Original Article

Neutrophil to lymphocyte ratio and albumin-bilirubin score for predicting the in-hospital mortality of hepatocellular carcinoma with acute upper gastrointestinal bleeding

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Background: Acute upper gastrointestinal bleeding (AUGIB) represents a major risk factor for mortality in patients with hepatocellular carcinoma (HCC) and liver cirrhosis. This retrospective observational study aimed to evaluate the prognostic performance of neutrophil to lymphocyte ratio (NLR) and albumin-bilirubin (ALBI) score for the assessment of in-hospital outcomes of cirrhotic patients with HCC and AUGIB.

Methods: All consecutive HCC patients with AUGIB were included in our study. The areas under the receiving operator characteristics curves (AUCs) of NLR, platelet to lymphocyte ratio (PLR), ALBI score, Child-Pugh score, and model of end-stage liver disease (MELD) score for predicting the in-hospital mortality were calculated.

Results: Overall, 191 HCC patients with AUGIB were included. In the overall analysis, the AUCs of NLR, PLR, ALBI score, Child-Pugh score, and MELD score were 0.74 (P=0.0007), 0.486 (P=0.8681), 0.78 (P<0.0001), 0.804 (P<0.0001), and 0.81 (P<0.0001), respectively. In the subgroup analysis of 112 patients with only hepatitis B virus-related HCC, the AUCs of NLR, PLR, ALBI score, Child-Pugh score, and MELD score were 0.723 (P=0.0169), 0.528 (P=0.8009), 0.772 (P<0.0001), 0.848 (P<0.0001), and 0.86 (P<0.0001), respectively. In the subgroup analysis of 58 HCC patients treated with endoscopic therapy for AUGIB, the AUCs of NLR, PLR, ALBI score, Child-Pugh score, and MELD score were 0.959 (P<0.0001), 0.536 (P=0.8544), 0.644 (P=0.4882), 0.717 (P=0.0349), and 0.917 (P<0.0001), respectively. In the subgroup analysis of 81 patients with infection, the AUCs of NLR, PLR, ALBI score, Child-Pugh score, and MELD score were 0.771 (P=0.0005), 0.53 (P=0.7702), 0.729 (P<0.0028), 0.772 (P<0.0001), and 0.759 (P=0.0037), respectively.

Conclusions: Patients with HCC and AUGIB have a high risk of in-hospital mortality, and NLR and ALBI score appear as promising predictors of adverse outcome. Future studies should prospectively evaluate

these scores, potentially in conjunction with other bio-markers, to improve prognostication in clinical practice.

Keywords: Hepatocellular carcinoma (HCC); bleeding; prognosis; survival; neutrophil to lymphocyte ratio (NLR); albumin-bilirubin score (ALBI score)

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor. The incidence of HCC is being increased over the last decades across the world (1). It was estimated that 782,000 new HCC cases and 745,000 deaths related to HCC occurred worldwide during 2012 (2). HCC is the third leading cause of death from cancer. A major complication of HCC is acute upper gastrointestinal bleeding (AUGIB) due to variceal bleeding or peptic ulcer (3). Both complications are related to the concomitant presence of liver cirrhosis as the major risk factor for HCC (4). The actual incidence of patients with HCC who present with variceal bleeding ranges from 1% to 13% (3,5,6). However, there are no established guidelines for the treatment of AUGIB in patients with HCC. Recently, the AASLD guidance statement suggests that the prevention and treatment of acute variceal bleeding in patients with HCC should follow the same principles as those without HCC (7). Furthermore, the prognosis of HCC patients with AUGIB remains unclear. Traditional prognosis scores for AUGIB have been prospectively evaluated in patients with non-variceal bleeding (8), but do not adequately predict the mortality risk in patients with liver cirrhosis or HCC (9).

Neutrophil to lymphocyte ratio (NLR) is a simple marker of inflammation that has been linked with the prognosis of gastrointestinal malignancy and other cancers such as non-small cell lung cancer (10-14). Recently, our meta-analysis indicated that NLR should be a major prognostic factor for HCC (15). Additionally, albumin-bilirubin (ALBI) score is a convenient model to assess the severity of liver dysfunction in patients with HCC (16) without the need of subjective variables, such as ascites and encephalopathy. Our recent study found that the prognostic performance of ALBI score was comparable with that of Child-Pugh score and model of end-stage liver disease (MELD) score for predicting the in-hospital mortality of AUGIB in liver cirrhosis without HCC (17).

Herein, we conducted a retrospective observational study to evaluate the prognostic performance of NLR and ALBI score in HCC patients with AUGIB.

Methods

This retrospective study was approved by the Medical Ethical Committee of the General Hospital of Shenyang Military Area. The approval number was No. k (2016) 18. The patient's informed written consent was waived because of the retrospective nature. The eligibility criteria were as follows: (I) all patients were consecutively admitted to the General Hospital of Shenyang Military Area between January 2012 and June 2014; (II) patients had a diagnosis of liver cirrhosis and HCC based on the history of chronic liver diseases, clinical manifestations, laboratory tests, and imaging tests (liver histology was required, if uncertain); and (III) patients had a diagnosis of AUGIB based on the occurrence of haematemesis and melena within 5 days before hospital admissions or positive occult blood on the stool at the first routine test after admissions. Source of AUGIB was not restricted, because not all patients underwent endoscopic examinations at their admissions. The endoscopic examination is dependent upon the patients' conditions, recommendations from physicians, and considerations from patients and their relatives. Some patients did not perform the endoscopic examination due to severe conditions. Some family members refused the endoscopic examinations due to advanced stage of HCC. The primary endpoint was the in-hospital mortality.

Data were reviewed regarding demographic profiles, causes of liver diseases, severity of bleeding, vital signs of hospitalized patients, routine laboratory data, treatment options of AUGIB (endoscopic ligation or sclerotherapy, vasoactive drug, and/or surgery, etc.), previous treatment options of HCC, in-hospital death, and causes of death from the electronic medical charts and calculated NLR, platelet to lymphocyte ratio (PLR), ALBI score, Child-Pugh score,

and MELD score. Another investigator checked the data accuracy.

The scores were calculated as follows: NLR = ratio of neutrophil to lymphocyte (18).

ALBI score = [$\log_{10}$ bilirubin (μmol/L) ×0.66] + [albumin (g/L) × (–0.085)] (19).

PLR = ratio of platelet to lymphocyte (20).

Child-Pugh score was calculated based on the severity of hepatic encephalopathy, grade of ascites, total bilirubin, albumin, and INR (21).

MELD score =9.57× ln[creatinine (μmol/L) ×0.01] + 3.78× ln[bilirubin (μmol/L) ×0.05] + 11.2× ln(INR) +0.643 (22).

We performed the statistical analyses in the SPSS software version 17.0 and MedCalc software version 11.4.2.0. Continuous and categorical data were expressed as the mean ± standard deviation (SD) in combination with the median with minimum and maximum and the frequency (percentage), respectively. The discriminative capacities of the NLR, PLR, ALBI score, Child-Pugh score, and MELD score for the in-hospital mortality were calculated by the receiving operator characteristics curve analyses and expressed as the areas under the receiving operator characteristics curves (AUC) with 95% confidence intervals (CIs). A best cut-off value was selected as the sum of sensitivity and specificity was maximal. The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predictive value (PPV), and negative predictive value (NPV) with 95% CIs were also calculated. Subgroup analyses were performed in patients with only hepatitis B virus-related HCC, in those treated with endoscopic therapy for AUGIB, and in those with and without infection. Due to the retrospective nature of our study, infection was arbitrarily identified based on the use of antibiotics. $P<0.05$ was considered statistically significant.

Results

A total of 191 HCC patients with AUGIB were included. The patient characteristics were shown in *Table 1*. A majority of patients were male (84.82%) and had hepatitis B virus infection (58.63%). Before admissions for AUGIB, 125 (65.45%) patients were on conservative treatment alone, 54 (28.27%) underwent interventional therapy alone, 8 (4.2%) underwent surgery alone, 2 (1.04%) underwent a combination of interventional therapy and surgery, 1 (0.52%) underwent sorafenib alone, and 1 (0.52%) underwent a combination of interventional therapy and sorafenib for the treatment of HCC. At our admissions, 135 (70.68%) patients were treated with somatostatin or octreotide, 91 (47.64%) received blood transfusion, and 58 (30.37%) underwent endoscopic therapy for the treatment of AUGIB. Additionally, 81 patients received antibiotics during their hospitalizations, who formed a group of infected subjects.

The in-hospital mortality was 10.47% (20/191). The diagnostic performances of the different scores were summarized in *Table 2*. The AUC of NLR for the in-hospital mortality was not significantly different from that of PLR (P=0.1425), Child-Pugh score (P=0.3810), MELD score (P=0.3230), or ALBI score (P=0.4938). The AUC of ALBI score for the in-hospital mortality was not significantly different from that of Child-Pugh score (P=0.5673) or MELD score (P=0.5520). The AUC of ALBI was superior to that of PLR (P=0.0126).

The in-hospital mortality in patients with only hepatitis B virus related HCC was 11.61% (13/112). The diagnostic performances of the different scores were summarized in *Table 2*. The AUC of NLR for the in-hospital mortality was not significantly different from that of PLR (P=0.2593), Child-Pugh score (P=0.2502), MELD score (P=0.1053), or ALBI score (P=0.5401). The AUC of ALBI score for the in-hospital mortality was not significantly different from that of PLR (P=0.0706), Child-Pugh score (P=0.2369), or MELD score (P=0.1776).

The in-hospital mortality in patients treated with endoscopic therapy for AUGIB was 3.4% (2/58). The diagnostic performances of the different scores were summarized in *Table 2*. The AUC of NLR for the in-hospital mortality was not significantly different from that of PLR (P=0.0678), MELD score (P=0.3213), or ALBI score (P=0.2365). The AUC of NLR was superior to that of Child-Pugh score (P=0.0002). The AUC of ALBI score for the in-hospital mortality was not significantly different from that of PLR (P=0.5497), Child-Pugh score (P=0.7791), or MELD score (P=0.3264).

The in-hospital mortality in patients without infection was 7.27% (8/110). The diagnostic performances of the different scores were summarized in *Table 2*. The AUC of NLR for the in-hospital mortality was not significantly different from that of PLR (P=0.7491), MELD score (P=0.0820), ALBI score (P=0.1238), or Child-Pugh score (P=0.2454). The AUC of ALBI score for the in-hospital mortality was not significantly different from that of PLR (P=0.0685), Child-Pugh score (P=0.9116), or MELD score (P=0.4814).

The in-hospital mortality in patients with infection

Table 1 Patient characteristics

Variables	N	Mean ± SD or Frequency (%)	Median (range)
Age (years)	191	57.64±10.36	56.98 (32 to 84)
Sex (male/female), n (%)	191	162 (84.82)/29 (15.18)	
Etiology, n (%)	191		
HBV alone		112 (58.63)	
HCV alone		8 (4.20)	
HBV + HCV		2 (1.04)	
Alcohol		14 (7.32)	
HBV + Alcohol		29 (15.18)	
HBV + HCV + Alcohol		3 (1.57)	
Others or unknown		23 (12.04)	
Ascites (no/mild/moderate – large), n (%)	190	89 (46.84)/18 (9.47)/83 (43.68)	
HE (no/grade I–II/grade III–IV), n (%)	189	174 (92.06)/8 (4.23)/7 (3.71)	
Previous treatment of HCC, n (%)	191		
Surgery		8 (4.18)	
Interventional treatment		54 (28.27)	
Molecular targeted drug		1 (0.52)	
Conservative treatment		125 (65.45)	
Interventional treatment + sorafenib		1 (0.52)	
Interventional treatment + surgery		2 (1.04)	
Number of tumor nodules (1/2/≥3), n (%)	87	52 (59.77)/2 (2.30) /33 (37.93)	
Diameter of tumor nodules (≤3/>3 cm), n (%)	63	16 (25.40)/47 (74.60)	
Distal extra-hepatic metastasis (yes/no), n (%)	191	7 (3.66)/184 (96.34)	
WBC (10^9/L)	188	6.49±4.81	5.2 (0.9 to 30.7)
RBC (10^{12}/L)	188	2.83±0.79	2.78 (0.79 to 4.79)
Hb (g/L)	188	85.6±26.23	80.5 (19 to 148)
PLT (10^9/L)	188	119.54±88.09	97.92 (17.06 to 633.33)
TBIL (μmol/L)	184	46.88±66.35	27.8 (6.8 to 447.2)
ALB (g/L)	185	29.47±6.37	29 (15 to 53)
ALP (U/L)	184	143.65±136.52	101.5 (26 to 964)
GGT (U/L)	184	136.74±141.19	95.5 (8 to 994)
ALT (U/L)	185	82.59±291.01	41 (7 to 3,845)
AST (U/L)	184	180.61±1,106.17	59 (9 to 15,000)
BUN (mmol/L)	181	8.84±6.22	7.21 (1.54 to 55.01)
Cr (μmol/L)	180	78.85±92.77	60 (25 to 1,189)

Table 1 (*continued*)

Table 1 (*continued*)

Variables	N	Mean ± SD or Frequency (%)	Median (range)
Na (mmol/L)	181	137.14±5.54	137.3 (109.2 to 160.1)
K (mmol/L)	181	4.05±0.56	4.02 (2.05 to 6.08)
PT (s)	173	17.02±4.61	15.7 (12.1 to 42.3)
INR	172	1.41±0.54	1.24 (0.89 to 4.70)
APTT (s)	173	43.55±10.96	42.1 (29 to 131.4)
AFP (ng/mL)	132	290.3±410.61	28.75 (0 to 1,000)
NLR	188	5.75±5.80	3.59 (0.8 to 36.6)
PLR	188	119.55±88.09	97.92 (17.06 to 633.33)
ALBI score	182	–1.53±0.66	–1.51 (–3.66 to 0.29)
Child-Pugh score	166	7.99±2.07	8 (5 to 14)
MELD score	169	8.64±8.09	7.24 (–6.45 to 40.95)
Treatment of AUGIB, n (%)	191		
Somatostatin or octreotide		135 (70.68)	
Sengstaken Blakemore tube		0 (0)	
Endoscopic therapy		58 (30.37)	
Blood transfusion		91 (47.64)	
RBC transfusion		86 (45.03)	
Amount of RBC transfused (u)	86	4.39±2.80	3.75 (1 to 16)
Death (yes/no), n (%)	191	20 (10.5%)/171 (89.5%)	
Cause of death, n (%)	20		
AUGIB		12 (60.0)	
Organ failure		8 (40.0)	

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALBI, albumin-bilirubin, APTT, activated partial thromboplastin time; AFP, alpha-fetoprotein; BUN, blood urea nitrogen; Cr, creatinine; GGT, gamma-glutamyl transpeptidase; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; Hb, hemoglobin; INR, international normalized ratio; MELD, model for end-stage liver disease; NLR, neutrophil-lymphocyte ratio; PLT, platelet; PT, prothrombin time; PLR, platelet-lymphocyte ratio; RBC, red blood cell; TBIL, total bilirubin; WBC, white blood cell.

was 14.81% (12/81). The diagnostic performances of the different scores were summarized in *Table 2*. The AUC of NLR for the in-hospital mortality was not significantly different from that of PLR (P=0.0876), MELD score (P=0.8082), ALBI score (P=0.4268), or Child-Pugh score (P=0.8738). The AUC of ALBI score for the in-hospital mortality was not significantly different from that of PLR (P=0.1126), Child-Pugh score (P=0.5237), or MELD score (P=0.7013).

Discussion

Various scoring systems of HCC have been proposed all over the world, such as Okuda stage firstly proposed in 1985 (23), BCLC stage firstly proposed in 1999 (24), the sixth edition of TNM stage that was jointly launched by the AACIF of Anti-Cancer in 2003 (25), and Japan Integrated Staging score (26), etc. However, there is no consensus regarding which system is the most suitable for evaluating the prognosis of HCC patients.

Table 2 Diagnostic performance of different scores

Variables	AUC (95% CI)	Cut-off value	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	P value
Overall analysis									
Neutrophil-lymphocyte ratio score	0.740 (0.671–0.801)	7.6	68.42 (43.4–87.2)	84.02 (77.6–89.2)	4.28 (3.1–5.9)	0.38 (0.2–0.8)	32.5 (18.6–49.1)	95.9 (91.4–98.5)	0.0007
ALBI score	0.780 (0.713–0.818)	–1.5516	94.44 (72.7–99.9%)	51.83 (43.9–59.7)	1.96 (1.6–2.4)	0.11 (0.02–0.7)	17.7 (10.7–26.8)	98.8 (93.7–100)	<0.0001
Platelet-lymphocyte ratio score	0.486 (0.413–0.560)	45.38	26.32 (9.1–51.2)	92.9 (87.9–96.3)	3.71 (1.9–7.9)	0.79 (0.4–1.5)	29.4 (10.3–56)	91.8 (86.6–95.5)	0.8681
Child-Pugh score	0.804 (0.735–0.861)	8	82.35 (56.6–96.2)	66.44 (58.3–74)	2.45 (1.9–3.1)	0.27 (0.09–0.8)	21.9 (12.4–34.1)	97.1 (91.6–99.4)	<0.0001
MELD score	0.810 (0.742–0.866)	8.5055	88.24 (63.6–98.5)	65.79 (57.7–73.3)	2.58 (2.1–3.2)	0.18 (0.05–0.7)	22.4 (13.1–34.2)	98 (93.1–99.8)	<0.0001
Subgroup analysis in patients with hepatitis B virus alone related HCC									
Neutrophil-lymphocyte ratio score	0.723 (0.629–0.804)	7.17	66.67 (34.9–90.1)	80.61 (71.4–87.9)	3.44 (2.3–5.2)	0.41 (0.2–1.0)	29.6 (13.5–50.6)	95.2 (88.1–98.7)	0.0169
ALBI score	0.772 (0.681–0.848)	-1.6676	100 (73.5–100)	44.68 (34.4–55.3)	1.81 (1.4–2.3)	0 (0)	18.8 (10.1–30.5)	100 (91.6–100)	<0.0001
Platelet-lymphocyte ratio score	0.528 (0.431–0.624)	45.38	33.33 (9.9–65.1)	91.84 (84.5–96.4)	4.08 (1.8–9.1)	8 (0.3–1.6)	33.3 (9.2–66.6)	91.8 (84.4–96.4)	0.8009
Child-Pugh score	0.848 (0.763–0.912)	8	91.67 (61.5–99.8)	67.05 (56.2–76.7)	2.78 (2.2–3.5)	0.12 (0.02–0.8)	27.5 (14.6–43.9)	27.5 (14.6–43.9)	<0.0001
MELD score	0.860 (0.778–0.920)	8.5055	100 (73.5–100)	64.84 (54.1–74.6)	2.84 (2.4–3.3)	0 (0)	27.3 (15–42.8)	100 (93.9–100)	<0.0001
Subgroup analysis in patients treated with endoscopic therapy for AUGIB									
Neutrophil-lymphocyte ratio score	0.959 (0.870–0.994)	7.17	100 (15.8–100)	90.91 [80–97]	11 (10.1–12)	0 (0)	28.6 (3.7–71.0)	100 (92.9–100)	<0.0001
ALBI score	0.644 (0.502–0.770)	–1.6786	100 (15.8–100)	44.23 (30.5–58.7)	1.79 (1.3–2.4)	0 (0)	6.5 (0.8–21.4)	100 (85.2–100)	0.4882
Platelet-lymphocyte ratio score	0.536 (0.399–0.670)	106.25	100 (15.8–100)	34.55 (22.2–48.6)	1.53 (1.1–2.2)	0 (0)	5.3 (0.6–17.7)	100 (82.4–100)	0.8544
Child-Pugh score	0.717 (0.569–0.838)	7	100 (15.8–100)	52.17 (36.9–67.1)	2.09 (1.6–2.8)	0 (0)	8.3 (1.0–27.0)	100 (85.8–100)	0.0349
MELD score	0.917 (0.803–0.976)	11.7876	100 (15.8–100)	85.42 (72.2–93.9)	6.86 (6.1–7.7)	0 (0)	22.2 (2.8–60.0)	100 (91.4–100)	<0.0001

Table 2 (*continued*)

Table 2 (*continued*)

Variables	AUC (95% CI)	Cut-off value	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	P value
Subgroup analysis in patients without infection									
Neutrophil-lymphocyte ratio score	0.628 (0.529–0.719)	7.17	42.86 (9.9–81.6)	93 (86.1–97.1)	6.12 (2.6–14.4)	0.61 (0.2–1.6)	30 (5.9–67.2)	95.9 (89.8–98.9)	0.3582
ALBI score	0.813 (0.725–0.813)	–1.5516	100 [59–100]	61.86 (51.4–71.5)	2.62 (2.2–3.1)	0 (0)	15.9 (6.6–30.1)	100 [94–100]	0.0001
Platelet-lymphocyte ratio score	0.517 (0.418–0.615)	31.72	28.57 (3.7–71)	100 (96.4–100)	0 (0)	0.71 (0)	100 (2.5–100)	95.2 (89.1–98.4)	0.9065
Child-Pugh score	0.804 (0.711–0.878)	8	71.43 (29–96.3)	73.03 (62.6–81.9)	2.65 (1.6–4.3)	0.39 (0.1–1.3)	17.2 (5.8–35.8)	97 (89.6–99.6)	0.0002
MELD score	0.854 (0.768–0.917)	10.7294	85.71 (42.1–99.6)	80.22 (70.6–87.8)	4.33 (3.1–6.0)	0.18 (0.03–1.1)	25 (9.8–46.7)	98.6 (92.7–100)	0.0001
Subgroup analysis in patients with infection									
Neutrophil-lymphocyte ratio score	0.771 (0.664–0.557)	7.89	83.33% (51.6–97.9)	73.91 (61.9–83.7)	3.19 (2.4–4.3)	0.23 (0.06–0.8)	35.7 (18.6–55.9)	96.2 (86.9–99.6)	0.0005
ALBI score	0.729 (0.616–0.823)	–1.1535	72.73 [39–94]	65.67 (53.1–76.8)	2.12 (1.4–3.2)	0.42 (0.1–1.2)	25.8 (11.9–44.6)	93.9 (82.5–98.7)	<0.0028
Platelet-lymphocyte ratio score	0.530 (0.416–0.642)	100.77	66.67 (34.9–90.1)	53.62 (41.2–65.7)	1.44 (0.9–2.3)	0.62 (0.3–1.4)	20 (9.1–35.6)	90.2 (76.9–97.3)	0.7702
Child-Pugh score	0.772 (0.656–0.864)	8	90 (55.5–99.7)	56.67 (43.2–69.4)	2.08 (1.5–2.8)	0.18 (0.03–1.2)	25.7 (12.5–43.3)	97.1 (85.1–99.9)	<0.0001
MELD score	0.759 (0.643–0.653)	8.4999	90 (55.5–99.7)	57.38 (44.1–70.0)	2.11 (1.6–2.8)	0.17 (0.03–1.1)	25.7 (12.5–43.3)	97.2 (85.5–99.9)	0.0037

ALBI, albumin-bilirubin; AUC, area under the curve.

Liver cirrhosis underlies HCC in approximately 80%-90% of cases worldwide (27). AUGIB is one of the most common complications and leading causes of death of liver cirrhosis and HCC. A multi-center case-control study has shown that patients with variceal bleeding and HCC have worse outcomes than those with variceal bleeding without HCC (28). Secondary prophylaxis offers the survival benefit for HCC patients. Therefore, we should pay more attention to the prevention and treatment of HCC patients with esophageal variceal bleeding. However, there is no consensus about the treatment of HCC with esophageal variceal bleeding (7). At the same time, the prognostic scoring system of HCC with AUGIB is still lacking.

Child-Pugh and MELD scores are important prognostic models for the assessment of liver cirrhosis complicating AUGIB. Our previous study found that the discriminative ability was not significantly different between the two scoring systems (29) and that the prognostic performance of the ALBI score was comparable with that of the Child-Pugh and MELD scores for the in-hospital mortality of AUGIB in liver cirrhosis without HCC (17).

In the present study, the target population has the following features: (I) all patients had a diagnosis of liver cirrhosis and HCC; (II) all patients presented with the clinical suspicion of AUGIB; (III) not all patients underwent endoscopic examinations to identify the sources of bleeding, partially because some family members refused the endoscopic examinations due to advanced stage of HCC.

To our knowledge, the present study is the first to explore the prognostic performance of NLR, ALBI, and PLR scores for the assessment of in-hospital mortality of HCC with AUGIB. The prognostic performance of NLR and ALBI score might be comparable to that of classical prognostic models in such patients.

Considering that endoscopic therapy is a mainstay treatment option for AUGIB in HCC patients, we performed a subgroup analysis of patients treated with endoscopic therapy for AUGIB and demonstrated that NLR score had an excellent prognostic performance (AUC =0.959). Certainly, we had to acknowledge only a small sample size and a very low proportion of patients who died during their hospitalizations in this subgroup. Therefore, the subgroup results should be further validated.

White blood cell and neutrophil reflect the underlying infection or stress related leukocytosis. However, since pancytopenia is common in cirrhosis, NLR should be more appropriate to reflect the underlying leukocytosis and possible infection. Thus, we performed two subgroup analyses according to the infection status. We found that NLR could significantly predict the in-hospital death of HCC patients with infection, but not that of HCC patients without infection. Notably, the absolute AUC of NLR is very close to that of Child-Pugh score and larger than that of MELD score in the subgroup analysis of infection alone. By comparison, after excluding infection, the absolute AUC of ALBI score is larger than that of Child-Pugh score, but smaller than that of MELD score. This might be because ALBI score should be more appropriate to reflect the underlying nutritional status and decompensated liver function, but not infection.

Additional limitations included (I) the long-term follow-up outcomes were lacking, (II) a substantial proportion of patients did not undergo the endoscopic examinations to disclose the source of AUGIB, and (III) the definition of infection is arbitrary.

In conclusion, patients with HCC and AUGIB have a high risk of in-hospital mortality, and NLR and ALBI score appear as promising predictive scores for adverse outcomes. Future studies should prospectively evaluate these scores, potentially in conjunction with other biomarkers, to improve the prognostication in clinical practice, because the combination of different scores (e.g., MELD score plus NLR) or the addition of other biomarkers (e.g., lactate) might further improve the predictive power of NLR or ALBI score in this setting (30).

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Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2017.10.02). Yasuhiko Sugawara serves as an unpaid editorial board member of *AME Medical Journal* from Aug 2017 to Aug 2019. Andrea Mancuso serves as an unpaid editorial board member of *AME Medical Journal* from Mar 2017 to Mar 2019. Fernando Gomes Romeiro serves as an unpaid editorial board member of *AME Medical Journal* from Apr 2017 to Apr 2019. Xingshun Qi serves as an Editor-in-Chief of *AME Medical Journal*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Medical Ethical Committee of the General Hospital of Shenyang Military Area. The approval number was No.k (2016) 18. The patient's informed written consent was waived because of the retrospective nature.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
2. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
3. Sayana H, Yousef O, Clarkston WK. Massive upper gastrointestinal hemorrhage due to invasive hepatocellular carcinoma and hepato-gastric fistula. World J Gastroenterol 2013;19:7472-5.
4. Rockey DC, Elliott A, Lyles T. Prediction of esophageal varices and variceal hemorrhage in patients with acute upper gastrointestinal bleeding. J Investig Med 2016;64:745-51.
5. Chen CH, Sheu JC, Huang GT, et al. Characteristics of hepatocellular carcinoma presenting with variceal bleeding. J Gastroenterol Hepatol 1998;13:170-4.
6. Yeo W, Sung JY, Ward SC, et al. A prospective study of upper gastrointestinal hemorrhage in patients with hepatocellular carcinoma. Dig Dis Sci 1995;40:2516-21.
7. Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017;65:310-35.
8. Dicu D, Pop F, Ionescu D, et al. Comparison of risk scoring systems in predicting clinical outcome at upper gastrointestinal bleeding patients in an emergency unit. Am J Emerg Med 2013;31:94-9.
9. de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743-52.
10. Yang X, Huang Y, Feng JF, et al. Prognostic significance of neutrophil-to- lymphocyte ratio in esophageal cancer: a meta-analysis. Onco Targets Ther 2015;8:789-94.
11. Zhang X, Zhang W, Feng LJ. Prognostic significance of neutrophil lymphocyte ratio in patients with gastric cancer: a meta-analysis. PLoS One 2014;9:e111906.
12. Li MX, Liu XM, Zhang XF, et al. Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Int J Cancer 2014;134:2403-13.
13. Peng B, Wang YH, Liu YM, et al. Prognostic significance of the neutrophil to lymphocyte ratio in patients with non-small cell lung cancer: a systemic review and meta-analysis. Int J Clin Exp Med 2015;8:3098-106.
14. Xiao WK, Chen D, Li SQ, et al. Prognostic significance of neutrophil-lymphocyte ratio in hepatocellular carcinoma: a meta-analysis. BMC Cancer 2014;14:117.
15. Qi X, Li J, Deng H, et al. Neutrophil-to-lymphocyte ratio for the prognostic assessment of hepatocellular carcinoma: A systematic review and meta-analysis of observational studies. Oncotarget 2016;7:45283-301.
16. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 2015;33:550-8.
17. Zou D, Qi X, Zhu C, et al. Albumin-bilirubin score for predicting the in-hospital mortality of acute upper gastrointestinal bleeding in liver cirrhosis: A retrospective study. Turk J Gastroenterol 2016;27:180-6.
18. Tang L, Li X, Wang B, et al. Prognostic Value of Neutrophil-to-Lymphocyte Ratio in Localized and Advanced Prostate Cancer: A Systematic Review and Meta-Analysis. PLoS One 2016;11:e0153981.
19. Chan AW, Kumada T, Toyoda H, et al. Integration of albumin-bilirubin (ALBI) score into Barcelona Clinic Liver Cancer (BCLC) system for hepatocellular carcinoma. J Gastroenterol Hepatol 2016;31:1300-6.
20. Condado JF, Junpaparp P, Binongo JN, et al. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) can risk stratify patients in transcatheter aortic-valve replacement (TAVR). Int J Cardiol 2016;223:444-9.

21. Jacob KA, Hjortnaes J, Kranenburg G, et al. Mortality after cardiac surgery in patients with liver cirrhosis classified by the Child-Pugh score. Interact Cardiovasc Thorac Surg 2015;20:520-30.
22. Krafcik BM, Farber A, Eslami MH, et al. The role of Model for End-Stage Liver Disease (MELD) score in predicting outcomes for lower extremity bypass. J Vasc Surg 2016;64:124-30.
23. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985;56:918-28.
24. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329-38.
25. Vauthey JN, Lauwers GY, Esnaola NF, et al. Simplified staging for hepatocellular carcinoma. J Clin Oncol 2002;20:1527-36.
26. Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). J Gastroenterol 2003;38:207-15.
27. Fattovich G, Stroffolini T, Zagni I, et al. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004;127:S35-50.
28. Ripoll C, Genescà J, Araujo IK, et al. Rebleeding prophylaxis improves outcomes in patients with hepatocellular carcinoma. A multicenter case-control study. Hepatology 2013;58:2079-88.
29. Peng Y, Qi X, Dai J, et al. Child-Pugh versus MELD score for predicting the in-hospital mortality of acute upper gastrointestinal bleeding in liver cirrhosis. Int J Clin Exp Med 2015;8:751-7.
30. Koch A, Buendgens L, Dückers H, et al. [Bleeding origin, patient-related risk factors, and prognostic indicators in patients with acute gastrointestinal hemorrhages requiring intensive care treatment. A retrospective analysis from 1999 to 2010]. Med Klin Intensivmed Notfmed 2013;108:214-22.

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