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The role of computed tomography for the prediction of esophageal variceal bleeding: Current status and future perspectives

Martino A *et al*. The role of computed tomography for the prediction of esophageal variceal bleeding.

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Abstract

Esophageal variceal bleeding (EVB) is a common complication related to portal hypertension associated with significant morbidity and mortality. Hepatic venous pressure gradient and esophagogastroduodenoscopy are currently recognized as the "gold standard" and the diagnostic reference standard for the prediction of EVB, respectively. In the last decade, computed tomography (CT) has been proposed as a promising modality for the non-invasive prediction of EVB. However, to date, evidence concerning the role of CT in this setting is still lacking.

The aim of our study was to comprehensively review the current evidence concerning the role of CT in predicting the risk of EVB.

Key Words: Esophageal variceal bleeding; Varicel upper gastrointestinal bleeding; Portal hypertension; Computed tomography; Computed tomography angiography.

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Core Tip: Esophagogastroduodenoscopy (EGD) is currently considered the diagnostic reference standard for the prediction of esophageal variceal bleeding (EVB) among cirrhotic patients. Recently, ==computed tomography (CT)== has emerged as a promising tool for the non-invasive prediction of EVB. Nevertheless, to date, evidence concerning the role of CT in this setting is still lacking. Thus, our study aimed to review the current evidence regarding the role of CT in the prediction of EVB.

INTRODUCTION

Variceal upper gastrointestinal bleeding (VUGIB) is one of the most severe and common complication related to portal hypertension (PH) occurring in patients affected by liver cirrhosis. The annual incidence of esophageal varices (EV) among cirrhotic patients is 7-8%, with a five-year cumulative incidence rate reaching approximately 20%. Furthermore, once EV develop, their risk of first bleeding is 5%-15% per year, being related to the severity of both PH and liver disease, and to the size and endoscopic appearance of EV[1-3].

Despite marked advances in its management during the last three decades, VUGIB is still a potentially life-threating event with a high morbidity and a 6-week mortality as high as 10-20%[4, 5]. Moreover, esophageal variceal bleeding (EVB) is a negative prognostic factor. Indeed, the mortality of patients sustaining a EVB is as high as 35% at 3 mo and 70% at 2 years [6, 7]. Thus, it is of paramount importance to carefully identify cirrhotic patients with a high-risk of EVB requiring prompt primary prophylaxis, in order to reduce first EVB incidence and improve the overall survival[8].

Nowadays, screening for EV by means of esophagogastroduodenoscopy (EGD) is suggested in decompensated cirrhotic patients, whereas primary prophylaxis is

recommended in patients with cirrhosis and medium-large size varices and in those with small size varices as long as they are classified as Child-Pugh C or have variceal red signs[9-13]. Currently recommended strategies for the EVB primary prophylaxis include the use of traditional non-selective beta-blockers (NSBB), carvedilol or endoscopic variceal ligation (EVL)[9-13]. However, the superiority of one prophylactic alternative over the others is controversial. Indeed, while EVL might be superior to pharmacological therapy regarding the prevention of the first bleeding episode, either traditional NSBB or carvedilol seem to play a more crucial role in the mortality reduction. Furthermore, although not routinely recommended as a first-line option, combined pharmacological and endoscopic primary prophylaxis has been reported to be capable to achieve a greater reduction in the risk of the first EVB episode[14]. Esophagogastroduodenoscopy (EGD) is currently regarded as the diagnostic reference standard for detecting the presence of EV and predicting their bleeding risk[9-13]. The North Italian Endoscopy Club index and its variations, composed of scores for Child-Pugh class, EV size, and red wale markings, are validated as significant predictors of first EVB [3, 15, 16].

However, EGD is invasive and capable to identify EV within only the superficial portions of intrinsic veins, ignoring the remaining esophageal venous plexuses [17]. Furthermore, only about a third of EVB patients have risk factors predictive of hemorrhage, such as large EV size, endoscopic red color signs, and severe liver dysfunction[3]. Finally, of note, inter-observer EV size agreement has been reported to be higher by the use of CT as compared to endoscopy[18, 19].

In addition to EGD, hepatic venous pressure gradient (HVPG) is recognized as the "gold standard" for the measurement of portal pressure, the prediction of the occurrence of EVB and other PH-related complications, and for the assessment of the response to pharmacological treatment[9, 10, 20]. Clinically significant PH, which is an at-risk condition for decompensation and EV development, is defined by HVPG ≥10 mmHg, whereas a gradient >12 mmHg defines severe PH, which is associated with a higher risk of EVB and mortality[11, 21]. Indeed, an HVPG threshold value >12 mmHg

was shown to be necessary for the occurrence of EVB[22, 23]. Furthermore, a decrease of baseline HVPG to ≤12 mmHg or by ≥20% by beta-blockers has been shown to be associated with a significant reduction in the risk of EVB and mortality [24].

However, HVPG is an invasive and expensive procedure, requiring high expertise. Thus, it is not readily and widely available in clinical practice, and its cost-effectiveness has been also questioned[25]. Moreover, the clinical utility of repeated monitoring HVPG after pharmacological therapy has not been established[26].

In this scenario, a promising role of computed tomography (CT) in the non-invasive prediction of VEB has been suggested. CT is commonly performed in cirrhotic patients, as in the case of hepatocellular carcinoma (HCC) screening/follow-up or first decompensation episode investigation. To date, CT angiography has shown good accuracy in the detection and grading of EV[27]. However, only a few studies have explored the utility of information provided by CT imaging to predict VEB, and evidence is still limited. Although CT is only a diagnostic modality, thus being not capable of supplanting EGD or HVPG in providing therapeutic and physiological data, it could potentially assist liver disease scores, HVPG, and EGD in a more effective prediction of EVB.

The aim of our study was to extensively review the current evidence with regard to the role of CT in the prediction of EVB among cirrhotic patients.

LITERATURE SEARCH

We performed a comprehensive literature search of the PubMed (MEDLINE) and EMBASE electronic databases up to June 2023, in order to identify relevant studies evaluating the role of CT in the prediction of EVB among cirrhotic patients. Studies evaluating the VE presence only or comparing CT findings with endoscopic grade of EV were not included in our review. The medical search strategy used the terms "computed tomography", "CT", "computed tomography angiography", "CTA", "multidetector computed tomography", "MDCT", "variceal upper gastrointestinal bleeding", "variceal upper gastrointestinal haemorrhage", "esophageal variceal

haemorrhage" and "esophageal variceal bleeding" in various combinations, using the Boolean operators AND, OR, and NOT. Search strategy was limited to non-animal studies conducted in adult population, and to articles written in English. Meeting abstracts, case reports/series (<10 cases), review articles, position papers, editorials, commentaries, and book chapters were excluded from our study.

The reference lists of pertinent identified studies and related review articles were carefully hand-searched in order to retrieve any additional eligible studies.

ROLE OF CT IN THE PREDICTION OF EVB

EVIDENCE

A total of 9 studies were included in our final analysis[28-36]. All of them were retrospective, single-center studies[28-36]. All but two European and one American studies, were from Asian countries. Intravenous contrast-enhanced CT, with at least one portal venous phase, was performed in all of the included studies. With the exception of one study[28], no contrast medium was orally administered in any of the included studies. Multidetector CT (MDCT) technology was adopted in most of the included studies[28, 30-32, 35, 36]. Main characteristics of the included studies are summarized in Table 1, 2 and 3.

In 2014, *Somsouk* et al. first retrospectively evaluated the role of MDCT angiography in predicting the occurrence of EVB among cirrhotic patients. A large maximal EV diameter was shown to be significantly associated with EVB. Furthermore, an MDCT threshold of <3 mm and ≥5 mm appeared to discriminate between low- and high-risk individuals, respectively. Other CT findings, including the size of the paraumbilical vein (PUV), the coronary vein, and the presence of ascites reached statistical significance, but less powerfully discriminated for VEB. Conversely, neither portal vein diameter nor spleen size showed significant association with EVB. Of note, the MELD score measured at the time of the CT execution was not significantly different between the bleeding and the control groups. However, among the included patients who experienced EVL, the average time between CT and EVB was 7 mo. Moreover, another

limitation of the study is the inclusion of patients undergoing EVB pharmacological prophylaxis in both the bleeding and the control groups[28].

Later on, *Ge* and colleagues showed not only EV diameter but also diameter of inferior mesenteric vein (IMV), posterior gastric vein, and short gastric vein were significantly correlated with EVB among HBV cirrhotic patients. For IMV and short gastric vein, the smaller the diameters, the higher hemorrhage rates were, whereas for EV and posterior gastric vein, the EVB rate was proportional to the diameter. Of note, the authors did not measure the EV diameter only, but a previously reported radiological score was adopted, providing the following 3 grades: a) 1: one varix less than 5 mm in diameter detected on the inner surface of the esophagus; b) 2: several varices less than 5 mm in diameter detected on the inner surface of the esophagus; c) 3: one varix 5 mm or greater in diameter, or varices occupying more than half the circumference of the esophagus [37]. Conversely, no significant correlation was found with portal vein, superior mesenteric vein, splenic vein, PUV, coronary vein, spleno-renal shunt, short gastric vein, and azygos vein. Notably, a significant difference in term of Child-Pugh was observed between the bleeding and the control group[29].

In 2017, *Calame et al* retrospectively evaluated the association between the presence/size of PUV on CT and a first EVB in 172 cirrhotic patients. The authors showed that a small/absent PUV was significantly associated with a first EVB. Moreover, the authors observed no case of first EVB in any patients with a PUV >10 mm, assuming that a large patent PUV may act in a transjugular intrahepatic portosystemic shunt-like manner, lowering portal venous pressure. The presence of an enlarged left gastric vein (LGV), i.e. when tortuous and >3 mm, was also significantly more frequent in patients with a first EVH. Conversely, LGV diameter and presence or diameter of spleno-renal shunt were not associated with first EVB. The study findings were in contrast with those from *Samsouk*[28], who reported a significant positive association of PUV diameter with EVB, as well with those from other groups who did not report any significant association between PUV and EVB[29, 32]. To be noted, the most common etiology of cirrhosis in both the bleeding and the control groups was alcoholic, in which the PUV prevalence is

probably higher as compared with other cirrhosis etiology, likely affecting the study outcomes. Moreover, Child-Pugh score was significantly different between the two groups[30].

Later on, a well-designed retrospective study from South Korea evaluated the utility of CT-measured liver volume for the prediction of EVB during primary prophylaxis with propranolol. Of interest, liver volume index, an estimated-to-actual liver volume index corrected for patients' body build, was shown to be significantly higher in the prophylaxis failure group, indicating that corrected liver volume was significantly smaller in patients without prophylaxis failure. Conversely, hepatic and spleen volumes were not significantly different between the case and control groups. Notably, neither Child-Pugh nor model for end-stage liver disease (MELD) scores were predictive of prophylaxis failure[31].

Subsequently, a single center retrospective study from Iran investigated the role of abdominal MDCT angiography in the prediction of EVB, comprehensively evaluating the value of different collateral veins. Intriguingly, the presence of EV on MDCT together with the presence and/or the size of various collaterals, including coronary, short gastric, paraesophageal, and paraesophageal draining, showed a significant relationship with EVB. The presence of EV on MDCT was defined as enhancing dots and linear structures within esophageal wall or protruded into the esophageal lumen [38]. In addition, size of main coronary vein, gastric fundus varices and IMV, and ascites also had significant correlation with EVH. Conversely, omental, perisplenic and spleno-renal collaterals, spleen size, PUV size/presence, size of portal vein, inferior vena cava, superior mesenteric vein and left renal vein did not show any significant association with EVB. However, of note, all of the above-mentioned CT features were also associated with EV presence, thus limiting their clinical usefulness in the prediction of EVB. Furthermore, the bleeding and non-bleeding groups significantly differed with regard to MELD score and Child-Pugh class[32].

In 2020, the largest included study from China retrospectively evaluated the accuracy of the diameter of EV, the number of cross-sectional EV, and the total cross-sectional area

of EV in the prediction of first EVB among 264 cirrhotic patients. All of these 3 EV indicators were shown to be significantly associated with first EVB. Of interest, the EV total cross-sectional area showed a higher accuracy, with a sensitivity of 0.75, a specificity of 0.73, and a critical point of 1.03 cm^2. The main limitation of this study was the absence of data regarding the liver function and the cirrhosis stage of the included patients[33].

Later on, *Peisen et al* failed to identify any significant correlation between hepatic perfusion index, portal venous perfusion, and splenic blood flow, measured by means of perfusion computed tomography, and EVB. However, of note, the study was limited by a very small sample size, including only a very few cases of EVB (8/66) and Child-Pugh class C patients (6/66). Indeed, the authors concluded that their results should be limited to patients in Child-Pugh class A and B[34].

In 2021, Wan and colleagues conducted a well-designed retrospective study in order to evaluate the role of CT-derived quantitative parameters of liver lobe volume in the prediction of first VEB. Caudate volume, caudate functional volume, caudate volume/total volume, and caudate functional volume/total functional volume were all shown to be significantly associated with first EVB. However, all these features were also associated with the EV severity. Moreover, given the rigorous inclusion criteria and the follow-up strategy, another study limitation was the small sample sizes of both the first-EVB and non-first EVB groups[35].

Finally, the same group investigated the potential of various quantitative CT-derived parameters, including EV grade, EV diameter, cross-sectional surface area, EV volume, spleen volume, splenic vein, portal vein, diameter of LGV, and the opening type of LGV, in predicting the risk of EVB. The EV grading system on CT images was made in accordance with the criteria proposed by Kim *et al*[39], classifying EV as I–IV mainly according to the EV diameter and their distribution around the inner wall. Although some of these CT parameters proved to be significantly associated with EV severity, none of them showed a significant association with EVB. However, as stated by the same authors, the enrolled study population was mainly composed of patients with

severe EV, bringing a potential bias of the study cohort, and large samples with more patients with mild to moderate EV would have been warranted to reach high-quality evidence for further validation[36].

CONCLUSION

As expected, EV diameter/grade was the CT feature significantly associated with EVB most frequently reported among the included studies[28, 29, 32, 33]. Conversely, with regard to major collateral vessels, LGV size/enlargement was shown to be significantly associated with EVB in only two of the included studies[28, 30]. PUV showed conflicting results in the prediction of EVB in two studies[28, 30]. As previously mentioned, this may be explained by an enrollment bias in the study from *Calame* et al, in which the alcoholic etiology of cirrhosis was prevalent[30]. Moreover, IMV size was shown to be a significant predictor of EVB in two studies[29, 32], while the size of posterior gastric vein and short gastric vein was demonstrated as such only in one study, respectively[29, 32]. Finally, none of the included studies found a significant association of spleno-renal vein with EVB occurrence.

Worth mentioning, portal-systemic collaterals development varies from patient to patient, being likely influenced by the etiology of cirrhosis, and with each subject showing his own pattern, either single or a combination of multiple collaterals[40, 41]. Moreover, with the exception of LGV, the value of these collaterals in the prediction of EVB has not been clearly established[41, 42].

EGD is currently regarded as the diagnostic reference standard for the prediction of VEB, being capable to identify high-risk EV, such as medium or large-sized, and small-sized with red wale markings EV[9]. Furthermore, primary prophylaxis against EVB is recommended in cirrhotic patients with high-risk EV and in those with small size EV who are classified as Child-Pugh C class[9-13]. Nevertheless, the occurrence of VEB during primary prophylaxis with propranolol has been reported in up to 30% of cases [11]. HVPG is considered the "gold standard" for the assessment of the response to pharmacological prophylaxis and may be adopted in order to reduce the rate of

primary prophylaxis failure[9, 10, 24]. However, HVPG is invasive and expensive. Moreover, it is not readily and widely available in routine clinical practice, and its cost-effectiveness and clinical usefulness have also been questioned[25, 26].

EGD is invasive, costly, and potentially associated with the risk of iatrogenic bleeding. With regard to high-risk EV identification, a lower inter-observer agreement of EGD has also been reported as compared with CT imaging[18, 19]. Moreover, frequent endoscopic screening may result in poor patients' compliance and loss of patients to follow-up[22, 43]. Despite these limitations, in our opinion, CT should not be intended to replace EGD in the prediction of EVB. Nevertheless, CT may be useful in the identification of patients with a very-high risk of EVB. Given that CT is increasingly performed with various indications among cirrhotic patients, it could potentially assist liver disease scores, HVPG, and EGD in a more effective prediction of EVB. Moreover, CT may be able to support clinicians in their daily practice in accurately identifying very high-risk patients for EVB, in whom a combined pharmacological and endoscopic primary prophylaxis may be systematically considered and/or a more aggressive therapeutic monitoring strategy may be adopted.

Of note, all of the included studies in our review demonstrated severe limitations, likely affecting the study outcomes. First of all, bleeding and control groups significantly differed in terms of Child-Pugh class and/or MELD score in three out of 9 studies[29, 30, 32], whereas liver disease scores were not reported in another study[33]. Second, their retrospective nature[28-36]. Lastly, their small sample size[28-36].

The role of CT in the prediction of VEB, especially by the measurement of various EV indicators and some collateral veins, appears to be promising and intriguing. However, to date, evidence is still lacking. In our opinion, large, multicenter prospective controlled trials with adequate follow-up, should be conducted in order to evaluate if the EVB prediction rate may be further improved by adding MDCT to currently validated modalities (i.e. liver disease scores combined with endoscopy and/or HVPG). Moreover, the capability of selected and standardizable MDCT parameters to predict EVB should be prospectively evaluated, adopting EGD with or without HVPG as the

reference standards. MDCT should be performed at the same time as the other validated modalities, without significant delay, and results should be stratified according to liver disease scores, endoscopic scores, and cirrhotic etiology. Of note, no significant differences in terms of liver disease severity, etiology, ongoing liver injury, or prophylactic therapy should be encountered between the enrolled groups. High morbidity and mortality rates still associated with EVB justify active research in this field.

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