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Predictive factors of failure to control bleeding and 6-week mortality after variceal hemorrhage in liver cirrhosis - a tertiary referral center experience

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ABSTRACT

Background: Mortality from variceal bleeding remains high despite the therapeutic progress in severe cirrhosis. Understanding the predictive factors of failure to control bleeding (FTB) and mortality assumes better future therapies. Comorbidities are thought to be important prognostic factors for variceal bleeding. Aim: To assess the factors associated with FTB and with 42-day mortality and to evaluate the influence of comorbidities on these patients' prognosis. Method: Patients with variceal bleeding admitted in a tertiary referral center were prospectively included in the study and followed over 6 weeks. CirCom score and Charlson index were used for the assessment of comorbidities. Results: Of the 138 patients included in the study, 27(19.5%) were considered to have FTB. Child C class (74.07% vs 32.43%, p<0.001), Meld score (20.5 vs 16.00, p=0.004) and creatinin level (1.04 vs 0.81, p=0.01) were associated with FTB, but only Child class was independently associated with FTB in multivariate analysis (OR=2.94, p=0.006). Mortality at 42 days (21.7%) was influenced by the severity of the dissease assessed through Child Class (76.66% vs 30.55%-Child C, p<0.001) and MELD score (21.00 vs 16.00, p<0.001). Creatinin level (1.00 vs 0.7, p=0.02) and acute kidney injury (26.66% vs 7.40%, p=0.009) were also prognostic factors for the 6-week mortality. Comorbidities didn't influence the mortality (CirCom>1 (16.7% vs 21.3%, p=0.76) and Charlson index>4 (36% vs 47.2%, p=0.41). Conclusion: The severity of cirrhosis is an important prognostic factor for FTB and 42-day mortality. Identifying the factors associated with early mortality may help selecting patients needing more than conventional therapy.

Keywords: variceal bleeding, cirrhosis, failure to control bleeding, mortality, predictive factors

INTRODUCTION

Acute variceal hemorrhage is a major complication of liver cirrhosis and is responsible for one third of cirrhosis deaths (Thuluvath, 2009; Sanyal, 2013). The Child Turcotte Pugh score and the Model for End Stage Liver Disease (MELD), proven to have a prognostic value in liver cirrhosis (Pugh et al., 1973; Kamath et al., 2001) have also been validated for the clinical course of variceal hemorrhage (Reverter et al., 2014; Chalasani et

al., 2002; Lee et al., 2002).

Although insufficiently validated, the presence of comorbidities cannot be ignored when discussing short-term mortality. Some research groups have already included in mixed scores the different variables that seem to influence the prognosis of liver cirrhosis patients (CirCom) (Jepsen et al., 2014).

On the other hand, the recent progress in the therapeutical means for variceal hemorrhage (band ligation, vasoactive medication, antibiotic treatment) (Graham and Smith, 1981; Carbonell et al., 2004; Chalasani et al., 2003; Thomopoulos et al., 2006; Stokkeland et al., 2006; D'Amico and De Franchis, 2003) has lead to a better control of bleeding; as a result, the natural history and prognosis of these patients can be different from the data published previously. The studies report values of mortality between 16 and 24% 6 weeks after the bleeding episode; these values have improved in the past few years but are still high enough to be disturbing and to motivate the continuing research on the risk factors and treatment. The key moment to calculate the prognosis is 6 weeks after the variceal hemorrhage, since the risk of death of patients after this threshold becomes similar to that of patients who have never bled (Sanyal, 2013; de Franchis and Primignani, 1992; Albillos, 2009).

The aim of this prospective, observational study was:

1. To assess the factors that are associated with failure to control bleeding and with 42-day mortality
2. To evaluate the influence of comorbidities on failure to control bleeding and 42-day mortality.

METHODS

Patient selection criteria

We included in the study all patients presented to the Emergency Department of a tertiary medical centre (The Regional Institute of Gastroenterology and Hepatology "Prof. Dr. Octavian Fodor", Cluj-Napoca, Romania) with upper gastrointestinal bleeding (UGIB) of variceal origin. It is worth mentioning that our hospital is the reference centre for the endoscopic treatment of upper digestive bleeding in the entire region (including almost 7 million inhabitants). The patient inclusion period spanned 8 months (November 2012 - July 2013) and all patients were prospectively followed over a period of 6 weeks. The inclusion criteria were the following: hematemesis and/or melena, liver cirrhosis diagnosis, bleeding of variceal origin, upper digestive endoscopy performed in the first 24 hours, age above 18 years. The patients who did not undergo endoscopy or did not have a variceal bleeding were excluded from the study.

Cirrhosis was diagnosed using unequivocal clinical (palmar erythema, spider nevi, gynecomasty, hepatomegaly with sharp anterior margin, splenomegaly, ascites, oedema, encepalopathy), laboratory and imaging criteria (irregular liver contour, splenomegaly, ascites, perigastric and pericholecystic collateral circulation and in the spleen hilum, recanalizaton of the round ligament). For defining the acute kidney injury (AKI), we used the 1,5mg/dL creatinin threshold.

The study was performed in accordance to the Helsinki declaration and was approved by the Ethics Committee of the Hospital. All patients signed an informed consent.

Patient management

Demographic and clinical data considered relevant for liver cirrhosis were recorded for each patient upon admission, as well as their comorbidities. Any arterial pressure below 90mmHg was defined as hypotension, while any heart rate above 100 beats/minute was considered tachycardia: hemodynamic instability was defined in the presence of at least one of these criteria.

Esogastroduodenoscopy was performed in each patient in the first 24 hours (between at least 20 minutes and at most 19 hours), at a mean of 3 hours 14 minutes from presentation (most patients were investigated in the first 12 hours, n=135, with an Olympus Exera II CLE165 equipment). After confirming the variceal site of the bleeding, band ligation and/or sclerotherapy (for gastric varices) were performed. In case of failure to control bleeding (FTB) or rebleeding, the endoscopy was repeated, as well as the band ligation. The balloon tamponade was used in case of massive bleeding where an effective endoscopic treatment could not be performed. Beside the endoscopic treatment, all patints received vasoactive medication (Sandostatin or Terlipressin) and all patients received antibiotic treatment (IV 3rd generation cephalosporins for at least 5 days). Rebleeding prevention (secondary prophylaxis) was started on the 6th day from the bleeding episode and was performed using Propranolol treatment and elastic ligatures.

When assessing comorbidities, we used both the CirCom (Jepsen et al., 2014) score, which quantifies conditions with impact on cirrhosis progression, as well as the Charlson comorbidity index (Charlson et al., 1987), which quantifies conditions with impact on any other disease (Supplementary table 1 and 2 below). Considering that all patients had liver cirrhosis, in calculating the Charlson index all patients were atributed at least 3 points. For each of the 2 scores used, the patients were divided into 2 groups: without comorbidities and with at least one comorbidity.

Supplementary **table 1.** CirCom score for comorbidities (Jepsen et al., 2014)

Number of points	Comorbidity
1	Chronic obstructive pulmonary disease
	Acute myocardial infarction
	Peripheral arterial disease
	Epilepsy
	Substance abuse other than alcoholism
	Heart failure
	Non metastatic or hematologic cancer
3	Metastatic cancer
	Chronic kidney disease

Supplementary **table II** – Charlson Index (Charlson et al., 1987)

Number of points	Comorbidity
1	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-stage organ damage
	Any tumor
	Leukemia
	Lymphoma
3	Moderate or severe liver disease
4	Metastatic solid tumor
	AIDS

Patient follow-up

All patients were followed for 6 weeks. The time interval used to define the acute bleeding episode was 5 days and failure to control bleeding was defined as follows: death or need to change therapy defined by one of the following criteria:

- Fresh hematemesis or NG aspiration of ≥100ml of fresh blood ≥2h after the start of a specific drug treatment or therapeutic endoscopy;
- Development of hypovolaemic shock
- 3g drop in Hb within any 24h period if no transfusion administered (Baveno V criteria) (de Franchis and Baveno, 2010).

Statistical analysis

The statistical analysis was performed using the SPSS software, version 20, Chicago, IL, USA. Nominal variables were characterized using frequencies. Quantitative variables were described by mean and standard deviation or by median and IQR, when appropriate. The level of statistical significance was set at $p<0.05$. Differences of frequencies between nominal variables were assessed with the chi-square test or Fischer exact test. Continuous variables were compared using the t Student or Mann–Whitney tests, when appropriate. Multivariate analysis was performed using logistic regression. We included in the univariate analysis the parameters reaching a significance level $p < 0.05$. The cutoff value was chosen for maximal sensitivity and specificity. We calculated the sensibility, specificity, positive predictive value and negative predictive values for the cutoff value of the score.

RESULTS

Between November 2012 and July 2013, 533 patients

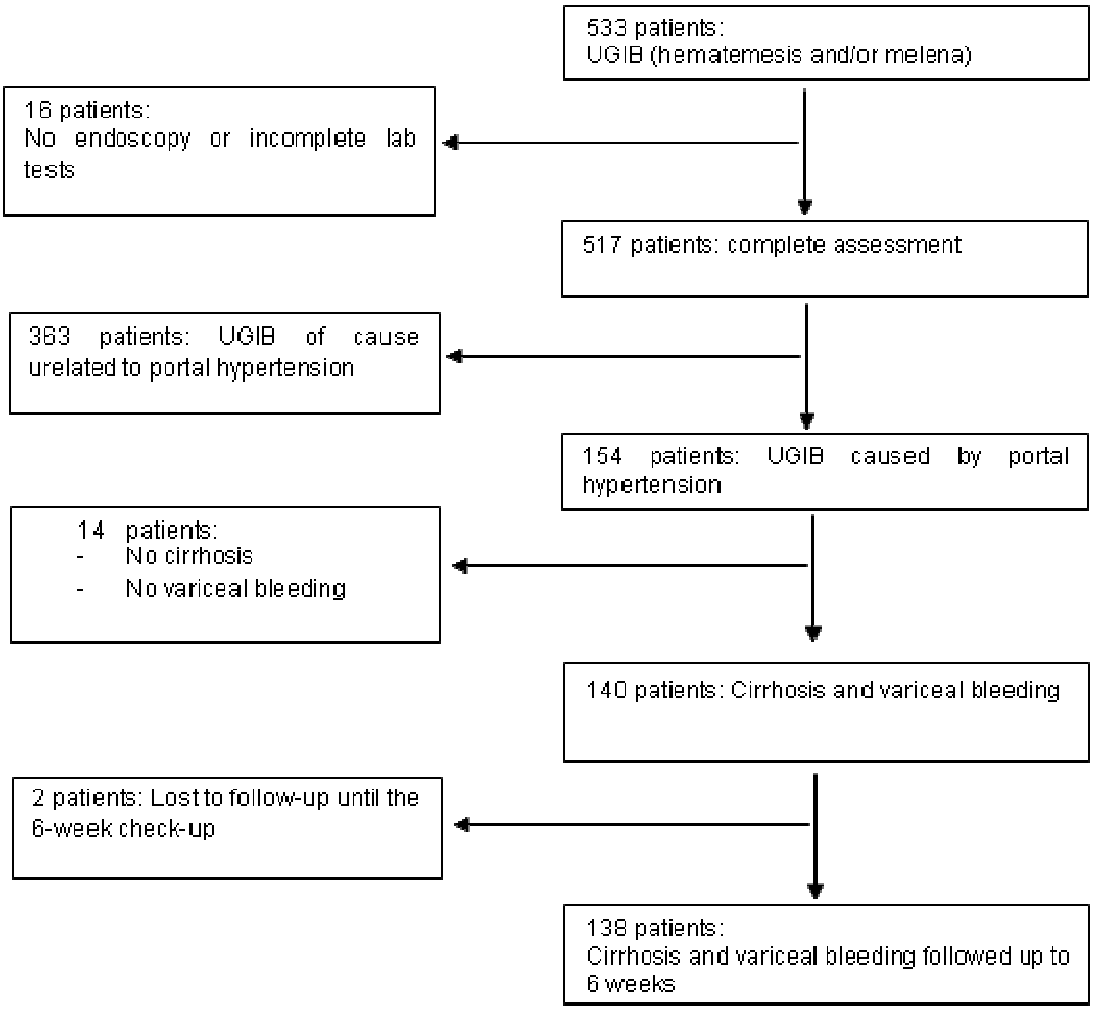

Figure 1. Study group composition and selection of patients presenting with UGIB to the Regional Institute of Gastroenterology and Hepatology "Prof. Dr. Octavian Fodor". UGIB: upper gastrointestinal bleeding

with upper gastrointestinal bleeding (hematemesis and/or melena) presented in the Emergency Department of the Regional Institute of Gastroenterology and Hepatology "Prof. Dr. Octavian Fodor". Of these, 16 did not undergo upper digestive endoscopy and were excluded from the study. In 154 patients, the cause of the UGIB was related to the portal hypertension, but 14 did not have cirrhosis or the origin of the bleeding was other than esophageal varices. The remaining 140 patients had both liver cirrhosis and variceal bleeding. Two patients were lost form the study until the 6-week check-up. It follows that 138 patients were included in the final analysis (figure 1).

Baseline characteristics of the patients included in the study are presented in table 1. The male gender was dominant, with a median age of 58 years; the ethanolic etiology was highly prevalent, the anemia found in patients was on the average of moderate severity and we found an equal distribution between Child B and C patients.

Failure to control bleeding

In our study group, 27 patients (19.5%) were considered to have failure of bleeding control. 16 patients (59.27%) of those with uncontrolled hemorrhage died, but all had been hemodynamically unstable at presentation. 8 of them had fresh hematemesis. A decrease of > 3g in hemoglobin 48 hours from the admission was found in 3 patients (11.11%). The factors associated with failure to control bleeding are presented in table 2. The mean time interval from the onset of symptoms to endoscopy was 25 hours for those who were treated successfully compared to 1 hour and 25 minutes for those who rebled or continued to bleed.

Table 1. Baseline characteristics of study group

Variable	Mean+ SD / Median (IQR)
Age (years)	58.00 (52.00; 65.00)
Gender (M) (%)	95 (68.8%)
Etiology (n, %)	
Viral	34 (24.6%)
Ethanolic	81 (58.7%)
Mixed	15 (10.9%)
Other	8 (5.8%)
Hemoglobin (g/dL)	9.30 (7.63; 11.50)
Platelets ($x10^9$)	101.00 (69.25; 130.00)
ALT (U/l)	28.00 (18.00; 43.50)
AST (U/l)	60.50 (40.00; 104.50)
Creatinin (mg/dL)	0.85 (0.61; 1.42)
Total bilirubin	2.70 (1.50; 6.55)
Albumin (g/dL)	2.92 ± 0.66
INR	1.88 (1.51; 2.60)
Ascites (n, %)	74 (53.6%)
Encephalopathy (n, %)	51 (37%)
Child (n, %)	
A	27 (19.6%)
B	55 (39.9%)
C	66 (40.6%)
MELD	16.00 (13.00; 20.00)

Table 2. Univariate analysis associated with failure to control bleeding

Variable	Failure to control bleeding		*p*
	Yes (n= 27)	No (n=111)	
First episode of bleeding (n, %)	21 (77.77%)	68 (61.26%)	0.16*
Arterial hypotension (n, %)	3 (11.11%)	5 (4.50%)	0.39*
Tachycardia (n, %)	16 (59.25%)	42 (37.83%)	0.07*
Hemodinamic instability (n, %)	17 (62.96%)	45 (40.54%)	**0.05***
Active bleeding at endoscopy	4 (14.81%)	30 (27.02%)	0.18*
High risk of FTB[§]	0 (0%)	12 (10.81%)	0.15*
Creatinin (mg/dL)	1.04 (0.73; 1.95)	0.81 (0.60; 1.32)	**0.01****
Creatinin >1.5	7 (25.92%)	9 (8.10%)	**0.02***
Total bilirubin (mg/dL)	4.10 (1.60; 10.00)	2.70 (1.47; 6.10)	0.15**
Albumin (g/dL)	2.60 (2.32; 2.95)	3.10 (2.60; 3.40)	**0.03****
INR	2.13 (1.59; 3.04)	1.83 (1.51; 2.22)	0.10**
Prothrombin time (s)	30.70 (22.15; 41.25)	25.00 (22.00; 31.00)	0.14**
Ascites (n, %)	17 (62.96%)	54 (48.64%)	0.38*
Hepatic encephalopathy (n, %)	18 (66.66%)	33 (29.72%)	**<0.001***
Child class (n, %)			
A	2 (7.40%)	25 (22.52%)	
B	5 (18.51%)	50 (45.04%)	**<0.001***
C	20 (74.07%)	36 (32.43%)	
MELD	20.5 (16.00; 26.00)	16 (13.00; 19.00)	**0.004****
Charlson	3 (3; 7)	3 (3; 6)	0.10 [¶]
Charlson≥4 (n, %)	1 (3.70%)	9 (8.10%)	0.70*
CirCom	0 (0; 2)	0 (0; 1)	0.41[¶]
CirCom≥1 (n, %)	4 (14.81%)	24 (21.62%)	0.60*

[§]High risk of failure to control bleeding = Child B+active bleeding
[¶]values expressed as median (min; max)
*values expressed as n (%)
**values expressed as median (25; 75 percentiles)
***values expressed as mean± SD
FTB= failure to control bleeding

Table 3. Multivariate analysis of factors associated with failure to control bleeding

Variable	Odds ratio	95% CI	p
Child class	2.94	1.34 to 6.43	**0.006**
Creatinin (mg/dL)	2.15	0.81 to 5.68	0.12
Hemodinamic instability	1.75	0.69 to 4.45	0.23

Table 4. Univariate analysis of factors associated with 42-day mortality

	42-days check-up		
Variable	**Dead (n= 30)**	**Survived (n=108)**	p
First episode of bleeding (n, %)	23 (76.66%)	66 (61.11%)	0.17*
Arterial hypotension (n, %)	3 (10%)	5 (4.6%)	0.50*
Tachycardia (n, %)	19 (63.3%)	39 (36.1%)	0.01*
Active bleeding during endoscopy (n, %)	10 (33.3%)	27 (25%)	0.49*
High risk of FTB [§] (n, %)	1 (3.33%)	11 (10.18%)	0.41*
Creatinin (mg/dL)	1 (0.7; 1.6)	0.7 (0.6;1)	0.02**
Creatinin >1.5 (n, %)	8 (26.66%)	8 (7.40%)	<0.001*
Total bilirubin (mg/dL)	3.9 (2.2; 6.2)	2.0 (1.3; 4.0)	<0.001**
Albumin (g/dL)	2.5 ± 0.5	3.00 ± 0.7	0.001***
INR	2.14 (1.66; 2.66)	1.60 (1.49; 1.89)	0.001**
Prothrombin time (s)	32.45 (26.9; 42.8)	24.50 (21.8; 29.3)	0.002**
Ascites (n, %)	20 (66.7%)	79 (73.2%)	0.64*
Hepatic encephalopathy (n, %)	21 (70%)	30 (27.8%)	<0.001*
Child class (n, %)			
A	1 (3.33%)	26 (24.07%)	
B	6 (20.00%)	49 (45.37%)	<0.001*
C	23 (76.66%)	33 (30.55%)	
MELD score	21 (17.5; 27.5)	16 (13; 19)	<0.001**
Charlson index	3 (3; 7)	3 (3; 6)	0.30[¶]
Charlson>4 (n, %)	11 (36.7%)	51 (47.2%)	0.41*
CirCom	0 (0; 2)	0 (0; 1)	0.54[¶]
CirCom>1 (n, %)	5 (16.7%)	23 (21.3%)	0.76*
Failure to control bleeding (n, %)	20 (66.66%)	5 (4.62%)	<0.001*

[§]High risk of failure to control bleeding = Child B+active bleeding
[¶]values expressed as median (min; max)
*values expressed as n (%)
**values expressed as median (25;75 percentiles)
***values expressed as mean± SD
FTB=failure to control bleeding

According to the clinical criteria of patients defined as high risk for failure to control bleeding (Child C or Child B plus active bleeding) (García-Pagán et al., 2010) in our population, only Child C class of severity significantly predicted the FTB (20 (74.07%) vs 36 (32.43%), p=0.002). Child B patients bleeding actively during endoscopy did not have a higher rate of FTB (p=0.15), neither when taken together Child B plus C who presented active bleeding (16 (59.25%) vs 44 (39.63%), p=0.10).

The CirCom score and Charlson index did not show any influence on FTB (p=0.47). Interestingly, we noticed that patients with lower Charlson scores had a higher rate of FTB (1 patient from the group with failure vs 9 patients from the group without failure, having at least one commorbidity, p=0.47). When we looked for any possible explanation, we found that the time from the first symptom to endoscopy was significantly lower in these patients (1.27±13.0 hours in the failure group vs 25.65±32.13 hours in the non-failure group, p=0.05). These data probably prove that patients at higher risk are transferred more rapidly to our unit.

In multivariate analysis, only the severity of the disease expressed through Child class was independently associated with failure to control bleeding (table 3). In order to avoid colinearity, we did not include encephalopathy, ascites or INR in multivariate analyses, since they are variables of the Child-Pugh score.

Forty-two day mortality

The next objective was to analyse the factors associated with 42-day mortality. Thirty patients (21.7%) died during

Table 5a. Multivariate analysis of factors associated with 42-day mortality (5a including Child class; 5b including MELD score)

Variable	Odds ratio	95% CI	p
Child class	4.28	1.87 to 9.77	**<0.001**
Creatinin (mg/dL)	2.64	1.00 to 6.91	**0.04**

Table 5b

Variable	Odds ratio	95% CI	p
MELD	1.10	1.01 to 1.21	**0.02**
Encephalopathy	4.23	1.50 to 11.94	**0.006**
Albumin (g/dL)	0.89	0.34 to 2.37	0.82

the first 6 weeks: 19 (63.3%) from uncontrolled bleeding, 9 (30%) due to hepatic failure and 2 (6.6%) due to ventricular fibrillation. As mentioned, 16 patients (53.33%) died in the first 5 days.

The factors associated with 42-day mortality are presented in Table 4 above.

Again, the most important factors associated with 42-day mortality are those related to the severity of the disease. The MELD score and the Child class were significantly associated in univariate analysis with death at 6 weeks after UGIB ($p<0.001$ in both cases). We found the MELD > 18 cutoff to be predictive of death (sensitivity 69%, specificity 72.6%).

It is worth mentioning that AKI had a significant influence on 6-week survival ($p=0.009$). In addition, AKI was significantly correlated with the presence of ascites ($p=0.01$). Failure to control bleeding at 5 days was also significantly associated with 42-day mortality ($p<0.001$). Of the patients defined as high risk for failure to control bleeding, only the Child C severity class had asignificant influence on mortality prediction ($p=0.001$). Patients from Child B class with active bleeding at endoscopy didn't have a higher mortality risk in our study ($p=0.41$), only when considering Child B plus C with active bleeding together (20 (66.66%) vs 40 (37.08%), $p=0.007$).

In order to avoid data colinearity, for multivariate analysis, we created two different models, one of them including the Child class while the other included the MELD score. In both models, we did not include the variables used for calculating Child and MELD scores, but only the score values, so as not to insert the variables twice in the analysis. In the first model, including the Child class, only the severity of the disease expressed by the Child score was independently associated with mortality at 6 weeks ($p=0.0005$, OR=4.28, 95% CI=1.87-9.77), while in the second model, the MELD score (OR=1.10, 95%CI=1.01-1.21, $p=0.02$) and encephalopathy (OR=4.23, 95%CI=1.50-11.94, $p=0.006$) were independently associated with mortality ($p=0.02$ and $p=0.006$ respectively) (Table 5a,b).

DISCUSSION

The present study proves that comorbidities (quantified using the Charlson and CirCom scores) do not influence the short-term prognosis of patients with variceal bleeding. The highest prognostic value is held by the liver function (Child and MELD scores) but the AKI should definitely not be neglected. We find the validation of the prognostic factors for patients with variceal bleeding on an Eastern European population to be essential, when we consider the geographical, genetic and lifestyle differences which greatly influence the etiology of liver cirrhosis and the pathology of variceal bleeding (Krige et al., 2005; Krige et al., 2007).

When assessing the 6-week mortality, the impossibility to control bleeding in the first days after the bleeding episode is of the utmost importance. Several studies have analysed the factors associated with *5*-day rebleeding or continued bleeding; some of these include active bleeding at endoscopy (D'Amico and De Franchis, 2003; Zhaov et al., 2002; Jalan and Hayes 2000), variceal size (Poynard et al., 1987), Child-Pugh class (Thomopoulos et al., 2006; D'Amico and De Franchis, 2003; Zhaov et al., 2002; Poynard et al., 1987; Sanders et al., 2002), hematocrit level (Bosch et al., 2008; D'Amico and De Franchis, 2003), bacterial infections (Zhaov et al., 2002; Bosch et al., 2008), hepatic encefalopathy (Ben-Ari et al., 1999), portal vein thrombosis (D'Amico and De Franchis, 2003), the presence of HCC (Bosch et al., 2008), hypoalbuminemia (Zhaov et al., 2002). Our study confirms these data (Table 2).

We also found the Child class and the MELD score as markers of cirrhosis severity to influence the 5-day prognosis. However, contrary to the previous reports, we did not find an influence of comorbidities (CirCom and Charlson indices) on the failure to control bleeding. Our results may be biased due to the small number of patients in the comorbidity group and to the low comorbidity scores. Nevertheless, it is important to

mention that AKI has a significant influence on the failure to control bleeding. Both the creatinin level itself and the association of kidney failure (defined as a creatinin level above 1.5mg/dL) were associated significantly to rebleeding at 5 days, maybe due to the severity of bleeding as well as that of the main condition. This particular fact has had little coverage in the literature so far. On the other hand, the correlation between kidney injury and ascites during liver cirrhosis is well known.

The significant diference in the time interval between the apparent bleeding and the moment of the endoscopy deserves to be mentioned. This interval was significantly shorter in patients who rebled or those with persistent bleeding, due to the more rapid transfer of severe patients to the endoscopy department. In multivariate sanalysis, only the Child class was significantly associated with failure to control bleeding, which is a marker of the real influence of the severity of the main disease.

At the 6-weeks check-up, the mortality in our group was 21.47%. Our results are similar to those reported by d'Amico et al. (2003) but higher than the 14.5 - 18.4% values reported in other studies (Carbonell et al., 2004; Chalasani et al., 2003; Thomopoulos et al., 2006; Boix et al., 2007).

In concordance with the previous reports, in our study the factors associated with 42-days mortality were mainly those depending on the liver function, such as the Child-Pugh (Thomopoulos et al., 2006; Sanders et al., 2002; Bosch et al., 2003; Yang et al., 2007) and MELD scores (Krige et al., 2006; Amitrano et al., 2005), total bilirubin (Lata et al., 2006; Hori et al., 2006), INR (Lata et al., 2006; Le Moine et al., 1992), ascites (Hori et al., 2006), hepatic encephalopathy (Sanders et al., 2002; Srikureja et al., 2005) or albumin (Lo et al., 2004). Regarding the endoscopic risk factors, we failed to demonstrate any association between active bleeding at endoscopy and FTB or 42-days death. However, as expected, the patients with FTB had higher 42-days mortality and the hemodynamic instability as a sign of severe bleeding was correlated with FTB, similar to previous reports (Chalasani et al., 2003; Thomopoulos et al., 2006).

Among the factors associated with both end-points we found that creatinine is strongly and independently associated with 42-days mortality in the model that did not include the MELD score. This finding is in concordance with other data, where renal failure is associated with a 7-fold increase in mortality, with half of patients dying in the first month (Fede et al., 2012). After the recent publication of the new criteria of AKI (Angeli et al., 2015), which discourage the use of the 1.5mg/dL threshold for serum creatinine, the biggest challenge is to diagnose AKI in the absence of a baseline serum creatinine. In our cohort, in the absence of baseline serum creatinine levels, we successfully identified patients with higher mortality using the 1.5mg/dL threshold. One of the limitations of our findings is that we did not look for any possibly associated infection at admission and its relation with AKI. However, all patients received prophylactic antibiotherapy and at discharge none had persistent renal failure.

The strongest factors associated with the end-points were the Child-Pugh and MELD score, and among the variables used in their calculation, the highest impact was held by creatinine for MELD and encephalopathy for the Child-Pugh score. Only encephalopathy among the Child-Pugh varibles (OR=3.84, 95%CI: 1.44-10.25, p=0.007) and only creatinine among the MELD score variables (OR=3.65, 95%CI: 1.40-9.51, p=0.008) were independently associated with 42-days mortality. Recently, the MELD score was proven to have the highest discriminative value for 42-days mortality prediction, with the best cut-off of 19 (Reverter et al., 2014, which is very similar to our cut-off value of 18. On the other hand, the Child score remains largely used in clinical practice and research, for being superior to other scores studied for the prediction of mortality of 6 weeks from a variceal bleeding (Sanders et al., 2002; Atkinson and Hurlstone, 2008; Angermayr et al., 2003). It is worth mentioning that both the score itself, as well as its variables were identified as predictive factors for bleeding (D'Amico et al., 2006). The score is easy to use at the bedside, requiring just a simple mathematical calculation, but has some disadvantages related to the subjective assessment of encephalopathy and ascites severity. However, it is generally accepted that liver function is the most important factor associated with short-term prognosis after variceal bleeding.

In our population, we failed to demonstrate any association between comorbidities quantified by the Charlson and CirCom scores and the 42-days prognosis. However, these score were created to predict long-term prognosis and, moreover, Charlson score is not dedicated to patients with cirrhosis. Acute kidney injury already present at admission appears to be an important prognosis factor but more studies are needed to confirm these findings. In addition, new diagnostic criteria need further validation in the setting of variceal bleeding.

This study has certain strengths and limitations. It reports the experience of a single referral center, which may be considered a limitation, but our institute is the referral center for treating variceal bleeding in a large region. Furthermore, the data were included prospectively and the patients were carefully followed for at least 6 weeks and therefore we consider the data to be representative for the Eastern-European region. On the other hand, we are aware of the absence of minimal invasive therapy of urgent decrease of portal hypertension (early TIPS), and consequently, this study has analysed only the factors associated with mortality and rebleeding in patients treated conservatively. In this context, the hepatic venous pressure gradient (HVPG)

was not assessed in our patients, so as to evaluate its influence on the failure to control bleeding and on mortality. Another limitation of the study is the lack of baseline serum creatinine values (before the bleeding) in order to apply the new diagnostic criteria of renal dysfunction (Angeli et al., 2015) and to better quantify the influence of renal dysfunction on prognosis.

CONCLUSION

Despite the substantial improvements made in the therapy of variceal bleeding, mortality remains high, especially in severe patients (Thabut et al., 2007). Identifying the factors associated with rebleeding and early mortality may help in selecting from the beginning the patients in need of more than just conventional therapy. New studies assessing the importance of portal venous pressure and even emergency vascular interventions are needed in order to improve the management of these patients.

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