Annals of Gastroenterology (2024) **37,** 303-312

Impact of blood transfusion on mortality and rebleeding in gastrointestinal bleeding: an 8-year cohort from a tertiary care center

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Abstract

Background The aim of this study was to investigate the impact of blood transfusion (BT) on mortality and rebleeding in patients with gastrointestinal bleeding (GIB) and whether BT at a threshold of ≤7 g/dL may improve these outcomes.

Methods A prospective study was conducted in patients admitted with GIB between 2013 and 2021. Antithrombotic (AT) use and clinical outcomes were compared between transfused and non-transfused patients, and between those transfused at a threshold of ≤7 vs. >7 g/dL. Multivariate analysis was performed to identify predictors of mortality and rebleeding.

Results A total of 667 patients, including 383 transfused, were followed up for a median of 56 months. Predictors of end-of-follow-up mortality included: age-adjusted Charlson Comorbidity Index, stigmata of recent hemorrhage (SRH), and being on anticoagulants only upon presentation (P=0.026). SRH was a predictor of end-of-follow-up rebleeding, while having been on only antiplatelet therapy (AP) upon presentation was protective (P<0.001). BT was not associated with mortality or rebleeding at 1 month or end of follow up. Among transfused patients, being discharged only on AP protected against mortality (P=0.044). BT at >7 g/dL did not affect the risk of short or long-term rebleeding or mortality compared to BT at ≤7 g/dL.

Conclusions Short- and long-term mortality and rebleeding in GIB were not affected by BT, nor by a transfusion threshold of ≤7 vs. >7 g/dL, but were affected by the use of AT. Further studies that account for AT use are needed to determine the best transfusion strategy in GIB.

Keywords Gastrointestinal bleeding, blood transfusion, mortality, rebleeding

Ann Gastroenterol 2024; 37 (3): 303-312

Conflict of Interest: None

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Received 9 September 2023; accepted 16 February 2024; published online 10 April 2024

DOI: https://doi.org/10.20524/aog.2024.0877

Introduction

Gastrointestinal bleeding (GIB) is a common medical emergency associated with significant morbidity and mortality [1,2]. Blood transfusion (BT) is an essential cornerstone in the management of GIB [3], and is administered to around 30-60% of patients with GIB [4-6]. The impact of BT on clinical outcomes in GIB is controversial. Several observational studies have suggested that BT may be associated with an increased risk of mortality and rebleeding, particularly in patients with portal hypertension [7,8]. Although these studies were limited by the fact that transfused patients are generally sicker than non-transfused ones, 2 recent studies that used propensity matching to compare

transfused and non-transfused patients suggested that BT does indeed increase the risk of mortality and rebleeding [9,10]. Furthermore, in a prospective study of patients presenting with GIB, BT was found to be an independent predictor of 1-year mortality [11].

The American College of Gastroenterology, European Society of Gastrointestinal Endoscopy, and British Society of Gastroenterology recommend a restrictive BT strategy for all patients with GIB, except those with hemodynamic instability or cardiovascular disease. Those recommendations were conditional to strong and were based on low-to-moderate quality evidence. This stems from a few randomized controlled trials (RCTs), systematic reviews, and meta-analyses suggesting that a restrictive BT strategy may be associated with better short-term survival and rebleeding risk compared to a liberal strategy [7,8,12]. It was not clear, however, if this applies to patients with non-variceal upper GIB (UGIB) [13,14], those with hemodynamic instability [14], severe GIB, lower GIB (LGIB) [15], or cardiovascular disease [16-18]. In addition, the definition of restrictive and liberal strategies was not uniform. Interestingly, a *post hoc* analysis by Nightingale *et al* proposed that the optimal BT threshold for reducing mortality in GIB may be higher than the one currently recommended by guidelines, and that mortality is related to the number of blood units transfused and the lowest hemoglobin (Hb) level patients reach [19].

Current guidelines have another limitation, as few studies examined the effects of antithrombotics (AT) on outcomes in transfused patients with GIB, and none have evaluated the long-term risk of rebleeding and mortality in relation to transfusion strategy. Consequently, the optimal transfusion strategy, including threshold and target Hb levels, remains uncertain. This study sought to address this gap by examining the association between BT thresholds and mortality and rebleeding rates in patients with all-cause overt GIB, while also considering the influence of AT medication.

Patients and methods

Study design

This was an observational, prospective cohort study of patients admitted to our tertiary care referral center with overt GIB between January 2013 and August 2021. All patients aged 18 years or older who were admitted with overt GIB were included.

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Data collection

Patients were interviewed by a member of the research team during the index admission or via phone call after discharge. To ensure reliable data collection, a structured questionnaire was administered. Interview data were supplemented with data retrieved from the medical record. Patient demographics (including age, sex and social history) and clinical variables (vital signs, severity of GIB, age-adjusted Charlson Comorbidity Index (CCI), and medications) were obtained from the patient interview upon admission and/or the medical records. We also documented laboratory results, imaging results, endoscopic findings and interventions, resuscitative measures and discharge medications from the medical records.

Follow up

Patients (or family members if the patient was deceased) were contacted by phone 1 month after discharge and then yearly until August 2021 to inquire about their outcomes, as well as any changes in their outpatient medications.

Definitions

Overt GIB was defined as either witnessed or reported melena, hematochezia, hematemesis, or coffee-ground emesis. UGIB was determined by the presence of coffee-ground emesis, hematemesis or melena, and/or stigmata of recent hemorrhage (SRH) detected by upper gastrointestinal endoscopy. LGIB was considered when hematochezia was reported and/or SRH was found in the colon by colonoscopy, in the absence of an upper source. Small-bowel GIB was identified when SRH was detected in the small bowel through endoscopy and/or other procedures (capsule endoscopy, balloon enteroscopy, after excluding UGIB and LGIB sources). All other events without a clearly identified bleeding site were considered unspecified GIB events. All cases of overt GIB were confirmed by gastroenterologists at the American University of Beirut Medical Center (AUBMC).

Drug use was considered recent if it occurred up to 7 days before hospitalization. AT medications upon presentation were categorized into antiplatelets only (AP), anticoagulants (AC) only, both AP and AC, and no AT therapy. Information on the resumption of AT was collected from the discharge orders in the medical records and was verified during the follow-up phone interview. Age-adjusted CCI was used to measure comorbidity.

Severe GIB was defined by the presence of any of the following: systolic blood pressure (SBP) <100 mmHg, >2 units of red blood cell transfused, or ≥2 units drop in Hb level. SRH was defined as the presence of any of the following during endoscopy: spurting blood, oozing blood, visible vessel, adherent blood clot, or a raised pigmented spot.

Definition of transfusion threshold

We compared outcomes between patients who were transfused at ≤7 g/dL (Group 1) and those who were transfused at >7 g/dL (Group 2). The exact timing of BT was obtained retrospectively from the medical record. All patients who had the lowest Hb of >7 g/dL and who were transfused were placed in Group 2. The medical records for all remaining patients with a drop of Hb to ≤7 g/dL were used to identify the Hb threshold that triggered BT. They were then distributed to either Group 1 or Group 2.

Definition of outcomes

Mortality and rebleeding were confirmed by reviewing the medical records and/or by phone interview with the patient and/or family members. The cause of death was determined based on a review of the medical record and/or by an interview with family members. Rebleeding was defined as a recurrence of overt bleeding occurring 24 h or longer after the initial endoscopic evaluation and/or hemostatic therapy and initial stabilization, accompanied by either a change in vital signs or a decrease in Hb concentration by 2 g/dL or more. Rebleeding events during the index hospitalization or requiring readmission were combined into a single variable.

Primary and secondary endpoints

Our primary endpoints were the impact of BT on mortality and rebleeding at 1 month and at the end of follow up in patients with GIB. Our secondary endpoints were: 1) the impact of BT on the composite outcome of rebleeding and/or mortality at 1 month and at the end of follow up; 2) the impact of transfusion threshold (Hb ≤7 vs. >7 g/dL) on 1-month and end-of-follow-up rebleeding and mortality; and 3) the impact of antiplatelet and anticoagulant therapy on 1-month and end-of-follow-up rebleeding and mortality in patients with GIB who received a BT.

Statistical analysis

The Statistical Package for Social Sciences (SPSS), version 28.0 was used for data entry, management and analyses. Data were described as numbers and percentages for categorical variables, whereas for continuous variables the mean ± standard deviation was calculated. The association between mortality, rebleeding, and other categorical variables was assessed using the chi-square test, whereas Student's *t*-test was used for associations with continuous variables. First, we examined the clinical presentation and outcomes of the whole cohort of patients with GIB and compared transfused patients to non-transfused patients, patients who were alive at the end of follow up to those who were deceased, and patients who had rebleeding to patients who did not. Cox regression analysis was used to determine the independent predictors of mortality and rebleeding. Variables that were found to be significant in the bivariate analyses were used in the multivariate analyses. We then focused specifically on transfused patients and assessed factors associated with short- and long-term mortality and rebleeding among transfused patients only. Similar regression analyses were performed to identify predictors of mortality and rebleeding among transfused patients. As a final step, we compared the baseline characteristics and outcomes of patients who were transfused at a lowest Hb of ≤7 g/dL (Group 1), and those who were transfused at a lowest Hb >7 g/dL (Group 2). For all regression models, a P-value of 0.05 was set for the entry of potential predictors into the model, whereas a P-value of 0.1 was set for removal from the model. The results included hazard ratios (HRs) and 95% confidence intervals (CIs). A P-value of <0.05 was considered statistically significant.

Ethical considerations

This study was approved by the institutional review board at AUBMC (Protocol number: IM.KB.12) and its protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in *a priori* approval by the institution's Human Research Committee. Written or verbal informed consent was obtained from each patient included in the study.

Results

Six hundred sixty-seven patients were admitted with overt GIB between January 2013 and August 2021. They were followed for a median of 56 months (interquartile range [IQR] 31-78). The distribution of total follow-up times is presented in Fig. 1. More than half of our patients had UGIB and more than half had severe GIB. As shown in Table 1, 419 patients (62.8%) were on AT therapy upon presentation with GIB, and 316 patients (51.2%) were discharged on AT therapy.

A total of 383 (57%) patients received BT during their hospitalization. Patients who were transfused had a higher age-adjusted CCI, were more likely to have had UGIB or severe GIB, and were more likely to have been admitted on AT (Table 1). Transfused patients were also more likely to have had SRH and to have had endoscopic therapy. Overall, end-of-follow-up mortality and rebleeding rates were 47.4% and 22.2%, respectively (Table 1). Short- and long-term mortality and rebleeding were higher in those who were transfused compared to those who were not. The most common causes of GIB are shown in Table 2.

Effect of BT on mortality

A comparison between patients who were alive and those who were deceased at the end of follow up allowed us to identify the factors associated with mortality. They included age-adjusted CCI, severe GIB, mean initial Hb and

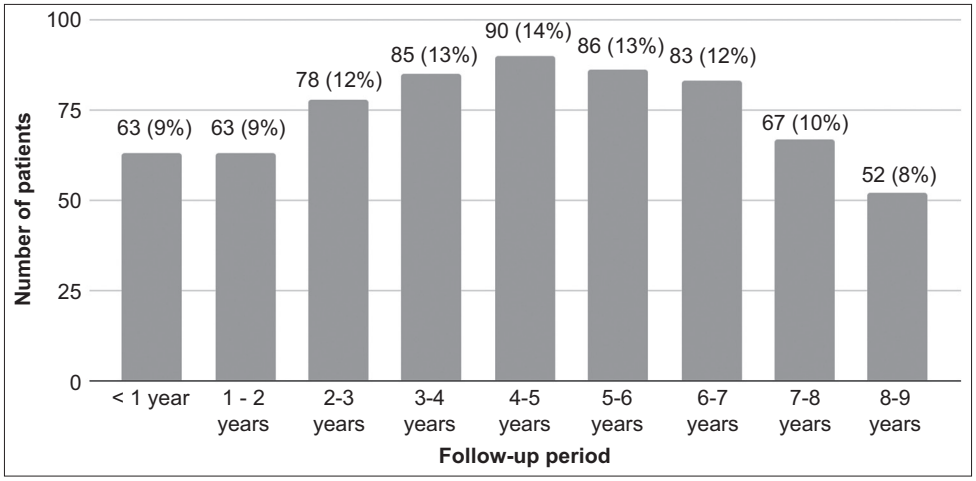

Figure 1 Distribution of total follow-up time in years for all patients in the cohort

SBP, a drop in Hb of ≥2 g/dL, BT, and being on only AC upon presentation. On multivariate analysis, the predictors of end-of-follow-up mortality were the age-adjusted CCI (HR 1.31, 95%CI 1.26-1.36; P<0.001), SRH (HR 1.37, 95%CI 1.06-1.78; P=0.015), and being on only AC upon presentation (HR 1.41, 95%CI 1.04-1.91; P=0.026). Having a higher lowest Hb was protective against mortality (HR 0.91, 95%CI 0.84-0.99; P=0.036). BT did not affect end-of-follow-up mortality (HR 1.32, 95%CI 0.92-1.91; P=0.126). As for the 1-month mortality, the only independent predictor was the age-adjusted CCI (HR 1.24, 95%CI 1.01-1.41; P=0.001).

Effect of BT on rebleeding

A comparison between patients who experienced rebleeding (22.2%) and those who did not (77.8%) suggested an association between rebleeding and the presence of SRH, BT, lower mean Hb during the index hospitalization, and a higher frequency of an initial Hb ≤7 g/dL (Table 3). Patients who rebled were less likely to have been on AP therapy upon admission. Subgroup analysis of various AT therapies revealed no significant association between a specific AP or AC and rebleeding. On multivariate analysis, the only independent predictor of 1-month rebleeding was SRH (HR 2.24, 95%CI 1.21-4.13; P=0.01), while a higher mean lowest Hb was protective (HR 0.79, 95%CI 0.65-0.97; P=0.02). Independent predictors of end-of-follow-up rebleeding were SRH (HR 1.64, 95%CI 1.13-2.39; P=0.009) and endoscopic therapy (HR 1.47, 95%CI 1.02-2.13; P=0.04), while having been on AP upon presentation was protective (HR 0.51, 95%CI 0.36-0.73; P<0.001). BT was not an independent predictor of rebleeding.

Effect of BT on the composite outcome of mortality or rebleeding

BT was not a predictor of the composite outcome of 1-month mortality or rebleeding (HR 0.78, 95%CI 0.41-1.48; P=0.45). Nor was it a predictor of the composite outcome of end-of-follow-up mortality or rebleeding either (HR 0.78, 95%CI 0.56-1.1; P=0.16).

Factors associated with mortality and rebleeding among transfused patients

Transfused patients who died were more likely to be older than those who survived, to have a higher age-adjusted CCI, a lower Hb during the index hospitalization, and to have been transfused ≥3 units of blood. They were also more likely to have been on only AC at presentation, and less likely to have been discharged on AP. Rebleeding rates did not differ significantly between the 2 groups. There was no significant difference in the proportion of patients transfused at a Hb threshold of ≤7 g/dL in patients who died compared to those who survived (44.6% vs. 50.9%, P=0.22). Patients who rebled were more likely to have SRH and less likely to be on AT. Surprisingly, they had a lower mean age-adjusted CCI. Being on AT upon discharge was not associated with a higher risk of rebleeding. A comparison of the clinical characteristics and outcomes of patients who were transfused at an Hb threshold of ≤7 g/dL (Group 1) to those transfused at an Hb of >7 g/dL (Group 2) is shown in Table 4. Patients in Group 1 were more likely to be women and to be taking AC upon presentation. They were also more likely to have had severe GIB, a lower mean initial Hb, and to have required a higher mean number of blood units. There was no difference in short- or long-term mortality or rebleeding between the 2 groups.

On Cox regression analysis, the only independent predictor of end-of-follow-up mortality among transfused patients was the age-adjusted CCI (HR 1.28, 95%CI 1.22-1.34; P<0.001) (Table 5). Being discharged on only AP was found to be protective against mortality (HR 0.69, 95%CI 0.489-0.991; P=0.044). BT at an Hb threshold of ≤7 g/dL did not affect mortality (HR 1.11, 95%CI 0.82-1.50; P=0.513). We did not identify any independent predictors of in-hospital mortality, and only the age-adjusted CCI was a predictor of 1-month

Table 1 Baseline characteristics of patients presenting with gastrointestinal bleeding who were transfused and those who were not transfused

Characteristics	All patients n=667	Transfused n=383	Non-transfused n=284	P-value
Female sex – no. (%)	246 (36.9)	148 (38.6)	98 (34.5)	0.274
Mean age – y (SD)	68.25 (16.2)	69.7 (15.1)	66.3 (17.4)	0.09
Age ≥75 y – no. (%)	286 (42.9)	169 (44.1)	117 (41.2)	0.450
Mean age-adjusted CCI – (SD)	4.77 (2.8)	5.26 (2.8)	4.11 (2.8)	<0.001
Cardiovascular diseases – no. (%)	315 (47.2)	197 (51.4)	118 (41.5)	0.011
Cirrhosis – no. (%)	51 (7.6)	34 (8.9)	17 (6)	0.165
GIB Location – no. (%)				
UGIB	370 (55.5)	233 (61.2)	137 (48.2)	0.002
LGIB	240 (36.0)	114 (29.9)	126 (44.4)	
SBP <100 mmHg – no. (%)	93 (13.9)	68 (17.8)	25 (8.8)	0.001
Mean initial SBP – mmHg (SD)	123.0 (21.8)	119.8 (20.9)	127.3 (22.2)	<0.001
Mean initial Hb – g/dL (SD)	9.7 (2.8)	8.2 (2.2)	11.8 (2.2)	<0.001
Mean lowest Hb – g/dL (SD)	8.4 (2.3)	7.1 (1.4)	10.2 (2.1)	<0.001
Initial Hb ≤9 g/dL – no. (%)	298 (44.7)	267 (69.7)	31 (10.9)	<0.001
Initial Hb ≤7 g/dL – no. (%)	125 (18.7)	124 (32.4)	1 (0.4)	<0.001
Drop of Hb ≥2 g/dL – no. (%)	231 (34.6)	150 (39.2)	81 (28.5)	0.004
Severe GIB – no. (%)	354 (53.1)	255 (66.6)	99 (34.9)	<0.001
Endoscopy performed – no. (%)	575 (86.2)	335 (87.5)	240 (84.5)	0.273
SRH – no. (%)	193 (28.9)	141 (43.0)	52 (22.5)	<0.001
Endoscopic therapy – no. (%)	200 (30.0)	132 (34.5)	68 (23.9)	0.003
AT upon presentation – no. (%)	419 (62.8)	258 (67.4)	161 (57.0)	0.005
AP only	220 (52.5)	125 (48.4)	95 (59.0)	0.065
AC only	110 (26.3)	70 (27.1)	40 (24.8)	
AP and AC	89 (21.2)	63 (24.4)	26 (16.1)	
AT on discharge* – no. (%)	316 (51.2)	185 (53.9)	131 (47.8)	0.130
AP only	180 (57.0)	103 (55.7)	77 (58.8)	0.303
AC only	99 (31.3)	56 (30.3)	43 (32.8)	
AP and AC	37 (11.7)	26 (14.1)	11 (8.4)	
Length of hospital stay – d (SD)	8.0 (21.0)	8.5 (11.6)	7.1 (29.2)	0.423
Mortality – no. (%)				
In-hospital	53 (7.9)	43 (11.2)	10 (3.5)	<0.001
1 month	81 (12.1)	62 (16.2)	19 (6.7)	<0.001
1 year	159 (23.8)	121 (31.6)	38 (13.4)	<0.001
End of follow up	316 (47.4)	226 (59.0)	90 (31.7)	<0.001
Rebleeding – no. (%)				
In-hospital	31 (4.8)	25 (6.9)	6 (2.2)	0.006
1 month	66 (10.3)	45 (12.4)	21 (7.5)	0.045
1 year	107 (16.6)	72 (19.8)	35 (12.5)	0.015
End of follow up	143 (22.2)	94 (25.8)	49 (17.6)	0.013

*Missing information about AT on discharge

CCI, Charlson Comorbidity Index; SRH, stigmata of recent hemorrhage; Hb, hemoglobin; AT, antithrombotic; AP, antiplatelet; AC, anticoagulant; UGIB, upper gastrointestinal bleeding; LGIB, lower gastrointestinal bleeding; SD, standard deviation

mortality (HR 1.28, 95%CI 1.16-1.42; P<0.001). Among transfused patients, the presence of SRH was a predictor of 1-month (HR 2.4, 95%CI 1.2-4.8; P=0.013) and end-of-follow-up rebleeding (HR 1.8, 95%CI 1.1-3.1; P=0.022), while the use of AP upon presentation was protective (HR 0.50, 95%CI 0.3-0.9; P=0.012). We could not identify any predictors of in-hospital rebleeding. Transfusion at an Hb threshold of ≤7 g/dL did not affect rebleeding rates.

Table 2 The 4 most common sources of UGIB and LGIB in patients who were transfused and those who were not transfused

Sources of bleeding	Non-transfused patients n=284	Transfused patients n=383
UGIB		
PUD – no. (%)	98 (34.5)	124 (32.4)
Esophageal varices – no. (%)	12 (4.2)	25 (6.5)
Luminal GI cancer – no. (%)	4 (1.4)	14 (3.7)
Dieulafoy – no. (%)	3 (1.1)	11 (2.9)
LGIB		
Diverticulosis – no. (%)	34 (12.0)	37 (10.0)
Hemorrhoids – no. (%)	21 (7.4)	15 (3.9)
Luminal GI cancer – no. (%)	13 (4.6)	6 (1.6)
AVM – no. (%)	7 (2.5)	22 (5.7)

UGIB, upper gastrointestinal bleeding; LGIB, lower gastrointestinal bleeding; PUD, peptic ulcer disease; GI, gastrointestinal; AVM, arteriovenous malformation

Effect of transfusion threshold on the composite outcome of mortality or rebleeding among transfused patients

On multivariate analysis, the age-adjusted CCI was a predictor of the composite outcome of 1-month mortality or rebleeding (HR 0.88, 95%CI 0.78-1.00; P=0.05). BT at a threshold of ≤7 g/dL did not predict 1-month (HR 0.57, 95%CI 0.25-1.28; P=0.17) or end-of-follow-up (HR 1.28, 95%CI 0.87-1.86; P=0.21) composite outcomes.

Effect of transfusion on mortality and rebleeding among patients with cardiovascular diseases

A subgroup analysis was performed on patients with cardiovascular diseases, comparing those who were transfused and those who were not. Although transfusion was associated with short- and long-term mortality on bivariate analysis—in-hospital mortality was 12.7% in transfused patients vs. 3.4% in non-transfused patients (P=0.006), 1-month mortality was 10.7% vs. 2.5% (P=0.009), 1-year mortality was 33.5% vs. 18.0% (P=0.003), and end of follow-up mortality was 62.9% vs. 44% (P=0.001)—it was not a significant predictor of mortality on Cox regression analysis, taking account of age-adjusted CCI, severe GIB, mean initial Hb and SBP, a drop of Hb of ≥2 g/dL, BT, and being on only AC upon presentation (HR 1.406, 95%CI 0.85-2.32; P=0.181). Furthermore, there was no association between transfusion and rebleeding in that subgroup.

Effect of transfusion on mortality and rebleeding among patients with Hb >7 g/dL at presentation

A subgroup analysis was conducted on patients presenting with an Hb level >7 g/dL. As in the entire cohort, transfusion in this subgroup was associated with both short-term and long-term mortality on bivariate analysis—in-hospital mortality was 12% vs. 3.5% (P<0.001), 1-month mortality was 12% vs. 3.5% (P<0.001), 1-year mortality was 30.5% vs. 12.7% (P<0.001), and end-of-follow-up mortality was 56.5% vs. 31.4% (P<0.001) for transfused vs. non-transfused patients, respectively. However, Cox regression analysis indicated that transfusion was not a significant predictor of mortality in these patients (HR 1.177, 95%CI 0.76-1.82; P=0.465). Additionally, no association was found between transfusion and rebleeding in this subgroup.

Discussion

Our study suggests that BT does not increase the risk of mortality or rebleeding in a cohort of patients with overt, primarily non-variceal GIB, the majority of whom were on AT therapy. However, independent predictors of mortality included age-adjusted CCI, SRH, and being on AC as the only AT. Among transfused patients, we found no significant difference in mortality or rebleeding rates between patients transfused at Hb ≤7 g/dL and >7 g/dL. The age-adjusted CCI was the only independent predictor of mortality among transfused patients, while being discharged on only AP was found to be protective. Continuing AP therapy in GIB patients who receive BTs might be protective against adverse outcomes.

The issue whether BT independently increases mortality in GIB has important clinical implications. However, this is complicated by the fact that patients who receive transfusions are typically sicker and have higher rates of severe hemorrhage. Previous studies have shown that BTs may be associated with higher mortality rates, particularly in patients with variceal hemorrhage [10,20-22]. The studies on non-variceal UGIB showed inconsistent results [22]. Our study, which included patients with UGIB, LGIB and only a small proportion of patients with variceal hemorrhage, found that BT did not affect long-term mortality, but increased 1-year mortality 3-fold, even after adjustment for confounders [11].

The age-adjusted CCI appears to be a predictor of mortality, independently of whether a patient with GIB was transfused or not. This is consistent with previous reports by our group (11) and by others [23]. Managing comorbidities through careful monitoring and treatment after a GIB episode may reduce long-term mortality. Additionally, the presence of SRH on endoscopy, as well as a lower Hb, are predictors of higher mortality in GIB. These factors may be surrogates of severe bleeding, which is associated with worse outcomes, and both are included in the validated Rockall and GBS scoring systems for predicting mortality [5,24,25]. Being on only AC at the time of GIB presentation is also an independent predictor of mortality [5]. However, the mechanism behind this is unclear, and there may be other confounders that were not accounted for.

In this study, BT in general and transfusing at Hb threshold of ≤7 g/dL did not lower the risk of rebleeding. The presence of SRH was a predictor of increased rebleeding risk both at 1 month and at the end of follow up, regardless of whether a patient was transfused or not. A lower Hb, which may indicate severe bleeding, was also associated with a greater risk of rebleeding. Interestingly, we note again that being on AP therapy upon presentation is protective against rebleeding. Although the underlying mechanism remains unclear, these

Table 3 Baseline clinical characteristics and outcomes of patients presenting with gastrointestinal bleeding who rebled and those did not rebleed

Characteristics	All patients N=643*	Patients who rebled N=143	Patients who did not rebleed N=500	P-value
Female sex – no. (%)	239 (36.4)	57 (36.5)	182 (36.4)	0.975
Mean age – y (SD)	67.8 (16.4)	67.09 (16.2)	68.08	0.513
Age ≥75 y – no. (%)	278 (42.4)	63 (40.4)	215 (43.0)	0.564
Mean age-adjusted CCI – (SD)	4.74 (2.86)	4.43 (2.5)	4.84 (3.0)	0.088
Cardiovascular diseases – no. (%)	304 (47.3)	70 (49)	234 (46.8)	0.650
Cirrhosis – no. (%)	50 (7.8)	17 (11.9)	33 (6.6)	0.037
GIB Location – no. (%)				
UGIB	361 (55.2)	91 (58.7)	270 (54.1)	0.115
LGIB	238 (36.4)	48 (31.0)	190 (38.1)	
SBP <100 mmHg – no. (%)	92 (14.0)	26 (16.7)	66 (13.2)	0.276
Mean initial SBP – mmHg (SD)	123 (21.8)	121.6 (21.7)	123.45 (21.9)	0.362
Mean lowest Hb – g/dL (SD)	8.47 (2.3)	7.99 (2.03)	8.62 (2.37)	0.001
Initial Hb ≤9 g/dL – no. (%)	288 (43.9)	74 (47.4)	214 (42.8)	0.308
Initial Hb ≤7 g/dL – no. (%)	118 (18.0)	37 (23.7)	81 (16.2)	0.033
Blood transfusion – no. (%)	373 (56.9)	103 (66.0)	270 (54.0)	0.008
Transfused				
1-2 units – no. (%)	210 (56.3)	55 (53.4)	155 (57.4)	0.209
3-4 units – no. (%)	113 (30.3)	29 (28.2)	84 (31.1)	
≥5 units – no. (%)	50 (13.4)	19 (18.4)	31 (11.5)	
Endoscopy performed – no. (%)	563 (85.8)	144 (92.3)	419 (83.8)	0.008
SRH – no. (%)	191 (34.9)	67 (48.6)	124 (30.3)	< 0.001
Endoscopic therapy – no. (%)	199 (30.3)	66 (42.3)	133 (26.6)	< 0.001
AT on presentation – no. (%)				
AP only	215 (46.2)	40 (35.7)	175 (49.6)	0.010
AC only	104 (29.4)	29 (28.7)	75 (29.6)	0.862
AP and AC	87 (25.8)	15 (17.2)	72 (28.8)	0.034
AT on discharge* – no. (%)				
AP only	175 (36.7)	36 (31.9)	139 (38.2)	0.223
AC only	97 (24.3)	26 (25.2)	71 (24.0)	0.798
AP and AC	37 (10.9)	8 (9.4)	29 (11.4)	0.608
Length of hospital stay – d (SD)	8.39 (26.3)	9.38 (34.7)	8.08 (23.13)	0.590
Mortality – no. (%)				
In-hospital mortality	48 (7.5)	11 (7.7)	37 (7.4)	0.907
One-month mortality	75 (11.7)	15 (10.5)	60 (12.0)	0.620
One-year mortality	152 (23.6)	29 (20.3)	123 (24.6)	0.284
End of follow up mortality	296 (46.0)	70 (49.0)	226 (45.2)	0.427

* 24 patients out of the 667 did not have data on rebleeding

CCI, Charlson Comorbidity Index; SRH, stigmata of recent hemorrhage; Hb, hemoglobin; AT, antithrombotic; AP, antiplatelet; AC, anticoagulant; UGIB, upper gastrointestinal bleeding; LGIB, lower gastrointestinal bleeding; SD, standard deviation

results suggest that AP therapy should be continued or resumed as soon as possible following a GIB episode.

Previously, several RCTs and meta-analyses have been published comparing restrictive and liberal transfusion strategies and suggesting that a restrictive strategy might protect against adverse outcomes in GIB [7,8,12]. Consequently, various clinical societies and guidelines have adopted a restrictive strategy. However, it remains unclear whether such a strategy is beneficial for patients with non-variceal UGIB, LGIB, severe or life-threatening hemorrhage, or those with cardiovascular disease. Our findings do not support the notion that restricting transfusion to a threshold of Hb ≤7 g/dL is more protective against mortality or rebleeding, compared to a higher threshold. Instead, decisions regarding transfusions, including the threshold and target Hb levels, should be individualized considering the severity of bleeding, hemodynamic compromise, and the patient's clinical characteristics and sensitivity to low blood oxygen saturation, such as in patients with cardiovascular and pulmonary diseases.

Table 4 Baseline characteristics and outcomes of patients who were transfused at a hemoglobin level of ≤7 g/dL during the course of their hospitalization (Group 1), and those who were transfused at a hemoglobin level >7 g/dL (Group 2)

Characteristics	Group 1 BT at Hb ≤7 g/dL n=133	Group 2 BT at Hb >7 g/dL n=250	P-value
Female sex – no. (%)	66 (49.6)	82 (32.8)	0.001
Mean age – y (SD)	71.8 (13.1)	68.6 (16.0)	0.960
Age ≥75 y – no. (%)	64 (48.1)	105 (42.0)	0.036
Mean age-adjusted CCI – (SD)	5.5 (2.7)	5.1 (2.8)	0.168
Cardiovascular or cerebrovascular diseases – no. (%)	61 (45.9)	114 (45.6)	0.961
Cirrhosis – no. (%)	11 (8.3)	24 (9.6)	0.667
GIB Location – no. (%)			
UGIB	80 (61.1)	153 (61.2)	0.827
LGIB	37 (28.2)	77 (30.8)	
Severe GIB – no. (%)	100 (75.2)	155 (62.0)	0.009
Mean initial Hb – g/dL (SD)	6.2 (1.0)	9.3 (1.9)	< 0.001
Initial Hb ≤9 g/dL – no. (%)	130 (97.7)	137 (54.8)	< 0.001
Initial Hb ≤7 g/dL – no. (%)	124 (93.2)	0 (0)	< 0.001
Mean lowest Hb – g/dL (SD)	6.0 (0.8)	7.8 (1.2)	< 0.001
Mean initial SBP – mmHg (SD)	118.2 (20.6)	120.7 (21.1)	0.276
SBP <100 mmHg – no. (%)	28 (21.1)	40 (16.0)	0.218
Mean blood units transfused – (SD)	3.53 (2.3)	2.17 (1.3)	< 0.001
Transfused			
1-2 units – no. (%)	47 (35.3)	167 (66.8)	< 0.001
3-4 units – no. (%)	59 (44.4)	60 (24.0)	
≥ 5 units – no. (%)	27 (20.3)	23 (9.2)	
Drop of Hb ≥2 g/dL – no. (%)	38 (28.6)	112 (44.8)	0.002
Endoscopy performed – no. (%)	119 (89.5)	216 (86.4)	0.387
SRH – no. (%)	48 (40.7)	93 (44.3)	0.526
Endoscopic therapy – no. (%)	48 (36.1)	84 (33.6)	0.625
AT on presentation – no. (%)	101 (75.9)	157 (62.8)	0.040
AP only	40 (30.1)	85 (34.0)	0.264
AC only	29 (21.8)	41 (16.4)	0.022
AP and AC	32 (24.1)	31 (12.4)	< 0.001
AT on discharge – no. (%)	71 (53.4)	114 (45.6)	0.247
AP only	30 (22.6)	73 (29.2)	0.998
AC only	25 (18.8)	31 (12.4)	0.034
AP and AC	16 (12.0)	10 (4.0)	0.001
Rebleeding – no. (%)			
In-hospital	11 (9.0)	14 (5.8)	0.250
1 month	16 (13.1)	23 (9.5)	0.293
1 year	28 (23.0)	44 (18.2)	0.281
End of follow up	46 (26.9)	48 (24.9)	0.254
Mortality – no. (%)			
In-hospital	17 (12.8)	26 (10.4)	0.482
1 month	24 (18.0)	38 (15.2)	0.472
1 year	46 (34.6)	75 (30.0)	0.358
End of follow up	87 (65.4)	139 (55.6)	0.063

*The remaining being either of small bowel origin or undetermined

Age-adjusted CCI, age-adjusted Charlson Comorbidity Index; GIB, gastrointestinal bleeding; SBP, systolic blood pressure; Hb, hemoglobin; SRH, stigmata of recent hemorrhage; AT, antithrombotic; AP, antiplatelet; AC, anticoagulant; SD, standard deviation

The majority of patients in our cohort were taking AT (67.3%) upon presentation, highlighting the importance of this factor in GIB. Our results suggest that resuming AP upon discharge was protective against end-of-follow-up mortality.

Table 5 Independent predictors of end-of-follow-up mortality on multivariate analysis in patients who were transfused (383 patients)

Mortality (reference: alive)				
Predictors	Hazard ratio	95%CI		P-value
		Lower	Upper	
Transfusion at Hb ≤7 g/dL	1.107	0.816	1.502	0.513
Mean age-adjusted CCI	1.279	1.220	1.340	<0.001
AC only at presentation	1.148	0.797	1.653	0.458
AP only at discharge	0.696	0.489	0.991	0.044

Hb, hemoglobin; age-adjusted; CCI, age-adjusted Charlson Comorbidity Index; AP, antiplatelet; AC, anticoagulant; CI, confidence interval

This is in accordance with the most recent literature advocating for early resumption of AP when indicated after an episode of GIB [5,26-33]. The protective effect of AP may be due to their cardiovascular benefits in patients with cardiovascular comorbidities. which could outweigh the risk of rebleeding [8]. On the other hand, being on AC alone was associated with a higher end-of-follow-up mortality, underscoring the importance of close monitoring and follow up for patents who develop GIB on AC. Our study did not find any protective effect of transfusing at a threshold of ≤7 g/dL against mortality or rebleeding. This may be because our cohort comprised a heterogeneous group of patients with non-variceal UGIB, LGIB, and a high prevalence of cardiovascular disease. A limited number of studies have studied the association between different AT classes and GIB-related mortality and rebleeding rates, including 1 study from the United Kingdom that investigated transfusion strategies in LGIB and found no difference in rebleeding rates between liberal and restrictive transfusion strategies.

The strengths of this study include its prospective design and the long-term follow up, which allowed for meticulous documentation of all factors that could affect mortality. The real-life practice setting of the study increases the generalizability of the findings, since patients with various comorbidities were included, unlike in tightly controlled RCTs. In addition, this study accounted for different classes of AT and the severity of GIB, which is often lacking in previous studies. The main limitation of the study is that it was not an RCT, but rather was based on observational data. Additionally, the study was conducted at a single tertiary care center, which may limit the external validity of the results. Moreover, although the use of AC upon presentation was found to be a predictor of mortality and resuming AP upon discharge was associated with a lower risk of rebleeding and mortality, the small sample size prevented comparisons between different subgroups of AT therapy.

In conclusion, this study showed that BT is not a predictor of short- or long-term mortality or rebleeding in patients with GIB. Furthermore, transfusing patients with GIB at an Hb level of ≤7 g/dL did not lead to better outcomes in terms of short term or long-term mortality or rebleeding risk, compared to transfusing at an Hb greater than 7 g/dL. In addition, our data suggest that AC adversely affects mortality, whereas AP protect against death and rebleeding in patients with GIB. These findings provide an important foundation for future RCTs to establish the most effective transfusion strategy for this patient population. While a restrictive approach may not be protective against mortality, other factors, such as age, comorbidities and AT use, have consistently been shown to impact outcomes. Guidelines should consider all these factors when deciding upon the optimal threshold and target for BT.

Summary Box

What is already known:

- Gastrointestinal bleeding (GIB) is a significant medical emergency with high morbidity and mortality
- Blood transfusion (BT) is a critical component in GIB management, but its impact on clinical outcomes remains controversial
- Current guidelines recommend a restrictive BT strategy for GIB patients, based on limited evidence from randomized controlled trials and systematic reviews
- The effects of antithrombotics on outcomes in transfused GIB patients are not well understood, and the optimal transfusion strategy remains uncertain

What the new findings are:

- In this cohort, BT was not found to increase the risk of mortality or rebleeding in patients with primarily non-variceal GIB
- No significant difference in mortality or rebleeding rates was observed between patients transfused at hemoglobin levels ≤7 g/dL and those transfused at higher levels
- Age-adjusted Charlson Comorbidity Index was a consistent independent predictor of mortality in GIB patients, regardless of transfusion status
- In patients with GIB, being on anticoagulant therapy is associated with increased mortality, while continuing antiplatelet therapy in patients with GIB who receive blood transfusion might be protective against mortality and rebleeding

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