ORIGINAL ARTICLE

Outcomes of Negative Computed Tomographic Angiography in Management of Gastrointestinal Bleeding: A Cross-sectional Study

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ABSTRACT

INTRODUCTION: Acute gastrointestinal bleeding is a common gastrointestinal emergency. Only limited studies are available regarding the clinical outcomes after computed tomographic angiography (CTA) mesentery showed negative for active bleed. This study aims to determine the clinical outcome of negative mesentery CTA in patients with clinically active acute gastrointestinal (GI) bleeding. **MATERIAL AND METHODS:** A cross-sectional study with a universal sampling method was used. Patients who underwent CTA to detect gastrointestinal bleeding in the National University Hospital of Malaysia from December 2015 until March 2021 were retrospectively analysed. The outcome of each patient, risk of re-bleeding, and 30-days mortality rate were evaluated and assessed. **RESULTS:** In total, 280 CTAs were performed on 232 patients, with 186 of them showing negative results on their first initial CTA. 40.8% (76/186) of those with negative initial CTA had recurrent bleeding and 73.6% (56/76) of them required active intervention. We found that the risk of re-bleeding is lower in the upper gastrointestinal group compared to the lower gastrointestinal group (OR=1.5, 95% CI: 0.877- 2.852, p: 0.128). The overall 30 days mortality rate after the first negative CTA was 23.1% (43/186). Among those patients who experienced re-bleeding, 32.8% (25/76) died within 30 days, with 18.4% (14/76) succumbing to massive bleeding. **CONCLUSION:** From our analysis, it can be concluded **that a** clinically active GI bleeding with negative mesentery CTA has a 40.8% chance to re-bleed with 23.1% 30-day mortality rate. Close observation and follow-up of this population is recommended due to high rate of active intervention needed.

Keywords
Angiography, Gastrointestinal Haemorrhage, Mesentery, Computed Tomography Angiography, Cross-Sectional Studies

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INTRODUCTION

Acute gastrointestinal bleeding is a common gastrointestinal emergency with potentially critical outcomes and can be divided into upper gastrointestinal bleeding (UGIB) and lower gastrointestinal bleed (LGIB). In the United Kingdom, the incidence of UGIB per year is 84-172/100 000 and 25/100 000 for LGIB.[1] In Malaysia, the incidence of UGIB is approximately 72/100,000.[2] The average mortality rate is approximately 10% with no significant improvement over the past 50 years.[3] There is also an increase in the trend of hospitalization rate due to gastrointestinal bleeding in the United States of America which is approximately 375 per 100 000 patients.[4]

According to 2012 United Kingdom National Institute of Health and Care Excellence (NICE) guidelines, endoscopy should be performed urgently in severe acute gastrointestinal bleeding patients, and within 24 hours of admission in stable gastrointestinal bleeding cases. If there is an episode of re-bleeding clinically, a repeat endoscopy should be offered for endoscopic treatment. Prompt referral to interventional radiology or surgery should be made if recurrent bleeding despite endoscopic treatment occurs.[3] In more than 10% of patients, recurrence of bleeding occurs after the initial endoscopic treatment.[5] When endoscopy fails, it is mostly due to the

large pooling of blood in the bowels or poor bowel preparation. Hence computed tomographic angiography (CTA) of the mesentery is used to detect the source of bleeding.

CTA has high sensitivity and specificity of 97% and 100% respectively using arterial and portal venous phase images.[6] CTA can also provide a precise source of bleeding and its possible causes, which is very useful in facilitating further management.[7] If the CTA is positive, patients will usually undergo either interventional procedures, repeat endoscopy, endovascular embolization, or open surgery hence improving their clinical outcomes and rate of survival. However, limited studies are available on the clinical outcomes after a negative CTA of the mesentery for active bleeding.

In this retrospective study, our research aims to assess the clinical outcomes of patients who had active acute GI bleeding with negative initial CTA of the mesentery. Hopefully, through this study, clinicians will be able to predict the potential cases of re-bleed based on specific risk factors that are going to be discussed.

MATERIALS AND METHODS

Patient

The study was conducted in a tertiary centre National University Hospital of Malaysia. A universal sampling of all 232 cases of acute gastrointestinal bleeding that underwent mesentery CTA from December 2015 to May 2021 were retrospectively analysed. The data lists and CTA reports were retrieved from Radiology Information System (RIS) and Caring Hospital Enterprise system (C-HETs). The medical records were retrieved from the hospital RIS, C-HETs system, and manually from the record unit department. Inclusion criteria were patients who were referred for radiological investigation due to clinical symptoms of acute gastrointestinal bleeding by the primary team, either upper or lower gastrointestinal bleeding. Patients were excluded for the following reasons: variceal gastrointestinal bleeding, traumatic gastrointestinal bleeding, and detailed information were unavailable. Data collection included patient demographics, comorbidities, location and causes of bleeding, clinical outcome, radiological or surgical procedure, hemodynamic status during the CTA, and survival at 30 days within a single admission.

CTA of Mesentery Examination

CT examinations were performed with a 160-slice Toshiba Prime Aquillion or 640-slice Toshiba One Aquillion CT scanners using a multi-phase protocol:

1. Plain phase: baseline 1-mm acquisition was performed from diaphragm to symphysis pubis without IV contrast.
2. Arterial phase: 100 ml iodinated contrast medium (Ultravist-370) was administered by intravenous bolus injection, using a 21-G branula, at 4 ml/s using a bolus tracking technique and the region of interest (ROI) is centred at the celiac artery. Once the intraluminal contrast reaches the HU of 180, it automatically triggers the machine and scan is performed with an acquisition of 1 mm with a slice interval of 0.8mm.
3. Portovenous (delayed) phase: scan was done at 65 seconds post contrast administration with the acquisition of 1-mm with a slice interval of 0.8mm.
4. Further delayed phase: usually 5 minutes after post-contrast administration, to see further pooling of contrast.

A CTA mesentery was considered positive when contrast blush is seen in the arterial phase with further pooling in the portovenous and delayed phases. And a negative CTA mesentery was when there is no contrast blush seen arterial phase and no pooling of contrast in subsequent phases.

Terminology and Definitions

UGIB was when the origin of the bleed is proximal to the ligament of Treitz, while LGIB was when the origin is distal to the ligament of Treitz. Common symptoms of UGIB include hematemesis and melena; whilst in LGIB the symptom is mainly haematochezia. The re-bleeding case was when a patient had recurrent similar symptoms of gastrointestinal bleeding, or when they were referred for other secondary symptoms such as a drop in haemoglobin (Hb) or requiring blood transfusion after an episode of recovery. The hemodynamic status of the patient at the time of bleeding was considered stable or unstable based on

criteria from the Rockall score which is tachycardia (pulse rate>100/min) and hypotension (systolic blood pressure <100mmHg).

Data Interpretation and Analysis

Descriptive summaries were used to evaluate the clinical outcome after the initial negative CTA and to determine the frequencies, percentages, median, standard deviation, and as well as 30-day mortality rate. The rates of re-bleeding between upper and lower gastrointestinal bleeding were also compared using the Chi-squared test. The risk for re-bleeding between these two groups was also calculated. The–relationship between multiple possible related comorbidities and the CTA outcome was calculated using binary logistic regression analysis and the Chi-squared test. Data collected from the study were analysed using a software program, Statistical Package for the Social Sciences (SPSS) version 26. The p-value <0.05 was taken as a statistically significant difference.

RESULTS

A total of 232 patients underwent a total of 280 CTA mesentery for acute GI. 28 patients had 2 CTAs, 6 patients had 3 CTAs, 2 patients had 4 CTAs and 1 patient had 5 CTAs. Of the 232 patients 147 were males (63.4%) with a mean age of 65.4 and a standard deviation (SD) of 14.8. Out of 232 patients, 129 (55.6%) had UGIB, and 103 (44.4%) had LGIB. The aetiologies for the UGIB cases were peptic ulcer disease (PUD) (61.2%), tumour-related (10%), inflammation (7.7%), overwarfarinization (4.6%), and others (16.3%), while the aetiologies of the LGIB group were diverticulum (36%), ulcer (13.6%), colitis/inflammatory bowel disease (8.7%), tumour-related (6.8%), polyps (4.9%), angiodysplasia/arteriovenous malformation/pseudoaneurys (4.9%), overwarfarinization (1%) and others (24.3%).

Out of the 232 patients who underwent CTA mesentery, 186 (80%) of them had a negative first CTA. And 101 (59%) of these negative initial CTA had no episode of further bleeding, of which 92 patients (83.6%) were discharged well, and 18 (16.3%) passed away due to other unrelated causes and complications. However, 76 out of those 186 (40.8%) patients had recurrent bleeding, of which 29 patients (38.1%) ended up with surgical intervention, 24 (31.5%) had mesenteric angiography and embolization including prophylactic embolization, 8 (10.5%) had diagnostic mesenteric angiography, 3 (4%) underwent endoscopy treatment, and 12 (15.8%) had supportive therapy. Unfortunately 25 (32.8%) of those with recurrent bleeding after their negative initial CTA died, of which 14 (18.4%) died due to direct cause of bleeding, either after intervention or supportive therapy, and 11 (14.4%) died from other causes such as sepsis or multiorgan failure. The results summary is shown in Figure 1. The outline of the outcome according to the location of bleeding is shown in Figure 2.

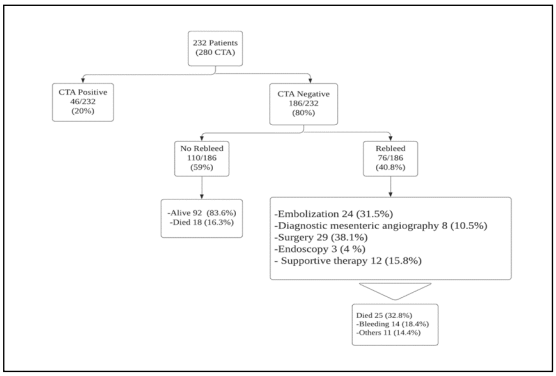

Figure 1. Flowchart of outcome summary of gastrointestinal bleeding after initial negative CTA.

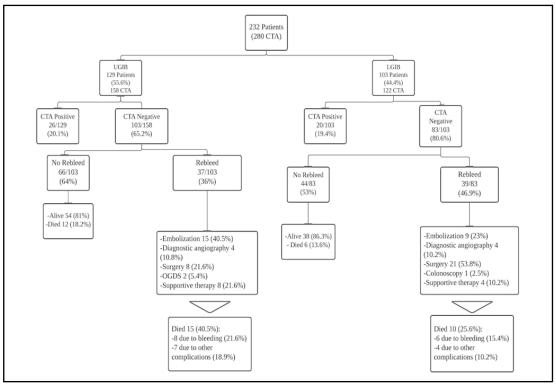

Figure 2. Flowchart of outcome summary of upper and lower gastrointestinal bleeding after initial negative CTA.

UGIB vs LGIB Re-bleeding Comparison

Within those without re-bleeding after the initial negative CTA, it was found that there was no significant difference between the upper and lower gastrointestinal groups; 66 out of 103 patients (64%) and 44 out of 83 patients in lower gastrointestinal bleeding (53%, p=0.127). The risk of re-bleeding after the first negative CTA is found to be lower in the upper gastrointestinal group as compared to the lower gastrointestinal group (OR=1.5, 95% CI: 0.877-2.852, *p*: 0.128).

In terms of the number of deaths directly related to bleeding following an episode of re-bleed, 8 patients (21.6%) were from the upper gastrointestinal group, and 6 (15.4%) were from the lower gastrointestinal group. They both showed rather similar mortality rate. So the decision whether or not to repeat CTA or directly go for intervention need to be weighed in equally in both cases.

30-Days Mortality Rate

The overall 30-day mortality rate for gastrointestinal bleeding after a negative initial CTA was 23.1% (43/186 patients). For those with re-bleeding after the negative first initial CTA, the mortality rate was 32.8% (25/76 patients), of which 18.4% (14/76) died directly due to bleeding; 5 after surgical intervention, 5 after mesenteric embolization, and 4 after supportive therapy. The remaining 11 (14.4%) deaths were due to other complications such as sepsis, myocardial infarction, and cancer-related. And of those who died directly due to bleeding episode following a negative initial CTA, there was not much difference either it was from UGIB or LGIB.

Most of the patients without re-bleed had a hospital stay of less than 7 days (82%). However, for those who had re-bleeding after the negative initial CTA, 39 out of the 51 patients who survived were admitted for more than 7 days (76.4%). The average total days of admission for this group was 13 days. Also important to note that most of these patients also had other health complications other than gastrointestinal bleeding per se such as sepsis and myocardial infarction.

Relation with Comorbidities

Binary logistic regression analysis assessing the association between CTA outcome and potential covariates or comorbidities is shown in Table I. All of these clinical predictors were analysed independently. While certain age group or patients with co-morbidities like end stage renal failure, coagulopathy and diabetes may have higher risk of gastrointestinal bleed, it is evident in our study that they are not significantly related to the result of their CT angiogram.

Table 1: Binary logistic regression analysis between covariates/comorbidities and CTA (n=232). *significant at p<0.05,

		CTA result of GI bleeding		Exp (B)	95% CI	*p* value
		Negative	Positive			
Age Category	15-30	8 (80%)	2 (20%)	0.375	0.051 - 2.772	0.337
	31-45	6 (60%)	4 (40%)			
	46-60	38 (80.9%)	9 (19.1%)			
	61-75	88 (85.4%)	15 (14.6%)			
	76-90	46 (74.2%)	16 (25.8%)			
Gender	Male	114 (77.6%)	33 (22.4%)	0.624	0.308 - 1.264	0.190
	Female	72 (84.7%)	13 (15.3%)			
Ethnicity	Malay	99 (81.1%)	23 (18.9%)			
	Chinese	76 (78.4%)	21 (21.6%)	1.189	0.613 - 5.602	0.608
	Indian	8 (80%)	2 (20%)			
	Others	3 (100%)	0 (0%)			
ESRF/CKD	No	144 (82.8%)	30 (17.2%)	0.547	0.272 - 1.098	0.09
	Yes	42 (72.4%)	16 (27.6%)			
Diabetes Mellitus	No	115 (81.0%)	27 (19.0%)	0.877	0.455 - 1.693	0.696
	Yes	71 (78.9%)	19 (21.1%)			
Hypertension	No	99 (80.5%)	24 (19.5%)	0.959	0.502 - 1.829	0.898
	Yes	87 (79.8%)	22 (20.2%)			
Coagulopathy	No	174 (81.3%)	40 (18.7%)	0.460	0.163 - 1.299	0.460
	Yes	12 (66.7%)	6 (33.3%)			
Haemodynamic	Stable	143 (80.8%)	34 (19.2%)	0.852	0.406 - 1.788	0.672
	Unstable	43 (78.2%)	12 (21.8%)			

DISCUSSION

Computed tomography angiography (CTA) of the mesentery is a widely used radiographic imaging to detect acute gastrointestinal bleeding mainly due to its availability in most tertiary hospitals, time-saving, and high accuracy to detect the bleeding point. The sensitivity and specificity of CTA were reported to be 97% and 100% respectively.[6,8] Our study focuses on the outcome of patients who presented with clinical symptoms of acute gastrointestinal bleeding but had a negative first initial CTA. In recent years, not many studies have been published regarding the clinical outcome after a negative CTA in gastrointestinal bleeding. Chan et al. in 2014 published their research regarding the prognostic indicator

of negative CTA and concluded that if no active gastrointestinal bleeding is detected in CTA, one can avoid unnecessary endovascular angiography intervention and supportive treatment might be sufficient.[1]

In this retrospective study, we found that the percentage of gastrointestinal re-bleeding cases in a single admission after the negative first CTA was 40.8%. This result was comparable to various studies from different other countries, with the re-bleeding rate after an initial negative study ranging from 27.4% to 51%.[1, 9-11] Some factors that may contribute to the re-bleeding episode in these patient include hemodynamic instability, cancer-related bleeding, the use of anticoagulants or antiplatelet medications and the performance status prior to admission.[1] All of these factors are associated with higher risk of bleeding to begin with hence would warrant a more vigilant monitoring. Almost three-quarters (73.6%) of the re-bleed group in our study population required further intervention, such as endovascular embolization, surgery, or an endoscopic treatment to stop the bleeding. A cross-sectional study in Korea also found quite a close number to our study, in which 60% of their study population required active intervention after a negative angiogram.[9] Chan et al. on the other hand showed that only a quarter (25%) needed further intervention to stop the bleeder.[1] In our setting, 31.5% had mesenteric angiography with embolization done to curb the recurrent bleeding in which mostly were prophylactic as localization of bleeding in angiography is even more challenging in a negative CTA cases. A few common factors making those with negative initial CTA needing active intervention include hemodynamic instability during the bleeding episode, overwarfarinization, and tumour-related bleeding.[1, 11] We can definitely relate with that as almost half of our patients (40%) needing active intervention after a re-bleeding episode was due to these factors; 27% were hemodynamically unstable, 9% had an underlying tumour, and 3.5% were overwarfarinized. However, these relationships require further in-depth research as it was not part of our study objectives.

Between the upper and lower gastrointestinal group, the rate of bleeding recurrence after a negative initial CTA was found to be higher in the LGIB group (46.9% vs 36%), with the risk of re-bleeding 1.5 times higher. The recently published data in 2020 by Fukuda et al also found a similar outcome[12] although some other studies observed a contradicted outcome in which bleeding recurrence was found to be higher in the upper gastrointestinal group.[1,13] The variable outcomes seen in these studies might be largely dependent on the expertise of the surgeons. On the other hand, the availability of medications like Proton-pump inhibitor (PPI) may contribute to the lesser bleeding recurrence in UGIB group.

The overall 30-day mortality rate of our study was 21.7% in the positive CTA group and 23.1% in the negative CTA group. In the negative CTA population, the 30-day mortality rate in the re-bleeding group was higher than in the non-rebleeding group (32.8% vs 16.3%). Mortality rate from this negative CTA group was reported to range from 8–48% in other centres.[1,7,9,12] Those who re-bleed and had UGIB after the first initial negative CTA had a higher mortality rate compared to the LGIB group (40.5% vs 25.6%). However, Chan et al., Fukuda et al. and Joo I et al. reported that the 30-day mortality rate was higher in the lower gastrointestinal group.[1,9,12] This conflicting result compared with our study was likely attributed to the more critically ill background of the upper gastrointestinal bleeding group in our population and faster surgical intervention in lower gastrointestinal bleeding. Although the 30-day mortality rate in the re-bleed group after their negative initial CTA was about one third of the studied population, only 18.4% of the death-related directly to massive bleeding, which is comparable to the previous study by Chan et al, Fukuda et al and Anthony et al.[1,7,12] The rest of the deaths were attributed to other complications and most of these patients had multiple comorbidities related to their mortality.

Several studies have shown that some specific comorbidities and factors could be the reasons for negative CTA in clinically positive gastrointestinal bleeding. Foley et al. concluded that in a hemodynamically stable patient, the result of an angiogram would likely to

be negative.[11] This is contrary to other studies that reported a significant association of age, haematocrit level and patients' heart rate (as manifestation of hemodynamic instability) with positive detection of bleeding on CTA.[14,15] And very recently, Sbeit et al. identified four parameters that were associated with positive bleeding on CTA which includes congestive heart failure, warfarin use, coagulopathy and low albumin level.[16] However, in our study, some of common comorbidities like hypertension, end stage renal failure, coagulopathy and hemodynamic stability were all shown not to be significantly related to the CTA result hence are not a suitable predictors of a positive CTA in those with clinical symptoms of gastrointestinal bleeding (Table I). Our result demonstrated that our patients had multiple variables which may interfere with the prognostication of the gastrointestinal bleeding outcome.

Finally, the variability in our study outcomes proved that managing gastrointestinal bleeding is ever challenging in general and our centre specifically. No fixed pathway or algorithm to find the cause of recurrent gastrointestinal bleeding is yet available, such as repeat CTA, tagged red blood cells (RBC) scan, and even diagnostic laparoscopy. However, a proposed diagnostic algorithm by Wortman JR et. al can be a useful guide. (Figure 3 & 4)

CONCLUSIONS

In our centre, a clinically positive gastrointestinal bleeding patient but with a radiologically negative CTA of mesentery has a 40.8% chance to re-bleed with a 30-day mortality rate of 23.1%. The lesson learnt from this study is that a negative initial CTA does not equate to no bleed. Hence, a close observation and follow-up in this group is highly recommended as the rate of these patients requiring active intervention is high with mortalities that may as well be prevented.

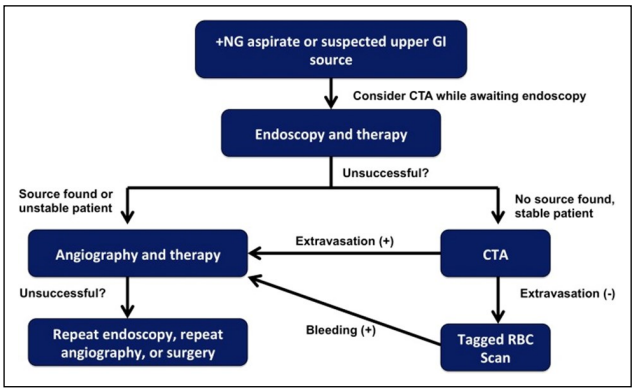

Figure 3. Proposed diagnostic algorithm for suspected upper GI bleeding cases[14]

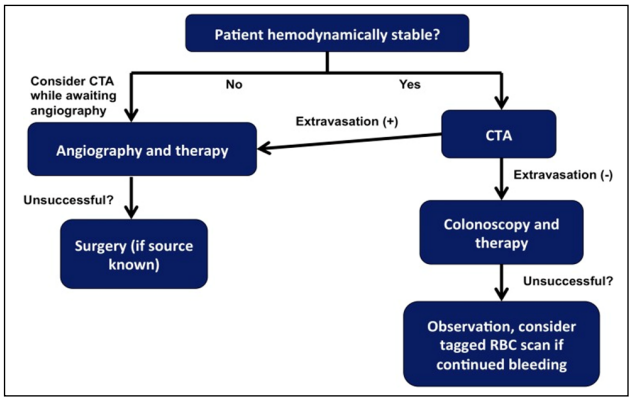

Figure 4. Proposed diagnostic algorithm for suspected lower GI bleeding cases[14]

LIMITATIONS

Since this study was a single centre retrospective study design, some of the data were difficult to obtain, as there was no direct contact with the primary physicians. Another limitation is that there was some variabilities in the clinical management of patients across different disciplines for example between surgical and medical patients.

RECOMMENDATIONS

A prospective and focused study of gastrointestinal bleeding with a larger sample size and standardized management algorithm should be conducted with collaborations from surgical and medical teams to evaluate the outcome.

CONFLICT OF INTEREST

No conflict of interest.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

Ethical approval for this study was obtained from the institution's Research and Ethics Committee (Ethical approval code: FF-2021-037). This is a retrospective cross-sectional study, so informed consent was waived.

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