

Predictors and Outcomes of Gastrointestinal Bleeding in Patients with Acute Myocardial Infarction

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Abstract

Background and objectives: The risk of gastrointestinal bleeding in patients hospitalized with acute myocardial infarction is higher due to antiplatelet and anticoagulant agents along with revascularization. There are limited data about predictors and implications of gastrointestinal bleeding in acute myocardial infarction. Our research aims to investigate the incidence, predictors, clinical outcomes associated with gastrointestinal bleeding in patients with acute myocardial infarction.

Patients and methods: Cross sectional study was conducted. All patients diagnosed with acute myocardial infarction at Tam Duc Heart hospital from January 2013 to March 2017 were enrolled.

Results: A total of 643 patients with acute myocardial infarction were included (67.2 ± 13.8 years). Gastrointestinal bleeding occurred in 9.5%. Multiple logistic regression analysis demonstrated that female (OR 2.21; CI95%: 1.02-4.74; $p=0.044$), pneumonia (OR 2.76; CI95%: 1.25-6.08; $p=0.012$), impaired renal function (OR 4.65; CI95%: 2.08-10.4; $p<0.001$) were independent predictors of gastrointestinal bleeding. Gastrointestinal bleeding was significantly associated with prolonged hospital stay (21.8 vs. 9.7 days; $p<0.01$), increased the need of transfusion (39.4% vs. 3.9%; $p<0.001$), higher in-hospital mortality (21.3% vs. 7.2%; $p<0.01$).

Conclusion: The rate of gastrointestinal bleeding was 9.5%. Female, pneumonia, impaired renal function were independent predictors in patients with acute myocardial infarction.

Keywords: Acute myocardial infarction; Gastrointestinal bleeding

Introduction

Gastrointestinal (GI) bleeding is an important cause of morbidity and mortality in the population as well as in patients with cardiovascular disease [1]. Many studies show that GI bleeding in acute myocardial infarction (AMI) has a worse prognosis, even in mild cases. In addition, the treatment of these patients including the combination of antiplatelet agents, thrombolysis, anticoagulant therapy increases the risk of bleeding, especially GI bleeding [1]. GI bleeding prolongs hospital stay, higher in-hospital mortality and 6-month mortality [2-4]. Despite advanced in diagnosis and treatment, mortality after GI bleeding is still around 10% during the last half decade and higher in-hospital mortality in severe patients [3].

At present, cardiovascular and GI physicians in our country have few reliable data on the frequency of GI bleeding, optimal treatment strategy and prognosis of GI bleeding in patients with AMI. Therefore, we found it necessary to perform this study to determine the risk factors and effect of GI bleeding in patients with AMI with three following objectives: to describe the clinical characteristics, laboratory test and treatment of GI bleeding in patients with AMI; to identify predictors of GI bleeding in patients with AMI; to determine and compare the rates of outcomes in patients with and without GI bleeding in patients with AMI.

Methods

Study design

It was a prospective cohort study.

Inclusion criteria

All patients diagnosed with acute myocardial infarction at Tam

Duc Heart hospital from January 2013 to March 2017 were enrolled in this study.

Exclusion criteria

Patients with uncompleted data were excluded from the study.

Definition

Acute myocardial infarction: Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above 99th percentile upper reference limit and with at least one of the following: Symptoms of ischaemia; New or presumed new significant ST-segment-T-waves (ST-T) changes or new left bundle branch block; Development of pathological Q waves in the ECG; Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; Identification of an intracoronary thrombus by angiography [5].

Gastrointestinal bleeding: Overt GI bleeding: at least one of three following symptoms:

- Hematemesis or blood in nasogastric tube

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Received August 16, 2018; Accepted August 24, 2018; Published August 31, 2018

Citation: Tran-Thi-Khanh T, Phan-Thi-Thuy D, Duong-Quy S (2018) Predictors and Outcomes of Gastrointestinal Bleeding in Patients with Acute Myocardial Infarction. J Vasc Med Surg 6: 368. doi: [10.4172/2329-6925.1000368](https://doi.org/10.4172/2329-6925.1000368)

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- Hematochezia

- Melena

Occult GI bleeding:

- Positive fecal occult blood (FOB) test

Hemoglobin drop of more than or equal to 2 g/dL without an identifiable extraintestinal source [6]

Anemia at admission: According to WHO (World Health Organization), anemia occurs when Hb<13 g/dL for men and Hb<12 g/dL for women.

Death: Including death and serious cases considered as death.

Statistical analysis

Statistics were performed with SPSS version 22.0 (Chicago; USA). The P value of <0.05 was considered significant for all tests. The χ^2 test to compare two ratios, t-test to compare two means. Non-standard deviation variable is described by median and interquartile range (IQR) (25%-75%). Significant clinical factors associated with GI bleeding were identified by univariable logistic regression analysis and then included in the multivariate logistic regression model with p<0.25.

Results

A total of 643 patients with AMI admitted to Tam Duc Heart hospital from January 2013 to March 2017 were included in the present study.

Study population

The anthropometric and clinical features of study subjects were presented in Table 1. The mean age was 67.2 ± 13.8 years old with 68.7% of male and 31.3% of female.

	Frequency (%)
N	643
Age	67.2 ± 13.8
Sex	
Male	442 (68.7%)
Female	201 (31.3%)
GI history	
Prior epigastric pain	13 (2.0%)
Prior peptic ulcer disease	54 (8.4%)
Prior GI bleeding	8 (1.2%)
NSAIDs medication	3 (0.5%)
Glucocorticoids medication	3 (0.5%)
Medical history	
Prior MI	48 (7.5%)
Prior PCI	46 (7.2%)
Prior CABG	9 (1.4%)
Prior heart failure	13 (2.0%)
Chronic renal failure	63 (9.8%)
Prior COPD	17 (2.6%)
Stroke	27 (4.2%)
Asthma	10 (1.6%)
Atherosclerosis factors	
Hypertension	434 (67.5%)
Diabetes	199 (30.9%)
Dyslipidemia	254 (39.5%)

Smoking	250 (38.9%)
Clinical characteristics	
Length of hospital stay. mean	10.93 ± 12
Admission heart rate (bpm)	81.6 ± 22.5
Admission systolic blood pressure (mmHg)	128.2 ± 30.2
Admission diastolic blood pressure (mmHg)	74.6 ± 17.7
Killip III, IV at admission	114 (17.7%)
Mechanical ventilator	77 (12.0%)
Vasopressors use	127 (19.8%)
Intra-aortic balloon pump	53 (8.2%)
Pneumonia	174 (27.1%)
Anemia at admission	214 (33.3%)
ST-segment elevation at admission	277 (43.1%)
GI bleeding	61 (9.5%)
Upper GI bleeding	16 (2.5%)
Lower GI bleeding	3 (0.5%)
Occult GI bleeding	42 (6.5%)
Treatment strategy	
Revascularization	493 (76.7%)
Medical management	150 (23.3%)
Endoscopy	9 (1.4%)
PPI drug use	615 (95.6%)
Outcome	
Death	55 (8.6%)
Survival	588 (91.4%)

Table 1: Anthropometric and clinical characteristics of study subjects.

Note: NSAID: Non-Steroid Anti-Inflammatory Drugs; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Graft; COPD: Chronic Obstructive Pulmonary Disease; GI: Gastrointestinal; PPI: Proton Pump Inhibitors.

Clinical features, laboratory test and treatment in AMI patients with and without gastrointestinal bleeding

All the clinical and biological data of AMI patients with and without gastrointestinal bleeding were presented in Table 2.

Treatment of gastrointestinal bleeding during hospitalization

All of the AMI patients with overt upper GI bleeding were controlled with high doses PPI (proton pump inhibitors) intravenously for 72 hours and switched to oral route. Occult GI bleeding were treated with intravenous or oral PPI. Four cases of GI bleeding were identified as acquired coagulation disorders due to multiple organ failure and/or thrombolytic therapy. These cases were supplemented with fresh frozen plasma, cryoprecipitated, and platelet concentrate.

In GI bleeding group, the time of event occurs on the second day with overt GI bleeding (IQR, 1-5) and upper GI bleeding (IQR, 1-7) and the third day with lower GI bleeding (IQR, 1-5). There were 9 (14.8%) patients underwent endoscopy (Table 3) and none of them had complications at the time of endoscopy (arrhythmia, hypotension, respiratory failure). The mean hemoglobin dropped from 11.0 ± 2.6 g/dL to 9.4 ± 2.0 g/dL. Most of patients didn't have ST-segment elevation at admission (60.7%). The need for transfusion is 24 cases (39.4%). The number for pack red blood cell needed was one unit on average. 8 (13.1%) patients had to stop anticoagulant therapy. Only one case underwent emergency endoscopy (<12 hours). Almost cases were performed endoscopy after cardiovascular stabilization. There wasn't recurrent GI bleeding during hospitalization. PPI was used in almost cases (98.4%).

Characteristics	Patients		P value
	With GI bleeding n=61	Without GI bleeding n=582	
Age, yrs	76.3 ± 10.4	66.2 ± 13.7	p <0.001
Female sex	35 (57.4%)	166 (28.5%)	p <0.001
Medical history			
Prior epigastric pain	3 (4.9%)	10 (1.7%)	p=0.091
Prior peptic ulcer disease	7 (11.5%)	47 (8.1%)	p=0.362
Prior GI bleeding	3 (4.9%)	5 (0.9%)	p=0.007
NSAIDs medication	0 (0%)	3 (0.5%)	p=0.574
Glucocorticoids medication	0 (0%)	3 (0.5%)	p=0.574
Prior MI	3 (4.9%)	45 (7.7%)	p=0.426
Prior PCI	7 (11.5%)	39 (6.7%)	p=0.169
Prior CABG	0 (0%)	9 (1.5%)	p=0.328
Prior heart failure	4 (6.6%)	9 (1.5%)	p=0.008
Chronic renal failure	17 (27.9%)	46 (7.9%)	p<0.001
Prior COPD	3 (4.9%)	14 (2.4%)	p=0.245
Stroke	5 (8.2%)	22 (3.8%)	p=0.102
Asthma	0 (0%)	10 (1.7%)	p=0.302
Hypertension	51 (83.6%)	383 (65.8%)	p=0.005
Diabetes	30 (49.2%)	169 (28.9%)	p=0.001
Dyslipidemia	14 (23%)	236 (40.6%)	p=0.007
Smoking	23 (37.7%)	231 (39.7%)	p=0.76
Admission heart rate (bpm)	91.1 ± 27.5	80.5 ± 21.7	p=0.005
Admission systolic blood pressure (mmHg)	124.9 ± 35.6	128.5 ± 29.5	p=0.373
Admission diastolic blood pressure (mmHg)	69.2 ± 19.9	75.1 ± 17.3	p=0.013
Killip III, IV at admission	23 (37.7%)	91 (15.6%)	p <0.001
Pneumonia	43 (70.5%)	131 (22.5%)	p <0.001
Anemia at admission	37 (60.7%)	177 (30.4%)	p <0.001
Vasopressors use	31 (50.8%)	96 (16.5%)	p <0.001
Mechanical ventilator	26 (42.6%)	51 (8.8%)	p <0.001
Intra-aortic balloon pump	13 (21.3%)	40 (6.9%)	p <0.001
ST-segment elevation at admission	24 (39.3%)	253 (43.5%)	p=0.536
LVEF <40% at admission	19 (31.1%)	107 (18.4%)	p=0.017
Troponin T _{hs} peak, mean (SD), pg/mL	4085.0 ± 7906.7	4142.8 ± 9416.9	p=0.963
Hb, mean (SD), g/dL	11.0 ± 2.6	13.4 ± 2.0	p<0.001
Platelet, mean (SD), Giga/L	243.8 ± 103.5	241.4 ± 80.6	p=0.862
PT, mean (SD), %	85.3 ± 21.2	93.0 ± 12.9	p=0.007
aPTT, mean (SD), s	34.2 ± 14.5	32.5 ± 13.5	p=0.367
Fibrinogen, mean (SD), g/L	4.1 ± 1.7	3.8 ± 1.9	p=0.189
Cholesterol, mean (SD), mmol/L	4.0 ± 1.4	4.8 ± 1.4	p<0.001
Triglycerid, mean (SD), mmol/L	2.0 ± 1.2	2.3 ± 1.8	p=0.165
HDL, mean (SD), mmol/L	1.0 ± 0.4	1.1 ± 0.4	p=0.122
LDL, mean (SD), mmol/L	2.6 ± 1.1	3.1 ± 1.8	p=0.025
AST, mean (SD), U/L	138.0 ± 370.4	100.6 ± 193.8	p=0.441
ALT, mean (SD), U/L	99.0 ± 271.7	60 ± 119.6	p=0.272
Creatinine, mean (SD), mg/dL	145.9 ± 79.0	107.9 ± 74.2	p=0.001
MDRD, mean (SD), ml/min/1.73m ²	49.4 ± 27.2	70.1 ± 23.3	p<0.001

Table 2: Clinical and biological data of AMI patients with and without gastrointestinal bleeding.

Note: NSAID: Non-Steroid Anti-Inflammatory Drugs; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Graft; COPD: Chronic Obstructive Pulmonary Disease; GI: Gastrointestinal; LVEF: Left Ventricular Ejection Fraction; MDRD: Modification of Diet in Renal Disease.

	Endoscopy	Number
Esophagogastroduodenoscopy	Gastric and duodenal ulcer Forest III	2
	Large lesser curvature gastric ulcer suspected cancer	1
	Erosive fundus	1
	Gastritis with multi-polyp	1
	Gastritis	2
Flexible sigmoidoscopy	Multi sigmoid ulcer	1
Colonoscopy	Caecum tumor	1

Table 3: Characteristics of patients with GI bleeding in endoscopy.

Predictors of GI bleeding in patients with AMI

In our study, we assessed the risk factors of GI bleeding in AMI patients by univariable logistic regression analysis and noted that all of the following conditions were correlated with GI bleeding (p<0.25) including age ≥ 70 years old, female, history of GI bleeding or heart failure or chronic renal failure or hypertension or diabetes mellitus or no smoking, at admission with heart rate ≥ 100 beat per minute, diastolic blood pressure<60 mmHg, anemia, Killip III, IV, thrombocytopenia<100000/mm³, PT<70s, renal failure with MDRD (Modification of Diet in Renal Disease)<60 ml/ph/1.73 m², left ventricular ejection fraction on echocardiography<40% and during hospital stay with mechanical ventilation, vasopressors use, IABP (intra aortic balloon pump), pneumonia. However, in multivariate logistic regression analysis, only females, pneumonia and impaired renal function were independent risk factors of GI bleeding (Figure 1).

Outcomes of study patients

In our present study, the group of AMI patients with GI bleeding had higher length of hospital stay than in group without GI bleeding (21.84 vs 9.79 days) (p<0.01). The rate of AMI patients with GI bleeding needed transfusion higher than in group without GI bleeding (39.4% vs 3.9%) (p<0.001).

The overall in-hospital mortality rate was 8.6%. The percentage of mortality in AMI patients with and without GI bleeding was 21.3%, 7.2%, respectively (p<0.001). AMI patients with GI bleeding was significantly increased in-hospital mortality with OR=3.48 (95% C.I. 1.75-6.93, p<0.001) compared to AMI patients without GI bleeding. We identified 5 independent predictors of in-hospital mortality in AMI patients when analysing multivariable logistic regression including diabetes mellitus, at admission with systolic blood pressure<90 mmHg; Killip III, IV; impaired renal failure, LVEF<40% (Figure 2).

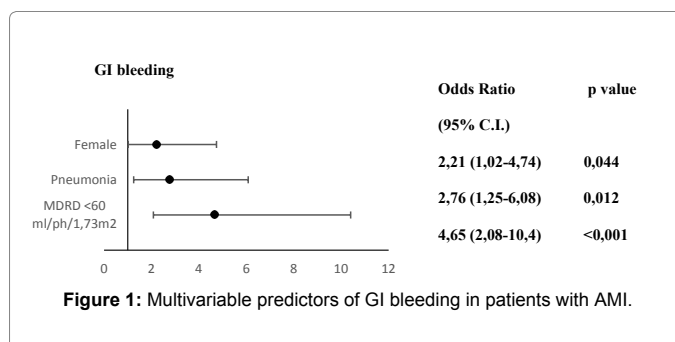
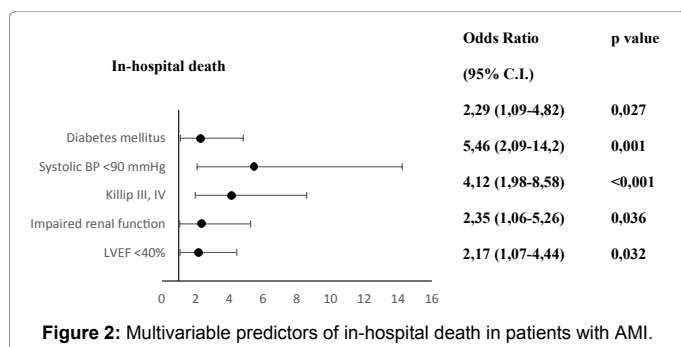


Figure 1: Multivariable predictors of GI bleeding in patients with AMI.



Discussion

The mean age of patients in this study was 67.2 ± 13.8 . The ratio on distribution of gender male:female was 2.2:1 and this result was compatible to previous studies on AMI. GI bleeding was observed in 9.5%, in which overt GI bleeding was 3.0% and occult GI bleeding was 6.5%. The proportion of GI bleeding reported in the previous studies about 1-9% in patients with AMI [2-4]. The rate of overt GI bleeding in AMI patients according to Guo was 2% [7], Ng was 2.7% [4] and Al-Mallah was 3.0% [3], which was similar to ours. Occult GI bleeding in our study accounted for the proportion of 6.5% higher than 2.6% Ng et al. [4], which may be due to different sampling methods. In addition, upper and lower GI bleeding were observed respectively on the second and third days. Therefore, we found that it is necessary to monitor hematocrit and hemoglobin (Hb) during treatment AMI on some high risks patients, especially in 7 first days.

In our study, the average age ($p < 0.001$), female gender, history of GI bleeding or heart failure or chronic renal failure or hypertension or diabetes ($p < 0.05$), tachycardia, low diastolic pressure, Killip III or IV, anemia, $EF < 40\%$ at admission, pneumonia, mechanical ventilation, vasopressors use, IABP ($p < 0.05$) in GI bleeding group was higher than that in non GI bleeding group. Our results were not different compared to others [2-4,6-10]. On biochemistry, mean values of Hb, PT, Cholesterol, LDL, MDRD at admission in GI bleeding group were significantly lower than that in non GI bleeding group ($p < 0.05$). Hypotension resulting from cardiac shock with hypoperfusion to gastric and intestinal mucosa will lead to mucosal erosions, increasing the likelihood of ulcers developing and subsequent bleeding [6].

The management of GI bleeding in AMI patients still has many difficulties. Anticoagulation and antiplatelet agents in the treatment of AMI patients increase risk of GI bleeding and, after that, GI bleeding can cause re-infarction. Previous studies showed that early endoscopy reduced re-bleeding and mortality [11,12]. In our study, only 14.8% patients were performed endoscopy. Most of them had gastritic and peptic ulcer disease on endoscopy. We found that it was necessary to resuscitation before endoscopy. Patients should be underwent diagnostic and therapeutic endoscopy within 24 hours, preferably after resuscitation and stable hemodynamic conditions.

In our study, multivariable analysis confirmed the association of female, pneumonia and impaired renal function with GI bleeding. Predictors of GI bleeding were age ≥ 75 years old, female, previous AMI, pneumonia, anemia at admission in the Guo's study [7] and previous GI bleeding, impaired renal failure with $MDRD < 60$ ml/ph/1,73 m², Killip IV at admission in the Chua's study [6]. Additionally, some of other risk factors composed of aspirin and/or NSAIDs use at home, organ dysfunction, dual antiplatelet agents and anticoagulant use [7,9,10,13].

Overall, the predictors of GI bleeding in AMI patients in our research were as the same as others. Our study found that female increased GI bleeding in AMI patients. Biological differences in platelet function and vascular reactivity, with different "response" to antithrombotic treatments account for most of these sex-based differences. In addition, gender-related difference associated with antithrombotic treatment due to lower body mass and renal function in women than men [14]. Consequently, the treatment related to anticoagulation should be in caution and pay attention to the dose on female patients due to their low body mass and high risk of bleeding.

Impaired renal failure was independent predictor of GI bleeding in our study. The percentage of acquired renal failure at the all stages in patients with acute coronary syndrome is about 30-40%, which make the prognosis severely and higher risk of bleeding. The patients with acute coronary syndrome had renal failure often have a high risk of bleeding because of anticoagulants overdose. Furthermore, renal dysfunction, which has been related to impairment of platelet aggregation and alteration of platelets' interaction with vessel wall, was also a risk factor for gastrointestinal bleeding [6]. Therefore, we realized that it is necessary to estimate glomerular filtration rates as soon as patients admitted to the hospital. Some of patients known to have renal failure or risk of renal impairment should avoid use some specific anticoagulants or need to reduce the dose reasonably.

Previous studies reported that pneumonia increased risk of GI bleeding [3,7]. The organ dysfunction was also one risk factor of GI bleeding. This may be a stress factor of gastro-duodenal ulceration. GI bleeding tends to occur in patients with underlying conditions such as anemia, renal failure and cardiac shock [10]. The mean hospital stay in this study showed that the AMI patients with GI bleeding had higher than those without GI bleeding, possibly due to prolonged GI bleeding treatment and antithrombotic therapy. In previous studies, GI bleeding prolonged hospital stay [6,9] and increased length of intensive care unit stay [7].

The overall mortality rate in the present study was 8.6% and in-hospital mortality in GI bleeding group was higher than in non GI bleeding group. AMI patients with GI bleeding group was 3.48 fold increased hospital mortality compared to AMI patients without GI bleeding group (95% CI; 1.75-6.93; $p < 0.001$). Some reports showed the higher mortality rate of GI bleeding in AMI patients, by 3-10% [2,3,6,9]. Our study found that most patients with GI bleeding were treated with high doses of PPI, transfusion and endoscopy when stabilizing cardiovascular condition. The univariable analysis showed the correlation between GI bleeding and in-hospital mortality, but this correlation seemed disappeared during multivariable analysis. Therefore, the cause of death in AMI patients was not due to GI bleeding but mainly due to cardiovascular events. Kirrkert reported that GI bleeding was not significantly associated with subsequent adverse major cardiac events, cardiac and all-cause mortality, recurrent MI, stroke or stent thrombosis [10]. The mortality in AMI patients was increased with hypotension, acute pulmonary oedema, cardiac shock, renal failure, decreased left ventricular function.

Conclusion

The rate of GI bleeding in AMI patients was 9.5%. Female, pneumonia, impaired renal failure with $MDRD < 60$ ml/ph/1,73 m² were independent predictors in AMI patients with GI bleeding. GI bleeding prolonged hospital stay, increased the need of transfusion and not a major risk of in-hospital mortality.

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