Non-invasive ultrasound-based diagnosis and staging of esophageal varices in liver cirrhosis. A systematic review of the literature published in the third Millenium

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Abstract

Introduction: Endoscopic surveillance of esophageal varices in patients with liver cirrhosis is expensive for the health system and uncomfortable for the patients. Recently, non-invasive ultrasound-based parameters seem to offer valuable information about the status of esophageal varices and thus challenge the need for repetitive endoscopic monitoring. Material and method: We have performed a systematic review of the literature published in PubMed from January 2000 until March 2012 over the role of ultrasound-based parameters on the evaluation of esophageal varices in patients with liver cirrhosis. Results: Eleven papers studied the role of gray-scale and Doppler ultrasound and two further studies analyzed the relationship between liver stiffness and staging of esophageal varices. The parameters that proved to be valuable for diagnosis of esophageal varices and reached statistical significance were: diameter of the spleen > 15 cm, congestion index of the portal vein > 0.154 cm×sec, portal hypertensive index > 2.08, liver stiffness > 43.97kPa, portal vein diameter > 13 mm, renal artery resistance index ≥ 0.7 and development of new porto-systemic collaterals. Other parameters such as: pattern of hepatic venous waveforms or flow parameters of the hepatic or splenic veins did not reach statistical significance. Conclusions: Although esophagogastroduodenoscopy remains the golden standard, there are some ultrasound-based parameters which, used within complex algorithms, may represent a viable alternative for the diagnosis and surveillance of esophageal varices in patients with liver cirrhosis.

Keywords: esophageal varices, esophagogastroduodenoscopy, abdominal ultrasound, non-invasive diagnosis, transient elastography

Introduction

Timely prediction of bleeding from esophageal varices (EV) in patients with liver cirrhosis represents a real challenge for the medical team and the proof of efficient surveillance. Nowadays, complete diagnosis of portal hypertension (PHT) requires measurement of the portal-to-systemic gradient, the parameter that gives the most accurate information about the development of EV [1-3]. Although measurement of this gradient is safe and has not been associated with vital risks [4], it still remains an invasive procedure which needs adequate logistics and training of the medical staff. Moreover, it is available in a limited number of specialized centers and is very much dependent on the expertise of the performing physician.

Present in 40% of patients with compensated and 60% of those with decompensated liver cirrhosis, EV are the result of a pressure gradient between the portal and caval venous systems [5]. The major risk associated with EV is represented by massive hemorrhage, the mortality rate of the first bleeding episode in these patients reaching up to 40% [6]. Performing an esophagogastroduodenoscopy (EGD) still remains the best way to diagnose and evaluate esophageal and gastric varices and the risk of variceal bleeding [7], EGD being recommended as the first line investigation at the initial diagnosis of liver cirrhosis by the most important leaders of opinion in gastroenterology (Baveno Consensus V, The American Association for the Study of Liver Disease, The British and French Society of Gastroenterology) [1,8-10]. EGD is however expensive for the health system and unpleasant for the pa-
tient, especially so when it has to be repeated frequently, within the framework of a screening program. Therefore, identification of alternative, non-invasive parameters for surveillance of EV in patients with liver cirrhosis would restrict its use only to those cases that necessarily need it, resulting in an increased compliance of the patients to surveillance protocol and a decreased risk of procedure-related complications and a reduced financial burden for the hospitals.

To date, there are a number of biochemical and imagistic parameters that have been used to predict the development of EV in patients with liver cirrhosis. Abdominal ultrasound offers an accurate assessment of the morphology of the liver and the portal system while evaluation of liver stiffness has been proven to offer a good degree of prediction for the final diagnosis of liver cirrhosis [11-13] and severity of portal hypertension [14,15]. Two other radiological investigations, abdominal contrast-enhanced computer tomography (CT) and magnetic resonance imaging (MRI), can also offer important information about the pattern of blood flow in the portal system and have been used successfully in this respect [16].

All the above mentioned parameters appear to be promising in the evaluation of PHT and may be regarded as alternatives to EGD in the risk assessment of bleeding from EV. Despite certain encouraging reports which showed a good correlation between these parameters and the grade of EV, to date there is no standardized, universally accepted non-invasive algorithm for the monitorization of EV, and EGD still plays the leading role in this respect. A clarification of the present status of knowledge in this field is necessary now, more than a decade after the beginning of the new Millenium, and for that reason we have decided to perform a systematic review of the literature on this subject.

**Material and method**

All papers published in MEDLINE (PubMed®, www.pubmed.org) from January 2000 until March 2012 in English, German and French languages were selected by the following search criteria: non-invasive diagnosis AND esophageal varices, ultrasonography (US) AND esophageal varices, US Doppler AND esophageal varices, liver stiffness AND esophageal varices, magnetic resonance imaging AND esophageal varices, computer tomography AND esophageal varices were analyzed in the abstract form.

**Including criteria.** From this initial group of articles those reporting on prospective trials that evaluated the role of non-invasive radiologic parameters for the diagnosis of EV in adults with liver cirrhosis confirmed either by liver biopsy or by a combination of clinical, biochemical and radiological criteria were selected. We have excluded papers in which measurement of the targeted parameter required a certain degree of invasiveness (introduction of an esophageal catheter for CT-esophagography) or those that were not purely imagistic (endoscopic capsule).

Other articles were excluded from our study because they have included patients with medication (beta-blocking treatment) or complications of the disease (EV banding or sclerization, thrombosis of the portal or splancnic vascular tree, recent or ongoing upper GI hemorrhage, cirrhosis-associated hepatocarcinoma, TIPS or liver transplantation) which can potentially change the pattern of portal blood flow. We have applied these inclusion criteria to increase the accuracy of data synthesis and reduce the risk of misinterpretations and biases.

The full-text version of papers that fulfilled the inclusion criteria were obtained on-line or in-paper at the libraries of the University of Medicine and Pharmacy, Cluj Napoca, România, University of Heidelberg, Germany, and University of Vienna, Austria. The data was collected systematically in standardized spreadsheets, sorted and analyzed accordingly. Due to the sparse number of papers and relatively reduced number of patients reported, it was not possible to perform a sound statistical analysis of the retrieved data. However, every time it was mentioned, the statistically significant results presented in the respective article were recorded and reported accordingly.

**Results**

**Selection of studies.** There were 464 potential references identified by the search criteria. Some of these were duplicates, most of the studies were not prospective and many of them did not fulfill the inclusion criteria.

In the end, after exclusion of duplicates and application of all inclusion and exclusion criteria, there were 11 papers that studied the role of ultrasound-based procedures (gray-scale and Doppler abdominal US) and two further articles that evaluated the role of liver stiffness in the prediction, evaluation and risk of rupture of EV (table I). The papers referring to the role of CT (1 paper [17]) or MRI (3 papers [18-20]) were not included in the study because they were retrospective and included patients that were already receiving medical treatment with beta-blocking agents. There was one paper which evaluated the role of spleen rigidity in the surveillance of EV [21] but it was excluded from our study because it reported on patients with previous episodes of upper-GI bleeding in their history or patients treated with beta-blocking agents, parameters defined as exclusion criteria for our study.
Table 1. Papers that studied the role of ultrasound based non-invasive parameters and Fibroscan for evaluation of esophageal varices in liver cirrhosis which were included in the review

<table>
<thead>
<tr>
<th>No</th>
<th>Author/Year/Country</th>
<th>Patients (n)</th>
<th>Etiology</th>
<th>Endoscopy findings (EV)</th>
<th>Investigated parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Joseph (2011) India</td>
<td>51</td>
<td>Alcohol=26, B,C virus=14, Others=11</td>
<td>Small=30, Large=21</td>
<td>Hepatic venous waveforms (right and middle hepatic vein)</td>
</tr>
<tr>
<td>2</td>
<td>Cherian (2011) India</td>
<td>229</td>
<td>Alcohol=97, B,C virus=58, Others=74</td>
<td>Absent=51, Small=97, Large=81</td>
<td>PV diameter</td>
</tr>
<tr>
<td>3</td>
<td>Kim (2010) Korea</td>
<td>280</td>
<td>B virus</td>
<td>Absent=156, Small=39, Medium=71, Large=14</td>
<td>Liver stiffness</td>
</tr>
<tr>
<td>4</td>
<td>Sarangapani (2009) India</td>
<td>106</td>
<td>Alcohol=63, B,C virus=25, Others=18</td>
<td>Absent=29, Small=26, Large=51</td>
<td>Spleen bipolar diameter, PV diameter</td>
</tr>
<tr>
<td>5</td>
<td>Berzigotti (2008) Italy</td>
<td>60</td>
<td>Alcohol=7, B,C virus=48, Alcohol + virus=2, Others=3</td>
<td>Absent=32, Small=20, Large=8</td>
<td>Nodular liver surface, PV (diameter, mean velocity, CIx), Superior mesenteric artery (mean velocity, PI), HARI, HAPI, SAPI, SARI, abdominal collaterals, abdominal flow of hepatic veins</td>
</tr>
<tr>
<td>6</td>
<td>Tarzamni (2008) Iran</td>
<td>85</td>
<td>Alcohol=2, B,C virus=52, Others=31</td>
<td>Absent=16, Small=50, Large=19</td>
<td>Spleen bipolar diameter, PV diameter, portal vein flow velocity, HARI, SARI, PHT index, Liver vascular index, CIx</td>
</tr>
<tr>
<td>7</td>
<td>Berzigotti (2008) Italy</td>
<td>126</td>
<td>Alcohol=46, B,C virus=61, Alc+vir=13, Others=6</td>
<td>Absent=43, Small=83</td>
<td>Abdominal collaterals (paraumbilical vein, left gastric vein, spleno-renal shunt, other collaterals)</td>
</tr>
<tr>
<td>8</td>
<td>Baig (2008) India</td>
<td>150</td>
<td>Alcohol=73, B,C virus=53, Others=24</td>
<td>Absent=44, Small=36, Medium=54, Large=16</td>
<td>Spleen bipolar diameter</td>
</tr>
<tr>
<td>9</td>
<td>Sharama (2007) India</td>
<td>101</td>
<td>Alcohol=36, B,C virus=32, Alc+vir=7, Others=26</td>
<td>Absent=12, Small=43, Large=46</td>
<td>PV diameter, Splenic vein diameter</td>
</tr>
<tr>
<td>10</td>
<td>Vizzutti (2007) Italy</td>
<td>46</td>
<td>C virus</td>
<td>Absent=16, Small=12, Large=18</td>
<td>Liver stiffness</td>
</tr>
<tr>
<td>11</td>
<td>Plestinia (2005) Croatia</td>
<td>99</td>
<td>Alcohol=83, B,C virus=13, Others=3</td>
<td>Small = 48, Medium=41, Large=10, Red sign positive=26, negative=73</td>
<td>PV (diameter, cross-sectional area, mean blood flow velocity, blood flow volume, perfusion pressure gradient, CIx)</td>
</tr>
<tr>
<td>12</td>
<td>Coli (2001) Italy</td>
<td>50</td>
<td>Alcohol=18, B,C virus=17, Alc+vir=6, Others=9</td>
<td>Absent=26, Present=24</td>
<td>RARI CIx</td>
</tr>
<tr>
<td>13</td>
<td>Shepis (2001) Italy</td>
<td>143</td>
<td>Alcohol=15, B,C virus=111, Others=17</td>
<td>Absent=80, Small=35, Medium=18, Large=10</td>
<td>PV (diameter, mean and maxim blood flow velocity, CIx), Spleen bipolar diameter</td>
</tr>
</tbody>
</table>
1. Gray-scale and Doppler abdominal ultrasound for evaluation of portal hypertension and esophageal varices.

A total number of 1200 patients with liver cirrhosis were investigated in those 11 papers selected for our study. The etiology of cirrhosis was alcoholic in 508 cases, viral (hepatitis B and hepatitis C) in 488 patients while 220 patients had other causes such as autoimmune hepatitis, hemochromatosis, Wilson disease or Budd-Chiari syndrome.

The classification of EV used by the authors of these studies was not homogenous and, therefore, it was difficult to compare the results; five studies used the 4 grades classification of EV [22-26], four used the 3 grades classification [8, 27-29], one study divided EV according to their size (small EV were considered those less than 5 mm while large EV had a size over 5 mm) [30] while one last study investigated only small EV according to the Beppu classification [31]. However, in the end, in order to increase the homogeneity of their final results, the same authors split the studied patients either in two groups (with EV vs. without EV or small EV vs. large EV) or in three groups (without EV vs. small EV vs. large EV). Small EV groups were considered EV grades I or II from the initial classification while large EV were those classified grade III or IV.

1.1. Morphological parameters as markers of portal hypertension

Seven of the total 11 papers evaluated the role of the bipolar diameter of the spleen and the diameter of the portal vein for prediction of EV status. These parameters are actually ultrasound-based non-invasive indirect markers of portal hypertension; they are currently used for evaluation of patients with liver cirrhosis and are rather easy to measure. At the same time the investigation is widely available, safe and repeatedly reproducible.

All 7 papers correlated the diameter of the bipolar diameter of the spleen with the development of EV and presence of large EV. Of these, three papers evaluated patients with compensated liver cirrhosis (no ascites, no encephalopathy) [8,24,27] and four papers studied all patients, both with compensated and decompensated liver cirrhosis [22,23,25,28].

The results of these studies are not homogenous and they are not powerful enough to allow an elaboration of the final conclusions (Tables II, III). There were studies which did find some statistically significant results, suggesting that a value of the bipolar diameter of the spleen over 15 cm could predict the presence of large EV [22] while a value of the portal vein diameter over 13 mm could be a sensitive parameter for the prediction of the

Table 2. Diagnostic performance of US (bipolar diameter of the spleen) for the diagnosis of EV by author. NS - not significant, NI - not investigated, 95%CI-confidence index

<table>
<thead>
<tr>
<th>Author</th>
<th>Berzigotti</th>
<th>Tarzamni</th>
<th>Shepis</th>
<th>Cherian</th>
<th>Sarangapani</th>
<th>Sharma</th>
<th>Baig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut-off values proposed for the bipolar diameter of the spleen (mm)</td>
<td>NS/NS</td>
<td>NS/&gt;150.5</td>
<td>NS/NS</td>
<td>&gt;150/ &gt;160</td>
<td>NI/&gt;138</td>
<td>NI/NS</td>
<td>&gt;112.5/NI</td>
</tr>
<tr>
<td>Se (%)</td>
<td>NS/NS</td>
<td>NS/79</td>
<td>NS/NS</td>
<td>NI/NI</td>
<td>NI/88.5</td>
<td>NI/NS</td>
<td>74.5/NI</td>
</tr>
<tr>
<td>Sp (%)</td>
<td>NS/NS</td>
<td>NS/NI</td>
<td>NS/NS</td>
<td>NI/NI</td>
<td>NI/83</td>
<td>NI/NS</td>
<td>68.2/NI</td>
</tr>
<tr>
<td>PPV</td>
<td>NS/NS</td>
<td>NS/NI</td>
<td>NS/NS</td>
<td>NI/NI</td>
<td>NI/83.3</td>
<td>NS/NS</td>
<td>84.9/NI</td>
</tr>
<tr>
<td>NPV</td>
<td>NS/NS</td>
<td>NS/NI</td>
<td>NS/NS</td>
<td>NI/NI</td>
<td>NI/70.5</td>
<td>NS/NS</td>
<td>52.6/NI</td>
</tr>
<tr>
<td>95% CI</td>
<td>NS/NS</td>
<td>NS/1.23-2.55</td>
<td>NS/NS</td>
<td>1.6-11.8/1.6-6</td>
<td>NI/NI</td>
<td>NS/NS</td>
<td>0.764/NI</td>
</tr>
</tbody>
</table>

Table 3. Diagnostic performance of US (diameter of the portal vein) for the diagnosis of EV by author

<table>
<thead>
<tr>
<th>Author</th>
<th>Berzigotti</th>
<th>Tarzamni</th>
<th>Shepis</th>
<th>Cherian</th>
<th>Sarangapani</th>
<th>Sharma</th>
<th>Plestina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut-off values proposed for the diameter of the portal vein (mm)</td>
<td>NS/NS</td>
<td>NS/NS</td>
<td>&gt;130/NI</td>
<td>&gt;130/NS</td>
<td>NI/&gt;13</td>
<td>NI/NS</td>
<td>NI/137.5</td>
</tr>
<tr>
<td>Se (%)</td>
<td>NS/NS</td>
<td>NS/NS</td>
<td>NI/NI</td>
<td>NI/NS</td>
<td>NI/76.5</td>
<td>NI/NS</td>
<td>NI/80</td>
</tr>
<tr>
<td>Sp (%)</td>
<td>NS/NS</td>
<td>NS/NS</td>
<td>NI/NI</td>
<td>NI/NS</td>
<td>NI/80</td>
<td>NI/NS</td>
<td>NI/78.4</td>
</tr>
<tr>
<td>PPV</td>
<td>NS/NS</td>
<td>NS/NS</td>
<td>NI/NI</td>
<td>NI/NS</td>
<td>NI/78</td>
<td>NS/NI</td>
<td>NI/NI</td>
</tr>
<tr>
<td>NPV</td>
<td>NS/NS</td>
<td>NS/NS</td>
<td>NI/NI</td>
<td>NI/NS</td>
<td>NI/78.6</td>
<td>NS/NS</td>
<td>NI/NI</td>
</tr>
<tr>
<td>95% CI</td>
<td>NS/NS</td>
<td>NS/NS</td>
<td>1.3-6.4/NI</td>
<td>1.1-5.3/NS</td>
<td>NI/NI</td>
<td>NI/NS</td>
<td>NI/0.877</td>
</tr>
</tbody>
</table>
The only paper which investigated the relationship between the porto-systemic circulation and the development, respectively enlargement of EV, was performed by Berzigotti [31]. She evaluated patients with liver cirrhosis every 6 months for a total duration of 55 months and demonstrated that the appearance of new collaterals on the ultrasound examination predicts aggravation of esophageal varices, findings proven by concomitant upper GI endoscopy. According to the authors, the worsening of findings during ultrasound screening should be considered a serious warning sign that is powerful enough to justify shortening of the time interval between two consecutive EGD in patients with liver cirrhosis. These results indicate that dynamic monitoring of the characteristics of collateral circulation is more important than the information offered by just a singular picture taken at a given time and that US is a valuable tool in this process through its ability to identify the modifications in the porto-systemic circulation and thus, to give information predictive for the aggravation of EV.

1.3. Ultrasound Doppler parameters of splanchnic and portal circulation

The portal and splanchnic hemodynamics have been intensely studied in the 80’s and 90’s, in an attempt to find non-invasive parameters that could accurately predict development of PHT and EV. There have been multiple attempts to find the best predictive protocol, starting from simple formulas to the most complex ones, that included various Doppler parameters. However, results were not up to expectations and even today, accurate diagnostic protocols for diagnosis and staging of EV are still waiting to be developed.

Various Doppler parameters have been described for the evaluation of EV in six of the 11 papers studied: Hepatic Artery Resistance Index (HARI), Hepatic Artery Pulsatility Index (HAPI), Splenic Artery Resistance Index (SARI), Splenic Artery Pulsatility Index (SAPI), Renal Artery Resistance Index (RAI), Renal Artery Pulsatility Index (RAPI), Congestion Index of the Portal Vein, Portal Hypertensive Index (PHT Index) and Liver Vein Blood Flow Speed Spectrum.

Although, according to these studies, HARI and SAPI have risen in patients with liver cirrhosis and PHT, there was no correlation between these parameters and the presence and development of EV. In the study from Berzigotti [27] HAPI was the only parameter which had a higher value in patients with EV compared with those without EV (1.72±0.44 versus 1.55±0.31); however, on the multivariate analysis, this variation did not reach statistical significance [27].

In the study of Tarzamni [24], the PHT Index > 2.08 was the only Doppler parameter to reach a high sensitiv-
ty (Se) (79%) for detection of large EV while all the other parameters (HARI, SARI, the vascular index of the liver) were not statistically significant. Proposed by Piscaglia [39], the PHT Index is calculated by the formula \((\frac{HARI \times 0.69}{SARI \times 0.87})/\text{portal vein mean velocity}\), a formula based on physiopathological considerations, starting from the idea that both impedance indexes in the liver and splenic arteries are well correlated with the portal resistance but with different coefficients.

Another parameter studied in PHT and EV respectively is the Congestion Index \((CI_x)\) of the Portal Vein first described by Moriyasu. This parameter represents the ratio between the cross-sectional area (cm\(^2\)) and the blood flow velocity (cm/sec) of the portal vein \(CI_x = \frac{pP}{4}/PV\text{mean}\), where \(P\) is the portal vein diameter and \(PV\text{mean}\) represents the mean portal flow velocity [40]. Moriyasu established a cut-off value that is diagnostic for each category of liver diseases, from acute hepatitis to liver cirrhosis \((CI_x\) cut-off value of 0.171±0.075cm×sec) and idiopathic PHT respectively \((CI_x\) cut-off value of 0.180±0.107cm×sec). A further development of the role of this parameter would be its prediction for presence of EV. Plestina et al [25] proved that at a cut-off value of 0.154 cm×sec, the \(CI_x\) has a sensibility (Se) of 70% and specificity (Sp) of 64.9% for the risk of bleeding from EV (grade III and IV and presence of red cherry spots). Similar results were published by Shepis [8] who also confirmed that the \(CI_x\) was significantly higher in the group of patients with EV than those without EV. There were also significant statistical differences of \(CI_x\) values among patients with small EV compared with those with medium and large EV [8]. All this data confirms that \(CI_x\) of the portal vein represents one of the most valuable Doppler parameter for prediction of presence and size of EV.

Coli [29], on the contrary, could not confirm the enthusiastic results mentioned above. He demonstrated that a cut-off value of \(CI_x \geq 0.12\)cm × sec was present in 50% of patients with VE and 30% of patients without VE and that, at this value (\(\geq 0.12\)cm × sec), \(CI_x\) with a specificity of 60% and sensibility of 60%, does not predict accurately PHT or presence of EV.

The Intraparenchymal Renal Artery Resistance Index (RARI) was investigated in a single paper [29] of those included in our review. For a RARI \(\geq 0.7\) there is a 70% probability for existence of EV and it was also shown that RARI is more accurate in the prediction of EV than the \(CI_x\) of portal vein. This is the only study demonstrating a relationship between RARI and the presence of EV and, for the moment, it opens a new chapter in the study of non-invasive parameters predictive for the presence of EV.

Another parameter investigated was the pattern of hepatic venous waveform. The measurements are relatively easy to perform and are associated with a less pronounced interobserver variability compared with other Doppler parameters. The study of Joseph T [30] performed on 51 patients with liver cirrhosis, of which 30 with small EV and 21 with large EV, has shown that the disappearance of the triphasic flow pattern had a high Se (95.23%) and negative predictive value (NPV) (95.23%) for the detection of large EV. However the positive predictive value (PPV) (42.6%) and Sp (10%) for this parameter were low and it ultimately failed to correlate accurately with the size of EV. One of the explanations for these findings and the equivocal results is that the hepatic veins flow waves are easily influenced by the phases of respiration and their accurate determination is very much dependant upon the study methodology.

Finally, we can conclude that certain Doppler parameters managed to offer valuable information regarding the diagnosis and stage of PHT and EV and among these the \(CI_x\) of portal vein and RARI seem to be the most promising. However, the data supporting their use in the non-invasive diagnosis and monitoring of EV requires further confirmation in other trials, on larger cohorts of patients and within homogenous study groups. In this respect, recording and analysis of data must be perfectly standardized (nul per os for minimum 8 hours and physical rest 20 min before the procedure, minimal presence of air in the colon and no massive ascites or significant liver steatosis) and requires advanced medical devices and specialized personal for accurate acquisition and interpretation of data. Further restrictions that can influence the end-results are related to the factors that alter the hemodinamic parameters such as vascular malformations, patent collaterals or use of various hemodinamically active drugs (beta-blocking agents, diurhetics, nitrates or nonsteroidal antiinflammatory drugs).

2. Transient elastography (Fibroscan) and esophageal varices

Ultrasoundographic measurement of liver stiffness is a very attractive non-invasive parameter for asessment of fibrosis in chronic liver diseases, being reproducible, operator-independent and well correlated with the degree of fibrosis [41]. It has already been demonstrated that in patients with histopathologically confirmed cirrhosis, the grade of EV is directly correlated with the degree of liver fibrosis, an increase of the latter being translated in a rise in the size of the former [42]. With these premises in mind, we have tried to evaluate if there is a cut-off value for liver fibrosis which can be used to predict presence or evolution of EV. For this sub-chapter of our review, we have added additional exclusion criteria, specific for the Fibroscan examination, namely: body mass index (BMI)
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> 35 kg/m², ALT or ASAT >100 UI, massive ascites or difficulty of measuring liver stiffness due to presence of interhepato-phrenic ascites. There were two papers [14,43] which fulfilled the inclusion criteria and were analyzed in this review. They included 326 patients in total with rather homogenous characteristics and liver cirrhosis of viral etiology. C virus in the study of Vizzutti [14] and B virus in the study of Kim [43]. EV were evaluated as small (minimal elevation of the venous wall from the esophageal mucosa), medium (tortuous veins which fill up less than a third of the esophageal lumen) and large (veins that occupy more than a third of the esophageal lumen). Kim has further classified EV in varices with high hemorrhagic risk (medium and large EV or small EV with red cherry spots), respectively EV without hemorrhagic risk. The examination protocol used for evaluation of liver stiffness was similar in both studies.

Kim BK [43] evidenced by multivariate statistical analysis that liver stiffness is well correlated with the risk of bleeding from EV. Patients with a value of liver stiffness up to 16.56±10.71kPa have a low risk of EV hemorrhage while those with values over 43.97±21.67 kPa have a significant risk of bleeding from EV (p<0.001, odds ratio 1.107; 95% confidence interval 1.074-1.142). The same study showed that there are two other parameters which have a statistically significant value in prediction of bleeding from esophageal varices: the bipolar diameter of the spleen > 14.34±2.08 cm and platelet count ≤ 82.2±37.6 (×10⁹/l). The next logical step was to use all these three parameters in a special formula which would provide better specificity and sensibility values for prediction of the risk of bleeding from esophageal varices. This new parameter was called LSPS (liver stiffness measurement – spleen diameter to platelet ratio score) and is calculated by the following formula: LSPS = liver stiffness measurement x spleen bipolar diameter / platelet count. When LSPS < 3.5 we can avoid endoscopy safely as the risk of bleeding from EV is small, whereas patients with LSPS >5.5 should be considered for appropriate prophylactic treatments. When LSPS is between 3.5 and 5.5 it is recommended to perform EGD monitoring of EV according to the present surveillance protocols.

Vizzutti [14] also showed that a value of liver stiffness ≥ 17.6 kPa correlates with severe PHT and has 66% NPV, 90% Se and 43% Sp for prediction of EV presence. Although they do provide some information, these values are far from being satisfactory. Moreover, Vizzutti could not duplicate in his study the results of Kazemi [42] which demonstrated that a liver stiffness < 19kPa can be correlated with the absence of EV grade ≥ II with 84% Se, 47% PPV and 93% NPV. We have to underline that the differences in the two studies reside in the selection criteria used to include patients in the study groups; while Vizzutti has remained with strict exclusion criteria, Kazemi included also patients treated with beta-blocking agents, a measure which actually dictated the exclusion of his paper from our review. This lack of homogeneity of the two papers could explain the difference in their final results.

The highly accurate studies of Kim and Vizzutti have shown that liver stiffness is a valuable parameter in the prediction of EV, especially when it is included in complex diagnostic algorithms.

At the end of our systematic evaluation of papers that investigated the role of ultrasound-based non-invasive parameters for diagnosis of esophageal varices we can conclude that in certain situations they offer information which, in selective settings, can be used for accurate prediction of presence and risk of bleeding from EV.

Presence of EV seems to be predicted by portal vein size > 13mm [8,22] and RARI ≥ 0.7 [29] while the risk of bleeding from EV is suggested by the following parameters: bipolar diameter of the spleen > 15cm [22], CI of portal vein > 0.154cm×sec [8,25], PHT index > 2.08 [24], liver stiffness > 43.97kPa [43] and appearance of new porto-systemic collaterals on dynamic ultrasound monitoring [31].

A value of liver stiffness ≤ 16.56kPa [43] or an CI of portal vein ≥ 0.12cm×sec [29] predict absence of EV and might be used as an indication for omission of EGD for surveillance of EV.

The pattern of liver vein blood flow [30] and values of HARI or SAPI [24,27] do not provide reliable information about the presence of EV or risk of bleeding from EV and, for the moment, cannot be used in this respect.

A particular conclusion of our study is that a combination of non-invasive parameters seems to be more accurate in the prediction of EV than the individual evaluation of each test. One direction for future development could be the development of integrated algorithms which use two or more non-invasive US and Doppler parameters alone or in combination with other markers of portal and splanhnic circulation for better prediction of the presence and evolution of esophageal varices.

Limitations of non-invasive parameters for prediction of esophageal varices

At the end of a systematic review on the role of ultrasound based diagnosis of EV, we notice that we are still faced with equivocal results which cannot match for the moment the accuracy of information offered by the EGD examination regarding the presence and grading of EV. There are certain parameters which have shown some promising results and, of these, measurement of
liver stiffness seems to be quite accurate in the prediction bleeding from EV. However, it is less valuable for the diagnosis of EV grade and does not match here the performance of EGD. Moreover, it is available only in highly specialized centers and requires advanced medical devices and highly trained medical staff.

A further disadvantage of the morphologic parameters used in the non-invasive evaluation of EV is that they rely mostly on the size of EV to predict the risk of bleeding. It is well known that even small EV can have a high risk of rupture if they are associated with negative prognostic features, such a cherry red spots. These aggravating features are easily identifiable by the EGD but very difficult to predict by the current non-invasive investigations [44]. One option could be to associate the endoscopic capsule to the ultrasonographic examinations but such a solution has its own disadvantages: high incidence of false negative results, overestimation or underestimation of EV grading (the esophageal lumen is not distended, it is difficult to assess how much of the lumen is occupied by the varices) and the high costs of the capsule itself [21].

A further limitation of non-invasive parameters is that they cannot be accurately calculated in all patients with liver cirrhosis. Patients with massive ascites cannot be evaluated by Doppler or with the Fibroscan, severe liver steatosis may negatively influence the accuracy of Doppler and liver stiffness evaluations while patients with BMI ≥35kg/m² are excluded by default from the measurement of liver stiffness because the thickness of their subcutaneous adipose tissue influences the validity of results.

Conclusions

The EGD remains the golden standard for the diagnosis and evaluation of the risk of bleeding from EV in patients with liver cirrhosis.

None of the non-invasive investigations used today managed to match the performance of EGD. Certain parameters (diameter of portal vein, liver stiffness, bipolar diameter of the spleen, CI of portal vein and PHT index) seem to offer valuable information regarding the presence, size and evolution of EV but the results are still equivocal. Other markers (development of new collaterals, RARI) emerge with promising results but they still need further evaluation on larger cohorts of patients.

Despite all inconveniences, there is a future for non-invasive parameters for the diagnosis and monitoring of esophageal varices. One of the possible directions of study for the future could be the development and implementation of complex predictive algorithms that include more markers, or mix these parameters with other markers of portal and splanchnic circulation.

Conflict of interest: none

References