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PORTAL HYPERTENSION IN CHRONIC NON-VIRAL LIVER DISEASE: CORRELATIONS BETWEEN ULTRASONOGRAPHIC AND ENDOSCOPIC ASPECTS

– ABSTRACT OF THE PhD THESIS –

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The doctoral thesis includes:

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- 323 bibliographic references.

In this abstract, the table of contents, the numbering of the selected figures and tables and the list of abbreviations are kept in the same form as in the doctoral thesis. The selective bibliography presented in the abstract includes 22 of the total of the 323 bibliographic references of the doctoral thesis.

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PERSONAL PART

ABBREVIATIONS

2D-SWE.GE = Real Time two-dimension ShearWave Elastography (General Electric)
2D-SWE = Real Time two-dimension ShearWave Elastography
AUROC = aria de sub curba ROC
CAP = Controlled Attenuation Parameter
CSPH = hipertensiune portală clinic semnificativă
CT = computer tomograf
DBPS = diametrul bipolar splenic
dLDH = diametrul lobului drept hepatic
DZ 2 = diabet zaharat tip 2
EDS = endoscopie digestivă superioară
FA = fosfataza alcalină
FGNA = ficat gras non-alcoolic
FIB-4 = Fibrosis-4 calculator
GGT = gama-glutamiltransferaza
GOV = varice gastrice
GPH = gastropatie portal-hipertensivă
HCC = hepatocarcinom
HDS = hemoragie digestivă superioară
HRV = varice cu risc crescut de sângerare
HTP = hipertensiune portală
HVPG = gradient venos hepatic
IMC = indice de masă corporală
IQR = interquartile range
LS 2D = rigiditatea hepatică măsurată prin elastometrie 2D-SWE
LS = rigiditate hepatică
NAFLD = non-alcoholic fatty liver disease
NASH = steatohepatită non-alcoolică
NFS = NAFLD fibrosis score
OR = odds ratio
PBH = puncție-biopsie hepatică
PLT = număr trombocite
pSWE = point ShearWave Elastography
RMN = rezonanță magnetică nucleară
ROI = regiune de interes
SS = rigiditate splenică
SSI = SuperSonic Imaging
TE = Elastometrie Tranzitorie
TGO = glutamat-oxalat transaminaza
TGP = glutamat-piruvat transaminaza
VE = varice esofagiene
VP = vena portă
VTQ = Virtual Touch Quantification

GENERAL CONSIDERATIONS

Chronic liver diseases and portal hypertension

Chronic liver diseases represent a major global problem, evolving with portal hypertension regardless of the aetiology. Identifying and staging the degree of liver fibrosis is a good prognostic indicator for optimizing the therapeutic strategy. The issue related to the non-invasive investigation of portal hypertension syndrome occurs in the context of a significant increase in the epidemiological load at a global level, but especially in Europe, in terms of chronic liver diseases. Analysing the worrying data from the literature on the importance of the presented phenomenon and given the fact that the techniques of exploration of portal hypertension have limitations, it is necessary to develop new methods or establish correlations between existing methods for a better assessment of the presence and degree of portal hypertension. optimization of the prophylactic and curative attitude.

Elastography in hepatology practice

Liver elastography is a non-invasive method of assessing increasingly widespread liver fibrosis, simple and rapid, easily accepted by patients, currently replacing liver biopsy-puncture. Transient elastography (FibroScan, Ecosens, Paris) is the first method that has been tested and validated to assess the degree of liver fibrosis, using dedicated equipment. The exploration correlates well with the histopathological assessment of liver fibrosis in chronic liver diseases of various aetiologies, including non-alcoholic fatty liver (NAFLD) and alcoholic liver disease (Wong et al., 2010), studies in the specialized literature confirming the accuracy of the method. in the detection of the degree of fibrosis and liver cirrhosis, independent of the aetiology (Bureau et al., 2008). Instead, controversy remains regarding the cut-off value for diagnosing advanced fibrosis and cirrhosis, a value that differs depending on the aetiology (Wong, 2013).

Spleen elastography represents a relatively new technique, in full assessment process. Assuming that splenomegaly and passive splenic congestion are directly related to portal hypertension, it has been suggested that spleen stiffness (SS) may reflect portal pressure more accurately than hepatic stiffness (LS) measurement. Studies have shown that the splenic parenchyma is much more rigid than the liver parenchyma, both in healthy subjects and in those with chronic liver disease (Stefanescu et al., 2011). A meta-analysis of 16 studies (1892 patients) comparing SS versus LS for predicting the presence of oesophageal varices showed that measuring splenic stiffness was more accurate than hepatic stiffness, suggesting that this technique may be useful for selecting patients with oesophageal varices. advanced liver disease requiring endoscopic assessment.

Non-alcoholic fatty liver and non-invasive assessment of patients

NAFLD is defined by the excessive accumulation of triglycerides at the level of the liver cell, which affects more than 5% of the number of hepatocytes, quantified histologically or by imaging (by nuclear magnetic spectroscopy) in the absence of secondary causes of steatosis: excessive alcohol consumption (> 30 g/day for men, respectively

> 20 g/day for women), hereditary diseases or the administration of medication with steatogenic potential (Chalasani et al., 2018).

In order to evaluate the presence of steatosis, the current guidelines recommend the use of two biological tests: FLI (*fatty liver index*) and NAFLD *liver fat score*. These scores are easy to calculate, use routine biological samples and simple clinical information. However, at this point, non-invasive tests do not have the ability to differentiate simple steatosis from non-alcoholic steatohepatitis (NASH), liver puncture-biopsy being the only validated method for the diagnosis of non-alcoholic steatohepatitis (EASL-EASD-EASO guidelines, 2016).

Various tests have been developed for this purpose, including biological tests (NAFLD fibrosis score, Fibrosis-4 calculator, APRI, BARD, AST / ALT ratio), biomarkers (ELF Panel, Fibrometer, Fibrotest, Hepascore), as well as imaging techniques: liver elastography based on ultrasonography and magnetic resonance elastography (MR-E).

According to the *Guide of the European Ultrasound Community* (EFSUMB) (Bamber et al., 2013, Cosgrove et al., 2013), the elastographic methods based on ultrasonography are divided into two categories, subdivided as following:

A. *Shear Wave Elastography* (quantitative):
    a. Transient Elastography (TE) – Fibroscan, Echosens – the only method that is not integrated into an ultrasonography system
    b. Point Shear wave Elastography (pSWE) using the ARFI (*acoustic radiation force impulse*) technology:
        1. Virtual Touch Quantification (VTQ-Siemens)
        2. Elast PQ (Philips)
    c. Real Time Shear Wave Elastography
        1. 2D-SWE (SuperSonic Imaging (SSI) Elastography-Aixplorer, GE, Toshiba)
        2. 3D SWE
B. *Strain Elastography* (qualitative) – Real-Time Elastography (RT-E) implemented on Hitachi systems.

These imaging techniques evaluate tissue deformability as a response to mechanical waves applied to the liver, through mathematical analysis and calculation of various stiffness parameters, such as: Young's modulus *(Transient Elastography), Shear Wave Velocity (ARFI)*. Regardless of the technique, the measured parameter is correlated with the histological stage of fibrosis, and these results objectify moderate to severe fibrosis with high accuracy.

CLINICAL, BIOLOGICAL AND ULTRASONOGRAPHIC PREDICTIVE FACTORS OF THE RISK OF ADVANCED FIBROSIS IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER. DESCRIPTIVE CLINICAL STUDY

Introduction

Starting from the epidemiological reality, according to which approximately a quarter of the population is affected globally by various forms of the non-alcoholic fatty liver pathology, with a prevalence of up to 6.5% of the active form of the disease represented by non-alcoholic steatohepatitis. (Younossi et al., 2016), it is easy to understand the growing concern about how the international scientific and professional community re-

sponds to the needs of these patients, especially with regard to the stratification of the risk of progression of the disease and the establishment of the monitoring program. The background elements that influence these professional attitudes are, on the one hand, the differential diagnosis of the type of liver disease and, on the other hand, the assessment of the degree of fibrosis. These two elements are perceived as the main objectives in the management of a newly diagnosed case (Castera et al., 2019).

Material and methods

We conducted a prospective study, with diagnostic strategy, which took place within the Institute of Gastroenterology and Hepatology of "Sfântul Spiridon" County Emergency Clinical Hospital of Iasi between January 2017-January 2019. The research was performed on a lot of 111 patients (82 - male, 29 - female), aged between 26 and 77 years old (mean age 54.92 years; p = 0.104) with a diagnosis of non-alcoholic fatty liver. The assessment of each subject included in the study comprised: medical history, complete clinical examination, laboratory tests, abdominal ultrasound, 2D-SWE.GE liver elastography.

For each subject included in the study, based on anthropometric and biological parameters, 3 scores with predictive value for the existence of advanced liver fibrosis were calculated: NAFLD fibrosis score (NFS), FIB-4 and BARD. The following cut-off values were used to grade the degree of fibrosis: <6,6 KPa (F0-F1), 6,6-7,9 KPa (F2), 8-10 kPa (F3),> 10,1kPa (F4), values suggested by Kim et al. (2016). We applied the Shapiro-Wilk test for normality in order to determine which of the analysed variables comply with the law of normal distribution (those for which the test gives statistically insignificant results). This step was necessary to be able to decide what kind of significance tests will be used later, in order to make comparisons between samples (in the case of variables that comply with the normal distribution law we will use the t-Student and ANOVA tests, and if the law of normal distribution is not observed, we will use the Mann-Whitney and Kruskal-Wallis tests).

Results

The relationship between the degree of steatosis and the values of the clinical and biological parameters in patients with non-alcoholic fatty liver was assessed, and there were statistically significant differences between the three categories of patients (S1 *vs.* S2 *vs.* S3) in the case of the following parameters: BMI (p = 0.000 *), GPT (.032 *), blood sugar (p = .004 *), dLDH (p = .001 *), VP (p = .000 *), DBPS (p = .000 *). There was no significant difference between patients with steatosis S1 and S2. The existence of statistically significant differences between patients with steatosis S1 and S3 was also observed for the parameters BMI (p = .000 *), dLDH (p = .036 *), VP (p = .000 *), DBPS (p = .005), respectively between S2 and S3 for the parameters BMI (p = .000 *), blood sugar (p = .004 *), dLDH (p = .003 *), VP (p = .000 *), DBPS (* p = .000).

Regarding the relationship between the degree of fibrosis and the values of clinical and biological parameters in patients with non-alcoholic fatty liver, it was found that there were statistically significant differences between the three categories of patients (F0-F1 *vs.* F2 *vs.* F3-F4) for the following parameters: BMI (p = 0.000 *), platelets (.015 *), albumin (p = .000 *), blood sugar (p = .000 *), dLDH (p = .048 *), VP (p = .000 *), DBPS (p = .000 *) (Table 5.XII). There were statistically significant differences noticed between F0-F1 and F2 for the parameters BMI (p = .037 *) and DBPS (p = .036 *), between F0-F1 and

F3-F4 for the parameters BMI (p = .000 *), platelets (p = .004 *), albumin (p = .000 *), blood sugar (p = .000 *), VP (p = .000 *), DBPS (p = .000 *), respectively between F2 and F3-F4 for the parameters albumin (p = .006 *), blood sugar (p = .000 *), VP (p = .001 *), DBPS (p = .001 *).

The statistical analysis of liver fibrosis stages showed the absence of statistically significant differences between male and female patients (p = .588). A statistically significant difference (p = .047 *) was noticed between patients under 50 years old *vs.* patients aged 50-60 years old *vs.* patients over 60 years old. It is noticed that in patients under 50 years old are more common cases of fibrosis of stage F0-F1 (52.5%), in those between 50-60 years old the most common cases of fibrosis are of stage F2 (38.5%), and in those over 60 years old the incidence of cases with F3-F4 stage fibrosis (37.8%) increases.

Correlations were determined between the investigated parameters and the degree of steatosis, as follows: (a) for the degree of steatosis S1, one noticed the existence of inversely proportional correlations, between the no. of platelets (r = -.9265, p = .008 *) and respectively directly proportional correlations between the degree of steatosis S1 and blood sugar (r = .9352, p = .006 *), triglycerides (r = .9723, p = .001 *) and DBPS (r = .9080, p = .012 *); (b) for degree S2 of steatosis, inversely proportional correlations were found between degree S2 and no. of platelets (r = -.3132, p = .046 *) and albumin (r = -. 5383, p = .001 *), respectively directly proportional correlations between degree S2 and DBPS (r = .5028, p = .001 *); (c) for the degree of steatosis S3, the existence of inversely proportional correlations was found between S3 and no. of platelets (r = -.3450, p = .005 *) and albumin (r = -. 4161, p = .001 *), respectively directly proportional correlations between S3 and blood sugar (r = .2984, p = .017 *), VP (r = .3612, p = .003 *), and DBPS (r = .3862, p = .002 *), respectively.

Subsequently, correlations were established between the investigated parameters and the degree of fibrosis as follows: (a) for fibrosis stages F0-F1 and F2, respectively, it was found that there were no statistically significant correlations between the investigated parameters and the degree of fibrosis; (b) for fibrosis stages F3 and F4, a statistically significant inversely proportional correlation (r = -. 4888, p = .005 *) was found with regard to the platelet count. No other statistically significant correlations were recorded between the investigated parameters and patients with an advanced fibrosis stage.

After identifying the risk factors, they were inserted into a binary logistic regression model of Forward LR type, in order to analyse their interdependence. The resulting logistic regression equation is: *Logit (P) = ln (P / (1-P) = -4.111 + 2,983 * Modified BMI + 1.198 * Modified blood sugar + 1.204 * Modified dLDH + 1.824 * Modified VP, where P = probability of develop S3 steatosis.*

Discussions

Taking into account the demographic parameters, Lonardo et al. (2015) conducted a meta-analysis that concluded that age and gender are major physiological factors of the risk of occurrence of NAFLD, along with race and genetic factors. Although data on the association between gender and the prevalence of NAFLD are contradictory, most studies in the specialised literature claim that the male gender is considered a risk factor for NAFLD, the prevalence being twice as high in males compared to females (Camhi et al., 2011). However, a very recent study conducted on lots of patients with non-alcoholic fatty liver reported a higher frequency (61.5%) of female patients (Castro et al., 2019).

In our study, the predominance of male patients (73,8%) was found among patients diagnosed with non-alcoholic fatty liver, a result similar to that presented by Camhi et al. (2011) and by most studies in the specialized literature. The number of male patients diagnosed with NAFLD was 2,8 times higher compared to female patients. If, as mentioned above, there was a higher number of male patients with NAFLD globally, our results regarding the share of both degrees of steatosis, as well as of significant fibrosis (F2, F3 and F4) in relation to the gender of the patients, did not show statistically significant differences between male and female patients, unlike Ciecko-Michalska et al. (2018), who reported a significantly higher prevalence of advanced fibrosis in male patients compared to female patients.

In the lot of patients with non-alcoholic fatty liver, a percentage of 60,7% of patients with BMI values over 30 kg/m^2 (obesity) was identified. A study performed by Castro et al. in 2019 identified a percentage of 82,1% of patients with NAFLD with associated metabolic syndrome. Also, McPherson et al. (2010) reported, for the patients with NAFLD assessed in their study, an average BMI value of 35 kg/m^2.

Regarding the relationship between the values of the monitored parameters and the numerical values obtained through elastometry, a study in the specialized literature claims that the value of the total score of the intensity of the modification of the ultrasound criteria for the diagnosis of hepatic steatosis does not correlate significantly with liver lobe diameters and the ANOVA analysis showed that there are no statistically significant differences between the level of diagnostic impression ("likely", "probable", "possible" steatosis) of steatosis and the dimensions of the anterior diameters of the hepatic lobes (Amzolini, 2012). In a comparative study of ultrasonography with histopathological confirmation, the specificity of the imaging examination is 77% and the sensitivity 88%, with an increase in sensitivity as the degree of fatty load of the liver increases (van Leeuwen, 2002).

Conclusions

1. The degree of hepatic steatosis assessed ultrasonographically correlates with liver enzymes, blood sugar, BMI and antero-posterior diameter of the right hepatic lobe.
2. The degree of liver fibrosis, assessed by 2D-SWE.GE elastometry, correlates with liver enzymes, blood sugar, platelet count, serum albumin value, BMI, portal vein diameter and bipolar spleen diameter.
3. Biological parameters (platelet count, serum albumin value), ultrasound (portal vein diameter, antero-posterior diameter of the hepatic right lobe, bipolar spleen diameter) and BMI can be used as predictors for the severity of hepatic steatosis and liver fibrosis.

COMPARATIVE ASSESSMENT OF LIVER FIBROSIS BY SHEAR WAVE ELASTOMETRY AND TRANSIENT ELASTOMETRY. DESCRIPTIVE CLINICAL STUDY

Introduction

The non-alcoholic fatty liver and its associated nosological framework affect over 90% of the obese population globally, and it is estimated that over 40% of the general population would have clinical-paraclinical elements suggesting the need to assess and

monitor possible suffering associated with steatosis. hepatic (Williams et al., 2011; Wong et al., 2012; Jiang et al., 2018). The way in which the hepatological professional community responds to these needs is undoubtedly a challenge.

The most advanced methods of non-invasive assessment of liver fibrosis through elastometry are transient elastography (TE) and shear-wave elastography (SWE), the latter being available in point shear-wave or bidimensional (2D-SWE) (Bamber et al., 2013, Castera et al., 2015). The main alternative technique to TE in the field of elastometry is 2D-SWE, which is considered to be a real technological progress. The method has several advantages, the most important of which is that of increased portability expressed by two-dimensional real-time imaging (Herrmann et al., 2018, Furlan et al., 2020).

The aim of the study was to evaluate the performance of the shear wave elastography method (2D-SWE.GE) in assessing the degree of liver fibrosis in patients with NAFLD, applying TE as a reference method.

Material and methods

The prospective study was carried out in the Institute of Gastroenterology and Hepatology within the County Emergency Clinical Hospital "Sfântul Spiridon" Iasi, between June 2019-December 2019, and targeted a group of 70 patients diagnosed with NAFLD who met the inclusion criteria. Of these, 8 patients were excluded (11.4%): 5 patients who did not meet the quality criteria of the measurements obtained by TE (7.14%) and 3 patients (4.28%) in whom the measurements performed by the method 2D-SWE.GE had an IQR> 30%. The final group consisted of 62 patients (30 - male, 32 - female), aged between 31 and 87 years (mean age 57.34 years). In relation to the BMI, patients were classified as: underweight (BMI < 18.5 kg/m^2); normal weight (BMI = 18.5 - 24.9 kg/m^2); overweight (BMI = 25-29.9 kg/m^2); and obese (BMI ≥ 30 kg/m^2).

Results

The estimated distribution of fibrosis degrees by transient elastometry (Fibroscan) was as follows: 31 patients diagnosed with absent or minimal F0-F1 fibrosis (50%), 10 patients with moderate fibrosis F2 (16.1%), 10 patients with advanced fibrosis F3 (16.1%), 11 patients with fibrosis F4 - cirrhosis (17.8%). The estimated distribution of fibrosis by 2D-SWE.GE elastometry was as follows: 30 patients diagnosed with absent or minimal F0-F1 fibrosis (48%), 16 patients with moderate F2 fibrosis (27.4%), 10 patients with advanced fibrosis F3 (16.5%), 6 patients with fibrosis F4 - cirrhosis (6.5%).

It is observed that the percentage of patients diagnosed with absent or minimal fibrosis is similar in the case of both elastometric methods of non-invasive diagnosis (48% *vs*. 50%). In contrast, in the case of advanced fibrosis, transient elastometry identifies a percentage of 17.8% of patients while 2D-SWE.GE elastometry identifies a lower percentage of patients (6.5%). Subsequently, it is observed that in 71% of the patients assessed the Results obtained by the two methods are concordant. Discordant results were recorded in 29% of cases: difference of one degree of fibrosis in 21% of patients, respectively difference > 1 degree in 8.1% of investigated cases.

To perform the multivariate analysis we used a binary logistic regression model, Forward LR type. We analysed the prediction accuracy for the presence of discrepancies between the two investigation methods. We find that the prediction accuracy is 68.6%. Of

the predictors that were introduced in the model, only CAP and GPT were identified as significant, of which the most important predictor was the degree of steatosis. Thus, although the constructed model is valid, it does not identify from the analysed parameters important predictors for the occurrence of discrepancies, except for a single significant predictor represented by CAP, with a risk of 1,017 (ie very low) - the risk of discordance changes by 1,017 times an increase of one unit in the score obtained by CAP assessment.

Discussions

In the present study, valid measurements were obtained in 95.7% of cases for the 2D-SWE.GE method and in 92.8% of cases for the TE method, respectively. The percentage of valid measurements is similar to that reported by Bende et al. (2017), a study that cites a percentage of valid measurements of 94.2% for the TE method and 95.8% for the 2D-SWE.GE elastometric method. Also, our Resultsle prove that by 2D-SWE elastometry the percentage of valid measurements is higher than that obtained by TE, our Results being similar to those reported by other authors (Cassinoto et al, 2014; Bende et al., 2017).

Analysing the results obtained in our study, we found that when all cases were analysed, regardless of the degree of fibrosis, the values of liver stiffness obtained through the two methods were similar, with no statistically significant differences ($p = 0.464$). On the other hand, when the Results were compared in relation to the degree of fibrosis assigned according to the assessment method, consistent results were obtained in 71% of the assessed patients. Discordant results were recorded in 29% of cases, in most cases with discordant results the difference being one degree of fibrosis. The total percentage of discrepancies recorded in our study was significantly higher compared to other research (Gerber et al., 2015; Kim et al., 2015; Thiele et al., 2016).

The BMI parameter was assessed as a possible cause of discrepancy between the results of the measurements by the two methods, as it is known that it is more difficult to obtain valid measurements by the TE method in overweight and obese patients (Ferraioli et al., 2012a). This disadvantage of transient elastometry was partially counteracted by the fact that the Fibroscan device with which the measurements were performed in our study is provided with separate probes for normal and obese patients, respectively, and the probe selection is made automatically by the device software. However, both in our study and in the specialized literature data, high BMI values were a predictor of discrepancy between the 2D-SWE and TE elastometric method (Yoon et al., 2014; Jeong et al., 2014; Piscaglia et al., 2016, Chang et al., 2016).

A second factor that influenced the concordance of the measurements by the two methods was the necroinflammatory activity, expressed by the TGO and GPT values, respectively. In our study, the discrepancy between the two elastometric methods was mainly influenced by the GPT level. Most studies in the specialized literature have reported that the presence of hepatic cytolysis influences the measured values of hepatic fibrosis and there is a directly proportional correlation between the level of transaminases and that of liver stiffness (Coco et al., 2007). However, there are studies that have not identified a link between liver enzyme levels and liver stiffness values (Elkrief et al., 2015, Piscaglia et al., 2016).

TE is a well-established method that has proven useful for the non-invasive assessment of liver fibrosis. The method has significant positive correlations with the stage of fibrosis, as demonstrated by clinical studies, and is very useful to exclude severe fibrosis and liver cirrhosis in patients with NAFLD (Shaheen et al., 2007, Fraquelli et al., 2007; Friedrich-Rust et al., 2008; Castera, 2009; Tsochatzis et al., 2011; Boursier et al., 2016,). These results led to the widespread recommendation of TE by practice guidelines for the diagnosis and management of patients with liver pathology (Klotz et al., 2014).

Due to the fact that Results similar to those obtained by TE (a method that is accepted by current guidelines) were recorded, 2D-SWE.GE elastometry can be considered a valid method of non-invasive assessment of liver fibrosis that is can legitimize assimilable as an investigative alternative equivalent to TE in the evaluative protocols of liver pathology.

Conclusions

1. 2D-SWE.GE and TE elastometry demonstrated comparable diagnostic performance of liver fibrosis.
2. Providing results similar to TE, a method that is accepted by current guidelines, 2D-SWE.GE elastometry can be considered a valid method for non-invasive assessment of liver fibrosis.
3. There are some discrepancies in the assessment of fibrosis stages between the two methods, their occurrence may be influenced by factors such as age, BMI, level of necroinflammatory activity and the presence, respectively, the degree of steatosis.

PERFORMANCE OF *SHEAR WAVE* ELASTOMETRY IN THE ASSESSMENT OF PORTAL HYPERTENSION. PROSPECTIVE CLINICAL STUDY

Introduction

The progression of liver fibrosis with a direct impact on the severity of portal hypertension (PH) is a pivotal element in terms of complications in cirrhotic patients, which significantly influences the mortality of these patients (de Franchis, 2010). The pathophysiological basis of the relationship between the progression of liver fibrosis and the morbidity and mortality of cirrhotic patients lies in the fact that the occurrence of major complications such as variceal haemorrhage, refractory ascites or hepato-renal syndrome is mainly due to increased portal pressure gradient. hepatic (Bosch, Garcia-Pagan, 2000).

The quantification in objective and reproducible functional parameters of this pathophysiological process has traditionally been performed by calculating the portal-suprahepatic pressure gradient with the establishment of the threshold of 10 mmHg, above which clinically significant portal hypertension (CSPH) was defined (Bosch et al., 2009, Ripoll et al., 2009). The Baveno VI consensus implemented transient elastography as a reproducible tool for risk assessment for the occurrence of CSPH, respectively to exclude the need for endoscopic screening of oesophageal varices (de Franchis, 2015).

Given the fact that so far elastography by 2D-SWE has enjoyed higher degrees of reception both in practice and in research in relation to related elastometric techniques, by identifying threshold values validated for the assessment of liver fibrosis, we can look at the technique 2D.SWE as a potentially useful and promising resource in assessing PH severity (Elkrief et al., 2015; Procopet et al., 2015; Kim et al., 2015; Jansen et al., 2017).

The aim of the study was to investigate the performance of splenic shear wave elastometry in the assessment of PH in patients with advanced chronic liver disease.

Material and method

Our study initially included 59 patients diagnosed with toxic and metabolic compensated liver cirrhosis. The study was a prospective one, carried out within the "Sfântul Spiridon" Hospital in Iași, Institute of Gastroenterology and Hepatology, in the period between January 2019-October 2019. After applying the inclusion and exclusion criteria, 48 patients remained enrolled in the study, patients who successively benefited from: complete biological profile, clinical and anthropometric assessment, abdominal ultrasonography, 2D.SWE.GE splenic elastography, diagnostic upper digestive endoscopy and screening of oesophageal varices. The Kolmogorov-Smirnov test was used to test the distribution of numerical variables. The mean value and standard deviation for numerically variable numerical variables were calculated. In cases with abnormal distribution, median and interval values were used. The Student's t test was used for group comparisons of continuous variables with normal distribution. Mann – Whitney U nonparametric tests were applied to variables with non-normal distribution. Group comparisons of categorical variables were performed using the Pearson test. ROC curves were calculated for the 2D-SWE.GE elastometric method. Positive predictive values (VPP - true positive / total cases), negative predictive values (VPN - true negative / total cases) and diagnostic accuracy (true positive cases + true negative / total cases) were calculated.

Results

There are statistically significant differences (p = .022 *) between male patients (74.3%) and female patients (30.8%) regarding the degree of damage by the presence of oesophageal varices. Consequently, we observe that a percentage of 10.4% of patients with compensated liver cirrhosis have gastric varices (GOV). There are no statistically significant differences (p = 0.190) between male and female patients in the presence of gastric varicose veins. 14.6% of patients with compensated liver cirrhosis have portal-hypertensive gastropathy. There are no statistically significant differences (p = 0.191) between male and female patients with GPH impairment.

Regarding the risk of bleeding, 37.5% of patients with compensated liver cirrhosis have high-risk varicose veins (HRV). There are statistically significant differences (p = 0.009 *) between male (48.6%) and female (7.7%) patients with varicose veins at high risk of bleeding (HRV). It is observed that there are statistically significant differences (p = 0.019 *) between the percentage of patients with varicose veins with high degree of bleeding (II-III) in relation to age.

The ROC curve was determined for SS values; the area under the curve is .987, p = .000 - so SS values are significant in identifying the risk of variceal haemorrhage. The

appropriate cut-off value is 17.95 - it has the best combination between sensitivity - 94.4% and specificity - 96.7% - according to Youden's coefficient - maximum value (sensitivity + specificity).

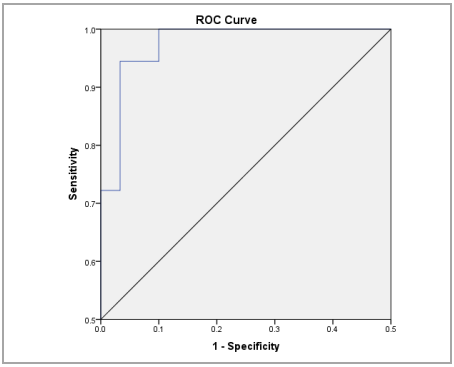

Fig. 6.16
ROC curve for SS values

For the multivariate analysis we used a binary logistic regression model, Forward LR type. For the diagnosis of varicose veins with an increased risk of bleeding, initially the prediction accuracy is 62.5%. All predictors introduced in the model are identified as significant, except GPT. The most important predictor is SS, followed by platelet count, CHILD = A, albumin and LS 2D.

The Hosmer-Lemeshow fit test indicates that the constructed model is viable, its Results being statistically insignificant (p = 1,000); the identified predictors increase the risk of HRV up to 95.8%, the share being important as a growth level and suggestive for the usefulness of the constructed regression model. Therefore, only one predictor was identified, namely SS, with a risk of 4,985: the risk of HRV changes 4,895 times to an increase by one unit of the SS value, according to the equation: Logit (p) = ln (p / (1- p) HRV) = -28,778 + 1,606 * SS, where p represents the probability that the patient will have HRV.

Discussions

Although numerous studies report a good correlation between spleen size and the presence of oesophageal varices (Berzigotti et al., 2008), other authors have shown that, although splenomegaly is commonly present in patients with liver cirrhosis, a significant percentage of patients with cirrhosis of the liver do not have varicose veins with an increased risk of bleeding (Ma et al., 2016; Manatsathit et al., 2018).

In the specialized literature a consensus has been reached on the use of Baveno VI criteria: patients with advanced chronic liver disease, with liver stiffness (measured by transient elastography) <20 kPa and platelet count> 150,000 have a low risk (<5%) to present varices with risk of bleeding (requiring endoscopic treatment) (Maurice et al., 2016; Silva et al., 2017). As a result, protocols based on the Baveno VI criteria suggest that Upper digestive endoscopy may be avoided in patients with advanced chronic liver disease with liver stiffness values below 20 kPa and platelet counts above 150,000/mm^3.

The rate of valid SS measurements by 2D-SWE.GE elastometry may be a limitation of studies of this type, if it is below 85%. The US guided assessment can increase the validation rate to over 90%, a result obtained (94%) in the study conducted by Colecchia et al. (2018). In the present study we obtained measurements valid in 88.8% of cases for the 2D-SWE.GE elastometric method, Results which are in accordance with the data in the specialized literature and honourable for the inaugural condition of the investigation in the institute.

In this context, the results of our study are consistent with data from the literature on the possibilities of using SS values in assessing portal hypertension and the presence of oesophageal varices. The results obtained in our study are similar to those reported by recent studies performed by 2D-SWE elastometry and pSWE elastometry, whose results recommend incorporating SS measurement into non-invasive algorithms by using validated software and optimized measurement scales to increase accuracy. diagnosis of portal hypertension in patients diagnosed with compensated liver cirrhosis (Berzigotti et al., 2017; Roccarina et al., 2018; Paternostro et al., 2019).

Conclusions

1. Patients with oesophageal varices at high risk of bleeding have significantly higher mean values of the portal vein and bipolar splenic diameter than those without a risk of bleeding; among the assessed clinical-biological parameters, platelets and Child Class are predictors of the increased risk of variceal bleeding;
2. Correlated hepatic and splenic stiffness in our study with haemorrhagic experiences can be used as predictors for the risk of variceal bleeding; to determine the risk of variceal bleeding, the calculated cut-off value of SS measured by 2D-SWE.GE elastometry is 17.95 kPa; this calculated value is lower than that reported in the specialized literature for transient elastometry (46 kPa).

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