American Journal of Emergency Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

The usefulness of the percentage of immature granulocytes in predicting in-hospital mortality in patients with upper gastrointestinal bleeding

Hüseyin Narcı [a,*], Mustafa Berkeşoğlu [b], Enver Üçbilek [c], Cüneyt Ayrık [a]

[a] Mersin University, Faculty of Medicine, Department of Emergency Medicine, Mersin, Turkey
[b] Mersin University, Faculty of Medicine, Department of General Surgery, Mersin, Turkey
[c] Associate professor, Mersin University, Faculty of Medicine, Department of Gastroenterology, Mersin, Turkey

ARTICLE INFO

Article history:
Received 13 October 2020
Accepted 13 December 2020
Available online xxxx

Keywords:
Immature granulocytes
Upper gastrointestinal bleeding
Mortality

ABSTRACT

Background: Upper gastrointestinal bleeding (UGIB) is an important health problem with a potentially life threatening course. Measurement of immature granulocytes percentage (IG %), reflecting the fraction of circulating immature granulocyte (IG), is associated with increased mortality in patients with systemic inflammation, or distress. The aim of this study was to evaluate whether the IG% is an effective predictive marker for estimating the in-hospital mortality for patients with UGIB admitting to the emergency department (ED).
Method: This retrospective study included patients with UGIB who admitted to the ED, between 01.01.2019 and 31.12.2019. The patients were divided into two groups as discharged and dead. The IG% and other parameters were recorded. The primary end point of the study was in-hospital mortality. Logistic regression model was used to determine the factors affecting mortality.
Results: This study included 149 patients, 94 of whom were men. The mean age of the patients was 64.5 ± 14.2. Twenty patients died during hospitalization and 129 were discharged. IG% was significantly higher in patients who died compared with patients who discharged. In the receiver operating characteristic (ROC) curves analysis to determine the in-hospital mortality, the cut-off value (>1%) for IG% level was found specificity (93.8%), sensitivity (100%), positive predictive value (PPV = 71.43%), negative predictive value (NPV = 100.00%) and area under curve (AUC = 0.98). Univariate logistic regression analysis showed that IG% was predicting in-hospital mortality (odds ratio, OR = 65.6, confidence interval, CI = 2.00–2152.6).
Conclusıons: High IG% levels may be used as a predictor of in-hospital mortality in patients with UGIB.

1. Introduction

Upper gastrointestinal bleeding (UGIB) is a common cause of emergency admissions, accounts for 36–172 of 100,000 people and has a mortality rate of up to 14% [1]. It is a serious, potentially life-threatening disease that causes approximately one million hospitalizations annually in the United States. Due to the high morbidity and mortality rates, physicians should evaluate and initiate the treatment of patients with UGIB as soon as possible [2]. Understanding the severity of disease may help predicting which patients will die. Various scoring systems are used to identify low and high risk patients in terms of mortality such as Glasgow-Blatchford score, Rockall Score and AIMS65 [3,4]. However, these scoring systems can be impractical and time-consuming to assess the patient in the emergency setting. In a nationwide study in the USA, only 30% of physicians were reported to be able to use risk scores in patients with UGIB [5]. Therefore, rapidly and easily available novel markers are needed to estimate the prognosis of patients with UGIB.

Immature granulocyte (IG) cells consist of promyelocyte, myelocyte, metamyelocyte, and are not found in peripheral blood under normal conditions except during pregnancy and newborn period [6]. They can be detected in the peripheral blood when the bone marrow is stimulated including the conditions bacterial infection, acute inflammatory diseases, surgical trauma, steroid use, and sepsis. The elevation of the immature granulocyte percentage (IG%) in the peripheral blood is directly related to the intensity of systemic inflammation [7]. Circulating hematopoietic progenitor cells may be also an early prognostic marker for mortality in patients presenting with traumatic hemorrhagic shock [8]. Delta neutrophil index (DNI) is another parameter derived from granulocyte count, reflects the fraction of IGs in circulation, and predicts 30-day mortality as an independent factor in patients with UGIB [9]. Measurement of IG% reflecting the fraction of circulating immature granulocytes, is associated with increased mortality in patients with systemic inflammation, or distress [6]. To the best of our knowledge, there are no published studies in the English literature on the prognostic significance of IGs in patients with UGIB.

* **Corresponding author at:** Department of Emergency Medicine, Mersin University, Faculty of Medicine, Mersin, Turkey.
E-mail address: hsnnarci@gmail.com (H. Narcı).

https://doi.org/10.1016/j.ajem.2020.12.039
0735-6757/

In this study, we aimed to investigate the efficacy of IG% in predicting in-hospital mortality in patients with UGIB admitted to the emergency department (ED).

2. Materials and method

2.1. Patients and study design

This retrospective study consisted of patients with UGIB admitting to ED of a university hospital, between 01.01.2019–31.12.2019. Our ED is a tertiary level emergency service and are approximately 100,000 visits annually. The study was approved by clinical research ethics committee (no:399/11, 2020). The data were obtained from the hospital electronic information system.

UGIB was defined as acute episode of hematemesis or melena in the 24 h prior to admission to the hospital. The inclusion criteria for the study were adult (>18 years-old) patients with UGIB who underwent an upper GI endoscopy. Exclusion criteria for the study were patients with any missing data, lower gastrointestinal bledding, current infection, immunodeficiency, hematological disorders, pregnant women, blood transfusion at another hospital, patients receiving chemotherapy and those receiving antibacterial therapy or vaccination within five days that could alter the levels of inflammatory markers. Of the 183 patients, 34 were excluded, and a total of 149 patients fulfilled the entry criteria and were selected for further analysis.

The patients were evaluated with regard to age, gender, symptoms (melena, hematemesis, hematochezia), comorbidity, length of hospital stay, blood pressure level, heart rate and laboratory results (leukocyte, platelet, immature granulocyte percentage (IG%), C-reactive protein (CRP), blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatinine. The patients were divided into two groups as discharged and died. All parameters were evaluated between groups. The primary end point of the study was in-hospital mortality.

2.2. Laboratory examination

Modern automated analyzers are available that can measure additional parameters, such as IG%. Blood samples for laboratory tests were collected within 2 h of admission. After blood samples were collected in the EDTA tube for the determination of leukocyte count, platelet count and IG%, measurements were performed on the automated blood cell analyzer (XN-1000, Sysmex Corp. Kobe, JAPAN). Reference values of parameters: Leukocyte (4500–11,000/mm^3), platelet (150000–400,000/mm^3), IG% (0–0.6%), AST (0–32 U/L), ALT (0–55 U/L), serum CRP (0–5 mg/L), BUN (15–50 mg/dL), creatinine (0.5–0.9 mg/dL).

2.3. Statistical analysis

In continuous variables, normality of distributions was tested with the Shapiro Wilk test. Mann Whitney *U* test was used to compare differences between two groups. Descriptive statistical data is given as minimum, maximum, median, and 25–75% percentages. Pearson chi-square and Likelihood Ratio chi-square tests were used for comparisons between the groups in categorical variables. Descriptive statistical data were stated as number (n) and percentage (%). ROC analysis was used to determine cut-off values of some parameters of discharged and died groups. Cut-off values, area under curve (AUC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were given as descriptive statistics. Binary logistic regression analysis was used to determine the risk factors causing death. Statistical significance value was taken as $p < 0.05$.

3. Results

A total of 149 patients, discharged ($n = 129$, 86.6%) and deaths ($n = 20$, 13.4%), were evaluated. The mean age of the patients was 64.5 ± 14.2. The mean age of the discharged patients was 64.1 ± 14.5, and the mean age of patients who death was 67.1 ± 12.1, and there was no statistically significant difference in terms of age ($p = 0.391$). Renal insufficiency (21.8%) was the most common comorbid condition among the patients. The most obvious symptoms of the patients were hematemesis (49.7%) and melena (43.0%). The endoscopic diagnosis in UGIB patients were peptic ulcus (71.8%), esophagogastric varice (21.7%), malignancy (4.4%) and dieulafoy lesion (2.01%) respectively (Dieulafoy lesion is a bleeding that develops as a result of the opening of a pulsatile arterial vessel from a mucosal tear area surrounded by normal mucosa) (Table 1).

When the laboratory parameters were evaluated among the patients who died and those who were discharged; IG% (1.95 vs. 0.5, $p < 0.001$), leukocyte (14,650 vs. 8580, $p < 0.001$), CRP (15.3 vs. 2.7, $p < 0.001$), INR (1.3 vs 1.04, $p = 004$), BUN (118.5 vs. 68.7, $p = 0.05$) and creatinine (1.52 vs 0.89, $p = 0.04$) values were higher in those who died. There was no statistically significant difference between the two groups in terms of hemoglobin, hematocrit and platelet values. The hospital stay was longer in the death group. In addition, systolic blood pressure was lower and heart rate was higher in the death group (Table 2).

In ROC analysis to determine in-hospital mortality; the cut-off value for IG% was determined as>1%, specificity (93.8%), sensitivity (100%), positive predictive value (71.43%) and negative predictive value (100%) (Table 3) (Fig. 1). The AUC values of IG%, CRP, leukocyte and BUN to predict in-hospital mortality were 0.98, 0.91, 0.77 and 0.69 respectively (Table 3).

IG% achieved the highest AUC, sensitivity, specificity PPV and NPV in predicting in- hospital mortality among parameters. There was significant difference comparing AUC values among IG% vs leucocyte ($Z = 3218$, $p = 0.001$), IG% vs BUN ($Z = 2876$, $p = 004$). There was no significant difference comparing AUC values between IG% and CRP ($Z = 1476$, $p = 140$). IG% was superior to leucocyte and BUN values.

When the risk factors affecting mortality are analyzed in the logistic regression analysis, the following parameters were associated with an increased in-hospital mortality; IG% (OR 65.6, CI 2.000–2152.59), leukocyte (OR1.0, CI 1.000–1.001), CRP (OR 1.7, CI 1.007–3.094) and BUN (OR 0.9, CI 2.000–2152.59) (Table 4).

Table 1
Demographic and clinical characteristics of the patients

Patient characteristics	Variables	n (%)
Gender	Male	94(63.1)
	Female	55(36.9)
Symptoms	Hematemesis	74(49.7)
	Melena	64(43.0)
	Hematochezia	11(7.4)
Causes of Bleeding	Peptic ulcus	107(71.8)
	Esophagogastric varice	32(21.7)
	Malignancy	7(4.4)
	Dieulafoy Lesion	3(2.01)
Comorbidity	Diabetes mellitus	45(19.6%)
	Renal failure	50(21.8%)
	Congestive heart failure	12(5.2%)
	Cerebrovascular Disease	8(3.4%)
	Atherosclerotic heart disease	21(9.1%)
	Hypertension	42(18.3%)
	Chronic liver disease	32(13.9%)
	Malignancy	19(8.2%)
Endoscopic treatment	Band ligation	17(41.4%)
	Sclerotherapy	19(46.3%)
	Epinephrine injection	3 (7.3%)
	Others	2 (4.8%)

Table 2
Comparison of laboratory values between patients who discharged from hospital and died at hospital

Parameters	Discharged(n = 129)	Dead(n = 20)	p
Age (years ±SD)	64.1 ± 14.5	67.1 ± 12.1	0.391
Leukocyte /μL	8580 (6130–12,355)	14,650 (10,507.5–18,497.5)	<0.001*
IG%	0.5 (0.1-0.6)	1.95(1.1–4.7)	<0.001*
Hemoglobin (g/dL)	8.8 (6.7–16.7)	8.7 (5.6–12.6)	0.334
Hematocrit (%)	26 (11–49)	27 (17–35)	0.309
Platelet count (/μL)	195,000 (13000–581,000)	220,000 (27000–338,000)	0.652
BUN(mg/dL)	68.7 (14.4–222.4)	118.5 (24–310)	0.005*
Creatinine (mg/dL)	0.89 (0.13–7.43)	1.52 (0.49–8.71)	0.004*
AST (U/L)	22 (4–240)	41.5 (5–462)	0.001*
ALT (U/L)	18 (3–249)	27.5 (3—200)	0.023*
INR	1.04 (0.76-5,34)	1.3 (0.9–5.61)	0.004*
CRP (mg/dL)	2.7(0.2–23)	15.3 (3–56)	<0.001*
SBP, mmHg	110 (70–167)	100 (80–136)	0.012*
DBP, mmHg	65 (32–105)	64 (31–84)	0.359
Heart rate, beats/min	84 (43–139)	100 (55–141)	<0.001*
LHS,days	3 (1—10)	6 (1–19)	<0.001*

DBP: Diastolic blood pressure, SBP: Systolic blood pressure, ALT: Alanine transaminase, AST: Aspartate transaminase, BUN = blood urea nitrogen, INR, international normalized ratio; LHS: Length of stay.
* $p < 0.05$ was considered statistically significant.

4. Discussion

We found that IG% was a strong predictor of in-hospital mortality in patients with acute UGIB admitted to the ED. Leukocyte, IG%, CRP, BUN, creatinine, and INR values were found higher in patients who died. AUC, specificity, and sensitivity of IG% were found to be significantly higher in determining in-hospital mortality in patients with UGIB. The comparison of AUC values of IG% was similar to CRP, whereas it was superior to leukocyte and BUN.

UGIB is one of the most common gastrointestinal emergencies. It is critical to recognize and manage the life-threatening cases. Studies on some parameters that are thought to be effective in determining prognosis in patients with UGIB are still ongoing. Some laboratory parameters are measured in patients with UGIB, may present some clues about the disease. In patients with UGIB, an initial lower hemoglobin value (less than 10 g/dL) has been associated with higher mortality rates. Lactate levels may help predict in-hospital mortality in patients with UGIB. The importance of BUN level has been known for a long time in patients with UGIB [10,11]. Kong et al. reported that leukocyte value was higher in patients who died due to UGIB [9]. In another study, high CRP levels in esophageal variceal hemorrhage patients without infection have been shown to be the predictor of mortality [12]. As seen in the studies mentioned above, a large number of biomarkers can guide the clinician about the severity of disease. The search for more accurate and novel biomarkers and new studies are ongoing to predict the prognosis. Recently, IGs have taken its place among these new biomarkers.

IG% is a parameter that is not well understood and partially neglected by physicians. This parameter can be measured inexpensively and quickly in the routine blood count. Recently, there are studies on IG % in the diagnosis and prognosis of diseases such as acute pancreatitis, acute appendicitis and sepsis [6,13,14,15]. However, there is only one study on the DNI that reflects the fraction of circulating immature granulocytes. Kong et al. reported that the elevation in DNI predicted 30-day mortality independently in patients with UGIB [9]. Park et al. reported that DNI has a prognostic effect for mortality in septic patients.

Table 3
Performance characteristics of laboratory parameters in determining in-hospital mortality

Variables	Cut-off	AUC (p)	Sensitivity	Specificity	PPV	NPV
IG%	>1	0.981 (0.0001)*	100.00 (83.01–100.00)	93.80 (88.14–97.28)	71.43 (51.33–86.74)	100.00 (96.97–100.00)
Leukocyte	>13,290	0.772 (0,0001)*	65.00 (40.79–84.55)	85.27 (77.96–90.89)	40.63 (23.71–59.35)	94.02 (88.06–97.55)
BUN	>115.7	0.694 (0.0049)*	60.00 (36.07–80.83)	82.95 (75.32–88.99)	35.29 (19.76–53.51)	93,04 (86.75–96.94)
CRP	>9.1	0.910 (0.0001)*	75.00 (50.89–91.25)	93.80 (88.14–97.28)	65.22 (42.74–83.58)	96.03 (90.98–98.68)

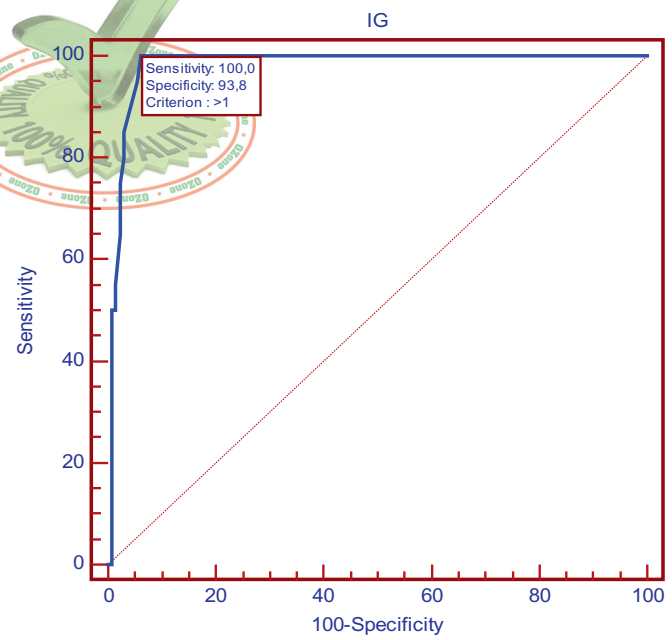

Fig. 1. Receiver-operating characteristics curve that shows the relationship between in-hospital mortality and IG%.

Table 4
The logistic regression analysis for the prediction of in-hospital mortality

Parameters	Odds ratio (OR)	%95 Confidence interval (CI)	p
Leukocyte	1.0	1.000–1.001	0.046
IG%	65.6	2.000–2152.6	0.019
BUN	0.9	0.881–0.999	0.045
CRP	1.7	1.007–3.094	0.047

They determined their sensitivity, specificity and AUC values for mortality as 70%, 78% and 0.84, respectively [16]. Bang et al. reported that the postoperative DNI value in trauma patients who had undergone emergency surgery may be a useful biomarker to predict mortality. They determined their sensitivity, specificity and AUC values as 85.7%, 84.4% and 0.887, respectively [17]. Karakulak et al. reported that IG% was effective in predicting in-hospital mortality in patients with acute pancreatitis. They determined sensitivity, specificity and AUC values as 97.2, 50% and 0.708 respectively [6]. In our study, IG% was found higher in patients who died than those who were discharged. High sensitivity, specificity and AUC (0.98) values in ROC analysis to determine the patients who died may increase the availability of this biomarker. Similarly, univariate logistic regression analysis showed that IG% is a strong predicting variable in-hospital mortality in this study. We believe that the lack of adequate studies on effectivity of IG% limits the clinical use of this useful biomarker in patient with UGIB.

Releasing mechanism of IGs to the peripheral circulation in patients with UGIB is not clearly understood. Hematopoietic system may try to adapt quickly by switching from a steady state to hematopoietic stress, such as severe infection or bleeding. Immature progenitor cells are released into the peripheral circulation in patients with hemorrhagic shock [18,19]. Baranski et al. showed that plasma levels of hematopoietic progenitor cells and granulocyte-colony stimulating factor (G-CSF) increased in rats with hemorrhagic shock [20]. We assumed that in UGIB, blood loss causes stress in the body, and as a result, an inflammatory reaction is triggered, which can increase the level of IGs in the peripheral blood.

Mortality in UGIB have been reported at different rates. Risk factors associated with mortality include hemodynamic instability during the admission to the ED, severe comorbidity, chronic or end-stage kidney disease, and old age [21]. It has been reported that the patients who died are often the result of comorbidity diseases such as coronary artery disease, kidney disease, malignancy and cirrhosis [22]. In our study, although our mortality rate seems to be high, it may not be appropriate to link the causes of death of patients to UGIB primarily. Undetectable infectious, organ failure and presence of comorbid diseases that may occur after hospitalization may have caused death.

Our study has several limitations: the results of our study were obtained from single center and retrospectively, serial measurements of immature granulocytes have not been performed, risk scores for UGIB have not been calculated in this study. Mortality rates for various diagnostic groups were not presented in the study. This could be a more important indicator of death. In addition, although measurement of IG% can be added to the blood count and easily performed, it is not currently available in all centers.

5. Conclusions

To our knowledge, this is the first study to show that IG% may be associated with in-hospital mortality in UGIH. According to the available data, the IG parameter provided the best sensitivity and specifity among all the tests examined. We concluded that IG% show promising results in terms of predicting in-hospital mortality in patients with UGIB. The IG% can be considered as a reliable initial measurement biomarker to predict prognosis in patients with UGIB. This potential marker can guide clinicians on the prognosis of UGIB without additional cost. Prospective, multicenter studies are needed to support the clinical use of IG%.

Financial support and sponsorship

Nil

Declaration of Competing Interest

There are no conflicts of interest.

References

[1] Strömdahl M, Helgeson J, Kalaitzakis E. Emergency readmission following acute upper gastrointestinal bleeding. Eur J Gastroenterol Hepatol. 2017;29:73–7.
[2] Nable JV, Graham AC. Gastrointestinal bleeding. Emerg Med Clin North Am. 2016; 34:309–25.
[3] Berger M, Divilov V, Teressa G. Lactic acid is an independent predictor of mortality and improves the predictive value of existing risk scores in patients presenting with acute gastrointestinal bleeding. Gastroenterology Res. 2019;12:1–7.
[4] Ebrahimi Bakhtavar H, Morteza Bagi HR, Rahmani F, Shahsavari Nia K, Ettehadi A. Clinical Scoring Systems in Predicting the Outcome of Acute Upper Gastrointestinal Bleeding; a Narrative Review. Emerg (Tehran). 2017;5:e36.
[5] Liang PS, Saltzman JR. A national survey on the initial management of upper gastrointestinal bleeding. J Clin Gastroenterol. 2014;48:93–8.
[6] Karakulak S, Narcı H, Ayrık C, Erdoğan S, Üçbilek E. The prognostic value of immature granulocyte in patients with acute pancreatitis [published online ahead of print, 2020 Mar 19]. Am J Emerg Med. 2020 S0735–6757(20)30170–4.
[7] Monteiro Júnior JGM. de Oliveira Cipriano Torres D, Filho DCS. Hematological parameters as prognostic biomarkers in patients with cardiovascular diseases. Curr Cardiol Rev. 2019;15:274–82.
[8] Kumar M, Bhoi S, Subramanian A, et al. Evaluation of circulating haematopoietic progenitor cells in patients with trauma Haemorrhagic shock and its correlation with outcomes. Int J Crit Illn Inj Sci. 2016;6:56–60.
[9] Kong T, In S, Park YS, Lee HY, Lee JW, You JS, et al. Usefulness of the Delta neutrophil index to predict 30-day mortality in patients with upper gastrointestinal bleeding. Shock. 2017;48:427–35.
[10] Amish Shah, Makini Chisolm-Straker, Aeri Alexander, Mohammad Rattu, Sean Dikdan, Alex F Manini. Prognostic use of lactate to predict inpatient mortality in acute gastrointestinal hemorrhage. Am J Emerg Med 2014;32:752–5.
[11] Nikolsky E, Stone GW, Kirtane AJ, George D. Dangas, Alexandra J Lansky, Brent McLaurin, gastrointestinal bleeding in patients with acute coronary syndromes: incidence, predictors, and clinical implications: analysis from the ACUITY (acute catheterization and urgent intervention triage strategy) trial. J Am Coll Cardiol. 2009;54: 1293–302.

[12] Ichikawa T, Machida N, Kaneko H, Oi I. A Fujino M. C-reactive protein can predict patients with cirrhosis at a high risk of early mortality after acute esophageal variceal bleeding. Intern Med. 2019;58(4):487–95.
[13] Park JS, Kim JS, Kim YJ, Kim WY. Utility of the immature granulocyte percentage for diagnosing acute appendicitis among clinically suspected appendicitis in adult. J Clin Lab Anal. 2018;32:e22458.
[14] Ayres LS, Sgnaolin V, Munhoz TP. Immature granulocytes index as early marker of sepsis. Int J Lab Hematol. 2019;41:392–6.
[15] Seok Y, Choi JR, Kim J, et al. Delta neutrophil index: a promising diagnostic and prognostic marker for sepsis. Shock. 2012;37(3):242–6.
[16] Park JH, et al. Delta neutrophil index (DNI) as a novel diagnostic and prognostic marker of infection: a systematic review and meta-analysis. Inflamm Res. 2017; 66:863–70.
[17] Bang HJ, Kim K, Shim H, et al. Delta neutrophil index for predicting mortality in trauma patients who underwent emergent abdominal surgery: A case controlled study. PLoS One. 2020;15(3) e0230149.
[18] Seita J, Weissman IL. Hematopoietic stem cell: Self-renewal versus differentiation. Wiley Interdiscip Rev Syst Biol Med. 2010;2:640–65.
[19] Francis WR, Ireland RE, Spear AM, et al. Flow cytometric analysis of hematopoietic populations in rat bone marrow. Impact of trauma and hemorrhagic shock. Cytometry A. 2019;95(11):1167–77.
[20] Baranski GM, Offin MD, Sifri ZC, et al. β-Blockade protection of bone marrow following trauma: the role of G-CSF. J Surg Res. 2011;170:325–31.
[21] Han YJ, Cha JM, Park JH, et al. Successful endoscopic hemostasis is a protective factor for Rebleeding and mortality in patients with nonvariceal upper gastrointestinal bleeding. Dig Dis Sci. 2016;61:2011–8.
[22] Thomopoulos K, Vagenas K, Vagianos C, et al. Changes in aetiology and clinical outcome of acute upper gastrointestinal bleeding during last 15 years. Eur J Gastroenterol Hepatol. 2004;16:177–82.