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Noninvasive assessment of portal hypertension in patients with alcoholic cirrhosis

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Background/aims: *Portal hypertension and development of esophageal varices is one of the major complications of liver cirrhosis. The aim of our study was to evaluate the possibility of the presence of esophageal varices and their size using biochemical and ultrasonography parameters in patients with alcoholic liver cirrhosis.* ***Material and Methods:*** *We included in our study 86 patients (74 males, mean age 55±7) with alcoholic liver cirrhosis. The control group consisted of 102 patients with cirrhosis of other etiologies. All patients underwent a complete biochemical workup, upper digestive endoscopy and ultrasonography examination. The right liver lobe diameter/albumin and platelet count/spleen diameter ratios were calculated. The correlation of the calculated ratios with the presence and degree of esophageal varices in patients with liver cirrhosis was also determined.* ***Results:*** *The mean value of right liver lobe diameter-albumin ratio was 6.15±1.77, and statistically significantly differed from values determined in the control group (4.97±1.68). The mean platelet count-spleen diameter ratio was 972.5±599.0 in alcoholic liver cirrhosis and 1055.9±821.3 in controls (p>0.05). In patients with alcoholic liver cirrhosis, none of the analyzed noninvasive markers was shown to be a good predictor of the presence and size of esophageal varices.* ***Conclusions:*** *Despite the important role of noninvasive markers in providing information pertinent to determination of esophageal varices in patients with liver cirrhosis, these markers have limited relevance in patients with alcoholic cirrhosis.*

Key words: Liver cirrhosis, alcohol, esophageal varices, portal hypertension, ultrasonography

Alkolik sirozlu hastalarda portal hipertansiyonun non – invaziv değerlendirilmesi

Amaç: *Portal hipertansiyon ve özofagusta varis gelişimi, karaciğer sirozunun ana komplikasyonlarından birisidir. Çalışmamızın amacı, alkolik karaciğer sirozlu hastalarda özofagus varis varlığı ve boyutlarının, biyokimyasal ve ultrasonografik parametreler kullanılarak öngörülmesidir.* ***Yöntemler:*** *Çalışmaya alkolik karaciğer sirozlu 86 hasta (74 erkek, ortalama yaş 55±7) alındı. Kontrol grubu olarak diğer etyolojilere bağlı 102 siroz hastası alındı. Bütün hastalara tam biyokimyasal çalışma, üst sindirim sistemi endoskopisi ve ultrasonografi uygulandı. Albumin/karaciğer sağ lobu çapı ve trombosit/dalak çapı oranları hesaplandı. Karaciğer sirozlu hastalarda hesaplanan oranların özofagus varisi varlığı ve derecesiyle korelasyonu araştırıldı.* ***Bulgular:*** *Ortalama karaciğer sağ lob çapı – albumin oranı 6,15±1,77 idi ve kontrol grubunda bulunan değer olan 4,97±1,68'den anlamlı şekilde farklıydı. Alkolik karaciğer sirozu hastalarında ortalama 972,5±599,0 olan trombosit sayısı – dalak çapı oranı, kontrollerde 1055,9±821,3 idi (p>0.05). Alkolik karaciğer sirozlu hastalarda analiz edilen non – invaziv belirteçlerin hiçbirisi özofagus varis varlığı ve boyutları açısından prediktif bulunmadı.* ***Sonuçlar:*** *Karaciğer sirozlu hastalarda, non – invaziv belirteçler özofagus varislerinin saptanmasına yönelik önemli role sahip olsa da, alkolik sirozda bu rol kısıtlıdır.*

Anahtar kelimeler: Karaciğer sirozu, alkol, özofagus varisleri, portal hipertansiyon, ultrasonografi

INTRODUCTION

Development of portal hypertension and esophageal varices is a serious consequence of liver cirrhosis that plays a crucial role in the disease progression from the pre-clinical to clinical phase of

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the disease. Portal hypertension is a contributing factor for the development of ascites and hepatic encephalopathy and a direct cause of variceal hemorrhage, increasing both the morbidity and mortality of these patients. Esophagogastric varices are, from the clinician's standpoint, the most important consequence of collateral circulation as a result of increased portal pressure. Previously published longitudinal studies reported that esophageal and/or gastric varices eventually develop in all cirrhotic patients (1,2), and once developed, they tend to increase in size and bleed (2). The estimated yearly rate of "new" varices' development ranges from 5–10% (1,3), while the rate of growth from small to large varices is between 5% and 30% according to different studies (3–6). The risk of bleeding is related to the size of varices, presence of "red signs" on their surface, and degree of liver insufficiency assessed by Child-Pugh score (7).

According to the literature, up to 20% of cirrhosis patients die due to variceal hemorrhage. Even if the patient survives an initial episode of variceal bleeding, the probability of another episode is high, and the rebleeding rate without treatment is 70% within one year. In a variceal rebleeding episode, the mortality rate augments to 33% (8). Bleeding episodes can be predicted by the variceal size and presence of red signs ("red cherry spots") on their surface during endoscopy (9,10). The incidence of variceal bleeding is reduced when nonselective beta-blockers are introduced into the therapy (11,12). Prophylactic endoscopic variceal ligation of large varices can also decrease the incidence of first variceal bleeding and mortality in patients with liver cirrhosis (13,14). Therefore, annual screening with endoscopy is highly recommended for patients with small esophageal varices, and it should be conducted once in two years in patients with liver cirrhosis without previously diagnosed varices (15,16). Nevertheless, repeated endoscopy examinations are unpleasant for patients, and they have a cost impact on health care insurance. Therefore, the sensitivity and specificity of numerous noninvasive parameters has been investigated in an attempt to find a noninvasive tool for assessment of the presence and size of esophageal varices and predict the risk of variceal bleeding. Despite promising results, some studies have suggested that noninvasive predictors are not reliable in alcoholic liver cirrhosis (17).

We aimed to identify noninvasive parameters based on ultrasonographic measurement and laboratory tests that could be used in the assessment of the presence and size of esophageal varices in patients with alcoholic liver cirrhosis.

MATERIALS AND METHODS

We conducted a prospective clinical study that included 86 patients treated for alcoholic liver cirrhosis in the Clinic for Gastroenterology and Hepatology, Clinical Center of Serbia. The control group consisted of 102 patients with liver cirrhosis of other etiologies. The diagnosis of cirrhosis was based on clinical features, laboratory test, imaging diagnostics, and whenever possible, on liver histology.

The following information was collected for each patient: age, gender, etiology of cirrhosis, laboratory parameters (serum albumin and platelet count), presence and degree of esophageal varices, and degree of liver function impairment by Child-Pugh classes. The cirrhosis etiology was classified as viral if hepatitis B surface antigen (HBsAg) or hepatitis C serum markers were positive. Positive immunological markers were characteristic for immunological liver disease. The other studied cases had liver cirrhosis of different etiology (Wilson's disease, α1 antitrypsin deficiency, hemochromatosis, etc.). If viral, immunological and other etiology factors were excluded and the personal history obtained from the patient indicated alcohol consumption of at least 50 g/day during the past five years, liver cirrhosis was considered as alcoholic.

All patients included in the study underwent ultrasonographic examination of the upper abdomen, and measurements of the right liver lobe diameter (RLLD) in the medioclavicular line, as well as of the spleen bipolar diameter (SD) were collected. Three measurements were performed for both parameters and the mean value was calculated and recorded by the same investigator in order to reduce the inter- and intra-observer errors in assessing diameters.

Using the laboratory and ultrasonographic values, we calculated two ratios: RLLD/serum albumin concentration and platelet count/SD, as previously published (13-15).

A single experienced endoscopist performed all esophagogastroduodenoscopy procedures and used grade I-IV classification to classify varices (16). Varices in the level of mucosa were recognized as grade I, and those smaller than 5 mm filling less

than 1/3 of the esophageal lumen were recognized as grade II. Grade III was attributed to varices larger than 5 mm filling more than 1/3 of the esophageal lumen, while grade IV varices occupied more than 2/3 of the esophageal lumen.

Patients with previous variceal bleeding, portosystemic shunts and those taking beta-blockers were excluded from the study, as well as patients with coexistent illness or infection that could influence liver and spleen size and laboratory findings relevant for this study.

Laboratory testing, ultrasonography examination and endoscopy were performed within one week. The Ethics Committee of our institution approved the study and all patients provided informed consent prior to inclusion in this investigation.

All collected data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 10.0). Basic descriptive statistics included means, standard deviations, ranges, and percentages. For correlation analysis, chi-square test, t-test, Mann-Whitney U test , as well as uni- and multivariate regression were used. Differences were considered statistically significant if p value was less than 0.05.

RESULTS

Clinical characteristics of patients included in our investigation are seen in Table 1.

The mean value of the calculated platelet count/SD ratio was not significantly different in patients with alcoholic liver cirrhosis compared to patients in the control group (972.5±599.0 vs. 1055.9±821.3, respectively, p>0.05).

The mean value of the calculated RLLD/serum albumin concentration ratio was significantly higher in patients with alcoholic liver cirrhosis than in the control group (6.15±1.77 and 4.97±1.68, respectively, p<0.001). Differences were observed in serum albumin and RLLD between the alcoholic and other etiology liver cirrhosis patients, but not in platelet count and SD, as seen in Figures 1-6.

Using multivariate regression, we assessed noninvasive markers as predictors of the presence and size of esophageal varices in both groups of patients. In patients with alcoholic liver cirrhosis, none of the markers analyzed proved to be predictive for either the presence and/or size of esophageal varices. In the control group of patients with liver cirrhosis due to other etiologies, statistically significant predictors of the presence of esophageal varices and their size were: RLLD/serum albumin concentration ratio, platelet count/SD ratio, as well as SD and platelet count (Table 2). In this group of patients, the RLLD/serum albumin concentration ratio was higher in patients with esophageal varices and increased with variceal size together with SD. Presence and size of esophageal varices were related to a decrease in platelet count and platelet count/SD ratio, respectively.

DISCUSSION

Portal hypertension is a progressive and, due to variceal bleeding, a potentially life-threatening

Table 1. Clinical characteristics, ultrasonographic measurements, biochemical data and indexes of patients

Parameters	Group Alcohol	Other cause	Significance
Sex M/F	74/12	50/52	p=0.000*
Age[c] X±SD (Med; min-max)	55.14±7.71 (55; 37-77)	49.94±16.68 (54; 17-79)	p=0.127
RLLD[b] X±SD (Med; min-max)	165.53±24.36 (166; 110-230)	151.12±20.26 (150; 110-210)	p=0.000*
Alb[c] X±SD (Med; min-max)	28.63±7.76 (27; 18-54)	32.61±7.67 (32; 15-50)	p=0.000*
Index RLLD-alb[c] X±SD (Med; min-max)	6.15±1.77 (5.71; 3.68-11.44)	4.97±1.68 (4.57; 2.76-10.56)	p=0.000*
SD[c] (mm) X±SD (Med; min-max)	144.91±29.29 (140; 110-240)	150.71±36.84 (150; 80-230)	p=0.276
Plt[c] x10^3 X±SD (Med; min-max)	131.38±68.53 (108; 27-357)	137.37±81.55 (117; 28-322)	p=0.987
Index Plt-SD[c] X±SD (Med; min-max)	972.5±599.0 (742.9; 117.4-2975)	1055.9±821.3 (787.9; 127.3-3362.5)	p=0.739

*Statistically significant; [a]Chi-square test; [b]t-test; [c]Mann-Whitney U test.
RLLD: Right liver lobe diameter. Alb: Albumin. SD: Spleen diameter. Plt: Platelets.

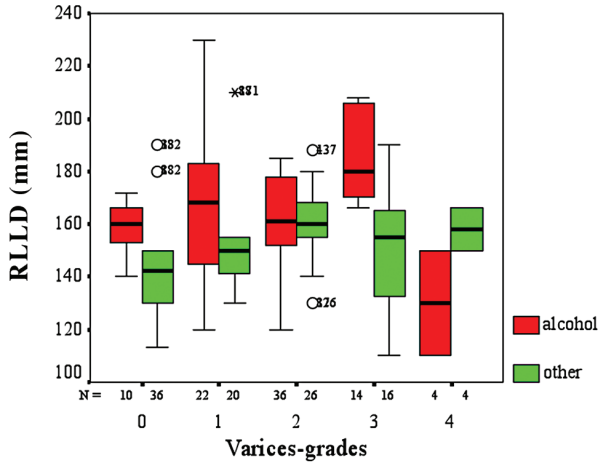

Figure 1. Right liver lobe diameter.

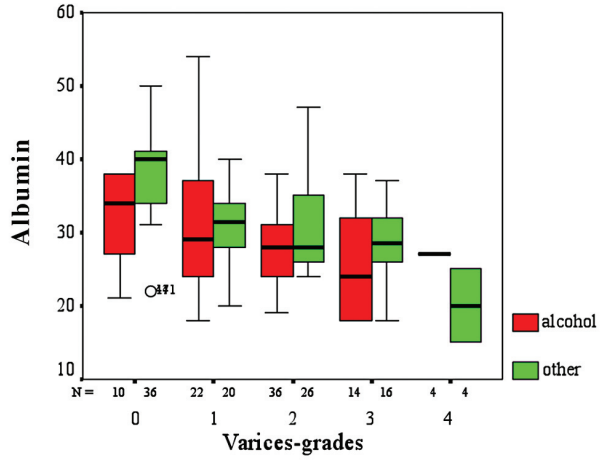

Figure 2. Albumin concentration.

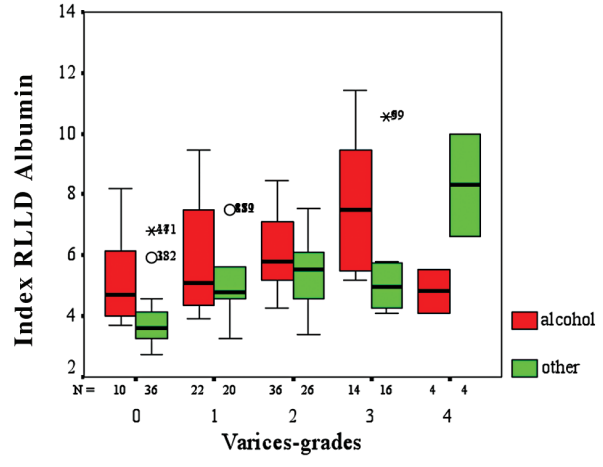

Figure 3. Right liver lobe diameter-albumin ratio.

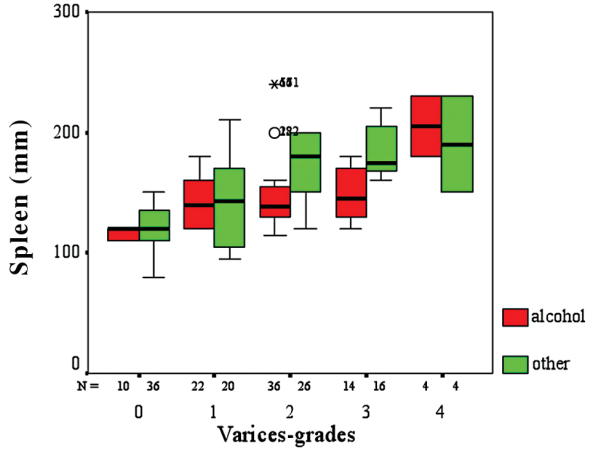

Figure 4. Spleen diameter.

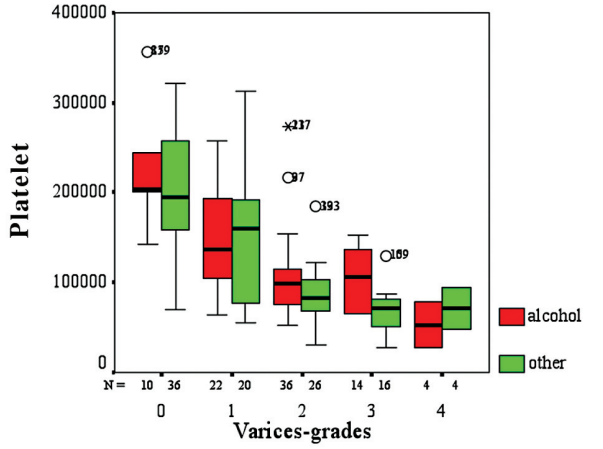

Figure 5. Platelet count.

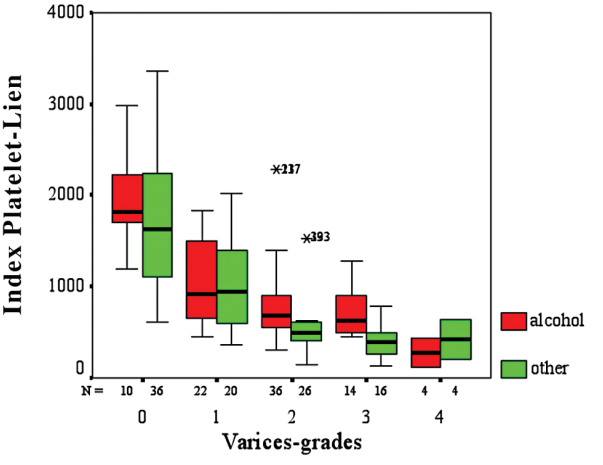

Figure 6. Platelet count-spleen diameter ratio.

complication of cirrhosis. Therefore, the management of liver cirrhosis patients with portal hypertension and subsequent gastrointestinal bleeding depends on the clinical stage of portal hypertension, ranging from prophylaxis to management of acute variceal hemorrhage when the objective is to

Table 2. Uni- and multivariate regression

	Alcohol				Other cause			
	Univariate	Multivariate			Univariate		Multivarıate (R^2=0,724)	
Parameters	#B (95%CI)	Significanse	B (95%CI)	Significanse	B (95%CI)	Significanse	B (95%CI)	Significanse
Sex	-0.892 (-1.493-(-0.291))	p=0.004*	-0.475 (-1.010-0.060))	p=0.081	0.026 (-0.456-0.508)	p=0.915	/	/
Age	0.020 (-0.009-0.048)	p=0.172	/	/	-0.008 (-0.023-0.006)	p=0.263	/	/
RLLD	0.002 (-0.007-0.011)	p=0.587	/	/	0.015 (0.004-0.027)	p=0.011*	-0.010 (-0.022-0.002)	p=0.088
Alb	-0.036 (-0.063-(-0.009))	p=0.010*	-0.016 (-0.055-0.022))	p=0.405	-0.091 (-0.117-(-0.065)	p=0.000*	-0.001 (-0.050-0.048)	p=0.965
Index RLLD-Alb	0.152 (0.032-0.272)	p=0.014*	0.041 (-0.124-0.205)	p=0.624	0.397 (0.276-0.519)	p=0.000*	0.285 (0.023-0.547)	p=0.033*
SD (mm)	0.015 (0.008-0.022)	p=0.000*	0.007 (-0.003-0.016)	p=0.180	0.023 (0.019-0.028)	p=0.000*	0.021 (0.015-0.028)	p=0.000*
Plt	0.000 (0.000-0.000)	p=0.000*	0.000 (0.000-0.000)	p=0.908	0.000 (0.000-0.000)	p=0.000*	0.000 (0.000-0.000)	p=0.000*
Index Plt-SD	-0.001 (-0.001-(-0.001))	p=0.000*	-0.001 (-0.002-0.001))	p=0.516	-0.001 (-0.001-(-0.001))	p=0.000*	0.001 (0.000-0.001)	p=0.018*

*Statistically significant; #Unstandardized Coefficients B
DPL: ??. Alb: Albumin. RLLD: Right liver lobe diameter. SD: Spleen diameter. Plt: Platelets.

control the acute episode and prevent rebleeding. The gold standard in the diagnosis of varices is esophagogastroduodenoscopy (18), but it is an invasive and costly diagnostic procedure. Therefore, several studies (1,15,19-26) have addressed the issue of identifying patients with varices by noninvasive or minimally invasive means, with the aim of avoiding endoscopy in those at low risk of having varices. Platelet count and spleen size were the most frequently explored noninvasive parameters.

The etiology of thrombocytopenia in liver disease cannot be attributed to a single cause with certainty. Even after decades of holding 'hypersplenism' as the major theory to explain low peripheral platelet counts in patients with liver cirrhosis, clarifying studies showing a correlation between portal pressure, spleen size, bone marrow production of platelets, platelet survival time, and peripheral platelet count are lacking. The evidence to date attributes thrombocytopenia in liver disease to the combined role of portal hypertension and splenic sequestration on the one hand and decreased thrombopoietin production by the diseased liver on the other (27).

Zaman (28) reported that patients with platelet counts of less than 88,000/mm^3 have a five-times greater likelihood of having large esophageal or gastric varices compared to the patients with higher platelet counts. Ng (21) identified a correlation between the presence of ascites, thrombocytopenia, hyperbilirubinemia, and larger varices in the Chinese population. Similarly, Chalasani (15) concluded that large esophageal varices are predictable in thrombocytopenic patients who have an enlarged spleen, while platelet count of less than 88,000/mm^3 indicates a higher risk for esophageal bleeding. Madhotra (16) reported that platelet count less than 68,000/mm^3 has larger discriminatory value. He also reported that 32% of patients had platelet counts of less than 68,000/mm^3 without detectable splenomegaly, which might be explained by insufficient synthesis of thrombopoietin. It is also indicated that platelet count and thrombopoietin level return to reference values following liver transplantation (29). Other potential explanations for this phenomenon are the presence of antithrombocyte antibodies and thrombocyte-associated immunoglobulin, which can be found in the sera of patients with liver diseases (30).

Qamar (31) suggested, based on results of both the cross-sectional and longitudinal evaluation of 213 cirrhosis patients, that platelet count cannot be used as an adequate noninvasive marker for gastroesophageal varices and that current guidelines for endoscopic screening should be followed. Patients with mild portal hypertension whose platelet count is over 100,000 have significantly lower incidence of large gastroesophageal varices and subsequent variceal hemorrhage. Therefore, platelet count is not useful as a surrogate measurement in the evaluation and treatment of patients with compensated cirrhosis.

In patients with alcoholic liver disease, platelet counts are difficult to interpret since the toxic effect of ethanol on platelets must be considered and active drinking taken into account. Ethanol has direct effects on the platelet lipids, the second messenger system (mediated by cAMP, inositol trisphosphate and diacylglycerol) and the phospholipase A2 system, all resulting in altered platelet aggregability (32). It is clear that alcohol, at a physiologically relevant concentration, has an inhibi-

tory effect on secondary platelet aggregation in the whole blood as well as in platelet-rich plasma (33).

The majority of studies indicate decreased platelet aggregability (34-36) although not all agree (37). Moreover, in alcoholic liver disease, malondialdehyde production (a by-product of prostaglandin synthesis) (34) and TXB2 production (38) are elevated. This could indicate an *in vivo* hyperaggregability possibly contributing to the thrombocytopenia (39).

Previously published data indicate different reliability of noninvasive assessment of portal hypertension related to the etiology of liver cirrhosis. It was reported that the use of noninvasive indicators is invalid for estimation of screening endoscopy necessity in patients with primary biliary cirrhosis and primary sclerosing cholangitis. The probability of presence of esophageal varices is lower in these patients if their platelet count is lower than 200,000/mm^3, possibly due to the fact that thrombopoietin production is preserved in primary biliary cirrhosis and primary sclerosing cholangitis (26,40).

It is now well documented that spleen size is in correlation with the grade of esophageal varices (22,41,42). Watanabe (43) calculated the splenic ratio (length x width x height of the spleen size on computed tomography), and showed that patients having a ratio over 963 cm^3 have esophageal varices, and that a high ratio may predict esophageal bleeding in patients with liver cirrhosis. It was concluded that ultrasonographic measurement of splenic craniocaudal diameter demonstrates lower inter- and intra-observer variability than Doppler sonographic assessment of hepatic flow (44,45).

By integration of two noninvasive parameters, namely platelet count and spleen size, into a single ratio, the pathophysiologic mechanisms are combined. Calculation of this ratio is very easy in routine clinical practice. Giannini with co-authors (19,20) reported the results of a retrospective and prospective study, concluding that this ratio is sensitive for prediction of the presence and size of esophageal varices. The same study group suggested, as especially important, the use of noninvasive parameters in the diagnostic algorithm for identifying patients without esophageal varices. A cut-off value of 909 was proposed for platelet count/spleen size ratio (20). Patients with a ratio greater than the cut-off value should not receive nonselective beta-blockers as prophylactic therapy because they are less likely to develop esophageal varices. These patients should undergo endoscopy less frequently, and this conclusion carries major medico-social importance.

Taking into account the results of previous studies in the field, we also combined laboratory and ultrasonographic parameters and calculated an original ratio. We reported for the first time the value of the RLLD/serum albumin concentration in the assessment of portal hypertension (46). We used serum albumin concentration as a parameter of liver function in combination with right liver lobe size. Our results were confirmed later by other authors (17).

The majority of the previously published studies analyzed noninvasive markers without discriminating the etiology. Using a similar methodology, Sen and Griffiths (17) indicated that platelet count, spleen size, and from these measures a calculated ratio can be used in the prediction of the presence of esophageal varices and their size in patients with cirrhosis due to hepatis C, but not chronic alcohol abuse. To the best of our knowledge, there are no similar studies.

The results of our study led us to conclude that the promising results of the previously published studies, which proposed identification of patients at higher risk for development of esophageal varices in an effort to select those in need of more frequent endoscopy, cannot be used for patients with alcoholic liver cirrhosis. Therefore, esophagogastroduodenoscopy remains the gold standard not only for initial diagnosis, but also for follow-up of varices in alcoholic liver cirrhosis patients.

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