Mortality Risk Factors in Acute Upper Gastrointestinal Bleeding

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ABSTRACT

Background: *Upper gastrointestinal bleeding (UGIB) is one of the emergency cases in gastroenterology. The mortality rate does not change in the last 4 decades, however, there is no precise data in Cipto Mangunkusumo Hospital. Identified risk factors are expected to increase early awareness and optimal planning in management of patients. This study was aimed to know the mortality risk factors in acute UGIB in Cipto Mangunkusumo Hospital.*

Method: *Case control study was performed between August and December 2011 by collecting and studying medical records of acute UGIB patients who were admitted and hospitalized between January 2003 and June 2011 in Cipto Mangunkusumo Hospital. Cases were acute UGIB patients who passed away during hospitalization in that period of time. Controls were patients who did not pass away and hospitalize in same period (date/month/year index). Samples were taken randomly with the proportion of case and control 1 : 2. Bivariate analysis was perfomed by chi-square test and continued with multivariate analysis.*

Results: *Study subjects consisted of 87 cases and 174 controls. Significant variables as risk factors were multiple comorbidities (OR = 2.66; 95% CI = 1.21-5.85), recurrent bleeding (OR = 9.07; 95% CI = 3.87-21.26), decreased consciousness (OR = 7.60; 95% CI = 1.94-29.88), endoscopy not performed (OR = 11.95; 95% CI = 4.75-30.11), and sepsis (OR = 4.83; 95% CI = 2.03-11.48).*

Conclusion: *Multiple co-morbidities, sepsis, decreased consciousness on hospital admission, and recurrent bleeding are mortality risk factors in acute UGIB. Mortality risk increases in patients, to whom endoscopy was not performed.*

Keywords: *UGI bleeding, risk factors, mortality*

ABSTRAK

Latar belakang: *Perdarahan saluran cerna bagian atas (SCBA) merupakan salah satu kegawatan di bidang gastroenterologi. Mortalitasnya tidak berubah dalam 4 dekade terakhir. Namun hingga saat ini di Rumah Sakit Cipto Mangunkusumo (RSCM) belum terdapat data yang pasti. Faktor risiko yang teridentifikasi diharapkan dapat meningkatkan kewaspadaan dini dan perencanaan optimal dalam tatalaksana pasien. Penelitian ini bertujuan untuk mengetahui faktor risiko kematian perdarahan akut SCBA di RSCM.*

Metode: *Penelitian kasus kontrol dilakukan pada bulan Agustus-Desember 2011 dengan mengumpulkan dan mempelajari catatan medik pasien yang mengalami perdarahan akut SCBA yang masuk dan dirawat pada periode Januari 2003-Juni 2011 di RSCM. Kasus adalah pasien dengan perdarahan akut SCBA yang meninggal saat dirawat. Kontrol adalah pasien yang tidak meninggal dan dirawat bersamaan dengan kasus (indeks tanggal/bulan/tahun), sampel diambil secara acak dengan perbandingan kasus dan kontrol sebesar 1 : 2. Analisis dilakukan secara bivariat dengan uji kai kuadrat dan dilanjutkan dengan uji multivariat.*

Hasil: *Subyek penelitian terdiri dari 87 kasus dan 174 kontrol. Variabel yang bermakna sebagai faktor risiko adalah komorbid multipel (OR = 2,66; IK 95% = 1,21-5,85), perdarahan berulang (OR = 9,07; IK 95% = 3,87-21,26), penurunan kesadaran (OR = 7,60; IK 95% = 1,94-29,88), tidak dilakukan endoskopi (OR = 11,95; IK 95% = 4,75-30,11), dan sepsis (OR = 4,83; IK 95% = 2,03–11,48).*

Simpulan: *Komorbid multipel, sepsis, penurunan kesadaran saat masuk ke rumah sakit, dan perdarahan ulang merupakan faktor risiko kematian pada perdarahan akut SCBA. Risiko kematian meningkat pada pasien yang tidak dilakukan endoskopi.*

Kata kunci: *perdarahan SCBA, faktor risiko, kematian*

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is one of cases, which needs to be taken into concern in gastroenterology. In America, this incident occurs in 50-150 per 100,000 people/year.[1-3] Mortality rate due to UGIB varies between 4-14% in line with patient's condition and given management.[1-3] Generally, UGIB in 80% cases can stop by itself, but 10% cases need intervention procedure to control the bleeding.[4] Thus, UGIB should always be considered as life-threatening condition.

Based on previous studies, there were several mortality predictors in UGIB, such as age above 60 years, hypoalbumin, unstable hemodynamic/ shock, prolonged prothrombin time, co-morbidity, adjusted blood requirement index (ABRI), aspirated blood in nasogastric tube, sepsis, consciousness state, increased blood urea nitrogen level, ongoing bleeding, bleeding in the hospital, recurrent bleeding, endoscopy stigma, and performed therapy, which all become consideration for the clinician in planning the management.[5-10]

Data on those factors as mortality risk factors in patients with UGIB in Indonesia is still unavailable. The most common etiology of UGIB in Indonesia is rupture of esophageal varices, while in foreign countries, it is due to peptic ulcer.[11] This different characteristic encourage to perform further studies in order to obtain mortality risk factors in UGIB in accordance with characteristic of population in Indonesia. This study was expected that UGIB mortality risk factors in hospitalized patients in Cipto Mangunkusumo Hospital would be identified, and thus, it was expected to increase early awareness and optimal planning in management of patients.

METHOD

A case control study was performed between August and December 2011 by collecting and analyzing medical records of acute UGIB patients hospitalized in January 2003 till June 2011 in Cipto Mangunkusumo Hospital, Jakarta. Inclusion criteria in this study were acute upper UGIB patients aged ≥ 18 years old and received standard empirical therapy and appropriate resuscitation procedure. Exclusion criteria in this study were patients discharged on their own will, incomplete risk factors data, and did not receive blood transfusion as indicated. Cases were acute UGIB patients who passed away during hospitalization in Cipto Mangunkusumo Hospital during that period of time. Controls were acute UGIB patients who did not passed away and still hospitalized in same period (date/month/year/date index). Controls were randomly taken as many as 2 people of acute UGIB patients who did not pass away.

Independent variable in this study are elderly, shock, multiple co-morbidities, need of transfusion, sepsis, decreased consciousness, hypoalbumin, increased prothrombin time, ABRI, repeated bleeding, and unperformed endoscopy. Dependent variable is mortality. Sample size in this study was 261 subjects, consisted of 87 subjects as cases and 174 subjects as controls and the ratio of case and control was 1 : 2. Obtained data was analyzed with SPSS computer software version 16.0. Further, chi-square test was used for bivariate and multivariate analysis. In case of $p < 0.025$ from bivariate analysis, multivariate analysis would further be conducted. This study has received ethical clearance from Ethical Research Committee in Medical Faculty University of Indonesia.

RESULTS

Subjects were mostly males, with the total of 171 (65.5%) patients, age group < 60 years was the most age group. Basic characteristics of patients are shown in Table 1. Table 2 reveals co-morbid conditions and mortality characteristics in patients, who looked well in case or control group with high proportion of acute kidney injury. While, bleeding manifestation many experienced by patients, both in case and control group was melena (Table 3).

Table 1. Basic characteristics of patients

Characteristic	Case n (%)	Control n (%)
Sex		
Male	55 (63.2)	116 (66.7)
Female	32 (36.8)	58 (33.3)
Age (years)		
≥ 60	23 (26.4)	58 (33.3)
< 60	64 (73.6)	116 (66.7)
History of drug use		
NSAID	9 (10.3)	23 (13.2)
Anticoagulant	1 (1.1)	1 (0.6)
Traditional herbs	17 (19.5)	34 (19.5)
Anti-aggresion	1 (1.1)	2 (1.1)
Steroid drug	3 (3.4)	4 (2.3)
Aspirin	4 (4.6)	4 (2.3)
Behavior		
Smoking	13 (14.9)	15 (8.6)
Alcohol consumption	10 (11.5)	18 (10.3)
Residence		
Jakarta	66 (75.9)	130 (74.7)
Others	21 (24.1)	44 (25.3)

NSAID: non-steroidal anti-inflammatory drug

Table 2. Characteristics of co-morbid conditions and mortality in patients

Characteristic	Case n (%)	Control n (%)
Unstable hemodynamic/shock	15 (17.2)	16 (9.2)
Decreased consciousness	21 (24.1)	5 (2.9)
Sepsis	40 (46)	5 (8.6)
Co-morbid conditions		
Pneumonia	51 (58.6)	34 (19.5)
CKD	31 (35.6)	27 (15.5)
Ashtma	2 (2.3)	39 (22.4)
Hypertension	18 (20.7)	39 (22.4)
Chronic liver disease		
Hepatitis B	4 (4.6)	25 (14.4)
Hepatitis C	4 (4.6)	29 (16.7)
Unknown	31 (35.6)	10 (5.7)
No data	48 (55.2)	110 (63.2)
AKI	65 (75.6)	157 (90.2)
Number of co-morbidities		
0	0 (0)	28 (17)
1	11 (12.6)	34 (21)
2	14 (16.1)	46 (28)
3	62 (71.3)	56 (34)
Onset to death (day)		
1-3	25 (28.7)	
> 3-7	30 (34.5)	
> 7	32 (36.8)	
Cause of death		
Septic shock	60 (69)	
Other	17 (19.5)	
Respiratory failure	10 (11.5)	

CKD: chronic kidney disease; AKI: acute kidney injury

Based on the type of therapy given, in the case group only 12.6% patients received diagnostic endoscopy and 3.4% patients received endoscopic therapy (Table 4). While, laboratory results in patients are shown in Table 5.

Table 3. Characteristics of bleeding manifestations in patients

Characteristic	Case	Control
	n (%)	n (%)
Onset of bleeding (day)		
≤ 1	43 (49.4)	89 (51.1)
> 1-3	23 (26.4)	41 (23.6)
> 3	21 (24.1)	44 (25.3)
Bleeding hystory (times)		
None	64 (75.3)	109 (62.6)
< 2	15 (17.6)	39 (22.4)
≥ 2	6 (7.1)	26 (15.0)
Bleeding manifestation		
Melena	42 (48.3)	93 (53.4)
Hematemesis	17 (19.5)	42 (24.2)
Hematemesis melena	28 (32.2)	39 (22.4)
Nasogastric aspirate	24 (27.6)	45 (25.9)
Recurrent bleeding	43 (49.4)	24 (13.8)

Table 4. Type of therapy administered to patients

Type of therapy	Case	Control
	n (%)	n (%)
Medicamentosa	87(100)	174 (100)
PPI	81(93.1)	169 (97.1)
H2A	8 (9.2)	13 (7.5)
PPI and H2A	5 (5.7)	9 (5.2)
Endoscopic therapy	3 (3.4)	50 (28.7)
Antibiotic	86 (98.9)	131 (75.3)
Diagnostic endoscopy	11(12.6)	111 (63.8)
Surgery	5 (5.7)	2 (1.1)
ABRI > 0.75	12 (13.8)	23 (13.3)
Amount of transfusion in 7 days* (cc)	500 (0-2,000)	509 (0-1,452)
Amount of transfusion* (cc)	510 (0-4,600)	509 (0-2,484)

PPI: proton pump inhibitor; H2A: hystamine type 2 antagonist; ABRI: adjusted blood requirement index; * median (min-max)

Risk factor sub-analysis in the presence of endoscopy procedure was also performed in patients with age group ≥ 60 years and age < 60 years old. The results showed that patient, to whom endoscopy procedure was not performed, has significant difference against mortality incidence due to UGIB. However, patients who underwent endoscopy were mostly in the age group ≥ 60 years compared to patients in the age group < 60 years.

Bivariate analysis exhibited association of risk factors in patients who underwent endoscopy with mortality due to UGIB, particularly OR = 12.17 (95% CI = 6.02–24.61; $p < 0.001$). Further multivariate analysis resulted in OR = 11.95 (95% CI = 4.75-30.11; $p < 0.001$) (Table 6).

Table 5. Characteristics of laboratory results in patients

Laboratory results	Case	Control
	% (SD)	% (SD)
AST > 2 x N	30 (34.5)	34 (19.5)
ALT > 2 x N	49 (56.3)	43 (24.7)
PT/C > 1.5 x C (second)	24 (27.6)	23 (13.2)
APTT/C > 1.5 x C (second)	24 (27.6)	23 (13.2)
Hypoalbumin < 3.5 (g/dL)	76 (87.4)	130 (74.7)
Initial hemoglobin# (g/L)	8.7 ± 3.6	8.5 ± 3.5
Final hemoglobin#(g/L)	9.4 ± 2.41	10.88 ± 1.47
Initial hematocrite# (%)	25.36 ± 9.3	25.51 ± 10.5
Final hematocrite# (%)	28.37 ± 7.07	32.49 ± 4.10
Albumin# (g/dL)	2.62 ± 0.64	3.05 ± 0.58
Prothrombine time# (second)	19.02 ± 12.6	15.71 ± 9.57
Leukocyte* (/uL)	11,400 (1,159-250,000)	9,200 (400-83,000)
Thrombocyte* (10^3/uL)	220,000 (327-854,000)	192,000 (3,500-849,000)
Ureum* (mg/dL)	69 (12-840)	40 (9-316)
Creatinin* (mg/dL)	1.3 (0.30-41.8)	1.0 (0.3-28.8)
AST* (U/L)	63 (8-1,627)	36.50 (5-644)
ALT* (U/L)	34 (6-902)	26.50 (3-944)
APTT* (second)	40 (23-180)	34.80 (12-590)

AST: aspartate transaminase; ALT: alanine aminotransferase; PT: prothrombin time; APTT: activated partial throboplastin time; C: control; AST/ALT > 2 x N: number of samples have AST level more 2 x than normal; #mean ± SD; *abnormal distribution was showed in SD (maximum-minimum)

Table 6. Results of bivariate and multivariate mortality risk factors in patients

Risk factor	Death (%)	Alive (%)	OR* (CI 95%)	OR# (CI 95%)
Age ≥ 60 year	23 (26.4)	58 (33.3)	0.72 (0.40–1.27)	
Unstable hemodynamic	15 (17.2)	16 (9.2)	1.38 (0.94–2.02)	
Multiple comorbidities ≥ 3**	62 (71.3)	56 (38.4)	3.98 (2.25–7.06)	2.66 (1.21-5.85)
ABRI > 0.75	12 (13.8)	23 (13.2)	1.05 (0.49-2.26)	
Sepsis**	40 (46)	15 (8.6)	9.02 (4.58–17.75)	4.83 (2.03-11.47)
Decreased consciousness**	21 (24.1)	5 (2.9)	10.69 (3.87–29.53)	7.60 (1.93-29.88)
Hypoalbumin	76 (87.4)	130 (74.7)	2.33 (1.14–4.79)	
PT ≥ 1.5 x C	24 (27.6)	23 (13.2)	2.50 (1.31–4.75)	
Recurrent bleeding**	43 (49.4)	24 (13.8)	6.10 (3.34–11.15)	9.07 (3.87-21.26)
Not performed endoscopy**	76 (87.4)	63 (36.2)	12.17 (6,02–24,61)	11.95 (4.74-30.10)

ABRI: adjusted blood requirement index; PT: prothrombin time; C: control; NA: not applicable; *bivariate analysis; **p < 0.025; #: multivariate analysis

DISCUSSION

There are some differences in the results of this study compared to previous studies. The mortality rate obtained in this study was 23-35%, which was higher compared to the previous study, 10-14%.[1-3] This was because the data included mortality in patients with UGIB on hospital admission and mortality due to UGIB occurred during hospitalization. Additionally, most of the study samples were less than 60 years of age. This is different compared to other countries, in which samples were mostly above 60 years old.[5,6] Other characteristic difference which also need to be stressed on was sepsis condition, which was more likely to be found in this study samples compared to samples in the study performed by Zimmerman et al.[12]

Other difference included increase of mortality risk as the age was older. Different with the study by Rockall et al, it was found that there was 2.34 times increase in the age of 60-79 years and increase 4.43 times in patients above 80 years old.[13] Bivariate analysis in the age variable ≥ 60 years old showed OR = 0.72, which means that age variable ≥ 60 years old has protective effect. However, results of 95% CI = 0.4-1.27; p = 0.25 showed that result was not statistically significant. Further analysis on risk factor difference in both age groups, was only one risk factor, endoscopy

procedure not performed, which revealed significant difference. In this study, the proportion of group aged ≥ 60 who underwent endoscopy examination was more compared to the group aged < 60 years. This might give the possible explanation on why elderly aged ≥ 60 years group had protective effect. Bleeding etiology can be found through endoscopy examination, so that endoscopy therapy and management according to the diagnosis can be performed. Furthermore, patients aged ≥ 60 years old received more specific attention from Division of Geriatric Department of Internal Medicine in Cipto Mangunkusumo Hospital, such as specific ward, phycisians, and paramedics, so the anticipation and management given would be better. However, to prove this further study need to be performed.

In the study by Rockall et al, risk factor of unstable hemodynamic condition is a significant risk factor for UGIB mortality, different with this study. This could be due to this condition was fewer in this study sample than in the study by Rockall et al, with 80.1% samples experienced unstable hemodynamic.[13]

Studies performed by Salimi et al and Kollef et al stated that increase of prothrombin time was one of the mortality predictors in gastrointestinal bleeding.[14,15] In this study, increase of PT/control > 1.5 x control only occurred in 18% of all study sample; this result was lower compared to the study conducted by Salimi et al.[14] In the bivariate analysis of this study, there was association between increase of prothrombin time and mortality, but multivariate analysis revealed no association. Results of block system multivariate analysis showed that decrease OR more than 10% occurred after adding recurrent bleeding variable. Thus, this variable was influenced by recurrent bleeding variable to cause mortality. Increase of prothrombin time need to be evaluated in association with liver disease co-morbidity in the study subjects. However, in this study, the proportion of hepatitis B and C was < 5% in case group and the diagnosis of cirrhosis was only 1% in the control group. This data need to be evaluated because in the control group, appearance of esophageal varices was found in 25.5% subjects. This disagreement may happen due to limited data in the medical records.

Hypoalbumin < 3.5 g/dL which is most frequently associated with several accompanying co-morbidities, particularly liver disease apparently does not play role in mortality risk factors in UGIB. However, if the cut off value of hypoalbumin is lowered to below 2.5 g/dL, the value was statistically significant, as obtained in the result of the study by Thomas et al.[6]

The characteristic of patients in this study since the beginning was thought to have varices as the cause of UGIB. Based on this, this study tried to evaluate the ABRI index. Apparently, bivariate analysis results showed there was no association between ABRI value > 0.75 and mortality. This is different with prospective study conducted by Naheed et al and Zuberi et al, who evaluated mortality risk in UGIB caused by varices.[16,17]

In this study, most of the sample in case group did not undergo endoscopy examination and endoscopy therapy. Reasons for not conducting endoscopy, included patients' bad condition, patients' family refuse the examination procedure, lack of funds, and unavailable examination schedule. Therefore, endoscopy diagnosis was unknown and patients did not receive appropriate intervention therapy. This was different with the studies by Rockall et al or Salimi et al, in which all study subjects underwent endoscopy examination.[13,14] Hence, risk factors of stigmata endoscopy, in which were stated in the literature to play role as mortality predictor, could not be analyzed due to incomplete data in the medical record.[18]

The strength of this study was on the different characteristic of samples compared to the previous studies, also founding of the service condition which had not completely in accordance with the guidelines.[19] Different risk factors compared to the previous studies, which were higher sepsis incidence, elderly, also hypoalbumin cut-off value need to be noted in treating acute UGIB in Cipto Mangunkusumo Hospital. This result can be used to evaluate operating procedures in Cipto Mangunkusumo Hospital, therefore in future we can use as base to anticipate mortality risk and increase service quality.

CONCLUSION

Significant mortality risk factors in UGIB include multiple co-morbidities, sepsis, decrease consciousness, and recurrent bleeding on hospital admission. While, elderly, increase prothrombin time, hypoalbumin, unstable hemodynamic during hospital admission, and ABRI were not proven as mortality risk factors. Mortality risk factors also increased if endoscopy was not conducted.

SUGGESTION

Significant risk factors need to be considered in taking decisions in management of patient with acute UGIB. Endoscopy procedure in acute UGIB need to

be performed in order to know the etiology of bleeding and further managed with endoscopy therapy. Results of this study could be used as the base for better study in evaluating the strength of association in the variable of acute UGIB mortality risk, which is in accordance with characteristic of Indonesian population.

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