

Upper Gastrointestinal Bleeding Associated with Myocardial Injury in Egyptian Patients: Frequency and Risk Factors

Emad F Hamid, Mohamed H Emara, Soha A El-Hawari, Amr A Ateya, Ahmad S Sherbeni

Emad F Hamid, Internal Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, 44519, Egypt

Mohamed H Emara, Soha A El-Hawari, Ahmad S Sherbeni, Tropical Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, 44519, Egypt

Amr A Ateya, Cardiology Department, Faculty of Medicine, Zagazig University, Zagazig, 44519, Egypt

Correspondence to: Mohamed H Emara, MD, Tropical Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, 44519, Egypt. emara_20007@yahoo.com

Telephone: +0201002724482

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ABSTRACT

AIM: The frequency and risk factors of myocardial injury after upper gastrointestinal bleeding in our community are unknown. The aim of this study was to investigate the frequency of myocardial injury in patients with first episode of upper gastrointestinal bleeding and to determine the risk factors for this simultaneous affection.

METHOD: One hundred and five patients with first episode of upper gastrointestinal bleeding were included. All patients were subjected to thorough history taking, clinical examination, routine investigations, treatment with blood transfusion and pharmacologic agents, abdominal ultrasonography, upper GIT endoscopy and studies of myocardial injury including electrocardiography (ECG), transthoracic echocardiography (TTE) and cardiac enzymes including creatine kinase (CK), creatine kinase-MB (CK-MB) and Troponin I (TnI). All patients were assessed for occurrence of myocardial injury, determination of risk factors and length of hospital stay.

RESULTS: A total of 39 patients (37.1%) developed myocardial injury. Patients with first episode of upper gastrointestinal bleeding with a history of liver cirrhosis, systemic hypertension, smoking, high body mass index (BMI) and hypertriglyceridaemia had a high risk of developing myocardial injury and longer hospital stay. Increased C-reactive protein, CK, CK-MB and Troponin I and deviated ST segment-T wave of ECG were the markers of this injury.

CONCLUSION: 37.1% of adult patients with first episode of upper gastrointestinal bleeding developed myocardial injury. Liver

cirrhosis, smoking, systemic hypertension and higher BMI were the predictors of this injury.

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Key words: Myocardial injury; Troponin I; Upper gastrointestinal bleeding; Liver cirrhosis

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INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is a common, potentially life threatening condition responsible for many hospital admissions and is associated with high mortality^[1] and despite the progress in endoscopic and intensive care therapies, the mortality remains unchanged; it results from increasing number of high-risk patients mainly the older ones with significant co-morbidity^[2].

Manifestations of acute myocardial injury in the circumstances of UGIB may be overshadowed by the severity of bleeding^[3], especially in critically ill patients^[4], and the classic chest pain in these patients may be absent, furthermore the associated manifestations like nausea and vomiting may be attributed to the UGIB rather than an underlying cardiac injury^[5].

Several cardiac impairments in cirrhotic patients were recognized and these include high-output heart failure (cirrhotic cardiomyopathy) with ventricular hypo-responsiveness in response to pharmacologic or physiologic stress^[6]. In addition, hemodynamic instability is often noticed in patients with variceal bleeding^[7]. These could potentiate subclinical heart failure and myocardial injury. Furthermore, terlipressin and vasopressin which have a coronary artery vasoconstricting effect and are used to treat bleeding varices may aggravate myocardial ischemia^[8].

To our knowledge, no studies focused on myocardial injury following UGIB in our Egyptian community, although UGIB is a frequent clinical entity in particular that of variceal origin and hence we aim by this study to investigate the frequency of myocardial injury in patients with first episode of UGIB and to determine the risk factors for this simultaneous affection.

MATERIALS AND METHODS

Patients

A total number of one hundred and five patients with first episode of UGIB were included in this study out of 835 patients admitted to the intensive care units of Internal and Tropical Medicine Departments, Zagazig University Hospitals during the period from June 2011 to May 2012, all had a preliminary diagnosis of acute upper gastrointestinal (GIT) bleeding.

Ethical Considerations

The study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Zagazig University. The patient or his custodian gave a written informed consent for the procedure of upper endoscopy after explaining the risk/benefit ratio as well as the expected hazards and interventions and other measures.

Study design

Prospective observational and analytic study.

Definitions

Upper gastrointestinal bleeding (UGIB): Refers to hemorrhage in the upper gastrointestinal tract above the ligament of Treitz (which connects the fourth portion of the duodenum to the diaphragm near the splenic flexure of the colon)^[9].

Myocardial injury was defined as the presence of any of the following^[10,11]:-

Serial ST segment-T wave deviation in two consecutive leads on ECG

Elevated CK-MB>4.9 ng/mL (normal, up to 4.9)

Troponin I (TnI)>0.01 ng/dL (normal, <0.01ng/mL)

Cirrhosis: The presence of liver cirrhosis was diagnosed by history of long-standing liver disease, clinical (stigmata of chronic liver disease), abdominal ultrasound^[12], and laboratory investigations (elevated bilirubin, prolonged prothrombin time, presence of varices in gastroendoscopic examination).

Re-bleeding: is the passage of hematemesis and/or melena with hemodynamic instability (tachycardia or hypotension) and decreased hemoglobin (Hb) measurement within three days of initial therapy^[13].

Patient management

All Patients with UGIB were admitted to the intensive care unit (ICU) with stepwise management plane according to current guidelines^[7]. Most of them underwent emergency upper GIT endoscopy within 24 hours after admission.

Exclusion criteria: Exclusion of patients with (1) Age younger than 18 years ($n=39$); (2) Patients with history of any heart disease ($n=128$); (3) Patients with recurrent attacks of UGIB ($n=563$).

The patients in the final analysis were classified into two groups:

Group (A): Patients of UGIB without myocardial injury (control group). It included 66 patients, 41 males and 25 females with mean age 52.8 ± 9.2 years; **Group (B):** Patients of UGIB and myocardial injury. It included 39 patients, 26 males and 13 females with mean age 52.9 ± 8.2 years.

All patients were subjected to: A: Thorough history taking: History of the present illness, past history of previous hospital admission and any medical disorders were taken. Special emphasis on history of liver diseases, previous attacks UGIB, previous endoscopy, smoking, alcohol intake, hypertension, anticoagulant therapy, and the use of non steroidal anti-inflammatory drugs (NSAIDs); B: Complete physical examination: Including assessment of the patients

for haemodynamic instability and clinical signs of poor perfusion; C: Laboratory Investigations: (1) Complete blood picture; (2) Liver function tests; (3) Renal function tests; (4) Bleeding profile: International normalized ratio (INR), Prothrombin time (PT) and Partial Thromboplastin Time (PTT); (5) Electrolytes (Na and K); (6) Arterial blood gases (ABG); (7) Lipid profile; (8) C-Reactive protein (CRP); (9) Abdominal ultrasonography; (10) Upper GIT endoscopy; and (11) Studies of Myocardial Injury: (i) Electrocardiography (ECG): was performed at admission and 4 hours later; (ii) Cardiac Enzymes: creatine kinase (CK), creatine kinase-MB (CK-MB), and Troponin I (TnI), were checked every 12 hours for three times after admission; (iii)- Trans-thoracic Echocardiography (TTE); and D: Reporting and analysis of all data regarding the therapy: Intravenous medications used to control bleeding (omeprazole, octreotide, terlipressin, or somatostatin), total amount of packed erythrocyte transfusion, length of hospital stay, and complications.

Statistical analysis

The χ^2 test or Fisher's exact test were used to examine the presence of myocardial injury by the distribution of general characteristics. Logistic regression was used to investigate the relationship between myocardial injury and other potential predictors that were significant in the univariate analysis. Data were analyzed using the SPSS statistical package. P value <0.05 was considered significant.

RESULTS

In this study 105 patients (12.6%) out of 835 patients met the inclusion criteria and have been analyzed. This is mainly due to exclusion of patients with recurrent attacks of UGIB ($n=563$). A total of 39 patients (37.1%) in this study developed myocardial injury (ST segment-T wave elevations, increased CK-MB and TnI). The age and gender distribution in both groups were not statistically significant. A positive relation toward the risk of myocardial injury is noticed for cases with history of smoking, hypertension, liver cirrhosis and those with high body mass index (BMI) (Table 1). Clinical assessment of patients showed no difference in the vital signs between both groups at the time of admission.

Table 1 General and clinical characteristics of both groups.

	Control ($n=66$)	Cases ($n=39$)	t	P
Age (years)				
≤55	37 (56.1%)	12 (30.8%)		
>55	29 (43.9%)	27 (69.2%)	1.7	0.1
Gender				
Male	41 (62.1%)	26 (66.7%)		
Female	25 (37.9%)	13 (33.3%)	0.2	0.6
BMI (kg/m²)	22.9±4.2	28.8±4.5	6.700	<0.000**
Hypertension	14 (21.2%)	26 (66.7%)	21.4	<0.001**
Smoking	20 (30.3%)	27 (69.2%)	15	<0.001**
Liver cirrhosis	37 (56.1%)	30 (76.9%)	4.6	0.03*
Use of NSAIDs	20 (30.3%)	9 (23.1%)	0.6	0.4
Pulse (beat/min)	92.6±19.9	88.5±20.2	-0.755	0.4
Mean arterial blood pressure (mmHg)	64.3±8.4	65.2±8.8	-0.992	0.3
Systolic blood pressure (mmHg)	88.3±10.6	90±10.2	0.471	0.63
Diastolic blood pressure (mmHg)	52.5±10.6	52.6±10.2	0.787	0.4
Respiratory rate/min	17.8±3.5	18.7±2.8	0.055	0.9
Temperature /°C	37.2±0.4	37.3±0.4	1.407	0.16

BMI= body mass index, *significant, **highly significant.

As regard the laboratory and therapeutic parameters of cases. None showed statistical significance in relation to the risk of cardiac injury. Neither the etiology of UGIB (variceal versus non-variceal) nor the use of splanchnic vasopressors (octreotide and terlipressin) seems to have a direct impact on myocardial injury in this study (Table 2).

Table 2 Comparison of laboratory and therapeutic factors in both groups.

	Control (n=66)	Cases (n=39)	t	P
Hemoglobin (gm %)	7.7±2.1	8.1±1.8	0.027	0.97
Platelets (×10 ⁹)	221±104.8	210.1±79	-0.061	0.95
Creatinine (mg/dL)	1.12±0.62	1.2±0.71	0.221	0.82
Total bilirubin (mg/dL)	1.6±1.5	2.2±2	1.263	0.2
Direct bilirubin (mg/dL)	0.72±0.5	1.01±1	1.487	0.1
Albumin (gm/dL)	3.2±0.82	3±0.83	-0.629	0.53
ALT (IU/L)	39.7±43.5	37.7±41.2	-1.654	0.1
AST (IU/L)	49.5±34.5	44.2±34.3	Mann-whitney	0.3
Lowest HCT	39.3 (7-212)	38.8 (7-160)	1147	
≤25	33 (50%)	14 (35.9%)	χ ²	P
>25	33 (50%)	25 (64.1%)	1.9	0.16
Endoscopy				
Variceal	39 (59.1%)	28 (71.8%)	1.6	0.19
Non-Variceal	27 (40.9%)	11 (28.2%)		
Octreotide/Terlipressin use	16 (24.2%)	16 (41.0%)	3.2	0.07

HCT= hematocrate value.

Table 3 Comparison of lipid profile and cardiac enzymes between both groups.

	Control (n=66)	Cases (n=39)	χ ²	p
LDL	115.9±25.4	121.7±24.8	1.139	0.2
HDL	43.5±7.6	44.4±8.2	0.571	0.5
CRP	2.1±3.7	6.4±3.9	5.588	<0.000**
TG	145.1±31.9	158±35.4	2.026	0.05*
CK (U/L)	217.1±223	427.4±346.6	3.784	<0.000**
CK (MB) (ng/mL)	1.97±0.8	4.7±5.4	4.050	<0.000**
TnI (ng/mL)	0.01±0.001	0.4±0.8	3.896	<0.000**

LDL: low density lipoprotein cholesterol; HDL: high density lipoprotein cholesterol; TG: triglycerides, *significant, **highly significant.

Analysis of the markers of myocardial injury showed increased serum levels of CRP, CK, CK-MB and TnI in the affected group (Table 3) together with ECG changes in 38% of them which were reflected by impaired ejection fraction on trans-thoracic echocardiographic assessment (Table 4).

Table 4 Comparison of ECG and trans-thoracic echocardiography between both groups.

	Control (n=66)	Cases (n=39)	χ ²	p
ECG (ST-T wave changes)	0 (0%)	15 (38.5%)	15	<0.001**
Trans-thoracic echo			T	P
LA	28.7±10.5	31.2±7.3	1.32	0.190
RVD	14.6±6.7	16.7±5.8	1.59	0.115
LVD	44.9±15.1	46.3±9	0.54	0.586
LVS	29.4±10	30.8±6.5	0.8	0.425
EF	51.9±18.2	58.5±11.6	2.03	0.04*
FS	28.4±10.3	32±7.7	1.75	0.082

LA: left atrial dimension; RVD: right ventricular dimension; LVD: left ventricular dimension in diastole; LVS: left ventricular dimension in systole; EF: ejection fraction; FS: fractional shortening, *significant, **highly significant.

The outcome analysis in this study is presented in terms of hospital stay, this mainly because no reported mortality in both groups up to two weeks follow-up period. Patients with acute myocardial injury tend to be admitted for longer period (11.5±3.5 days) in the ICU even when the UGIB is controlled. Furthermore, the medications used in treatment of acute myocardial injury have no risk of re-bleeding.

Table 5 Comparison of the outcome between diseased and control groups.

	Control (n=66)	Cases (n=39)	t	p
Hospital stay (days)	4.3±1.5	11.5±3.5	14.2	<0.001**
blood transfusion (units)	2.1±2.3	1.8±2.4	Mann-whitney 1187	0.4
Re-bleeding	1 (2.6%)	5 (7.6%)	1	0.2

**highly significant.

Table 6 Logistic regression for potential confounders among the cases.

	OR	P	95% Confidence Interval	
			Lower Bound	Upper Bound
Age	1.448	0.229	-0.690	2.884
Gender	2.029	0.154	-0.466	2.944
HCT	0.687	0.407	-4.591	1.863
Variceal cause	0.401	0.526	-2.634	5.150
Liver cirrhosis	4.872	0.03*	-5.740	2.035
History of NSAIDs use	0.979	0.323	-1.107	3.365
Hypertension	7.057	0.008*	-4.335	-0.654
Smoking	5.425	0.020*	-3.728	-0.321
Octreotide/Terlipressin use	0.448	0.503	-2.692	1.321

HCT= hematocrate value; *significant.

DISCUSSION

Myocardial injury after UGIB is frequently ignored because the signs and symptoms may be over shadowed by the severity of UGIB^[5]. Several studies showed that this process is common, especially in critically ill patients^[13].

Upper gastrointestinal bleeding may predispose to myocardial ischemia/infarction because the massive UGIB compromises myocardial perfusion and the reflex tachycardia increases myocardial oxygen consumption^[5].

The frequency of acute myocardial injury in this study was 37%, frequency higher than other studies. Emenike *et al*^[4] reported rate of 13% in American patients while Iser *et al*^[14] reported rate of 19% in Australian patients. The discrepancy in the figures can be explained on the basis of included patients, where in the Emenike study they included only 83 patients while in the second study they used higher cut off for TnI (0.5 ng/dL versus 0.01 ng/dL in our study). Another study from Taiwan^[15] reported rate of 40.64%, although they used higher cut off values for cardiac enzymes than we used in our study (CK-MB>12 U/L, or TnI>0.2 ng/dL) yet they enrolled higher number of patients (155 versus 105 in our study).

In our study, the age and gender are not risk factors for acute myocardial injury in patients with first episode of UGIB. Obese patients with high BMI are at increased risk to develop acute myocardial injury while they experience their first bleeding episode. Although other studies have identified the older age as a risk factor for acute myocardial injury in patients with UGIB^[15], another study showed that younger age patients with a history of significant alcohol use are less likely to develop cardiac complications when compared to older patients^[16].

Also in our study, we found that there was a significant difference between patients with myocardial injury and those without myocardial injury as regard coronary artery disease (CAD) risk factors including systemic hypertension, smoking, BMI and hypertriglyceridaemia. These factors are considered to be predictive risk factors of simultaneous UGIB and myocardial injury, as the results are closely similar to previous studies, which showed that presence of two or more risk factors for CAD or a previous clinical history of CAD are among the factors that may help to stratify patients who are at increased risk of morbidity and mortality with GIT hemorrhage^[4,17].

Our study revealed that liver cirrhosis showed significant difference between both groups. Univariate analysis revealed that liver cirrhosis is a risk factor in UGIB patients for developing myocardial injury. These results are supported by findings of Pateron *et al*^[18] they investigated 32 patients with liver cirrhosis and showed that 10 patients (32%) had slightly elevated TnI (range, 0.06-0.25 ng/dL) and developed myocardial injury although the exact mechanism remains unknown. Also Taiwanese patients with liver cirrhosis and more than 2 risk factors of CAD are likely to develop acute

myocardial injury after UGIB^[15].

This study revealed that there was no significant difference between both groups as regard the use of NSAIDs, lowest HCT, initial Hb, and number of blood transfusion units, vital signs and creatinine level. Although initial and minimum HCT levels ($\leq 25\%$ vs $>25\%$) were not significant predictors for UGIB patients to develop myocardial injury, it is still important to consider the necessity of adequate blood transfusion before performing gastroendoscopy, which further increases heart load and may exacerbate the acute myocardial injury. However in another study, it is found that UGIB patients with acute myocardial injury had significantly lower presenting hematocrits (26.0 ± 1.3 vs 30.5 ± 0.8 ; $p=0.007$), and lower lowest hematocrits in the first 48 h (22.3 ± 0.9 vs 25.1 ± 0.5 ; $p=0.01$) than those without acute myocardial injury^[6].

Our study showed that there is a significant difference between UGIB patients with myocardial injury and those without as regard hospital stay (mean duration, 4.3 ± 1.5 vs. 11.5 ± 3.5 days; $p < 0.001$). These results are in agreement with a previous study which showed that UGIB patients with acute myocardial injury tend to have longer stay in the ICU (7.9 ± 2.2 vs 4.0 ± 0.4 days; $p=0.09$) than those without acute myocardial injury^[6]. And that is why some authors drawn a recommendation for older patients with UGIB and those with comorbidities to be monitored in the ICU^[16].

The mortality in both groups (up to 2 weeks after the first episode of UGIB) were comparable, this is probably due to sticking to the guidelines in treatment of both patient groups and better monitoring in the ICU.

In conclusion, UGIB patients with a history of liver cirrhosis and other cardiac risk factors including systemic hypertension, smoking, high BMI and hypertriglyceridaemia had a high risk of simultaneously developing myocardial injury and longer hospital stay.

Monitoring by ECG and cardiac enzymes, including TnI, is recommended in high risk patients with UGIB, even if no cardiac complaints are present. Further studies are necessary to investigate the exact mechanisms by which liver cirrhosis precipitates myocardial injury during UGIB.

REFERENCES

- 1 Fallah MA, Prakash C, Edmundowicz S. Acute gastrointestinal bleeding. *Med Clin North Am* 2000; **84**(5): 1183–1208.
- 2 Bělohávek J, Hrubý M, Polák F, Bortlík M. Nonvariceal acute upper digestive tract hemorrhage--therapeutic approach. *Cas Lek Cesk* 2001; **140**(10): 295-298
- 3 Cappell MS. Gastrointestinal bleeding associated with myocardial infarction. *Gastroenterol Clin North Am* 2000; **29**: 423–444
- 4 Emenike E, Srivastava S, Amoateng-Adjepong Y, al-Kharrat T, Zarich S, Manthous CA. Myocardial infarction complicating gastrointestinal hemorrhage. *Mayo Clin Proc* 1999; **74**: 235–241
- 5 Cappell MS. A study of the syndrome of simultaneous acute upper gastrointestinal bleeding and myocardial infarction in 36 patients. *Am J Gastroenterol* 1995; **90**: 1444–1449
- 6 Ma Z, Lee SS. Cirrhotic cardiomyopathy: getting to the heart

- of the matter. *Hepatology* 1996; **24**: 451–459
- 7 Sorbi D, Gostout CJ, Peura D, Johnson D, Lanza F, Foutch PG, Schleck CD, Zinsmeister AR. An assessment of the management of acute bleeding varices: a multicenter prospective member-based study. *Am J Gastroenterol* 2003; **98**: 2424–2434
- 8 Lee MY, Chu CS, Lee KT, Lee HC, Su HM, Cheng KH, Sheu SH, Lai WT. Terlipressin-related acute myocardial infarction: a case report and literature review. *Kaohsiung J Med Sci* 2004; **20**: 604–608
- 9 Cuellar RE, Gavaler JS, Alexander JA, Brouillette DE, Chien MC, Yoo YK, Rabinovitz M, Stone BG, Van Thiel DH. Gastrointestinal tract hemorrhage: The value of a nasogastric aspirate. *Arch Intern Med* 150:1381-1384, 1990.
- 10 Beyne P, Bouvier E, Werner P, Bourgoin P, Logeart D, Alliot L, Daïkha H, Vidaud M. Emergency department triage of patients with acute chest pain: definition of cardiac troponin I decisional value to manage patients without electrocardiographic evidence of ischemia. *Clin Chem Lab Med* 2004; **42**: 556–559
- 11 Pagani F, Bonetti G, Stefani F, Cuccia C, Panteghini M. Determination of decision limits for ACS: systems cardiac troponin I. *Clin Chem Lab Med* 2000; **38**: 1155–1157
- 12 Aubé C, Oberti F, Korali N, Namour MA, Loisel D, Tanguy JY, Valsesia E, Pilette C, Rousselet MC, Bedossa P, Rifflet H, Maïga MY, Penneau-Fontbonne D, Caron C, Calès P. Ultrasonographic diagnosis of hepatic fibrosis or cirrhosis. *J Hepatol* 1999; **30**(3): 472-478
- 13 Bellozzo F, Fagiuoli S, Pavei A, Gregory SA, Cati A, Silverj E, Plebani M, Zaninotto M, Mancuso T, Iliceto S. Anemia and ischemia: myocardial injury in patients with gastrointestinal bleeding. *Am J Med* 2005; **118**: 548–451
- 14 Iser DM, Thompson AJ, Sia KK, Yeomans ND, Chen RY. Prospective study of cardiac troponin I release in patients with upper gastrointestinal bleeding. *J Gastroenterol Hepatol* 2008; **23**(6): 938-942
- 15 Wu IC, Yu FJ, Chou JJ, Lin TJ, Chen HW, Lee CS, Wu DC. Predictive risk factors for upper gastrointestinal bleeding with simultaneous myocardial injury. *Kaohsiung J Med Sci* 2007; **23**(1): 8-16
- 16 Prendergast HM, Sloan EP, Cumpston K, Schlichting AB. Myocardial infarction and cardiac complications in emergency department patients admitted to the intensive care unit with gastrointestinal hemorrhage. *J Emerg Med* 2005; **28**(1): 19-25
- 17 Bhatti N, Amoateng-Adjepong Y, Qamar A, Manthous CA. Myocardial infarction in critically ill patients presenting with gastrointestinal hemorrhage: retrospective analysis of risks and outcomes. *Chest* 1998; **114**: 1137–1142
- 18 Pateron D, Beyne P, Laperche T, Logeard D, Lefilliatre P, Sogni P, Moreau R, Langlet P, Elman A, Bernuau J, Valla D, Erlinger S, Lebrec D. Elevated circulating cardiac troponin I in patients with cirrhosis. *Hepatology* 1999; **29**: 640–643

Peer reviewer: Qi-Quan Zhou, Department of High Altitude Disease, College of High Altitude Military Medicine, Third Military Medical University; Key Laboratory of High Altitude Medicine, Ministry of Education, 30 gaotanyan street, Shapingba area, Chongqing 400038, China.