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Predictors of In-Hospital Mortality in patients with hepatocellular carcinoma and Acute Variceal bleeding

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Abstract

Introduction: Detection of hepatocellular carcinoma (HCC) in cirrhotic patients remains a serious, unsolved problem, and the risk factors for acute variceal bleeding (AVB) in HCC patients remain unclear. This study aimed to determine the in-hospital mortality (IHM) and factors influencing the clinical outcomes of AVB in patients with liver cirrhosis and HCC.

Methods: This was a retrospective, non-randomized, clinical study that was conducted in 2014. The study was conducted on 70 patients with liver cirrhosis and HCC presenting by acute upper gastrointestinal bleeding (AUGIH). All patients were examined endoscopically within 24 hours from presentation and bleeding varices accounted for AUGIH. Full medical history, clinical examination, and laboratory and radiologic data were collected from admission charts, and hospital medical records were statistically analyzed with SSPS version 22.

Results: Thirty-two patients (45.7%) survived and 38 died (54.3%). Survivors are more likely to be Child-Pugh class A or B, and the non-survivors were class C. The Model for End-Stage Liver Disease (MELD) was highly predictive of IHM at an optimized cut-off value of ≥ 12.9. Higher esophageal varices grades and presence of active bleeding on index endoscopy were significant ($p < 0.01$) in the non-survivors compared to survivors. Complications of liver cirrhosis and associated major comorbidity were significantly higher ($p < 0.01$) in the non-survivors than the survivors. Univariate logistic regression analysis identified higher Grade Esophageal Varices and number of transfused packed red blood cells units as two independent predictors of IHM.

Conclusions: IHM was particularly high (54.3%) among HCC patients with AVB who had MELD score > 12.9, higher grade Esophageal Varices, active bleeding on index endoscopy, more increased needs for blood transfusion, longer hospital stay, decompensated liver disease with major comorbidity.

Keywords: acute upper gastrointestinal bleeding, MELD score, complications of liver cirrhosis, hepatocellular carcinoma, prognosis

1. Introduction

Hepatocellular carcinoma (HCC) has a 5-year survival rate as low as 5% because it is an aggressive primary malignancy of the liver (1). Throughout the world, it is the third leading cause death from cancer. In the United States, it is the ninth leading cause of cancer deaths, with an average annual percentage change of incidence rate of 3.5%. Most cases of HCC are due to chronic liver disease caused by hepatitis B and C (78%) (2). A common complication experienced by patients with HCC is gastrointestinal (GI) bleeding. The common etiologies associated with underlying cirrhosis and/or tumor invasion of portal vein are peptic ulcer disease, variceal bleeding due to portal hypertension, which can cause thrombosis and portal hypertensive gastropathy (3). In the prospective study of Yeo et al. (4), 53% of HCC patients who presented with GI bleeding had a non-variceal source of bleeding, and the remainder had variceal bleeding. Variceal hemorrhage occurs in 25 - 40% of patients with cirrhosis (5).

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A mortality rate of 30% is associated with each episode of active variceal hemorrhage (6, 7). Also, patients who survive an episode of active bleeding have a 70% risk of recurrent hemorrhage within one year (8). Both liver cirrhosis and portal vein thrombosis (PVT) due to the progression of HCC, can occur in HCC patients (9). The incidence rate of portal hypertension reported in earlier studies was about 30% in patients with HCC, but portal hypertension was evaluated as in these studies using clinical parameters instead of portal vein pressure measurement, resulting in the estimation of a higher frequency of portal hypertension in these patients (10, 11). The treatment of HCC (12) is affected directly by portal hypertension, contributing to a poor prognosis (13). The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) have established guidelines that indicate that liver cirrhosis with portal hypertension is a relative contraindication for hepatic resection because of the high risk liver failure after the operation (14-17). Randomized, controlled trials have shown that mortality from variceal bleeding in cirrhosis has decreased over the past 3 decades from about 50% to 20 - 30%, but this figure is still remarkably high (18, 19). Improved supportive measures, early administration of drugs to reduce the portal pressure, the widespread use of emergency endoscopic treatment, and, more recently, the use of the salvage transjugular intrahepatic portosystemic shunt (TIPS) are credited with this important reduction in mortality among patients with cirrhosis and upper digestive bleeding. Most deaths do not result from the failure of haemostasis, either medically or surgically, but mainly from comorbidities, poorly tolerated blood loss, and the resultant complications (19-21). The aim of the present study was to determine the in-hospital mortality and the factors that influence the clinical outcome of acute variceal bleeding in patients with liver cirrhosis and HCC.

2. Material and Methods

2.1. Study setting

This was a retrospective, hospital-based study conducted at Theodor Bilharz Research Institute (TBRI), and it included 70 patients with liver cirrhosis and HCC presenting with acute upper gastrointestinal bleeding (AUGIH) in the period from November 1, 2013, to December 31, 2014. All of the patients were admitted to the intensive care unit in the Hepatogastroenterology Department.

2.2. Eligibility criteria

Patients were considered for enrollment in the study if they have liver cirrhosis and HCC and met at least one criterion: 1) Hematemesis, defined as either one or more than one episode of vomiting either fresh blood or a coffee ground-like material, along with either hypotension (systolic BP 100 mmHg), or orthostasis (20 mmHg decline in systolic BP from lying supine to standing, or an increase in heart rate of 20 bpm from lying supine to standing), 2) Reported or observed melena with a diagnostic esophagogastroduodenoscopy (EGD), 3) Hematemesis and melena with a diagnostic EGD.

2.3. Data collection and methods

The diagnosis of HCC was confirmed by computed tomography (CT) or magnetic resonance (MR) findings after abdominal ultrasound scanning. Diagnosis of main PVT also was based on dynamic CT or MR. The hepatic reserve status of each patient was accessed at the time of presentation according to Pugh’s modification of Child’s classification and MELD score. Admission and post admission data, including demographic features, presenting symptoms, comorbidity, results of laboratory, radiographic, and endoscopic tests, blood transfusion records and treatments were collected retrospectively. EGD was done in the first 24 hours as an emergency procedure unless contraindicated. The endoscopic components of the database included identification of the bleeding lesion, description of stigmata of bleeding, method of endoscopic hemostasis, if any, and the number of therapeutic attempts. Outcomes recorded complications and mortality. All of the data of the patients were registered and statistically analyzed.

2.4. Research ethics

The local institutional review board at the institute approved this study, and all patients gave written informed consent according to the ethical guidelines of the 1975 Declaration of Helsinki.

2.5. Statistical analysis

All the data of the patients were registered mean ± SE and statistically analyzed with SPSS version 22.0 (SPSS-IBM, USA). Comparisons between groups were made using Fisher's exact and the chi squared tests for categorical variables and the Mann-Whitney tests for continuous variables. Two-sided p-value less than 0.05 were considered statistically significant. Multivariate models were adjusted for age, gender, diagnosis, blood units, MELD score, and

serum sodium at registration. The ability of the scoring systems to discriminate between hospital survivors and non-survivors was assessed by using the area under the receiver operating characteristic (AUROC) curve.

3. Results

In our cohort, 70 patients with post-hepatitic liver cirrhosis and HCC were admitted to the ICU due to acute upper GI bleeding with bleeding attributed to esophageal varices. Demographic, clinical, and laboratory data are shown in Tables 1 and 2. Thirty-two patients survived (45.7%) and 38 died (54.3%). While the survivors and those who died were similarly matched with regard to age, ethnicity, and etiology of cirrhosis (HCV or HBV), the survivors and the in-hospital mortality (IHM) cases were found to be different according to Child-Pugh classification ($p = 0.05$) and MELD score ($p = 0.01$). Those who survived were more likely to be Child A or B with mean MELD scores of 16.61 ± 1.40, and the non-survivors were Child class C with a mean MELD score of 22.14. Recurrent bleeding was found to have a statistically significant difference ($p < 0.01$) in non-survivors compared to survivors. Non-survivors required more transfusion of packed red blood cells and longer stays in the ICU than the survivors ($p < 0.001$).

Table 1. Demographic and Clinical variables in survivors and non-survivors

Characteristic		All patients	Survivor	Non- Survivor
Age (years)		59.63 ± 1.30	60.95 ± 1.85	58.06 ± 1.78
Male/Female ratio		56/14	22/10	34/4
Cirrhosis secondary to HCV, n (%)		63 (90.0)	30 (42.86)	33 (47.14)
Cirrhosis secondary to HBV, n (%)		7 (10.0)	2 (2.86)	5 (7.14)
Cirrhosis + HCC + PVT, n (%)		15 (21.4)	9 (12.8)	6 (8.6)
Child-Pugh scores (X ±SE)		8.98 ± 0.32	8.84 ± 2.38	9.11 ± 0.47
Child-Pugh class	A, n (%)	14 (20.0)	5 (7.14)	9 (12.86)
	B, n (%)	26 (37.14)	15 (21.43)	11 (15.71)
	C, n (%)	30 (42.85)	12 (17.14)	18 (25.71)*
MELD scores, (X ±SE)		19.62 ± 1.12	16.61 ± 1.40	22.14 ± 1.71**
Ascites	No, n (%)	32 (45.7)	15 (21.4)	17 (24.3)
	Yes, n (%)	38 (54.3)	17 (17.1)	21 (30.0)**
Bleeding	Hematemesis, n (%)	55 (78.6)	28 (40.0)	27 (38.6)
	Melena, n (%)	7 (10.0)	1 (1.4)	6 (8.6)
	Hematemesis + melena, n (%)	8 (11.4)	3 (4.3)	5 (7.1)
	1st Attack	38 (54.3)	21 (30.0)	17 (24.3)
	Recurrent bleeding	32 (45.7)	11 (15.7)	21 (30.0)**
Units of PRBC transfused		2.10 ± 0.25	1.9 ± 0.23	2.60 ± 0.74*
ICU Admission Days		1.24 ± 0.10	0.97 ± 0.13	1.45 ± 0.15**

Data were represented as Mean ±SE, *$p < 0.01$, **$p < 0.001$

Table 2. Laboratory parameters at time of admission in survivors and non-survivors

Variables	All patients	Survivor	Non- Survivor
Albumin (g/dL)	2.47 ± 0.11	2.54 ± 1.40	2.41 ± 1.51
Creatinine (mg/dL)	1.66 ± 0.18	1.39 ± 0.22	1.89 ± 1.69
Bilirubin (mg/dL)	5.03 ± 0.59	4.37 ± 0.75	5.57 ± 0.88
Alanine aminotransferase (ALT) (SGPT), (U/L)	116.50 ± 21.9	87.75 ± 26.45	140.71 ± 33.46*
Aspartate aminotransferase (AST) (SGOT), (U/L)	69.63 ± 12.77	44.63 ± 5.73	90.68 ± 22.60*
PT (seconds above control)	9.72 ± 1.10	7.43 ± 1.03	11.65 ± 1.79*
International normalized ratio (INR)	1.77 ± 0.09	1.62 ± 0.11	1.91 ± 0.13
White blood cells (WBC), (mm^3)	10.58 ± 0.94	9.69 ± 1.01	11.33 ± 1.51
HB (g/dL)	10.06 ± 1.10	9.36 ± 0.38	10.65 ± 2.01
Platelet count ($\times 10^3$ / mm^3)	138.38 ± 14.68	162.65 ± 28.37	117.94 ± 12.19
Natremia	128.84 ± 0.96	129.56 ± 1.54	128.24 ± 1.21

Data were represented as Mean ± SE, *$p < 0.01$

Endoscopic findings in survivors and non-survivors is presented in Table 3. The presence of complications of liver cirrhosis or associated major comorbidity and risk of IHM are shown in Tables 4 and 5, respectively. Survivors and non-survivors were different according to the presence of ascites ($p < 0.01$), size of the spleen ($p < 0.01$), diabetes mellitus ($p < 0.05$), and chest infection ($p < 0.05$). Non-survivors are more likely to be ascetic with larger spleens, associated with diabetes mellitus and chest infection. Univariate logistic regression analysis identified two independent predictors of IHM, i.e., the number of units of packed red blood cells transfused and Esophageal Varices Grade (Table 6).

Table 3. Endoscopic findings in survivors and non-survivors

Variables		All patients, n (%)	Survivors, n (%)	Non- Survivors, n (%)
Esophageal Varices (Grade)	GI	6 (8.6)	1 (1.43)	5 (7.14)
	GII	12 (17.1)	5 (7.14)	7 (10.0)
	GIII	13 (18.6)	7 (10.0)	6 (8.6)
	GIV	35 (50)	15 (21.43)	20 (28.57)*
	Eradicated	4 (5.7)	4 (5.7)	0
Gastric	Gastric Varices	24 (34.3)	11 (15.7)	13 (18.6)
	Portal hypertensive gastropathy (PHG)	38 (54.3)	18 (25.7)	20 (28.57)
	Gastric ulcer (GU)	6 (8.6)	2 (2.9)	4 (5.7)
	Gastric carcinoma	2 (2.9)	1 (1.4)	1 (1.4)
Endoscopic Treatment	Band ligation (BL)	32 (45.7)	12 (17.1)	20 (28.6)
	Histoacryl (HA)	24 (34.3)	11 (15.7)	13 (18.6)
	Injection sclerotherapy (IS)	13 (18.6)	9 (12.9)	4 (5.7)
	Argon plasma coagulation	1 (1.4)	0	1 (1.4)
Bleeding at Endoscopy		38 (54.3)	10 (14.3)	28 (40.0)**

*Fisher's test ($p < 0.02$). **$p < 0.01$

Table 4. Complications of liver cirrhosis and risk of mortality

Complication	All patients, n (%)	Survivor, n (%)	Non- Survivor, n (%)
Ascites	38 (54.3)	17 (24.3)	21 (30.0)*
Hepatic encephalopathy	17 (24.28)	9 (12.85)	8 (11.43)
SBP	4 (11.4)	1 (1.43)	3 (4.3)
HRS	11 (15.71)	5 (7.14)	6 (8.57)
PVT	15 (21.4)	9 (12.9)	6 (8.5)
Enlarged Spleen	55 (78.57)	22 (31.43)	33 (47.14)*

*$p < 0.01$

Table 5. Associated major comorbidity and risk of mortality

Associated Diseases, n (%)	All patients, n (%)	Survivor, n (%)	Non- Survivor, n (%)
Hypertension	8 (11.43)	2 (2.86)	6 (8.57)
Diabetes mellitus	26 (37.14)	12 (17.14)	14 (20.0)*
Neurological	7 (10.0)	2 (2.86)	5 (7.14)
Chest infection	9 (12.9)	2 (2.86)	7 (10.0)*
Cardiovascular	7 (10.0)	3 (4.28)	4 (5.71)
NSAIDs	3 (4.28)	1 (1.43)	2 (2.86)

*$p < 0.05$

Table 6. Logistic regression analysis of independent predictors of mortality

Variable	Odds Ratio	CI (95%)	p-value
Bags	1.38	1.034-1.452	<0.01
Esophageal Varices Grade	1.67	1.124-1.234	<0.01

The accuracy of MELD and Child–Pugh score in predicting IHM after variceal bleeding is shown in Table 7. MELD score was highly predictive of mortality at an optimized cut-off value of $\geqslant$ 12.9 (sensitivity 77.8%, specificity 80%) and Child cut-off value of $\geqslant$ 10.9 (sensitivity 50%, specificity 96.7%). AUROC for MELD and Child–Pugh score =

0.797 and 0.836, respectively. Differences between MELD's AUROC and that of Child-Pugh were statistically significant ($p < 0.01$).

Table 7. Areas under the curve for the Meld and Child-Pugh score

Method	Cut-Off	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV
MELD	≥ 12.9	0.797 (0.679–0.915)	77.80	80.00	80.00	77.80
Child	≥ 10.9	0.836 (0.697–0.975)	50.00	96.70	71.40	92.40

4. Discussion

According to the fourth Baveno Consensus Workshop, mortality predictors of esophageal varices bleeding are an area of further research as there is still no consensus on a model that accurately predicts the survival of cirrhotic patients with bleeding varices (22). In addition to the severity of the bleeding episode itself, mortality risk in patients with Esophageal Varices bleeding has a strong association with the severity of the underlying hepatic disease and associated major comorbidity. In our cohort, IHM in patients with liver cirrhosis and HCC admitted to the ICU duo to Esophageal Varices bleeding was 54.3%. Non-survivors suffered from more severe cirrhosis and poor hepatic reserve as indicated by Child class C and higher MELD score compared to those who survived. This finding was consistent with that of Magliocchetti et al. and Chen et al., who showed that the Child-Pugh score, albumin level, and encephalopathy correlated with survival (23, 24). The more severe cirrhosis in the former group of patients was somewhat expected because variceal bleeding is often a direct result of portal hypertension caused by underlying severe cirrhosis rather than the presence of HCC per se (23). Mortality was particularly high in Child class C patients who required longer hospital stays and more blood transfusions, which was consistent with other studies (25, 26). The prognosis of patients with HCC and GI involvement is poor because of massive bleeding and/or hepatic failure. In one series, the median survival was four weeks (26), and, in a second study, no patient survived beyond nine months (27). Compared with other studies on cirrhotic HCC patients with acute variceal bleeding, our results revealed a worse outcome (28, 29). It may be explained by poor hepatic reserve as indicated by Child class C and higher MELD score, advanced tumor stage of our patients, higher portal venous pressure, presence of more complications of liver cirrhosis and associated major comorbidity. The reported in-hospital mortality rate of 20.5% in cirrhotic HCC patients with variceal bleeding appeared to be within the reported range of 20–30% mortality rate for variceal bleeding patients in general, irrespective of the presence of HCC (30). This figure may be an underestimate of the true mortality rate (28, 31). The presence of ascites, sepsis, and elevated serum creatinine was statistically significant in non-survivors compared to the survivors. These findings are in accordance with those of Patch et al., who found six factors to have independent prognostic value for death, i.e., moderate to severe ascites, need for ventilation, white blood cell count, platelet count, partial thromboplastin time, and creatinine (32-34). In a large retrospective study of cirrhotics with variceal bleeding, raised serum creatinine, post-gastroscopy re-bleeding, presence of HCC and encephalopathy were found to be independent predictors of mortality (35). Hyponatremia has classically been considered relevant only at a serum sodium level < 130 mEq/L in patients with cirrhosis (36). Serum sodium was an independent risk factor for mortality in HCC patients evaluated for liver transplantation (37), and MELD-Na was better than MELD in the prediction of survival in unresected HCC patients (38). In our study, there was no statistically significant difference between survivors and non-survivors concerning hyponatremia. This can be explained by the limited sample size. The presence of active bleeding on index endoscopy was statistically significant in non-survivors compared to the survivors, a factor that also was reported in the series of Bamba et al. (26). Grade IV Esophageal Varices was statistically significant in non-survivors compared to the survivors, and esophageal varices grade was an independent predictor of in-hospital mortality. These findings were in accordance with those of Park et al. (39), who reported three risk factors for variceal bleeding, i.e., the size of varix, presence of red color sign, and heavy alcohol consumption. In their series, these factors had independent correlations with first variceal hemorrhage, and patients with large varices showed approximately three times higher bleeding risk than those with small varices. The development of two major complications, variceal bleeding and HCC, was significantly correlated with decreased survival rate (41). In our series, patients with recurrent bleeding showed a statistically significant difference ($p < 0.01$) between survivors and non-survivors. The occurrence of rebleeding was significantly associated with mortality, a factor also reported in the series of Bamba et al. (26), who reported that advanced Child score, MELD score ⩾ 18, the number of units transfused during the first 24 hours, the presence of ascites, an active bleeding at initial endoscopy, high transaminase levels, and low serum sodium were predictive of early mortality. These parameters also were consistent with other studies (41). In our study, the presence of gastric varices had no statistically significant difference between survivors and non-survivors. It can be explained by the

limited number of gastric varices in our study and most patients with gastric variceal bleeding were gastroesophageal varices, type 1 (appear as continuations of esophageal varices along the lesser curve of the stomach) and had a lower risk of mortality compared with other types of gastric varices. These findings were in accordance with those of Han et al. (30), who demonstrated that, in comparison with gastric variceal bleeding, esophageal variceal bleeding was an independent predictor of intra-hospital mortality. Portal vein thrombosis resulting from tumor infiltration might have also contributed to the high portal venous pressure and led to more severe bleeding in some cases, but it has no statistically significant difference between survivors and non-survivors in our study. It can be explained by the small number of cases with PVT in the two groups. In patients with HCC complicated by PVT, the tendency for concurrent severe variceal bleeding was attributed to the increased resistance to portal outflow by tumor thrombus and to the formation of arterioportal shunting, which aggravated portal hypertension by augmenting portal flow from arterial vessels (23). Co-morbid conditions can affect the outcome of HCC patients presenting with acute variceal bleeding. In our study, the presence of diabetes mellitus and chest infection had a statistically significant difference in non-survivors compared to survivors. We also found a longer hospital stay and greater blood transfusion in the non-survival group compared to the survivors. Also, Chojkier et al. found that co-morbid conditions and greater transfusion requirements showed a striking association with mortality (33). The higher mortality rate in patients with diabetes was due to the complications of diabetes mellitus and to the increased risk of hepatocellular failure in long-term follow up (38). Hyperglycemia induces splanchnic hyperemia, increases portal pressure, and may increase the risk of variceal bleeding (39, 40). In our study, MELD scores were more predictive of mortality than the Child–Pugh scores. The AUROC of MELD and Child–Pugh scores were statistically different ($p < 0.01$). MELD scores were highly predictive of mortality at an optimized cut-off value of 12.9 (sensitivity 77.8%, specificity 80%). These results were different from those of Amitrano et al. (41), who found that both MELD and Child scores were predictive of short-term mortality in HCC cirrhotics with bleeding Esophageal Varices. In their series, patients with MELD score >15 had a significantly worse survival rate than patients with MELD < 15. In the study of Bamba et al. (26), a MELD score $\geqslant$ 18 was predictive of early mortality. It might be explained by the different characteristics of the patients. HVPG > 20 mmHG measured at admission has been documented to be an important prognostic factor predictive of treatment failure in AVB (36). Non-invasive predictors of mortality and treatment failure can select cases for HVPG measurement. We recommend prophylactic band ligation and eradication of Esophageal Varices in HCC patients with MELD scores >12.9, high grades of Esophageal Varices, and associated major comorbidity if the HVPG > 20 mmHG. Also TIPS should be used to rescue HCC patients with intractable variceal bleeding, as this technique can decrease portal pressure and may lead to cessation of torrential variceal bleeding as well as prevent further re-bleeding. However, due to the limited number of cases in our study and its retrospective nature, further research is still needed in large-scale, prospective trials.

5. Conclusions

In-hospital mortality was particularly high among HCC cirrhotics with acute variceal bleeding. The number of units of packed red blood cell transfused, MELD score at cut-off value > 12.9, high grade of Esophageal Varices and active bleeding on index endoscopy, associated major comorbidity were highly predictive of IHM. We recommend prophylactic band ligation and eradication of Esophageal Varices in HCC patients with MELD score >12.9, high grade Esophageal Varices and associated major comorbidity if the HVPG > 20 mmHg. Also TIPS should be used to rescue HCC patients with intractable variceal bleeding. However, due to the limited number of cases in our study and retrospective nature, further research in larger prospective trials is still needed.

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Conflict of Interest:
There is no conflict of interest to be declared.

Authors' contributions:
All authors contributed to this project and article equally. All authors read and approved the final manuscript.

References

1) El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999; 340: 745-50. doi: 10.1056/NEJM199903113401001, PMid: 10072408

2) Centers for Disease Control and Prevention (CDC). Hepatocellular carcinoma - United States, 2001-2006. MMWR Morb Mortal Wkly Rep. 2010;59: 517-20. PMid: 20448528
3) Sayana H., Yousef O. and Clarkston WK. Massive upper gastrointestinal hemorrhage due to invasive hepatocellular carcinoma and hepato-gastric fistula. World J Gastroenterol. 2013; 19 (42): 7472-5. doi: 10.3748/wjg.v19.i42.7472, PMid: 24259980, PMCid: PMC3831231
4) Yeo W, Sung JY, Ward SC, Chung SC, Lee WY, Li AK, et al. A prospective study of upper gastrointestinal hemorrhage in patients with hepatocellular carcinoma. Dig Dis Sci. 1995; 40: 2516-21. doi: 10.1007/BF02220435, PMid: 8536505
5) Smith JL, Graham DY. Variceal hemorrhage: a critical evaluation of survival analysis. Gastroenterology 1982; 82: 968. PMid: 7037525
6) De Dombal FT, Clarke JR, Clamp SE, et al. Prognostic factors in upper GI bleeding. Endoscopy 1986; 18:6s. doi: 10.1055/s-2007-1018418, PMid: 3519197
7) Graham DY, Smith JL. The course of patients after variceal hemorrhage. Gastroenterology 1981; 80: 800. PMid: 6970703
8) Grace ND. Prevention of initial variceal hemorrhage. Gastroenterol Clin North Am.1992; 21:149. PMid: 1349004
9) Bettinger D., Knuppel E, Euringer W, Spangenberg HC, Rossle M, Thimme R and Schultheiss M. Efficacy and safety of transjugular intrahepatic portosystemic shunt (TIPS) in 40 patients with hepatocellular carcinoma. Aliment. Pharmacol.Ther. 2015; 41(1): 126-36. doi: 10.1111/apt.12994, PMid: 25329493
10) Ruzzenente A, Valdegamberi A, Campagnaro T, et al. Hepatocellular carcinoma in cirrhotic patients withportal hypertension: is liver resection always contraindicated? World J. Gastroenterol. 2011; 17: 5083–8. doi: 10.3748/wjg.v17.i46.5083, PMid: 22171142, PMCid: PMC3235591
11) Santambrogio R, Kluger MD, Costa M, et al. Hepatic resection for hepatocellular carcinoma in patients with Child-Pugh's A cirrhosis: is clinical evidence of portal hypertension a contraindication? HPB 2013; 15: 78-84. doi: 10.1111/j.1477-2574.2012.00594.x,PMid: 23216782, PMCid: PMC3533715
12) Kanwal F, Befeler A, Chari RS, et al. Potentially curative treatment inpatients withhepatocellular cancer–results from the liver cancer research network. Aliment Pharmacol Ther.2012; 36: 257–65. doi: 10.1111/j.1365-2036.2012.05174.x, PMid: 22670798
13) Villanueva C, Piqueras M, Aracil C, et al. A randomized controlled trial comparing ligation and sclerotherapy as emergency endoscopic treatment added to somatostatin in acute Variceal bleeding. J. Hepatol. 2006; 45: 560-7. doi: 10.1016/j.jhep.2006.05.016, PMid: 16904224
14) Singal AK, Jampana SC, Singal V, KuoYF. Hepatocellular carcinoma predicts in-hospital mortality from acute variceal hemorrhage among patients with cirrhosis. J Clin Gastroenterol. 2012; 46: 613–9. doi: 10.1097/MCG.0b013e318256b670, PMid: 22772741
15) European Association For The Study Of The Liver; European Organization For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J. Hepatol. 2012; 56: 908-43. doi: 10.1016/j.jhep.2011.12.001, PMid: 22424438
16) Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020–2. doi: 10.1002/hep.24199, PMid: 21374666, PMCid: PMC3084991
17) Bettinger D, Knuppel E, Euringer W, Spangenberg HC, Rossle M, Thimme R, et al. Efficacy and safety of transjugular intrahepatic portosystemic shunt (TIPS) in 40 patients with hepatocellular carcinoma." Aliment Pharmacol Ther. 2015; 41(1): 126-36. doi: 10.1111/apt.12994, PMid: 25329493
18) Pagliaro L, D'Amico G, Pasta L, Tine` F, Aragona E, Politi F, et al. Efficacy and efficiency of treatments in portal hypertension. In: de Franchis R, ed. Portal Hypertension II. Proceedings of the second Baveno International Consensus Workshop on Definitions, Methodology and Therapeutic Strategies. Oxford: Blackwell Science 1996; 159-179.
19) D'Amico G, De Franchis R, and a Cooperative Study Group. Upper Digestive Bleeding in Cirrhosis. Post-therapeutic Outcome and Prognostic Indicators. Hepatology 2003;38: 599-612. doi: 10.1053/jhep.2003.50385, PMid: 12939586
20) El-Serag HB, Everhart JE. Improved survival after variceal hemorrhage over an 11-year period in the Department of Veterans Affairs. Am J Gastroenterol. 2000; 95: 3566-73. doi: 10.1111/j.1572-0241.2000.03376.x, PMid: 11151893
21) Chalasani N, Kahi C, Francois F, Pinto A, Marathe A, Bini EJ, et al. Improved patient survival after acute variceal bleeding: a multicenter, cohort study. Am J Gastroenterol. 2003; 98: 653-9. doi: 10.1111/j.1572-0241.2003.07294.x, PMid: 12650802

22) Garcia-Tsao G, D´Amico G, Abraldes JG. Predictive models in Portal Hypertension. In Portal Hypertension Proceedings of the fourth Baveno International Consensus Workshop on methodology of diagnosis and treatment. Ed de Franchis R. 2006; 47-100.
23) Chen CH, Sheu JC, Huang GT, et al. Characteristics of hepatocellular carcinoma presenting with variceal bleeding. J Gastroenterol Hepatol. 1998; 13:170-4. doi: 10.1111/j.1440-1746.1998.tb00633.x, PMid: 10221819
24) Magliocchetti N, Torchio P, Corraco G, Arico S, Favilli S. Prognostic factors for long-term survival in cirrhotic patients after the first episode of liver decompensation. Ital. J. Gastroenterol Hepatol. 1997; 29:38-46. PMid: 9265577
25) D'Amico G, Garcia-Tsao G. and Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. Journal of Hepatology 2006; 44, 217-31. doi: 10.1016/j.jhep.2005.10.013, PMid: 16298014
26) Bambha K, Kim WR, Pedersen R, et al. Predictors of early rebleeding and mortality after acute variceal hemorrhage in patients with cirrhosis. Gut 2008; 57, 814-20. doi: 10.1136/gut.2007.137489, PMid: 18250126
27) Maruyama A, Murabayashi K, Hayashi M, Nakano H, Isaji S, Uehara S, et al. Hepatocellular carcinoma complicated by gastrointestinal hemorrhage caused by direct tumor invasion of stomach. J. Hepatobiliary Pancreat. Surg. 2004; 6: 90-3. doi: 10.1007/s005340050089
28) Nicoll AJ, Ireton HJ, Crotty B. Gastrointestinal bleedingfrom hepatocellular carcinoma invading the stomach. J. Gastroenterol Hepatol. 2004; 9: 533-5. doi: 10.1111/j.1440-1746.1994.tb01290.x
29) Chen CH, Sheu JC, Huang GT, Lee HS, Yang PM, Wong JM. Characteristics of hepatocellular carcinoma presenting with variceal bleeding. J. Gastroenterol. Hepatol. 2004;13: 170-4. doi: 10.1111/j.1440-1746.1998.tb00633.x
30) Han ML, Chen CC., Wu MS, et al. Predictors of in-hospital mortality after acute varicealbleeding in patients with hepatocellular carcinoma and concurrent main portal vein thrombosis. Journal of Gastroenterology and Hepatology 2004; 29: 344-51. doi: 10.1111/jgh.12341, PMid: 23870023
31) Lang BH, Poon RT, Fan ST, Wong J. Outcomes of patients with hepatocellular carcinoma presenting with variceal bleeding. Am. J. Gastroenterol. 2004; 99: 2158-65. doi: 10.1111/j.1572-0241.2004.40336.x, PMid: 15554997
32) Sarin SK, Kumar A, Angus PW, Baijal SS, Baik SK, Bayraktar Y. Diagnosis and management of acute variceal bleeding: Asian Pacific Association for Study of the Liver recommendation. Hepatol. Int. 2004; 5: 607-24. doi: 10.1007/s12072-010-9236-9, PMid: 21484145, PMCid: PMC3090560
33) Chojkier M, Laine L, Conn HO, Lerner E. Predictors ofoutcome in massive upper gastrointestinal hemorrhage. J Clin Gastroenterol. 2004; 8:16-22. doi: 10.1097/00004836-198602000-00005
34) Patch D, Nikolopoulou V, McCormick A, Dick R, Armonis A, Wannamethee G. Factors related to early mortality after TIPS for failed endoscopic therapy in acute variceal bleed. J Hepatol. 1997; 28:454-60. doi: 10.1016/S0168-8278(98)80320-6
35) Conn HO. Quantifying the severity of hepatic encephalopathy. In: Conn HO, Bircher J. Eds. Hepatic Encephalopathy: Syndromes and Therapies. Bloomington Illinois: Medi-Ed Press. 1997; 13-26.
36) Meza-Junco J, Montano-Loza AJ, Baracos VE, Prado CM, Bain VG, Beaumont C, et al. Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. J Clin Gastroenterol. 2013; 47: 861-70. doi: 10.1097/MCG.0b013e318293a825, PMid: 23751844
37) Hsu CY, Huang YH, Hsia CY, Su CW, Lin HC, Loong CC, et al. A new prognostic model for hepatocellular carcinoma based on total tumor volume: the Taipei Integrated Scoring System. J Hepatol. 2010; 53: 108-17. doi: 10.1016/j.jhep.2010.01.038, PMid: 20451283
38) Lo GH. The use of transjugular intrahepatic portosystemic stent shunt (TIPS) in the management of portal hypertensive bleeding. Journal of the Chinese Medical Association 1997;77 395-402. doi: 10.1016/j.jcma.2014.05.010, PMid: 25028297
39) Park DK, Um SH, Lee JW, et al. Clinical significance of variceal hemorrhage in recent years inpatients with liver cirrhosis and esophageal varices. Journal of Gastroenterology and Hepatology 2004; 19, 1042-51. doi: 10.1111/j.1440-1746.2004.03383.x, PMid: 15304123
40) Sarin SK, Laiioid, Saxena SP, Murif NS, Makwana UK. Prevalence, Classification and Natural History of Gastric Varices: A Long-term Follow-up Study in 568 Portal Hypertension Patients. Hepatology 1992; 16 (6).1343-9.
41) Amitrano L., Guardascione M A, Bennato R, Manguso F, Balzano A. MELD score and hepatocellular carcinoma identify patients at different risk of short-term mortality among cirrhotics bleeding from esophageal varices. Journal of Hepatology. 2005;42, 820-5. doi: 10.1016/j.jhep.2005.01.021, PMid: 15885352