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Future directions of noninvasive prediction of esophageal variceal bleeding: No worry about the present computed tomography inefficiency

Zhang YH *et al.* Future directions of predicting EVB noninvasively

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Abstract

In this editorial, we comment on the minireview by Martino A, published in the recent issue of *World Journal of Gastrointestinal Endoscopy* 2023; 15 (12): 681-689. We focused mainly on the possibility of replacing the hepatic venous pressure gradient (HVPG) and endoscopy with noninvasive methods for predicting esophageal variceal bleeding. The risk factors for bleeding were the size of the varices, the red sign and the Child-Pugh score. The intrinsic core factor that drove these changes was the HVPG. Therefore, the present studies investigating noninvasive methods, including computed tomography, magnetic resonance imaging, elastography, and laboratory tests, are working on correlating imaging or serum marker data with intravenous pressure and clinical outcomes, such as bleeding. A single parameter is usually not enough to construct an efficient model. Therefore, multiple factors were used in most of the studies to construct predictive models. Encouraging results have been obtained, in which bleeding prediction was partly reached. However, these methods are not satisfactory enough to replace invasive methods, due to the many drawbacks of different studies. There is still plenty of room for future improvement. Prediction of the precise timing of bleeding using various models, and extracting the texture of variceal walls using high-definition

imaging modalities to predict the red sign are interesting directions to lay investment on.

Key Words: Esophageal variceal bleeding; Prediction; noninvasive; Computed tomography; Hepatic venous pressure gradient; Endoscopy

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Core Tip: Current imaging techniques, especially computed tomography, are helpful for describing some of the characteristics that may explain the severity of portal hypertension. However, studies on radiomics have not achieved good results in accurately predicting variceal bleeding. In future studies, more delicate features of the images (especially the texture of variceal walls) could be focused on to reveal subtle signs of correlation.

1 **INTRODUCTION**

Esophageal variceal bleeding (EVB) is one of the deadliest complications of portal hypertension^[1,2], and is usually secondary to portal hypertension-triggering diseases, one of which is liver cirrhosis. Therefore, accurately recognizing and grading the severity of esophageal varices (EVs) is critical for prognostic prediction and the selection of prophylactic treatment. Generally, the scopes of dealing with EVs include: (1) identifying the existence of EVs; (2) correctly grading the severity of EVs; (3) accurately predicting the bleeding risk within a certain period of time; and (4) administering prophylactic treatment. In this editorial, the main topic that we focus on is the former three scopes. Endoscopic examination usually provides direct visualization of EVs, which is the gold standard, while computed tomography (CT) or magnetic resonance imaging (MRI) and corresponding angiography provide indirect

evidence. Although the severity of EVs can be evaluated by signs of enlargement and tortuosity of the varices, the hepatic venous pressure gradient (HVPG) defines the true essence of varices, namely, increased venous pressure. ⁵ When the HVPG surpasses 10 mmHg, clinically significant portal hypertension (CSPH) occurs^[3]. In regard to bleeding risk, both invasive and noninvasive techniques have been proposed in recent decades.

While the HVPG is able to provide the exact number of intravenous pressure, it is invasive, costly, and requires special facilities and expertise. Several investigations have been performed in recent decades to identify noninvasive predictive modalities. Encouraging results have been obtained across the globe, although these results are not satisfactory enough to replace HVPG and endoscopy. In the following paragraphs, we provide a mini discussion on invasive and noninvasive modalities and shed some light on future directions.

MODALITIES FOR EVALUATING EVB RISK

Currently, high-risk EVs are defined as medium-to-large EVs with red signs and late-stage liver disease^[4,5]. Bleeding relies mostly on the intravariceal pressure and wall tension^[6]. The HVPG and endoscopy ⁸ constitute the backbone for pressure evaluation. Endoscopic characteristics, such as the size of the varices and the presence of the red sign, may help predict the chance of bleeding^[7]. However, these signs occur in only approximately 30% of bleeding varices^[8]. There is a debate over the predictive value of the HVPG for bleeding because bleeding and nonbleeding varices may have similar high pressures^[9]. Additionally, large varices may not indicate proportionally high pressures. Since the indications of the Gold standards (HVPG and endoscopy) are not absolute, why do we not find some less invasive evaluation tools? Over the years, efforts to investigate noninvasive alternatives for HVPG evaluation have been made.

Radiological examinations, the most commonly applied techniques in clinical settings (*i.e.*, CT, MRI, and endoscopic ultrasound), have been investigated for their ability to stratify EVs and determine the risk of EVB. These modalities are good at describing the shape and distribution of vasculatures and organs beyond the esophageal wall. T1 MR

6
liver image and splenic artery velocity correlated well with the HVPG ($r = 0.90$)^[10]. As Martino A *et al* illustrated in the review we are now commenting upon, CT can be used to evaluate the size of entire varices, while endoscopy can be used to reveal only the portions protruding into the lumen. CT can also reveal other branches of the portal venous system and collateral veins. However, the evidence showing correlation between CT radiomics features and the HVPG or EVB risk is not solid.

Ultrasound elastography [*i.e.*, transient elastography, two dimensional elastography (2D-SWE)^[11]] and magnetic resonance elastography^[12] are reliable methods for liver stiffness measurement (LSM). LSM has a fair ability to distinguish CSPH (AUC = 0.90) and is correlated with the HVPG (coefficient = 0.783), although it cannot be used to estimate the exact HVPG^[13]. However, the predictive value of LSM for the size of varices is relatively low.

Moreover, laboratory test results are also candidates for prediction. A decade ago, researchers tried to exploit metabolic data to predict HVPG and found that the homeostasis model assessment index was associated with high risk of EVB^[14]. Ibrahim *et al*^[15] reported that the serum vWF antigen level and vWF antigen/platelet ratio (VITRO) could help stratify the risk of bleeding, with AUCs of 0.982 and 0.843, respectively, although this study had a small sample size. Kothari *et al*^[16] argued that the platelet count-to-spleen diameter ratio and FIB-4 index might be useful for predicting EVB, with AUCs of 0.78 and 0.74, respectively.

Since a single parameter, either radiological or laboratory, is insufficient to predict EVB, combinations of different modalities were studied. Liang *et al*^[17] proposed a statistical model named SSL-RS, which consists of 7 the spleen diameter, splenic vein diameter, and lymphocyte ratio, to predict the red sign. The authors showed that the sensitivity and specificity could be greater than 70%. Another team tried to manipulate an ANN model, which included both demographic and laboratory parameters, to estimate the 1-year EVB risk^[18]. The model was able to perform the prediction with an AUC of 0.959. Recently, two other models were proposed. A nomogram combining several laboratory markers with computed tomography portal vein diameter had an

AUC of 0.893^[19], while another model combining radiomics, CT and clinical features reached a predictive AUC of 0.89^[20]. The better performance of the combination of parameters reveals at least one fact, which is, that EVB is a consequence of multiple factors.

CAN NONINVASIVE MODALITIES REPLACE HVPG AND ENDOSCOPY?

As mentioned above, endoscopic manifestations and the Child-Pugh score are risk factors indicative of possible EVB. Although the HVPG is the core factor that determines EVB risk, it is already reflected in these two indicators. An increased HVPG is a consequence of increased liver stiffness and disease progression. The stages of disease can be described using symptoms, physical signs, laboratory tests and radiography. The size of EVs can be determined by CT or MRI, although the sensitivity of identifying varices is limited. Therefore, the remaining question concerns the pressure and tension of the varices. The ultimate goal of describing different factors using multiple modalities, *e.g.* demographics, radiomics, and laboratory test results, is to reach as closely as possible to the real HVPG. Therefore, replacement is possible. CT or MRI has partly replaced endoscopy for assessing the size of varices. However, the efficacy of the present models is not enough to have a stable and reliable correlation with the HVPG, and the present radiological techniques cannot describe the delicate superficial characteristics. However, we do not need to worry too much, plenty of improvement will occur.

FUTURE DIRECTIONS FOR IMPROVING NONINVASIVE PREDICTIVE MODALITIES

Much has been done to improve the predictive ability of noninvasive modalities. Accurate measurement and stratification are helpful for precision medicine^[21]. The goal must be to represent features equivalent to the HVPG and endoscopy using noninvasive methods. There are many directions to be taken in future researches.

One interesting question is how precise could one modality be in predicting when EVB may occur, instead of just determining the bleeding risk. The present risk stratification system could only identify the chances of EVB within one year for the population. This may be helpful for clinical decisions with regard to administering prophylactic treatments. However, for individuals, this approach is insufficient. Patients would like to know precisely when (although not possible scientifically) and under what conditions may they experience the first EVB. Instead of the already known risk factors discussed above, are medication, food intake, sports and other activities candidate factors that may ultimately determine the final bleeding event? Future models may take these factors into consideration.

Another question, from the perspective of endoscopy, is how to detect the red sign noninvasively. Put differently, how can the precise characteristics of the variceal walls be better delineated using high-definition imaging? One of the foci may be on superficial varices protruding into the esophageal lumen, which are responsible for bleeding. Researchers may also study the radiological features of variceal surfaces, *e.g.* the change in the variceal wall thickness and variceal wall textures, which may indicate points of weakness. In addition, the distribution pattern and 3D structural shapes of varices may also be taken into consideration. However, these methods may require imaging techniques with higher resolution. Deep learning is a promising method for integrating all these data, and might bring us some surprise one day.

Of course, appropriate study design may provide better and convincing evidence. It will be better should the study be well designed in a cohort way, with a statistically significant sample size to provide a more conclusive result.

CONCLUSION

The present imaging techniques (including CT) can provide a primary prediction for EVB. However, these methods are far from useful in actual clinical application. Future studies are needed to explore features that are equivalent to the real HVPG and

endoscopic presentations. Combinations of different modalities to accomplish this goal are still encouraged.

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