Incidence, Predictors, and Outcomes of Gastrointestinal Bleeding in Patients Admitted With ST-Elevation Myocardial Infarction

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Gastrointestinal bleeding (GIB) complicating ST-elevation myocardial infarction (STEMI) poses significant management challenges and may be associated with poor outcomes. We sought to evaluate the incidence and outcomes of GIB in STEMI patients using a nationwide database. We identified adults admitted with STEMI between in the National Inpatient Sample (2003 to 2016), and compared the morbidity, mortality, resource utilization, and cost in patients with and without GIB. We assessed rates of endoscopy referral and its associated with mortality. Among 1,450,696 weighted STEMI hospitalizations, 32,624 (2.2%) were complicated with GIB. Patients with GIB were older, and had distinctive characteristics compared to those without GIB. Older age, cardiogenic shock; history of peptic ulcer disease, cirrhosis, anemia, or alcohol use disorder were the strongest predictors of GIB during STEMI hospitalizations. In-hospital mortality was higher in the GIB group (28.2% vs 11.1%, p <0.001). The excess mortality associated with GIB persisted after propensity-score matching, and in sensitivity analyses excluding patients who underwent coronary intervention >24-hours after admission, and those transferred to another hospital. Post-STEMI GIB was associated with more strokes and acute kidney injury, longer hospitalizations, and higher cost. In a logistic regression analysis, GIB was independently associated with mortality (odds ratios [OR] 1.91, 95% confidence interval [CI] 1.85 to 1.97, p <0.001). There was a correlation between undergoing endoscopy and lower in-hospital mortality (unadjusted OR 0.27; 95% CI, 0.24 to 0.29; adjusted-OR 0.30; 95% CI, 0.27 to 0.33; p <0.001). In conclusion, GIB complicating STEMI is uncommon but is associated with excess morbidity, mortality, resource utilization and cost. Referral to endoscopy in this cohort may be associated with reduced in-hospital mortality. **(Am J Cardiol 2019;124:343−348)**

Gastrointestinal bleeding (GIB) is a major healthcare burden resulting in 250,000 to 300,000 hospitalizations, 15,000 to 30,000 deaths, and over $1 billion in direct annual expenditure in the United States.[1,2] A non-negligible proportion of patients who experience GIB are hospitalized with other primary acute cardiovascular illnesses such as myocardial infarction, stroke, or pulmonary embolism.[3−9] Gastrointestinal bleeding complicates 0.6% and 3.9% of acute myocardial infarction admissions, and confer an excess risk of short-term mortality among these patients.[3,7,10−14] However, studies evaluating the incidence and impact of GIB on patients with acute myocardial infarction are limited to single center reports and/or included heterogeneous groups of patients with ST- and non-ST elevation myocardial infarction. Patients with ST-elevation myocardial infarction (STEMI) constitute a high risk cohort of patients that is characteristically different from the non-ST elevation myocardial infarction cohort. Nonetheless, data on the incidence and outcomes of GIB in STEMI patients are scarce. Hence, we aimed to utilize a contemporary nationwide database to assess the incidence and predictors of GIB among patients admitted with STEMI, and the impact of post-STEMI GIB on in-hospital morbidity, mortality, resource utilization and cost.

Methods

The national inpatient sample (NIS) was used to derive patient-relevant information between January 1st, 2003 and December 31st, 2016. The NIS is the largest, publicly available, all-payer, claims-based database that contains clinical and resource utilization information on patient discharges from approximately 1000 nonfederal hospitals in 46 states. These data is stratified to represent ∼20% of United States (US) inpatient hospitalizations across different hospital and geographic regions (random sample). National estimates of the entire US hospitalized population were calculated using the Agency for Healthcare Research and Quality (AHRQ) and weighting methods. The study was exempt by the institutional review board because the NIS is a publically available de-identified database.

Patients aged 18 years or above who were hospitalized with a principle diagnosis of STEMI with or without GIB

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were identified using *International Classification of Diseases*-Ninth and Tenth Revision-Clinical Modification (ICD-9-CM and ICD-10-CM) codes (Online Table 1).

The study has the following end points: (1) Temporal trends in the incidence of GIB after STEMI. (2) Predictors of GIB among patients admitted with STEMI. (3) In-hospital complications, mortality, resource utilization, and cost of STEMI in patients with and without GIB. (4) Rates of referral to endoscopy and the association between endoscopy and in-hospital mortality.

Weighted national estimates were used in all statistical analyses. The Cochrane-Armitage test was used to assess the statistical significance of the temporal trend incidence of GIB in patients with STEMI. Patients were categorized into GIB complicating STEMI and STEMI without GIB. Descriptive statistics were presented as frequencies with percentages for categorical variables. Mean, standard deviation, median, 25th and 75th percentiles were reported for continuous measures. Baseline characteristics were compared using Pearson-chi-squared test and Fisher's exact test for categorical variables and an independent-samples *t* test for continuous variables. To account for potential confounders and reduce the effect of selection bias, a propensity score-matching model was developed using logistic regression to derive 2 matched groups for comparative outcomes analysis. Patients admitted with STEMI with or without subsequent GIB were entered into a nearest neighbor 1:1 variable ratio, parallel, balanced propensity-matching model (caliper of 0.01) without replacement to ensure perfect matching. Comparative analyses were then conducted between the 2 groups. Matched continuous variables were presented as means with standard deviations and compared using a paired-samples *t* test. Univariate logistic regression was performed to estimate odds ratios (ORs) with 95% confidence intervals (CIs) to determine predictors of in-hospital mortality in patient admitted with STEMI.

To assess robustness, we performed two sensitivity analyses limiting our analysis to two sub-cohorts of patients. First, a cohort of STEMI patients who underwent primary percutaneous coronary intervention (PCI) within 24 hours of admission. The rational for this analysis is that diagnostic codes of STEMI and GIB are not associated with timing of event in the NIS. It is possible that some patients were initially admitted with GIB and then developed STEMI during the hospitalization, and including those patients might have confounded our results. We hence limited the analysis to patients with STEMI undergoing PCI within 24 hours of admission to minimize this chance. Second, a cohort of STEMI patients who were not transferred to another facility. The rational for this analysis is that NIS does not track patients across hospitals. It is possible that some patients may have presented with STEMI to one facility, received thrombolytic therapy, and were then transferred to another. Hence, we limited the analysis to those treated at the initial facility to avoid under- or overestimation of the patient's subsequent events.

Results

Between 2003 and 2016, a total of 1,450,696 weighted STEMI hospitalizations were identified in the NIS. Of those, 32,624 (2.2%) were complicated with GIB. The incidence of GIB after STEMI decreased over time from 2.7% in 2003 to 2.0% in 2016 (p_{trend} <0.001) (Figure 1). Patients who suffered GIB were older (73 ± 14 vs 68 ± 15; p <0.001), were more likely to be female 44.9% vs 36.8%, p <0.001, had a higher prevalence of pre-existing anemia, renal insufficiency, chronic lung disease, vascular disease, cirrhosis, coagulopathy, atrial fibrillation/flutter, and cardiogenic shock (Table 1).

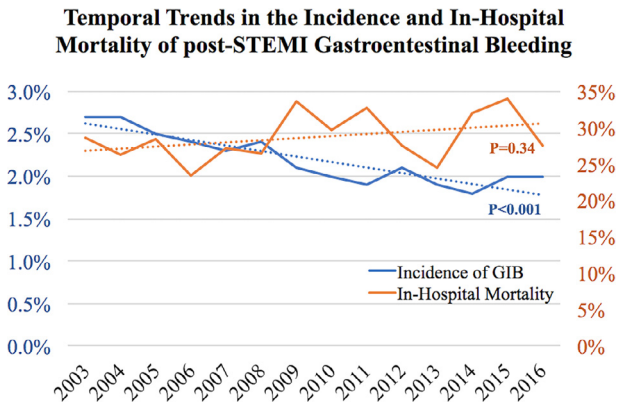

Figure 1. Temporal trends in the incidence and in-hospital mortality of gastrointestinal bleeding in patients admitted with ST-elevation myocardial infarction.
p value in the orange line indicates absence of statistical significance of the trend of in-hospital mortality over time. p value in the blue line indicates statistical significance of the trend in the incidence of GIB.

In a logistic regression analysis, older age, history of peptic ulcer disease, pre-existing anemia, cirrhosis, alcohol use disorder, and cardiogenic shock were the strongest predictors of GIB in patients admitted with STEMI (Table 2). Other significant predictors included female gender, black race, chronic kidney disease, obstructive lung disease, peripheral vascular disease, atrial fibrillation, inflammatory bowel disease, mechanical circulatory support use, and non-private insurance. Chronic anticoagulation and undergoing PCI did not predict GIB.

Compared with patients who did not experience GIB, those with GIB had higher incidence of in-hospital mortality (28.2% vs 11.1%, p <0.001), which persisted over time (P_{trend} = 0.34) (Figure 1). Patients with GIB had higher incidence of key complications, were less likely to be discharged home, had longer hospital stays, and higher cost (Table 3).

After propensity score matching, baseline characteristics were well matched between the two groups (Online Figure 1). In-hospital mortality remained significantly higher in the GIB group (28.3% vs 20.4%, p <0.001), who also experienced significantly higher rates of in-hospital complications (Table 4). Patients with GIB had a 50% increase in hospital length of stay and accrued a 50% higher cost of their hospitalization.

In a cohort of STEMI patients who underwent percutaneous coronary intervention within 24 hours of admission (a pure cohort in whom STEMI was the principle diagnosis), and in another cohort of patients who were not transferred to another hospital, patients who suffered GIB after STEMI had significantly higher in-hospital mortality in both sensitivity analysis cohorts (22.8% vs 5.3%, and

Table 1
Baseline characteristics of the study population

Baseline characteristics	GI bleeding		p Value
	No N = 288,056 NE = 1,418,072	Yes N = 6,632 NE = 32,624	
Age - Mean ±SD (Years)	66±15	73±14	<0.001
Male	63.2%	55.1%	<0.001
Race			<0.001
White	77.5%	76.9%	
Black	8.5%	9.2%	
Hispanic	7.5%	7.0%	
Diabetes mellitus	29.6%	28.8%	0.002
Hypertension	59.2%	53.0%	<0.001
Prior sternotomy	5.0%	5.5%	<0.001
Chronic kidney disease	10.9%	19.8%	<0.001
Chronic lung disease	16.7%	22.5%	<0.001
Peripheral vascular disease	7.4%	11.0%	<0.001
Atrial fibrillation/flutter	15.0%	24.0%	<0.001
Coagulopathy	4.0%	10.3%	<0.001
Conduction disorders	5.5%	6.3%	<0.001
Smoker	23.3%	12.9%	<0.001
Peptic ulcer disease	0.2%	0.6%	<0.001
Liver cirrhosis	0.3%	1.3%	<0.001
Inflammatory bowel disease	0.3%	0.5%	<0.001
Anemia	11.5%	33.3%	<0.001
Mechanical circulatory support	9.4%	16.6%	<0.001
Cardiogenic shock	9.5%	23.9%	<0.001
Received PCI	51.0%	37.9%	<0.001
Underwent endoscopy			
EGD	1.0%	12.5%	<0.001
Colonoscopy	0.2%	4.3%	<0.001
Primary payer			<0.001
Medicare/Medicaid	58.7%	76.0%	
Private insurance	30.7%	17.5%	
Self-pay/No charge/other	10.6%	6.6%	

GI; gastrointestinal, N; number, NE; national weighted estimate, SD; standard deviation, PCI; percutaneous coronary intervention, EGD; esophagogastroduodenoscopy.

32.6% vs 12.3%, p <0.001, respectively). In addition, the occurrence of GIB similarly had a substantial negative impact on complications rates, length of stay, non-home discharges and cost in both analyses (Online Tables 2, 3).

In a logistic regression analysis, GIB was an independent predictor of mortality (OR 1.91, 95% CI 1.85 to 1.97, p <0.001) (Table 5). Other significant predictors included older age, female gender, black race, renal insufficiency, pulmonary disease, cirrhosis, vascular disease, atrial fibrillation, coagulopathy, and cardiogenic shock (Table 4).

Few patients (n = 3,288; 10%) who had post-STEMI GIB underwent endoscopy during their hospitalizations. Among these patients, a total of 5,481 endoscopic procedures (74.7% upper endoscopy, 25.3% lower endoscopy) were performed. Timing of endoscopy was within 2 days, between 3 and 7 days and beyond 7 days in 39.3%, 39.6%, and 20.1%, respectively. Patients who underwent endoscopic evaluation for a source of the bleeding had higher survival to discharge (89.3% vs 69%, p <0.001) and lower complication rates than those who did not undergo endoscopic evaluation (Online Table 4). In a logistic regression analysis, undergoing endoscopic evaluation for GIB was associated with improved in-hospital mortality in patients with STEMI (unadjusted OR

Table 2
Univariate logistic regression analysis for predictors of gastrointestinal bleeding among patients admitted with ST-elevation myocardial infarction

Predictors of GIB	OR	95% CI		p Value
		Lower	Upper	
Age group (year)				
18-44	Ref	Ref	Ref	Ref
45-65	1.51	1.40	1.63	<0.001
66-84	2.12	1.98	2.29	<0.001
>85	2.39	2.20	2.5	<0.001
Female	1.09	1.06	1.12	<0.001
White	Ref	Ref	Ref	Ref
Black	1.11	1.06	1.16	<0.001
Hispanic	1.06	1.01	1.12	0.012
Diabetes mellitus	0.88	0.86	0.91	<0.001
Hypertension	0.73	0.71	0.75	<0.001
Chronic kidney disease	1.30	1.26	1.35	<0.001
Obstructive lung disease	1.18	1.15	1.22	<0.001
Peripheral vascular disease	1.16	1.12	1.21	<0.001
Atrial fibrillation/flutter	1.24	1.20	1.27	<0.001
Peptic ulcer disease	2.64	2.2	3.05	<0.001
Liver cirrhosis	2.5	2.30	2.89	<0.001
Inflammatory bowel disease	1.75	1.47	2.08	<0.001
Pre-existing anemia	2.88	2.80	2.96	<0.001
Mechanical circulatory support	1.23	1.19	1.28	<0.001
Use of glycoprotein IIb/IIIA inhibitors	1.07	1.03	1.11	0.002
Obesity	0.70	0.66	0.74	<0.001
Alcohol use disorders	1.82	1.71	1.95	<0.001
Percutaneous coronary intervention	0.77	0.75	0.79	<0.001
Cardiogenic shock	2.42	2.34	2.51	<0.001
Primary payer				
Private insurance	Ref	Ref	Ref	Ref
Medicare/medicaid	1.33	1.28	1.39	<0.001
No Charge/self-pay/other	1.11	1.05	1.17	<0.001

GIB; gastrointestinal bleeding, OR; odds ratio, CI; confidence interval, Ref; reference.

0.27; 95% CI 0.24 to 0.29; adjusted OR 0.30; 95% CI, 0.27 to 0.33; p <0.001). In comparing patients undergoing GI intervention versus those who did not undergo GI intervention, those in the GI intervention group were younger, had a higher prevalence of co-morbidity, and were more likely to receive PCI (Online-Table 5).

Table 3
In-hospital outcomes of STEMI patients stratified by the occurrence of gastrointestinal bleeding (Unmatched cohorts)

In-hospital outcomes	GI bleeding		p Value
	No N = 288,056 NE = 1,418,072	Yes N = 6,632 NE = 32,624	
Death	11.1%	28.2%	<0.001
Acute kidney injury	11.0%	29.8%	<0.001
New dialysis requirements	0.7%	2.5%	<0.001
Stroke	1.5%	3.5%	<0.001
Blood transfusion	5.8%	29.3%	<0.001
Nonhome discharge	25.8%	41.5%	<0.001
LOS-Median (25%, 75%)	3 (2,6)	6 (3,10)	<0.001
Cost-Mean ± SD $	21,372 ± 23,552	30,752 ± 42,802	<0.001

GI; gastrointestinal, N; number, NE; national weighted estimate, LOS; length of stay, SD; standard deviation, $; US dollar.

Table 4
In-hospital outcomes of STEMI patients stratified by the occurrence of gastrointestinal bleeding (Propensity score matched cohorts)

In-hospital outcomes	GI bleeding		p Value
	No N = 5,266 NE = 25,916	Yes N = 4,746 NE = 23,382	
Death	20.4%	28.3%	<0.001
Acute kidney injury	20.2%	29.7%	<0.001
New dialysis requirements	1.5%	2.4%	<0.001
Stroke	2.4%	3.5%	<0.001
Blood transfusion	10.9%	29.2%	<0.001
Nonhome discharge	39.3%	41.3%	<0.001
LOS-Median (25%, 75%)	4 (2-8)	6 (3-10)	<0.001
Cost-Mean±SD $	24,376 ± 31,270	30,667 ± 42,669	<0.001

GI; gastrointestinal, N; number, NE; national weighted estimate, LOS; length of stay, SD; standard deviation, $; US dollar.

Discussion

To our knowledge, this is the largest nationwide analysis examining the incidence and outcomes of GIB in patients admitted with STEMI. The main findings of our study are: (1) Gastrointestinal bleeding among patients with STEMI is uncommon and has decreased significantly from 2003 to 2016; (2) Post-STEMI GIB is, however, associated with excess in-hospital morbidity, mortality, resource utilization, and cost of care; and (3) Referral for endoscopy may be associated with improved in-hospital outcomes.

The outcomes of patients presenting with STEMI have improved over time due to the improvement in systems of care (e.g., symptom recognition, door-to-balloon time, etc.), and due to the advances in primary PCI techniques and their wide spread adoption.[16] However, due to the acuity of their presentation and the high prevalence of major co-morbidities among them, STEMI patients constitute a tenuous cohort whose outcomes may be substantially impacted by noncardiovascular in-hospital complications. For example, developing major infection during the hospitalization among STEMI patients is associated with 3 to 5 fold increase in short-term mortality.[9] In another example, acute diabetes decompensation is associated with a 32% increase in in-hospital mortality.[10] Similarly, the occurrence of GIB in patients admitted with STEMI has been shown to be attendant with excess morbidity and mortality in several studies. However, these studies were limited by their modest sample size, and the inclusion of heterogeneous groups of patients.[8,11,12,15,17–20] Our study aimed to assess the nationwide trends in the incidence and outcomes of acute GIB following STEMI.

Our findings suggest a temporal decrease in the incidence of GIB after STEMI, following similar a downward trend in the incidence of GIB overall.[3] Albeit reassuring, the 2% rate of post-STEMI GIB remains significant (>2,000 patients annually) given the substantial increase in morbidity and mortality in these patients. Our study showed that GIB was associated with higher adjusted risks of death (38.5%), new dialysis requirement (58%), and stroke (46.5%) in rigorously propensity matched cohorts of STEMI patients with and without GIB. Hence, identifying modifiable variables that can predict the occurrence of GIB in STEMI patients and/or those that can improve their outcomes is warranted.

In keeping with other studies, our analysis confirmed that age, female sex, pre-existing anemia, use of Glycoprotein IIb/IIIa inhibitors, chronic renal insufficiency, coagulopathy, and liver disease were independent predictors of GIB in STEMI patients.[11,15,17,21] Additionally, we identified peptic ulcer disease, inflammatory bowel diseases, and alcohol use disorder as significant independent predictors of post-STEMI GIB. Although most of these factors are non-modifiable, their recognition allows better risk stratification and possibly prompts more aggressive management in order to minimize the substantial associated morbidity and mortality.

The safety and effect of referral to endoscopy ± prompt intervention in STEMI patients with acute GIB remains unknown. However, patients with acute GIB following STEMI might be perceived as extreme risk patients who are more prone to periendoscopy complications.[22] Hence, diagnostic ± interventional endoscopy may often be withheld in these patients. Our study shows that among patients who suffered GIB following STEMI, those who underwent endoscopy (albeit a small minority) had substantially better survival to discharge. Although the impact of selection bias in this group cannot be eliminated, prior smaller studies have shown that endoscopic evaluation of GIB is associated with improved outcomes among patients admitted with STEMI and those admitted with acute ischemic stroke.[3,4,23] Hence, despite the limitation of this analysis, our finding suggests a possible positive impact of endoscopy on the outcomes of STEMI patients who develop subsequent GIB.

Table 5
Univariate logistic regression analysis for predictors of in-hospital mortality among patients admitted with ST-elevation myocardial infarction

Predictors	OR	95% CI		p Value
		Lower	Upper	
Age group				
18-44	Ref	Ref	Ref	Ref
45-65	1.64	1.57	1.70	<0.001
66-84	3.19	3.06	3.32	<0.001
>85	5.97	5.72	6.23	<0.001
Female	1.13	1.12	1.15	<0.001
White	Ref	Ref	Ref	Ref
Black	1.17	1.15	1.20	<0.001
Hispanic	0.99	0.97	1.02	0.611
Diabetes mellitus	1.03	1.02	1.05	<0.001
Hypertension	0.68	0.67	0.68	<0.001
Chronic kidney disease	1.55	1.53	1.58	<0.001
Chronic lung disease	1.04	1.02	1.06	<0.001
Peripheral vascular disease	1.05	1.03	1.08	<0.001
Atrial fibrillation/flutter	1.13	1.11	1.14	<0.001
Coagulopathy	1.11	1.08	1.14	<0.001
Liver cirrhosis	2.41	2.23	2.61	<0.001
Mechanical circulatory support	1.30	1.27	1.33	<0.001
Gastrointestinal bleeding	1.91	1.85	1.97	<0.001
Cardiogenic shock	8.34	8.19	8.49	<0.001
Primary payer				
Private insurance	Ref	Ref	Ref	Ref
Medicare/medicaid	1.38	1.35	1.41	<0.001
Self-pay/no charge/other	1.43	1.39	1.47	<0.001

OR; odds ratio, CI; confidence interval, Ref; reference.

Current guidelines from American Society for Gastrointestinal Endoscopy (ASGE) do not support routine endoscopy in the post-STEMI timeframe. Guidelines do seem to suggest that there may be mortality benefit in the setting of significant GIB, however, benefits in the setting of an occult bleed is unclear. As with any intervention, cases must be considered individually, and the risk of endoscopy should outweigh the risk of withholding the procedure through a multidisciplinary approach.[24]

The NIS does not include data as to whether or not patients are currently on proton pump inhibitors (PPI) after STEMI or at the time of GIB, however GI prophylaxis is recommended by the ACCF/AHA as well as the European Society of Cardiology (ESC) as a class IB recommendation, particularly those on DAPT therapy.[25,26]

Our study has a number of limitations. First, the NIS is derived from hospital claims data and subject to the shortcomings of other administrative data sets. Inconsistencies related to over- or under-coding are possible but AHRQ quality control measures should minimize these possibilities. Also, the ICD-9 codes used in our study have been used and/or validated in several prior studies.[27,28] Second, we used the principle diagnosis of STEMI to identity our study cohort. Hence, our data may not reflect the incidence or outcomes of GIB among patients who were admitted for another reason and suffered an STEMI during the hospitalization (i.e., those with STEMI as a secondary diagnosis). Along these lines, the NIS does not allow us to capture more granular information regarding the timing of GIB relative to STEMI, severity of GIB or criteria used. Again, the use of the ICD-9 codes has been validated in prior studies for GIB. Third, the NIS collect data on ICD-coded diagnoses and procedures but lack details on the antithrombotic and/or antiplatelet regimens used during the hospitalization and also laboratory values. The possible confounding impact of these missing data cannot be excluded. Despite this limitation, there is no plausible clinical database that allows temporal assessment of the incidence and outcomes of GIB at the national level to our knowledge. Even dedicated disease specific databases such as the Cath-PCI registry do not contain information about both cardiac and endoscopic procedures. As such, we believe that this study offers important insights into a high risk cohort of patients in whom data to guide optimal therapy are scarce.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.008.

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