

Clinical Predictors of Arterial Extravasation, Rebleeding and Mortality Following Angiographic Interventions in Gastrointestinal Bleeding

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ABSTRACT

Background & Aims: The aim of this study was to identify clinical and imaging predictors of arterial extravasation, post embolization rebleeding and 30-day mortality in gastrointestinal (GI) bleeding.

Method: This retrospective study included 114 patients who underwent angiography for upper or lower GI bleeding. Multivariate logistic regression was used to identify clinical and imaging predictors.

Results: Angiography demonstrated arterial extravasation in 22 patients (19%) and embolization was performed in 48 (42%) patients including prophylactic embolization in 26 (56%). Fall in hemoglobin level from baseline was an independent predictor of arterial extravasation with 65% increased odds for every unit drop (OR 1.65, 95%CI 1.13-2.40, $p=0.01$). Age <60 years was a negative predictor of rebleed within 30-days (OR 0.94, 95%CI 0.89-1.00, $p=0.04$). Patients with a history of malignancy were more likely to rebleed (OR 4.4, 95%CI 1.06-18.36, $p=0.04$). Hemodynamic instability prior to angiography (OR 13.22, 95%CI 1.65-106.07, $p=0.02$), history of malignancy (OR 1.36, 95%CI 1.49-10.49, $p=0.01$), number of units of platelets transfused (OR 1.42, 95%CI 1.02-1.97, $p=0.04$) and rebleed after angiography (OR 46.8, 95%CI 4.80-456.14, $p<0.01$) were predictors of 30-day mortality. Prophylactic embolization was not a predictor of rebleed or 30-day mortality.

Conclusions: This paper identified important clinical predictors of arterial extravasation, rebleed and 30-day mortality in GI bleedings, which will assist in patient selection and help to improve the overall angiographic management of GI bleeding.

Key words: Embolization – upper gastrointestinal bleeding – lower gastrointestinal bleeding – mesenteric angiography.

Abbreviations: CT: computed tomography; CTA: computed tomography angiography; FFP: fresh frozen plasma; GI: gastrointestinal; INR: International Normalized Ratio; IRB: institutional review board; PACS: Picture Archiving and Communication System; pRBC: packed red blood cells; PT: prothrombin time; TAE: transcatheter angiographic embolization.

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INTRODUCTION

Acute gastrointestinal (GI) bleeding results in over 300,000 hospitalizations annually in the United States, which amounts to 1-2% of all admissions [1]. The costs of inpatient management of acute GI bleeding approach \$1 billion dollars each year [2]. Upper GI bleeding is responsible for most of these admissions, estimated at 100 cases per 100,000 persons [3]. Lower GI tract bleeding has a much lower incidence of 20-27 per 100,000,

representing only 24% of all GI bleedings [3]. Persons over the age of 60 represent 35-45% of all cases, and this proportion continues to increase [3].

The significance of GI bleeding is underscored by a mortality rate of 5-12%, which has not changed significantly in the past five decades [4]. Endoscopic intervention remains the primary modality for treatment of non-variceal GI bleeding. When endoscopic intervention fails or is not possible, angiographic or surgical intervention is warranted [3, 5]. Angiographic intervention is preferred over surgical treatment as it preserves the bowel and is minimally invasive. A major limitation for transcatheter angiography is the high incidence of negative studies that fail to identify or localize the bleeding [6]. Previous studies have shown negative angiograms in as many as 52% of cases [7]. This makes appropriate selection of patients for angiographic intervention a critical component

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in the management of GI bleeding. Another limitation of angiographic intervention is the incidence of rebleeding after embolization, estimated to be about 33% for upper GI and 21% for lower GI bleeding [8, 9]. Identification of patients at risk of rebleeding would greatly help in the better management of these patients. The aim of this study was to identify any clinical or imaging factors that predict a positive angiogram in non-variceal GI bleeding. Secondary aims of the study were to identify any clinical or imaging predictors of rebleeding after embolization and 30-day mortality.

MATERIAL AND METHODS

This is an IRB approved retrospective study of 114 patients from two institutions, who underwent angiography for GI bleeding. Patients were identified using billing and coding data from 12/2010 to 12/2015. Inclusion criteria included all cases of upper or lower, non-variceal bleeding across all age groups and genders, admitted for angiography. All patients underwent endoscopy prior to angiography. Exclusion criteria were cases of variceal bleeding or patients with cirrhosis. Data were extracted from electronic medical records, PACS and outside imaging. All data were collected and analyzed by five of the authors.

Collected data included patient demographics, hemodynamic parameters, baseline hemoglobin, coagulation studies, platelets, blood type, transfusions, CT angiogram and nuclear medicine study findings, lowest hemoglobin (Hb) recorded within the 24 hours preceding the procedure, anticoagulation if any, intervention type, angiographic findings including interventions, embolization material, occurrence of rebleeding and 30-day mortality.

A multivariate regression analysis was used for the identification of any factors that predicted positive angiogram, rebleed or 30-day mortality. Linear regression analysis allowed for identification of several independent variables and their relationship to our dependent variables, in this case positive angiogram, rebleed, or 30-day mortality. IBM SPSS software was used for all statistical analysis. Multiple independent variables comprising patient age, site of GI bleed, history of malignancy, anticoagulation therapy, Hb on admission, drop in Hb from baseline, platelet count, recent transfusion, hemodynamic instability, and rebleed status were input into the software to compare to dependent variables which included positive angiogram, rebleed, and 30-day mortality. Chi squared test and *t*-test were used for analysis of categorical and continuous variables respectively.

RESULTS

Patient background

Data collection resulted in an unselected, consecutive cohort of 114 patients who underwent angiography between 12/2010 to 12/2015 for upper or lower GI bleeding. The mean age of patients was 63 years (SD 17.1) and 59 (52%) were female. Clinical examination localized the site of bleeding to the upper GI tract in 57 (50%) patients, the lower GI tract in 54 (47%) patients, and in 3 (3%) patients the site was not localized. Thirty-six (32%) had a documented history of malignancy,

and 13 (11%) presented malignancies of gastrointestinal organs. Eight (7%) patients were on warfarin therapy and 3 (3%) were on heparin at the time of angiography (Table I). Final diagnosis was upper GI bleeding in 10 (9%), lower GI bleeding in 20 (18%), malignancy in 15 (13%), ulcers in 14 (12%), Dieulafoy lesion in 2 (2%), duodenal hematoma in 2 (2%), pseudoaneurysm in 5 (4%), diverticulitis in 15 (13%), angiodysplasia in 3 (3%), segmental arterial mediolysis syndrome in 1 (1%), unspecified in 24 (21%), related to a dive injury in 1 (1%), and esophageal perforation in 1 (1%).

Table I. Characteristics of patients undergoing angiography for clinically suspected GI bleeding

| | Mean | SD or % |
|--------------------------|------|---------|
| Age (years) | 63 | 17.1* |
| Female | 59 | 52% |
| History of malignancy | 36 | 32% |
| Nadir Hb (g/dL) | 7.2 | 1.5* |
| Drop in Hb (g/dL) | 3.6 | 2.2* |
| pRBCs transfused (units) | 4.96 | 5.6* |

*: Standard Deviation; pRBCs: packed Red Blood Cells; Hb: Hemoglobin.

Patient status at angiography

Mean nadir of Hb during admission was 7.2 g/dL (SD 1.5) with a mean baseline Hb of 10.7g/dL (SD 1.7); the mean drop in Hb was 3.6 g/dL (SD 2.2). Mean platelet count was 123,000/ μ L (SD 86,000). Mean INR was 1.28 (SD 0.47). In the 24 hours prior to angiography, 55 (60% of 92 with data available) required transfusion of packed red blood cells (pRBCs) and they received a mean 4.96 units (SD 5.6). Twenty-five of 86 (29%) patients required platelet transfusion prior to angiography with a mean of 2.4 units (SD 1.9) transfused. Fresh Frozen Plasma (FFP) was required in 45 of 86 (52%) and mean of 12.2 units (SD 23) was transfused. Patients were considered hemodynamically unstable if they were on vasopressors or had a systolic BP less than 90 mmHg. At the time of angiography, 35 (41%) patients were hemodynamically stable, and afterward 47 (57%). There was a significant decrease in the proportion of hemodynamically unstable patients after angiography ($p < 0.01$).

Angiography

Angiography demonstrated extravasation in 22 patients (19%), 12 of these were upper GI bleedings and 10 were lower GI bleedings. Embolization was performed on a total of 48 (42%) patients. Technical success was achieved in 98% of cases, with only 1 out of 48 patients demonstrating blood flow distal to the coil. Coils were the most commonly used material for embolization, which were used in 41 (87%) patients. Coils alone were used in 27 (57%), coils with gelfoam in 14 (30%), gelfoam alone in 6 (13%) and vascular plug in one case. Prophylactic embolization was done in 26 patients (56%). The vessel for prophylactic embolization was selected based on endoscopy, CT angiogram or nuclear medicine (NM) findings. On logistic regression, the fall in Hb from baseline was predictive of arterial extravasation on angiogram (OR 1.65, 95% CI 1.13-2.40, $p = 0.01$). Other hematological parameters such as platelet count, PT, or INR were not predictive of extravasation ($p = 0.98$,

0.15, 0.05, respectively). The quantities of pRBCs, platelets, or FFP transfused were not predictive of positive angiogram ($p=0.99, 0.99, 0.64$, respectively) (Table II).

Table II. Results of angiography performed on patients with clinically suspected GI bleeding

| | Number of Patients | % |
|-------------------------------|--------------------|-----|
| Active arterial extravasation | 22 | 15% |
| Prophylactic embolization | 26 | 58% |
| Embolization material | | |
| Coils | 27 | 57% |
| Coils+Gelfoam | 14 | 30% |
| Gelfoam | 6 | 13% |
| Vascular plug | 1 | 2% |

Seventeen patients (15%) underwent CTA prior to angiography with 5 (29%) positive studies. Forty-two patients (37%) underwent 99-Tc-tagged red blood cell scan prior to angiography and 26 (62%) were positive. Using logistic regression, neither positive CTA nor scintigraphy were predictive of demonstration of extravasation on angiography (CTA: OR 2.0, 95% CI 0.21-18.33, $p=0.54$; scintigraphy: OR 0.79, 95% CI 0.15-4.09, $p=0.78$).

Post angiography course

After angiography, the mean length of stay was 20.7 days (SD 40). Rebleeding occurred within 30-days in 14 of the 41 patients for whom follow-up data were available. There were 22 (20%) deaths within 30 days. Younger patients (<60 years) were significantly less likely to have rebleeding within 30-days (OR 0.94, 95%CI 0.89-1.00, $p=0.04$). Patients with a history of malignancy were more likely to rebleed within 30-days (OR 4.4, 95%CI 1.06-18.36, $p=0.04$). There was not a significant difference in the rate of rebleeding between upper or lower GI source of bleeding. (OR 1.11, 95%CI 0.29-4.31, $p=0.88$). Material used during embolization did not predict the likelihood of recurrent GI bleed within 30-day follow-up ($p=0.81$) (Table III).

Table III. Potential predictors of rebleeding occurrence within 30 days of endovascular embolization in patients with clinically determined GI bleeding

| Parameter | OR | 95% CI |
|---------------------------|------|------------|
| Age | 0.94 | 0.89-1.00 |
| Location | 1.11 | 0.29-4.31 |
| Prophylactic embolization | 1.44 | 0.39-5.27 |
| Material | NA | $p=0.81^*$ |

*p-values given where 95% CI not applicable

Rebleeding within 30 days of angiography was predictive of 30-day mortality (OR 46.8, 95%CI 4.80-456.14, $p<0.01$). Hemodynamic instability at the time of angiography was found to be a predictor of 30-day mortality (OR 13.22, 95%CI 1.65-106.07, $p=0.02$). Presence of a known malignancy was

associated with increased 30-day mortality (OR 1.36, 95%CI 1.49-10.49, $p=0.01$). Interestingly, the number of units of platelets transfused was a predictor of 30-day mortality (OR 1.42, 95%CI 1.02-1.97, $p=0.04$). Prophylactic embolization was not associated with increased mortality at 30-days (OR 1.47, 95%CI 0.37-5.96, $p=0.59$), nor was it associated with an increased risk of rebleeding within 30 days (OR 1.44, 95%CI 0.39-5.27, $p=0.59$). There was not a significant difference in mortality between upper, lower, and clinically unlocalized gastrointestinal bleeding ($p=0.19$) (Table IV).

Table IV. Potential predictors of 30-day mortality in patients undergoing endovascular embolization for clinical GI bleeding.

| Parameter | OR | 95% CI |
|---------------------------|-------|-------------|
| Rebleed | 46.8 | 4.80-456.14 |
| History of malignancy | 1.36 | 1.49-10.49 |
| Location | NA | $p=0.19^*$ |
| Prophylactic embolization | 1.47 | 0.37-5.96 |
| Hemodynamic instability | 13.22 | 1.65-106.07 |

*p-values given where 95% CI not applicable

DISCUSSION

Endoscopy is the primary diagnostic and therapeutic modality for the management of upper and lower GI bleeding [10]. Common causes of non-variceal upper GI bleeding include ulcers, esophagitis, erosions, and Mallory-Weiss lesions, all of which are amenable to endoscopic treatment [11]. It is technically difficult for the endoscopist to access much of the small bowel and visualization of lesions can be limited in the presence of extensive hemorrhage or poor bowel preparation [12]. Failure of endoscopic management is positively associated with lesion number, size, location, and the amount of blood in the bowel [9, 13]. It is estimated that up to 16% of upper GI and 25% of lower GI bleedings require invasive intervention beyond endoscopy using transcatheter arterial embolization (TAE) or surgery [3, 5]. TAE is preferred to surgical interventions as it is less invasive and preserves the bowel [14-16].

The role of angiography is larger in lower GI bleeding than in upper GI bleeding, where endoscopic failure is relatively rare. Angiography demonstrates luminal extravasation or mucosal blush in up to 61% cases of suspected upper GI bleeding and in up to 50% of acute lower GI bleeds [6]. Initial technical success rates of TAE are as high as 93% for upper GI bleedings [9]. These numbers are similarly high for lower GI bleeding; 95% initial success of embolization and 76% remaining free of bleeding after 30 days [8]. Previous studies have shown negative angiograms with failure to localize active extravasation in as many as 52% of cases [6, 7]. The low rate of positive angiographic studies is a more vexing problem in the management of lower GI bleeding than in upper GI bleeding, where empirical embolization has been found to be safe and effective. Selection of appropriate patients for angiography is a critical component of GI bleeding management due to the relatively low sensitivity of the procedure, the risk, albeit low, associated with angiography and the need for contrast exposure [17].

A number of clinical and laboratory parameters have been studied as predictors of extravasation and outcome in GI bleedings. Our study found that the drop in Hb, rather than the absolute Hb level is an independent predictor of a positive angiogram in GI bleeding (OR 1.65, CI 1.128-2.403, $p=0.010$). For every unit drop in the Hb value, there is a 65% increase in the odds of finding active extravasation on angiogram. Other investigators have found that the number of units of packed red blood cells and amount of fresh frozen plasma transfused in the 24 hours before angiography were positively associated with positive extravasation on angiography, with each unit of pRBC transfused increasing the probability of a positive angiographic study by 30% [18]. Abbas et al. [19] found that patients with lower GI bleeding requiring more than 5 units of blood in the 24 hours preceding angiography were significantly more likely to demonstrate extravasation on angiography. Hemodynamically unstable patients (systolic blood pressure at time of angiography less than 90 mm Hg) have also been found by multiple investigators to be significantly more likely to demonstrate extravasation on angiography [7, 20, 21]. Interestingly, one group found that angiographies performed outside of standard working hours at their center's interventional center were more likely to demonstrate extravasation [22].

One of the important limitations of angiographic intervention in GI bleeding is the occurrence of rebleeding after embolization. In a review of 15 studies with 819 patients with upper GI bleeding, treated with angiographic intervention, the rate of rebleeding was documented at 33%: half of bleedings responded to repeat embolization [9]. Similarly, in a review of 15 studies with 309 patients with lower GI bleeding, the rate of rebleeding was estimated at 21% [8]. The rate of rebleeding in this study was 36%, which is comparable to the above studies. Patients younger than 60 years were slightly less likely to have rebleeding compared to those over the age of 60 (OR 0.95, $p=0.04$). Patients with known malignancy were at least 4 times more likely to rebleed within 30 days of procedure (OR 4.4, $p=0.04$), which is consistent with the findings of others demonstrating a strong proclivity for malignancy-associated GI bleeding to recur [23]. Interestingly, in one small study of patients with malignancy-associated GI bleeding, in which a majority of patients experienced recurrent bleeding after embolization, all recurrent bleedings occurred at sites other than the initial, embolized, source of bleeding [24].

The overall mortality from GI bleeding ranges from 5-12% [4]. In a study of 362 patients with upper GI bleeding, Kelbl et al. [25] showed the mortality for hospital inpatients to be 39.0% compared to 11.1% for outpatients. Our study found a 30-day mortality rate of 20.7% and the presence of hemodynamic instability prior to the angiogram was associated with a 13 times increased odds of death within 30-days. Rebleeding within 30 days was associated with more than 45 times increased odds of 30-day mortality (OR 46.8). Also, as expected, the presence of malignancy was an independent predictor of mortality. Interestingly, the number of units of platelets transfused was a predictor of mortality (OR 1.42). This is likely related to the comorbidities associated with thrombocytopenia rather than the effects of platelet transfusion itself. Comorbidities,

especially malignancies are well known as a predictor of poor outcomes in acute GI bleeding [20, 21].

In addition to clinical and laboratory assessments, many diagnostic imaging modalities have been studied for their usefulness in triaging GI bleeding patients for angiography. Diagnostic imaging modalities for GI bleeding include NM scintigraphy, computed tomographic angiography (CTA), and angiography. Historically, the 99-Tc tagged red blood cell scan has been the primary modality for localizing bleedings that are not seen by endoscopy. The sensitivity and specificity of this method have been reported as ranging from 78.6%-97% and 70.4%-100%, respectively [26]. Though extremely sensitive, the length of time required for this study makes scintigraphy of limited utility in severe acute GI bleedings [27]. Furthermore, the anatomic quality of information obtained from the positive studies is limited, with 22% of positive studies being falsely localizing [28]. The utilization of tagged red cell scans was low in this cohort (42, 37%) and its sensitivity and specificity for identifying extravasation on angiography were 57.1% and 39.5%, respectively. A tagged red blood cell study had a negative predictive value for a positive angiography of 83.3%, and a positive predictive value of 14.8%. This study showed that a positive tagged red cell scan is not a reliable predictor of active extravasation on angiography. This finding is related to the different sensitivity detected by two studies, where red cell scan can detect bleeding rate as low as 0.04 mL/min compared to angiography which needs bleeding rate of 0.5 mL/min to be positive [29, 30]. Similar to these findings, prior studies have shown that tagged red blood cell scintigraphy is not helpful as a screening tool for selecting patients who are most likely to benefit from angiography [31].

CT angiography has more recently become more popular for the evaluation of GI bleeding as it is rapid, noninvasive, and allows accurate localization of bleeding site. A meta-analysis including 672 patients found CTA to have a sensitivity and specificity of 85% and 92%, respectively, for the detection of active bleeding [32]. One small study found CTA to be somewhat helpful in triaging patients for angiography: out of their patients with negative CTA, 80% experienced spontaneous resolution of bleeding without further intervention, while 80% of patients with a positive CTA required endovascular or surgical intervention [33]. The rate of CTA utilization prior to angiography was very low in our cohort (17 patients, 15%). Our study found CTA to have a sensitivity and specificity for positive angiography of 40% and 76.9%, respectively. The positive predictive value of CTA for positive angiography was 40% and the negative predictive value was 76.9%. The low numbers of CTA utilized in the series makes these numbers less reliable.

The main limitation of our study is its retrospective design. The timing between the presentation of the acute bleeding and angiography was not investigated and this could potentially lower the rate of detection of active extravasation in case of long delays or intermittent bleeding. Similarly, the timing between CTA, NM, and angiography was not measured and could have had an impact on sensitivity and specificity of CTA and NM on angiography.

CONCLUSION

This study shows that the degree of drop in Hb from baseline, rather than absolute Hb value is an independent predictor of active extravasation on angiogram, with a 65% increase in the odds of extravasation for every unit of Hb drop. Age less than 60 years was a negative predictor of rebleeding and malignancy increased the risk of rebleeding by more than four times. Rebleeding within 30 days of an angiography is a significant predictor of mortality, which increased the odds of death by 45 times. The presence of hemodynamic instability before angiogram increased the risk of 30-day mortality by 13 times. As might be expected, malignancy was also an independent predictor of 30-day mortality.

Conflicts of interest: None of the authors have any conflicts of interest to declare.

Authors' contributions: P.M., S.V. and G.N. contributed to study design and planning, analysis of imaging, and carried out the interventions concerned. J.M. compiled and analyzed data and wrote the greater part of the manuscript. A.B.D. contributed to data analysis and the writing and proofing of the manuscript. M.L. contributed to the statistical analysis of the data. A.N. and R.H. contributed to data gathering and wrote an initial version of the manuscript.

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