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 informations 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: Althought 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 porto-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 recomended 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 Millennium, 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 splanchic 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 rigidity 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>Spleen bipolar diameter, 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, Splenic vein diameter</td>
</tr>
<tr>
<td>5</td>
<td>Berzigotti (2008) Italy</td>
<td>60</td>
<td>Alcohol=7, B,C virus=48, Others=3</td>
<td>Absent=32, Small=20, Large=8</td>
<td>Nodular liver surface, PV (diameter, mean velocity, CI_x), 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, CI_x</td>
</tr>
<tr>
<td>7</td>
<td>Berzigotti (2008) Italy</td>
<td>126</td>
<td>Alcohol=46, B,C virus=61, Alc+virus=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+virus=7, Others=26</td>
<td>Absent=12, Small=43, Large=46</td>
<td>PV diameter, Splenic vein diameter, Spleen bipolar diameter, Abdominal collaterals</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>Plestina (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, CI_x)</td>
</tr>
<tr>
<td>12</td>
<td>Coli (2001) Italy</td>
<td>50</td>
<td>Alcohol=18, B,C virus=17, Alc+virus=6, Others=9</td>
<td>Absent=26, Present=24</td>
<td>RARI, CI_x</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, CI_x), 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 |
|---|---|---|---|---|---|---|---|
| **Author** | Berzigotti | Tarzamni | Shepis | Cherian | Sarangapani | Sharma | Baig |
| Cut-off values proposed for the bipolar diameter of the spleen (mm) | NS/NS | NS/>150.5 | NS/NS | >150/>160 | NI/>138 | NI/NS | >112.5/NI |
| Se (%) | NS/NS | NS/79 | NS/NS | NI/NI | NI/>88.5 | NI/NS | 74.5/NI |
| Sp (%) | NS/NS | NS/NI | NS/NS | NI/NI | NI/>83 | NI/NS | 68.2/NI |
| PPV | NS/NS | NS/NI | NS/NS | NI/NI | NI/>83.3 | NI/NS | 84.9/NI |
| NPV | NS/NS | NS/NI | NS/NS | NI/NI | NI/>70.5 | NI/NS | 52.6/NI |
| 95% CI | NS/NS | NS/1.23-2.55 | NS/NS | 1.6-11.8/1.6-6 | NI/NI | NI/NS | 0.764/NI |

| Table 3. Diagnostic performance of US (diameter of the portal vein) for the diagnosis of EV by author |
|---|---|---|---|---|---|---|
| **Author** | Berzigotti | Tarzamni | Shepis | Cherian | Sarangapani | Sharma | Plestina |
| Cut-off values proposed for the diameter of the portal vein (mm) | NS/NS | NS/NS | >130/NI | >130/NS | NI/>13 | NI/NS | NI/137.5 |
| Se (%) | NS/NS | NS/NS | NI/NI | NI/NS | NI/>76.5 | NI/NS | NI/80 |
| Sp (%) | NS/NS | NS/NS | NI/NI | NI/NS | NI/>80 | NI/NS | NI/78.4 |
| PPV | NS/NS | NS/NS | NI/NI | NI/NS | NI/>78 | NI/NS | NI/NI |
| NPV | NS/NS | NS/NS | NI/NI | NI/NS | NI/>78.6 | NI/NS | NI/NI |
| 95% CI | NS/NS | NS/NS | 1.3-6.4/NI | 1.1-5.3/NS | NI/NI | NI/NS | NI/0.877 |
presence of EV [8,22]. Other studies did not identify any statistical significance for any of the parameters described above [26,27]. These differences could signify that it is actually difficult to predict the presence and grading of EV only by the interpretation of the bipolar diameter of the spleen and portal vein but they can also be the result of an interpretation bias due to the use of different methodologies in different studies and the lack of standardization in the study protocols. The most accurate evaluation is obtained when measurements are performed in an identical setting in all patients: the same plane of ultrasonographic section, the same phase of respiration, same etiology of cirrhosis, same race and phenotype for all patients. In clinical practice it is difficult to achieve such a tight selection of patients. For instance, among the articles selected for our study, only two gave specific information about the protocols used for the acquisition of morphological parameters of the portal vein; Plestina et al [25] calculated a mean of two different values for the portal vein diameter, one taken at 1 cm and the other one at 2 cm distal from portal vein bifurcation, while Berzigotti [27] used the protocol already described by Sabha C [32]. None of the studied papers described which was the plane for measurement of the bipolar axis of the spleen but in all cases it was specified that the maximum value of the parameter was recorded.

1.2. Collateral circulation

Abdominal porto-systemic collateral circulation is present in roughly one third of patients with liver cirrhosis [33]. Some of these collaterals, such as the left gastric vein and the spleno-renal shunt, have a direct correlation with the development of EV while recanalisation of the paraumbilical vein is more frequently a sign of decompensated liver disease [34]. The correlation between recanalisation of the paraumbilical vein and development of EV is controversial; some authors have shown that recanalisation of the paraumbilical vein is a sign of severe portal hypertension and therefore is associated with the development of EV while others consider that recanalisation reduces the pressure in the porto-systemic collaterals and acts as a protective role on variceal development and rupture [35-38].

In our study we identified three papers with relatively homogenous study groups which used ultrasound techniques to correlate the presence of abdominal collateral circulation with presence or absence of EV and the size of EV, respectively [26,27,31]. All studies have shown that the collateral circulation does not act as an indirect marker for the presence of EV since it can be present both in patients with EV and in those without EV [26,27,31]. 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 Pulsatility Index (SARI), Splenic Artery Resistance 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 /([HARI ×0.69]×(SARI×0.87))// 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 (CIx) of the Portal Vein first described by Moriyasu. This parameter represents the ratio between the cross-sectional area (cm²) and the blood flow velocity (cm/sec) of the portal vein CIx=(P²/4)/PV×mean, where P is the portal vein diameter and PV×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 (CIx cut-off value of 0.17±0.075 cm²×sec) and idioptic PHT respectively (CIx cut-off value of 0.18±0.107 cm²×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 cm²×sec, the CIx 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 CIx was significantly higher in the group of patients with EV than those without EV. There were also significant statistical differences of CIx values among patients with small EV compared with those with medium and large EV [8]. All this data confirms that CIx 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 CIx ≥ 0.12 cm²×sec was present in 50% of patients with VE and 30% of patients without VE and that, at this value (≥ 0.12 cm²×sec), CIx 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 ≥ 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 CIx 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 CIx 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 aquisition 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 hemodicamically 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 prequisites 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)
> 35 kg/m², ALAT 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 > 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 splanchnic 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 of 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 $\geq 35$kg/m$^2$ 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


