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Can "Attenuation Subtraction", a Computed Tomography Scan-Based Factor, be Used as a Predictor of High-Risk Esophageal Varices in Cirrhotic Patients? A Retrospective Cohort Study

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ABSTRACT

Background and Aims: Liver cirrhosis is a severe condition that can result in complications such as portal hypertension and esophageal varices (EVs). While current guidelines recommend screening for EVs, existing procedures are often invasive, costly, and occasionally unreliable. This study aims to develop a CT-based predictor for identifying high-risk esophageal varices group (HRG) in cirrhotic patients, offering a noninvasive, safe, and cost-effective alternative that integrates seamlessly into routine follow-up without requiring additional resources or time.

Methods: The study retrospectively analyzed data from 2016 to 2021 of cirrhotic patients referred to a hospital in Tehran. Experienced professionals analyzed factors related to CT scans, and patients were categorized into high-risk and non-high-risk varicose veins groups by endoscopy. The main sample size for the study was 62 patients with an average age of 50.2 ± 11.5 years. Also, we aimed to determine a diagnostic cutoff and externally validated it in a separate statistical population (29 patients).

Result: The study found that liver attenuation subtraction, Child-Pugh score, and direct visualization of esophageal varices in CT scans were significant factors in predicting high-risk esophageal varices. The study showed that a liver attenuation subtraction of 14.5 HU (CI 95%: 0.949–1) with an inverse relationship could predict high-risk esophageal varices with high accuracy.

Conclusion: The study indicated that liver "Attenuation Subtraction" in CT scans distinguishes high-risk and non-high-risk esophageal varices. Furthermore, external validation demonstrated that this cutoff value is generalizable to other statistical populations. We pinpoint an indicator of high-risk esophageal varices in patients with cirrhosis devoid of invasiveness and peril and do not impose supplementary expenses or time beyond the customary monitoring of cirrhotic patients.

Abbreviations: DV-CT, direct visualization on CT scan; EGV, esophago-gastric varices; EV, esophageal varices; HRG, high-risk variceal group; HU, Hounsfield unit; IKHC, Imam Khomeini Hospital Complex; NHRG, non-high-risk variceal group; PVD, portal vein diameter; ROI, region of interest; SMVD, superior mesenteric vein diameter; SRC, splenorenal collateral; SVD, splenic vein diameter; SV, spleen volume; UGE, upper gastrointestinal endoscopy; USE/MRE, ultrasound or magnetic-resonance elastography.

1 | Introduction

Liver cirrhosis is associated with numerous complications that significantly impact patient prognosis. Among these, portal hypertension is the most critical, playing a key role in the development of esophageal varices (EVs). The presence of EVs is particularly concerning, as variceal bleeding is often life-threatening in cirrhotic patients [1–3].

Current guidelines recommend screening for EVs during cirrhosis diagnosis, with follow-up endoscopic evaluations every 1–3 years if no varices are detected. However, endoscopy is invasive, costly, and unreliable in identifying EVs [4, 5]. The formation of EVs is believed to result from elevated resistance to blood flow and advanced hepatic fibrosis [6]. Understanding intrahepatic hemodynamics is, therefore, crucial for assessing the progression of EVs. Abdominal dynamic contrast-enhanced multi-detector-row computed tomography (ADCE-MDCT) has proven useful not only for detecting hepatocellular carcinoma and evaluating liver morphology but also for assessing portal vein thrombosis, EVs, and hemodynamic changes [7–9].

Approximately 30% of cirrhotic patients with EVs develop high-risk esophageal varices (HRG), which require prophylactic interventions such as endoscopic variceal ligation (EVL) or β-blockers to prevent life-threatening variceal bleeding [10, 11]. In a healthy liver, injected contrast material is distributed between the hepatic extracellular space (ECS) and the hepatic sinusoids before clearing through the hepatic vein [12, 13]. However, in cirrhotic livers, hepatocyte damage and fibrosis lead to sinusoidal narrowing, increased extracellular matrix deposition, and decreased microvascular permeability, resulting in delayed hepatic enhancement and prolonged contrast retention in the hepatic parenchyma [14–16]. These hemodynamic changes are reflected as attenuation differences in CT imaging, particularly during the portal and equilibrium phases [17–19].

We hypothesized that the degree of hepatic fibrosis-related hemodynamic alterations could be quantified through attenuation subtraction, which calculates the difference between hepatic parenchymal CT values (Hounsfield units) in the equilibrium and portal phases. This approach may provide a more precise assessment of intrahepatic hemodynamic changes caused by fibrosis.

Given the longstanding need for accurate, noninvasive methods to predict EV development before endoscopic examination, we propose that attenuation subtraction in abdominal CT imaging with a four-step contrast injection protocol could serve as a valuable screening tool. This technique can reduce unnecessary endoscopies by identifying HRG in cirrhotic patients, offering a novel, cost-effective, and opportunistic approach to EV detection. Accordingly, this study aims to evaluate the predictive value of liver attenuation subtraction for identifying HRG in cirrhotic patients.

2 | Materials and Methods

2.1 | Study Design, Patients, and Data Collection

This retrospective study, conducted from 2016 to 2021, examined patients diagnosed with cirrhosis referred to the gastroenterology clinics of Imam Khomeini Hospital Complex (IKHC) in Tehran. The study specifically included cirrhotic patients who had undergone upper gastrointestinal endoscopy (UGE) or endoscopic treatment for esophageal variceal bleeding within 4 months following a four-phase abdominal CT scan. The inclusion criteria ensured that the study focused on patients with recent imaging and endoscopic evaluations, allowing for a reliable assessment of the relationship between CT-based parameters and EVs.

To maintain the integrity of the analysis, patients who had received abdominal interventions between the CT scan and UGE, such as trans-arterial embolization or percutaneous radiofrequency ablation for liver cancer, were excluded. Additionally, individuals who had undergone any form of abdominal surgery, as well as those with a prior history of endoscopic treatment for EVs or splenectomy before the CT scan, were not included in the final analysis (Figure 1). After applying these criteria, 62 patients, with a mean age of 50.2 ± 11.5 years, were eligible for evaluation. Among them, 39 (62.9%) were male, and 23 (37.1%) were female.

The analysis of CT parameters, including attenuation subtraction, was conducted by expert radiologists specializing in abdominal and pelvic imaging using the hospital's INFINITT PACS system. Additional clinical information was extracted from the hospital database, including the etiology of chronic liver disease, Child-Pugh and MELD scores, and endoscopic findings. This comprehensive data set allowed for a thorough investigation of the relationship between imaging biomarkers and EVs.

All endoscopic procedures were performed by a specialized gastroenterologist with 12 years of experience. Endoscopic findings classified patients into HRG and NHRG (Non-high-risk variceal group). The grading of EVs followed the criteria established by the Japanese Research Society for Portal Hypertension, where grade 2 varices (beaded appearance) and grade 3 varices (oblique course and tumor-like tortuosity) were designated as high-risk. Furthermore, patients requiring urgent interventional endoscopy, including band ligation or sclerotherapy, were also categorized in the HRG group due to their increased likelihood of variceal hemorrhage [20].

By systematically comparing CT-derived parameters and clinical data between the HRG and NHRG groups, this study aimed to identify reliable, noninvasive predictors of HRG. The findings could contribute to optimizing screening strategies and potentially reducing the need for unnecessary endoscopic examinations. The study was conducted according to ethical guidelines and received approval from the AJA (Islamic Republic of Iran Army (Artesh)) University of Medical Sciences ethical committee under the ethics approval ID IR.AJAUMS.REC.1402.190. Informed consent was obtained from all participants before data collection.

2.2 | Liver Computed Tomography Protocol and Administration of Contrast

Liver CT examinations for following up on all cirrhotic patients to rule out hepatocellular carcinoma (HCC) were performed with an MX16-slice Philips scanner. A total of 100 mL of contrast material (IOHE XOL (OPAQUESOL) 350 Shahid Ghazi Pharmaceutical Co., each 1 mL containing 350 mg Iodine) was

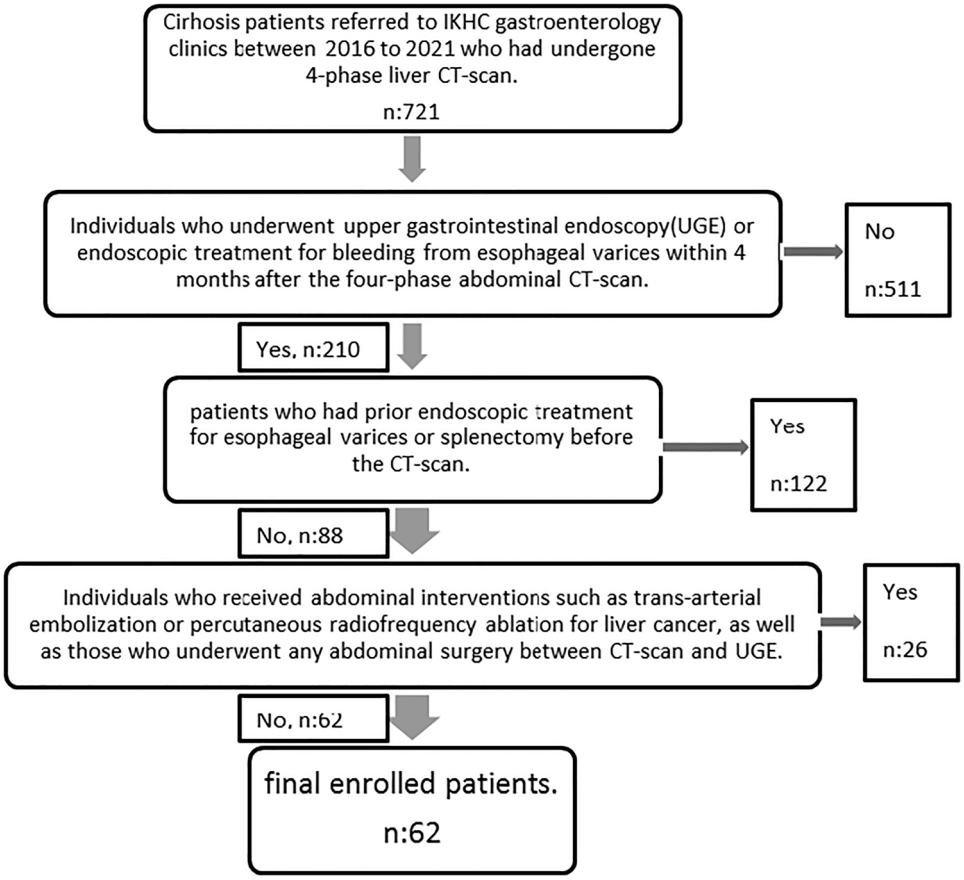

FIGURE 1 | Patient's enrollment (main sample).

administered intravenously with an automatic injector (Dual shot alpha 7-Nemato) at a rate of 2.5 mL/s. Images were obtained at 0, 25–28, 70, and 130–150 s after the contrast material injection, representing the non-contrast, late arterial, portal venous and equilibrium phases, respectively. Subsequently, images were obtained from the dome of the liver to the bottom of the Ischial bone during a single breath-hold. CT scanning parameters were as follows: 16 detector rows; pitch, 1.00; 120–130 kvp;. The raw data obtained a transverse image with a slice thickness of 1.25 or 2.5 mm and Fov 450–500 mm. No patients received oral contrast material.

2.3 | Assessment

An abdominopelvic radiologist (f.s) with 10 years of experience plus a general radiologist with 4 years of experience (mmmt) independently interpreted the liver CT images. A skillful gastroenterologist (with 12 years experience) had performed esophageal endoscopy and interpreted the results to (1) observe endoscopic visible esophageal varices and define the high-risk group of esophageal varices as (grade 2 or 3) according to the grading criteria outlined by the Japanese Research Society for Portal Hypertension [20], plus a group of EVs which needed acute subsequent interventional endoscopy for preventing hemorrhage (band ligation or sclerotherapy), (2) The hepatic parenchyma's CT "attenuation subtraction" was determined by measuring the delta HU using circular ROIs of approximately 2 cm^2 in three specified areas (S3, S7, and S8 on the porta hepatis cross-section; avoiding apparent vessels and focal lesions). As a result, the mean CT value(HU) of these three specified areas was measured in both the portal and equilibrium phases. Then we subtracted the mean CT value of the equilibrium phase from that of the portal phase(entitled "the attenuation subtraction") [21], (3) evaluate the maximum diameter of portal vein, superior mesenteric vein(SMV), and splenic vein in equilibrium phase, (4) estimate intrahepatic portosystemic shunt in portal phase, (5) assess spelenorenal collateral in equilibrium phase, (6) The spleen's largest dimension was measured in the right-to-left (x), ventral-to-dorsal (y), and cranial-to-caudal (z) directions. The "$x*y*z*0.52$" measurements obtained, considered to represent the patient's approximate splenic volume, (7) determine the presence of prominent vascular structure on the mucosal aspect of the esophagogastric lumen as EV (DV-CT: direct visualization on CT scan).

2.4 | External Validation

External validation was employed to assess the predictive role of "Liver Attenuation Subtraction" in high-risk esophageal varices among patients with cirrhosis. For this purpose, 29 patients (with mean age of 48.1 ± 11.9 years, 16 (55.2%) males and 13 (44.8%) females) with liver cirrhosis who met the inclusion criteria and did not meet the exclusion criteria, similar to the main study population, were selected as the "external validation population" from another university-affiliated hospital, namely shariati hospital, in Tehran, between 2020 and 2023. The abdominal and pelvic CT

imaging protocol, including the timing of contrast agent administration, was almost identical to that of the primary study population. Additionally, the CT scanner used (16-slice HITACHI scanner) had the analogous settings (16 detector rows; pitch, 1.00; 110–120 kvp; The raw data obtained a transverse image with a slice thickness of 1.25 or 2.5 mm and FOV 400–450 mm). The evaluation of CT scans for calculating Liver Attenuation Subtraction was performed using the hospital's Marco PACS system and followed the previously described method, conducted by a different abdominopelvic radiologist. Furthermore, endoscopic data for categorizing patients into HRG and NHRG were extracted from the hospital database. All endoscopic procedures were performed by a skilled gastroenterologist distinct from the main study samples.

2.5 | Statistical Analysis

Our research focuses on individuals diagnosed with cirrhosis who sought treatment at the gastroenterology clinics of Imam Khomeini Hospital in Tehran from 2016 to 2021. The sample size for this investigation consisted primarily of 56 patients, as determined by the study by Inkouchi et al. [21] and a specific formula (with 95% confidence interval and 90% test power):

$$n = ((Z_{(1-\alpha/2)} + Z_{(1-\beta)})^* (S_1^2 + S_2^2))/(\mu_1 - \mu_2)^2$$

A 10% increase was added to account for potential errors in project implementation stages, resulting in a final sample size of 62 ($n = 62$) for this retrospective cohort study. The determination of diagnostic cutoff involves the use of ROC analysis and assessment of sensitivity, specificity, as well as positive and negative predictive values. In addition, a comparison of the area under the ROC curves (AUC) between the main sample and the external validation sample was conducted to compare the cutoff values. Statistical significance is indicated by a 95% confidence interval (CI) and p values less than 0.05. All statistical analyses are conducted utilizing SPSS software version 22. Moreover, univariable analysis was conducted using an independent t-test or Fisher's exact probability test for parametric variables and χ^2 and Mann–Whitney tests for non-parametric variables. Additionally, multivariable analysis was performed using the stepwise regression method.

3 | Result

This study included 62 patients, with an average age of 50.2 ± 11.5 years, who met the inclusion criteria. Among the participants, 39 (62.9%) were male and 23 (37.1%) were female. Among these, 35 patients were found to belong to high-risk esophageal varices (HRG), and the other 27 patients had non-high-risk esophageal varices (NHRG) (Table 1). Two experienced and independent radiologists collected radiological data, showing a significant correlation with a Cohen's Kappa coefficient of approximately 0.88, showing an excellent correlation between the results. In univariable data analysis, factors such as liver attenuation subtraction (8.4 ± 3.1 vs. 19.3 ± 5.9 HU), spleen volume (1009.4 ± 680.3 vs. 592.2 ± 272 cubic centimeters), Child-Pugh score A/B/C (0/12/23 vs. 5/11/11), and direct visualization of esophageal varices in CT scan (DV-CT Positive/Negative) (35/0 vs. 13/14) were found to significantly differentiate between high-risk esophageal varices and non-high risk esophageal varices. In a multivariable analysis, Stepwise Regression was employed to examine the four factors (Table 2) sequentially. The study's findings revealed that among the aforementioned factors, only the attenuation subtraction of the liver, DV-CT, and Child-Pugh score with probability coefficients of 0.001, 0.009, and 0.02 significantly predict a high risk of esophageal varices. Furthermore, ROC curve analysis was utilized in this study to determine a diagnostic cutoff point for liver attenuation subtraction (Figure 2). We used Youden's index, which determines the Maximum of (Sensitivity + (1 − Specificity)) as an optimal cut point in ROC; at this point, we have the most significant area under the curve. These investigations demonstrated that a liver attenuation subtraction of 14.5 HU could predict a high risk of esophageal varices with sensitivity, specificity, positive predictive value, and negative predictive value of 97.1%, 88.9%, 91.9%, and 96%, respectively. The area under the AUC curve was also found to be 0.979 (CI 95%: 0.949–1).

In external validation sample, 16 patients (55.2%) had NHRG esophageal varices, while 13 patients (44.8%) had HRG varices (Table 3). The diagnostic cutoff value for "Attenuation Subtraction" in this patient group was 14.75 HU, which predicted high-risk esophageal varices with a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 99%, 81.2%, 81.4%, and 98%, respectively. The area under the ROC curve (AUC) was 0.986 (CI 95%: 0.952–1). When comparing the AUC of the primary study population and the external validation population, no significant difference was observed (p value = 0.8). (Figure 3) Therefore, it can be concluded that the predictive role of "Attenuation Subtraction" in high-risk esophageal varices is generalizable to other statistical populations.

4 | Discussion

This study included 62 patients (main sample) who met the inclusion criteria, enabling a comprehensive evaluation of potential predictors for HRG. Multivariate analysis identified liver attenuation subtraction, Child-Pugh score, and direct visualization of EVs on CT (DV-CT) as significant differentiators between HRG and NHRG. Also, 29 patients were examined as an external validation sample to investigate liver attenuation subtraction.

Consistent with previous findings, our results demonstrated that cirrhotic patients exhibited reduced hepatic enhancement in the portal venous phase and a slight increase during the equilibrium phase [13, 17, 18]. These changes reflect intrahepatic hemodynamic alterations due to increased resistance in intrahepatic vessels caused by hepatic fibrosis. Attenuation subtraction was introduced to capture these variations in blood flow and contrast distribution between the portal and equilibrium phases.

A key strength of this study was its focus on intrahepatic hemodynamic changes in cirrhotic patients with EVs, aiming to predict HRG through attenuation subtraction. Our findings revealed that patients with HRG exhibited a greater reduction in liver attenuation subtraction, with a cutoff value of 14.5 Hounsfield units. External validation demonstrated that this cutoff value is generalizable to other statistical populations. This cutoff suggests that lower attenuation subtraction values

TABLE 1 | Clinical and radiological data of the patients (main sample).

	HRG ($n = 35$)	NHRG ($n = 27$)	Univariable p value	Multivariable
Age	50.7 ± 11.1	49.6 ± 12.2	NS	
Sex (M:F)	23:12	16:11	NS	
HBV/HCV	8/2	8/0	NS	
CPS: A/B/C	0/12/23	5/11/11	0.02	0.02
MELDS	21.6 ± 4.9	20.5 ± 6.4	NS	
Spleen volume (cm^3)	1009.4 ± 680.3	592.2 ± 272.0	0.001	NS
Liver attenuation subtraction (HU)	8.4 ± 3.1	19.3 ± 5.9	0.001	0.001
PVD	13.7 ± 4.4	13.3 ± 2.8	NS	
SVD	10.9 ± 5.2	10.2 ± 4.7	NS	
SMVD	13 ± 2.7	12.3 ± 2.2	NS	
SRC (P:N)	25:10	16:11	NS	
IPS (P:N)	3:32	2:25	NS	
DV-CT (P:N)	35:0	14:13	0.001	0.009

Note: mean ± standard deviation.
Abbreviations: CPS, Child-Pugh score; CT, P/N, positive/negative; DV-CT, direct visualization of oesophagogastric varices on portal phase; HCV/HBV, hepatitis C virus/hepatitis B virus; HRG, high-risk variceal group; HU, Hounsfield unit; IPS, intrahepatic portosystemic shunt; MELDS, model for end-stage liver diseases score; M/F, male/female; NHRG, non-high-risk variceal group; NS, not significant; PVD, portal vein diameter (mm); SMVD, superior mesenteric vein diameter (mm); SRC, splenorenal collaterals; SVD, splenic vein diameter (mm).

TABLE 2 | Stepwise regression analysis data (main sample).

Step	Parameter	Action	χ^2 LR	p value	R^2	AIC	BIC
1	Liver attenuation subtraction	entered	26.7	0.001	0.599	48.5	57.1
2	DV-CT	entered	2.4	0.009	0.630	23.9	32.4
3	CPS	entered	2.1	0.02	0.662	22.2	28.6

Abbreviations: AIC, akaike information criterion; BIC, bayesian information criterion; CPS, Child-Pugh score; DV-CT, direct visualization of varices on the portal phase CT; LR, likelihood ratio.

could indicate more severe liver fibrosis, which is associated with a higher risk of variceal bleeding. Additionally, advanced cirrhosis was linked to lower whole blood viscosity, hematocrit levels, and platelet counts, factors that have been independently associated with hypovolemic shock in cirrhotic patients experiencing variceal bleeding [22].

In addition to attenuation subtraction, DV-CT emerged as a significant predictor of HRG. Our findings align with those of Perri et al., who demonstrated that using abdominal CT as a primary screening tool for large and high-risk varices could be an accurate and cost-effective alternative to endoscopy [23]. Moreover, CT imaging allows for assessing extra-luminal pathology, which may influence treatment decisions. Similar studies by Wan et al. and Yu et al. further support the role of CT in evaluating EVs, suggesting that it may provide complementary diagnostic information alongside endoscopy [24, 25].

Our study also identified the Child-Pugh score as a significant predictor of HRG, a finding consistent with research by Gomaa et al. [26]. This scoring system evaluates bilirubin, albumin, INR, hepatic encephalopathy, and ascites, with some variables assessed subjectively and others through laboratory tests. However, our results contrast with studies conducted by Inkouchi et al., Cherian et al., and Tafarel et al., which did not find a significant correlation between the Child-Pugh score and HRG [21, 27, 28].

Conversely, the MELD score, a widely used system incorporating INR, bilirubin, and creatinine to assess disease severity, was not found to be a reliable predictor of HRG in our study. These findings are consistent with those reported by Tafarel et al. and Mottaez and Ahadi, who also observed no significant correlation between MELD scores and variceal risk stratification [28, 29]. However, Gomaa et al. reported conflicting results, suggesting that the MELD score could be a reliable predictor of HRG [26].

Furthermore, spleen volume (SV) was investigated as a potential differentiator, but our results indicated no significant association with HRG. This contrasts with findings from Sarangapani et al. and Yu et al., who reported a positive correlation between SV and variceal risk [30, 31]. A possible explanation for this discrepancy is the occurrence of multiple infarcts in the spleen of patients with advanced cirrhosis, which may lead to a reduction in spleen size despite worsening disease progression [32].

Similarly, our study did not identify portal vein diameter (PVD) as a significant predictor of HRG, aligning with findings from

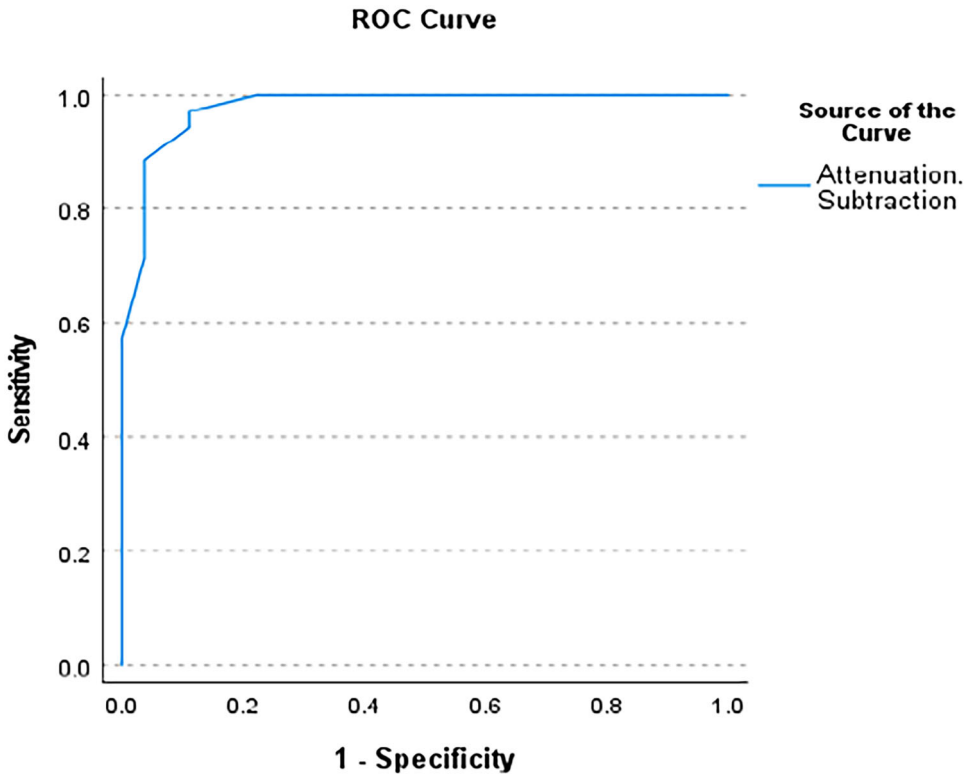

FIGURE 2 | ROC curve of liver attenuation subtraction (main sample). The liver attenuation subtraction has a cutoff point of 14.5, demonstrating a sensitivity of 97.1% and a specificity of 88.9%. Its positive predictive value is 91.9%, and its negative predictive value is 96%. The area under the curve is recorded at 0.979 with a 95% confidence interval of (0.949–1). A lower liver attenuation subtraction correlates with a higher risk of bleeding in esophageal varices, indicating an inverse relationship between the two.

TABLE 3 | External validation report.

Variables	Main samples	External validation samples	*p* value
Gender	Male: 39 (62.9%) Female: 23 (37.1%)	Male: 16 (55.2%) Female: 13 (44.8%)	0.3
Age	50.2 ± 11.5	48.1 ± 11.9	0.4
HRG/NHRG	HRG: 35 (56.4%) NHRG: 27 (43.6%)	HRG: 13 (44.8%) NHRG: 16 (55.2%)	0.2
Liver attenuation subtraction	14.2 ± 6.9	13.1 ± 7.1	0.5
ROC (AUC)	0.979	0.986	0.8

Abbreviation: AUC, area under the curve; HRG, high-risk variceal group; NHRG, non-high-risk variceal group; ROC, receiver operating characteristic curve.

Zardi et al. [33]. However, research conducted by Sarangapani et al., Sudha Rani et al., and Farooqi et al. suggested that PVD could be a relevant parameter for predicting large, high-risk varices [30, 34, 35].

Finally, splenic vein diameter (SVD) was also investigated as a potential predictor, but was not found to be a reliable differentiator of HRG in our study. This finding contrasts with results reported by Cherian et al. and Jha et al., who identified a significant correlation between SVD and HRG [27, 36].

Overall, our study highlights liver attenuation subtraction, DV-CT, and Child-Pugh score as the most significant differentiators of HRG. In contrast, factors such as MELD score, SV, PVD, and SVD were unreliable predictors. These findings emphasize the potential of noninvasive CT-based markers in the risk stratification of EVs, offering an alternative screening method that may help reduce the need for frequent endoscopic examinations.

4.1 | Limitations

This study has several limitations. First, a fixed contrast injection volume of 100 cc was administered to all patients, regardless of their weight, which may have introduced variability in contrast enhancement. Second, in the CT scan protocol, the portal phase may not have been captured precisely in some cases, with early portal venous (late arterial) imaging being used instead. Third, there is variability in the timing of the equilibrium phase across different medical

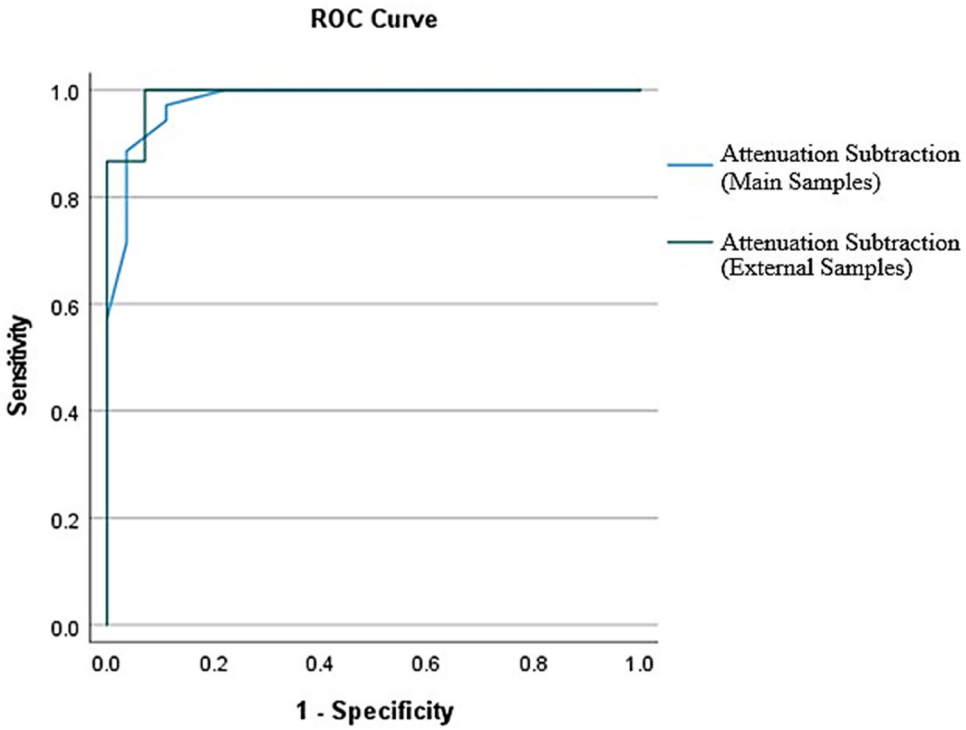

FIGURE 3 | Main and external samples ROC curves together.

centers, and minor differences in Hounsfield unit (HU) measurements exist between CT scanners from various manufacturers. Lastly, although the sample size was determined using a standard formula based on a reference study, it remains relatively small, which may limit the generalizability of the findings.

4.2 | Strengths

A key strength of this study is that it was conducted at Imam Khomeini Hospital complex in Tehran, a leading referral center for cirrhosis in Iran. This setting provided a representative sample of the Iranian population, enhancing the study's clinical relevance. Furthermore, external validation in another university-affiliated hospital demonstrated that "liver attenuation subtraction" cutoff value is generalizable to other statistical populations Additionally, the study focused on identifying a noninvasive, safe, and cost-effective predictor for HRG, which could be seamlessly integrated into routine follow-up without imposing additional costs or time burdens on cirrhotic patients.

5 | Conclusion

The findings of this study highlight liver attenuation subtraction, Child-Pugh score, and the presence of EVs on CT scans as significant differentiators between HRG and NHRG. In contrast, other variables, including SV, SVD, PVD, superior mesenteric vein diameter (SMVD), splenorenal collaterals (SRC), and MELD score, were not reliable predictors of HRG. These results suggest that CT-based attenuation subtraction could serve as a valuable noninvasive screening tool for the early identification of HRG in cirrhotic patients.

Author Contributions

Mohammad Mersad Mansouri Tehrani: supervision, data curation, writing – review and editing. **Nasser Bahari:** formal analysis and methodology. **Kian Goudarzi:** writing – original draft. **Faeze Salahshour:** conceptualization and methodology. **Babak Shekarchi:** conceptualization, supervision, resources and methodology. **Mohammad Masih Mansouri-Tehrani:** writing – original draft. **Majid Nouri:** resources.

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Ethics Statement

Human Ethical Approval ID for this study is IR.AJAUMS. REC.1402.190, from AJA (Islamic Republic of Iran Army (Artesh)) University of Medical Sciences ethical committee.

Consent

Informed consent of the patient's participation was obtained.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data and materials that support the findings of this study are available from the corresponding author, upon reasonable request.

Transparency Statement

The lead author Babak Shekarchi affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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