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# The association between red blood cell transfusion and outcomes in patients with upper gastrointestinal bleeding

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## Abstract

**Background:** The benefits of transfusion for acute upper gastrointestinal bleeding (UGIB) have not been well established; however, previous studies suggest that transfusion is associated with adverse outcomes. We performed an observational study using a 10-year database to analyze the association between red blood cell (RBC) transfusion and outcomes in patients with UGIB in the emergency department (ED).

**Method and findings:** All adult patients with UGIB were identified through diagnostic codes. Hospital mortality was the primary outcome; further bleeding was the secondary outcome. Logistic regression, propensity analyses, and conditional logistic regression were performed to determine factors associated with outcomes. Of 59,188 enrolled patients, 31.6% ($n = 18,705$) received RBC transfusions within 24 h following presentation to the ED. Hospital mortality was noted in 3.9 and 10.6% of the patients in the non-RBC transfusion and RBC transfusion groups, respectively ($P < 0.001$). RBC transfusion was associated with increased mortality risk (unadjusted odds ratio (OR) 2.95, 95% confidence interval (CI) 2.75–3.16; $P < 0.001$) among all patients and in the propensity-matched cohort (unadjusted OR 1.55, 95% CI 1.39–1.72; $P < 0.001$). Further bleeding was noted in 5.6 and 33.8% of the patients in the non-RBC transfusion and RBC transfusion groups, respectively ($P < 0.001$). RBC transfusion was associated with increased risk of further bleeding (unadjusted OR 8.60, 95% CI 8.16–9.06; $P < 0.001$) among all patients and in the propensity-matched cohort (unadjusted OR 2.58, 95% CI 2.37–2.79; $P < 0.001$).

**Conclusion:** RBC transfusion was significantly associated with increased rates of hospital mortality and further bleeding in patients with UGIB. Although our findings have strengths, these results are not generalizable to all patients presenting with UGIB, especially patients presenting with exsanguinating bleeding. Additional prospective trials to guide optimal transfusion strategies in UGIB patients are needed.

## Introduction

Acute upper gastrointestinal bleeding (UGIB) is a common emergency medical condition with an annual incidence of 50 to 200 cases per 100,000 individuals, and a mortality rate ranging from 3 to 14%[1–3]. UGIB is a typical indication of red blood cell (RBC) transfusion, and accounts for ~11–14% of all RBC transfusions in England[4,5]. Acute blood loss results in decreased tissue perfusion and oxygen delivery; thus, blood transfusion, which improves hemostasis and restores oxygen delivery in massive exsanguinating hemorrhage, is considered life-saving[6,7]. However, most patients with UGIB experience mild to moderate hemorrhage without evidence of hemodynamic instability. According to one survey

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conducted in the United Kingdom in 2007, 62% of admitted patients with UGIB were hemodynamically stable; hence, the patients did not have a heart rate > 100 bpm nor had a systolic blood pressure < 100 mmHg[8]. Another investigation from Canada reported that 68.4% of nonvariceal patients with UGIB had no features of hemodynamic compromise[9]. In such circumstances, the benefit and effectiveness of transfusion remain unclear.

Randomized trials involving patients who had hip surgery[10], cardiac surgery[11], or were critically ill[12] have demonstrated that a lower threshold for transfusion is safe, without adversely influencing outcomes. Whether this finding applies to patients with UGIB is uncertain. Observational cohort studies have suggested that transfusion is associated with an increased risk of further bleeding, but not death, in patients with UGIB[9,13]. Recently, a large single-center, randomized controlled trial conducted in Spain revealed significantly reduced rates of mortality and further bleeding with a lower threshold for transfusion in patients with acute UGIB[14]. However, a multi-center, cluster-randomized trial conducted in the United Kingdom showed no significant difference in clinical outcomes between restrictive (transfusion when hemoglobin level is <8 g/dL) and liberal (transfusion when hemoglobin level is <10 g/dL) transfusion strategies[15]. With these inconsistent results, the benefit or harm of RBC transfusion in patients with UGIB remains inconclusive. Thus, we report the findings of a propensity analysis, which aimed to determine the association between RBC transfusion and clinical outcomes, including hospital mortality and further bleeding, from a large sample of patients with UGIB.

## Methods

### Data source

This study used the electronic medical records of the Chang Gung Research Database (CGRD), which consists of de-identified data designed for research purposes that are stored in a secure server for data analysis. The CGRD currently contains data from six different branches of Chang Gung Memorial Hospital, with two medical centers, three regional hospitals, and one local hospital, distributed in northern, central, and southern Taiwan. The CGRD uses a computerized system to record all key clinical information, including treatment, diagnoses, prescriptions, laboratory results, procedure information, demographics, vital signs, date of consultation, date of hospital admission, and date of discharge. All patient records in the CGRD are anonymized to protect patient confidentiality. A unique reference number is allocated to each individual patient, facilitating data retrieval and further analysis. This study protocol was approved by the Institutional Review Board of the Chang Gung Medical Foundation Institutional Review Board (IRB No: 201600990B0). Informed consent was waived, as the data used in this study were anonymized.

### Study design

We performed a retrospective cohort study. All adult patients (>18 years old) admitted to the emergency department (ED) between January 2006 and December 2015 with evidence of UGIB were reviewed. UGIB was identified in the CGRD using the physician-assigned International Classification of Diseases 9th revision (ICD-9) codes. We included possible diagnoses of UGIB, such as peptic ulcer hemorrhage (531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, and 534.6), bleeding gastritis and/or duodenitis (535.01, 535.11, 535.21, 535.31, 535.41,535.51, 535.61, and 535.71), and gastrointestinal hemorrhage (578) (Supplementary Table 1). Only ED ICD-9 coding was used as the defining index diagnosis in the present study. We also included possible diagnoses of liver cirrhosis, such as alcoholic cirrhosis of liver (571.2), cirrhosis of liver without mention of alcohol (571.5), biliary cirrhosis (571.6), esophageal varices with bleeding (456.0), esophageal varices without mention of bleeding (456.1), esophageal varices in diseases classified elsewhere (456.2), hepatic coma (572.2), portal hypertension (572.3), hepatorenal syndrome (572.4), and other sequelae of chronic liver disease (572.8) (Supplementary Table 1). The index date was defined as the date of ED admission with the presentation of UGIB. Patients with incomplete data and those who developed UGIB during hospital stay, but were admitted because of other diseases, were excluded.

### Definition for RBC transfusion

The RBC transfusion group consisted of patients who received RBC transfusions within 24 h following presentation to ED. The non-RBC transfusion group consisted of patients who were not classified into the RBC transfusion group.

### Definition of shock

Shock was defined as systolic blood pressure < 90 mmHg at the ED triage.

### Definition of variceal bleeding

Acute variceal bleeding was defined via endoscopy in accordance with Baveno II-III criteria when endoscopy showed active hemorrhage (spurting or oozing) from any varices, the presence of a white nipple or a clot over any varices, or the presence of blood in the stomach with varices as the only potential source of bleeding[16].

### Outcomes

The primary outcome was hospital mortality; the secondary outcome was further bleeding. Further bleeding

**Table 1 Basic characteristics of all 59,188 patients**

| Characteristic | Non-RBC transfusion group | | RBC transfusion group | | Standardized difference | *P* value |
|---|---|---|---|---|---|---|
| | *N* = 40,483 (68.4%) | | *N* = 18,705 (31.6%) | | | |
| | *N* | % | *N* | % | | |
| Male | 27,293 | 67.4 | 12,617 | 67.5 | 0.0007 | 0.93 |
| Age > 65 years | 18,067 | 44.6 | 9822 | 52.5 | 0.1582 | <0.001 |
| Ischemic heart disease | 4240 | 10.5 | 2170 | 11.6 | 0.0359 | <0.001 |
| Myocardial infarction | 992 | 2.5 | 577 | 3.1 | 0.0387 | <0.001 |
| Heart failure | 2855 | 7.1 | 1729 | 9.2 | 0.0802 | <0.001 |
| Cerebrovascular accidents | 2594 | 6.4 | 1187 | 6.3 | −0.0025 | 0.78 |
| Peripheral vascular disease | 1170 | 2.9 | 648 | 3.9 | 0.0327 | 0.0002 |
| Renal disease | 8145 | 20.1 | 4723 | 25.2 | 0.1227 | <0.001 |
| Malignancy | 8375 | 20.7 | 5561 | 29.7 | 0.2094 | <0.001 |
| Ulcer disease | 19,185 | 47.4 | 9272 | 49.6 | 0.0436 | 0.8288 |
| Liver cirrhosis | 8121 | 20.1 | 5845 | 31.2 | 0.2583 | <0.001 |
| Child A | 2376 | 5.9 | 1057 | 5.7 | −0.0093 | 0.29 |
| Child B | 4044 | 10.0 | 2702 | 14.4 | 0.1364 | <0.001 |
| Child C | 1701 | 4.2 | 2086 | 11.2 | 0.2633 | <0.001 |
| Upper gastrointestinal bleeding history | 5218 | 12.9 | 2936 | 15.7 | 0.0803 | <0.001 |
| Variceal bleeding | 7969 | 19.7 | 5330 | 28.5 | 0.2071 | <0.001 |
| Hb < 10 g/dl | 16265 | 40.2 | 14283 | 76.4 | 0.7881 | <0.001 |
| INR > 1.5 | 2500 | 6.2 | 2575 | 13.8 | 0.2554 | <0.001 |
| Shock at ED | 2773 | 6.8 | 2702 | 14.4 | 0.2481 | <0.001 |
| Rockall score > 2 | 26,779 | 66.1 | 15,674 | 83.8 | 0.4161 | <0.001 |
| Daytime | 21,515 | 53.1 | 9932 | 53.1 | −0.0009 | 0.91 |
| Weekend | 10,673 | 26.4 | 4925 | 26.3 | −0.0008 | 0.93 |
| PPI use | 4157 | 10.3 | 10,376 | 55.5 | 1.0977 | <0.001 |
| Terlipressin use | 846 | 2.1 | 3874 | 20.7 | 0.6128 | <0.001 |
| Hospital 1 | 2466 | 6.1 | 37 | 0.2 | −0.3426 | <0.001 |
| Hospital 2 | 4493 | 11.1 | 2174 | 11.6 | 0.0165 | 0.06 |

**Table 1** continued

| Characteristic | Non-RBC transfusion group | | RBC transfusion group | | Standardized difference | *P* value |
|---|---|---|---|---|---|---|
| | *N* = 40,483 (68.4%) | | *N* = 18,705 (31.6%) | | | |
| | *N* | % | *N* | % | | |
| Hospital 3 | 17,994 | 44.5 | 6859 | 36.7 | −0.1589 | <0.001 |
| Hospital 4 | 5416 | 13.4 | 3720 | 19.9 | 0.1755 | <0.001 |
| Hospital 5 | 9711 | 24.0 | 5170 | 30.5 | 0.1472 | <0.001 |
| Hospital 6 | 403 | 1.0 | 205 | 1.1 | 0.0099 | 0.26 |
| Year 2006 | 3073 | 7.6 | 1090 | 5.8 | −0.0705 | <0.001 |
| Year 2007 | 4753 | 11.7 | 1968 | 10.5 | −0.0388 | <0.001 |
| Year 2008 | 4445 | 11.0 | 2217 | 11.9 | 0.0274 | 0.0018 |
| Year 2009 | 3645 | 9.0 | 1935 | 10.3 | 0.0454 | <0.001 |
| Year 2010 | 3317 | 8.2 | 1340 | 7.2 | −0.0387 | <0.001 |
| Year 2011 | 4362 | 10.8 | 2149 | 11.5 | 0.0227 | 0.0098 |
| Year 2012 | 4412 | 10.9 | 1897 | 10.1 | −0.0247 | 0.0055 |
| Year 2013 | 4332 | 10.7 | 1982 | 10.6 | −0.0034 | 0.71 |
| Year 2014 | 4085 | 10.1 | 2206 | 11.8 | 0.0546 | <0.001 |
| Year 2015 | 4059 | 10.0 | 1921 | 10.3 | 0.0081 | 0.36 |

Daytime: from 8:00 a.m. to 5:00 p.m.; Weekend: Saturday and Sunday
*RBC* red blood cell, *Child A, B, C* Child–Pugh classification A, B, C (Child A denotes good hepatic function, Child B denotes intermediate hepatic function, and Child C poor function), *Hb* hemoglobin, *INR* international normalized ratio, *ED* emergency department, *PPI* proton pump inhibitor

was defined as that which required repeated esophagogastroduodenoscopy (EGD) after the initial resuscitation or initial endoscopic therapy, angiographic embolization, or operation to stop the bleeding. These patients were followed throughout the hospital course until in-hospital death or rebleeding episode. Admitted patients were followed for 30 days after discharge to determine if death occurred.

### Covariates

Baseline medical conditions, including heart failure, renal disease, malignancy, ulcer disease, liver cirrhosis, ischemic cardiac disease, previous stroke, peripheral arterial disease, and previous gastrointestinal bleeding, were included as dichotomous covariates in the analysis. For each patient, all diagnosis records dated before the individual index date were retrieved using ICD-9 codes (Supplementary Table 1) from the CGRD for the identification of baseline medical conditions. The medical condition of each patient was determined based on outpatient department ICD-9 codes or discharge ICD-9 codes (if the patient had been admitted to the hospital). The Child–Pugh classification system was used to classify the severity of cirrhosis[17]. Proton pump inhibitor (PPI) use was defined as the use of any intravenous PPI (including omeprazole, esomeprazole, and pantoprazole) for at least 72 h. Terlipressin use was defined as the use of intravenous terlipressin for at least 72 h. Patients were considered to be using aspirin use and undergoing novel oral anticoagulant (NOAC) therapy if these were prescribed for >30 days. Patients were considered to be using non-steroid anti-inflammatory drug (NSAIDs) if these were prescribed for >7 days.

#### *Rockall score*

The Rockall score was calculated for all patients. The Rockall score (range, 0–11) is a risk-stratification system for assessing the risk of further bleeding or mortality in patients with UGIB; a score $\leqq 2$ suggests a low risk of death, while a score $> 5$ suggests a high risk of further bleeding[18,19].

### Statistical analysis

RBC transfusion was not randomly allocated in the patient population; thus, we created a propensity score for RBC transfusion and controlled for potential confounding and selection biases[20]. Using multivariable logistic regression analysis, wherein patient outcome was not taken into account, a propensity score for RBC transfusion was determined. A full logistic regression model was fit with RBC transfusion as a dependent variable and every variable in Table 1 as independent variables. A propensity score for RBC transfusion for each patient was calculated using the logistic regression equation. The propensity score represented the probability that a patient with UGIB would receive a RBC transfusion. The scores were generated from the model for caliper matching, using a caliper distance of 0.01 without replacement[21,22]. Based on the propensity score, we matched the patients with UGIB who received RBC transfusion to those who did not receive RBC transfusion at a ratio of 1:1.

Balance between the RBC transfusion and non-RBC transfusion groups in the propensity-matched population was assessed using standardized differences for each covariate included in the model. A standardized difference of less than 0.1 was considered to indicate negligible correlation between the matched-control group and the binary variable[23].

Group differences were evaluated with Mann–Whitney $U$-tests, Student's $t$ tests, and $\chi^2$ or Fisher's exact tests. Using the data for all UGIB cases, three logistic regression models were fitted using hospital mortality and further bleeding as dependent variables. Using the data for the propensity-matched patients, four types of conditional logistic regression models were fitted with hospital mortality and further bleeding as dependent variables. A two-tailed, $P$ value $< 0.05$ was considered statistically significant. All analyses were conducted using the SAS Enterprise Guide (version 5.1; SAS Institute, Cary, NC).

### Sensitivity analysis

To test the robustness of the main results, several additional analyses were conducted. First, multiple imputation using multivariate normal distribution (Markov Chain Monte Carlo) was performed to evaluate the potential influence of missing data[24]. Second, a subgroup analysis with complete data set was also conducted by stratifying pre-existing heart disease into myocardial infarction, ischemic heart disease and heart failure, and stratifying liver cirrhosis into Child–Pugh classification A, B, C.

### Survival analyses

We used the Kaplan–Meier (KM) method to analyze the 30-day survival of admitted patients with and without RBC transfusion, and the log-rank test was performed to examine the differences in survival. Cox proportional hazard models were used to compute the hazard ratios (HRs) of admitted patients and subgroup patients for death by 30 days.

## Results

### Study population

Figure 1 illustrates the patient selection process. A total 63,740 patients with UGIB who presented to the ED during the study period were identified, of which 61,240 were >18 years old. The vital signs and laboratory data of 2052 (3.3%) adult patients were incomplete; thus, they

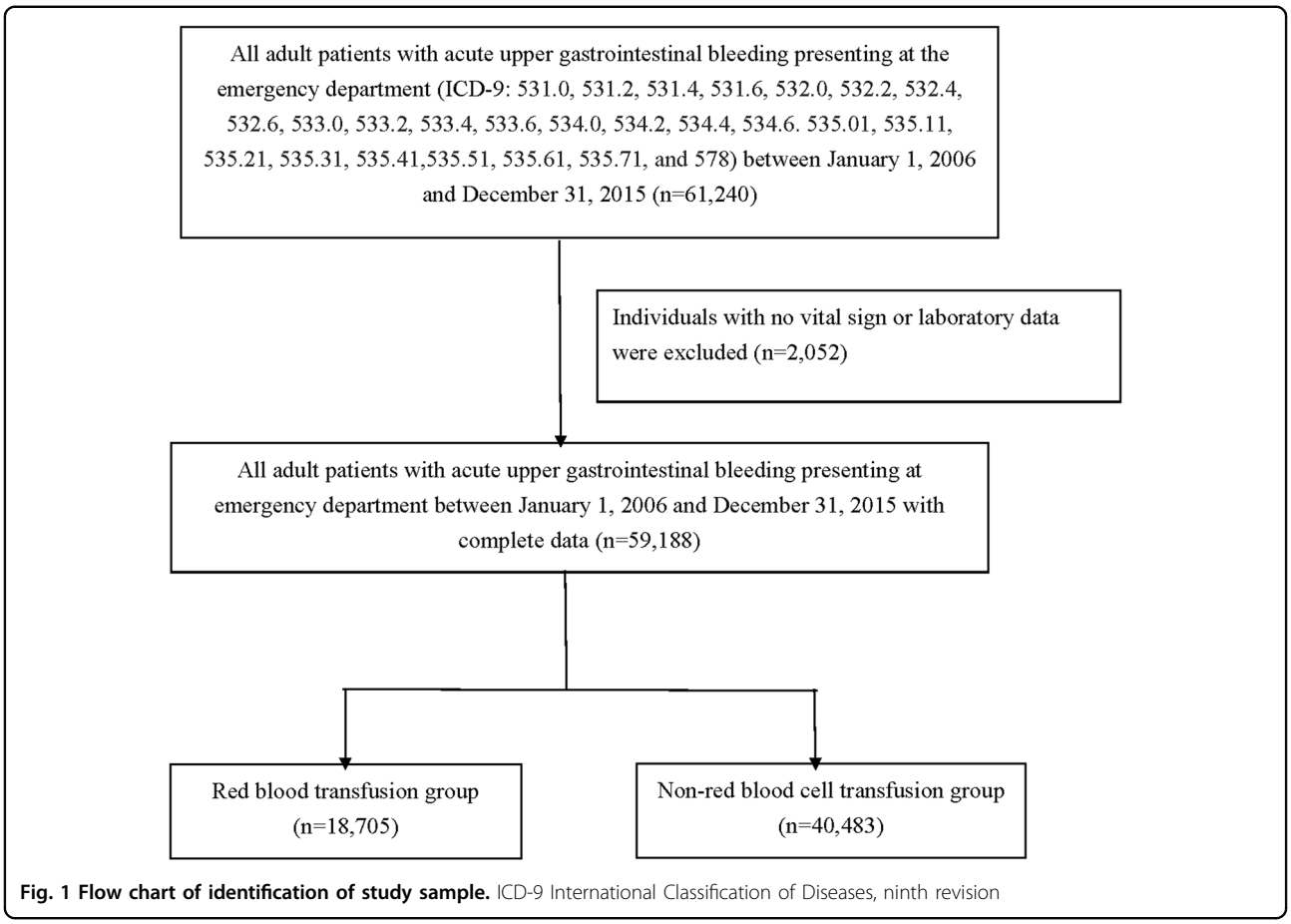


**Fig. 1 Flow chart of identification of study sample.** ICD-9 International Classification of Diseases, ninth revision

were excluded. A total of 59,188 patients constituted the study cohort. Of the 59,188 patients, 6.0% ($n = 3535$) died, 7.4% ($n = 4387$) were admitted to the ICU, and 14.5% ($n = 8602$) experienced further bleeding. In addition, 31.6% ($n = 18{,}705$) received RBC transfusions within 24 h following presentation to the ED. The median units of RBC transfused within 24 h in the RBC transfusion group was 3 (interquartile range; IQR: 2–5). In our current study, upper endoscopy (EGD) was performed on all (59,188) patients but only 52,185 (88.2%) patients underwent EGD within 24 h of admission and 7003 (11.8%) did not undergo EGD within 24 h. A total of 7962 (13.5%) patients received endoscopic therapy. A total of 784 patients (1.3%) used aspirin, 2394 patients (4.0%) used NSAIDs, and 50 patients (0.08%) used NOAC. Table 1 provides the demographic characteristics and comorbidities of the RBC transfusion and non-RBC transfusion groups. Significant differences between the groups were noted in most variables. Patients who received no RBC transfusion had a lower rate of hospital mortality and further bleeding than those with RBC transfusion (3.9 vs. 10.6, $P < 0.001$; 5.6 vs. 33.8, $P < 0.001$, respectively).

After matching, the standardized differences for patient and hospital baseline characteristics between RBC transfusion and non-RBC transfusion groups were all <0.1 (Table 2), indicating a small magnitude of difference. In the matched cohort, 6.8% of the patients in the non-RBC transfusion group and 7.8% of patients in the RBC transfusion group received intravenous terlipressin for at least 72 h. In the matched cohort, the groups did not differ in the proportion of variceal bleeding (7.3% non-RBC transfusion group vs. 7.8% RBC transfusion group). The proportions of patients from hospital 1, hospital 2, hospital 3, hospital 4, hospital 5, and hospital 6, were not significantly different between the matched groups (standardized difference = 0.0369, −0.0428, 0.0116, −0.0036, 0.0204, and −0.0008, respectively). Similarly, the proportions of visits in the year 2006, year 2009, and year 2015 were not significantly different between the matched groups (standardized difference = 0.0352, 0.0296, and −0.0335, respectively).

Table 3 summarizes the outcomes according to RBC transfusion or non-RBC transfusion among all patients with UGIB. In the initial unadjusted model, there were significant group differences in hospital mortality and further bleeding (all $P < 0.001$) (Table 3). RBC transfusion was associated with higher rates of hospital mortality and further bleeding in all the three models.

**Table 2 Basic characteristics in the matched cohort**

| Characteristic | Non-RBC transfusion group | | RBC transfusion group | | Standardized difference |
|---|---|---|---|---|---|
| | *N* = 11,060 | | *N* = 11,060 | | |
| | *N* | % | *N* | % | |
| Male | 7308 | 66.1 | 7312 | 66.1 | 0.0008 |
| Age > 65 years | 5903 | 53.4 | 5882 | 53.2 | −0.0038 |
| Ischemic heart disease | 1371 | 12.4 | 1371 | 12.4 | 0 |
| Myocardial infarction | 378 | 3.4 | 351 | 3.2 | −0.0137 |
| Heart failure | 1075 | 9.7 | 1064 | 9.6 | −0.0034 |
| Cerebrovascular accidents | 852 | 7.7 | 777 | 7.0 | −0.0260 |
| Peripheral vascular disease | 364 | 3.3 | 393 | 3.6 | 0.0144 |
| Renal disease | 2769 | 25.0 | 2861 | 25.9 | 0.0191 |
| Malignancy | 3043 | 27.5 | 2924 | 26.4 | −0.0242 |
| Ulcer disease | 5581 | 50.5 | 5562 | 50.3 | −0.0034 |
| Liver cirrhosis | 2940 | 26.6 | 2958 | 26.8 | 0.0037 |
| Child A | 593 | 5.4 | 622 | 5.6 | 0.0115 |
| Child B | 1471 | 13.3 | 1442 | 13.3 | −0.0078 |
| Child C | 876 | 7.9 | 894 | 8.1 | 0.0060 |
| Upper gastrointestinal bleeding history | 1818 | 16.4 | 1774 | 16.0 | −0.0108 |
| Varices bleeding | 2830 | 25.6 | 2811 | 25.4 | −0.0039 |
| Hb < 10 g/dl | 7240 | 65.5 | 7403 | 66.9 | 0.0312 |
| INR > 1.5 | 1123 | 10.2 | 1180 | 10.7 | 0.0169 |
| Shock at ED | 1282 | 11.6 | 1292 | 11.7 | 0.0028 |
| Rockall score > 2 | 8915 | 80.6 | 8831 | 79.9 | −0.0191 |
| Daytime | 5913 | 53.5 | 5904 | 53.4 | −0.0016 |
| Weekend | 2822 | 25.5 | 2949 | 26.7 | 0.0262 |
| PPI use | 3643 | 33.0 | 3432 | 31.3 | −0.0409 |
| Terlipressin use | 733 | 6.6 | 846 | 7.7 | 0.0397 |
| Hospital 1 | 18 | 0.16 | 37 | 0.33 | 0.0345 |
| Hospital 2 | 1650 | 14.9 | 1465 | 13.3 | −0.0481 |

**Table 2** continued

| Characteristic | Non-RBC transfusion group | | RBC transfusion group | | Standardized difference |
|---|---|---|---|---|---|
| | *N* = 11,060 | | *N* = 11,060 | | |
| | *N* | % | *N* | % | |
| Hospital 3 | 4100 | 37.1 | 4097 | 37.0 | −0.0006 |
| Hospital 4 | 2272 | 20.5 | 2367 | 21.4 | 0.0211 |
| Hospital 5 | 2865 | 25.9 | 2935 | 26.5 | 0.0144 |
| Hospital 6 | 155 | 1.4 | 159 | 1.4 | 0.0031 |
| Year 2006 | 655 | 5.9 | 736 | 6.7 | 0.0302 |
| Year 2007 | 1186 | 10.7 | 1162 | 10.5 | −0.0070 |
| Year 2008 | 1174 | 10.6 | 1193 | 10.8 | 0.0056 |
| Year 2009 | 914 | 8.3 | 984 | 8.9 | 0.0226 |
| Year 2010 | 867 | 7.8 | 903 | 8.2 | 0.0120 |
| Year 2011 | 1308 | 11.8 | 1322 | 12.0 | 0.0039 |
| Year 2012 | 1127 | 5.1 | 1129 | 5.1 | 0.0006 |
| Year 2013 | 1277 | 11.6 | 1201 | 10.9 | −0.0218 |
| Year 2014 | 1324 | 12.0 | 1298 | 11.7 | −0.0073 |
| Year 2015 | 1228 | 11.1 | 1132 | 10.2 | −0.0281 |

Daytime: from 8:00 a.m. to 5:00 p.m.; weekend: Saturday and Sunday
*RBC* red blood cell, *Child A, B, C* Child–Pugh classification A, B, C (Child A denotes good hepatic function, Child B denotes intermediate hepatic function, and Child C poor function), *Hb* hemoglobin, *INR* international normalized ratio, *ED* emergency department, *PPI* proton pump inhibitor

**Table 3 Logistic regression analysis (RBC transfusion group vs non-RBC transfusion group) among all 59,188 patients**

| | Hospital mortality | | | Further bleeding | | |
|---|---|---|---|---|---|---|
| **Analysis** | **Odds ratio** | **95% CI** | ***P* value** | **Odds ratio** | **95% CI** | ***P* value** |
| Unadjusted | 2.95 | 2.75–3.16 | <0.001* | 8.60 | 8.16–9.06 | <0.001* |
| Adjusted for selected variables [a] | 2.24 | 2.09–2.41 | <0.001* | 7.55 | 7.13–7.99 | <0.001* |
| Adjusted for all covariates [b] | 1.77 | 1.62–1.94 | <0.001* | 4.80 | 4.48–5.15 | <0.001* |
| Multiple[b] imputation | 1.02 | 1.024–1.031 | <0.001* | 1.18 | 1.17–1.19 | <0.001* |

[a]Selected variables included sex, age > 65 years, ischemic heart disease, myocardial infarction, heart failure, cerebrovascular accidents, peripheral vascular disease, renal disease, malignancy, ulcer disease, liver cirrhosis, INR > 1.5, variceal bleeding, shock at emergency department presentation, Rockall score > 2 and upper gastrointestinal bleeding history.
[b]All variables in Table 1 included as covariates. For model with hospital mortality, further bleeding was added as a covariate.
* indicates a p value < 0.05, which is statistically significant.

**Table 4 Conditional logistic regression (RBC transfusion group vs non-RBC transfusion group) among 23,326 propensity-matched patients**

| | Hospital mortality | | | Further bleeding | | |
|---|---|---|---|---|---|---|
| **Analysis** | **Odds ratio** | **95% CI** | ***P* value** | **Odds ratio** | **95% CI** | ***P* value** |
| Unadjusted | 1.54 | 1.39–1.71 | <0.001* | 3.43 | 3.16–3.72 | <0.001* |
| Adjusted for propensity | 1.53 | 1.37–1.70 | <0.001* | 3.42 | 3.15–3.71 | <0.001* |
| Adjusted for propensity and selected variables[a] | 1.62 | 1.45–1.82 | <0.001* | 3.96 | 3.61–4.37 | <0.001* |
| Adjusted for propensity and all covariates[b] | 1.67 | 1.48–1.88 | <0.001* | 4.26 | 3.85–4.71 | <0.001* |

[a]Selected variables included sex, age > 65 years, ischemic heart disease, myocardial infarction, heart failure, cerebrovascular accidents, peripheral vascular disease, renal disease, malignancy, ulcer disease, liver cirrhosis, INR > 1.5, variceal bleeding, shock at emergency department presentation, Rockall score > 2, and upper gastrointestinal bleeding history.
[b]All variables in Table 1 included as covariates. For model with hospital mortality, further bleeding was added as a covariate.
* indicates a p value < 0.05, which is statistically significant.

**Table 5 Subgroup unconditional logistic analysis of hospital mortality and further bleeding in RBC transfusion group vs non-RBC transfusion group**

| | Hospital mortality | | | Further bleeding | | |
|---|---|---|---|---|---|---|
| analysis | Unadjusted Odds ratio | 95% CI | p value | Unadjusted Odds ratio | 95% CI | p value |
| Subgroup by pre-existing heart disease | | | | | | |
| Myocardial infarction | 2.57 | 1.81–3.65 | < 0.001* | 7.66 | 5.34–10.9 | < 0.001* |
| Ischemic heart disease | 2.75 | 2.26–3.33 | < 0.001* | 6.78 | 5.74–8.01 | < 0.001* |
| Heart failure | 2.61 | 2.05–3.33 | < 0.001* | 6.57 | 5.29–8.16 | < 0.001* |
| Subgroup by liver cirrhosis | | | | | | |
| Child A | 1.74 | 1.32–2.29 | < 0.001* | 8.03 | 6.60–9.78 | < 0.001 |
| Child B | 2.09 | 1.79–2.42 | < 0.001* | 7.47 | 6.60–8.47 | < 0.001* |
| Child C | 1.17 | 0.99–1.42 | 0.06 | 5.97 | 5.08–7.00 | < 0.001* |

*Child A, B, C* Child–Pugh classification A, B, C (Child A denotes good hepatic function, Child B denotes intermediate hepatic function, and Child C poor function)
* indicates a p value < 0.05, which is statistically significant.

Table 4 summarizes the outcomes according to RBC transfusion or non-RBC transfusion among propensity-matched patients. In the initial unadjusted model, there were significant differences in hospital mortality and further bleeding (all $P < 0.001$) (Table 4). RBC transfusion was associated with higher rates of hospital mortality and further bleeding in all four conditional regression models.

Supplementary Table 2 summarizes the outcomes of transfusions according to different hemoglobin levels.

Supplementary Table 3 summarizes the characteristics and outcomes of the nonvariceal UGIB group and variceal UGIB group.

After matching all variables in Table 1 and an additional five variables, that underwent endoscopy within 24 h; endoscopic therapy; aspirin use; NSAID use; and NOAC use, a new matched cohort composed of 20,716 patients was developed. Supplementary Table 4 summarizes the outcomes according to RBC transfusion or non-RBC transfusion among newly matched patients. RBC transfusion was still associated with higher rates of hospital mortality and further bleeding in all the four models (all $P < 0.001$).

Supplementary Table 5 summarizes the outcomes according to RBC transfusion or non-RBC transfusion among all patients with UGIB. After including all variables in Table 1 and an additional five variables, that underwent endoscopy within 24 h; endoscopic therapy; aspirin use; NSAID use; and NOAC use, in the logistic regression model, similar results were obtained. RBC transfusion within 24 h following presentation to ED was still associated with increased rate of mortality and further bleeding (OR: 1.80, 95% CI: 1.64–1.97, $P < .001$; OR: 11.25, 95% CI: 8.83–14.35, $P < .001$, respectively).

### Sensitivity analysis

The results of multiple imputation presented a similar positive association of RBC transfusion with increased rate of hospital mortality and further bleeding (Table 3).

In subgroup analysis among all patients with UGIB, a positive association of RBC transfusion was still noted with increased rate of hospital mortality and further bleeding in patients with myocardial infarction, ischemic heart disease and heart failure, in cirrhotic patients with Child–Pugh classification A and B (Table 5).

### Survival analysis

In our cohort, a total of 35,801 (60.5%) patients were admitted to the hospital for further management of UGIB and of those admitted patients, a total of 30,342 (84.8%) patients had complete follow-up records. Figure 2 demonstrates a KM curve for 30-day survival for admitted patients. The probability of survival was higher in the non-RBC transfusion group than in the RBC transfusion

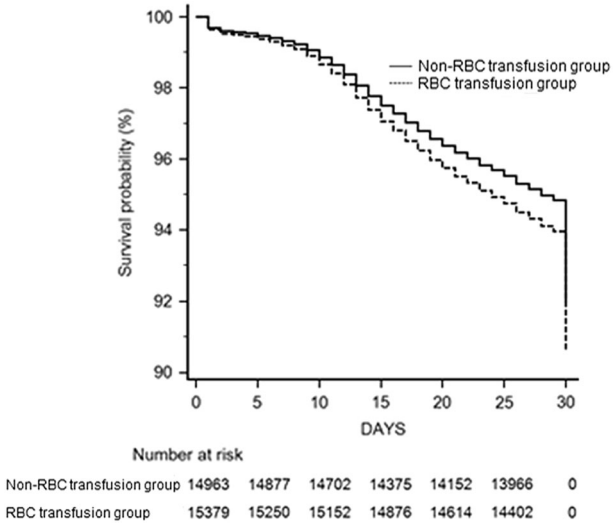


**Fig. 2** Kaplan–Meier (KM) curve for 30-day survival for admitted patients

group ($P < 0.001$ by log-rank test). Figure 3 shows the HRs, with 95% confidence intervals for death by 30 days according to subgroups.

## Discussion

To our knowledge, this is the first multi-center observational study with a large-sample size that focuses on RBC transfusion in patients with UGIB using a propensity-matched approach. The present results demonstrate that RBC transfusion is significantly associated with higher rates of hospital mortality and further bleeding among patients with UGIB. Our findings are consistent with those in previous observational or randomized studies in other settings, suggesting that RBC transfusion does increase mortality and could worsen outcomes[10,12,25]. Moreover, cumulating evidence supports that a liberal RBC transfusion strategy in critically ill patients is associated with increased mortality; thus, the transfusion threshold should be lower[12,25,26].

The current international consensus on the management of UGIB recommends a hemoglobin level <7 g/dL as the threshold for the indication of blood transfusion[27], which is lower than the previously recommended threshold of <10 g/dL[28]. In patients with variceal bleeding, the threshold for blood transfusion is a hemoglobin level <8 g/dL[29]. However, these recommendations are largely based on expert opinions[30] or international guidelines for transfusion in critically ill patients without UGIB[12,25,31]. Two large randomized trials on UGIB have been performed in recent years. One large randomized trial of patients with UGIB (the Barcelona trial), as reported in Villanueva et al.[14]. showed a significant decrease in mortality with a restrictive transfusion strategy (RBC transfusion with hemoglobin < 7 g/dL), especially in patients with a peptic ulcer or Child–Pugh class A or B liver cirrhosis. However, another large randomized cluster trial (the TRIGGER trial), as reported in Jairath et al.[15]. showed a non-significant reduction in RBC transfusion and difference in clinical outcomes, despite rapid recruitment and high protocol adherence. The differences in the results of the Barcelona and TRIGGER trials may be explained by several reasons, including differences in the proportion of patients with peptic ulcer and variceal bleeding (with a higher proportion of variceal bleeding in the Barcelona trial), differences in the RBC transfusion threshold in the restrictive group (hemoglobin <7 g/dL in the Barcelona trial versus <8 g/dL in the TRIGGER trial), greater protocol adherence in the restrictive group of the Barcelona trial, the exclusion of patients with major comorbidities (including ischemic heart disease, vascular disease and stroke) in the Barcelona trail, and differences in the number of trial centers (single center in the Barcelona trial and multi-center in the TRIGGER trial). Despite these differences, both Barcelona and TRIGGER trials showed that the restrictive transfusion strategy is at least safe and feasible in acute UGIB. However, a large randomized trial to assess the effectiveness of transfusion strategies for acute UGIB is still essential. Nevertheless, the results of our large-sample, retrospective, multi-center study also revealed that patients in the non-RBC transfusion group had a lower rate of hospital mortality, as well as a lower rate of further bleeding. In addition, after adjusting to selected important clinical variables of acute UGIB, including sex, age > 65 years, ischemic heart disease, myocardial infarction, heart failure, cerebrovascular accidents, peripheral vascular disease, renal disease, malignancy, ulcer disease, liver cirrhosis, an international normalized ratio (INR) > 1.5, variceal bleeding, shock at ED presentation, Rockall score > 2, and UGIB history, or adjusting to all variables listed in Table 1, RBC transfusion remained an independent unfavorable prognostic factor in patients with acute UGIB. Thus, the present study provides additional evidence that a restrictive transfusion strategy may significantly improve outcomes in patients with acute UGIB.

Several possible mechanisms could explain the increased mortality and unfavorable outcomes in the liberal transfusion strategy, including coagulation abnormalities and clot rupture due to the repletion of blood volume to compensate for hypotension and immunomodulation[32]. Moreover, in the present study, non-RBC transfusion was also associated with a lower rate of further bleeding, which is consistent with previous reports[9,13]. A recent randomized control study revealed a significantly lower rate of further bleeding in the conservative transfusion group compared to that in the non-conservative transfusion group[14]. In addition, an observational study conducted in Australia showed that RBC transfusion was associated

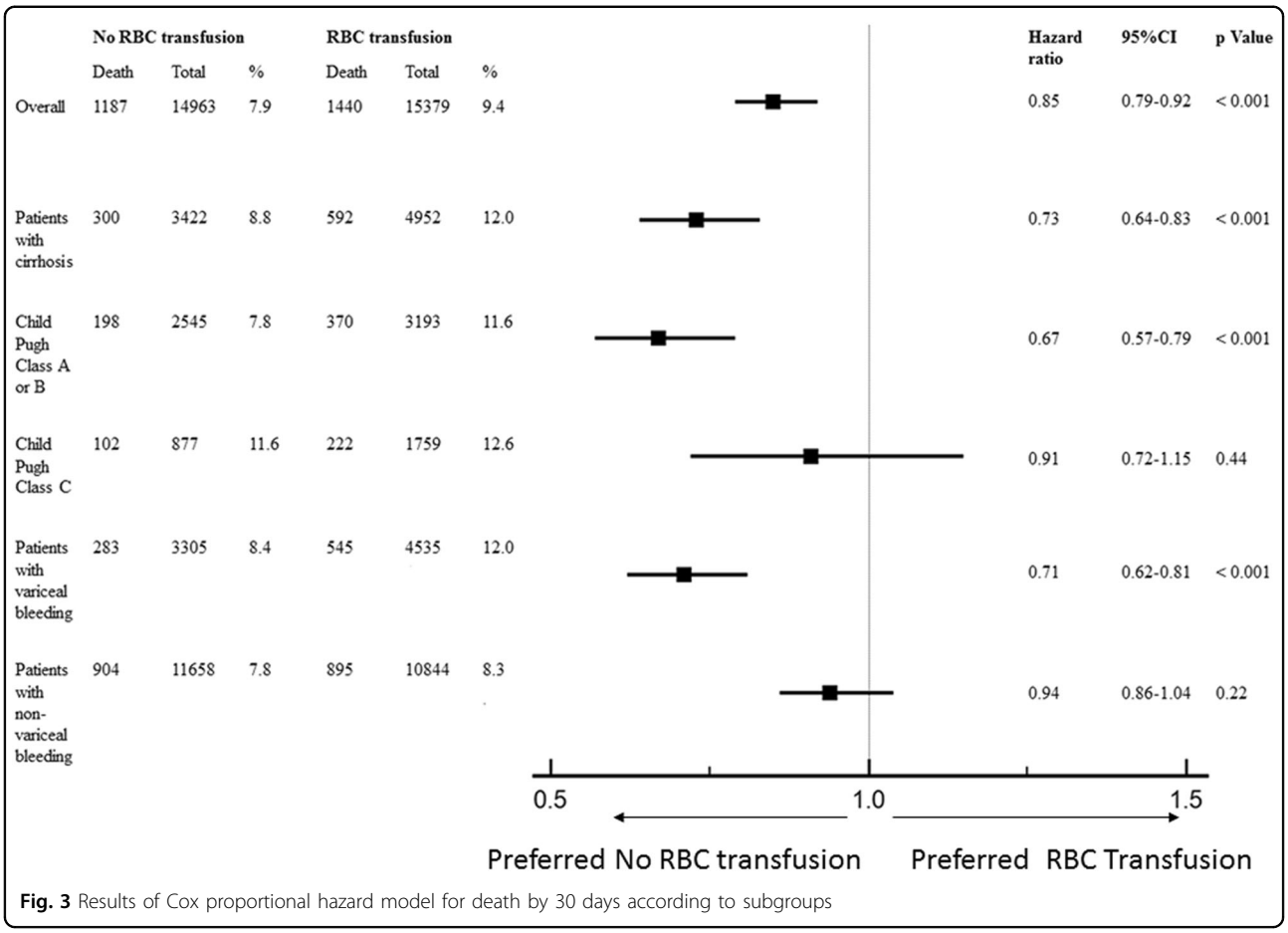


**Fig. 3** Results of Cox proportional hazard model for death by 30 days according to subgroups

with an increased rate of further bleeding in patients with nonvariceal UGIB[33]. However, the exact underlying mechanisms have not been well established. Furthermore, a liberal transfusion strategy in cirrhotic patients with variceal bleeding results in a higher rate of further bleeding, which may be due to the deterioration of pre-existing portal hypertension[34]. Similarly, a small randomized trial reported an increased rate of further bleeding in patients with acute nonvariceal UGIB who received blood transfusion following hemorrhage, which may be due to an impaired hypercoagulable response[35].

The present study has several potential limitations. First, this is a retrospective observational study; unmeasured confounders may exist and a causal inference of the observed associations could not be explained. Second, our study included only patients with UGIB admitted to the ED; thus, our findings might not be applicable to all patients with UGIB. UGIB in patients admitted to the hospital wards could reflect a more complex condition, as UGIB is typically not a major disease, but is more likely a complication of other severe or critical illnesses. Thus, further investigations including all patients with UGIB are warranted.

## Conclusion

In this multi-center, observational study of patients with UGIB, RBC transfusion was associated with higher rates of hospital mortality and further bleeding. Although our findings have strengths, these results are not generalizable to all patients presenting with UGIB, especially patients presenting with exsanguinating bleeding. Additional prospective trials to guide optimal transfusion strategies in UGIB patients are needed.

## Study Highlights

**What is current knowledge?**

- RBC transfusion is controversial in upper gastrointestinal bleeding (UGIB).

**What is new here?**

- This study demonstrates RBC transfusion is associated with increased rate of hospital mortality and further bleeding in overall UGIB patients, patients with pre-existing heart disease and cirrhotic patients with Child–Pugh classification A and B.

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## Conflict of interest

**Guarantors of the article:** Yi-Chuan Chen and Ming-Szu Hung had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
**Specific authors' contributions:** Y.C.C. conceived the study, designed the method, managed the data, including quality control, and drafted the manuscript. C.T.H. conceived the study, designed the method, provided statistical advice on study design and analyzed the data, chaired the data oversight committee, and drafted the manuscript. L.C.L. conceived the study, designed the method and supervised the conduct of the data collection. K.Y.H. conceived the study, designed the method, and supervised the conduct of the data collection. M.S.H. conceived the study, designed the method, managed the data, including quality control, provided statistical advice on study design and analyzed the data, and drafted the manuscript. All authors approved the final version of the manuscript. M.S.H. takes responsibility for the paper as a whole.
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