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Esophageal varices on computed tomography and subsequent variceal hemorrhage

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Abstract

Purpose—Endoscopy is recommended to screen for esophageal varices in patients with cirrhosis. The objective of this study was to identify features on abdominal CT imaging associated variceal hemorrhage (VH).

Methods—A case–control study was performed among patients with cirrhosis who had a CT scan. Consecutive patients who experienced VH were included as cases, and patients without VH served as controls. Two radiologists recorded the maximal esophageal varix diameter in addition to other measures of portal hypertension at CT.

Results—The most powerful CT parameter associated with VH was the esophageal varix diameter (5.8 vs. 2.7 mm, $p < 0.001$; adjusted OR 1.84 per mm, $p = 0.009$). 63% of individuals with VH had a maximal varix diameter ≥5 mm compared to 7.5% of cirrhotic patients without VH ($p < 0.001$). In contrast, the proportion of individuals whose largest varix was <3 mm was 7.4% among VH cases compared to 54.7% among controls ($p = 0.001$). The varix diameter powerfully discriminated those with and without VH (C-statistic 0.84).

Conclusions—A large esophageal varix diameter is strongly associated with subsequent VH. A threshold of <3 and ≥5 mm appears to identify patients with cirrhosis at low and high risk for hemorrhage.

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Keywords

Portal hypertension; Variceal hemorrhage; CT; Cirrhosis

Background

Patients with cirrhosis are at increased risk for variceal hemorrhage (VH). Patients sustaining a VH have poor outcomes; notably, their mortality is as high as 35% at 3 months and 70% at 2 years [1, 2]. Strategies to prevent VH have been studied extensively and include endoscopic band ligation and nonselective β-blockers [3, 4]. To reduce the risk of VH, current guidelines recommend risk stratification with an upper endoscopy. However, there are costs and risks associated with endoscopy and moderate sedation, particularly in patients with cirrhosis [5–7]. Indeed, while identification of high risk individuals is important, risk stratification should be performed considering risks, benefits, and costs.

Patients with cirrhosis often undergo multiphase computed tomography (CT) scans to screen for hepato-cellular carcinoma as a part of their routine clinical management. Findings suggestive of portal hypertension are common (esophageal varices, splenomegaly, ascites, and enlargement of the portal vein or the presence of enlarged collateral vessels). Previous studies have examined the correlation between CT findings and endoscopy and have shown that the variceal size agreement between radiologists is better than agreement between endoscopic interpretations [8–10]; however, to date, studies have not directly examined features of CT imaging associated with VH.

Methods

Study design

We performed a nested case–control study of patients with clinical cirrhosis seen one single-center VA Medical Center from January 2002 to August 2007.

Cases

Case patients with VH were identified from the administrative database by ICD-9 codes based on an inpatient hospitalization for variceal bleeding. VH was confirmed by chart review, including typical clinical presentation and endoscopic findings at the time of hospitalization. All cases of VH were defined by upper gastrointestinal hemorrhage and an endoscopy revealing esophageal varices with stigmata of recent hemorrhage or the absence of other identifiable source of bleeding. All patients included as cases also had a CT scan available for review prior to the hospitalization for VH.

Controls

The control group consisted of consecutive patients with cirrhosis who had CT imaging and endoscopy to assess for esophageal varices. We selected controls with a short time interval between the two tests to allow for agreement between CT and endoscopy (45 days). All individuals in the control group had clinical evidence of cirrhosis although liver biopsies were not routinely performed. Factors that could have altered the appearance of varices on CT were excluded such as a previous VH, endoscopic band ligation, or liver transplantation. After endoscopy, the standard practice was to prescribe empiric β-blocker therapy for patients with at least moderate sized esophageal varices unless they were intolerant. The indication for CT imaging for the majority of individuals was hepatocellular carcinoma screening.

Measurements

Laboratory values for all individuals were abstracted within 30 days of the CT scan. These parameters included total bilirubin, INR, creatinine, sodium, and platelet count. To standardize the definition and interpretation between radiologists, twenty different abdominal multidetector CT (MDCT) cases of similar patients with cirrhosis were reviewed by both readers (one attending radiologist and one trainee) together. Each reader then independently analyzed each of the CT scans in the study. Readers were blinded to the patient's medical history, including any history of VH.

Axial CT images were evaluated for the following parameters: maximum short axis diameter of the largest esophageal varix, degree of coronary vein enlargement, diameter of the paraumbilical veins, maximum short axis diameter of the portal vein, presence of ascites, and finally the maximum dimension of the spleen was measured. An esophageal varix was defined as an intramural enhancing nodular tubular structure which may protrude into the lumen of the esophagus or run adjacent to the inner esophageal mucosa (Fig. 1).

MDCT scans of the abdomen and pelvis were retrospectively reviewed and had been performed with variable slice thickness ranging from 1.25 to 5 mm. 67% of the studies were performed using a 5-mm slice thickness. 30% were performed with a 2.5-mm slice thickness, and the remaining 3% were performed with a 1.25-mm slice thickness. 46% of the studies were performed on an 8-MDCT scanner (LightSpeed Ultra, GE Healthcare), 44% were performed on a 16-MDCT scanner (LightSpeed 16, GE Healthcare), 7% were performed on a 64-MDCT scanner (LightSpeed VCT, GE Healthcare), and 3% were performed on a 4-MDCT scanner (LightSpeed Plus, GE Healthcare).

Eighty-six percent of the studies were performed using a multiphase liver protocol with low osmolar iodinated intravenous contrast [Omnipaque™ (iohexol) 350, GE Healthcare] injected at a rate of 3 mL/s using a power injector (EZEM). Precontrast images were obtained through the upper abdomen from the diaphragm to the iliac crests. This was followed by image acquisition during the late arterial phase initiated 45 s after contrast injection covering the same region. Portal venous phase imaging was initiated 90 s after contrast injection with coverage extended to the ischial tuberosities. The remaining studies were performed with a standard abdominal protocol during the portal venous phase of enhancement, imaging from the diaphragm to the ischial tuberosities initiated at ~70 s after the injection of low osmolar iodinated intravenous contrast [Omnipaque™ (iohexol) 350, GE Healthcare] at a rate of 3 mL/s, using a power injector (EZEM). Only 17% of the studies received positive oral contrast [MD-Gastroview™ (diatrizoate megulamine and diatrizoate sodium solution) 240 mL Mallinckrodt Inc].

Statistical analysis

Patient demographics, baseline chemistries, etiologies, the model for end-stage liver disease (MELD) score, and CT measurements were tabulated and compared using *t*-or nonparametric tests for continuous variables, and Chi square or Fisher's exact test for categorical variables. For the primary analysis, the association between CT findings and VH was analyzed using the average measurements of the two CT readers. The MELD score was calculated using the standard formula: $11.2 \times \ln(\text{INR}) + 9.57 \times \ln(\text{creatinine, in mg per dL}) + 3.78 \times \ln(\text{bilirubin, in mg per dL}) + 6.43$, with a lower limit of 1 for all variables and a maximum MELD score of 40 [11, 12]. Graphical methods were used to assess the associations of continuous measures with case or control status, in order to detect non-linearities.

Multivariable logistic modeling was used to determine whether other CT measures, including portal vein size, ascites, and splenomegaly, or laboratory measures including INR, platelets, sodium, and creatinine, might be used in place of or along with CT characteristics of esophageal varices. We assessed interactions between candidate predictors. A final model was selected using backwards deletion with a relatively strict retention criterion of $p < 0.05$, to avoid over-fitting.

Since our primary purpose is accurate prediction of VH, we were most interested in markers that powerfully discriminated between those with and without disease. The area under the receiver-operator curve, or C-statistic, was used to summarize the predictiveness of each parameter and the final model for VH. The C-statistic is a measure of a prognostic test's ability to correctly assign an individual with the adverse outcome to the higher risk strata. To inform clinical decision making, we tabulated sensitivity and specificity for a range of possible thresholds for VH.

For CT measurements to be replicated and implemented in the community, the measurements must have fair agreement between readers. We used the linear weighted κ-statistic to estimate inter-observer agreement for variceal diameter and other significant parameters by CT. Weighting was used because 1 mm differences during measurement were credited for their similarity.

STATA Version 11 (Stata Corp., College Station, TX, USA) was used for all analyses. This study was approved by the committee on human research at the University of California, San Francisco (Approval #: 10-02944).

Results

Baseline characteristics

We identified 27 consecutive patients with cirrhosis who had an outpatient CT scan prior to sustaining a VH. 53 individuals with cirrhosis who underwent CT with no VH during the time interval served as the control population. 96% of the cohort was men (Table 1). Among the individuals who experienced a VH, the average time between CT and VH was 7 months. The average time in the control group from the date of the CT was 33 months (range 2–53 months).

Comparing the baseline characteristics of subjects who sustained a VH with those who did not, only albumin concentration was significantly different between the two groups (2.9 vs. 3.4, respectively, $p = 0.003$). There was a trend toward older age and increased alcohol use in patients with VH, which did not meet statistical significance.

CT parameters associated with VH

CT scan findings and measurements are shown in Table 2. The most powerful parameter associated with VH was the diameter of the largest esophageal varix (5.8 vs. 2.7 mm, OR 2.21, 95% CI 1.51–3.23; C-statistic 0.84, 95% CI 0.74–0.94). The short axis diameter of the esophageal varix was associated with a high C-statistics and powerfully discriminated between cases and controls. There was good inter-observer agreement for the diameter of the largest esophageal varix with a κ_w of 0.67 (Supplemental Table S1). Multiple other findings reached statistical significance but less powerfully discriminated for VH. These included the size of the paraumbilical veins, the coronary vein, and the presence of ascites. The portal vein size and spleen size were not significantly different between the two groups. Of note, the MELD score measured at the time of the CT scan was not significantly different between cases and controls.

In the multivariable analysis, the diameter of the largest esophageal varix remained independently associated with VH (OR 1.84 per mm, 95% CI 1.16–2.92, $p = 0.009$). This model included variables significant in the univariate analysis such as the largest diameter of the left gastric or paraumbilical veins, ascites, serum albumin, and liver nodularity. While ascites was more common among cases compared to controls, it was not an independent predictor of VH in the multivariable analysis.

Performance of varix diameter thresholds

We explored the thresholds for the diameter of the largest esophageal varix that discriminated high and low risk individuals using graphical (Fig. 2) and statistical methods (Table 3). A CT threshold of ≥5 mm was present in 63% of the VH cases and in only 7.5% of the control population (OR = 20.8, 95% CI 5.77–75.2, $p < 0.001$). In contrast, a CT threshold of <3 mm was observed in 7.4% of VH cases and 55% of the control group (OR = 0.066, 95% CI 0.014–0.31, $p = 0.001$). Between 3 and 5 mm, an interval associated with 30% of cases of VH and 38% of controls, the performance of CT scan in this area is equivocal (OR = 0.69, 95% CI 0.26–1.88, $p = 0.47$). Refined test characteristics at each millimeter threshold can be found in Supplemental Table S2.

Two cases of VH occurred in which the diameter of the varix was assessed to be less than 3 mm. One individual was admitted 1 month after the CT scan with a VH. He had three columns of moderately sized esophageal varices during endoscopy and was banded along with treatment for gastric antral vascular ectasia. His MELD score was 10 and platelet count was 118. The two radiologists identified the largest measuring varix at 2 and 3 mm, respectively. The second patient was admitted for VH 3 months after the CT scan, had two columns of small esophageal varices on endoscopy but also had gastric varices. The patient had small ascites, nodular liver, and a thickened distal esophagus. No varices were detected on the CT scan. His MELD score was 12. Both patients were selected as VH cases but it is possible that they bled from gastric varices and antral ectasias.

Discussion

To date, several studies have evaluated the correlation between CT measurements and endoscopic grading of varices, but no studies have explored the utility of information provided by CT imaging to predict VH. Endoscopy has traditionally been accepted as the gold standard predictor of VH but is invasive, costly, and requires sedation. Results from our study show that the most powerful CT parameter associated with VH is the diameter of the largest esophageal varix. Other findings were informative, such as the presence of ascites, the diameter of a paraumbilical or left gastric vein and liver nodularity; however, the diameter of the largest varix remained the most robust predictor and reproducible measure between radiologists for VH in this study.

We identified two important thresholds that may improve clinical decision making. Individuals with small (<3 mm) or undetectable esophageal varices on CT scan were unlikely to experience a VH (OR 0.066). This threshold is important because only a small proportion (7.5%) of individuals with VH had a “normal” CT of the esophagus. A sensitive cut-point provides a mechanism to “rule out” disease. When an EV diameter <3 mm was compared against the grade of esophageal varices during elective outpatient endoscopy, none of the 36 individuals had greater than small varices. Therefore, varices <3 mm on CT appear be at low risk of hemorrhage and may obviate an invasive endoscopy for risk stratification.

In contrast, varices ≥5 mm identified high risk individuals. 63% of the VH cases had varices exceeding this threshold compared to 7.5% of the control group (OR 20.8). When this

degree of CT abnormality was present in the control group, the majority of endoscopies demonstrated varices of moderate size or greater. This suggests that endoscopy may not be necessary in this situation, and an argument could be made for empiric β-blockers initiation for primary prophylaxis against VH. This point is controversial, and would need to be confirmed by prospective studies, but nonetheless may eventually be shown to be useful clinically. As such, in addition to accurately risk stratifying patients, CT scans have the potential to decrease resource utilization.

Several studies have correlated CT and endoscopy findings but our study is the first to correlate CT and VH events. A cut-point of 5 mm was previously shown to have approximately 90% sensitivity and 50% specificity for large varices [8–10]. The inter-observer agreement between radiologists in this study was better than between endoscopists for the evaluation of varices. Indeed, the agreement between endoscopists was at best fair (κ = 0.36). Another study used a 3-mm threshold for varices on CT to accurately predict the presence of large varices on EGD [13]. Neither of the previous studies used multiple thresholds to risk stratify patients, which may effectively allocate EGD to those who need it most. Another competing technology is capsule endoscopy, which has been studied to identify patients with moderate or large esophageal varices [14, 15]. It has demonstrated good performance but incurs additional cost deterring its role as a screening tool [16]. All in all, CT imaging may offer the most consistent quantitative measurements with important clinical implications.

There are several limitations to this study. First, the control group is inherently different from the hemorrhage cases and can be prone to selection bias. To address selection bias, we sampled consecutive patients with cirrhosis to develop the cases and control group. A representative control group that represents the population at risk allows for rigorous comparison of the predictive qualities of the CT parameters, and allows for adjustment in the multivariate model to assess the independent contribution of each parameter to the outcome. Bias may also exist due to the use of β-blockers. We attempted to reduce treatment bias by blinding the radiologists from the endoscopic findings as they reread the CT scans; however, it is possible that residual bias (e.g., β-blocker or banding effects) may exist. Second, CT scan measurements posed several issues in the current study. As this was a retrospective study the technology and protocols, as demonstrated in our study, tend to change over time, increasing the variability in findings in a single individual and between individuals. Other findings on CT can also reduce the precision of the measurement of a varix such as the presence of a hiatal hernia, thickening or compression of the distal esophagus and the administration of positive oral contrast. Inter-observer agreement may have been impacted by the quality of the underlying image, which when zoomed, impacted resolution secondary to pixilation. As technology and quality of the images improve, these limitations should decrease over time.

In conclusion, a large maximal esophageal varix diameter is strongly associated with esophageal VH. A threshold of <3 mm and ≥5 mm appears to discriminate between low and high risk individuals, respectively. The clinical implications of these thresholds would be best evaluated in the context of a prospective cohort study first to confirm the prognostic value of these size intervals, the value of repeated measurements, and subse quently, to identify which individuals may avoid endoscopy and others who may be empirically started on primary prophylaxis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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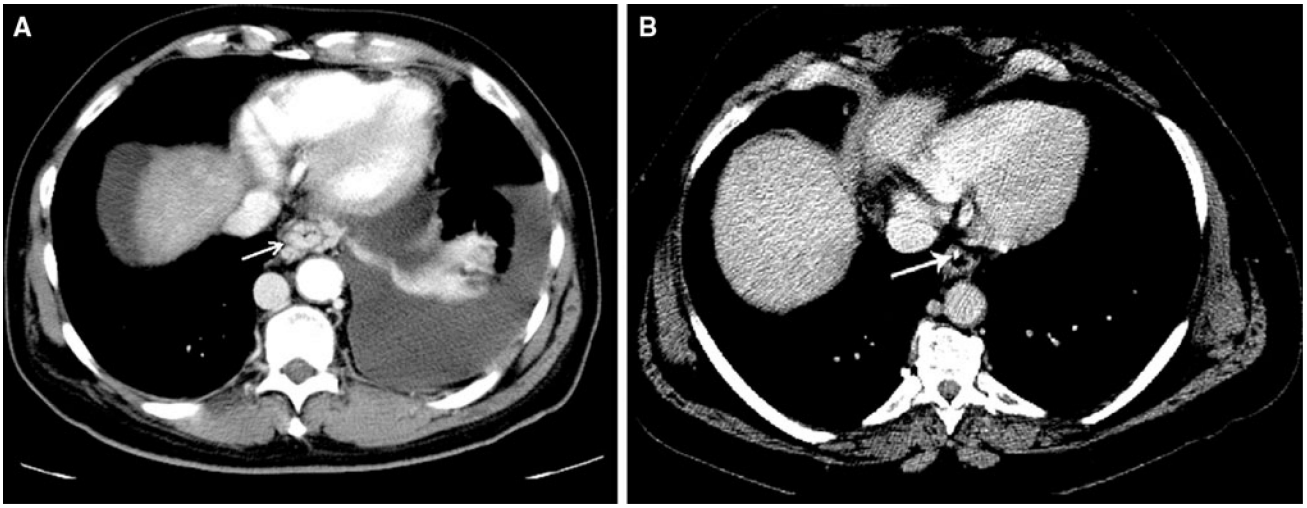

Fig. 1.
CT measurement of esophageal varices. Image **A** shows >5 mm esophageal varices that subsequently bled, the esophageal varix in **B** were 3 mm by CT evaluation and did not bleed.

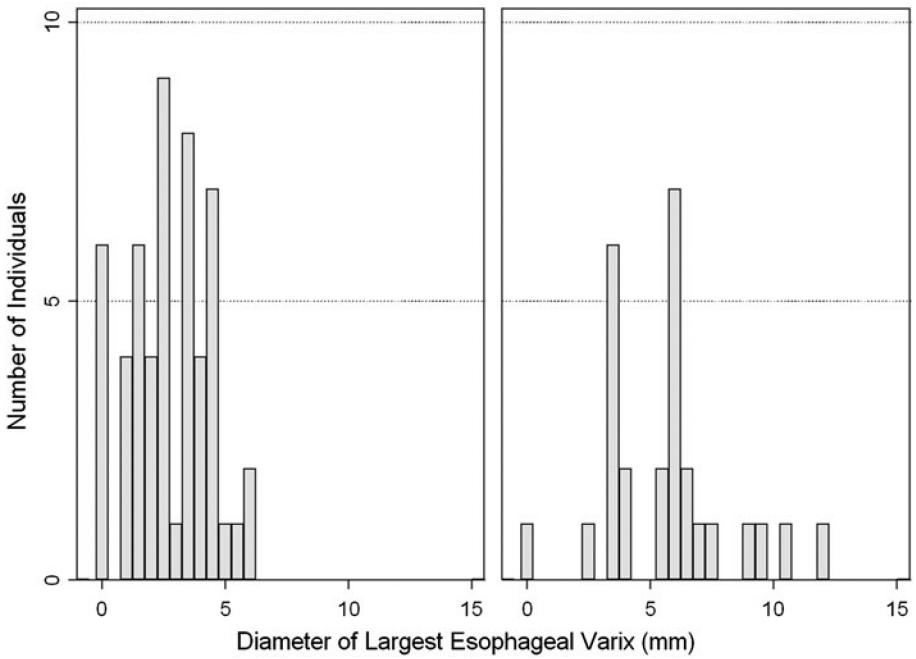

Fig. 2.

Histogram of the diameter of the largest luminal esophageal varix between cases (*right*) and controls (*left*).

Table 1

Baseline characteristics of subjects with and without VH

	Cases	Controls	*p* value
Subjects (no.)	27	53	
Male (%)	96	96	0.99
Age (mean)	58	55	0.075
β-Blocker (%)	67	51	0.20
Laboratory (mean)[a]			
Platelet count (k/μL)	130	148	0.42
Sodium (mmol/L)	138	137	0.25
Creatinine (mg/dL)	0.96	0.88	0.09
Albumin (g/dL)	2.9	3.4	0.003
INR	1.18	1.14	0.48
Total bilirubin (mg/dL)	1.9	1.8	0.91
AST (U/L)	102	75	0.13
ALT (U/L)	70	68	0.94
Etiology (%)			
HCV antibody	71	77	0.57
HBsAg positive	0	9.4	0.12
Alcohol use[b]	83	64	0.09

INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen

[a] Seven individuals did not have laboratory data available within 30 days of CT scan, 3 among cases, and 4 among controls

[b] Includes current and previous alcohol use

Table 2

Measurements of CT parameters in cases and controls

CT finding	VH cases	Controls	Odds ratio	95% CI	*p* value	C-statistic
Largest vessel diameter (mm)						
Esophageal varix	5.8	2.7	2.21	1.51–3.23	< 0.001	0.84 (0.74–0.94)
Coronary vein	2.3	1.6	3.47	1.71–7.05	0.001	0.75 (0.65–0.85)
Paraumbilical vein	1.9	1.1	3.36	1.75–6.44	< 0.001	0.79 (0.69–0.89)
Portal vein	16.5	16.5	1.01	0.84–1.23	0.89	0.50 (0.35–0.64)
Other findings						
Spleen size (cm)	14.5	13.5	1.05	0.94–1.16	0.39	0.61 (0.46–0.76)
Any ascites (%)	74	25	8.8	3.10–25.0	< 0.001	0.76 (0.65–0.86)

Table 3

Odds ratios for VH associated with esophageal diameter intervals

Intervals (mm)	Cases (%)	Controls (%)	Odds ratio	95% CI	*p* value
<3.0	7.4	54.7	0.066	0.014–0.31	0.001
3.0–4.9	29.6	37.8	0.69	0.26–1.88	0.47
≥5.0	63.0	7.5	20.8	5.77–75.2	<0.001