Impact of Anemia on the Outcomes of Endoscopic Intervention in High-Risk NUGIB Patients

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Abstract

Background: It is common for high-risk, non-variceal upper gastrointestinal bleeding (NUGIB) patients coexisting anemia, but the role of anemia on the prognosis of endoscopic intervention is not clear. The aim of this study was to assess the impact of hemoglobin level on outcomes of endoscopic intervention in high-risk NUGIB patients.

Methods: A retrospective study was performed on high-risk (Glasgow-Blatchford score ≥7) NUGIB patients who underwent endoscopic intervention within 24h of presentation. Patients were divided into three groups based on hemoglobin level before intervention: severe (<7g/dl), moderate (7g/dl ≤hemoglobin <9g/dl) and mild (≥9g/dl) group. Outcomes included mortality, length of ICU stay, re-bleeding rate, procedural adverse events, length of hospital stay, adverse events and transfusion requirement.

Results: A total of 156 patients received endoscopic intervention were identified, 88 in the severe group, 45 in the moderate group, and 23 in the mild group. The total mortality rate in 45 days was 2%, and the re-bleeding rate was 21%. There was no significant difference in mortality, re-bleeding rate or length of ICU stay among the three groups. The average days of hospitalization in the severe group was significantly longer than that of the moderate group (13 *vs* 8, $P < 0.05$). No adverse events occurred. Low hemoglobin level was a predictor for more red-cell transfusion (OR=5.94, 2.69-13.11) and plasma transfusion (OR=2.34,1.21-4.51).

Conclusions: Anemia does not affect the mortality and rebleeding of endoscopic intervention in high-risk NUGIB patients, but is associated with more transfusion and longer hospitalization.

Background

Acute upper gastrointestinal bleeding (UGIB) is a common disease with an estimated incidence of 48–160 cases per 100,000[1]. Despite advances in endoscopic and intensive treatment in recent years, NUGIB (non-variceal UGIB) is still associated with a 2 to 10 percent mortality rate[2, 3]. Appropriate endoscopic intervention can effectively diagnose the etiology of NUGIB, followed by endoscopic intervention, and directly improve the prognosis of NUGIB patients[4–6]. The Glasgow-Blatchford Score (GBS) has been acknowledged as the most accurate prediction score system for therapeutic intervention and mortality[7]. Patients with a GBS score < 3 who do not need hospitalization are considered low-risk, whereas patients with a GBS score ≥ 7 are considered high-risk and recommended to undergo urgent endoscopy within 24 hours; this is considered to be the best score to predict mortality and demand for urgent endoscopic intervention[7, 8].

In clinical practice, lower hemoglobin levels in NUGIB patients are usually associated with severe clinical episodes, including mortality, recurrent hemorrhage and blood transfusion [1, 8–12]. In high-risk patients, anemia is relatively common, but the role of anemia on the prognosis of endoscopic intervention remains unclear. Recently, Cho et al. reported that the time of emergency endoscopy was considered as an

independent factor on the mortality but not re-bleeding in the high-risk NUGIB patients in a retrospective study [8]. However, the effect of anemia as an independent factor on the outcomes of endoscopic intervention in the high-risk condition is still unclear.

In this article, a retrospective single-center study was conducted to investigate the effects of anemia on prognosis of endoscopic intervention in high-risk NUGIB patients.

Methods

Study design and inclusion criteria

This retrospective study was performed in West China hospital, Sichuan University, China, from January 2008 to December 2018. In order to observe the outcomes of acute high-risk NUGIB patients with fast and fierce bleeding in the study, we included only patients with angiogenic hemorrhage, including peptic ulcer and Dieulafoy disease. All patients were ≥ 17 years old and underwent emergent endoscopic intervention within 24 h for overt hematemesis and/or melena at the emergency center. High-risk was defined as a GBS score ≥ 7. All patients had the records necessary for this research. Patients were divided into three groups based on hemoglobin level: severe (< 7 g/dl), moderate (7 ≤ hemoglobin < 9 g/dl) and mild (≥ 9 g/dl). Patients with a recent history of trauma or surgery in the prior month, combined with severe comorbidity, including acute coronary syndrome, symptomatic peripheral vasculopathy, stroke, transient ischemic attack, chronic heart failure, respiratory failure, lower gastrointestinal bleeding, and pregnant or lactating women, were excluded. These data were collected from the HIS by our team members.

Data collection

The data collected included demographic, clinical and laboratory findings, and endoscopic interventions. Demographic findings included age and sex of patients. Clinical findings included the population of patients experiencing hemorrhagic shock during the hospital stay, hospitalization days, mortality, and re-bleeding, adverse effects related to the endoscopic intervention and transfusion requirements among the different groups. The bleeding source, the Forrest category, and hemostatic interventions were recorded by endoscopic examination. GBS scores were calculated based on laboratory and endoscopic findings. Laboratory findings included the hemoglobin levels of patients during admission at the emergency center, the time within 24 hours before endoscopic intervention, and the lowest level of hemoglobin during hospitalization. They also included the last recorded international normalized ratio (INR), prothrombin time (PT), and platelets of patients within 24 hours before endoscopic intervention.

Outcomes

The outcomes included both therapeutic outcomes and transfusion requirements. The therapeutic outcomes were defined and documented as the mortality within 45 days, the number of patients who went to ICU, the re-bleeding rate in 30 days, procedural adverse events 72 hours post-intervention, duration of ICU stay, and duration of hospitalization. Transfusion requirements included the number of

patients who underwent transfusion, and the total amount of transfusion for each patient. The transfusion requirements for red-cell, platelet and plasma were recorded.

Statistical analysis

Continuous variables are expressed as median (range) and underwent a normal distribution test first. If the data were normally distributed, one-way analysis of variance (ANOVA) was performed among the three groups. Otherwise, the Wilcoxon rank-sum test was performed. The qualitative indexes were described by the frequency and percentage and the chi-squared test was used. Logistic regression model was used to analyze the correlation between hemoglobin and the transfusion requirement. $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS 20 (SPSS, Chicago, IL, USA).

Results

Baseline characteristics

Of 156 patients met the criteria, 88 were in the severe group, 45 in the moderate group, and 23 patients in the mild group, with hemoglobin levels of < 7 g/dl, 7 ~ 9 g/dl and ≥ 9 g/dl, before endoscopic intervention, respectively. The details of baseline characteristics are shown in Table 1. The median age of the whole group was 60 (17–92) years old. Twenty patients (13%) were female and 136 patients (87%) were male (Table 1). About half of the patients (44%) experienced shock during the hospital stay. There was no significant difference among the three groups in age, gender and shock ($P > 0.05$). The bleeding source of the ulcer location was identified in all patients. The location of bleeding source was observed to be in the stomach (76 patients, 49%), duodenum (76 patients, 49%) and anatomic stoma (8 patients, 5%). Several patients had more than one bleeding source. The median GBS score in the entire group was 10 (7–17). The Forrest category of all patients was evaluated. Patients with a Forrest category of IIB made up the largest group among all patients (44%), while patients with IA made up the smallest (2%). There was no significant difference in bleeding source, GBS score and Forrest category among the three groups ($P > 0.05$). A total of 111 (71%) patients underwent endoscopic hematemesis, including thermal, mechanical and injection hematemesis. Fifty-six (37%) patients underwent only one kind of hematemesis, 44 (28%) underwent two kinds, and 11 (7%) underwent three kinds. There was no significant difference in endoscopic hematemesis among the three groups.

Table 1 Baseline Characteristics

	Severe n=88	Moderate n=45	Mild n=23	Total n=156
Gender				
Men	76 (86)	39 (87)	21 (91)	136 (87)
Women	12 (14)	6 (13)	2 (9)	20 (13)
Age	60 (17-92)	61 (17-86)	53 (22-85)	60(17-92)
Shock	45 (51)	18 (40)	6 (26)	69 (44)
Bleeding Source				
Duodenum	37 (42)	28 (60)	12 (52)	76 (49)
Gastric	47 (53)	19 (42)	10 (43)	76 (49)
Stomas	6 (7)	1 (2)	1 (4)	8 (5)
GBS score	10 (7-13)	10 (7-17)	11 (7-17)	10 (7-17)
Forrest level				
IA	1 (1%)	2 (4%)	0 (0%)	3(2%)
IB	18 (20%)	7 (16%)	0 (0%)	25(16%)
IIA	30 (34%)	25 (56%)	13 (57%)	68(44%)
IIB	5 (6%)	1 (2%)	2 (9%)	8(5%)
III	8 (9%)	3 (7%)	2 (9%)	13(8%)
Dieulafoy disease	26 (30%)	7 (16%)	6 (26%)	39(25%)
Hemostasis				
None	26 (30)	15 (33)	4 (17)	45 (29)
Single				
Thermal	5 (6)	7 (16)	6 (26)	18 (12)
Mechanical	16 (18)	5 (11)	5 (22)	26 (17)
Injection	6 (7)	4 (9)	2 (9)	12 (8)
Multiple				
Dual	29 (33)	10 (22)	5 (22)	44 (28)
Tri	6 (7)	4 (9)	1 (4)	11 (7)

Data are given as medium (range) or number (percent)

*No significant difference in each characteristic among the three groups（P>0.05).

Biochemical results was shown in Table 2. Coagulation function among the three groups was evaluated including the platelet count, INR and PT before endoscopic intervention. The platelet level in the mild group (146 cells x 10^3/ml, range, 36 to 258) was lower than that in the moderate group (177 cells x 10^3/ml， range, 37 to 479) (P = 0.02, Table 2). The INR level in the mild group (1.03, range, 0.871 to 35) was significantly higher than in the severe group (1.18, range, 0.81 to 10.4) (P = 0.00). There was no significant difference in other routine coagulation function among the three groups.

The hemoglobin level at admission, 24 hours before intervention, and lowest value during hospital stay was included in the biochemical result (Table 2). Before endoscopic intervention, the median of hemoglobin in the entire cohort was 68 (34–126) g/ml. The median hemoglobin level in the entire cohort at administration was 73 (25–155) g/ml. The median of the lowest hemoglobin level during hospital stay in the entire cohort was 5.8 (1.7–12.6) g/dl. The administration hemoglobin level was similar in the

moderate and the mild group, (P = 0.09), but all other hemoglobin levels in the groups were significantly different from the other groups, as shown in the Table 2.

Table 2 Laboratory parameters

	Severe	Moderate	Mild	Total	*P* value		
	n=88	n=45	n=23	n=156	1 *vs* 2	1 *vs* 3	2 *vs* 3
Platelet (cells x 10^3/ml)	139 (27-429)	177 (37-479)	146 (36-258)	150 (527-479)	0.15	0.60	0.02
INR	1.18 (0.81-10.4)	1.10 (0.87-11.5)	1.03 (0.871-35)	1.14 (0.81-11.5)	0.06	0.00	0.09
PT	13.5 (10-26.4)	12.8 (10-129.4)	12.1 (9.7-15)	13 (0-129.4)	0.06	0.00	0.15
Hemoglobin Level (g/dl)							
At Administration	6.7 (2.5-15.5)	7.4 (4.4-11.6)	11.6 (6.5-14.0)	7.3 (2.5-15.5)	0.00	0.00	0.09
Before intervention	6.0 (3.4-6.9)	7.5 (7.0-8.9)	10.3 (9.1-12.6)	6.8 (3.4-12.6)	0.00	0.00	0.00
Lowest Value During Hospital Stay	5.3 (1.7-7.2)	6.7 (4.3-9.3)	9.7 (3.6-12.6)	5.8 (1.7-12.6)	0.00	0.00	0.00

Data are given as medium (range) or number (percent)

1 *vs* 2: severe group *vs* moderate group.

1 *vs* 3: severe group *vs* mild group.

2 *vs* 3: moderate group *vs* mild group.

Therapeutic outcomes

The therapeutic outcomes included mortality and length of hospital stay (ICU and general ward). Details are shown in Table 3. The mortality in the entire cohort was 2% (three patients), and all of the deceased belonged to the severe group. There was no significant difference in mortality among the three groups (P > 0.05). None of these patients experienced adverse effects related to the endoscopic intervention.

Table 3
Therapeutic outcomes

	Severe n = 88	Moderate n = 45	Mild n = 23	Total n = 156	*P* value		
Mortality in 45 Days	3 (3)	0	0	3 (2)	0.31		
Popularity Went Into ICU	10 (11)	9 (20)	1 (4)	20 (13)	0.15		
Rebleeding rate in 30 days	20 (23)	11 (24)	2 (9)	33 (21)	0.80		
Hospital Staying					1 *vs* 2	1 *vs* 3	2 *vs* 3
No. of Days in ICU	0 (0–70)	0 (0–28)	0 (0–7)	0 (0–70)	0.09	0.31	0.20
No. of Days in Hospital	13 (3-111)	14 (6–49	8 (4–46)	12 (3-111)	0.00	0.00	0.61
Data are given as medium (range) or number (percent)							
1 *vs* 2: severe group *vs* moderate group.							
1 *vs* 3: severe group *vs* mild group.							
2 *vs* 3: moderate group *vs* mild group.							

Twenty patients were admitted to the ICU, ten in the severe group, nine in the moderate group, and one in the mild group (Table 3). The chi-squared test showed that there was no significant difference in the number of patients staying in the ICU among the three groups. The median time that a patient stayed in the ICU was 1.62 days in the entire cohort. There was no significant difference among the three groups ($P > 0.05$). No patients in the cohort reported procedural adverse events related to the endoscopic intervention.

All patients experienced a hospital stay. The number of days of hospital admission in the severe group (13 days, range, 3 to 111) was significantly greater than in the moderate group (14, range, 6 to 49) and the mild group (8, range, 4 to 46) ($P < 0.05$) (Table 3).

Transfusion requirements

In the entire cohort, 114 patients (73.08%) underwent blood transfusion. The details of the transfusion requirement are shown in Table 4. The percentage of patients who received red-cell transfusion was 88% (77/88). Each group was significantly different from the others ($P < 0.05$). The median red-cell transfusion was four (0–58) units per patient in the entire cohort. Each group was significantly different from the others ($P < 0.05$). Only a small number (4%) of patients underwent platelet transfusion in the entire cohort

and the median was 0 (0–4) cells x 10^3/ml per patient (Table 3). There was no significant difference in the transfusion population and the amount of transfusion among the three groups ($P > 0.05$).

Table 4
Transfusion Requirement

	Transfused	Severe	Moderate	Mild	Total	1 *vs* 2	1 *vs* 3	2 *vs* 3
Red-cell	Units	6 (0–48)	3 (0–58)	0 (0-12.5)	4 (0–58)	0.01	0.00	0.02
	No. of patients	77 (88)	30 (67)	7 (30)	114 (73)	0.04	0.00	0.01
Platelet	Units	0 (0–4)	0 (0–3)	0 (0–0)	0 (0–4)	0.48	0.24	0.38
	No. of patients	5 (6)	1 (2)	0	6 (4)	0.36	0.24	0.47
Plasma	Volume (ml)	150 (0-5800)	0 (0-6250)	0 (0-1600)	0 (0-6250)	0.12	0.00	0.10
	No. of Patients	47 (53)	17 (38)	5 (21)	69 (44)	0.09	0.09	0.18
Data are given as medium (range) or number (percent)								
1 *vs* 2: severe group *vs* moderate group.								
1 *vs* 3: severe group *vs* mild group.								
2 *vs* 3: moderate group *vs* mild group.								

Nearly half of the patients (44%) received plasma transfusion in the entire cohort. The median of plasma transfusion was 0 (0–6,250) ml per patient. There was significant difference in the mild group 0 (0–1,600) and the severe group 150 (0–5,800) ($P = 0.00$).

The hemoglobin level at different times (≥ 7 g/dl *vs* < 7 g/dl) was evaluated with the logistic analysis model (Table 5). Low hemoglobin level at administration, before intervention and the lowest level during hospital stay were predictors for further RBC transfusion and plasma transfusion. The odds ratio, 95% CI and *P* values are shown in Table 4.

Table 5
Correlation test of transfusion with hemoglobin level

Correlation with RBC transfusion	Odd ratio	95% CI	*P* value
At administration (< 7 g/dl)	4.22	1.85–9.62	0.00
Before intervention (< 7 g/dl)	5.94	2.69–13.11	0.00
Lowest during stay (< 7 g/dl)	8.89	3.51–22.52	0.00
Correlation with plasma transfusion			
At administration (< 7 g/dl)	2.22	1.16–4.23	0.02
Before intervention (< 7 g/dl)	2.34	1.21–4.51	0.01
Lowest during stay (< 7 g/dl)	3.81	1.67–8.69	0.00

Discussion

In the present study, anemia in high-risk NUGIB patients was not associated with therapeutic outcomes of endoscopic intervention in mortality, re-bleeding rates,adverse effect and days in ICU. The span of hospitalization in the severe group was significantly longer than in the moderate and mild groups ($P < 0.05$). In addition, anemia in high-risk NUGIB patients underwent endoscopic intervention tended to be associated with more transfusion.

Hemoglobin level has been considered as an independent factor on the outcomes of NUGIB patients [1, 8–12]. However, the impact of hemoglobin level in high-risk patients underwent endoscopic intervention has not been clarified. In the entire cohort, 56.4% (88/156) patients had hemoglobin < 7 g/L, 28.9% (45/156) between 7 ~ 9 g/dl and 14.8% (23/156) ≥ 9 g/dl before endoscopic intervention, supporting that anemia is the common symptom of high-risk NUGIB patients.

No significant difference was found in mortality, re-bleeding rates,adverse effect and days in ICU among 3 groups of high-risk NUGIB patients underwent endoscopic intervention. In our study, the baseline of each group was comparable, including age, gender, shock, location of bleeding, endoscopic treatment and GBS score with the median of 10. The mortality rate was 2%, and all three patients were in the severe group, which was comparable to the reported NUGIB mortality of about 1–5% [13]. The re-bleeding rate (21%) was higher than in other researches (about 10%) [13, 15, 16]. This difference may be related to the higher proportion of high-risk patients with Forrest I, Forrest IIa/b and Dieulafoy patients in this study. The percentage of ICU admission in this study (13%) is similar to the results of other research (13.2%), supporting the efficacy of endoscopic intervention[14]. Studies have shown that AIMS65, a clinical prediction factor that includes albumin, INR, mental status, systolic BP and age, but not hemoglobin level[15], is the best predictor for ICU admission[14]. This may explain why there is no difference in ICU admission among the three groups. On the contrary, the median span of hospitalization in the severe group was significantly longer than in the mild group. This was acceptable since patients in the severe

group need more time for comprehensive treatment and drug treatment in hospital, which are also indispensable for UGIB therapy[16]. Overall, our results showed that anemia did not associate with the mortality and rebleeding of high-risk NUGIB patients underwent endoscopic intervention.

There is no doubt about the benefits of RBC transfusion for patients with severe UGIB improving the tissue oxygen supply in the circulation. A target threshold for red cell transfusion of 7–9 g/dl for severe UGIB patients (known as the restrictive transfusion strategy) is popularly recommended [9, 17]. In our cohort study, most patients were treated following the recommendation of restriction transfusion[4, 18], except for two older patients who were had RBC transfused at the condition of hemoglobin higher than 9 g/dL. The transfusion requirements among the mild, moderate and severe groups were statistically different and increased successively. Correlation tests showed that low hemoglobin level at administration, before intervention, and the lowest level during hospital stay were predictors for further RBC transfusion and plasma transfusion. Therefore, under the effective and safe endoscopic intervention, blood transfusion is still an indispensable strategy for high-risk patients with anemia.

Studies have shown that massive bleeding can cause the loss of a large amount of blood-clotting factor and platelets, causing the coagulation function to decrease, especially in those with an acute condition[19]. Consistently, our studies reported that the INR and PT of severe patients were statistically higher than in mild patients. Compared with the thrombocytopenia frequently seen in populations with liver cirrhosis and hematologic malignancies, platelets in the severe group were not significantly different from the mild group, whereas platelets in the moderate group were significantly higher than in the mild group[20–22].

Our study had several limitations. First, selection bias existed in this retrospective single-center study at a tertiary academic hospital. Patients with variceal bleeding and serious comorbidities were not included in the cohort study. Therefore, the external validity of the result is limited, owing to these inclusion and exclusion criteria. Second, the interventions were all performed by experienced endoscopists in the tertiary center. Their extensive experience optimized diagnosis and treatment and reduced the rate of adverse events, which led to the excessively low mortality and complication rates in this study. Third, the sample size of this study was quite small, since severe bleeding with urgent endoscopic intervention is rare in the general population. However, in our study, characteristics, GBS score and endoscopic hemostasis of patients among 3 groups were comparable, which supported the impact of anemia as an independent factor to affect the outcomes of endoscopy. Based on our retrospective study, further prospective multicenter studies looking into the comparative outcomes of patients with severe anemia should be the next step to verify our findings and determine the appropriate hemoglobin threshold for safe and effective endoscopic procedures.

Conclusion

Severe anemia is a common symptom in high-risk NUGIB patients. Anemia does not affect the mortality and rebleeding of endoscopic intervention in high-risk NUGIB patients, but is associated with more

transfusion and longer hospitalization. Therefore, we cautiously suggest that high-risk NUGIB patients with severe anemia under endoscopic intervention is safe and effective, based on endoscopic examinations performed by an experienced endoscopist, and effective comprehensive therapy.

Abbreviations

UGIB
upper gastrointestinal bleeding; NUGIB:non-variceal upper gastrointestinal bleeding; GBS:Glasgow-Blatchford score

Declarations

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Not applicable.

Authors' contributions

LL conducted the study and designed the study. JT drafted the manuscript and interpreted data. SB and TL collected the data. All authors have read and approved the final draft submitted.

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by Human Research Ethics Committee of West China Hospital, Sichuan University, China with NO.2019(1024).

Consent for publication

Consent was obtained from all subjects whose imaging data were published in this study.

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