Original Article

Risk factors of in-hospital mortality among patients with upper gastrointestinal bleeding and acute myocardial infarction

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Abstract

Background/Aims: Patients with simultaneous upper gastrointestinal bleeding (UGIB) and acute myocardial infarction (AMI) have higher mortality than patients with either GIB or AMI. We aimed to assess the incidence and risk factors of in-hospital mortality in patients with UGIB and AMI.

Patients and Methods: A total of 243 patients with UGIB and AMI were enrolled during 2012–2017. Clinical and laboratory data were collected and analyzed for clinical characteristics and potential risk factors of in-hospital mortality.

Results: Among the 243 patients, 60 in-hospital deaths were observed (in-hospital mortality rate of 24.7%). Patients who died were older than the survivors (78.7 ± 6.6 vs. 72.6 ± 10.5 years, $P < 0.001$). Compared with survivors, patients who died showed increased peak white blood cell (WBC) count (9.74 ± 4.72 vs. 7.60 ± 2.91 × 10^9/L, $P = 0.002$), serum creatinine levels [134 (106, 190) vs. 97 (79, 125) mmol/L, $P = 0.014$], peak blood urine nitrogen levels (16.31 ± 8.48 mmol/L vs. 9.86 ± 6.33 mmol/L, $P < 0.001$), and peak brain natriuretic peptide (BNP) amounts [13,250 (6071, 30,000) vs. 3598 (728, 12,842) pg/mL, $P < 0.001$]. Meanwhile, patients who died also displayed lower minimum hemoglobin levels (78.3 ± 21.1 vs. 86.3 ± 22.3 g/L, $P = 0.018$) and minimum platelet counts (184.3 ± 79.1 vs. 214.6 ± 80.1 × 10^9/L, $P = 0.013$). In multivariable logistic analysis, age [OR (95% CI) =1.118 (1.053–1.186), $P < 0.001$], peak WBC count [OR (95% CI) =1.252 (1.113–1.407), $P < 0.001$], minimum platelet count [OR (95% CI) = 0.994 (0.989–1.000), $P = 0.032$], and peak BNP levels [OR (95% CI) =3.880 (1.761–8.550), $P = 0.001$] were independent predictors of in-hospital mortality.

Conclusions: Patients with UGIB and AMI had a high in-hospital mortality, which was independently associated with age, peak WBC count, minimum platelet count, and peak BNP levels.

Keywords: Acute myocardial infarction, in-hospital mortality, risk factors, upper gastrointestinal bleeding

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Access this article online	
Quick Response Code:	Website: www.saudijgastro.com
	DOI: 10.4103/sjg.SJG_492_17

How to cite this article: He L, Zhang J, Zhang S. Risk factors of in-hospital mortality among patients with upper gastrointestinal bleeding and acute myocardial infarction. Saudi J Gastroenterol 2018;24:177-82.

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) and acute myocardial infarction (AMI) are common but serious medical emergencies that cause synergistic sequelae.[1-5] Yavorski *et al.*[6] found a UGIB incidence of 36 per 100,000 people; the overall mortality of UGIB was 7–10%, and increased along with age in both males and females. Wilcox *et al.*[7] found that the 30-day mortality rates of gastrointestinal bleeding (GIB) and AMI were 2.5% and 4.4% in hospitalized patients, respectively.

According to AMI guidelines,[8-12] reperfusion followed by medical therapy (e.g., aspirin, clopidogrel, and statin) is the gold standard for AMI treatment, but while clopidogrel and aspirin in combination may reduce the risk of cardiovascular events, they increase the risk of hemorrhage.[13-18] Myocardial infarction and acute GIB (upper and lower GIB, hereafter referred to as UGIB and LGIB, respectively) occurring simultaneously is well documented. In a multicenter, case-controlled study, 36 patients with combined GIB and AMI were assessed.[19] The study showed that patients with simultaneous UGIB and AMI had significantly greater mortality than either GIB or AMI controls. The incidence of AMI with UGIB has steadily increased following the recommendations for aggressive dual antiplatelet therapy.[20] Puymirat *et al.* demonstrated that hospitalized elderly AMI patients receiving low molecular weight heparin (LMWH) present decreased bleeding and higher survival compared with those using nonfractioned heparin (UFH).[21] In agreement, bleeding during hospitalization was shown to be correlated with a high 5-year mortality in patients with AMI.[22]

Age, a previous history of GIB (upper or lower) and/or anemia, chronic kidney disease, respiratory failure, severe heart failure, and gastrointestinal cancer are demonstrated risk factors for GIB among patients with AMI after PCI.[23] Nevertheless, no guidelines presently define the causes, risk factors, and treatment principles in UGIB with AMI. Therefore, the aim of this study was to assess the frequency of in-hospital mortality in patients with UGIB and AMI, and determine the potential risk factors for this condition.

PATIENTS AND METHODS

Patients

This was a retrospective analysis of hospitalized patients with UGIB and AMI during the January 2012 to January 2017 period at the emergency department of a local Chinese hospital. The inclusion criterion was confirmed admission diagnosis of non-ST segment elevation AMI[24] with subsequent UGIB,[5,25] treated with conservative treatments only and without percutaneous coronary intervention. Patients with a positive fecal occult blood test but no visible melena or without any other clinical evidence of UGIB were excluded. The patients did not undergo gastroscopy after UGIB, but they discontinued antiplatelet therapy and were given proton pump inhibitors (PPIs). This study was approved by the ethics committee of our institution.

Data collection

Clinical history, medication, and laboratory data were collected. Laboratory data were recorded at admission and after 12, 24, and 48 h, and included peak values of white blood cell (WBC) count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, serum creatinine (SCr), blood urea nitrogen (BUN), brain natriuretic peptide (BNP), creatine kinase (CK), and creatine kinase muscle B (CK-MB), and minimum values of red blood cell (RBC) count, hemoglobin, and platelets for all patients.[19]

Study endpoint

The main study endpoint was in-hospital mortality from all causes, including cardiac death, sudden death, stroke, and multiple organ failure. The various risk factors for mortality were assessed as well.

Statistical analysis

Categorical data were presented as frequencies (percentages) and compared using the Chi-square test or Fisher's exact test, as appropriate. Normally distributed continuous data were presented as mean ± standard deviation, and non-normally distributed parameters as median and interquartile range (IQR). The unpaired *t*-test and Mann–Whitney U-test were used for assessing normally and non-normally distributed parameters, respectively. Variables significantly associated with mortality in univariate analysis were entered into a multivariate logistical regression model to identify risk factors of in-hospital mortality. Data were analyzed using the SPSS 17.0 statistical software (IBM, Armonk, NY, USA), and $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

Based on both inclusion and exclusion criteria, 243 UGIB patients with AMI were included in the current study. Among them, 60 died (in-hospital mortality rate of 24.7%). As shown in Table 1, the Patients who died were older than the survivors (78.7 ± 6.6 vs. 72.6 ± 10.5 years, $P < 0.001$). Compared with survivors, the Patients who

died showed increased peak white blood cell (WBC) count (9.74 ± 4.72 vs. 7.60 ± 2.91 × 10^9/L, $P = 0.002$), serum creatinine levels [134 (106, 190) vs. 97 (79, 125) mmol/L, $P = 0.014$], peak blood urine nitrogen levels (16.31 ± 8.48 mmol/L vs. 9.86 ± 6.33 mmol/L, $P < 0.001$), and peak brain natriuretic peptide (BNP) amounts [13,250 (6071, 30,000) vs. 3598 (728, 12,842) pg/mL, $P < 0.001$]. Meanwhile, Patients who died also displayed lower minimum hemoglobin levels (78.3 ± 21.1 vs. 86.3 ± 22.3 g/L, $P = 0.018$) and minimum platelet counts (184.3 ± 79.1 vs. 214.6 ± 80.1 × 10^9/L, $P = 0.013$). The remaining parameters, including sex, red blood cell levels, transaminase levels, blood glucose amounts, history of medication, hypertension, diabetes mellitus, coronary heart disease, and blood transfusion treatment had similar values in both groups.

Risk factors of in-hospital mortality in patients with upper gastrointestinal bleeding and acute myocardial infarction

Multivariable logistic regression analysis was used to determine the independent risk factors for in-hospital mortality. The variables showing statistically significant differences between the death and survivor groups were selected for analysis [Table 2]. The included variables were age, peak WBC, minimum hemoglobin, minimum platelet, peak Cr, peak BUN, and peak BNP (BNP levels were log-transformed before data analysis). Interestingly, age [OR (95% CI) =1.118 (1.053–1.186), $P < 0.001$], peak WBC count [OR (95% CI) =1.252 (1.113–1.407), $P < 0.001$], minimum platelet count [OR (95% CI) = 0.994 (0.989–1.000), $P = 0.032$], and peak BNP levels [OR (95% CI) =3.880 (1.761–8.550), $P = 0.001$] were significantly associated with in-hospital mortality.

DISCUSSION

This study strongly suggests that UGIB with AMI leads to high in-hospital mortality, with age, peak WBC count, minimum platelet count, and peak BNP amounts representing significant risk factors of mortality. These findings provide a basis for improving the clinical management of such patients.

In this retrospective study, the mortality of patients with UGIB and AMI was 24.7%. The ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial demonstrated that GIB is strongly associated with 30-day all-cause mortality (hazard ratio [HR]: 4.87 [IQR 2.61 to 9.08], $P < 0.0001$), cardiac mortality (HR: 5.35 [IQR 2.71 to 10.59], $P < 0.0001$), and composite ischemia (HR: 1.94 [IQR 1.14 to 3.30], $P = 0.014$).[26] Shalev *et al.* demonstrated that UGIB in patients with ACS is associated with markedly increased overall mortality, with a 30-day mortality rate of 33%. Moreover, previous peptic disease and use of combined anti-platelet therapy, especially in conjunction with heparin, are strong risk factors for mortality.[2] In UGIB and MI, bleeding represents the main symptom, and hypotension, tachycardia, and hematemesis are commonly found; independent of other epidemiological parameters, the mortality rate of combined GIB and MI is higher than that of each individual condition.[19] Lee *et al.* showed that mortality of patients with AMI and

Table 1: Patient demographic and clinical characteristics

	Patients who died	Survivors	*P*
n	60	183	NA
Age (years)	78.7±6.6	72.6±10.5	<0.001
Males (*n*, %)	37 (61.7)	131 (71.6)	0.149
WBC counts (×10^9/L)	9.74±4.72	7.60±2.91	0.002
RBC counts (×10^{12}/L)	2.71±0.68	2.92±0.79	0.081
Hemoglobin (g/L)	78.34±21.14	86.27±22.25	0.018
Platelet (×10^9/L)	184.29±79.06	214.63±80.07	0.013
ALT (U/L)	22 (12, 58)	19 (13, 34)	0.141
AST (U/L)	32 (21, 69)	29 (21, 54)	0.264
Glucose (mmol/L)	9.59±5.53	8.44±4.06	0.145
SCr (mmol/L)	134 (106, 190)	97 (79, 124.5)	0.014
BUN (mmol/L)	16.31±8.48	9.86±6.33	<0.001
BNP (pg/mL)	13,250 (6071, 30,000)	3598 (728,12,842)	<0.001
CK (U/L)	216 (79.5, 377.25)	164 (77, 488)	0.373
CKMB (ng/mL)	7.1 (3.8, 17.625)	6.6 (1.9, 34.15)	0.856
Troponin I (ng/mL)	1.60 (0.44,9.35)	1.62 (0.14, 7.93)	0.649
Medication history (*n*, %)			
Aspirin	23 (38.3)	75 (41.0)	0.716
Clopidogrel	15 (25.0)	48 (26.2)	0.850
PPI	9 (15.0)	17 (9.3)	0.214
Comorbidity (*n*, %)			
Hypertension	39 (65.0)	106 (57.9)	0.332
Diabetes mellitus	25 (41.7)	55 (30.1)	0.097
Coronary heart disease	30 (50.0)	81 (44.3)	0.439

Note: Values are presented as number (%), mean±SD, or Median (IQR); ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BNP: Brain natriuretic peptide; CK: Creatine kinase; CK-MB: Creatine kinase muscle B; PPI: Proton pump inhibitor; RBC: Red blood cell; SCr: Serum creatinine; BUN: Blood urea nitrogen; WBC: White blood cell

Table 2: Logistic regression analysis of risk factors for mortality

Variables	OR (95% CI)	*P*
Age	1.118 (1.053-1.186)	<0.001
Peak WBC	1.252 (1.113-1.407)	<0.001
Min Hemoglobin	0.985 (0.965-1.005)	0.140
Min Platelet	0.994 (0.989-1.000)	0.032
Peak SCr	1.001 (0.997-1.005)	0.578
Peak BUN	1.025 (0.961-1.093)	0.457
Peak BNP	3.880 (1.761-8.550)	0.001

BNP: Brain natriuretic peptide; BUN: Blood urea nitrogen; CI: Confidence interval; OR: Odds ratio; SCr: Serum creatinine; WBC: White blood cells

nonvariceal UGIB was only 8.7%, much lower than in the present study,[27] but no gastroscopy was performed in the present study and we could not distinguish patients with nonvariceal UGIB from those with variceal UGIB.

As shown above, age, peak WBC count, minimum platelet count, and peak BNP were independent risk factors for in-hospital mortality in patients with UGIB and AMI. To our knowledge, this is the first study revealing the associations of peak WBC count, minimum platelet count, and peak BNP with in-hospital mortality in UGIB with AMI. Previous studies showed that MI occurs frequently in patients with GI hemorrhage and admitted to an ICU. Age above 65 years and two or more risk factors for coronary artery disease have been shown to identify the patients at greatest risk of MI.[28] Al-Mallah *et al.* showed that 3% (80/3045) of patients with ACS develop clinically significant GIB. In the latter study, the risk factors of GIB were found to be older age, female gender, smoking status, peak troponin I amounts, and a history of heart failure, diabetes, and/or hypertension; in-hospital mortality was significantly higher in ACS patients with GIB versus those without (36% vs. 5%, $P < 0.001$).[29] Wu *et al.* also found that women and patients below 65 show fewer comorbidities compared with older individuals or men.[30]

Several studies have indicated that proton pump inhibitors significantly reduce major bleeding incidence in patients treated with dual antiplatelet therapy, especially among those with additional risk factor(s) for bleeding.[17,31,32] Nevertheless, Gaspar *et al.* and Kim *et al.* found that PPI in addition to aspirin and clopidogrel after ACS is not associated with a better prognosis.[33,34] In agreement, we found that the mortality rate in patients treated with aspirin, clopidogrel, and PPIs after ACS was not significantly different from that of patients without PPIs. Interestingly, a large Chinese trial demonstrated that AMI risk in patients with coronary artery disease increases by two-fold after UGIB.[30]

As shown above, multiple factors were associated with high mortality in patients with UGIB and AMI. It should be noted that UGIB and AMI are both clinical conditions and each has high mortality. In addition, treatment methods for UGIB and AMI are partially contradictory. Previous studies demonstrated that endoscopy is relatively safe for the diagnosis and management of UGIB in patients with AMI.[35,36] Yachimski *et al.* also supported endoscopy prior to cardiac catheterization in patients with AMI and overt UGIB; this strategy resulted in fewer deaths and reduced complications.[37] Lin *et al.* concluded that, in patients with concomitant UGIB and AMI, urgent endoscopy is most beneficial in patients with UGIB as the initial event, as well as in those presenting with hematemesis and hemodynamic instability.[38] Nevertheless, to avoid medical tangles, doctors often choose a relatively conservative therapy. Finally, there are no definitive guidelines for the management of patients with such unique scenarios and most practitioners rely on empiric treatment.

A few limitations should be mentioned for this study. First, this was a retrospective analysis, with inherent shortcomings. Some risk factors of UGIB and AMI mortality could not be assessed; indeed, albumin[39,40] and alcohol[41,42] could not be analyzed in the present study. Moreover, the treatment and disease severity was not consistent in the study population, but the treatment principles were consistent. In addition, relatively few patients with AMI and UGIB were included, and very small amounts of data were available on endoscopy efficacy. Finally, these patients were usually treated with conservative therapy, so there were few coronary angiography and coronary computed tomography angiography (CTA) data in the record. Bedside echocardiography generally could not be used as the clinical evaluation basis due to many factors such as availability and economical reasons. Hence, the heart conditions could only be estimated based on the levels of blood myocardial enzymes and BNP. Therefore, the present findings should be interpreted with caution.

CONCLUSION

The in-hospital mortality rate of patients with UGIB and AMI was very high. Age, peak WBC count, minimum platelet count, and peak BNP levels were shown to be independent risk factors of in-hospital mortality.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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