Digestive Diseases and Sciences (2019) 64:2381–2383
https://doi.org/10.1007/s10620-019-05731-2

EDITORIAL

Sound Conclusions: How Splenic Elastography May Decrease the Need for Endoscopic Variceal Surveillance

Federico Ravaioli[1] · **Antonio Colecchia**[2]

Published online: 17 July 2019

Portal hypertension (PH), a common complication of advanced hepatic cirrhosis, is often accompanied by esophageal varices that can be the source of torrential hemorrhage. In recent years, regular endoscopic variceal surveillance (EVS) combined with prophylactic banding or clipping has decreased the incidence of variceal hemorrhage. One issue is that EVS requires periodic upper endoscopy (EGD) that carries inherent risk and inconvenience to the patient and costs to the healthcare system. To address the issue of patient stratification for EVS, the consensus workshop on definitions, methodology, and therapeutic strategies on PH held in Baveno, Italy, considered this issue. In the latest (sixth) iteration, De Franchis et al. [1] have for the first time highlighted noninvasive tests useful for identifying patients requiring EVS to identify esophageal varices needing treatment (VNT). These experts concluded that patients with liver stiffness measurement (LSM), assessed by transient elastography (TE, FibroScan® Echosens, Paris, France) < 20 kPa and a platelet count > 150×10^9/L have a low (< 5%) prevalence of VNT, thus effectively risk-stratifying this population, consequently avoiding or postponing the need for EVS. One problem, however, is that LSM values vary by operator, technique, and the type of machine used, confounding the calculation.

Since publication, most of the research in this field has been focused on validating and implementing these criteria in order to increase the number of patients who can benefit from a noninvasive approach and who can avoid or postpone EGD [2]. For the first time last year, the authors combined the measurement of spleen stiffness (SSM), as assessed by TE, with the Baveno VI criteria in a diagnostic algorithm aiming to improve its performance. The algorithm was tested in a cohort of > 500 patients with advanced chronic liver disease (ACLD), demonstrating that is possible to correctly identify VNT while decreasing the number of EGDs needed to identify VNT [3].

In this issue of *Digestive Diseases and Sciences,* Karagiannakis and colleagues [4] report for the first time how SSM measured using ultrasonic two-dimensional shear wave elastography (2D-SWE) improves the ability of the Baveno VI criteria to risk-stratify cirrhotic patients for the presence of VNT, safely reducing the number of unnecessary EGDs. The authors not only confirmed our findings [3] but also showed that the measurement of SSM alone can reduce, in a cohort of cirrhotic patients, the number of unnecessary EGDs performed. Identifying new specific SSM cutoffs for 2D-SWE, they were able to spare more than 40% of EGDs in a cirrhotic cohort of 71 patients, achieving a missed VNT rate < 5%, an arbitrary threshold included in the Baveno recommendations [1]. It is well known and well validated that SSM is superior to LSM for identifying patients not only with clinically significant PH (CSPH) but also in the identification of its main complications such as VNT [5, 6].

The main strengths of this study are that for the first time with a 2D-SWE technique, SSM can correctly identify VNTs and consequently increase the number of patients who can safely avoid endoscopic variceal surveillance. Lacking an external validation and a well-calibrated multivariate model, the possibility of using the proposed cutoffs in the near future is excluded.

This paper [4], once again highlights that the assessment of spleen parameters, such as SSM, more reliably reflects portal pressure due to the structural changes that occur in the spleen due to congestion and hyperplasia. The condition of splenic hyperplasia, with increased blood flow, participates in the hyperdynamic circulatory PH syndrome that characterizes the extra-hepatic phase of PH development leading to the development of VNT [7]. Nevertheless, up to now, SSM assessment has been mostly ignored, considered as

✉ Antonio Colecchia
antonio.colecchia@aovr.veneto.it

[1] Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

[2] Gastroenterology and Hepatology Unit, Borgo-Trento University Hospital, Verona, Italy

a "stepchild" of LSM, not yet entering into daily clinical practice of general hepatologists [6]. One of the most frequent criticisms of SSM that could have led to this state is its feasibility, since, as noted in the present publication [4], that the unsuccessful examination rate remains around 10% even if 2D-SWE machines are used. These data are consistent with other recent publications that have used the same elastography technique, although with slightly superior results than SSM according to the success rates of TE [6]. Nonetheless, in cases in which for this reason the number of patients excluded could affect the results and consequently the conclusions drawn, an intention-to-diagnose approach should be considered [3].

Although these are important results, we have a few comments on the design and methods used, which we hope will improve the generalizability of these excellent results to other cohorts and settings. The first point is with regard to the patient selection. Indeed, the authors included only cirrhotic patients, based on the evidence of advanced fibrosis by histological or by clinical/laboratory assessment, without indicating objective criteria. As recommended by the Baveno workshop [1], the appropriate population for this kind of study would be patients with compensated ACLD (cACLD) with LSM > 10 kPa. This selection bias could explain the low number of patients that fulfilled the Baveno VI criteria and the absence of significant differences in LSM between patients with and without VNT.

Another more important point concerns the methods used to identify the SSM cutoffs. The authors did not state in their publication how they derived the new cutoffs (33.7 and 35.8 kPa) for SSM by 2D-SWE, respectively. Classically, in order to identify new cutoffs, they should carefully apply rules, based primarily on a well-calibrated and sensibly validated multivariate predictive model that enable the identification of variables associated with the condition under study [3, 8]. Subsequently, the clinically significant variables emerged should be used to identify new cutoffs, maximizing for at least one of the operating parameters: sensitivity (> 95%), negative predictive value (NPV > 95%), or negative likelihood ratio (< 0.05) [1]. Once the new cutoff has been identified and validated internally, external validation in an independent cohort is mandatory in order to strengthen the generalizability of these results to clinical practice. A suitable methodological approach should be performed when analyzing data relating to the proposal of new specific cutoffs based on the specific ultrasound elastography instrumentation used; only then will it be possible to improve the knowledge on the application of these noninvasive methods in clinical practice and to minimize the "background noise" produced by poorly conducted research. This aspect has recently been evaluated by studies that have demonstrated how LSM values and cutoffs widely validated with TE cannot be translated to other diagnostic instruments [9]. In the future, the issue of machine-dependent thresholds should also be addressed for SSM assessment with differing elastography methods.

The reader should also bear in mind that in the most recent published articles, the definitions (and rate) of missed VNTs proposed (and shown) differed according to the denominator chosen [8], leading to false equivalence among articles. For this reason, when choosing the definition of the rate of VNTs missed, authors of future studies should consider and show the most restrictive (and least optimistic) definitions; these definitions should consider as the numerator the number of VNTs missed and as the denominator the total number of patients with VNT or the total number of endoscopies spared [8].

Despite the limitations mentioned above, the paper of the Karagiannakis' s group [4] has important clinical implications since SSM alone is able to reduce the need for endoscopic surveillance comparable with the recently proposed expanded Baveno VI criteria [2]. Recently, it has been found that these expanded criteria could be influenced by an unsatisfactory rate of missed VNTs (> 5%), considered unsafe criteria compared to the Baveno VI or SSM approach [10, 11].

In conclusion, we hope that future larger studies evaluating SSM also with 2D-SWE can confirm, as just published by different independent groups worldwide, the efficacy and accuracy of SSM as a noninvasive assessment of PH and for patient stratification for VNT screening. This could lead this "Cinderella" technique to finally find its "glass slippers" in that it would become routine for the identification of CSPH and its complications and, therefore, rightly be included in future guidelines.

Acknowledgments The authors would like to thank Dr. Katherine Johnson for constructive proofreading of the manuscript.

Author's contribution All the authors have approved the final version of the article, including the authorship list. All the authors contributed to the writing of this paper.

Compliance with Ethical Standards

Conflict of interest AC has served as a speaker for Jazz Pharmaceuticals, and as a consultant and an advisory board member for Alfasigma and Jazz Pharmaceuticals.

References

1. de Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI consensus workshop—stratifying risk and individualizing care for portal hypertension. *J Hepatol*. 2015;63:743–752. https://doi.org/10.1016/j.jhep.2015.05.022.
2. Augustin S, Pons M, Maurice JB, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated

advanced chronic liver disease. *Hepatology*. 2017;66:1980–1988. https://doi.org/10.1002/hep.29363.
3. Colecchia A, Ravaioli F, Marasco G, et al. A combined model based on spleen stiffness measurement and Baveno VI criteria to rule out high-risk varices in advanced chronic liver disease. *J Hepatol*. 2018;69:308–317. https://doi.org/10.1016/j.jhep.2018.04.023.
4. Karagiannakis DS, Theodoros V, Evgenia K, Elissavet C, Papatheodoridis G V, Vlachogiannakos J (2019) The role of spleen stiffness measurement by 2D-shear wave elastography in ruling out the presence of high risk varices in cirrhotic patients. *Dig. Dis. Sci.* (Epub ahead of print). https://doi.org/10.1007/s10620-019-05616-4.
5. Ravaioli F, Montagnani M, Lisotti A, Festi D, Mazzella G, Azzaroli F. Noninvasive Assessment of portal hypertension in advanced chronic liver disease: an update. *Gastroenterol Res Pract*. 2018;2018:1–11. https://doi.org/10.1155/2018/4202091.
6. Berzigotti A. Non-invasive evaluation of portal hypertension using ultrasound elastography. *J Hepatol*. 2017;67:399–411. https://doi.org/10.1016/j.jhep.2017.02.003.
7. Colecchia A, Ravaioli F, Marasco G, Festi D. Spleen stiffness by ultrasound elastography. In: Berzigotti A, Bosch J, eds. *Diagnostic methods for cirrhosis and portal hypertension*. Cham: Springer; 2018:113–137. https://doi.org/10.1007/978-3-319-72628-1.
8. Calès P, Buisson F, Ravaioli F, et al. How to clarify the Baveno VI criteria for ruling out varices needing treatment by noninvasive tests. *Liver Int*. 2018. https://doi.org/10.1111/liv.13945.
9. Piscaglia F, Salvatore V, Mulazzani L, et al. Differences in liver stiffness values obtained with new ultrasound elastography machines and Fibroscan: A comparative study. *Dig Liver Dis*. 2017. https://doi.org/10.1016/j.dld.2017.03.001.
10. Dajti E, Ravaioli F, Colecchia A, Marasco G, Calès P, Festi D. Are the expanded Baveno VI Criteria really safe to screen compensated cirrhotic patients for high-risk varices? *Dig Liver Dis*. 2019;51:456–457. https://doi.org/10.1016/j.dld.2018.12.013.
11. Stafylidou M, Paschos P, Katsoula A, et al. Performance of Baveno VI and expanded Baveno VI criteria for excluding high-risk varices in patients with chronic liver diseases: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2019. https://doi.org/10.1016/j.cgh.2019.04.062.