

Scores prédictifs de la mortalité précoce par hémorragie digestive d'origine variqueuse chez le cirrhotique

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R É S U M É

Introduction: L'hémorragie digestive variqueuse, principale complication de l'hypertension portale au cours de la cirrhose, est associée à un risque de mortalité précoce élevé estimé entre 15 et 20%. Ceci souligne la nécessité de modèles prédictifs permettant d'identifier les patients à haut risque posant l'indication à une prise en charge thérapeutique plus agressive.

But : Était d'évaluer la performance de 4 scores pour la prédiction du risque de mortalité précoce par hémorragie digestive chez les cirrhotiques et de les comparer au score de référence, le Child-Pugh. Il s'agissait du score de Rockall, du score Glasgow-Blatchford, du score MELD et du score MELD-Na.

Méthodes : Nous avons mené une étude rétrospective colligeant, sur une période de 15 ans, de janvier 1999 à décembre 2014, 87 cirrhotiques admis au service de Gastro-entérologie de l'hôpital Charles Nicolle pour une hémorragie digestive haute par rupture de varices œsophagiennes ou gastriques.

Résultats : 56 hommes et 31 femmes ont été inclus dans cette étude. L'âge moyen était de 59 ans. La cirrhose était classée dans 85% des cas en stade B ou C selon le score Child-Pugh. La valeur moyenne des scores Rockall, Glasgow Blatchford, MELD et MELD-Na, était respectivement égale à 6.19, 10.91, 17.6 et à 20. La mortalité précoce était de 30%. La valeur moyenne de tous les scores calculés dans notre étude était significativement plus élevée chez les patients décédés précocement ($p < 0.001$). Le score MELD-Na avait la meilleure sensibilité et la meilleure spécificité pour la prédiction de la mortalité précoce comparé aux autres scores et en particulier au score de référence Child-Pugh sans différence statistiquement significative (Aire sous la courbe ROC : MELD-Na=0.867, $p < 0.001$; Child-Pugh=0.809, $p < 0.001$; Rockall=0.777, $p = 0.001$; Glasgow-Blatchford=0.761, $p < 0.001$; MELD=0.838, $p < 0.001$). La valeur prédictive seuil du score MELD-Na était égale à 19 avec une sensibilité de 70% et une spécificité de 82%.

Conclusion : les quatre scores sont performants pour prédire la mortalité précoce chez le cirrhotique avec hémorragie digestive variqueuse.

M o t s - c l é s

Cirrhose, hémorragie, mortalité, scores

S U M M A R Y

Introduction: The variceal bleeding, main complication of portal hypertension during cirrhosis, is associated with high early mortality risk estimated between 15 and 20%. This highlights the necessity of predictive models that allow identifying high-risk patients raising the issue of a more aggressive therapeutic care.

Objective: To assess the performance of four scores for the prediction of cirrhotic patients' high early mortality risk due to digestive hemorrhage and to compare them to the Child-Pugh reference score.

Methods: We collected 87 cirrhotic patients admitted to the Gastroenterology Department of Charles Nicolle Hospital for a high digestive hemorrhage by rupture of gastric or esophageal varicose veins.

Results: 56 men and 31 women were included in this study. The average value of Rockall, Glasgow Blatchford, MELD and MELD-Na scores, was respectively equal to 6.19, 10.91, and 17.6 and at 20. Early mortality was 30%. The average value of all the scores was significantly higher with the prematurely deceased patients ($p < 0.001$). The MELD-Na score had higher sensitivity and specificity for the prediction of premature mortality compared to the other scores but without statistical significantly difference (Area under the ROC curve: MELD-Na=0.867, $p < 0.001$; Child-Pugh=0.809, $p < 0.001$; Rockall=0.777, $p = 0.001$; Glasgow-Blatchford=0.761, $p < 0.001$; MELD=0.838, $p < 0.001$). The predictive value of the cut-off MELD-Na score was equal to 19 with a sensitivity of 70% and a specificity of 82%.

Conclusion: The studied four scores had a good predictive value of early mortality risk by varicose digestive hemorrhage with cirrhotic patients.

Key - words

Cirrhosis, Bleeding, Mortality, Scores.

The high digestive bleeding, by rupture of gastric or esophageal varicose veins, main complication of portal hypertension during cirrhosis, is associated with a high early mortality risk estimated between 15 and 20% [1, 2]. This highlights the necessity of predictive models that allow stratifying the cirrhotic patients with varicose hemorrhage according to the early mortality risk so as to adapt the initial care. Many studies proved the MELD score interest (Model for end-stage liver disease) in order to assess the prognostic of cirrhotic patients following-up a digestive bleeding [3, 4].

OBJECTIVE

To assess the performance of 4 scores for the prediction of cirrhotic patients' high early mortality risk due to digestive bleeding and to compare them to the Child-Pugh score considered as reference. It's about the Rockall score, the Glasgow-Blatchford score, the MELD score and the MELD-Na score.

METHODS

Population studied:

We collected data in our retrospective study, over a 15-year-period, from January 1999 to December 2014, the cirrhotic patients admitted for a high digestive bleeding, by rupture of gastric or esophageal varicose veins. The cirrhosis diagnosis was brought about either on non-invasive criteria, facing the association of clinic-biological signs of hepatic-cellular failure, of clinic-endoscopic signs relating to portal hypertension and to signs compatible to imagery, either on the data provided by anatomic-pathological examination of hepatic biopsy. The varicose origin of digestive bleeding was either confirmed by the endoscopic exploration made urgently or retained as bleeding etiology facing a cirrhotic patient known as carrier of gastric or esophageal varicose, when the high digestive endoscopy couldn't be carried out. When the endoscopic exploration was done, the diagnosis of a digestive bleeding was retained in front of an active bleeding coming from a varicose, the presence of a platelet plug or of an ulcer at the top of a varicose, or the presence of blood in the digestive cavities associated to esophageal varices or still facing the absence of other lesions that might be at the origin of bleeding. The cirrhotic patients, whose medical history wasn't complete, making it impossible the calculation of the different predictive score, were excluded from this study.

The retrospective data collection was done according to a fiche bearing many parameters : the patients' epidemiologic characteristics, the les co-morbidities, the cirrhosis etiology, the presence of a hepatic-cellular carcinoma, the history of varicose bleeding, the physical examination data at the admission, the data of the initial biological assessment, the data of the high endoscopic

exploration and its achievement deadline relating to the admission, the bases of the therapeutic care, the evolution throughout the hemorrhagic episode and the average deadline for the follow-up. These different clinic-biological and endoscopic parameters allowed us calculating the Child-Pugh score, the Rockall score, the Glasgow-Blatchford score, the MELD score and the MELD-Na score. All the patients received a treatment by Octréotide associated with an antibiotic-prophylactic treatment. The failure of the first-line treatment based on the perfusion of vasoactive drugs associated or not to an endoscopic treatment of varicose was defined by the non-control of bleeding or a premature recurrence, that is to say within the 5 days following the first hemorrhagic episode. The early mortality was defined by a death happening within the six weeks following the digestive hemorrhage episode [5].

Statistical study:

The data collection was carried out with the software SPSS version 19. The quantitative variables were compared by test t of Student. The differences were judged significant when the probability p was inferior or equal to 0, 05. Mortality was evaluated by the actuarial survival curve according to the Kaplan Meier model. The comparison of the survival curves was done by the Log rank test. The sensitivity and the specificity of the different scores were established thanks to the ROC curves. The area under the curve was determined for each score. Comparison of ROC curves was done used the statistical software Medcalc using the DeLong method.

RESULTS

Eighty seven cirrhotic patients were included. The patients' main characteristics at admission are represented in Table n°1. Among 73% (n=64) of the patients included, it was about a first digestive hemorrhage episode by rupture of gastric and esophageal varicose veins. The varicose hemorrhage was inaugural of cirrhosis in 40% of the cases (n=35) and it complicated the known varicose veins in 33% (n=29) of the cases. There was the matter of a relapse in 26% of the cases (n=23) with an average deadline of 7.37±6.78 months relating to the last episode of digestive hemorrhage with extremes going from 1 month to 24 months. 13% of the patients included (n=11) presented a state of shock during their admission. Half of the patients have a hemoglobin figure of ≤8g/dl. A high digestive endoscopy couldn't be done with 78 patients out of the 87 included initially, that is to say 90% among them. For the 9 patients who were not explored patients by endoscopy, it was about the known cirrhotic patient's bearers of esophageal varices grade II or III. Two among them had already presented a varicose bleeding. The endoscopic exploration couldn't be done with these patients because of, essentially, of a

rapid death after admission, of an instable hemodynamic state, of a continuous bleeding or still of a deep alteration of the conscience state.

Table 1: Patients' characteristics at admission

Age years	59 (± 13)
Male % (n)	64 (56)
Co-Morbidities % (n)	
Diabetes	32 (28)
Blood pressure 25 (22)	
Chronic kidney failure	5 (4)
Heart failure	2 (2)
Cirrhosis Etiologies % (n)	
Viral B	27 (24)
Viral C	29 (25)
Alcoholic or others	44 (38)
Varicose hemorrhage history % (n)	26 (23)
Exteriorization mode of hemorrhage % (n)	
Hematomas	91 (79)
Melina	59 (51)
hemodynamic parameters, average value	
Pulse	89.85 \pm 12.8
systolic blood pressure (mmHg)	111 \pm 18.5
diastolic blood pressure (mmHg)	66.6 \pm 11.6
biological parameters, average value	
Hemoglobin (g/dL)	7.9 \pm 2.2
Platelets (el/mm ³)	106264.36 \pm 59839.6
INR	1.94 \pm 0.98
TP	52.43 \pm 17.48
Plasmatic urea (mmol/L)	10.10 \pm 7.85
Creatininemia (μ mol/L)	110.4 \pm 102.35
Natremia (mmol/L)	135.5 \pm 5.36
ALAT (UI/L)	53.1 \pm 74.82
Total bilirubinemia (μ mol/L)	67.59 \pm 107.57
Albuminemia (g/L)	27.2 \pm 5.11
Ascites % (n)	68 (58)
Hepatic-cellular carcinoma % (n)	9 (8)
Hepatic Encephalopathy % (n)	21 (18)
Infection at admission % (n)	
Infection of ascetic fluid	9 (8)
Urinary infection	2 (2)

The main observations of the high endoscopic exploration as well as the bases of the therapeutic care are summarized in Table n°2. In the majority of the cases, that is to say 91% of the patients (n=71), the high digestive bleeding was secondary to a rupture of esophageal varices. These varicose veins were classified in grade II or III. When the bleeding came from a gastric varicose vein, there was the matter, in all cases, of varicose veins classified GOV 2. An intravenous perfusion by vasoactive drugs was implemented with all the patients. The only

molecule used was Octréotide at the dose of 25 μ g/h. An antibio-prophylaxy was systematically prescribed with all the patients either by Ofloxacin at the dose of 400mg/j, either by Ceftriaxone at the dose of 3-4g/j. An endoscopic treatment of gastric and esophageal varicose veins was realized in 72% of the cases (n=63). The achievement deadline was in average 6, 53 \pm 4, 7 days with extremes going from 1 to 19 days following the varicose bleeding. The esophageal varices were treated in the quasi-totality of the cases by elastic ligation. Sclerotherapy was done with only one patient. Out of the 7 patients who were bleeding from the gastric varices classified GOV 2, only two were treated by injection of biological glue. A failure of the treatment based on the medical treatment associated or not to an endoscopic treatment was noted in 18,5% (n=16) of the cases. Ten patients (n=9) presented a premature relapse. At admission, 85% (n=74) of the patients presented a severe hepatic-cellular failure with a cirrhosis classified stage Child-Pugh B or C.

Table 2 : Endoscopic observations and therapeutic care

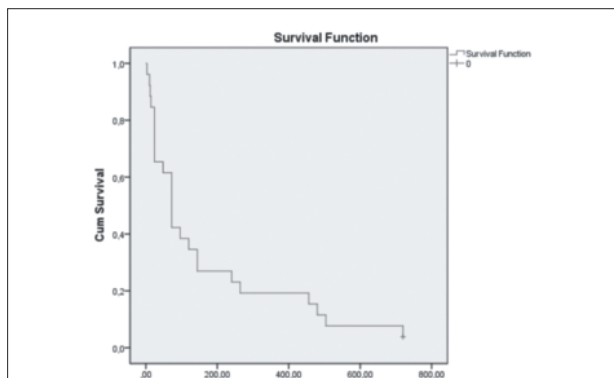
Endoscopic exploration % (n)	90 (78)
Achievement deadline relating to admission % (n)	
≤ 12 hours	52 (40)
] 12- 24 hours]	33 (25)
> 24 hours	15 (5)
Origin of bleeding % (n)	
Esophageal varicose veins	91 (71)
Gastric varicose veins	9 (7)
Active bleeding % (n)	14 (11)
Stigmata of recent bleeding % (n)	23 (18)
Medical treatment % (n)	
Vasoactive drugs	100 (87)
Antibiotoprohylaxy	100 (87)
Number of patients requiring transfusion of CG % (n)	45 (39)
Number of CG transfused in average	2.2 \pm 1.06
Endoscopic treatment % (n)	72 (63)

The average value of Child-Pugh score as well as those of Rockall, Glasgow-Blatchford, MELD and MELD-Na scores is reported in Table n°3.

In average, the patients were followed-up over a period of 26,24 \pm 28,57 months with extremes from 2 to 168 months. The average mortality deadline throughout the hemorrhagic episode was equal to 277,68 days with extremes going from 3 hours to 5 years. Throughout the period studied, all the patients were followed-up till the 6th Week following the hemorrhagic episode. We managed thus to individualize the patients deceased prematurely. The early mortality rate was 30%. The average survival of these patients throughout the hemorrhagic episode was 171,34 hours. The survival actuarial frequency at 100 hours (4,16days) and at 200 hours (8, 33 days) was respectively equal to 50% and to 27% (Figure n°1).

Table 3 : Average value and extremes of calculated scores

	Average Value	Extremes
Score Child-Pugh	8.82 \pm 2.34	[5-14]
Score Rockall	6.19 \pm 1.87	[3-10]
Score Glasgow-Blatchford	10.91 \pm 3.43	[3-18]
Score MELD	17.6 \pm 8.7	[7-40]
Score MELD-Na	20 \pm 8.6	[8-40]

**Figure 1** : Survival curve of prematurely deceased patients

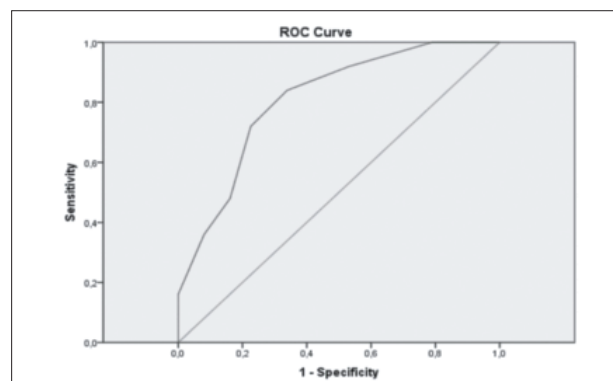
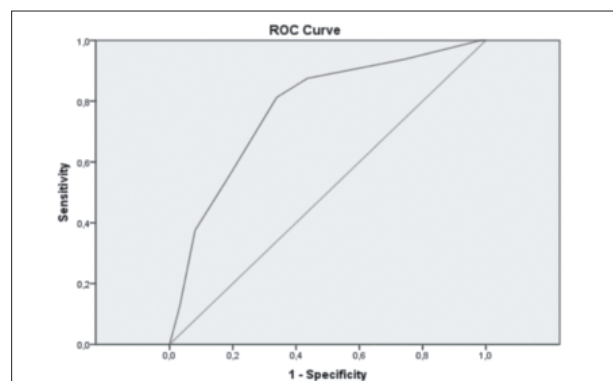
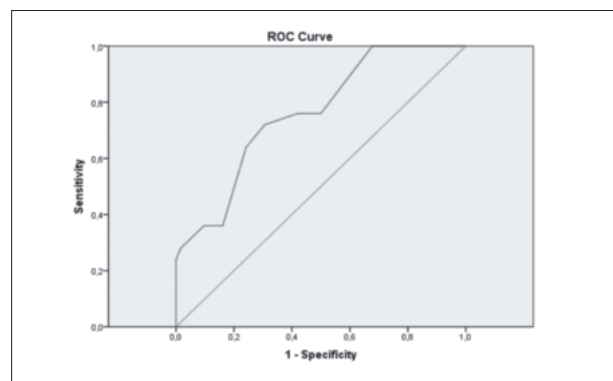
Cataclysmic digestive bleeding was the main cause of early death described in 14 cases. The hepatic encephalopathy was the cause of death with 5 patients, the liver/ kidney syndrome with 3 patients and a septic state of shock with 2 patients. There was the matter of a multi-visceral failure with 2 patients.

Predictive value of the different scores at the 6-week mortality:

Basing our research-study on premature mortality, we subdivided the patients into two groups: those prematurely deceased following the varicose hemorrhage and those deceased later than the 6-week deadline. We compared the average mean of the different scores calculated between the 2 groups thanks to a variance analysis. All the scores were significantly higher with the prematurely deceased cirrhosis patients (Table n°4). We then assessed the sensitivity and the specificity of each of the scores calculated for the prediction of premature mortality (Figures n° 2, 3, 4, 5, 6).

The score Child-Pugh, the score Rockall, the score Glasgow-Blatchford, the score MELD and the score MELD-Na were all actually significantly predictive of premature mortality ($p \leq 0,001$). With an area under the superior ROC curve, the score MELD-NA was the most sensitive and the most specific among the different scores calculated (Table n°5), but the comparison of ROC curves showed no statistical differences between the five scores (Figure n°7). The predictive threshold value of the score MELD-Na was equal to 19 with a sensitivity of 70% and a

specificity of 82%. There was hence a difference at the limit of significance for early mortality between the patients with a score MELD-Na ≥ 19 in comparison with those of the score MELD-Na which was inferior to 19 ($p=0,07$) (Figure n°8).

**Figure 2** : ROC curve of score Child-Pugh**Figure 3** : ROC curve of score Rockall**Figure 4** : ROC curve of score Glasgow-Blatchford

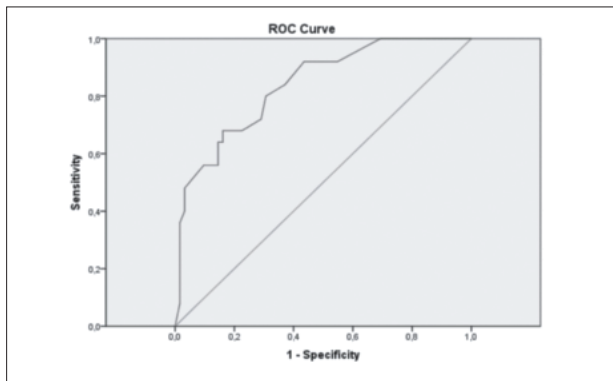


Figure 5 : ROC curve of score MELD

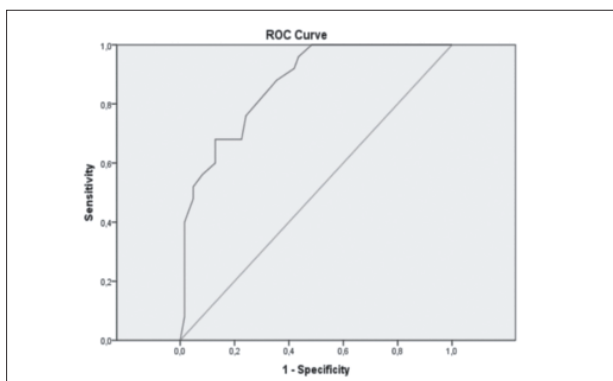


Figure 6 : ROC curve of score MELD-Na

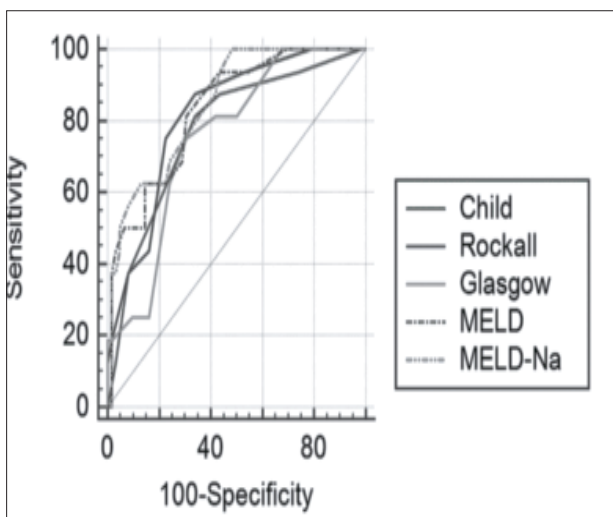


Figure 7 : Comparison of ROC curves of the five scores

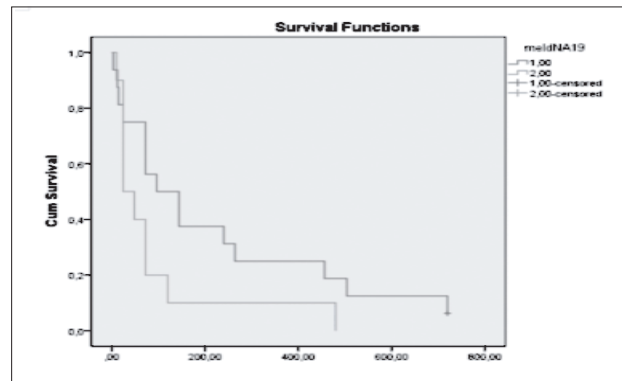


Figure 8 : Survival curve according to the threshold value of score MELD-Na

Table 4 : Correlation between the scores calculated and premature mortality

	Early death		p
	Yes	No	
Score Child-Pugh	10.68 ±2.13	8.08 ±2	<0.001
Score Rockall	7.68 ±1.7	5.8 ±1.7	<0.001
Score Glasgow-Blatchford	13.24 ±3.16	9.98 ±3.1	<0.001
Score MELD	25.35 ±9.6	14.48 ±6	<0.001
Score MELD-Na	28.08 ±8.14	16.8 ±6.37	<0.001

Table 5 : Area under the ROC curve of the different calculated scores

	Area under the curve	95% CI	p
Score Child-Pugh	0.809	[0.714 - 0.904]	<0.001
Score Rockall	0.777	[0.649 - 0.904]	0.001
Score Glasgow-Blatchford	0.761	[0.654 - 0.868]	<0.001
Score MELD	0.839	[0.749 - 0.928]	<0.001
Score MELD-Na	0.867	[0.791 - 0.943]	<0.001

DISCUSSION

In our series, the mortality rate at 6 weeks was 30%. This rate was significantly higher relating to those reported in the literature [3, 6]. This is probably linked to the difficulties with the access to the elastic ligature kits at the beginning of the experience, the majority of the patients classified Child-Pugh B or C, and no saving treatment such as a TIPS could be suggested. Early mortality following the varicose digestive bleeding has neatly decreased thanks to the development of therapeutic means, yet the 6-week mortality remains rather high. Many authors tried to identify the different criteria allowing individualizing the patients called high-risk patients so as to adapt the initial care and to indicate a premature TIPS realized within 24 to 72 hours following the digestive hemorrhagic episode [5,7].

However, there is no specific predictive model allowing classifying the cirrhosis patients according to risk of early mortality following a varicose hemorrhage episode and proposing adapted therapeutic strategies notably for those identified as high-risk patients. The score Child-

Pugh is considered as the reference score. Many authors adopted the Garcia-Pagan and al. Criteria based on the score Child-Pugh defining the cirrhotic patients with a high-risk of death within the six weeks following a digestive hemorrhage episode by rupture of gastric or esophageal varicose veins [7,8]. It is as a consequence then that a premature TIPS was indicated in case of cirrhosis classified Child B in presence of active bleeding or classified Child C. These criteria were retained by the latter Baveno consensus published in 2015 [5]. Nevertheless, it was not identified as a prognostic factor of premature mortality by varicose digestive bleeding and its sensitivity were quite inferior to the other clinic parameters and to the score MELD [6]. For that, we suggested assessing the predictive value of many scores and comparing them to the score Child-Pugh.

The score Rockall was largely used for the ulcerous hemorrhages [9]. In our study, this score was significantly higher with the prematurely deceased patients (7, 68 versus 5, 8; $p < 0,001$) and predictive of the 6-week mortality, yet inferior to the score Child-Pugh. This score was validated for the assessment of the prognosis of cirrhosis patients following a digestive bleeding by rupture of gastric or esophageal varicose veins by certain studies [10]. The score Glasgow-Blatchford is notation system calculated before the endoscopic exploration allowing identifying not only the endoscopic patients with a risk of hemorrhage relapse or death following a high digestive hemorrhage, but also those requiring a blood transfusion or a surgery or endoscopic homeostasis gesture [11]. Many authors validated the use of this score and confirmed its interest to classify the patients admitted with a high digestive hemorrhage table, whether it is of varicose origin or not, with low or high risk of relapse and of mortality so as to adapt the initial care [12-14]. We calculated the score Glasgow-Blatchford with our patients. By applying this score, our patients are straight away classified with the high risk group of relapse and mortality. Actually, the hepatic failure is sided by two points, whatever its severity level, which might limit the prognostic sensitivity of the score Glasgow-Blatchford with the cirrhotic patients [15]. In our study, the score Glasgow-Blatchford was significantly associated with early mortality ($p < 0,001$) and had a good sensitivity and a good predictive specificity of the 6-week mortality risk, but which remains inferior to the score Child-Pugh. We did not find in the literature any similar study assessing the predictive value of the score Glasgow-Blatchford for the early mortality risk by varicose digestive hemorrhage with the cirrhosis patients. As a result, it seems to be of a weak contribution for the prognosis assessment with the subgroup of cirrhotic patients.

The score MELD is significantly associated with the degree of the cirrhosis severity and predictive of mortality at 3 months and useful for the prognostic assessment of the different complications associated with cirrhosis [16-

18]. It takes into consideration as well, contrary to the Child-Pugh, the kidney function which is a major prognostic factor with the cirrhotic patient [19]. In our study, the score MELD had an average value of $17,6 \pm 8,7$ points and it was significantly predictive of early mortality ($p < 0,001$). Our results match with the conclusions of numerous studies assessing the predictive value of the score MELD for premature mortality by varicose digestive hemorrhage with the cirrhotic patients [3, 6, 19-21]. In the Bamba and al. study, the score MELD was significantly predictive of early mortality [6]. The authors equally identified a threshold value of the score MELD ≥ 18 allowing defining the patients with a high 6-week risk of mortality ($p < 0,001$). This meets the conclusions drawn by Jairath and al. in their national audit carried out in 212 British hospitals and published in 2014 [19]. Actually, the score MELD was predictive of premature mortality ($p < 0,001$) and a score ≥ 18 was equally identified as a threshold value defining the high risk patients. In the Amitrano and al. study, the score MELD was equally predictive of the 6-week mortality but the threshold value defining the high risk patients was, indeed, superior or equal to 15 [20]. We compared the score MELD to the score Child-Pugh. The score MELD revealed to be superior to the score Child-Pugh for the prediction of the 6-week mortality, following a varicose digestive hemorrhage with the cirrhotic patients. With the prognostic value comparable, or even superior, in our study as in the literature, the score MELD could be proposed as alternative to the score Child-Pugh, for the prediction of the 6-week mortality in case of varicose digestive hemorrhage with the cirrhotic patient [3, 6, 19-21].

We assessed the predictive value of the score MELD-Na. Actually, the hyponatremia is the reflection of hemodynamic troubles throughout the cirrhosis and often associated with a refractory ascite. The prognostic superiority of the score MELD-Na was essentially validated in case of the initial low score MELD in presence of an ascite or of an hepatic encephalopathy as well as in certain clinic situations such as an onset of hepatic-cellular failure or the follow-ups of TIPS [22-24].

The results analysis also allowed us identifying a threshold value for the score MELD-Na. A score ≥ 19 defined the high risk cirrhotic patients with premature mortality with a difference for the average survival at the limit of significance ($p = 0.077$). This threshold value had a sensitivity of 70% and a specificity of 82%. The only study bearing on the predictive value of the score MELD-Na for mortality following a varicose hemorrhage is that of Wang and al. who assessed the prognostic value of the score MELD-Na for mortality at 3 months and at a year compared to the score Child-Pugh and to the score MELD. The score MELD-Na had a predictive value significantly higher ($p < 0,05$) [25]. Our study is the first in the literature, to research the predictive value of the score

MELD-Na for the 6-month mortality, following a varicose hemorrhage episode with the cirrhotic patient and comparing its sensitivity and its specificity to those of the score Child-Pugh and the score MELD as well as the scores Rockall and Glasgow-Blatchford. This score appeared to be the best as it was based on objective biological and clinical variables easily accessible. It could then allow, from admission, stratifying the cirrhotic patients presenting a varicose hemorrhage according to the premature mortality risk and identifying the high risk patients requiring a more aggressive care.

CONCLUSION

The score MELD and the score MELD-Na seem to be of superior prognostic value compared to the score Child-Pugh for the prediction of early mortality by varicose hemorrhage with the cirrhotic patient. These two scores based on objective and easily accessible variables, will be then a precious tool allowing individualizing, from their admission for a hemorrhage by rupture of gastric and esophageal varicose veins, the premature mortality high risk cirrhotic patients.

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