Observational Study

Safety of gastrointestinal endoscopy in patients with acute coronary syndrome and concomitant gastrointestinal bleeding

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Author contributions: Campbell DR and Clarkston WK were the study’s senior authors; they contributed to interpreting the data, writing, critical reviewing, and editing of the manuscript; Elkafrawy AA contributed to the conception, study design, literature review, and drafting of the manuscript; Ahmed M and Alomari M performed the literature review and drafted the manuscript; Elkaryoni A contributed to the study design and to develop the analytic plan; Kennedy KF extracted the data and performed the statistical analysis; all authors reviewed and approved the final manuscript.

Institutional review board statement: The study population was identified from the Healthcare Cost and Utilization Project databases (HCUP). The HCUP databases are sponsored by the Agency for Healthcare Research and Quality.

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Abstract

BACKGROUND
Gastrointestinal bleeding (GIB) is a major concern in patients hospitalized with acute coronary syndrome (ACS) due to the common use of both antiplatelet medications and anticoagulants. Studies evaluating the safety of gastrointestinal endoscopy (GIE) in ACS patients with GIB are limited by their relatively small size, and the focus has generally been on upper GI bleeding (EGD) only.

AIM
To evaluate the safety profile and the hospitalization outcomes of undergoing GIE in patients with ACS and concomitant GIB using the national database for hospitalized patients in the United States.

METHODS
The Nationwide Inpatient Sample database was queried to identify patients hospitalized with ACS and GIB during the same admission between 2005 and 2014. The International Classification of Diseases Code, 9th Revision Clinical Modification was utilized for patient identification. Patients were further classified into two groups based on undergoing endoscopic procedures (EGD, small intestinal endoscopy, colonoscopy, or flexible sigmoidoscopy). Both groups were compared regarding demographic information, outcomes, and comorbidities. Multivariate analysis was conducted to identify factors associated with mortality and prolonged length of stay. Chi-square test was used to compare categorical variables, while Student’s t-test was used to compare continuous variables. All analyses were performed using SAS 9.4 (Cary, NC, United States).

RESULTS

A total of 35612318 patients with ACS were identified between January 2005 and December 2014. 269483 (0.75%) of the patients diagnosed with ACS developed concomitant GIB during the same admission. At least one endoscopic procedure was performed in 68% of the patients admitted with both ACS and GIB. Patients who underwent GIE during the index hospitalization with ACS and GIB had lower mortality (3.8%) compared to the group not undergoing endoscopy (8.6%, P < 0.001). A shorter length of stay (LOS) was observed in patients who underwent GIE (mean 6.59 ± 7.81 d) compared to the group not undergoing endoscopy (mean 7.84 ± 9.73 d, P < 0.001). Multivariate analysis showed that performing GIE was associated with lower mortality (odds ratio: 0.58, P < 0.001) and shorter LOS (-0.36 factor, P < 0.001).

CONCLUSION

Performing GIE during the index hospitalization of patients with ACS and GIB was correlated with a better mortality rate and a shorter LOS. Approximately two-thirds of patients with both ACS and GIB undergo GIE during the same hospitalization.

Key Words: Gastrointestinal endoscopy; Gastrointestinal bleeding; Acute coronary syndrome; Safety; Outcomes; Mortality

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Core Tip: Less than 1% of hospitalized patients have concomitant acute coronary syndrome (ACS) and gastrointestinal bleeding (GIB). However, the combination of these two conditions is reported to be associated with increased morbidity and mortality. Studies evaluating the safety and hospitalization outcomes of gastrointestinal endoscopy (GIE) in patients with ACS and GIB are limited and conflicting. This analysis was designed to evaluate GIE safety and efficacy in patients with ACS and GIB. This study concluded that GIE in patients hospitalized with ACS and GIB is both safe and associated with lower mortality as well as a shorter hospital stay.

Citation: Elkafrawy AA, Ahmed M, Alomari M, Elkaryoni A, Kennedy KF, Clarkston WK, Campbell DR. Safety of gastrointestinal endoscopy in patients with acute coronary syndrome and concomitant gastrointestinal bleeding. World J Clin Cases 2021; 9(5): 1048-1057
URL: https://www.wjgnet.com/2307-8960/full/v9/i5/1048.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i5.1048

INTRODUCTION

Gastrointestinal bleeding (GIB) is associated with increased morbidity and mortality. The annual incidence of upper GIB in the United States is estimated to be 65 per 100000 individuals, and between 0.7% and 3% of patients with acute coronary syndrome (ACS) develop GIB. GIB in patients with ACS is associated with a higher 30-d mortality rate (9.6%) as compared to ACS patients without GIB (1.4%). Studies
Elkafrawy AA et al. GIE in ACS with GIB

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Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: United States

Peer-review report’s scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: July 24, 2020

First decision: September 14, 2020

Revised: October 1, 2020

Accepted: January 6, 2021

Article in press: January 6, 2021

Published online: February 16, 2021

P-Reviewer: Chen YD, Guo JS, Ju SQ, Karayiannakis AJ, Wang K

S-Editor: Zhang H

L-Editor: A

P-Editor: Xing YX

Patients older than 18 years of age with the diagnosis of ACS and GIB (upper and/or lower GIB) were included in the study. ACS was defined as acute myocardial infarction, subendocardial infarction, and acute coronary occlusion without infarction. Patients with chronic ischemic heart disease without an ACS associated diagnosis, peptic ulcer without hemorrhage, acute duodenal ulcer without hemorrhage, gastric ulcer without hemorrhage, and esophageal varices without bleeding were excluded.

The study population was identified from the Healthcare Cost and Utilization Project databases (HCUP). The Agency for Healthcare Research and Quality sponsors the HCUP database. The NIS database is the largest HCUP database, and it contains unweighted data from over seven million hospital admission each year. The data represent a 20% random sample of participating hospital discharges from 46 states. The NIS database is de-identified and available to the public. Thus, it is not considered human subject research and is exempted from review by the institutional review board. To assure a meaningful study cohort, the investigators agreed upon a minimum study cohort of 250,000 admissions. International Classification of Diseases (ICD)-9 codes were transitioned to ICD-10 codes in the last quarter of 2015. To assure consistency and data integrity, the study was designed only to include ICD-9 codes. Therefore, the study population and variables of interest (Table 1) between January 2005 and December 2014 were evaluated as in subsequent years, ICD-10 codes were used to populate the NIS database.

Endoscopic studies of the upper and/or lower GI tract are frequently required to: (1) Identify the anatomic site of bleeding; (2) Identify the lesion; and (3) Intervene to control bleeding.

The dilemma endoscopists often face is determining how safe an endoscopic procedure is in a patient with ACS. The current study was designed to evaluate on a large scale the safety and outcomes associated with the performance of endoscopic procedures during the same hospitalization with ACS and concomitant GIB.
Table 1: Comparison between 2 groups regarding undergoing gastrointestinal endoscopy

|                                | Total (n = 269483) | Patients underwent endoscopy (n = 183409) | Patients without endoscopy (n = 86073) | P value |
|--------------------------------|--------------------|------------------------------------------|---------------------------------------|---------|
| Mean age at admission          | 72.32 ± 11.72      | 72.82 ± 11.41                            | 71.27 ± 12.29                        | < 0.001 |
| Males                          | 178111 (66.1)      | 120040 (65.4)                            | 58070 (67.5)                         | < 0.001 |
| Females                        | 91372 (33.9)       | 63369 (34.6)                             | 28003 (32.5)                         |         |
| Race                           |                    |                                          |                                       | < 0.001 |
| Caucasian                      | 185713 (79.1)      | 127623 (79.5)                            | 58089 (78.1)                         |         |
| African American               | 17453 (7.4)        | 11555 (7.2)                              | 5898 (7.9)                           |         |
| Hispanic                       | 16362 (7.0)        | 10710 (6.7)                              | 5652 (7.6)                           |         |
| Other                          | 15338 (6.5)        | 10639 (6.6)                              | 5652 (7.6)                           |         |
| Mortality                      | 14448 (5.4)        | 7027 (3.8)                               | 7421 (8.6)                           | < 0.001 |
| Length of stay                 | 6.99 ± 8.49        | 6.59 ± 7.81                              | 7.84 ± 9.73                          | < 0.001 |
| Primary expected payer         |                    |                                          |                                       | < 0.001 |
| Medicare                       | 198925 (73.9)      | 137580 (75.1)                            | 61344 (71.4)                         |         |
| Medicaid                       | 12590 (4.7)        | 7864 (4.3)                               | 4726 (5.5)                           |         |
| Private                        | 45991 (17.1)       | 30558 (16.7)                             | 15433 (18.0)                         |         |
| Self-pay                       | 6407 (2.4)         | 3900 (2.1)                               | 2507 (2.9)                           |         |
| No charge                      | 578 (0.2)          | 318 (0.2)                                | 261 (0.3)                            |         |
| Other                          | 4642 (1.7)         | 2971 (1.6)                               | 1672 (1.9)                           |         |
| Location/teaching status of hospital |              |                                          |                                       | < 0.001 |
| Rural                          | 26040 (9.7)        | 19100 (10.5)                             | 6939 (8.1)                           |         |
| Urban nonteaching              | 119321 (44.5)      | 82796 (45.4)                             | 6939 (8.1)                           |         |
| Urban teaching                 | 122779 (45.8)      | 80650 (44.2)                             | 42129 (49.2)                         |         |
| Region of hospital             |                    |                                          |                                       | 0.022   |
| Northeast                      | 49463 (18.4)       | 34252 (18.7)                             | 15212 (17.7)                         |         |
| Midwest                        | 64974 (24.1)       | 44079 (24.0)                             | 20895 (24.3)                         |         |
| South                          | 100860 (37.4)      | 68653 (37.4)                             | 20895 (24.3)                         |         |
| West                           | 100860 (37.4)      | 68653 (37.4)                             | 17759 (20.6)                         |         |
| Shock                          | 24171 (9)          | 13172 (7.2)                              | 10999 (12.8)                         | < 0.001 |
| Mechanical ventilation         | 24705 (9.2)        | 12736 (9.2)                              | 11969 (13.9)                         | < 0.001 |
| Blood transfusion              | 145939 (54.2)      | 102484 (55.9)                            | 43455 (50.5)                         | < 0.001 |

Table 1 compares demographics and main outcomes between patients who underwent gastrointestinal endoscopy and the group who did not undergo endoscopy. Values are presented as n (%).

**Statistical analysis**

Continuous variables were described using mean ± SD, while categorical variables were described using proportion (percentage). Chi-square test was used to compare categorical variables, while Student’s t-test was used to compare continuous variables. Multivariate analysis was done using logistic regression models to decrease bias and adjust for possible confounding factors. Statistical analysis was performed by a biomedical statistician. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, United States).
RESULTS

General characteristics
A total of 35612318 patients with ACS were identified between January 2005 and December 2014, and 269483 (0.75%) of the patients with ACS developed GIB during the same index admission. At least one GIE procedure was performed in 183248 (68%) patients with concomitant GIB and ACS, and outcomes in these patients were compared to the 86235 patients who did not undergo any endoscopic procedures (Figure 1). Males comprised 66.1% of the study population, while females comprised 33.9%. The mean age of the study population was 72.3 years, 79.1% were Caucasian, 7.4% African American, and 7.0% were Hispanic.

Outcomes
In the study cohort, undergoing GIE procedure was associated with reduced mortality (3.8%) in comparison to (8.6 %) in the group not having an endoscopic procedure (95%CI: -5.2, -4.4), (P < 0.001). Hospital length of stay (LOS) was shorter in patients who underwent gastrointestinal endoscopic procedures (mean 6.59 ± 7.81 d) in comparison to the group who did not undergo endoscopy (mean 7.84 ± 9.73 d) (95%CI: -1.42, -1.10), (P < 0.001). Shock was present in 7.2% of patients undergoing GIE compared to 12.8% in patients not undergoing endoscopy (95%CI: -6.1, -5.1), (P < 0.001) while 6.9% of patients were mechanically ventilated from the first group as compared to 13.9% in the group not undergoing endoscopy (95%CI: -7.5, -6.5), (P < 0.001). 55.9 % of patients who underwent GIE received blood transfusions in comparison to 50.5% of patients not undergoing endoscopic procedures (95%CI: 4.5, 6.3) (P < 0.001). Refer to Table 1 for comparison between both groups. Other compared comorbidities are detailed in Supplementary Table 1.

Multivariate analysis
Multivariate logistic regression models were used to predict factors associated with increased mortality and LOS. GIE was associated with less mortality; odds ratio (OR) of 0.58 (95%CI: 0.53-0.63) (P < 0.0001). Coagulopathy, shock, and mechanical ventilation were associated with higher mortality, OR of 1.76, 3.03, and 9.16, respectively (P < 0.0001). Regarding LOS, performing endoscopy was associated with a shorter LOS by -0.36 factor (beta weight) (95%CI: -0.56, -0.16) (P < 0.001). Congestive heart failure, shock, and mechanical ventilation were associated with prolonged LOS by 1.57, 3.16, 8.48 factor, respectively (beta weight). Refer to Tables 2 and 3 for all variables included in the logistic regression models.

DISCUSSION
Similar to previous studies, the results of this analysis found that 0.75% of patients admitted during a ten-year period with ACS develop GIB. Previous studies estimated the prevalence of GIB in ACS patients between 0.7% and 3%[3-5]. Performing GIE (EGD, small intestinal endoscopy, colonoscopy, or flexible sigmoidoscopy) in patients with ACS and GIB was associated with significantly lower mortality and a shorter hospitalization stay in comparison to the group not undergoing endoscopic procedure. The selection of endoscopic procedures depended on the clinical impression of the gastroenterologist. Since patients with hematochezia may be experiencing brisk upper GIB or lower GI hemorrhage, some patients required evaluation with more than one endoscopic procedure. For that reason, all types of endoscopic procedures commonly used in the management of GIB were included in this study without stratification. One of the challenges in this study was to determine whether the patients who did not undergo GIE were at excessive risk for an endoscopic procedure or whether they developed complications (shock, respiratory failure, etc.) as a result of not having had an endoscopic procedure performed. A temporal relationship between performing endoscopy, presence of shock, mechanical ventilation, and other comorbid confounding factors could not be evaluated in this database. However, the association between performing GIE and better outcomes was statistically significant in the logistic regression models in the presence of these comorbidities.

GIB complicating ACS is a complex clinical scenario with sparse data to direct evidence-based guidelines on proper management. A recent study reported that the use of antplatelet therapy, malignancy, renal impairment, heart failure, previous peptic ulcer disease, and abnormal activated partial thromboplastin time were predictors of GIB following ACS[19]. Pioppo et al[20] concluded that non-variceal upper
| Predictor                   | Odds ratio, 95%CI       | P value  |
|-----------------------------|-------------------------|----------|
| GIE                         | 0.58 (0.53, 0.63)       | < 0.0001 |
| Age                         | 1.03 (1.03, 1.03)       | < 0.0001 |
| Female                      | 0.99 (0.9, 1.08)        | 0.7729   |
| Race (Caucasian)            | 0.9 (0.83, 0.99)        | 0.0225   |
| DM                          | 0.71 (0.64, 0.79)       | < 0.0001 |
| CHF                         | 1.13 (1.02, 1.26)       | 0.0186   |
| Coagulopathy                | 1.76 (1.57, 1.98)       | < 0.0001 |
| Anemia                      | 0.85 (0.76, 0.96)       | 0.0069   |
| Liver disease               | 1.75 (1.51, 2.02)       | < 0.0001 |
| Renal failure               | 1.32 (1.2, 1.44)        | < 0.0001 |
| Diagnosis of cancer         | 1.76 (1.41, 2.19)       | < 0.0001 |
| Shock                       | 3.03 (2.72, 3.38)       | < 0.0001 |
| Mechanical ventilation      | 9.16 (8.33, 10.07)      | < 0.0001 |
| Blood transfusion           | 0.9 (0.82, 0.99)        | 0.0314   |
| Tobacco smoking             | 0.71 (0.63, 0.8)        | < 0.0001 |
| Alcohol abuse               | 1.19 (1.01, 1.41)       | 0.0400   |

Multivariate logistic regression model for predictors of mortality in patients hospitalized with acute coronary syndrome and concomitant gastrointestinal bleeding. Performing gastrointestinal endoscopy was included along with other variables and comorbidities that can affect mortality. GIE: Gastrointestinal endoscopy; DM: Diabetes mellitus; CHF: Congestive heart failure.

GIB in hospitalized patients with ACS was correlated with higher mortality, a longer length of stay, and increased hospitalization charges. Several studies have evaluated the safety of upper endoscopy shortly after ACS (usually within 30 d) and concluded it could be safely performed. The current study assessed the safety of endoscopic procedures during the same admission as ACS, and those admissions averaged approximately eight days. Al-Ebrahim et al. reported complications occurred in 25% of patients undergoing endoscopy. However, mortality was not reported in that study, and only a small number of patients met the inclusion criteria. Lim et al. evaluated major and minor complications following performing EGD within 30 d of ACS. They found no major complication, while minor complications occurred in 31% of the patients.

Another study concluded that undergoing upper GIE before cardiac catheterization was associated with a lower death rate when done for overt upper GIB. Additionally, Modi et al found that colonoscopy performed in the same admission for patients with STEMI and concomitant GIB was associated with lower mortality as compared with no intervention.

A meta-analysis by Cena et al evaluated the safety and benefits of performing GIE after myocardial infarction. It demonstrated that endoscopic procedures are safe and beneficial in stable patients with GIB after recent MI and should be performed without delay. A more recent meta-analysis found higher rates of cardiac complications following endoscopy in ACS patients. However, that study included endoscopic retrograde cholangiopancreatography and endoscopic ultrasound, which may have increased the rates of complications.

Several predictors of GIB in patients with ACS have been identified, including; older age, diabetes, hypertension, previous peptic ulcer disease, and dual antiplatelet therapy. In the study reported herein, the presence of coagulopathy, chronic heart failure, liver disease, renal failure, shock, and mechanical ventilation are associated with increased mortality.

A recently published study concluded that performing endoscopy in ACS patients was associated with better outcomes. However, it was not limited to the patients with GI hemorrhage and included other indications for performing endoscopy. The current analysis highlights the safety and superior outcomes of undergoing
### Table 3 Factors associated with length of stay (multivariate analysis)

| Label                  | Beta weight, 95% CI for LOS | P value |
|------------------------|----------------------------|---------|
| GIE                    | -0.36 (-0.56, -0.16)        | < 0.001 |
| Age                    | -0.01 (-0.02, 0)            | 0.0059  |
| Sex (female)           | 0.34 (0.2, 0.48)            | < 0.0001|
| Race (Caucasian)       | -0.47 (-0.62, -0.32)        | < 0.0001|
| DM                     | -0.8 (-0.95, -0.66)         | < 0.0001|
| CHF                    | 1.57 (1.35, 1.8)            | < 0.0001|
| Coagulopathy           | 1.39 (1.04, 1.74)           | < 0.0001|
| Anemia                 | 0.07 (-0.11, 0.26)          | 0.4333  |
| Liver disease          | 0.28 (-0.05, 0.61)          | 0.0945  |
| Renal failure          | 1.41 (1.24, 1.59)           | < 0.0001|
| Diagnosis of cancer    | 0.56 (0.08, 1.04)           | 0.0228  |
| Shock                  | 3.16 (2.73, 3.59)           | < 0.0001|
| Mechanical ventilation | 8.48 (7.96, 9)              | < 0.0001|
| Blood transfusion      | -0.69 (-0.9, -0.49)         | < 0.0001|
| Tobacco smoking        | -1.58 (-1.77, -1.38)        | < 0.0001|
| Alcohol abuse          | -0.77 (-1.08, -0.47)        | < 0.0001|

Multivariate logistic regression model for predictors of length of stay (LOS) in patients hospitalized with acute coronary syndrome and concomitant gastrointestinal bleeding. Performing gastrointestinal endoscopy was included along with other variables and comorbidities that can affect LOS. LOS: length of stay; GIE: Gastrointestinal endoscopy; DM: Diabetes mellitus; CHF: Congestive heart failure.

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**Figure 1** Diagram illustrating the number and percentage of patients with acute coronary syndrome and concomitant gastrointestinal bleeding in the same admission and also shows the number and percentage of patients who underwent gastrointestinal endoscopy. ACS: Acute coronary syndrome; GI: Gastrointestinal.

Gastrointestinal endoscopic procedures in the specific setting of ACS and GIB.

**Limitations**

Like all retrospective database studies, the usual concerns apply (selection bias, confounding, reliability of data, etc.). The diagnoses of diseases, comorbidities,
outcomes, and procedures were identified using ICD-9 CM and ICD-9 PCS codes. Coding accuracy and missing data are potential sources of bias. The inability to review the individual medical records to validate the data may have led to inaccuracies. The temporal relationship between the performance of endoscopic procedures and confounding comorbidities could not be evaluated. However, the logistic regression models allowed for evaluation for comorbidities and minimization of possible confounding factors. Despite these limitations, the large sample size (269,483 patients with concomitant ACS and GIB), wide geographic representation, variable size, and type of hospital (community vs. academic) enhance the generalizability of the findings.

CONCLUSION

This large retrospective analysis found that over a ten year period, 0.75% of patients admitted with ACS developed significant GIB. An endoscopic procedure was performed during the same hospitalization in the majority of the 269,483 patients experiencing ACS and gastrointestinal hemorrhage. Patients with ACS who underwent GIE had lower mortality (3.8%) compared to patients who did not undergo endoscopic procedures (8.6%). Undergoing GIE in these patients during the same hospitalization was not only safe but was also correlated to lower mortality and a shorter hospital stay. The study confirms GIE can be safely performed in the majority of patients with ACS and concomitant GIB. The analysis highlights the need for future prospective controlled studies to determine the optimal time for intervention in patients with concomitant ACS and GIB and whether different modalities of endoscopy are equally safe. However, it’s unlikely such a study will ever be completed given the requisite enrollment numbers combined with current and other studies demonstrating the safety and superior outcomes with the same hospitalization endoscopy.

ARTICLE HIGHLIGHTS

Research background
Gastrointestinal bleeding (GIB) in patients with acute coronary syndrome (ACS) is reported to be associated with increased morbidity and mortality.

Research motivation
Large scale studies investigating the safety profile and hospitalization outcomes of undergoing gastrointestinal endoscopic (GIE) procedure in hospitalized patients with ACS and GIB are limited and conflicting.

Research objectives
This large scale study assesses the safety and utility of performing GIE in hospitalized patients with concomitant ACS and GIB.

Research methods
The Nationwide Inpatient Sample database was queried to identify patients hospitalized with ACS and GIB during the same admission between 2005 and 2014 using ICD-9 codes. The study cohort was further categorized into two groups based on undergoing GIE. Outcomes of interest were compared between both groups. Multivariate analysis was conducted to predict factors associated with increased mortality and prolonged length of stay.

Research results
Patients with both ACS and GIB during the same admission who underwent GIE had a lower mortality rate (3.8%) in comparison to the group without endoscopy (8.6%). Patients who underwent GIE had a shorter hospital stay (mean 6.59 ± 7.81 d) contrasted to those not undergoing endoscopic procedure (mean 7.84 ± 9.73 d). Multivariate regression analysis showed that undergoing GIE in this cohort was an independent predictor of lower mortality and shorter hospital stay.

Research conclusions
Undergoing GIE in patients presenting with ACS and GIB during the same index
admission was associated with lower mortality as well as a shorter hospital stay.

**Research perspectives**

Future prospective studies are needed to evaluate the optimal time for intervention in patients with concomitant ACS and GIB and whether different modalities of endoscopy and endoscopic interventions are equally safe.

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