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EPIDEMIOLOGICAL ASPECTS AND RISK FACTORS IN THE OUTCOME OF VARICEAL ESO-GASTRIC BLEEDING AT CIRRHOSIS PATIENTS

Motto:
"Ab uno disce omnes"
(From one sample, we judge the rest)
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Abstract: *The epidemiological aspects and risk factors in the outcome of upper gastrointestinal bleeding were analyzed in a prospective study of 268 patients with liver cirrhosis. The hemorrhagic episode has a negative prognostic in the immediate outcome, with 96 deaths (35.82%), p<0,01.*
In the acute phase of bleeding appeared 36 deaths (13.40 %); others were registered after recurrent hemorrhage (48 cases, 17.23%), or after sclerotherapy or surgical treatment of varices (12 cases, 4.47%).
Patients in advanced stage of cirrhosis – Child C stage – (n=124), registered the highest death toll (n=76, 61.29%, p<0.01).
High potential risk factors responsible for death included: altered general status (p<0.01), jaundice (p<0.01), increased seric level of total bilirubin (over 3 mg%, p<0.01), encephalopathy (p<0.05). Among these risk factors, the highest sensitivity belongs to jaundice (83.33%), and total highest positive predictive value belongs to seric and total bilirubin (over 3mg %), with 64.28% value.

Key words: *upper GI Bleeding; cirrhosis; esophageal varices; risk factors; epidemiology*

Introduction

One of the main public health problems with special epidemiological interest – both at the national and the international level – is liver cirrhosis.

Frequently caused by a hepatitis or chronic alcohol use, accompanied by portal hypertension and varices, the prevalence of cirrhosis is upscaling. Gastrointestinal bleeding from portal hypertension carries the highest mortality, ranging from 30 to 40 percent, and has an equally high rate of recurrence (1).

Cirrhosis is associated with a hyperdynamic circulatory state characterized by peripheral and splachnic vasodilatation, decreased mean arterial pressure and increased cardiac output (2).

Table 1. Risk factors for variceal hemorrhage (hepatic vein pressure gradient) (3,4,5,6)

	High		Low	
Portal pressure	HVPG > 12 mm Hg		HVPG < 12 mm Hg	
Varix size and location	Large esophageal varices		Isolated varices in fundus of stomach	
Variceal appearance on endoscopy ("red signs")	Red walemarks	Cherry spots	Hematocystic spots	Diffuse erithema
Degree of liver failure	Child Pugh class C cirrhosis			
Presence of ascites	Present		Absent	

Methods

In the prospective study of the 268 patients we examined different factors, regarding: *clinical data* (age, gender, presence of jaundice, ascites, encephalopathy and altered status), *antecedents* – former upper gastrointestinal bleeding, existence of toxic intake, *characteristic of bleeding* (hematemesis, melena, hematochezia, and associated signs). Hematochezia in the setting of upper GI hemorrhage implies that a minimum of 1000 ml of blood is entering the upper GI tract; red hematemesis with concomitant hematochezia are suggestive for massive brisk bleeding, in this case the mortality being around 30%.

1 *The origins of hemorrhage* – esophageal varices, gastric varices/ portal hypertensive gastropathy, gastric peptic ulcer).

2 *Evolution* – according to the type of treatment.

We used the Child-Pugh classification of patients, by means of 5 criteria: serum albumin, bilirubin, ascites, encephalopathy and protrombin time (each factor has values on a 1 to 3 scale representing the gravity; the final value is the sum of all values for that patient; Child-Pugh A = 5-6, Child-Pugh B = 7-9, Child-Pugh C = 10-15).

The management of hemorrhage comprised 4 main objectives:

1. rapid and effective resuscitation of the patient through i.v./central lines, transfusions of blood to insure an optimal hemodynamic;

2. definitive control of bleeding with medical therapy (hemostats), Sengstaken-Blackmore tube, endoscopic banding and sclerotherapy and the last resource – surgery. Sustaining the liver function and prevention and/or treatment of associated complications was don in the resuscitation unit, in order to fight-off the encephalopathy, cerebral edema,

infection and increase the immunity (7,8);

3. treatment of the cause;
4. prevention of rebleeding (recurrent hemorrhage).

The statistical analysis was made with χ^2 (chi square) test.

Results

In our paper, the most frequent cause of hemorrhage were ruptured esophageal varices (n=175, %). The clinical and laboratory findings pointed out that the Child-Pugh C stage was met in most cases (n=124).

With definitive hemostasis obtained only in 172 patients, there were 96 deaths (35.82%) registered.

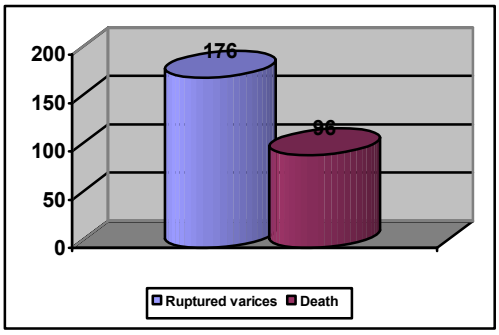

Figure 1. Deaths in esophageal varices
χ^2= 6.6
p<0.01

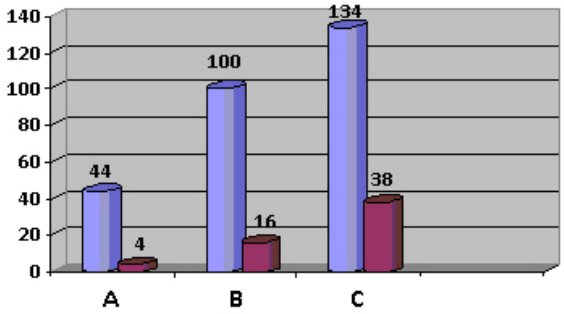

Figure 2. Deaths in Child-Pugh Classification
χ^2= 13.56
p<0.01

There were 88 deaths (p<0.01) due to the ruptured varices; off the total 96 deaths, 36 were registered the acute phase the disease, 48 after an recurrent hemorrhage and other 12 following local hemostasis.

Highest number of deaths was in C stage of cirrhosis (II), p<0.01 patients with altered general condition (figure 3, p<0.01), encephalopathy (figure 4, p<0.05) or jaundice (figure 5, p<0.01).

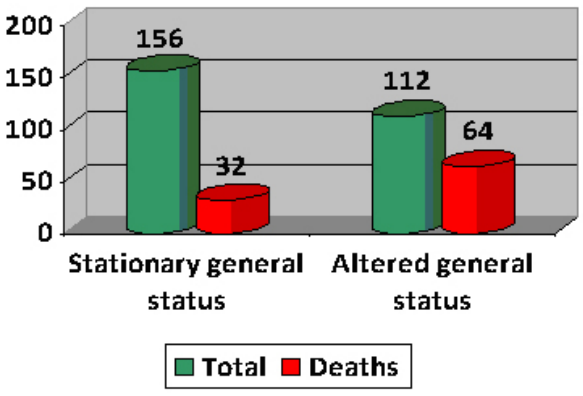

Figure 3. Deaths related to general condition
χ^2= 9.53
p<0.01

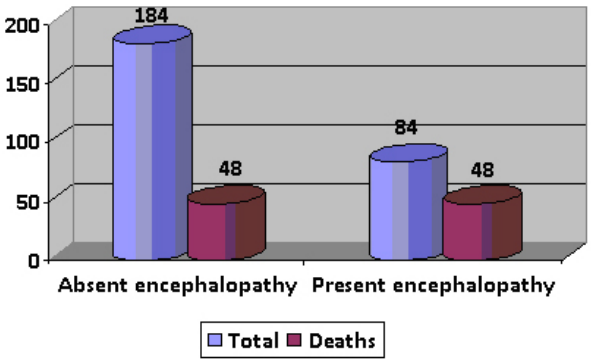

Figure 4. Deaths related to encephalopathy
χ^2= 6.05
p<0.05

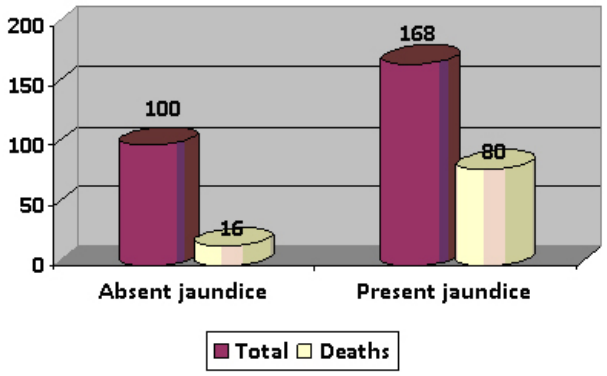

Figure 5. Deaths related to jaundice
$\chi^2 = 9.53$
$p<0.01$

As figured, the main cause of death remains the ruptured varix; upper GI hemorrhage remained the primordial aggravation for patients in Child-Pugh stage B, C, the ensuring hepatico-renal insufficiency being the lethal element.

Table 2. Generalities

Characteristics		Total	Deaths	χ^2
Gender	Female	76 (28.38%)	16 (21.05%)	2.51
	Male	192 (71.62%)	80 (41.66%)	
Age	< 60 years	184 (68.65%)	60 (32.60%)	0.65
	> 60 years	84 (31.35%)	36 (42.70%)	
Type of bleeding	Hematemesis	200 (74.62%)	72 (36%)	0.016
	Melena	44 (16.42%)	16 (36.36%)	
	Combined	24 (8.95%)	8 (33.33%)	
Arterial blood presure	Normal	184 (68.12%)	68 (36.95%)	1.79
	Decreasing	64 (23.83%)	20 (32.25%)	
	Under 80 mm Hg	20 (7.46%)	18 (90%)	
Bleeding cause	Varices	176 (65.62%)	88 (50%)	11.24 p<0.01
	Portal hypertension gastropathy	88 (32.83%)	8 (9.09%)	
	Others (peptic ulcer)	4 (1.4%)	0	
Treatment type	Medical (including Sengstaken-Blackmoore tube)	124 (46.24%)	27 (21.77%)	2.17
	In recurrent hemorrhage	48 (17.91%)	48 (100%)	
	Sclerotherapy	8 (5.97%)	2 (25%)	
	Surgery (resections, ligatures)	44 (16.42%)	4 (9.09%)	
Child-Pugh classification	A	44 (16.42%)	4 (9.99%)	13.56 p<0.02
	B	100 (37.31%)	16 (16%)	
	C	124 (46.27%)	76 (61.27%)	

Statistical significance was relevant for several risk factors, as early predictors, with key roles in triggering the deaths of cirrhosis patients with upper GI bleeding:

1. altered general status ($p<0.01$)
2. stage C of Child-Pugh classification of cirrhosis ($p<0.01$)
3. anatomical cause of hemorrhage ($p<0.01$)
4. serum bilirubin over 3 mg% ($p<0.001$)
5. encephalopathy ($p<0.05$).

The highest sensibility belonged to jaundice (83.33%), while the positive predictive value (<50%) belonged to serum bilirubin >3mg%.

Discussions

It is stated that approximately 1/3 of cirrhosis patients will develop in one stage of evolution an upper GI hemorrhage and in the vast majority of cases (approximately 80%) it will be due to variceal bleeding; auxiliary lesions may be present, like hypertensive portal gastropathy (30-40%) or peptic ulcer (7-10%) (9,10,11,12).

Similar percentages were obtained in our study (see table 2).

New varices develop in 5-15% patients with cirrhosis (each year), and enlarge by 4%-10% each year. Of the 30-40% patients who develop variceal bleeding, only 40 to 50 percent of actively bleeding varices will spontaneously stop bleeding (7,13,14).

This variability of phenomena requires attentive statistical analysis.

Regarding the risk of rupturing varices, the endoscopic data collected by NIEC (North Italian Endoscopic Club) established a predictability of the hemorrhage onset; varices with the size bigger than 5 mm, associated with "red dots" have a greater bleeding risk than small varices (70% opposed to 7%), $p<0.001$ (10,15,16,17,18). The stage of cirrhosis, with impairment of hemostasis, will directly influence the gravity of hemorrhage; the hepatic venous pressure higher than 12 mm Hg will induce the increase of the bleeding risk (9,19).

Table 3. Clinical and endoscopic findings

Characteristics		Total	Deaths	χ^2
Antecedents	Hemorrhage	Yes: 144 (53.73%)	52 (36.11%)	0.02
		No: 4 (46.27%)	44 (35.48%)	
	Ascites	Yes: 164 (61.19%)	48 (29.26%)	1.97
		No: 104 (38.81%)	48 (46.15%)	
	Use of aggressive drugs	Yes: 124 (83.58%)	76 (33.92%)	0.527
		No: 44 (16.42%)	20 (45.45%)	
Clinical exam	Altered general status	Yes: 112 (41.79%)	64 (57.14%)	9.53 p<0.01
		No: 156 (58.21%)	32 (20.51%)	
	Jaundice	Yes: 168 (62.68%)	80 (47.11%)	6.91 p<0.01
		No: 100 (37.32%)	16 (16%)	
	Ascites	Yes: 160 (59.47%)	60 (37.50%)	0.12
		No: 104 (40.63%)	36 (33.33%)	
	Encephalopathy	Yes: 84 (31.34%)	48 (57.14%)	6.045 p<0.05
		No: 184 (68.66%)	48 (26.08%)	
Endoscopical data	Ruptured varices	Yes: 176 (65.67%)	88 (50%)	6.6 p<0.01
		No: 92 (34.33%)	8 (8.69%)	

The 32 cirrhotic patients in our study, with fast decreasing blood pressure, registered a mortality of n=10 (31.25%), while the mortality scored to 90% (n=9), for the 10 patients hospitalized in hemorrhagic shock: international data acknowledges also high percentage mortality (approximately 20%) for the cirrhosis patients with severe upper GI bleeding (12).

The anemia, with low hematocrit value, and also maintaining the blood pressure only with saline i.v., can facilitate and increase the severity of bleeding (20). Likewise, in *table 4*, in our study, patients with hematocrit value under 25%, registered 88 deaths

(59.09%).

Table 4. Laboratory findings (data)

Characteristics		Total	Deaths	χ^2
Hematocrit value	>25%	180 (67.16%)	44 (45.83%)	0.20
	<25%	88 (32.89%)	52 (59.09%)	
Bilirubin	<3 mg/dl	156 (58.21%)	24 (15.38%)	16.98 p<0.001
	>3 mg/dl	112 (41.79%)	72 (64.27%)	
Prothrombin time	>40%	184 (69.42%)	64 (34.27%)	0.068
	<40%	84 (31.34%)	32 (38.09%)	
Albumin	>3g%	156 (58.21%)	44 (28.20%)	2.36
	<3g%	112 (41.79%)	52 (46.42%)	
Liver transaminases (ALT, AST)	<100 U/L	160 (59.76%)	52 (32.5%)	N
	>100 U/L	108 (40.29%)	44 (40.74%)	
Blood urea nitrogen	<60 mg%	164 (61.19%)	58 (35.36%)	N
	>60 mg%	104 (38.8%)	38 (38.46%)	
Sodium (Na^+)	>130 mEq/L	192 (71.64%)	64 (33.33%)	N
	>130 mEq/L	76 (28.35%)	32 (42.1%)	
Potassium (K^+)	>3 mEq/L	198 (73.83%)	72 (37.5%)	N
	<3mEq/L	70 (26.11%)	24 (34.28%)	

N – not significant

Directives are to use blood transfusions in upper GI bleeding at the cirrhotic patients with hematocrit value less than 25%, eventually frozen plasma.

The highest positive predictive value belongs to serum bilirubin levels higher than 3 mg% ($p<0.001$). One other predictive factor is recurrent hemorrhage which is present in 50% of the complicated cirrhosis (with anterior bleeding). Another issue is *infection*, with clear predictive role in the early recurrence of hemorrhage; infection is proved in 60-70% of cirrhosis patients and is caused by the lower immunity of these patients, the catheterization of body cavities, assisted ventilation. That was justification for the compulsory introduction of antibiotic protection in the therapeutic protocol.

The Baveno criteria were used to demarcate the recurrent hemorrhage: *zero time* is considered the full stop of bleeding, with no blood on nasogastric tube, no bleeding on endoscopy and stable vital signs for 24 hours. Early recurrent hemorrhage is considered premature bleeding after *zero time*; recurrent hemorrhage implies that after 10 days from *zero time*, there is hemorrhage that necessitates at least 2 units of blood at 6 hours interval, or hemostasis with red blood or endoscopy with bleeding stigmata (21,22).

With at least 30,000 deaths in USA, the hospitalization rate of 1/1000 and the 8-10% mortality, the upper GI bleeding remains in the focus of clinical teams of experts. In Europe, there is an incidence of 45-100 hospitalizations/100000 for upper GI bleed, with a case ratio of 3:2 males versus females; its incidence strongly correlates with increased age, 20 to 30 times higher in 70-80 year old patients compared with patients in the second decade of life. The lethality in Europe averages around 4-5% for less than 60 years old patients to more than 20% in patients over 80 years old. The mortality range for gastro-esophageal varices is 4-20% (22).

The remarkable issue is the unlowering curve of upper GI bleed mortality in the past 25-30 years, in disregard to the technical progresses – medical, endoscopical therapy that should have contributed to lessen the hemorrhage. The explanation dwells in the fact that the highest percentage of upper GI bleeding occurs in the elderly, with a rather sever

prognostic due to comorbidities, anticoagulant medication (over 45% of patients with upper GI bleed have over 60 years).

Varices frequently complicate end-stage liver disease, with more than 30% compensated cirrhotic patient and 60% decompensate cirrhotic having varices at the time of diagnostic.

Definitive hemostasis (n=124, 61.17%) used medical measures, endoscopy or surgical intervention (23).

The therapeutically protocol is represented in table 5.

Table 5. Therapeutical management stabilization

1. Stabilization with i.v. fluids, reverse coagulopathy.
2. Initiation with octreotide or vasopressin with nitrates.
3. Endoscopic evaluation with sclerotherapy or banding.
4. Multiple endoscopic sessions for variceal obliteration or TIPS/ surgical shunt/ angiographic shunt/ liver transplant.
5. Secondary prophylaxis with nonselective β-blockers ± nitrates.

During initial hemodynamic stabilization, the clinician must devise on orderly approach that will expedite diagnosis and treatment. Consulting a team of specialists that includes the internist, gastroenterologist, surgeon and interventional radiologist may provide the optimal management for the patient.

Conclusions

Upper GI bleeding is the most frequently met in cirrhosis patients with ruptured varices ($p<0.01$), the prognostic is not propitious in the immediate evolution of the hemorrhage ($p<0.01$), because of the high death toll (35.81%).

Most death were noted in the advanced stages (Child-Pugh stage C), $p<0.01$.

The risk factors in initiation of deaths were: encephalopathy ($p<0.05$), jaundice ($p<0.01$), altered general status ($p<0.01$), serum bilirubin level over 3 mg% ($p<0.001$).

The greatest sensibility belonged to jaundice (83.33%) and the highest positive predictive value belonged to serum bilirubin values over 3 mg% (64.28%).

Table 6. Risk factors in immediate evolution of hemorrhage of cirrhotic (24,25)

	Total	Deaths	Sensibility	Positive predictive value
Encephalopathy	84	48	50%	57.14%
Altered general status	112	64	66.66%	57.14%
Jaundice	168	80	83.33%	47.61%
Bilirubin >3 mg%	112	72	75%	64.28%
Child-Pugh C stage	124	76	79.16%	61.29%

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