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Independent Predictors of In-hospital Re-bleeding, Need of Operation and Mortality in Acute Upper Gastrointestinal Bleeding

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Abstract: Prediction of outcome is difficult in patients with acute upper gastrointestinal bleeding (AUGIB). Some factors have been proposed in this regard with varying accuracy. This study aimed to investigate probable predictors of in-hospital outcome in patients with AUGIB. One hundred sixty four patients with AUGIB were studied prospectively in Tabriz Imam Reza Teaching Centre. All these patients were evaluated endoscopically by an expert. Patients' age, gender, presenting complains, transfusion, clinical findings and previous medical history were compared between survived vs. expired, re-bled vs. non re-bled and operated vs. non operated patients. There were 117 males and 47 females with the mean age of 57.12±17.32 (range: 32-78) years in this study. Hematemesis was the sole independent predictor of in-hospital mortality (82.1 vs. 100%; $p<0.001$). In univariate analysis, however, female gender, major hemorrhage and previous neurological disease were associated with higher rate of expiration. Comparing two re-bled and non re-bled groups, hematemesis (76.5 vs. 95.9%; $p = 0.003$) and need of transfusion >2U (36.1 vs. 71.4%; $p = 0.006$) were independent predictors of re-bleeding. In univariate analysis, hematocrit <30%, major hemorrhage and previous history of hepatic disease or hypertension were predictive of re-bleeding. In comparison between operated and non operated groups no significant predictor was detected. In conclusion, this study showed that presence of hematemesis at the time of admission and need of transfusion >2U were independent predictors of poor outcome in patients with AUGIB.

Key words: Acute upper gastrointestinal bleeding, mortality, recurrence, prognostic factors, hematemesis, transfusion

INTRODUCTION

Acute upper gastrointestinal bleeding (AUGIB) is one of the major underlying causes of hospitalization in the West with an estimated annual incidence of 0.1%. The reported incidence is wide and is reported to be 50 to 150 episodes per 100000 individuals per year (Rockall *et al*., 1995; Sarkar *et al*., 1992). Furthermore, the associated mortality rate ranges between 10-14% in different settings (Braunwald *et al*., 2005; Cameron *et al*., 2002). However, it is thought that by on-time and appropriate management, such as endoscopic approaches in the hands of expert endoscopists (Fakheri *et al*., 2010), 9 out of 10 patients with even massive AUGIB could be saved (Kashyap *et al*., 2005). By now, different studies have focused on possible prognostic parameters in these patients, albeit with heterogeneous and inconclusive consequences (Schemmer *et al*., 2006). There are various underlying causes for this indefiniteness, many origins from methodological shortcomings such as retrospective instead of prospective studies, insufficient power due to small sample size, complexity of evaluated factors with statistical errors, lack of multivariate analysis, heterogeneous group of patients, etc. (Gilbert, 1990; Kalula *et al*., 2003). An acceptable prognostic model is believed to be accurate, simply applicable and accurate in different populations. Available data in this regard, however, mostly lack these specifications and need to be revised in methodologically proper studies (Badel *et al*., 2011; Wee, 2011; Greenspoon and Barkun, 2010). This study aimed to evaluate most possible prognostic factors in patients with AUGIB in a prospective setting. In addition to survival, predictors of re-bleeding and need of operation were also investigated which have rarely or never been studied in patients with AUGIB.

MATERIALS AND METHODS

Study design and patients: In this prospective study, all 182 consecutive patients with an initial diagnosis of AUGIB referred to emergency department in Imam Reza Hospital, Tabriz, Iran; were recruited from January 2011

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through the end of June 2011. Patients with AUGIB due to a previous surgery (n = 4) or endoscopic interventions (n = 2), as well as those with a positive history of recent anticoagulant use (n = 12) were excluded. This study was approved by the ethics committee of Tabriz University of Medical Sciences. Written consent was obtained from patients.

Procedures: Hemodynamically unstable patients were temporarily stabilized initially with serum therapy or transfusion of Packed Cells (PC) in emergency department. After thorough examination and taking past medical history, complete blood cell count, as well as determining of blood group, serum glucose, coagulation factors, renal and liver function tests and any other necessary laboratory test as per request of associated physician were performed. All the patients were endoscopically evaluated by a skilled physician.

Variables: Patients' age, sex, Age, presenting complains, amount of transfusion and past medical history including accompanying disease were documented. These variables were compared within hospital stay period between survived vs. expired, re-bled vs. non re-bled and operated vs. non operated cases. Orthostatic hypotension was defined as a systolic blood pressure decrease of at least 20 mmHg or a diastolic blood pressure decrease of at least 10 mmHg and/or increased pulse rate more than 15 beat /min within 3 min after standing up (Braunwald *et al*., 2005). Major hemorrhage was considered when a systolic blood pressure lower than 100 mmHg and/or orthostatic change were present (Klenzak *et al*., 1996). All other terminologies such as AUGIB, re-bleeding, hematemesis, melena, hematochezia, etc. were defined according to the criteria of American Society of Gastrointestinal Endoscopists (ASGE) (Silverstein *et al*., 1981). All patients with severe hemorrhage and/or probable esophageal varices were evaluated endoscopically within 5 h after stabilization and the remaining within 24 h post-admission. Management and treatment of patients was in accordance with accepted guidelines (Braunwald *et al*., 2005).

Statistical analysis: Data were analyzed using the SPSS statistical software package (version 15.0; SPSS Inc, Chicago). The Chi square or Fisher's exact test were employed when appropriate for qualitative data. For quantitative data the Independent samples t-test was used. The logistic regression test was used for multivariate analysis. p-value≤0.05 was considered statistically significant.

RESULTS

One hundred sixty four patients with AUGIB, 117 males and 47 females with the mean age of 57.12±17.32 (range: 32-78) years were studied. At presentation there were 138 patients with hematemesis, 110 with melena, 16 with hematochezia, 70 with hematocrit level less than 30% and 51 with major hemorrhage (i.e. presence of hypotension, n = 35 and/or orthostatic change, n = 19). Previous accompanying medical conditions were ischemic heart disease (44 patients), hepatic disease (27 patients), neurological disease (24 patients), DM (22 patients), HTN (15 patients), pulmonary disease (6 patients), renal disease (6 patients) and malignancy (8 patients). Transfusion over 2 U of packed red blood cell was indicated in 78 patients. In 35 patients endoscopic treatment was tried, leading to stop of bleeding in 8 patients. Remaining 27 patients underwent open surgery. As a result, 19 patients expired after surgery. Conservative treatments were employed for other 129 cases. Nineteen patients re-bled during hospital stay (Table 1).

Comparing different variables between survived and expired patients showed comparable results in term of age of patients (>60 year), blood transfusion (>2U), hematochezia, level of hematocrit (<30%) and previous diseases except for neurological abnormalities. On the other hand, percentage of female cases (67.9 vs. 14.8%, p = 0.003), with hematemesis (100 vs. 82.1%, p<0.001), major hemorrhage (68.4 vs. 26.2%, p<0.001) and neurological disease (31.6 vs. 12.4%, p = 0.04)

Table 1: Characteristics and general data of the studied population with acute upper gastrointestinal bleeding

Variables	Characteristics	No (%)
Age (year)	≤60	77 (47)
	60 <	87(53)
Gender	Male	117(71.3)
	Female	47(28.7)
Findings at presentation	Hematemesis	138(84.1)
	Melena	110(67.1)
	Hematochezia	16(9.8)
	Hematocrit < 30%	70(43.7)
	Major hemorrhage*	51(31.1)
	Hypotension	35(21.3)
	Orthostatic changes	19(11.6)
Accompanying disease	Ischemic heart disease	44(26.8)
	Hepatic disease	27(16.5)
	Neurological disease	24(14.6)
	Diabetes mellitus	22(13.4)
	Hypertension	15(9.1)
	Pulmonary disease	6(3.7)
	Renal disease	6(3.7)
	Malignancies	8(4.9)
Need of transfusion (>2U)		78(46.7)
Treatment	Endoscopic approach only	8(4.9)
	Endoscopic approach and open surgery	27(16.4)
	Conservative measures	129(78.7)
Mortality		19(11.6)
Re-bleeding		49(29.9)

*Systolic blood pressure <100 mmHg and/or orthostatic changes

Table 2: Comparing variables between survived and expired patients with acute upper gastrointestinal bleeding

Variables	Survived (n = 145)	Expired (n = 19)	p-value *	p-value**
Age (>60 years)	66(4.5)	11(57.9)	0.22	-
Gender (Male)	109(75.2)	8(42.1)	*0.003*	0.51
Blood transfusion (>2U)	67(46.2)	11(57.9)	0.34	-
Hematemesis	119(82.1)	19(100)	0.04	<0.001
Melena	101(69.7)	9(47.4)	0.06	-
Hematochezia	14(9.7)	2(10.5)	0.99	-
Hematocrit (<30%)	60(41.4)	10(52.6)	0.35	-
Major hemorrhage	38(26.2)	13(68.4)	<0.001	0.38
Previous ischemic heart disease	37(25.5)	7(36.8)	0.30	-
Previous hepatic disease	21(14.5)	6(31.6)	0.09	-
Previous neurological disease	18(12.4)	6(31.6)	0.04	0.45
Previous diabetes mellitus	18(12.4)	4(21.1)	0.29	-
Previous hypertension	15(10.3)	0(0)	0.22	-
Previous pulmonary disease	6(4.1)	0(0)	0.98	-
Previous renal disease	5(3.4)	1(5.3)	0.53	-
Previous malignancy	6(4.1)	2(10.5)	0.23	-

Data presented as frequency (percentage), *Univariate analysis, **Multivariate analysis, p≤0.05 is statistically significant

Table 3: Comparing variables between patients with and without acute upper gastrointestinal re-bleeding

Variables	Without re-bleeding (n = 119)	With re-bleeding (n = 49)	p-value*	p-value**
Age (>60 years)	50(42)	27(55.1)	0.11	-
Gender (Male)	86(72.3)	31(63.3)	0.12	-
Blood transfusion (>2U)	43(36.1)	35(71.4)	<0.001	0.006
Hematemesis	91(76.5)	47(95.9)	0.007	0.03
Melena	78(65.5)	32(65.3)	0.75	-
Hematochezia	10(8.4)	6(12.2)	0.57	-
Hematocrit (<30%)	42(35.5)	28(57.1)	0.02	0.09
Major hemorrhage	23(19.3)	28(57.1)	<0.001	0.12
Previous ischemic heart disease	30(25.2)	14(28.6)	0.74	-
Previous hepatic disease	13(10.9)	14(28.6)	0.006	0.19
Previous neurological disease	14(11.8)	10(20.4)	0.17	-
Previous diabetes mellitus	16(13.4)	6(12.2)	0.77	-
Previous hypertension	14(11.8)	1(2)	0.04	0.43
Previous pulmonary disease	3(2.5)	3(6.1)	0.37	-
Previous renal disease	4(3.4)	2(4.1)	0.99	-
Previous malignancy	5(4.2)	3(6.1)	0.70	-

Data presented as frequency (percentage), *Univariate analysis, **Multivariate analysis, p≤0.05 is statistically significant

was significantly higher in expired patients comparing with survived ones. In multivariate analysis, however, only hematemesis was an independent risk factor of mortality in patients with AUGIB (p<0.001) (Table 2).

In comparing studied variables including age (>60 year), gender, presence of melena and hematochezia and previous medical conditions except for hepatic disease and HTN, patients with and without re-bleeding after treatment were statistically comparable. However, frequency of patients who received blood transfusion more than 2U (71.4 vs. 36.1%, p<0.001), those with hematemesis (95.9 vs. 76.5%, p = 0.007), decreased level of hematocrit below 30% (57.1 vs. 35.5%, p = 0.02) and major hemorrhage (57.15 vs. 19.3%, p<0.001) and with previous history of hepatic disease (28.6 vs. 10.9%, p = 0.006) and normal blood pressure (98% vs. 91.2%, p = 0.04) was significantly higher in re-bled case than those who did not re-bleed. Comparing the significantly different variables in multivariate analysis revealed that only higher blood transfusion (>2U) and presenting with hematemesis were the independent predictors of re-bleeding in patients with AUGIB (p = 0.006 and 0.03, respectively) (Table 3).

Table 4: Comparing variables between operated and nonoperated patients with acute upper gastrointestinal bleeding

Variables	Nonoperated (n = 156)	Operated (n = 8)	p-value
Age (>60 years)	75(48.1)	2(25)	0.28
Gender (Male)	110(70.5)	7(87.5)	0.44
Blood transfusion (>2U)	73(46.8)	5(62.5)	0.48
Hematemesis	131(84)	7(87.5)	0.98
Melena	105(67.3)	5(62.5)	0.72
Hematochezia	15(9.6)	1(12.5)	0.57
Hematocrit (<30%)	64(41)	6(75)	0.07
Major hemorrhage	47(30.1)	4(50)	0.26
Previous ischemic heart disease	42(26.9)	2(25)	0.98
Previous hepatic disease	26(16.7)	1(12.5)	0.55
Previous neurological disease	23(14.7)	1(12.5)	0.99
Previous diabetes mellitus	21(13.5)	1(12.5)	0.99
Previous hypertension	15(9.6)	0(0)	0.98
Previous pulmonary disease	5(3.2)	1(12.5)	0.26
Previous renal disease	5(3.2)	1(12.5)	0.26
Previous malignancy	8(5.1)	0(0)	0.98

Data presented as frequency (percentage), p≤0.05 is statistically significant

When the studied variables were compared between operated and nonoperated patients, no differenced received a statistically significant level even in univariate analysis (Table 4).

DISCUSSION

In the present study, two independent predictors of re-bleeding were identified in patients with AUGIB including need of transfusion greater than 2 units and hematemesis as a presenting complain. This is in line with previous reports indicating that the need of higher load of transfusion is usually a sign of more mischievous upper gastrointestinal hemorrhage (Zaragoza Marcet *et al*., 2002; Terdiman and Ostroff, 1997). However, it is quantified in our study; i.e., >2 unit of packed red blood cell may predict a poor outcome in terms of retreatment requirement. Zaragoza Marcet *et al*. (2002) concluded that initial extensive hemorrhage may be sign of re-bleeding in patients with AUGIB. This could be considered equal to hematemesis at presentation which was also an independent predictor of re-bleeding in our patients. Other parameters such as a decreased hematocrit, presence of major hemorrhage and a previous history of

hepatic and neurological diseases were only significant predictors of re-bleeding in univariate analysis. These findings were confirmed in other studies, as well (Adamopoulos *et al*., 2003; Arora *et al*., 2002; Blatchford *et al*., 2000; Al-Akeely *et al*., 2004; Zuckerman, 2000). In the current study, presence of hematemesis at admission was the sole independent risk factor for in-hospital mortality in patients with AUGIB; whereas female gender, major hemorrhage and previous renal disease were just dependent predictors of poor outcome. In agreement with our result, Mavares *et al*. (1993) also found that patients with AUGIB and initial hematemesis, poor outcome is more expected than those without hematemesis on presentation. This finding might be justified by this fact that hematemesis is a sign of massive hemorrhage in AUGIB. In the present study, major hemorrhage was incorporated into model as a systolic blood pressure lower than 100 mmHg and/or presence of orthostatic change (Klenzak *et al*., 1996). This approach takes both factors in to account as a single parameter and hence, possibility of type II error would be declined. Indeed, this error is a major limitation of many previous reports which investigated possible predictors of outcome in patients with AUGIB. There was no significant difference between operated and nonoperated patients with regard to the studied variables in present study. To the best of our knowledge, there is no similar report in the literature. Low number of operated cases could be regarded as a limitation of our study. So, further studies with larger sample size could further elucidate the issue. We acknowledge short follow-up of patients. However, it should be born in mind that in-hospital prognosis constitutes a very important share of debates on patients with AUGIB. This was appropriately covered in this prospective, methodologically fitted survey.

CONCLUSION

Initial hematemesis and need of transfusion >2U are two important and independent predictors of poor outcome in short-term in patients with AUGIB. As the booth factors could readily be documented at the time of admission, they could be considered as simple and handy indicators to identify high risk patients.

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