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**PhD THESIS**  
**NON INVASIVE EVALUATION OF PORTAL  
HYPERTENSION**

**SUMMARY**

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## INTRODUCTION

Portal hypertension (PH) is one of the most feared complications of liver cirrhosis being diagnosed when hepatic venous pressure gradient (HVPG) has a value of  $>5$  mmHg. Clinically significant portal hypertension (CSPH) is established when HVPG is  $> 10$  mmHg.

Development of CSPH is a major step in the natural history of patients with compensated advanced chronic liver disease (ACLD) and it is associated with PH-related complications, such as ascites or esophageal varices (EV). The measurement of HVPG is the gold standard method to ascertain the presence and significance of PH, but because it is invasive and not widely available, it is difficult to perform in daily clinical practice.

In recent years, the arsenal of non-invasive methods available for the evaluation of PH has increased. Ultrasound based elastography techniques were used over the past years to assess liver fibrosis severity and steps have been made to assess their value to predict CSPH.

Liver stiffness (LS) is a well-known non-invasive marker that has been studied as a predictor for PH, studies being performed mainly with TE (FibroScan; EchoSens, Paris, France) but also with other techniques, suggesting a very good correlation between LS measurements (LSM) and the presence of PH. A more recently introduced non-invasive marker is spleen stiffness (SS). In the last years, various studies focused on the evaluation of spleen stiffness measurement (SSM) and its correlation with PH and showed a clear and reproducible correlation between SSM and the presence and severity of PH.

The present research aims to establish the performance of spleen and liver stiffness together with ultrasonography and biological markers, as non-invasive markers for predicting the presence as well as the severity of EV in patients with compensated liver cirrhosis.

**Key words:** portal hypertension, esophageal varices, liver stiffness, spleen stiffness

## GENERAL PART

The diagnosis of portal hypertension can be made directly by invasive methods, or indirectly by using non-invasive markers.

HVPG represents the current gold standard for the evaluation of hepatic venous pressure gradient and it is an invasive technique that requires venous catheterization.

Upper digestive endoscopy (EGD) is the gold standard method for the diagnosis of EV, GV and portal hypertensive gastropathy in patients with liver cirrhosis. Both techniques are invasive, unpleasant and quite difficult for the patient to accept.

Therefore, non-invasive, easily reproducible and cost-efficient techniques for substituting invasive methods, in some specific situations, are certainly welcome. The most used markers for this purpose are serum markers, ultrasound parameters, hepatic and splenic elastography or combined models including these markers.

Elastography-based imaging techniques have received considerable attention in recent years for the non-invasive assessment of tissue mechanical properties. These techniques are assessing changes in soft tissue elasticity and are giving qualitative and quantitative information about the elasticity of the interrogated tissue. Ultrasound elastography has shown promising results, being well-validated methods for the non-invasive assessment of liver fibrosis. Subsequently, numerous studies have evaluated the performance of these methods for the non-invasive evaluation of PH by evaluating hepatic or spleen stiffness, and the results are promising.

**Transient elastography (TE)** is the first ultrasound-based elastography technique that was introduced for the evaluation of liver fibrosis, having the largest body of evidence by far. LS evaluated with TE is a well-known non-invasive marker that has been studied as a predictor for PH. Studies found correlations between LS and the presence of EV and even between LS values and variceal size. More than that, Baveno VI consensus suggested that the

combination of LSM  $<20$  kPa by TE and platelet count  $>150\ 000/\text{mm}^3$  could help to avoid endoscopy in patients with advanced liver disease, as the possibility of having HRV is very low ( $<5\%$ ) when these criteria are fulfilled.

In the last years, various studies focused on evaluating SSM and its correlation with PH. Studies demonstrated a definite and reproducible correlation between SSM by TE and the presence of PH.

**Point shear wave elastography (pSWE)** is an ARFI-based technique that allows the direct visualization of the parenchyma. Two types of pSWE have been more thoroughly evaluated, the ones developed by Siemens (Virtual Touch Quantification) and by Philips (ElastPQ). Currently, other manufacturers also offer pSWE on their systems: Esaote, Hitachi, and Samsung.

For the evaluation of PH, the most studied pSWE technique is VTQ. Although the results are inconsistent among studies, the majority concluded that LS using pSWE.VTQ is a useful marker for predicting PH. Not as much data are available regarding the evaluation of SS as a predictor of PH using ElastPQ. A recent study showed that SS significantly correlated with portal pressure ( $R = 0.489$ ,  $p < 0.001$ ).

### **2D shear wave elastography (2D-SWE)**

The majority of the published studies that evaluated the performance of LS for predicting PH, used 2D-SWE.SSI, showing that LS has a good performance for predicting PH. Fewer studies are available regarding the performance of 2D-SWE.GE. Stefanescu et al. showed that LS by 2D-SWE.GE was highly correlated with HVP (r = 0.704;  $p < 0.0001$ ). There are a limited number of studies that have evaluated SS assessed by means of 2D-SWE as a predictor of PH. In a recent study, SSM  $< 35.8$  kPa assessed with 2D-SWE.SSI was found to exclude the existence of HRV with an NPV of 91.3% (AUC-0.85). In a larger study, SS evaluated with 2D-SWE.SSI was able to predict the presence of any grade EV with an AUC of 0.8 and HRV with an AUC of 0.78, respectively.

## **SPECIAL PART**

The main objectives of the thesis were:

1. To establish the feasibility and performance of liver stiffness evaluated by means of a pSWE elastography technique (ElastPQ) to predict the presence and severity of esophageal varices in patients with compensated liver cirrhosis.
2. To establish the feasibility and performance of liver stiffness assessed by means of 2D-SWE (GE) to predict the presence and severity of esophageal varices in patients with compensated liver cirrhosis.
3. To establish the feasibility and performance of spleen stiffness evaluated by means of 2D-SWE (GE) to predict the presence and severity of esophageal varices in patients with compensated liver cirrhosis.
4. To establish the feasibility and performance of spleen stiffness evaluated by means of a pSWE technique (VTQ) to predict the presence and severity of esophageal varices in patients with compensated liver cirrhosis.
5. To compare the performances of 2D-SWE (GE) and pSWE (VTQ) for the evaluation of spleen stiffness as a non-invasive marker for predicting the presence and severity of esophageal varices.
6. To compare the performance of spleen stiffness versus liver stiffness for predicting portal hypertension.
7. To elaborate a multi-parametric score consisting of elastographic, ultrasonographic and biological markers for predicting the presence and the severity of esophageal varices

## **MATERIAL AND METHOD**

In the present research, we included a number of 555 subjects, aged between 31-81 years (median 59) of which 237 (42.7%) men and 318 (57.3%) women. The study was conducted in the Department of Gastroenterology and Hepatology, County Emergency Clinical Hospital „Pius Brînzeu”, Timișoara, Romania, between January 2018 and November 2019, and included only subjects that were previously diagnosed with compensated liver cirrhosis based on clinical, biological, ultrasonography and elastography criteria (liver TE > 12.5 kPa).

Initially, a prospective study that included 149 patients in whom we evaluated the performance of LS as a non-invasive marker for predicting the presence and severity of esophageal varices was performed.

In the second part of the research, we conducted a prospective study, that included a number of 406 subjects in whom we evaluated liver and spleen stiffness with two different elastography techniques, as non-invasive markers for predicting PH and a prediction score using these elastography markers along with biological and ultrasonography markers was formulated.

All subjects included underwent abdominal US, elastography evaluation and upper endoscopy. The presence and the grade of EV, as well as the presence of gastric varices (GV) or portal hypertensive gastropathy, were recorded. HRV were defined as grade I with cherry red spots, grade II and III esophageal varices and gastric varices. The elastography measurements were performed by experienced operators, blinded to the upper digestive endoscopy results.

Inclusion criteria for all subjects were: the ability to provide informed consent, age  $\geq 18$  years old, previous diagnosis of compensated liver cirrhosis based on clinical, biological and elastography (LS by TE >12.5 kPa) criteria.

Exclusion criteria were: LS by TE  $\leq 12.5$  kPa, patients with ascites, aminotransferases higher than 3 times the upper level of normal, patients with

signs of biliary obstruction, liver congestion secondary to heart failure, patients with focal liver lesions and patients with non-cirrhotic PH.

Informed consent for both elastography measurements and upper endoscopy was obtained from all the participants. The study was approved by the institutional review board and the Ethics Committee and was performed in accordance with the World Medical Association Declaration of Helsinki, revised in 2000, Edinburgh.

LSM and SSM were performed using two different elastography techniques: pSWE (VTQ and ElastPQ) and 2D-SWE (GE), following the recommendations of the latest guidelines.

## RESULTS

The performance of LS as a non-invasive marker for predicting the presence and severity of EV was evaluated using two different elastography techniques. First, we performed a study on 61 subjects in whom LS was evaluated using ElastPQ and the number of platelets was also recorded. The best LS and thrombocytes cut-off values for ruling out HRV in this study group were  $LS \leq 11.96$  kPa (Se-96.3%, Sp-39.3 %, PPV-56.6%, NPV-92.9%) and thrombocytes  $\geq 126\ 000$  (Se-81.4%, Sp-57.5 %, PPV-61.1%, NPV-79.2%).

Subsequently, in a study that included 88 subjects with advanced chronic liver disease (LSM by means of 2D-SWE.GE  $\geq 8.2$  kPa) we evaluated the utility of LS values assessed by 2D-SWE.GE and platelet count as non-invasive markers for ruling out the presence of EV. The best LS cut-off value performed with 2D-SWE.GE and thrombocytes cut-off value for ruling out the presence of any grade EV were  $LS \leq 12.5$  kPa (Se-84%, Sp-61.7 %, PPV-61.8%, NPV-4%) and thrombocytes  $\geq 125\ 000$  ( Se-93.3%, Sp-77.2 %, PPV-48.8%, NPV-94.4%). Using platelet count and 2D-SWE-GE cut-off values, 78.5% (22/28) of patients from the control group were correctly classified as having or not EV (AUROC 0.73,  $p < 0.01$ ).

The performance of SS for predicting the presence and severity of EV was evaluated in a prospective study that included 107 subjects in whom SS was assessed by means of two different elastography techniques: pSWE (VTQ) and 2D-SWE (GE). The optimal SS cut-off values for predicting HRV were :  $SS \leq 13.2$  kPa (AUC-0.84, Se-87.5%, Sp-69 %, PPV-66%, NPV-88.9%) for 2D-SWE.GE and  $SS \leq 2.91$  m/s (AUC-0.9, Se-85%, Sp-75.8 %, PPV-70.8%, NPV-88%) for pSWE.VTQ, respectively. Based on AUROC comparison (AUC-0.84 vs. AUC-0.90), no difference between the performance of the two techniques for predicting HRV ( $p=0.16$ ) was found.

Subsequently, a study that compared the performance of SS vs. LS as non-invasive markers for predicting the presence of EV was performed in 90 subjects with compensated liver cirrhosis who underwent both SSM and LSM by means of 2D-SWE.GE. Based on AUROC comparison, SS performed significantly better than LS to predict the presence of EV ( $p=0.0253$ ).

Finally, a study that evaluated the performance of SS and LS along with other non-invasive markers for HRV prediction was performed on 132 subjects with compensated liver cirrhosis, in whom we evaluated SS and LS by means of 2D-SWE.GE. Subsequently, we divided the subjects into two distinct groups. Data from the first group (101 patients) were used to assess the predictive value of SS, LS and SSZ for the presence of HRV and data from the second group were used for score validation. 41/101 (40.6 %) subjects from this group had HRV.

The optimal cut-off values (highest sum of sensitivity and specificity) of SS, LS and SSZ for predicting HRV were:  $SS \geq 13.2$  kPa (AUC-0.84, Se-87.8%, Sp-68.3 %, PPV-65.5%, NPV-89.1%);  $LS \geq 12.1$  kPa (AUC-0.86, Se-85.3%, Sp-68.3 %, PPV-64.8%, NPV-87.2%) and  $SSZ \geq 12.9$  cm (AUC-0.71, Se-85.3%, Sp-48.3 %, PPV-53%, NPV-82.%)

In both univariate and multivariate regression analysis, SSM, LSM and SSZ were associated with HRV (all  $p<0.001$  for univariate analysis, respectively  $p=0.0019$ ,  $p=0.0365$  and  $p=0.0046$  in multivariate analysis).

Using these factors as predictors, by multiple regression analysis we obtained the following score for predicting HRV:  $0.053 \times SS + 0.054 \times LS + 0.059 \times SSZ - 1.84$ . The optimal cut-off value of our score for predicting HRV was  $>0.34$  (AUROC- 0.93; Se-87.8%; Sp - 80%; PPV- 75%; NPV- 92.3%,  $p < 0.001$ ).

By comparing the AUROC's, the score performed better than each independent marker for predicting HRV ( $p=0.0091$ ;  $p=0.0341$ ;  $p<0.0001$ , respectively).

Subsequently, a smaller study was performed on 77 subjects with compensated liver cirrhosis, who underwent SS and LS measurements with 2D-SWE.GE and were put together along with spleen size and thrombocytes in the framework of a score. In univariate analysis, SSM, LSM, spleen size and thrombocytes were associated with the presence of EV, all  $p < 0.0001$ . In multivariate analysis, the model including SSM, LSM, spleen size and thrombocytes had the following p-values:  $p=0.01$ ,  $p=0.01$ ,  $p=0.03$  and  $p=0.01$ . Using these factors as predictors, by multiple regression analysis, a prediction score was obtained for predicting the presence of EV:  $EV = 0.04 \times SSM + 0.06 \times LSM + 0.04 \times \text{spleen size} - 1 \times 10^{-6} \times \text{thrombocytes} - 1.17$ .

The score was calculated for all the subjects and the best cut-off value for predicting the presence of EV was  $>0.48$  (AUROC=0.9, Se=95.8%, Sp=96.3%, PPV=97.9%, NPV=92.9%).

Regarding the feasibility of the elastography methods that were used, both ElastPQ and 2D-SWE. GE are feasible elastography techniques for the evaluation of LS, with a feasibility of 98.3% for ElastPQ and between 94.4-100% for 2D-SWE.GE. The feasibility for the evaluation of SS was 94.4% for pSWE.VTQ and between 95.4- 98.7% for 2D-SWE.GE.

## DISCUSSIONS

The development of CSPH together with its complications represents an important event in the evolution of patients with ACLD that modifies both the

subsequent management and the patient's prognosis therefore assessing PH status is important and essential.

In recent years, different approaches have been used in order to identify non-invasive methods for diagnosing the degree of liver fibrosis and consequently recognizing cirrhosis, varices, or CSPH. Among the different modalities, including serum biomarkers of fibrosis and physical approaches that measure LS, TE and real-time elastography have achieved wide acceptance, have been shown to possess excellent performance, and are currently incorporated as a valuable tool in the assessment of chronic liver disease.

All the elastography methods that were used, for evaluating both LS and SS, had very good feasibility. The good feasibilities of pSWE (VTQ, ElastPQ) and 2D-SWE were confirmed by previously published studies.

LS is one of the most validated non-invasive markers for diagnosing liver fibrosis and has been found to correlate with the presence and the severity of EV by many authors.

Regarding the performance of LS by ElastPQ for predicting HRV, for a cut-off value of 11.96 kPa we obtained an AUROC of 0.67, but very good values for Se and NPV, which makes LS a useful marker for ruling out the presence of HRV. For a cut-off value of platelets of 126,000, we obtained an AUROC of 0.7 for HRV prediction but as in the case of LS, the sensitivity and NPV values were good thus if the platelets are > 126 000 we can rule out the presence of HRV with a NPV of almost 80%. Garcovich et al., in a recently published study, showed quite similar results regarding the performance of LS by ElastPQ and thrombocytes values for predicting varices needing treatment (VNT). Regarding the performance of LS by 2D-SWE.GE for predicting EV, for a cut-off value of 12.5 kPa we obtained and AUROC of 0.69 with good Se and NPV values, which makes LS a useful marker for ruling out the presence of EV. Better results were found in another study of the present research that also evaluated the performance of LS by 2D-SWE.GE on a larger number of

subjects. For a cut-off value of 12.1 kPa, the AUC for ruling out the presence of HRV was 0.86, results that are similar to those found in other published studies. There is a limited number of studies regarding the performance of LS by 2D-SWE.GE for predicting the presence of EV and besides, the results are quite inconsistent among these studies, but they are encouraging, so further studies are needed.

So far, liver elastography has proved to be a very good prognostic marker for the presence of CSPH and HRV, but considering the fact that there are many situations in clinical practice when LS is impossible to measure, SS represents a reliable alternative. We performed a study and evaluated the diagnostic accuracy of SS by two different elastography techniques: pSWE (VTQ) and 2D-SWE (GE) for predicting the presence of HRV and good diagnostic accuracy was found (AUROC 0.84 and 0.90, respectively;  $p=0.1606$ ), with no differences between the techniques. The good performance of SS assessed using pSWE techniques (VTQ) was also confirmed by studies. Due to the fact that there are no studies that used 2D-SWE.GE technique for the evaluation of SS, we compared the results of the present study with those of studies that evaluated SS using a 2D-SWE technique implemented on different ultrasound systems, and the results are quite similar to those published in the literature.

When it comes to evaluating PH using non-invasive makers, probably one of the most important controversies is the superiority of SS over LS or vice versa and the results are quite inconsistent among studies, although the majority of them concluded that SS is superior to LS. We also performed a study regarding this aspect, as a part of this research, and concluded that SS by 2D-SWE.GE is superior to LS for predicting the presence of any grade EV, but in another study we found no differences between the performances of LS and SS also by 2D-SWE.GE for predicting the presence of HRV.

The fact that both SS and LS are useful markers for predicting EV and even their severity has already been well validated by studies, but another

disputed aspect regarding the non-invasive evaluation of PH is whether the use of several markers together in the framework of a score is superior to their individual use.

As a part of this research a study that evaluated the accuracy of three non-invasive markers for predicting HRV, alone or combined, was performed and concluded that a multi-parametric score that combined LS, SS along with spleen size, performed better for predicting HRV as compared to each parameter individually ( $p=0.0091$ ;  $p=0.0341$ ;  $p<0.001$ , respectively). This aspect has also been retrieved in other studies.

When it comes to using several parameters for HRV prediction, the platelet count is a very used parameter along with other well-known parameters. In the present study, platelet count was not an independent predictor of HRV but was an independent predictor of any grade EV. Given the fact that this score was intended to predict HRV, the thrombocyte values were excluded. Instead, a smaller study was performed on 77 subjects and showed that a multi-parametric score that combines LS and SS by 2D-SWE.GE along with spleen size and thrombocyte values had a great performance for predicting any grade EV. Although many aspects remain in a gray area, most of the studies reinforce the idea that the use of a combination of multiple non-invasive markers leads to increased diagnostic performance.

The arsenal available for the assessment of PH has increased in recent years with the advent of several non-invasive markers, besides the classical and invasive HVPG and endoscopy. Because these techniques are not widely available and invasive, new, non-invasive and easily reproducible techniques are needed, especially in a patient with a newly diagnosed ACLD, when screening with non-invasive markers is preferable in order to define the best timing to perform endoscopy or other invasive techniques.

Regarding the markers the present research proposed, we strongly believe that they have the potential to satisfy this request, either alone or in combination.

## CONCLUSIONS

1. Both ElastPQ and 2D-SWE (GE) are feasible elastography techniques for the evaluation of liver stiffness and LS evaluated with these techniques showed good performance for predicting the presence and severity of EV.

2. Both pSWE (VTQ) and 2D-SWE (GE) are feasible elastography techniques for the evaluation of spleen stiffness. The main causes that led to SSM failure regardless of the elastography technique that was used were small spleen size and high BMI.

3. Spleen stiffness assessed by means of 2D-SWE (GE) and pSWE (VTQ) showed good performance for predicting the presence and severity of EV. No difference between the performances of SS assessed with 2D-SWE (GE) or pSWE (VTQ) for predicting HRV was found.

4. Spleen stiffness had superior accuracy for predicting any grade EV compared to LS, but no significant difference was found for the prediction of HRV.

5. The optimal cut-off values (highest sum of sensitivity and specificity) of SS and LS assessed with 2D-SWE (GE) for predicting HRV are  $SS \geq 13.2$  kPa (AUC- 0.84) and  $LS \geq 12.1$  kPa (AUC- 0.86). The optimal cut-off value (highest sum of sensitivity and specificity) of SS assessed with pSWE (VTQ) for predicting HRV is  $SS \geq 2.91$  m/s (AUC- 0.9).

6. A multi-parametric prediction score that included SS and LS assessed with 2D-SWE (GE) and spleen size performed better than each independent marker for predicting HRV.