TITLE: Red blood cell transfusion is associated with further bleeding and fresh frozen plasma with mortality in non-variceal upper gastrointestinal bleeding

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Financial support: Supported by a Targeted Research Fund Grant from the Western Australian Department of Health. John K. Olynyk is the recipient of a National Health & Medical Research Council of Australia Practitioner Fellowship (1042370).

Disclosures: None

Conflict of interest: The authors declare that they have no conflicts of interest relevant to the manuscript submitted to TRANSFUSION

Abstract word count: 250

Body of text word count: 3800

Author Contributions: Conceived and designed the study: KSu KSp OA AM JS ML JO.
Acquisition of data: KSu KSp FL AM JO.
Analysis and interpretation of data: KSu KSp AM OA ML JO.
Wrote the first draft of the manuscript: KSu KSp.
Critical revision of the manuscript for important intellectual content: KSu KSp OA ML JO.
All authors read and approved the final manuscript.

SHORT TITLE: Adverse transfusion outcomes in GI bleeding

Abstract

Background: Blood products are commonly transfused for patients with non-variceal upper gastrointestinal bleeding (NVUGIB). While concerns exist about further bleeding and mortality in subsets of patients receiving red blood cells (RBCs) transfusion, the impact of non-RBC blood products has not previously been systematically investigated. The aim of the study was to investigate the associations between blood products transfusion, further bleeding and mortality after acute NVUGIB.

Study Design and Methods: Retrospective cohort study examining further bleeding, 30-day and one-year mortality in adult patients who underwent gastroscopy for suspected acute NVUGIB between 2008 and 2010 in three tertiary hospitals in Western Australia. Survival analysis was performed.

Results: 2,228 adults (63% male) with 2,360 hospital admissions for NVUGIB that met the inclusion criteria. Median age at presentation was 70 years (range 19 to 99 years). 30 day mortality was 4.9% and one-year mortality 13.9%. Transfusion of four or more units of RBCs was associated with greater than ten times the odds of further bleeding in patients with hemoglobin >90g/L (OR 11.9; 95% CI 3.1-45.7; p=<0.001), but was not associated with mortality. Administration of five or more units of fresh frozen plasma (FFP) was associated with increased 30-day (HR 2.8; 95% CI 1.3-5.9; p=0.008) and one year mortality (HR 2.6; 95% CI 1.3-5.0; p=0.005) after adjusting for coagulopathy, comorbidity, Rockall score and other covariates.

Conclusion: In this large, multicentre study of NVUGIB, RBC transfusion was associated with further bleeding but not mortality, while FFP transfusion was associated with increased mortality in a subset of patients.

Keywords: non-variceal upper gastrointestinal bleeding; red blood cell transfusion, fresh frozen plasma, survival analysis, mortality, gastrointestinal bleeding

Introduction

Acute non-variceal upper gastrointestinal bleeding (NVUGIB) is a common medical emergency associated with significant morbidity, mortality, and substantial health care costs. Despite recent advancements in endoscopic hemostasis, the 30-day mortality from upper gastrointestinal bleeding (UGIB) remains 5% to 14% [1-3]. Males and the elderly appear to be most vulnerable to UGIB [3].

Transfusion practice for acute UGIB is largely empiric [4], however with declining blood donations relative to demand, better evidence for blood transfusion is needed [5]. Gastrointestinal blood loss, primarily UGIB, accounts for 21% of red blood cell (RBC) transfused in Western Australia (WA) {personal communication, WA Patient Blood Management Program}. Whilst transfusion may be life-saving in massive UGIB, there is little evidence to support its use in less severe bleeding. An observational study from the UK reported that 19% of patients who received an early RBC transfusion had an initial hemoglobin (Hb) of >80g⁄L, and satisfactory hemodynamic status [6].

A recent randomized controlled trial concluded that there was a reduction in mortality in patients with UGIB under a restrictive RBC transfusion strategy compared with a more liberal transfusion strategy [7]. Large observational studies from the UK and Canada concluded that RBC transfusion for UGIB was associated with increased rates of rebleeding but not mortality [6, 8]. By contrast, another UK study reported increased 30-day and 2-year mortality after RBC transfusion [9].

Although RBC transfusion has been associated with increased short-term morbidity and mortality, little is known about outcomes following administration of fresh frozen plasma (FFP) or platelets in NVUGIB. Even in critically ill patients, current guidelines for FFP and platelet transfusion are weak [10, 11]. Consequently, we aimed to examine for associations between blood products transfusion (RBC, FFP and platelets), further bleeding and mortality at 30 days and 1 year after acute NVUGIB.

Materials and Methods

Study design

This was a retrospective cohort study of all patients who underwent gastroscopy for an acute NVUGIB event at three WA tertiary hospitals that have on-call endoscopic services, over a three year period (2008-2010). Institutional ethics review board approval was granted by the human research ethics committees of the WA Department of Health, Curtin University, Fremantle Hospital, Royal Perth Hospital and Sir Charles Gairdner Hospital.

Cohort selection

Study participants were identified from electronic medical records of all gastroscopy procedures carried out in the three participating hospitals during the study accrual period 1 January 2008 to 31 December 2010. Inclusion criteria were age 18 years and over at presentation with hematemesis and/or melena. Day case and outpatient procedures and patients with portal hypertensive gastropathy or varices were excluded. Patients were followed-up for 29-65 months, until the study censor date of 31 May 2013.

Data collection

A medical chart review was conducted for eligible acute NVUGIB admissions by dedicated research nurses. Detailed admission and procedural data, including presenting symptoms and signs, laboratory results, medications, comorbidity, time from bleed to gastroscopy, endoscopic findings and treatment and any requirements for surgery or radiological intervention were collected. The volumes and types of transfused blood products, infused colloid or crystalloid products used prior to first gastroscopy were also collected.

Further data on patients were obtained from an extraction of person-level linked hospital morbidity records, patient blood management and death registration records from the Data Linkage Branch of the WA Department of Health. These included patient socio-demographic variables, previous history

of UGIB and comorbidities, total blood product use per admission and dates of death. All analyses were performed on de-identified data.

Variable definitions

Acute UGIB admission-specific variables recorded included the in- or out-of hospital location at the time of bleeding, transfer from a peripheral hospital, presenting symptoms and signs, cardio-respiratory or neurological comorbidity and sequelae of the bleeding episode. Additional comorbidity information was defined using International Classification of Diseases (ICD)-10-AM [12] codes to create Elixhauser binary indicators from conditions recorded during in-patient hospitals stays within the year prior to and including the acute UGIB admission [13].

A post-endoscopy Rockall risk score was calculated for each acute UGIB admission[14]. The Rockall score was designed to predict the risk of mortality in UGIB and takes into account patient age, comorbidity, diagnosis, shock and evidence of bleeding. In cases where systolic blood pressure or heart rate at admission was missing the patient was given a zero score in the shock domain. The comorbid domain of the Rockall risk score was assigned using specific comorbid conditions present at time of admission (ICD-10-AM codes: I50 I20-I25 C77-C79 K72 K704 N17-N19). Patients with a one-year history of congestive heart failure, peripheral vascular disease, metastatic solid tumours or weight loss were also assigned a Rockall comorbidity score of two as these conditions were found empirically to be associated with increased odds of mortality after adjusting for age and all comorbidity.

The Child-Pugh Class, used as measure of prognosis in chronic liver disease, was calculated for admissions with documented liver disease. Admissions where data on bilirubin and serum albumin levels at admission were missing were classified as unknown Child-Pugh score.

Coagulopathy at time of admission was defined as moderate with an international normalised ratio (INR) >1.2 and/or platelet count <150,000/mm^3 and severe with INR>1.5 and/or platelet count $\leq$=50,000/mm^3. The lowest documented haemoglobin (Hb) associated with the NVUGIB episode prior to the first gastroscopy was categorised as <70g/L, 70-90 g/L and >90 g/L. Lowest Hb for the admission

was similarly categorised. These categories were chosen to match that used as a trigger for transfusion in the recent randomised controlled trial[7]. Renal and liver biochemistry and fibrinogen values were recorded. The volumes of colloid and crystalloid fluid resuscitation, RBC, FFP, cryoprecipitate and platelets transfused prior to first gastroscopy and over the complete admission were recorded. An early RBC, FFP or platelet transfusion was defined as being prior to first gastroscopy.

A detailed record of medications at admission, including anticoagulant and antiplatelet medication, was classified into 41 categories loosely based on the Australian Pharmaceutical Benefits Scheme drug classes. Treatment with Vitamin K, Prothrombinex, proton-pump inhibitors, (PPI), Octreotide or Terlipressin prior to gastroscopy, gastroscopy-related information including duration of procedure, type and site of the bleeding lesion, Forrest criteria [15], endoscopic, radiologic or surgical procedures undertaken to arrest the bleeding, and post-gastroscopy morbidities were recorded. Calendar year of admission and individual hospital was also available.

Blood product preparation

RBC and all blood components used in the study hospitals were obtained from the Australian Red Cross Blood Service (ARCBS) in Western Australia.

RBCs for transfusion were obtained by removing most of the plasma after centrifuging whole blood collected into citrate phosphate dextrose anticoagulant. The shelf life (time available for use) was up to 42 days and they were stored at 2-6 degrees centigrade. All RBCs were leucodepleted. When required, RBCs were released from ARCBS at 7-8 days post collection. The average age of red cells transfused in Western Australia was 24 days.

Apheresis or single donor platelets in Western Australia accounted for 75% of supply. The remaining adult doses of donor platelets were derived from pooled buffy coats derived from four ABO identical donors and resuspended in a nutrient additive solution to produce a pooled platelet component. Both apheresis and pooled platelets were leucodepleted during or soon after collection and they are also irradiated before release from the Blood Service[16].

FFP was derived from either a collection of whole blood or apheresis plasma. FFP was not leucodepleted. To be suitable for clinical purposes, whole blood plasma was separated from the whole blood unit within 6 hours of collection. The freezing process commenced within 18 hours of collection. All FFP was frozen to a core temperature below -30ºC within 1 hour of commencement of the freezing process.

FFP in Australia is not yet pathogen inactivated by photo inactivation or solvent detergent treatment but there is a strong framework to ensure safety with regards to transfusion transmitted infections evident in globally low ARCBS residual rates of transmission as judged by mandatory testing.

A unit of FFP contains all coagulation factors including the labile plasma coagulation Factors VIII and V. An adult dose contained approximately 200 IU of Factor VIII. FFP can be stored for 12 months at -25ºC or below[16].

Outcome measures

The principal outcome measures were early further bleeding, 30-day and conditional one-year mortality after the last NVUGIB hospitalisation. Early further bleeding was defined by further hematemesis or passage of fresh melaena and a) a gastroscopy-confirmed lesion that was bleeding or showed signs of recent bleeding occurring after the initial gastroscopy but during the same hospitalisation, b) a post-gastroscopy radiological hemostatic intervention, c) evidence of surgical repair of an upper gastrointestinal lesion in the same admission and at a later date than first gastroscopy, or d) readmission to hospital within 30 days of discharge with another acute NVUGIB. One year mortality outcomes were conditional upon surviving the first 30 days post first gastroscopy.

Statistical methods

Logistic regression models were used to investigate factors associated with odds of early further bleeding. The lack of independence that arose from some patients having had multiple acute NVUGIB admissions was accounted for by using a clustered sandwich variance estimator. Models were fitted using a purposeful stepwise approach and final models only included variables that were significant

at the 0.05 level (parsimonious approach) except for forced inclusion of variables indicating units of RBCs, Platelets and FFP. Plausible interactions were investigated where appropriate. Chi-square tests were used to assess equality of proportions and nonparametric k-sample equality of medians test used to asses medians. The level of collinearity between variables included in regression models were assessed using the conditioning of the matrix procedure available in Stata.

Survival analysis was performed from the time of first gastroscopy in the last NVUGIB admission for each patient until date of death or census times (30 days or one-year). Data were incorporated into the counting process format so that the timing of multiple gastroscopies was taken into account. Cox models were used to identify factors associated with mortality outcomes using a parsimonious approach except for forced inclusion of blood product variables. Schoenfeld residuals were used to test for violation of the proportional hazards assumption.

Results

We identified 2,238 patients with 2,371 acute NVUGIB hospitalisations that met the inclusion criteria (Figure 1). Eleven admissions were missing an admission Hb result and these were excluding leaving 2360 acute NVUGIB hospitalisations for 2228 patients. Most patients (n=2,122; 95%) experienced a single NVUGIB admission. The cohort was predominantly male (63%), with median age of 70 years (range 19 to 99 years). Approximately one-quarter (n=650; 28%) were transferred from a peripheral general hospital where emergency endoscopy was not available. Seventeen percent (n=408) of acute UGI bleeds occurred in patients who were already hospitalised for other reasons. At admission, 24% (n=568) of patients were not taking PPI, anti-platelet, anti-coagulant or H2 antagonist medications. More than half of the patients presented with Hb $\leq$90g/L and these patients tended towards more coagulopathy, higher Rockall scores, active bleeding, female gender and older age. (Table 1). Overall mortality was 4.9% (95%CI: 4.0-5.8), 13.8% (95%CI: 12.5-15.3) and 19.6% (95%CI: 18.0-21.3) at 30 days, one year and two years respectively.

Volume resuscitation and blood product use prior to first gastroscopy

Early volume resuscitation prior to first gastroscopy occurred in 97% (n=2,280) admissions, including 57% with RBC, 13% with FFP and 3% with platelet transfusion (Table 1). Overall, 63% (n=1,482) of admissions involved RBC transfusion. Crystalloid was delivered prior to first gastroscopy in most admissions (n=2197; 93%) with over 55% receiving 2000ml or more (n=1,310). Colloid was used pre-gastroscopy in 11% of NVUGIB admission (n = 268) and cryoprecipitate in 18 (0.8%) admissions.

Gastroscopy findings

Most UGI lesions showed no endoscopic features of a recent bleed (Table 1). Fourteen percent of gastroscopies identified active or oozing bleeding and the remaining 20% had stigmata of recent haemorrhage ranging from flat, pigmented lesions (n=61) to visible blood vessels (n=192). Over 46% (n=1,098) of acute NVUGIB were associated with ulcer disease. Other findings included esophagitis, gastritis or duodenitis in 23% (n=538), Mallory-Weiss tears 5.8% (n=136), angiodysplasia 4.6% (n=109), UGI cancers 2.1% (n=49), Dieulafoy lesions 1.4% (n=34) and Cameron's ulcers 0.5% (n=12). Bleeding from surgical anastomotic sites, polyps and unspecified lesions were also rarely noted. In 1.1% (n=26) of admissions, bleeding could not be attributed to a site or lesion, despite fresh blood being observed.

Early further bleeding

Early further bleeding requiring treatment was observed in 116 (4.9%) patients. Multivariable logistic regression was used to identify patient characteristics and clinical management practices that were associated with odds of further bleeding (Table 2). A significant interaction between Hb and RBC units transfused was present in this model. Patients presenting with low Hb (≤ 70g/L) were more likely to experience further bleeding compared to those with Hb >90g/L when no early RBC units were transfused OR 7.2; 95%CI 2.0-25.9). However, the effect of RBCs on further bleeding varied depending on the admitting Hb level. For patients admitted with a Hb $\leq$=90 g/L there was no association between the number of RBC units transfused pre-gastroscopy and the odds of early further bleeding. This was not the case for patients admitted with a Hb>90 g/L where there was a linear association of increasing

odds of early further bleeding with increasing units of pre-gastroscopy transfused. Duodenal ulcers, perforated ulcers, upper GI cancer, Dieulafoy lesions, an in-hospital UGIB, and UGI lesions with stigmata of high risk of rebleed or necessitating endoscopic therapy were more likely to experience further bleeding. Coagulopathy or being on warfarin at presentation was not associated with further bleeding in this cohort.

30-day mortality

One hundred and eight (4.9%) patients died within 30 days of first gastroscopy for an acute NVUGIB, with most deaths (n=74) occurring in hospital. UGI conditions, including cancer, were the cause or contributory cause of death noted on the death certificate in 35% (n=38) of deaths within 30 days. An additional 12% (n=13) were attributed to other digestive system disorders; 21% (n=23) non-upper GI cancer; and 15% (n=17) to disorders of the circulatory system.

In a multivariate Cox survival model that included multiple comorbidity indicators and coagulopathy status, a significantly increased 30-day mortality was observed for patients transfused with five or more units of FFP with some evidence of an increasing linear association observed (Table 3). Further investigation showed that 11/89 (12.4%) patients who received 5+ units of FFP had a complication following transfusion/infusion/injection (ICD 10 T80 code) or post procedural respiratory disorder (ICD 10 J95 code) recorded for the hospital admission compared to 6/313 (1.9%) patients who received between 1 and 4 units of FFP.

The association of platelet transfusion with 30-day mortality was observed to be modified by serum albumin levels at admission. For patients with a serum albumin < 35 at admission, platelet transfusion was not associated with increased rate of dying. However, for patients admitted with a serum albumin $\geq$=35, the rate of dying was 7 times faster for those who received three or more units of platelets during the admission. No association between the volume of RBC transfused and 30 day mortality was observed in this cohort (Table 3). The survival models also estimated increased 30-day mortality was associated with admissions requiring longer duration gastroscopy, gastroscopy performed in ICU

and patients who experienced post gastroscopy cardiac complication, increasing Rockall score, increasing age, moderate coagulopathy, metastatic cancer, liver disease and use of anti-psychotic medication at admission. Hb at admission or lowest recorded Hb during the admission was not associated with 30-day survival outcomes.

One-year conditional survival outcomes

The association of FFP, RBC and platelets with longer term survival outcomes was investigated. A further 200 deaths occurred after 30 days but within one year of the date of first gastroscopy in the last NVUGIB admission. Upper GI conditions, including cancers, accounted for 14% of deaths, while non-UGI cancers (35%) and vascular disease (22%) accounted for most other deaths.

Patients transfused with five or more units of FFP during their last UGIB admission had almost 2.5 times the rate of dying during the following year, provided that they survived the first 30 days and after accounting for coagulopathy related variables (INR, platelets and warfarin). Moderate and severe coagulopathy at time of admission were associated with poorer one year survival outcomes but only in patients not on warfarin at admission. Coagulopathy in the presence of warfarin was not associated with one's survival. There was no evidence that RBC transfusion, platelet transfusion was associated with long-term conditional mortality (Table 4).

Increasing Rockall score, increasing age, increasing length of stay in hospital, liver disease, malignancy, taking anti-anaemic, diuretics or antibiotics at admission and finding Mallory-Weis tears at gastroscopy were also associated with increased rates of dying within one year.

Discussion

In this large multicenter study of acute NVUGIB, early RBC transfusion was associated with increased odds of further bleeding while increased mortality was observed in a subset of patients transfused

with multiple units of FFP. The strengths of this study were the large sample size from three tertiary referral hospitals and complete follow-up resulting from linkage to multiple registries including hospital admissions and death registry. Limitations include the observational design which means that residual confounding from unmeasured or unknown confounders could not be accounted for which limits the ability to draw causal inference of the observed association.

Our finding of increased further bleeding with early RBC transfusion partly supports those of other observational studies [6, 8] and randomized trials[7, 17], however we observed that the risk was limited to patients who presented with Hb >90g/L. There are a number of mechanisms postulated to explain the increased mortality and morbidity with a liberal transfusion strategy. These include abnormalities in coagulation, clot rupture when hypotension is eliminated by repletion of blood volume, immunomodulation and changes in storage lesion[18]. Unique to our study was the finding of increased odds of further bleeding with increasing RBC administration in patients with Hb >90g/L when compared to otherwise identical patients who did not receive RBCs. We found no association between further bleeding and increasing RBC administration in patients presenting with Hb$\leq$=90g/L. Whilst our observations are broadly consistent with the observations of Villanueva et al[7], they add to the original Spanish study by demonstrating a Hb level above which further bleeding is much more likely to occur if RBCs are administered.

In the local Australian setting, RBC transfusion to Hb >90g/L was at the discretion of various physicians and probably reflects the previous recommendations to transfuse to Hb ≥100g/L[19, 20]. More recent guidelines published after this study period state that RBC transfusion should not be dependent on Hb concentration alone, but a whole patient assessment that includes decompensated liver disease, age and comorbidity[21]. The observed further bleeding rate of 4.9% was less than that reported in other observational studies[6, 8], although this in part may be due to differences in defining a further bleed. Our study needed confirmation of further bleed with endoscopy. However, it could also reflect a shift in blood transfusion attitudes and practice following the local introduction of evidence-based patient blood management in one of the tertiary hospital included in this study[22].

The 30-day mortality rate of 5% reported here is consistent with studies from Europe[23], Canada[24]and Asia[25] while the 19.5% two-year mortality rate is a little less than the 26% reported in the UK[9]. RBC transfusion was not associated with 30-day or conditional 1-year mortality in our study, similar to that reported by two other observational studies[6, 8]. This contrasts with a randomised trial that found increased 45-day mortality in patients assigned to a liberal transfusion strategy (Hb threshold 90g/L) compared to patients allocated to a more restrictive transfusion strategy (Hb threshold 70g/L)[7]. The trial selection criteria included acute variceal bleeding but excluded patients at low risk for mortality, with massive exsanguinating bleeding, symptomatic coronary, cerebral or peripheral vascular disease, transfusion within 90 days, recent trauma or surgery, and lower GI bleeding. By contrast, our study included all severities of NVUGIB examined with gastroscopy though we were not privy to specific factors triggering the clinical decision to administer blood products.

The use of five or more units of FFP was associated with poorer 30-day and one-year survival outcomes with more post procedural respiratory disorders and transfusion related events being recorded. The value of FFP on survival outcomes has been questioned in trauma, intensive care and cardiac surgery patients[26-28]. Reported adverse effects of transfusion include transfusion-associated lung injury and circulatory overload, with the risk of acute lung injury being higher in patients who received FFP and platelets than in those who received only RBCs[29]. The association of FFP with mortality in our study was independent of RBC transfusion and was dose-dependent.

Recent Australian guidelines recommend that FFP transfusion in the setting of major RBC transfusion be guided by both the coagulation profile and clinical scenario, with an INR of >1.5 likely reflecting a coagulopathy requiring correction by FFP and /or other coagulation factors [30] although in one study involving trauma patients requiring a non-massive transfusion (<10 units packed RBCs within 12 hours after admission) the administration of more than 6 units of FFP compared with no transfusion was associated with a 12-fold increase in the rate of ARDS and 6-fold increase in multiorgan dysfunction syndrome with no improvement in survival[31].

The association of FFP with increased mortality remained even after one year which is more difficult to reconcile biologically. However, the observational nature of this study means that unmeasured and unknown variables related to mortality could be confounding the role of FFP and one year mortality. While poorer longer term outcomes with FFP use have been reported in a trauma setting[32] in this study it is possible that unmeasured reasons that triggered the use of FFP in these patients rather than the FFP *per se* is playing a role. Elucidation of the factors involved is beyond the scope of the current study and requires further evaluation.

There has been concern regarding adverse patient outcomes and the longer storage time of red cells transfused especially in the critical care setting. The average age of RBCs received by patients in our study was 24 days. This topic has been reviewed elsewhere[33, 34] , but to date there have been no consistent adverse findings determined from the transfusion of older stored RBCs to alter clinical practice.

The stringent quality control in the collection, preparation and administration of RBCs and other blood products in Western Australia mitigates against reduced product quality as a contributor to the adverse outcomes[16],

In conclusion, early RBC transfusion was associated with increased further bleeding in NVUGIB patients presenting with Hb >90g/L. Massive transfusion with FFP, but not RBC transfusion, was associated with increased mortality outcomes for patients. While a causal relationship between FFP use and mortality cannot be drawn, judicious use of FFP guided by the coagulation status of the patient is advisable. Randomized clinical trials are necessary to examine the benefit versus risk of FFP transfusion in NVUGIB patients.

ACKNOWLEDGEMENTS

We would like to thank Dr Nick Kontorinis, Head of Department, Royal Perth Hospital and Dr Hooi Ee, Head of Department, Sir Charles Gairdner Hospital for their support in the conduct of this study. We also thank our research nurses Peter Murray, Susan Hodson, Ruth Dempsey and Jenny Kava for data collection and patient record reviews.

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Table 1. Patient characteristics and findings during NVUGIB admissions (n=2360)

	All n=2360		Haemoglobin at admission (g/L)						p-value
			≤=70 (n=417)		>70-90 (n=833)		>90 (n=1010)		
	No.	%	No.	%	No.	%	No.	%	
Sex									
Male	1,505	63.9	273	60.3	514	60.7	718	67.9	0.001
Female	852	36.1	180	39.7	333	39.3	339	32.1	
Median Age (IQR)	70	56-81	73	59-82	73	62-82	66	53-78	<0.001
Coagulopathy									
None	1325	56.1	185	44.4	428	51.4	712	64.4	<0.001
INR>1.2 or Platelets≤=150‡	659	27.9	133	31.9	249	29.9	277	24.8	
INR>1.5 or Platelets≤=50‡	376	15.9	99	23.7	156	18.7	121	10.8	
RBC pre-gastroscopy									
None	1055	44.7	34	8.2	149	17.9	872	80.1	<0.001
1 unit	212	9.0	24	5.8	106	12.7	82	7.3	
2 units	489	20.7	66	15.8	322	38.7	101	7.8	
3 units	259	11.0	105	25.2	128	15.4	26	2.2	
4 units	201	8.5	116	27.8	66	7.9	19	1.8	
5+ units	144	6.1	72	17.3	62	7.4	10	0.8	
FFP pre-gastroscopy									
None	2051	86.9	319	76.5	704	84.5	1028	93.0	<0.001
1 unit	83	3.5	30	7.2	37	4.4	16	1.2	
2 units	162	6.9	50	12.0	62	7.4	50	4.4	
3 units	14	0.6	4	1.0	4	0.5	6	0.5	
4 units	33	1.4	7	1.7	19	2.3	7	0.6	
5+ units	17	0.7	7	1.7	7	0.8	3	0.3	
Platelets pre-gastroscopy									
None	2280	96.6	385	92.3	799	95.9	1096	98.8	<0.001
1 unit	58	2.5	20	4.8	29	3.5	9	0.8	
2 units	16	0.7	9	2.2	3	0.4	4	0.3	
3+ units	6	0.3	3	0.7	2	0.2	1	0.1	
Gastroscopy findings									
UGI pathology, no blood	1556	65.9	230	55.2	508	61.0	818	74.2	<0.001
Stigmata of RH	476	20.2	94	22.5	195	23.4	187	16.7	
Active bleeding	328	13.9	93	22.3	130	15.6	105	9.1	
Rockall score									
<3	946	40.1	107	25.7	255	30.6	584	53.6	<0.001
3-4	622	26.4	106	25.4	223	26.8	293	26.2	
5-7	630	26.7	159	38.1	281	33.7	190	16.6	
≥=8	162	6.9	45	10.8	74	8.9	43	3.6	

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	All n=2360		Haemoglobin at admission (g/L)						p-value
			<=70 (n=417)		>70-90 (n=833)		>90 (n=1010)		
	No.	%	No.	%	No.	%	No.	%	
Total RBC in admission									
None	878	37.2	16	3.8	66	7.9	796	73.7	
1 unit	120	5.1	4	1.0	45	5.4	71	6.2	
2 units	456	19.3	27	6.5	302	36.3	127	10.4	
3 units	208	8.8	69	16.5	107	12.8	32	2.5	<0.001
4 units	262	11.1	106	25.4	119	14.3	37	3.1	
5 units	125	5.3	50	12.0	59	7.1	16	1.2	
6+ units	311	13.2	145	34.8	135	16.2	31	2.8	
Total FFP in admission									
None	1958	83.0	286	68.6	662	79.5	1010	91.3	
1 unit	68	2.9	22	5.3	28	3.4	18	1.5	
2 units	167	7.1	45	10.8	76	9.1	46	4.2	<0.001
3 units	21	0.9	11	2.6	7	0.8	3	0.2	
4 units	57	2.4	15	3.6	29	3.5	13	1.0	
5+ units	89	3.8	38	9.1	31	3.7	20	1.8	
Platelets in admission									
None	2171	92.0	347	83.2	757	90.9	1067	96.3	
1 unit	106	4.5	32	7.7	47	5.6	27	2.4	<0.001
2 units	46	1.9	20	4.8	16	1.9	10	0.8	
3+ units	37	1.6	18	4.3	13	1.6	6	0.6	

RH= recent haemorrhage, FFP = fresh frozen plasma, RBC = Red Blood Cells, ‡Platelets = x 1000 /mm^3.

IQR = Inter-quartile range

Table 2. Factors associated with odds of early further bleeding following an UGIB admission as estimated by a logistic regression model with robust variance estimators (n=2370 admissions)

	OR	95%CI	p-value
Hb at admission <70g/L†			
No pre-gastroscopy RBC	1.0	-	-
1 unit RBC	0.23	0.03 - 2.16	0.201
2 units RBC	0.60	0.15 - 2.34	0.462
3 units RBC	0.75	0.20 - 2.81	0.670
4 units RBC	0.63	0.17 - 2.31	0.482
5+units RBC	0.57	0.15 - 2.21	0.418
Hb at admission ≥=70g/L and ≤=90g/L†			
No pre-gastroscopy RBC	1.0	-	-
1 unit RBC	0.59	0.20 - 1.71	0.329
2 units RBC	0.65	0.29 - 1.44	0.289
3 units RBC	0.86	0.33 - 2.24	0.754
4 units RBC	0.88	0.33 - 2.32	0.796
5+units RBC	0.60	0.18 - 1.99	0.403
Hb at admission >90g/L†			
No pre-gastroscopy RBC	1.0	-	-
1 unit RBC	1.59	0.31 - 8.17	0.580
2 units RBC	1.15	0.23 - 5.74	0.864
3 units RBC	4.15	0.70 - 24.47	0.116
4 units RBC	11.89	3.09 - 45.74	<0.001
5+units RBC	15.85	2.36 - 106.67	0.004
Coagulopathy at admission			
None	1.0	-	-
INR>1.2 or Platelets≤=150,000/mm^3	0.86	0.51 - 1.43	0.556
INR>1.5 or Platelets≤=50,000/mm^3	1.51	0.74 - 3.06	0.256
On warfarin at admission (yes vs no) (n=264)	0.93	0.41 - 2.10	0.857
In hospital bleed (yes vs no) (n=408)	2.15	1.34 - 3.44	0.002
Endoscopic therapy required (yes vs no) (n=665)	2.44	1.56 - 3.83	<0.001
Active bleed / high risk stigmata (yes vs no) (n=221)	1.85	1.10 - 3.14	0.021
Findings on gastroscopy (yes vs no)			
Dieulafoy lesion (n=37)	2.87	1.14 - 7.18	0.025
Duodenal ulcer (n=563)	2.67	1.72 - 4.14	<0.001
Perforated ulcer (n=42)	4.95	2.13 - 11.49	<0.001
Upper GI cancer (n=75)	4.58	2.04 - 10.28	<0.001

† Units of early RBC were entered into this model as an interaction term with Hb (g/L) at admission, hence the association of early RBC with odds of further bleeding is shown for the three different levels of Hb at admission.

Pre-gastroscopy units of fresh frozen plasma, units of platelets, Rockall score, year of admission, and presence of chronic liver disease were also tested for association with further bleeding but were not significant (p>0.05) and not included in the final model. The number of patients for each variable in the model are indicated if not already shown in Table 1.

Table 3. Factors associated with 30-day mortality from first gastroscopy during last admission as estimated from a Cox survival model (n=2228 patients).

		HR	95%CI	p-value
Rockall score				
	<3	1.00	ref	.
	3-4	3.58	1.58 - 8.11	0.002
	5-7	2.88	1.26 - 6.58	0.012
	≥8	7.74	3.28 - 18.25	<0.001
Age at admission (years)		1.03	1.02 - 1.05	<0.001
Morbidity indicators at admission				
No liver disease (n=2014)		1.00	ref	.
Child-Pugh Class A (n=65)†		2.14	0.89 - 5.17	0.090
Child-Pugh Class B (n=90)		2.29	1.19 - 4.44	0.014
Child-Pugh Class C (n=40)		1.95	0.64 - 5.97	0.241
Malignant disease (n=58)		4.08	2.12 - 7.85	<0.001
Anti-psychotic medication (n=73)		3.58	1.84 - 6.97	<0.001
Procedural factors (Yes versus No)				
Gastroscopy > 25 minutes (n=567)		2.08	1.38 - 3.13	<0.001
Post-gastroscopy cardiac complications (n=24)		2.33	1.18 - 4.59	0.014
Performed in ICU (n=78		2.83	1.08 - 7.42	0.035
Coagulopathy at admission				
None		1.00	1.00 – 1.00	.
INR>1.2 or Platelets≤=150,000/mm^3		1.93	1.19 - 3.11	0.007
INR>1.5 or Platelets≤=50,000/mm^3		1.07	0.58 - 1.98	0.833
Total RBC in admission				
None		1.00	1.00 – 1.00	.
1 unit		0.61	0.18 - 2.10	0.436
2 units		0.69	0.34 - 1.41	0.309
3 units		0.74	0.32 - 1.69	0.474
4 units		0.72	0.33 - 1.55	0.404
5+ units		0.84	0.44 - 1.61	0.606
Total FFP in admission				
None		1.00	1.00 – 1.00	.
1-2 units		1.33	0.72 - 2.48	0.366
3-4 units		1.61	0.64 - 4.01	0.310
5+ units		2.77	1.30 - 5.91	0.008
Total platelets in admission				
Serum albumin ≥=35 (n=1543)	No platelets	1.00	ref	.
	1 -2 unit platelets	1.74	0.61 - 4.95	0.296
	3+ units platelets	7.62	2.22 - 26.10	0.001
Serum albumin <35 (n=817)	No platelets	1.00	ref	.
	1 -2 unit platelets	0.64	0.30 – 1.36	0.249
	3+ units platelets	1.50	0.63 – 3.60	0.363

† Child-Pugh score could not be calculated for 19 patients with liver disease due to missing blood chemistry data and the HR for this group are not shown.

Table 4. Factors associated with one-year mortality conditional upon surviving first 30 days since date of first gastroscopy in last UGIB admission (n=2120).

		HR	95%CI	p
	Rockall score			
	<3	1.00	ref	.
	3-4	1.65	1.07 - 2.55	0.023
	5-7	2.13	1.38 - 3.29	0.001
	≥8	2.68	1.54 - 4.67	<0.001
	Age at admission (years)	1.02	1.01 - 1.04	<0.001
	Morbidity indicators at admission	1.00	ref	.
	No liver disease (n=1930)	1.00	1.00 - 1.00	.
	Child-Pugh Class A (n=59)†	3.25	1.78 - 5.93	<0.001
	Child-Pugh Class B (n=78)	2.48	1.46 - 4.21	0.001
	Child-Pugh Class C (n=36)	1.49	0.61 - 3.65	0.377
	Malignant disease (yes vs no) (n=41)	4.87	2.80 - 8.48	<0.001
	Anti-anaemic medication (yes vs no) (n=292)	1.60	1.25 - 2.03	<0.001
	Diuretic & potassium sparing medication (yes vs no) (n=405)	1.35	1.03 - 1.78	0.033
	Antibiotics (yes vs no) (n=81)	1.80	1.17 - 2.77	0.008
	Admission-related factors	1.00	ref	.
	Length of hospital stay (^-0.5)	0.90	0.83 - 0.97	0.006
	Mallory-Weis tear cause of UGIB (n=145)	2.00	1.19 - 3.36	0.008
	Coagulopathy at admission			
On warfarin (n=257)	None	1.00	ref	.
	INR>1.2 or Platelets<=150,000/mm^3	0.28	0.02 - 3.17	0.304
	INR>1.5 or Platelets<=50,000/mm^3	1.12	0.26 - 4.83	0.883
Not on warfarin (n=1863)	None	1.00	ref	.
	INR>1.2 or Platelets<=150,000/mm^3	1.42	1.01 - 2.00	0.046
	INR>1.5 or Platelets<=50,000/mm^3	2.24	1.28 - 3.92	0.005
	Total RBC in admission			
	None	1.00	ref	.
	1 unit	1.01	0.55 - 1.86	0.975
	2 units	0.79	0.51 - 1.21	0.277
	3 units	0.82	0.47 - 1.42	0.471
	4 units	0.64	0.38 - 1.08	0.097
	5+ units	0.78	0.49 - 1.24	0.297
	Total FFP in admission			
	None	1.00	ref	.
	1-2 units	0.96	0.59 - 1.58	0.878
	3-4 units	1.11	0.52 - 2.35	0.791
	5+ units	2.57	1.33 - 4.96	0.005
	Total platelets in admission			
	None	1.00	ref	.
	1-2 unit platelets	0.72	0.42 - 1.26	0.252
	3+ units platelets	0.36	0.12 - 1.11	0.076

† Child-Pugh score could not be calculated for 17 patients with liver disease due to missing blood chemistry data and the HR for this group are not shown.

Figure 1. Flowchart of inclusion and exclusion criteria.