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INTERVENTIONAL RADIOLOGY

Recent use of NSAID and NOAC medications are associated with a positive CT arteriogram

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Abstract

Background Computed tomography angiography (CTA) is a diagnostic modality utilized in patients with suspected active lower gastrointestinal (GI) bleeding. CTA use in clinical practice is limited by the risk of contrast-induced nephropathy, and the loss of patients from direct physician observation while undergoing the test. Identifying clinical predictors of a positive result would be useful in guiding physician utilization of CTA studies.

Methods We performed a single-center retrospective study to determine which clinical predictors are associated with a positive CTA. Binary logistical regression modeling was used to identify the independent predictors and the results were expressed as adjusted odds ratios with corresponding 95% CI .

Results 262 patients met inclusion criteria and there were 61 (23.3%) positive CTA exams. In unadjusted analysis those who were CTA positive were more likely to require management in the intensive care unit (85.2% vs. 14.8%, $p<0.01$) and being CTA positive was associated with a significantly increased in-hospital mortality (14.8% vs. 4.5%, $p<0.01$). The use of a novel oral anticoagulant (NOAC) in the week prior to presentation was associated with a positive CTA after adjustment for confounders (adjusted odds ratio = 3.89; 95% CI 1.05–14.43). Similarly, the use of a non-steroidal anti-inflammatory drug (NSAID) was associated with a positive CTA (OR 2.36; 1.03–5.41). Only 8% of patients experienced contrast-induced nephropathy.

Conclusion Use of either NOACs or NSAIDs in the previous week is independently associated with a positive CTA in the setting of acute lower GI bleeding. CTA exams appear to confer a low risk of contrast-induced nephropathy.

Keywords Computed tomography angiography · Gastrointestinal bleeding · Contrast-induced nephropathy

Abbreviations

CKD	Chronic kidney disease
CIN	Contrast-induced nephropathy
CTA	Computed tomography angiography
GIB	Gastrointestinal bleeding
LGIB	Lower gastrointestinal bleeding
NOAC (DOAC)	Novel oral anticoagulant (direct oral anticoagulant)
NSAID	Non-steroidal anti-inflammatory drug

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Introduction

Acute gastrointestinal bleeding (GIB) remains a leading cause of morbidity and mortality, responsible for over half a million combined inpatient hospitalizations per year in the United States [1, 2]. Due to the diverse etiologies of acute GIB, diagnostic and therapeutic evaluation requires obtaining a clinical history in conjunction with endoscopic and radiologic testing. In cases where the bleeding is suspected to be in the upper gastrointestinal (GI) tract (anatomically defined as a source proximal to the anatomic ligament of Treitz), upper endoscopy is the recommended initial test [3].

For cases of suspected acute lower GIB, computed tomography angiography (CTA) has proven to be a useful diagnostic test. CTA is capable of detecting active intestinal blood loss as slow as 0.3 milliliters/min, allowing expedient and precise localization of the site of luminal bleeding which subsequently may be amenable to invasive angiography or therapeutic endoscopy [4]. Compared to diagnostic colonoscopy, it offers the advantages of not requiring a bowel preparation and is non-invasive [4]. Despite these advantages, the accuracy of CTA in clinical practice remains inconsistent, with studies suggestive of a sensitivity ranging from 38 to 100% in prospective series [5–7]. Furthermore, CTA is not entirely innocuous as it requires sending potentially actively bleeding patients out of clinical attention and exposing them to risks of intravenous contrast-mediated nephropathy (CIN). The American Colleges of Gastroenterology and Radiology both recommend consideration of CTA in those with acute GIB who have "high risk" clinical features that may predict a worse outcome [4, 8]. Some of these are defined as presence of hemodynamic instability, age > 60 and presence of gross blood on rectal exam. Both societies concede, however, that the recommendations for the use of CTA in these settings are based on low quality, limited data [8].

Therefore, a clinical unmet need is improving the diagnostic yield of CTA by identifying predictors of active GIB. Based on our review of the literature, there are no studies which have identified clinical variables predictive of a positive CTA in acute GIB. The primary aim of our study was to identify independent predictors of a positive CTA, thereby assisting clinicians faced with ordering this test. A second aim was to report on the rate of CIN as a result of CTA and to identify predictors of this adverse event.

Methods

Patients and methods

Using our hospital's inpatient electronic medical record, we identified all patients that underwent a CTA for the evaluation of acute GIB between 1/2014 and 9/2016. To identify cases, we cross-referenced appropriate International Classification of Disease -9 and 10 codes (ICD-9/ICD-10) for acute GIB with the Current Procedural Terminology CPT and ICD-10 codes for CTA (see supplementary table). We included patients age ≥ 18 who presented either with bleeding to our emergency room or those who developed bleeding while admitted to the hospital for another indication. Clinical bleeding was defined as passage of bright red blood per rectum, passage of clots or passage of melenic stool. We eliminated cases in which there was ambiguity as to whether the CTA was performed for acute GIB or a competing reason (e.g. acute mesenteric ischemia). All CTA exams were performed with the identical protocol used by our institution's radiology department which includes a bolus administration of 100 mL of iodinated intravenous contrast at a rate of 4 mL/second to highlight the mesenteric arterial vasculature (duration of 30 s). The arterial phase was followed by a venous phase scan (duration of 70 s). The constructed images were then interpreted by a radiologist. A CTA study was considered positive when there was extravasation of contrast in the arterial phase with or without pooling of contrast in the lumen of the GI tract in the venous phase.

Clinical parameters and demographic features at the onset of clinical bleeding were obtained using information available in the patient medical record. We recorded medications used prior to the onset of bleeding and calculated a Charlson Comorbidity Index. Initial vitals and lab studies were gleaned from the first assessment in the emergency room or the first set taken after acute GIB was identified for an inpatient. Both physician and nursing documentation is part of the electronic record so that the timing of the onset of acute GIB for inpatients could be determined within a narrow window. The information for the entire hospitalization was recorded for each patient with a determination of the final cause of acute GIB. We also recorded the results of additional studies performed for the evaluation and treatment of acute GIB such as endoscopy and Tc-99 tagged RBC scintigraphy. We were specifically interested in contrast-induced nephropathy and recorded, where available, the creatinine clearance for the 2 days following the CTA in keeping with the criteria for CIN [9]. For patients undergoing multiple CTAs (in the setting of recurrent bleeding), we only included information from their first study.

Statistical analysis

The primary outcome variable of interest was a positive CTA study in the setting of acute GIB.

We first dichotomized patients based on the results of the CTA. We performed univariate comparisons of continuous data between groups using unpaired *t* tests after assessment for normality with histograms. For non-parametric continuous data, we compared medians and calculated interquartile ranges. For dichotomous data comparisons, we used Fisher's Exact test or Chi square where appropriate. We selected significant (p set at ≥ 0.1) potential predictor variables from the univariate analysis and entered them into a binary logistic regression model and controlled for relevant confounders. The binary outcome variable was CTA positive or negative. From this model, we calculated the adjusted odds ratio and associated 95% confidence interval for each predictor variable. The Hosmer–Lemeshow test was used to assess the fitness of the model. Descriptive and inferential statistics were performed using SPSS v. 24. A 2-tailed p value of ≤ 0.05 was considered significant for this portion of the analysis.

Results

After eliminating cases meeting exclusion criteria (Fig. 1), we identified 262 individuals who underwent CTA for the evaluation of acute GIB. Table 1 highlights the characteristics of this study group. Overall, there were 61 (23.3%) positive studies. There were no significant differences between the CTA + vs. CTA—groups with respect to gender and age. Roughly a quarter of patients in both groups presented > 24 h after the onset of GIB and about 20% for both groups occurred in the inpatient setting. In both groups, roughly half of the cases presented during the evening or weekend. With respect to platelet and coagulation factor inhibitors, those who were CTA+ were significantly more likely to be taking a novel oral anticoagulant (NOAC) medication (8.2% vs. 2.5%, $p = 0.04$). CTA + patients were also more likely to be taking an NSAID although this was not significant in univariate analysis (18.0% vs. 10.0%, $p = 0.09$). There were no significant differences in hemodynamic parameters, initial lab values such as hemoglobin, creatinine, INR, or the Charlson Comorbidity Index scores between those who were CTA + vs. CTA—(all $p > 0.05$) (Table 1). CTA + status was strongly associated with a poor outcome. Those who were CTA + were far more likely to require management in the intensive care unit (85.2% vs. 14.8%, $p < 0.01$). Additionally, on univariate analysis, CTA + was associated with a significantly increased in-hospital mortality (14.8% vs. 4.5%, $p < 0.01$).

In logistic regression analysis, use of a NOAC in the week prior to presentation was significantly associated with CTA + after adjustment for age, gender, initial systolic blood pressure, heart rate, hemoglobin and Charlson Comorbidity Index (adjusted odds ratio [aOR] 3.89; 95% CI 1.05–14.43). Similarly, the use of an NSAID was associated with CTA + after the same adjustments (aOR 2.36; 1.03–5.41).

Additional studies after CTA

Findings on CTA+ studies are used as a guide to direct further studies which could be both diagnostic and therapeutic. Figure 2 highlights the results of selective mesenteric arteriography ± embolization for the 61 patients that were

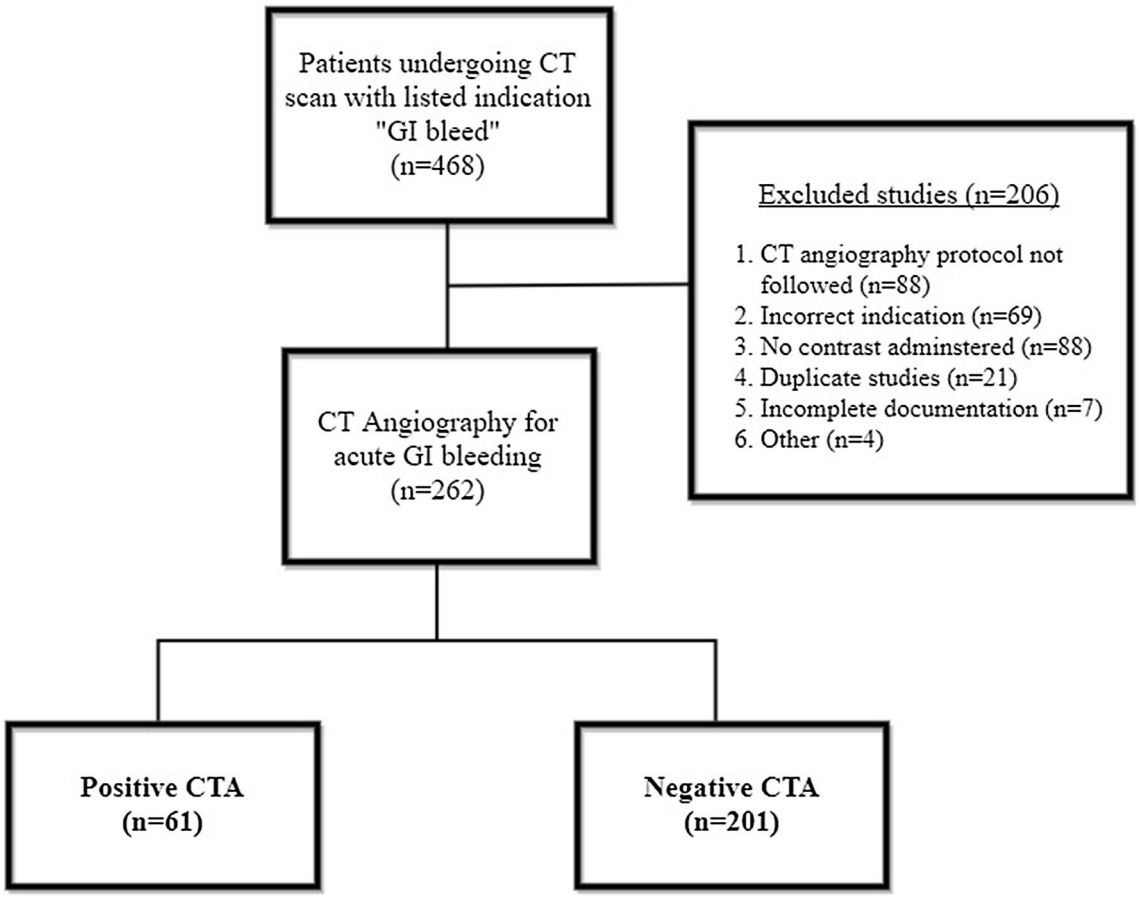

Fig. 1 Flow diagram showing inclusion and exclusion of studies

Table 1 Baseline characteristics of patients

	CTA Positive $n=61$	CTA Negative $n=201$	P value
Male (%)	47.5	50.7	0.66
Age (SD)	65.9 (13.7)	65.8 (14.8)	0.99
Bleeding onset before admission (%)			0.30
< 24 h	60.7	49.2	
> 24 h	21.3	27.9	
Inpatient	18.0	22.9	
Median door to CTA, h (IQR)	4.25 (3.0–8.125)	5.0 (3.0–8.5)	0.24
Median number of bloody BM (IQR)	2 (1.0–3.5)	2 (1.0–4.0)	0.55
Time of day (%)			0.42
7a–6p weekdays	48.3	42.4	
Off hours	51.7	57.6	
Cirrhosis (%)	9.8	8.0	0.64
Use within past 7 days (%)			
Aspirin	47.5	45.3	0.76
NSAID	18.0	10.0	0.09
NOAC	8.2	2.5	0.04
Warfarin	13.1	9.0	0.34
Values prior to CTA, mean (SD)			
Systolic blood pressure	120.4 (25.2)	124.4 (25.1)	0.28
Heart rate	93.8 (25.2)	93.9 (20.2)	0.99
Hemoglobin (g/dl)	9.5 (2.4)	9.9 (2.9)	0.34
Platelet count (1000/μL)	234 (141)	245 (117)	0.52
INR	1.29 (0.56)	1.29 (0.79)	0.99
Creatinine (mg/dl)	1.35 (1.18)	1.58 (1.83)	0.35
Charlson comorbidity index	4.39 (2.6)	4.49 (2.6)	0.80
Clinical outcome (%)			
ICU admission	85.2	14.8	< 0.01
Surgery	14.8	8.0	0.11
Death	14.8	4.5	< 0.01

CTA computed tomography angiography, *INR* International normalized ratio, *ICU* intensive care unit, *NSAID* non-steroidal anti-inflammatory drug, *NOAC* novel oral anticoagulant

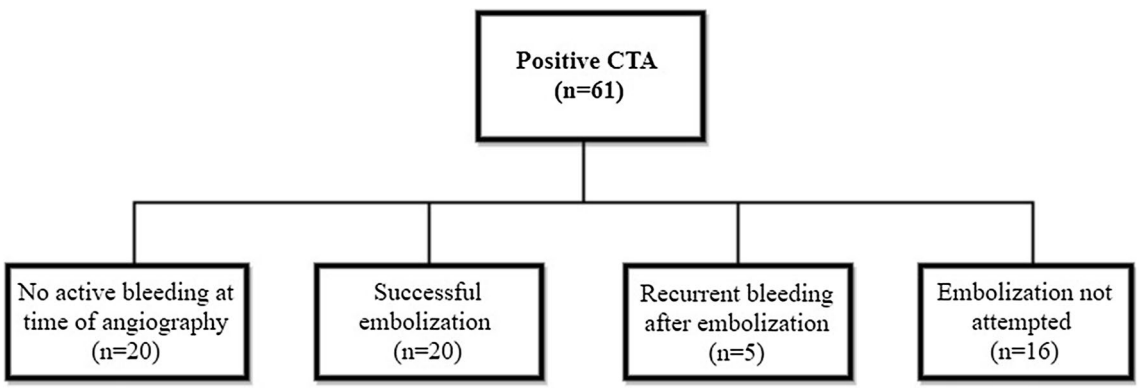

Fig. 2 Outcomes after positive CT Arteriogram

CTA+. Overall, 20 (32.8%) patients did not have a bleeding source identified. Of the remaining 41 patients with an active bleeding source seen by invasive angiography, 25 (61.0%) underwent successful culprit vessel embolization. Five (20%) patients experienced recurrent bleeding despite initial successful embolization. However, 4 of 5 had self-limited bleeding while one required endoscopic hemostasis. For 16 (39.0%) patients, embolization was not attempted due to various reasons including severe arterial stenosis ($n=1$), identified sites of bleeding that were clinically determined to be more amenable to endoscopic therapy ($n=11$) such as a rectal Dieulafoy's lesion, and the decision to elect for supportive care ($n=4$).

After embolization, depending on the results of angiography, along with the clinical history and hospital course, a significant portion of patients underwent further studies to visualize the luminal GI tract. Table 2 shows the extent of endoscopic evaluation in both the CTA+ and CTA− groups. Patients in the CTA+ group required fewer endoscopic studies compared to the CTA− group (64% vs 76%). Table 3 highlights the endoscopic findings noted in the respective groups. The majority of patients in both CTA+ and CTA− groups had no identifiable lesion on endoscopic evaluation (59% and 61%, respectively). Luminal ulcers (e.g. PUD), vascular lesions (e.g. angioectasias) and intraluminal masses were the most common endoscopic findings in the CTA+ group while colitis and luminal ulcers were the most common endoscopic lesions seen in the CTA− group. The rate of endoscopic therapy was higher in the CTA+ group compared to the CTA− group (17% vs 7%). Active bleeding diverticuli were seen in only 2% of endoscopic exams performed in the CTA− group.

Table 3 Endoscopic findings in patients who underwent CTA

	Positive CTA ($n=61$)	Negative CTA ($n=201$)
No discrete lesion	32 (59%)	134 (61%)
Luminal ulcers (e.g. PUD, SB & rectal)	10 (19%)	16 (7%)
Vascular lesions (e.g. AEC or Dieulafoy)	3 (6%)	10 (5%)
Colitis	2 (4%)	22 (10%)
Luminal mass	3 (6%)	11 (5%)
Colonic diverticular bleeding (active)	0	5 (2%)
Bleeding hemorrhoids	0	4 (2%)
Other (varix, PHG, hemobilia, post-polypectomy bleeding)	2 (4%)	5 (2%)
Presence of blood in lumen without source	2 (4%)	14 (6%)
Total number of procedures	54	221

AEC angioectasia, *PHG* portal hypertensive gastropathy, *PUD* peptic ulcer disease, *SB* small bowel

Contrast-induced nephropathy

We used the standard criteria for acute kidney injury defined as a rise in the serum creatinine concentration (Cr) by ≥ 0.3 mg/dl by 48 h post exposure to intravenous contrast [9]. Patients on dialysis were not included in the analysis. 206 patients remained after we excluded 20 patients on dialysis prior to CTA, and 36 patients without a 48 h post-CTA Cr. Only 17 (8.3%) patients met the definition of CIN at 48 h post-CTA. Their mean rise in Cr was 0.69 ± 0.52 mg/dl with only 2 patients having a rise by ≥ 1.0 mg/dl. Patients who developed CIN had a significantly higher baseline Cr than those who did not (1.9 ± 1.7 vs 1.1 ± 0.6 mg/dl; $p<0.001$). In a binary logistic regression model, for every 1.0 mg/dl increase in the baseline Cr, the adjusted risk of CIN roughly doubled (OR 2.1; 1.35–3.59) after adjusting for age, baseline systolic blood pressure, hemoglobin, and Charlson Comorbidity index.

Discussion

CT angiography is a minimally invasive, rapidly available diagnostic modality that has been shown to detect active bleeding rates of as low as 0.3 ml/min with >90% sensitivity and specificity [10–12]. However, the clinical accuracy of CTA in detecting active GIB remains suboptimal, with reported detection rates of as low as 38% [5, 7]. The

Table 2 Endoscopic evaluation in patients who underwent CTA

	Positive CTA ($n=61$)	Negative CTA ($n=201$)
Number of patients who underwent endoscopic evaluation, *n* (%)	39 (64%)	152 (76%)
Total number of procedures performed in each group, *n*	54	221
Number of procedures requiring endoscopic therapy, *n* (%)	9 (17%)	16 (7%)
Upper endoscopy, *n* (%)	20 (37%)	93 (42%)
Lower endoscopy, *n* (%)	27 (50%)	122 (55%)
Video capsule endoscopy, *n* (%)	2 (4%)	2 (1%)
Double balloon enteroscopy, *n* (%)	5 (9%)	4 (2%)

discordance between the inherent capability of CTA and the observed clinical performance highlights the inability of the ordering clinician to predict which patient will have a positive study with a reasonable pre-test probability. The American College of Gastroenterology offers suggestions to consider CTA in patients with high risk clinical features such as age >60 and signs of hemodynamic compromise but these recommendations are supported by very low-quality evidence [8].

The aim of our study was to identify clinical variables that can be used to predict a positive CTA result in patients admitted with acute lower GIB. The previous literature has identified a decrease in hematocrit [13] and a transfusion requirement [14] as a predictors of extravasation during invasive angiography but there are no dedicated studies looking at clinical predictors for CTA. We compiled a large number of objective parameters such as hemoglobin, creatinine, number of units of blood transfused, presentation vital signs, use of anti-platelet medications and anticoagulants along with historical parameters such as prior endoscopic reports identifying potential sources of gastrointestinal bleeding. To our knowledge, this is the first study to examine a comprehensive list of variables in patients undergoing CTA for acute lower GIB.

We demonstrated that the use of NSAIDs and NOACs were independent predictors of a positive CTA. Interestingly, the use of warfarin did not demonstrate a statistically significant difference in CTA results. Our findings may be due to the observation that NOAC drugs have a predisposition for causing GIB in comparison to other anticoagulants and anti-platelet medications in certain populations [15]. This is hypothesized to be related to the increased luminal concentration of NOAC drugs particularly in the lower gastrointestinal tract which can exert topical effects on the intestinal mucosa and increase the likelihood of bleeding from pre-existing lesions [16]. While we did observe NOACs to be a predictor of a positive CTA, larger scale studies should be done to further investigate the degree of this risk and whether this population should be considered for early visceral angiography or undergo direct visceral angiography without first obtaining a CTA. Similarly, NSAID drugs have been shown to be strongly associated with an increased risk of acute GIB from sources unrelated to peptic ulcer disease such as diverticulosis—the leading cause of acute lower GIB [17]. NSAIDs have shown to also be associated with recurrent diverticular bleeding [18]. When looking at aspirin use, there was no statistically significant difference in CTA results – a finding consistent with current accepted guidelines to continue aspirin for secondary prevention in patients admitted with lower GIB [8].

In our cohort, clinical variables such as systolic blood pressure, heart rate, time from onset of bleeding to administration of CTA were not predictive of a positive result. Inpatient onset of clinical bleeding was also not associated with a positive CTA result. One would expect that these markers could identify earlier and more severe bleeding, thereby increasing the pre-test probability of a positive result, but this was not observed in our study. Probable explanations for these findings relate to the transient and intermittent nature of most etiologies of lower GIBs (e.g. diverticular) [19]. Secondly, the colon has the ability to store a large amount of blood [20] and a patient who may pass bright red blood per rectum may not necessarily have active arterial extravasation of blood at that moment leading to negative CTA results despite the clinical suspicion of "active" bleeding.

Our results also showed that CTA may be a clinically useful prognostic tool in patients presenting with acute GIB. We found that patients who had a CTA + result were much more likely to require ICU admission than those who had a negative CTA result (85.2% vs 14.8%, $p < 0.01$). This suggests that CTA + patients are more ill and require a higher level of clinical monitoring. This finding is consistent with previous studies showing a lower risk of re-bleeding after an initial negative CTA and therefore a more conservative management strategy may be used [21]. However, we do suspect that an association between CTA + and ICU admission may partly be influenced by the result of the test itself. We also found in unadjusted analysis that CTA + patients experienced a fourfold increased odds of mortality.

One of the concerns with CTA, especially in the setting of acute GI blood loss, is the risk of contrast-induced nephropathy (CIN). Defined as an acute form of renal function impairment following administration of intravenous contrast, the risk of CIN has been reported to range from <1% of patients without risk factors to upwards of 30% in those with significant risk factors such as underlying hypovolemia and chronic kidney disease (CKD) [21, 22]. In our study population, roughly 8% of patients developed CIN after undergoing CTA, mostly in the group with underlying CKD. Baseline elevation in creatinine was the principle risk factor for developing CIN after controlling for relevant risk factors. Although further studies on this are warranted and awareness of the risks of CTA are still important, this suggests that the risk of CIN in patients with bleeding and hypovolemia is not dis-similar from other studied populations (e.g. those undergoing cardiac catheterization) and that the concern for CIN should not outweigh the potential benefit for most patients with acute GIB [22].

Our study has a number of strengths. The study sample was large and homogeneous due to our inclusion/exclusion criteria. Our study model evaluated common clinical variables and therefore reflected the use of real world diagnostic information that would be available to all clinicians in a hospital setting. We provide detailed radiologic and endoscopic data for patients after their CTA, whether positive

or negative. This information is particularly useful in the CTA negative study group as clinicians often wrestle with deciding on the next diagnostic step after a negative result.

Our study also had limitations. Due to the retrospective methodology, there is a risk for selection bias. For example, in real time, there may be other factors which we did not measure that lead a physician to consider a CTA. For example, an elevated baseline creatinine may deter some clinicians from ordering a CTA in the setting of suspect GI bleeding. Another limitation is that our results are from a single center. CTA protocols vary from institution to institution and our results may, therefore, not be generalizable. Furthermore, the etiologies of acute GIB presenting to our hospital may differ from other regions, and therefore, the performance of CTA could vary with a different mix of diagnoses. While we did identify the use of NOACs to be associated with a higher rate of positive CTA, a low absolute number of patients on NOAC therapy limited the precision of the estimated risk. From our data, we had also hoped to derive and validate a clinical prediction model to aid clinicians in the use of CTA in the setting of GI bleeding. There were no significant hemodynamic or laboratory differences between CTA+ and CTA- results, and therefore, modeling was not possible.

In conclusion, the recent use of non-steroidal anti-inflammatory drugs and novel oral anticoagulants independently predicts a CTA + in the setting of acute GI bleeding. Other clinical parameters such as hemodynamic status, transfusion requirement and timing of onset of bleeding to CTA performance did not reveal a statistically significant difference. A CTA + result portends a worse clinical outcome with increased in-hospital mortality. The risk of contrast-mediated kidney injury in patients with acute GI blood loss undergoing CTA is not increased in comparison to other diagnostic settings in which intravenous contrast is administered. Our findings highlight the diagnostic strengths and limitations of CTA in the setting of gastrointestinal bleeding and hopefully will promote further studies to clarify its future role.

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