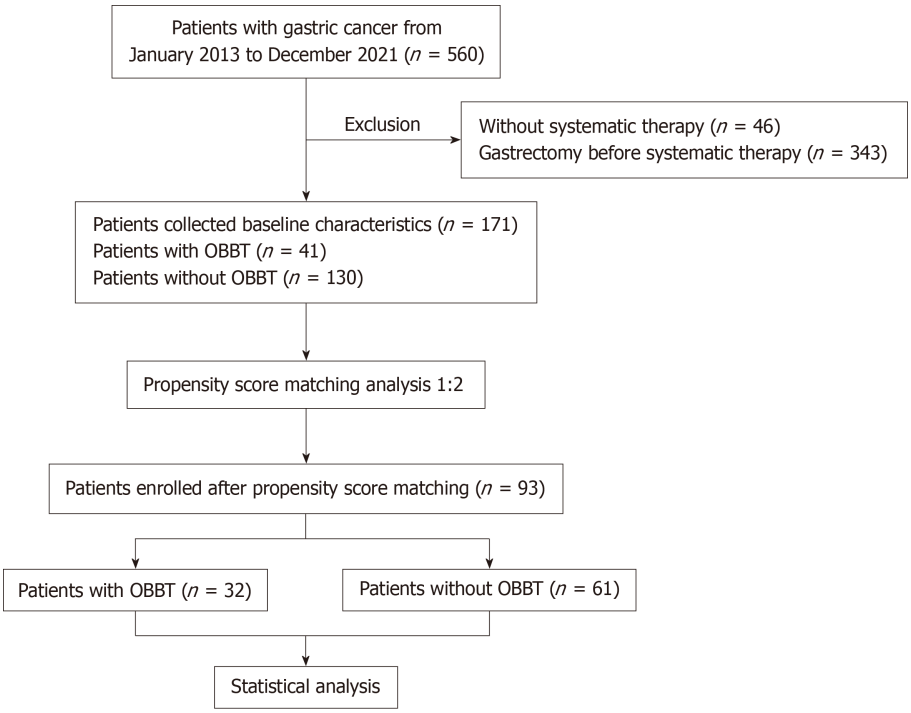


**Figure 1 Flow diagram of selection of eligible patients.** OBBT: Overt bleeding before treatment.

the current study, many patients could not be evaluated by the ORR because of the lack of target lesions.

The mOS of patients with OB in the present study was longer than that of patients who received hemostatic strategies such as endoscopic hemostasis, transcatheter embolotherapy, and radiotherapy in several other studies[3,4,10,21]. On the one hand, systematic therapy may be more effective than local therapy for advanced or metastatic GC/GEJC. On the other hand, this study enrolled patients receiving systematic therapy who were usually hemostatic or hemodynamically stable and had a better performance status.

Neoplasms usually result in bleeding from diffuse mucosal erosion or ulceration or from cancer invasion into underlying vessels of the stomach wall. The process can be exacerbated or accelerated by many risk factors. The current study revealed that drinking history was a risk factor for OBAT in GC/GEJC patients. Researchers have reported that alcohol consumption over a long period of time can stimulate the gastric mucosa, and increased the risk of GC[22-24]. In this study, most patients had stopped drinking upon the diagnosis of malignancy, and thus, they had not experienced acute alcohol damage to the gastric mucosa during anticancer treatment. Nevertheless, the chronic mucosal changes caused by long-term alcohol stimulation may exacerbate the occurrence of hemorrhage in GC patients with gastric mucosa lesions after chemotherapy.

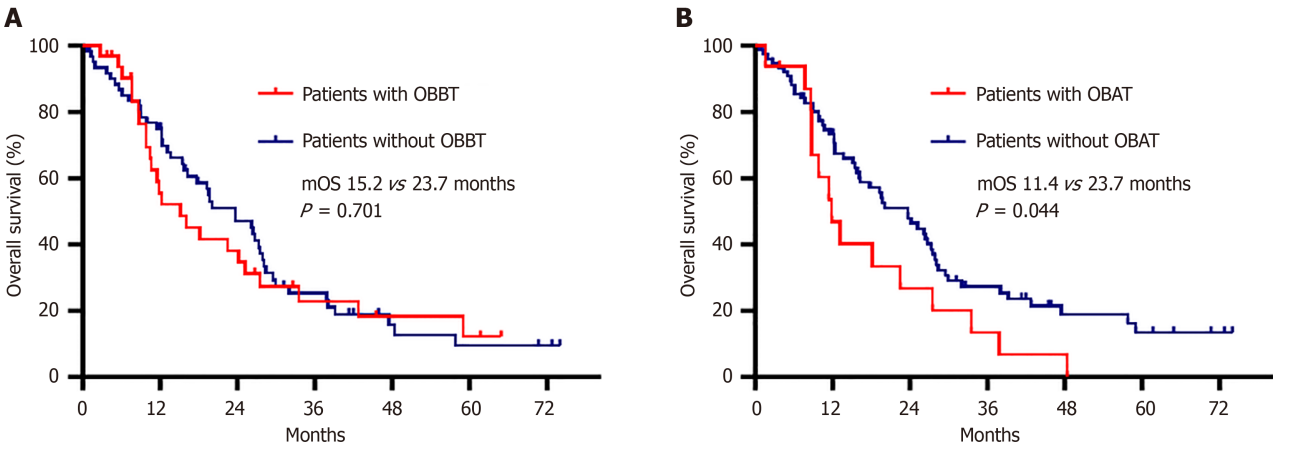


**Figure 2 Kaplan Meier curves of overall survival.** A: Overall survival (OS) of gastric cancer (GC)/gastroesophageal junction cancer (GEJC) patients according to overt bleeding before treatment; B: OS of GC/GEJC patients according to overt bleeding after treatment. OBBT: Overt bleeding before treatment; OBAT: Overt bleeding after treatment; mOS: Median overall survival.

Prior studies has shown that an ECOG-PS ≤ 1 was associated with better chemotherapy tolerance than an ECOG-PS = 2 [25]. The ECOG-PS of most patients was 0 or 1 in this study, and only a few patients had an ECOG-PS = 2. However, the rate of ECOG-PS = 2 was significantly greater in the group with OBBT than in the group without OBBT (19.5% *vs* 4.6%, *P* = 0.010) before PSM. To reduce the bias of the ECOG-PS on TRAEs in this study, we added the ECOG-PS score as a matching variable in the PSM analysis. In this study, the rates of all grade AEs and grade ≥ 3 AEs were 93% (80/86) and 37.2% (32/86) in patients with ECOG-PS ≤ 1, and 100% (7/7) and 57.1% (4/7) in patients with ECOG-PS = 2, respectively, without statistical significance (*P* > 0.05).

The rebleeding rate was 31.3% (10/32) for patients with OBBT in the current study, similar to other studies[3,10]. The bleeding rate varied across different primary tumor locations in the study. A previous study reported similar phenomena [2]. The difference could be related to unequal erosion caused by the acidic medium of the stomach, which was different in each stomach part. Because all patients in this study were at AJCC stage III-IV (T3-T4 and N +), we did not analyze the relationships between the bleeding rate and the T, N or tumor stage categories.

The occurrence of OBAT in patients with OBBT was greater than that in patients without OBBT [31.3% (10/32) *vs* 9.8% (6/61), *P* = 0.009]. Although OBBT was a risk factor for OBAT, only 31.3% of patients with OBBT experienced OBAT, and most patients with OBBT achieved hemostasis after systematic therapy. This may explain why OBAT was associated with shorter survival, whereas OBBT did not affect the mOS.

There were several shortcomings in this study. First, it was retrospective, and there may have been omissions in data collection and selection bias. Second, the study was conducted at a single center and the sample size was small. Finally, the various regimens for the patients may have led to analytical bias with respect to TRAEs and survival. Ultimately, we look forward to conducting a prospective study in GC patients with OB to identify more effective treatments.

## CONCLUSION

In conclusion, this study revealed that the mOS for GC/GEJC patients who received systematic treatment with OBBT was similar to that for those without OBBT, but the mOS for GC/GEJC patients with OBAT was worse than that for GC/GEJC patients without OBAT. The DCR and TRAEs were similar for patients with and without OBBT. Therefore, we should actively control bleeding and choose appropriate treatment plans for GC/GEJC patients with OBBT. It is also essential to prevent bleeding in GC/GEJC patients after systematic treatment in order to prolong their survival.

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## FOOTNOTES

**Author contributions:** Cao BS and Yao YH conceived and designed the study; Yao YH, Liu ZT, Yu JY, Xiao Y and Li Q performed data collection; Yao YH and Zhang H performed statistical analysis; All the authors contributed to the data interpretation; Yao YH written the first draft of the manuscript; All the authors revised and edited the final manuscript.

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