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The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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ORIGINAL ARTICLE

Retrospective Study

Risk factors for hemocoagulase-associated hypofibrinogenemia in patients with gastrointestinal bleeding

Fei Zou, Mian-Tao Wu, Yong-Yi Wang

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Abstract

BACKGROUND

With the widespread use of hemocoagulase in patients with gastrointestinal bleeding, clinicians have become increasingly concerned about coagulation disorders associated with this medication. Risk factors for hypofibrinogenemia associated with hemocoagulase are poorly understood.

AIM

To determine risk factors for hemocoagulase-associated hypofibrinogenemia in patients with gastrointestinal bleeding.

METHODS

We performed a retrospective analysis of the medical documentation of hospitalized patients treated with hemocoagulase for gastrointestinal bleeding. Hypofibrinogenemia was defined as a decrease in plasma fibrinogen concentration to less than 2.0 g/L. The included patients were divided into two groups: acquired hypofibrinogenemia group and non-hypofibrinogenemia group. We used logistic regression analysis to identify potential risk factors and established risk assess-

ment criteria by employing a receiver operating characteristic curve.

RESULTS

There were 36 patients in the acquired hypofibrinogenemia group and 73 patients in the non-hypofibrinogenemia group. The hypofibrinogenemia group showed higher rates of intensive care unit admissions (P = 0.021), more female patients (P = 0.005), higher in-hospital mortality (P = 0.027), larger hemocoagulase doses (P = 0.026), more Packed Red Cells transfusions (P = 0.024), and lower baseline fibrinogen levels (P < 0.000). Binary logistic regression was employed to examine the risk factors associated with acquired hypofibrinogenemia. The analysis revealed that baseline fibrinogen [odds ratio (OR) 0.252, 95%CI: 0.137-0.464, P < 0.000], total hemocoagulase doses (OR 1.074, 95%CI: 1.015-1.137, P = 0.014), and female gender (OR 2.856, 95%CI: 1.015–8.037, P = 0.047) were statistically significant risk factors.

CONCLUSION

Higher doses of total hemocoagulase, female gender, and a lower baseline fibrinogen level were risk factors for hemocoagulase-associated hypofibrinogenemia in patients with gastrointestinal bleeding.

Key Words: Hemocoagulase; Gastrointestinal bleeding; Hypofibrinogenemia; Risk factors; Snake venom

Core Tip: In order to identify risk factors for hemocoagulase-associated hypofibrinogenemia, a retrospective study analyzing data from 109 patients with gastrointestinal bleeding was conducted. We found that higher doses of total hemocoagulase, female gender, and a lower baseline fibrinogen level were risk factors for hemocoagulase-associated hypofibrinogenemia in patients with gastrointestinal bleeding.

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INTRODUCTION

Gastrointestinal bleeding (GIB) encompasses various instances of bleeding within the gastrointestinal tract. Manifestations of GIB, particularly when characterized by a rapid blood loss, may include vomiting red blood, vomiting black blood, bloody stool, or black stool[1,2]. Additional symptoms may involve abdominal discomfort, respiratory distress, a pallid complexion, or episodes of syncope. It is noteworthy that individuals experiencing minimal blood loss may remain asymptomatic[1,2].

GIB is commonly classified into three types: Upper GIB (UGIB), lower GIB (LGIB), and middle GIB (MGIB)[1,2]. Causes of UGIB include peptic ulcer disease, esophageal varices resulting from liver cirrhosis and cancer, among other factors[2]. Causes of LGIB involve hemorrhoids, cancer, and inflammatory bowel disease, among other contributing factors[2]. Causes of MGIB comprise inflammatory bowel disease, Meckel's diverticulum, and small bowel neoplasms[2,3]. The primary interventions for GIB include resuscitation, intravenous fluids, use of proton pump inhibitors, and blood transfusions. Endoscopy of the upper or lower gastrointestinal tract is typically recommended within 24 hours, facilitating both diagnosis and treatment[4].

Hemocoagulase, a hemostatic preparation originating from snake venom, is widely used for bleeding disorders in China. Currently, several hemocoagulase products have received approval from China's National Medical Products Administration[5-7]. These products consist of Slounase (based on viper venom), Hemocoagulase for injection (based on *Agkistrodon halys pallas* venom), Haemocoagulase Agkistrodon for injection (based on *Agkistrodon acutus* venom), and Hemocoagulase *Bothrops Atrox* for injection (based on *Bothrops atrox* venom)[5-7]. These hemocoagulase agents can effectively treat GIB, traumatic bleeding, surgical hemorrhage, and other bleeding disorders[8,9]. Their proven efficacy lies in diminishing bleeding duration and transfusion needs[5,8,9].

Hemostasis by hemocoagulase is achieved through two primary mechanisms: Enzymatic cleavage of fibrinogen's α-subunit into α-peptide and fibrin, followed by polymerization into insoluble fibrin polymers and fibers facilitated by factor XIII. Additionally, hemocoagulase suppresses factor XIII release, thereby reducing the likelihood of thrombus formation[10,11].

In treating GIB, hemocoagulase is an effective agent, and can be administered both intravenously and locally *via* endoscopy[5,8-10]. Nevertheless, it is important to emphasize that the utilization of hemocoagulase has the potential to induce acquired hypofibrinogenemia. This, in turn, may contribute to a serious exacerbation of bleeding manifestations. Although there are documented cases of this complication, the risk factors for hypofibrinogenemia induced by hemocoagulase administration are not well understood[9,12,13]. Our research aimed to address this knowledge gap by exploring

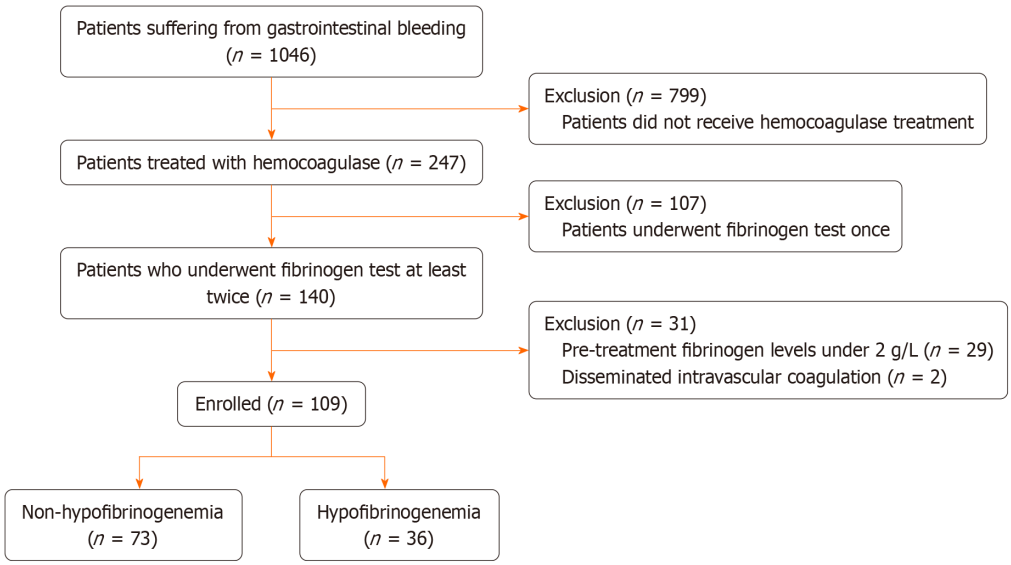

Figure 1 Flow diagram of this study.

potential risk factors associated with hemocoagulase-induced hypofibrinogenemia in GIB patients. We hope that this study will provide meaningful insights to healthcare practitioners.

MATERIALS AND METHODS

This retrospective investigation, carried out at the First Affiliated Hospital of Chongqing Medical and Pharmaceutical College, was a single-center observational cohort study. The study received approval from the hospital's Medical Ethics Committee, adhering to the ethical principles described in the Declaration of Helsinki. Due to the study's retrospective nature, the necessity to obtain informed consent was exempted[14].

Design and study population

We identified 1046 in-patients suffering from GIB between July 2020 and July 2023. Of these patients, 937 were excluded according to the following criteria: (1) Lack of hemocoagulase treatment; (2) Absence of coagulation status monitoring despite being treated with hemocoagulase; (3) Pre-treatment fibrinogen levels less than 2 g/L; and (4) Diagnosed with disseminated intravascular coagulation. To determine the risk factors associated with hemocoagulase-induced hypofibrinogenemia, we conducted a case-control study, analyzing data from patients who experienced GIB and received hemocoagulase therapy. Acquired hypofibrinogenemia was our principal outcome. Using this outcome as a criterion, we partitioned patients into two groups: Those exhibiting hypofibrinogenemia and those not presenting this condition (Figure 1). We then investigated the correlation between hemocoagulase-induced hypofibrinogenemia and pertinent variables such as patient demographics, causes of bleeding, and laboratory tests, among others.

Data collection

We extracted patients' clinical data from the digital medical record system. Subsequently, we analyzed the data comprising demographics (age, sex, body mass index), cumulative hemocoagulase dosage, duration of hemocoagulase use, GIB etiological factors, admission to the intensive care unit (ICU), concomitant medications, site of bleeding, in-patient mortality, transfusions and laboratory tests.

Definitions

The fibrinogen assay used in this study had a reference range of 2-4 g/L. Consistent with the laboratory's established parameters, we defined hypofibrinogenemia as any plasma fibrinogen concentration lower than 2 g/L. This disorder was subsequently categorized into mild (ranging from 1 to 2 g/L), moderate (ranging from 0.5 to 1 g/L), and severe (lower than 0.5 g/L) phases[15]. Additionally, we defined severe blood loss as hemorrhage leading to hemorrhagic shock or any extent of blood loss causing unstable vital signs[1,2].

Hemocoagulase preparations, dosage and administration route

We utilized the hemocoagulase agent known as Hemocoagulase for Injection (Avanc Pharma, Jinzhou, Liaoning, China). Each Klobusitzky unit (KU) of this hemocoagulase was administered intravenously after diluting in 10 mL of 0.9% saline solution. The hemocoagulase could also be injected intramuscularly after diluting in 2-5 mL of the same saline solution. The administration frequency varied from one to five times daily depending on the individual patient's health status.

Statistical analysis

We employed SPSS version 23.0 for data analysis, and a P value less than 0.05 was considered statistically significant. Missing data were replaced using the series mean. Continuous variables, which were not normally distributed, were delineated as medians along with interquartile ranges; categorical variables were represented as rates (in percentages). We used the χ^2 test or Fisher's exact test to compare categorical variables; the Mann-Whitney U test was used to evaluate continuous variables that were not normally distributed. Variables that displayed significant differences between the hypofibrinogenemia group and non-hypofibrinogenemia group were incorporated into a multivariate logistic regression model to determine possible risk factors for hemocoagulase-associated hypofibrinogenemia. To predict hypofibrinogenemia, the receiver operating characteristic (ROC) curve was utilized, and parameters (the optimal cut-off, sensitivity, and specificity) within the ROC curve were determined using the Youden index.

RESULTS

A total of 109 patients were included in the study and divided into two groups. The acquired hypofibrinogenemia group, also known as the case group, comprised 36 patients, while the non-hypofibrinogenemia group, also referred to as the control group, consisted of 73 patients. Following the administration of hemocoagulase, we noted a range in hypofibrinogenemia severity: 22 patients (20.2%) presented mild conditions, 13 patients (11.9%) demonstrated moderate levels, and severe hypofibrinogenemia was observed in one patient, accounting for 0.9%.

Comparisons of baseline demographics and clinical characteristics

Table 1 summarizes the baseline demographics and clinical characteristics in the two groups. No significant differences were found between the two groups in terms of age and body mass index. Similarly, there were no significant differences in bleeding sites, duration of treatment, and administration of concomitant drugs (Table 1). However, admissions to the ICU were notably higher in the hypofibrinogenemia group compared to the non-hypofibrinogenemia group (5.5% *vs* 22.2%; P = 0.021; Table 1). The hypofibrinogenemia group also had a higher percentage of female patients (32.9% *vs* 61.1%; P = 0.005), along with an increased incidence of severe blood loss (9.6% *vs* 41.7%; P < 0.000) and in-hospital mortality (19.2% *vs* 38.9%; P = 0.027; Table 1). Median total hemocoagulase doses were significantly higher in the hypofibrinogenemia group (3.0 *vs* 5.0 KU; P = 0.026; Table 1 and Figure 2A). Bleeding from esophagogastric varices was more prevalent in the hypofibrinogenemia group (4.1% *vs* 27.8%; P = 0.001; Table 1). Packed red cells (PRC) transfusion rate was significantly higher in the hypofibrinogenemia group (23.3% *vs* 44.4%; P = 0.024; Table 1). Laboratory tests showed that the hypofibrinogenemia group had lower baseline fibrinogen levels (4.11 *vs* 2.20 g/L; P < 0.000; Figure 2B), lower fibrinogen levels after treatment (3.83 *vs* 1.23 g/L; P < 0.000), lower platelet count (PLT) (202 *vs* 122.5 × 10^9/L; P = 0.001), and higher total bilirubin (TBil) (11.00 *vs* 15.87 μmol/L; P = 0.003; Table 1). No significant differences were observed in other laboratory tests between the two groups (Table 1).

Risk factors related to acquired hypofibrinogenemia

In the multivariate analysis, we included the following variables which showed significance at P < 0.05 during univariate analysis: Total hemocoagulase doses, esophagogastric varices, baseline fibrinogen, PLT, sex, and TBil. Moreover, we incorporated treatment duration into the multivariate analysis, despite its P value exceeding 0.05 in the univariate analysis, as a previous study on hemoptysis showed that this variable was associated with acquired hypofibrinogenemia [16].

The multivariate analysis with logistic regression suggested that baseline fibrinogen [odds ratio (OR) 0.252, 95%CI: 0.137-0.464, P < 0.000], total hemocoagulase doses (OR 1.074, 95%CI: 1.015-1.137, P = 0.014), and female gender (OR 2.856, 95%CI: 1.015-8.037, P = 0.047) were risk factors for hypofibrinogenemia induced by hemocoagulase (Table 2). To assess the predictive capacity of both the total doses of hemocoagulase and baseline fibrinogen level for hemocoagulase-associated hypofibrinogenemia, the ROC curve was employed. The area under the receiver operating characteristic curve was 0.630 for total hemocoagulase doses (95%CI: 0.520-0.740, P = 0.028), and was 0.850 for the baseline fibrinogen level (95%CI: 0.769-0.931, P < 0.000; Table 3). The optimal cutoff point, sensitivity, and specificity on the ROC curve were determined by selecting the threshold corresponding to the largest Youden index. For total hemocoagulase doses, the cutoff value was 3.5 KU, with a sensitivity of 63.9% and a specificity of 57.5%. For baseline fibrinogen level, the cutoff value was 3.012 g/L, with a sensitivity of 77.8% and a specificity of 80.8% (Table 3).

DISCUSSION

To our knowledge, this is the first study to determine the risk factors for hemocoagulase-related hypofibrinogenemia in patients with GIB. Hemocoagulase is a complex of thrombin-like enzymes originating from snake venom. The extensive examination of hemocoagulase spans multiple decades, with the earliest known form, Reptilase (batroxobin), emerging in the 1950s. To date, multiple hemocoagulase products have been commercialized globally, with widespread use in bleeding disorders[6,17].

In the terminal phase of the blood coagulation process, fibrin formation is crucial; hemocoagulase accelerates the conversion of fibrinogen into fibrin monomers, thereby playing a pro-hemostatic role similar to human thrombin. At present, hemocoagulase is extensively used to mitigate traumatic hemorrhage, respiratory system bleeding, and

Table 1 Demographics and clinical characteristics, *n* (%)

Variables	Non-hypofibrinogenemia (*n* = 73)	Hypofibrinogenemia (*n* = 36)	*P* value
Age (years)	76.0 (66.5-82.0)	73.0 (57.3-81.0)	0.29
Sex, female	24 (32.9)	22 (61.1)	0.005[a]
Body mass index (kg/m^2)	20.3 (19.1-21.8)	20.3 (19.2-20.3)	0.183
Total hemocoagulase doses (KU)	3.0 (1-6.5)	5.0 (2.0-11.8)	0.026[a]
Treatment duration (days)	2 (1-5)	3 (1-6.8)	0.1
ICU admission	4 (5.5)	8 (22.2)	0.021[a]
Total deaths	14 (19.2)	14 (38.9)	0.027[a]
Severe blood loss	7 (9.6)	15 (41.7)	0.000[a]
Bleeding location			
Upper gastrointestinal	25 (34.2)	17 (47.2)	0.190
Small bowel	1 (1.4)	1 (2.8)	1.0
Lower gastrointestinal	5 (6.8)	1 (2.8)	0.667
Unknown site of bleeding	42 (57.5)	17 (47.2)	0.310
Cause of bleeding			
Esophagogastric varices	3 (4.1)	10 (27.8)	0.001[a]
Malignant neoplasm	21 (28.8)	8 (22.2)	0.467
Peptic ulcer	10 (13.7)	2 (5.6)	0.341
Ischemic bowel disease	3 (4.1)	0 (0)	0.549
Severe infection	22 (30.1)	8 (22.2)	0.384
Unexplained GIB	14 (19.2)	8 (20.2)	0.710
Concomitant drugs			
Cephalosporin	12 (16.4)	7 (19.4)	0.697
Carbopenems	10 (13.7)	3 (8.3)	0.618
CSS	48 (65.8)	27 (75.0)	0.327
Vitamin K1	5 (6.8)	3 (8.3)	1.0
Tranexamic acid	4 (5.5)	3 (8.3)	0.876
Transfusion			
PRC	17 (23.3)	16 (44.4)	0.024[a]
FFP	6 (8.2)	7 (19.4)	0.166
Laboratory tests			
Baseline FIB (g/L)	4.11 (3.18-5.44)	2.20 (2.00-2.96)	0.000[a]
Post-hemocoagulase FIB (g/L)	3.83 (2.81-5.16)	1.23 (0.67-1.62)	0.000[a]
PLT (× 10^9/L)	202 (137.5-277.5)	122.5 (79-216.75)	0.001[a]
WBC (× 10^9/L)	9.08 (7.11-12.38)	8.00 (5.79-11.51)	0.285
ALT (U/L)	19.00 (14.20-37.78)	20.13 (12.50-34.85)	0.867
AST (U/L)	28.04 (19.90-39.89)	27.89 (20.18-54.28)	0.556
TBil (μmol/L)	11.00 (8.32-20.08)	15.87 (11.51-39.84)	0.003[a]

[a]$P < 0.05$.

KU: Klobusitzky unit; ICU: Intensive care unit; GIB: Gastrointestinal bleeding; CSS: Carbazochrome sodium sulfonate; PRC: Packed red cell; FFP: Fresh frozen plasma; FIB: Fibrinogen; PLT: Platelet; WBC: White blood cells; ALT: Alanine transaminase; AST: Aspartate transaminase; ALB: Albumin; TBil:

Total bilirubin.

Table 2 Multivariate analyses for the risk factors of hemocoagulase-related hypofibrinogenemia

Variables	OR	95%CI	*P* value
Baseline fibrinogen	0.252	0.137-0.464	0.000[a]
Total hemocoagulase doses	1.074	1.015-1.137	0.014[a]
Sex	2.856	1.015-8.037	0.047[a]

[a]*P* < 0.05.
OR: Odds ratio.

Table 3 Receiver operating characteristic curve analysis of baseline fibrinogen and total hemocoagulase doses: Area under the receiver operating characteristic curve, sensitivity, specificity, and optimal cutoff points

Variables	AUC	95%CI	*P* value	Cut-off	Sensitivity	Specificity
Baseline fibrinogen	0.850	0.769–0.931	0.000[a]	3.012	77.8%	80.8%
Total hemocoagulase doses	0.630	0.520–0.740	0.028[a]	3.5	63.9%	57.5%

[a]*P* < 0.05.
AUC: Area under the receiver operating characteristic curve.

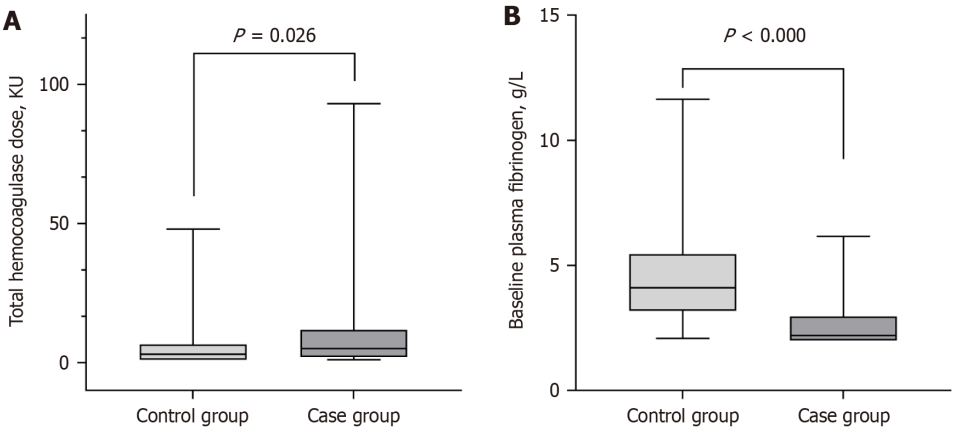

Figure 2 Comparison in the non-hypofibrinogenemia group (control group) *vs* the hypofibrinogenemia group (case group). A: Comparison of total hemocoagulase doses administered in the non-hypofibrinogenemia group (control group) *vs* the hypofibrinogenemia group (case group); B: Comparison of baseline fibrinogen in the non-hypofibrinogenemia group (control group) *vs* the hypofibrinogenemia group (case group). KU: Klobusitzky unit.

gastrointestinal hemorrhage. Additionally, it plays a preventative role in bleeding complications predominantly stemming from invasive operations. Nevertheless, according to post-marketing studies, hemocoagulase may trigger bleeding associated with hypofibrinogenemia. The current literature on hemocoagulase-related hypofibrinogenemia consists mainly of case reports, with a notable absence of case-control studies[13,18-20].

Our research showed that in patients with GIB, the administration of hemocoagulase may cause acquired hypofibrinogenemia, which was noted in 33% of cases. Before the use of hemocoagulase, fibrinogen levels in all patients were within the normal range. However, following the administration of hemocoagulase, hypofibrinogenemia was noted in 36 patients. In addition, we observed that patients who developed hypofibrinogenemia exhibited more severe blood loss, a higher rate of PRC transfusions, and an increased mortality rate compared to those without hypofibrinogenemia. This suggests that the development of hypofibrinogenemia following hemocoagulase use may result in heightened transfusion needs, and an elevated risk of bleeding and death. In previous studies, a case report detailed the propensity for bleeding in a patient with hemoptysis, caused by hypofibrinogenemia related to long-term hemocoagulase therapy[20]. Moreover, Zhou[13] identified seven patients with hypofibrinogenemia after colonic polypectomy, which was performed following the administration of hemocoagulase; three of these patients had lower gastrointestinal hemorrhage; Notably, no decrease in fibrinogen levels was observed in the 13 patients who did not receive hemocoagulase[13]. The findings of these studies

were generally consistent with those of ours. In addition, as hemocoagulase has the potential to induce hypofibrinogenemia, coagulation monitoring and prompt treatment adjustment are necessary for patients. However, coagulation monitoring for all patients is impractical as this would significantly increase medical costs. Therefore, it is important to identify patients at high risk of developing hypofibrinogenemia. In view of this, our study specifically focused on the risk factors associated with the development of hypofibrinogenemia following the administration of hemocoagulase in GIB patients. We identified several risk factors, including total hemocoagulase doses (≥ 3.5 KU), female gender, and a lower baseline fibrinogen level (≤ 3.012 g/L). We believe that these risk factors can help identify patients at high risk of developing hypofibrinogenemia and that patients with GIB who have any of these risk factors require strict coagulation monitoring and prompt treatment adjustment.

Although our research provides meaningful insights, it did have some limitations. First, the single-institution retrospective nature of our study resulted in a limited number of participants. This may constrain the generalizability of our results. Second, there might be factors that could potentially influence the precision of our study. For example, there was uncertainty surrounding the timing and frequency of coagulation function tests. Lastly, due to insufficient laboratory test data, a significant number of GIB patients were not included (for instance, a variety of milder cases were left out as post-treatment coagulation function assessments were not available). This could potentially lead to selection bias.

CONCLUSION

In patients with GIB, the occurrence of acquired hypofibrinogenemia following treatment with hemocoagulase is associated with a higher likelihood of severe bleeding, increased likelihood of admission to the ICU, and a higher mortality rate compared to those who do not develop acquired hypofibrinogenemia. Higher doses of total hemocoagulase, female gender, and a lower baseline fibrinogen level are risk factors for hemocoagulase-associated hypofibrinogenemia in patients with GIB. We recommend that GIB patients with any of these risk factors receive coagulation monitoring and prompt treatment adjustments during hemocoagulase administration.

FOOTNOTES

Author contributions: Wang YY proposed the concept of this study; Zou F was responsible for the literature review, methodology, data acquisition, and manuscript writing; Wu MT handled data analysis and manuscript review; All authors have read and approved the final manuscript.

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