Predictors of myocardial injury in patients with cirrhosis presenting with upper gastrointestinal bleeding

Rehab Shaheen[a], Tarek Gouda[a], Monir Bahgat[b], Tarek Selim[c], Hazem Hakim El-Beltagy El-Menshawy[b], Elsayed Awad[d]

Departments of [a]Internal Medicine, Critical Care, [b]Internal Medicine, Hepatology and Gastroenterology, [c]Clinical Pathology, Faculty of Medicine, Mansoura University, Mansoura, [d]Department of Anaesthesia and ICU, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Correspondence to Hazem Hakim El -Beltagy El-Menshawy, Specialized Medical Hospital, Mansoura University, Mansoura, Egypt.
Tel: +20 110 010 0066;
e-mail: hzhzhkhk@yahoo.com

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Background
Myocardial injury in conditions other than coronary artery disease (CAD), known as type 2 myocardial infarction, is mostly related to mismatch between myocardial oxygen supply and demand. Cirrhotic patients with acute upper gastrointestinal bleeding (UGIB) are usually hemodynamically unstable. Hypovolemia, hypotension, and decreased oxygen-carrying capacity as consequences of UGIB may precipitate subclinical heart failure and myocardial injury.
Aim of work
Assessment of the prevalence and potential risk factors of myocardial injury in patients with liver cirrhosis with acute UGIB.
Patients and methods
The study was conducted on 132 patients diagnosed with liver cirrhosis presenting by UGIT bleeding at Mansoura University Hospitals during one year. Patients were divided into 2 groups: group 1 (76 patients) with myocardial injury or ischemic heart disease and group 2 (60 patients) without.
Results
The incidence of myocardial injury in this study (elevated troponin levels above cutoff value and/or ECG changes) was 55% of patients. Troponin I was positive in 25% of patients. ECG ischemic changes were found in 36.3% of patients in the form of ST-segment deviation or T-wave inversion. On univariate analysis, predictors of myocardial injury in patients with UGIB included MELD score and variceal source of GI bleeding. On multivariate analysis variceal source of GI bleeding is an independent predictor of myocardial injury. Variceal bleeding was found in 95 % of the ischemic group versus 63% in the other group.
Conclusion
More than half of the study patients presented with UGIB have suffered from unnoticed subclinical myocardial injury. Variceal source of GI bleeding was found to be an independent predictor of myocardial injury.

Keywords:
GI bleeding, liver cirrhosis, myocardial injury

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Introduction

Acute upper gastrointestinal bleeding (UGIB) is a leading health problem. Approximately 150 for each 100 000 adults experience this problem every year [1]. Approximately 60% of the attacks of bleeding in patients with cirrhosis are due to variceal causes [2]. Type 2 myocardial infarction (MI) is defined as myocardial necrosis owing to inequity in coronary blood flow in the face of increased myocardial oxygen demand. Recognition of this type has increased with widespread use of increasingly sensitive troponin assays [3]. Hypovolemia, decrease in blood pressure, and decreased oxygen-carrying capacity as consequences of acute gastrointestinal bleeding contribute to myocardial ischemia and necrosis [4], precipitating in mostly subclinical heart failure and myocardial injury [5]. Many studies revealed that major upper or lower gastrointestinal hemorrhage is associated with MI in ~30–49% of cases in ICUs causing a mortality rate of ~5–10% [6].

Aim of work

The aim is to assess the prevalence and potential risk factors of myocardial injury in patients with liver cirrhosis presenting with acute UGIB.

Patients and methods

This prospective study underwent from March 2017 to March 2018 at Hematemesis and Melena Units, Mansoura University Hospitals. It involved 132

patients (99 males and 33 females) diagnosed with liver cirrhosis presenting with upper gastrointestinal tract (GIT) bleeding. According to the presence or absence of myocardial injury, patients were divided into two groups:

(1) Group 1: with myocardial injury or ischemic heart disease (IHD) (76 patients).
(2) Group 2: without myocardial injury or IHD (60 patients).

Inclusion criteria

This study was conducted on all patients with liver cirrhosis presenting with acute upper GIT bleeding (hematemesis and/or melena).

Exclusion criteria

Patients with a history of coronary heart disease, chronic renal insufficiency, septic shock, cerebral stroke, and hematological malignancy were excluded.

Ethical concerns

Oral informed consents were obtained from the patients or their relatives participating in this study after informing them about the steps of the study. The study was approved by the Ethical Committee of Faculty of Medicine Mansoura University.

Methods of the study

Between March 2017 and March 2018, 132 patients diagnosed with liver cirrhosis presenting with upper GIT bleeding were considered eligible for analysis in this study. Patients were divided into two groups, as previously described, which were subjected to thorough medical history taking (stressing on age; sex; smoking; hypertension; diabetes mellitus; history of previous attacks; history of IHD; presentation with hematemesis, melena or both; and presence of anginal chest pain) and thorough examination (including vital signs and abdominal and cardiopulmonary examination). Both groups were subjected to standardized 12-lead ECG and cardiac troponin-I measurement on admission and 12 h later. Severity of liver disease and UGIB were determined according to Child–Turcot–Pugh (CTP) score [7], model for end-stage liver disease (MELD) score [8], and Rockall score [9]. All patients within 24 h from UGIB, except for those who refused or were contraindicated (irritable or shocked patients), underwent upper gastrointestinal endoscopy as an essential demonstrative and restorative device.

Scores calculation

(1) CTP score [7].

2 Measure	1 Point	2 Points	3 Points
Total bilirubin (μmol/l) (mg/dl)	<34 (<2)	34–50 (2–3)	>50 (>3)
Serum albumin (g/dl)	>3.5	2.8–3.5	<2.8
Prothrombin time, prolongation (s) odds ratio (OR)	<4.0	4.0–6.0	>6.0
International normalized ratio (INR)	<1.7	1.7–2.3	>2.3
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy	None	Grades I–II	Grades III–IV

Class A (5–6), Class B (7–9), and Class C (10–15).

(2) MELD score: MELD=3.8[log serum bilirubin (mg/dl)]+11.2[log INR]+9.6 [log serum creatinine (mg/dl)]+6.4 [10].

(3) Rockall score.

Variables	Score 0	Score 2	Score 3
Shock	No shock	Systolic blood pressure<100	
Comorbidity	Nil major	Congestive heart failure, IHD, and major morbidity	Renal failure, liver failure, and metastatic cancer
Diagnosis	Mallory-Weiss	GI malignancy	
Evidence of bleeding	None	Blood, adherent clot, and spurting vessel	

The total score is calculated by simple addition. A score less than 3 carries good prognosis, but a total score more than 8 carries high risk of mortality [9].

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package, version 21 (SPSS Inc., Chicago, IL, USA). Qualitative data were expressed as count and percent. Quantitative data were initially tested for normality using Kolmogorov–Smirnov and Shapiro–Wilk test, with data being normally distributed if P value more than 0.050. Quantitative data were expressed as mean±SD if normally distributed or median and interquartile range if not. Regarding data comparison, for qualitative data for two groups (2×2) table, χ^2 test (or Fisher's exact test) was used. Regarding qualitative data for more than two groups (e.g. 2×3 table), χ^2 test (with Bonferroni's method to adjust P values when comparing column proportions) was used. For quantitative data between

Table 1 Baseline data of both groups

Parameters	IHD group (*N*=72)	Non-IHD group (*N*=60)	χ^2	*P* value
Age [median (IQR)] (years)	58 (52.5–69.4)	56.5 (50.5–64.5)	–1.098	0.272**
Sex [*n* (%)]			0.489	0.484***
Male	51 (70.8)	48 (80)		
Female	21 (29.2)	12 (20)		
Smoking history [*n* (%)]			1.650	0.259***
Nonsmokers	54 (75)	54 (90)		
Smokers	18 (25)	6 (10)		
HTN [*n* (%)]			0.058	1.0***
Nonhypertensive	63 (87.5)	51 (85)		
Hypertensive	9 (12.5)	9 (15)		
DM [*n* (%)]			0.171	0.679***
Nondiabetic	51 (70.8)	39 (65)		
Diabetic	21 (29.2)	21 (35)		
Pulse (mean±SD) (beats/min)	100.8±16	96.2±9.5	–1.136	0.262*
Recurrent attacks [*n* (%)]			0.00	1.00***
No	36 (50)	30 (50)		
Yes	36 (50)	30 (50)		
Systolic BP [median (IQR)] (mmHg)	100 (90–110)	110 (90–127)	–0.717	0.473**
Diastolic BP (mean±SD) (mmHg)	64.58±14.738	68.50±15.652	0.853	0.398*
Hematemesis [*n* (%)]			1.474	0.356***
No	12 (16.7)	3 (5)		
Yes	60 (83.3)	57 (95)		
Melena [*n* (%)]			2.265	0.217***
No	6 (8.3)	15 (25)		
Yes	66 (91.7)	45 (75)		
Child score [Median (IQR)]	9.5 (7–10.75)	8 (7–9.75)	–0.943	0.346**
MELD score	14±3.479	11.89±2.904	–2.156	0.037*
Rockall score	5.33±1.958	5.16±1.47	–0.298	0.767*
White blood count (cell/mm)	8850 (5550–13 450)	8350 (6025–10 625)	–0.259	0.795**
Hemoglobin (mean±SD) (g/dl)	7.724±1.9128	8.658±2.0153	1.277	0.208*
Mean corpuscular volume (mean±SD) (Fl)	80.81±11.826	83.84±9.529	0.327	0.745*
Platelet count (cell/mm)	120 000 (94 000–183 000)	103 500 (74 000–152 000)	–0.637	0.524**
INR (mean±SD)	1.456±0.2081	1.188±0.1349	–3.726	0.01*
Albumin (g/dl)	2.547±0.5257	2.465±0.5308	–0.106	0.916*
Bilirubin level (mg/dl)	1.95 (0.8–2.875)	1.34 (0.725–2.95)	–0.271	0.786**
ALT (U/l)	43 (29.5–83.75)	36.5 (21–59)	–1.038	0.299**
Creatinine (mg/dl)	1.1 (0.4–1.5)	0.9 (0.8–1.3575)	–1.103	0.270**
Troponin on admission (pg/ml)	221.9 (185.75–278.25)	169 (98.25–192.25)	–3.583	0.000**
Troponin level after 12 h (pg/ml)	233.5 (191–298.5)	159 (108–202)	–3.513	0.000**

ALT, alanine aminotransferase; BP, blood pressure; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; INR, international normalized ratio; IQR, interquartile range; MELD, model for end-stage liver disease. **P* value was computed by independent samples *t* test. ***P* value was computed by Mann–Whitney *U* test. ****P* value was computed by χ^2 test.

two groups, independent samples *t* test was used if data were normally distributed in both groups, and the nonparametric alternative Mann–Whitney *U* test was used if not. Standard logistic regression was used to predict the likelihood of a diagnosis using only one predictor, and standard logistic regression analysis was used to calculate the OR with its 95% confidence interval. Multivariable logistic regression was used to create a prediction model of the likelihood of a diagnosis to detect the significant 'independent' predictors with their OR (95% confidence interval). Results were considered as statistically significant if *P* value less than or equal to 0.050.

Results

A total of 132 patients (99 males and 33 females) were involved in this trial, with an age range of 43–79 years (mean±SD, 59.29±9 years). They were divided into two groups according to myocardial injury presence. Both groups were comparable in their baseline characteristics as shown in Table 1, whereas the main outcomes are shown in Fig. 1, Tables 2 and 3, and predictors for myocardial injury in the context of UGIB are shown in Tables 4 and 5. INR, MELD score, and variceal bleeding were statistically significantly higher in IHD groups than non-IHD group. Presence of

variceal bleeding has an 11-fold increased odds of occurrence of ischemia. The logistic regression model was statistically significant, χ^2 (2)=9.235, *P* value=0.010. The model explained 28.1% (Nagelkerke R^2) of the variance in coronary ischemia and correctly classified 69.2% of cases. Sensitivity was 75%, specificity was 63.2%, positive predictive value was 68.2%, and negative predictive value was 70.6%. Of the two predictor variables, variceal bleeding as a source of bleeding was statistically significant. Patients variceal bleeding had 10.5 times higher odds to exhibit coronary ischemia.

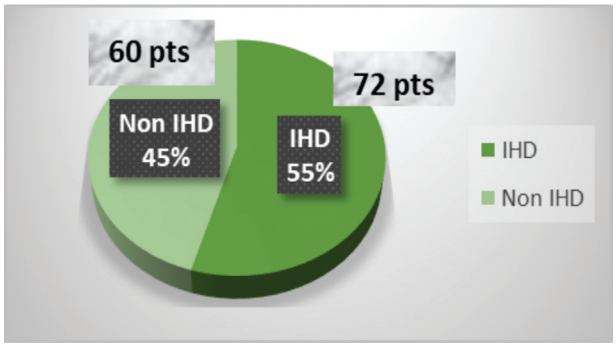
Discussion

Patients with cirrhosis with UGIB are unstable hemodynamically most of the time, which may precipitate to subclinical heart failure and myocardial injury [11]. The current study revealed that the incidence of myocardial injury (elevated troponin levels above cutoff value and/or ECG changes) was seen in 55% (72) of patients, in contrast to Emenike *et al.* [6], who found that the frequency of myocardial injury was seen in 13%. This result can be explained by that in the Emenike study myocardial injury was diagnosed by enzymatic elevation plus ECG changes, whereas in our study, the presence of any of them is enough for the diagnosis. Troponin-I, which is considered as a superior biologic marker to identify myocardial ischemia in gastrointestinal bleeders, was positive in 25% (33) of patients compared with 12% in the study by Bellotto *et al.* [12], 8.4% in Wu *et al.* [13], and 19% in Iser *et al.* [14].

ECG ischemic changes were found in 36.3% (48) of patients in the form of ST-segment deviation or T-wave inversion compared with 24% in the study by Emenike *et al.* [6]. In the study by Wu *et al.* [13], the percentage of myocardial injury was 40.46% using high cutoff troponin value (500 pg/ml), and in the study by Hamid *et al.* [15], 37% of the patients were reported to have myocardial injury. In the mentioned study, the number of patients included was 105 versus 132 in our study. Regarding age and sex, patients diagnosed with having myocardial injury were older, and mostly males were more affected than those without myocardial injury. However, age and sex were not significant predictors of myocardial injury in cirrhotic cases presented with GIT bleeding, which was in parallel to the reports by Bellotto *et al.* [12] and Hamid *et al.* [15].

Hypertension, diabetes mellitus, and smoking had no significant statistical difference between the ischemic and the nonischemic groups, which is in agreement with Bellotto *et al.* [12]. This result is in contrast to the

Figure 1



Number of patients diagnosed±IHD. IHD, ischemic heart disease.

Table 2 Serum troponin and ECG results

Parameters	Statistical value [*n* (%)]
Positive troponin on admission	24 (18.2)
Positive troponin after 12 h	33 (25)
Ischemic changes in ECG	48 (36.4)

Table 3 Endoscopic findings in studied patients

Parameters	IHD group (60 patients) [*n* (%)]	Non-IHD group (57 patients) [*n* (%)]	χ^2	*P* value
Source of bleeding				
Variceal	57 (95)	36 (63.2)	6.059	0.020*
Nonvariceal	3 (5)	21 (36.8)		
PHG				
Yes	15 (25)	24 (42.1)	1.283	0.257*
No	45 (75)	33 (57.9)		
Active spurting				
Yes	18 (30)	3 (5.3)	4.048	0.090*
No	42 (70)	45 (94.7)		
Ulcer on varices				
Yes	6 (10)	9 (15.8)	0.292	0.58*
No	54 (90)	48 (84.2)		

IHD, ischemic heart disease; PHG, portal hypertensive gastropathy. **P* value was computed by independent samples *t* test.

studies by Bhatti *et al.* [4] and Prendergast *et al.* [16] who proposed that these factors are the only variables capable of predicting myocardial injury. This discrepancy could be explained by the small proportion of the patients who were smokers, diabetic, and hypertensive in our study. The type of MI in our study is type 2 MI, which results from an inequity between the actual blood supply and the need of oxygen without CAD.

Regarding clinical data, Prendergast *et al.* [16] found that patients presented with hematemesis were less likely to develop complicated course that could result in ICU admission, cardiac complications, and even death than those presented with melena or hematochezia. However, in our study, we found no significant difference between the two groups regarding the presenting sign (hematemesis and/or melena) or the first or recurrent attacks. Severity of blood loss could be estimated by the presence of hypotension and reflex tachycardia. In this study, admission heart rate in patients with myocardial injury was 100.8±16 versus 96.2±9.5 in the other group. Systolic blood pressure/diastolic blood pressure in the ischemic group was 100 (90–110)/64.58±14.7, and in the nonischemic group was 110 (90–127)/68.50±15.6. However, there is no significant difference between the two groups regarding heart rate and blood pressure. This result is in same line with those of Bellotto *et al.* [12], Prendergast *et al.* [16], and Hamid *et al.* [15].

Regarding laboratory data, the patient group with myocardial injury had hemoglobin level of 7.724±1.9 in contrast to 8.658±2 in the other group, but with no significant difference, which was similar to what was reported in Prendergast *et al.* [16] and Hamid *et al.* [15] study. In contrast to our study, the study by Bellotto *et al.* [12] found that minimum hemoglobin during admission was positively correlated with myocardial ischemia, but in our study, we used hemoglobin on admission only. INR was significantly higher in the ischemic group than the nonischemic one to be 1.456 ±0.2 versus 1.188±0.13, respectively. This result can be explained by that increased INR is a self-determining prognostic factor of mortality in patients without anticoagulant drugs, as in Kırıs *et al.* [10]. Activated coagulation, inflammation, neurohumoral stimulation, and liver failure are related to elevated INR [17]. Regarding scoring systems, ischemic group had a Child score of 9.5 (7–10.75) in contrast to 8 (7–9.75) in the other group. Rockall score has been done also to be 5.33±1.958 in the ischemic group and 5.16±1.47 in the nonischemic group. However, there is no significant difference between the two groups regarding CTP and Rockall score. MELD score was significantly higher in the ischemic than the nonischemic group. The MELD had been initially established to evaluate the short-term mortality in cirrhotic cases scheduled to undergo transjugular intrahepatic porto-systemic shunts [18]. The importance of MELD is increased to involve ranking of liver transplantation [19].

More lately, data have been found proposing that the MELD score could be used as a new biomarker of medical and cardiovascular hazards, surprisingly in cases who do not have known liver disease [20,21]. MELD score has been lately recognized to be related to predominant CVD in patients with nonalcoholic fatty liver disease [22]. MELD-Na score is known to be linked to an elevated possibility of major adverse CV events including CV death, nonfatal MI, angina in need for hospital admission, PCI, CABG, stroke, or transient ischemic attack [23]. MELD score has been found to have a significant elevation in nonsurvived cases of ACS who underwent PCI than those who survived [10].

Regarding endoscopic findings, the source of bleeding was found to be a significant predictor of myocardial injury. Variceal bleeding was found in 95% of the ischemic group versus 63% in the other group. This result is in agreement with Wu *et al.* [13]. However, Bellotto *et al.* [12] and Prendergast *et al.* [16] showed insignificant difference between the group diagnosed with IHD and the other group; this may be explained by small number of patients diagnosed as variceal bleeders, that is, 26 of 227 in the Belloto study, and only four of 68 patients in the Prendergast study. Other endoscopic findings were that active spurter in 30% of ischemic patients and 5.3% in nonischemic group. Portal hypertensive gastropathy has been found in 25% of patients with myocardial injury versus 42% of those without myocardial injury. None of these variables were statistically different between the two study groups. On multivariable logistic regression analysis involving MELD score and variceal bleeding as compared with nonvariceal bleeding on the likelihood of having coronary ischemia, variceal bleeding was an independent predictor of myocardial injury.

Conclusion

In conclusion, our trial revealed that more than half of the study patients presented with UGIB have had unnoticed subclinical myocardial injury. Predictors of

myocardial injury in patients with UGIB must concern MELD score and variceal source of GI bleeding as our study revealed that they are independent risk factors. So, frequent monitoring, careful fluid resuscitation, and blood transfusion in addition to ECG should be taken into account for every patient presenting with UGIB.

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Conflicts of interest

There are no conflicts of interest.

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