Egyptian Journal of Radiology and Nuclear Medicine

RESEARCH

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The role of shear wave elastography in differentiation between benign and malignant portal vein thrombosis in hepatocellular carcinoma

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Abstract

Background: Hepatocellular carcinomas (HCC) most commonly complicate liver cirrhosis and it may coexist with malignant portal vein invasion (PVI) that minimizes its possible treatment opportunities and negatively affects its prognosis. However, liver cirrhosis may also be associated with non-tumoral portal vein thrombosis (PVT) particularly in decompensated cirrhosis. Thus, discrimination between tumoral and non-tumoral PVT most preferably by non-invasive imaging techniques is mandatory before treatment decision. Based on the concept of changing tissue elasticity according to tissue pathological changes, Shear wave elastography (SWE) could quantitatively assess tissue stiffness in malignant PVI. We aimed in this work to evaluate the performance of SWE as a novel fast non-invasive diagnostic modality for malignant PVI in cirrhotic patients with HCC.

Results: Seventy-eight HCC patients with PVT included in this prospective cross-sectional study, tumoral and non-tumoral PVT were differentiated using triphasic CT and/or dynamic MRI, then SWE was blindly and independently done for all included patients. non-tumoral PVT was present in 21.8% of our HCC patients mostly in decompensated cirrhosis. All of our evaluated predictor factors were evaluated by univariate logistic regression analysis to identify the significant factors in prediction of malignant PVI (SWE, AFP, HCC size, HCC multi-focality, and PVD). By using the multivariate logistic regression we identified that the most independent significant factors were SWE and PVD (sig.: 0.012 and 0.045 respectively). SWE was evaluated versus the criteria of PVT and we found that malignant PVI has significant higher SWE values than benign non-tumoral PVT (sig: 0.012). Two cutoff values were calculated for SWE using ROC curve; the 1st cutoff point was selected to rule in malignant PVI for values $\geq$ 13 kps, while the 2nd cutoff point was selected to rule out malignant PVI for values $\leq$ 9 kps with a significant discriminatory performance (AUC: 0.984; sig: 0.000).

Conclusions: SWE could be used as a novel fast and non-invasive indicator of malignant portal vein invasion in cirrhotic patients with HCC especially for values $\geq$ 13 kps and particularly if coexists with larger values of PVD and AFP.

Keywords: Shear wave elastography, Portal vein thrombosis, Hepatocellular carcinoma, Diagnosis

Background

Hepatocellular carcinoma (HCC) is considered as the most common primary liver malignancy that arises in the background of liver cirrhosis. It is well known that the advanced stages of HCC have great implications on both

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patients' morbidity and mortality. Macrovascular tumor invasion is often associated with the advanced stages of HCC. It usually has very poor prognosis, and at the same time, it significantly minimizes the possible therapeutic options for HCC patients especially the curative locoregional modalities [1–4].

Patients with liver cirrhosis especially those with Child–Pugh grade B or C also have a tendency to develop non-malignant portal vein thrombosis (PVT) in up to 16% of cirrhotic patients, which could be treatable, therefore, the accurate differentiation between tumoral portal vein invasion and non-tumoral PVT is mandatory at the time of HCC diagnosis and staging [5, 6].

The reference or the gold standard for the diagnosis of portal vein tumor invasion is histopathology; however, it is often not feasible or accepted in routine clinical practice due to its dangerous complications or sampling errors [7]. Consequently, the noninvasive characterization of PVT at the time of HCC diagnosis is considered as a hopeful surrogate diagnostic options using different contrast enhanced imaging modalities as triphasic computed tomography (CT) or dynamic magnetic resonance imaging (MRI) [8]. Elastography is considered as a new diagnostic modality that assesses the soft tissue's properties to resist a force-induced deformation due to its intrinsic stiffness. Pathological tissues tend to be less elastic than the surrounding healthy tissue. Shear wave elastography (SWE) is one of the most advanced elastography techniques; it depends on measuring shear waves propagation, and allows evaluating tissue stiffness in a quantitative way relying on the measurement of the velocity of shear waves [9, 10]. In this study, we tried to differentiate between benign and malignant portal vein thrombosis in cirrhotic patients complicated with hepatocellular carcinoma using shear wave elastography; as a new non-invasive technique.

Methods

Study design and setting

This was a diagnostic accuracy cross sectional study that was conducted in accordance to Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines [11]. It was conducted at hepatology unit of internal medicine department and hepatoma unit of diagnostic and interventional radiology department at our university hospitals. All our participants were consecutively selected in the period from October, 2019 to October, 2021.

Participants and data collection

Eighty nine cirrhotic patients proved to be complicated with HCC and associated with PVT (either benign or malignant), were consecutively referred to our hepatology unit for clinical assessment. All patients were evaluated for the study eligibility criteria before enrollment that were fulfilled in 78 cirrhotic patients after exclusion of 11 patients; 4 cirrhotic patients were excluded due to presence of tense ascites, 3 patients were excluded due to morbid obesity, 3 patients were excluded due to concomitant hepatic encephalopathy, and one uncooperative patient. All included patients were firstly evaluated accurately using history, clinical evaluation, demographic criteria (age and gender), laboratory parameters [alanine aminotransferase (ALT), aspartate aminotranferase (AST), serum albumin, serum bilirubin, international normalized ratio (INR), Child–Pugh grade, hemoglobin, white blood cells, platelets, serum creatinine and alpha fetoprotein (AFP)] and the imaging criteria [HCC focality, HCC size, portal vein diameter (PVD), and nature of PVT]. Then, all participants were blindly referred to diagnostic radiology department for assessment of PVT using P-SWE by a highly experienced operator. All these are illustrated in the participant's flowchart (Fig. 1).

Assessment of malignant criteria of portal vein thrombosis

The malignant criteria of HCC and PVT were assessed using triphasic computed tomography (used in 68 patients) or dynamic magnetic resonance imaging (used only in 10 patients). The malignant PVT was proved if it revealed arterial hyper-enhancement with delayed and venous washout [1, 6, 7].

Assessment of shear wave elastography of portal vein thrombosis

Assessment of SWE of portal vein thrombi were performed using iU22 US system (iU22, Philips Medical systems, Bothell, WA, USA), which can assess stiffness by p-SWE. It was done using a convex transducer C5-1 (1–5 MHz; C5-1, Philips Healthcare) through intercostal route in a supine position with the corresponding arm maximally abducted to widen intercostal space for better examination. Some patients underwent p-SWE in left or right lateral position for better access to liver or portal vein with holding their breath during time of examination for about 5 s. The maximum penetration depth of ElastPQ was 8 cm and the ROI was presented as a rectangular area measured 5×15 mm. The measures were taken from the main trunk, right and left branches of thrombosed portal veins. We considered the value of an average of 5–8 valid successful measurements. The velocity of the propagated shear wave in the ROI was automatically translated to stiffness in kilopascals (kPa) for PVT. As shown in Figs. 2 and 3.

Statistical analysis methods

We used IBM SPSS; version 23 statistic software (IBM, NY, USA) for description and statistical analysis of our

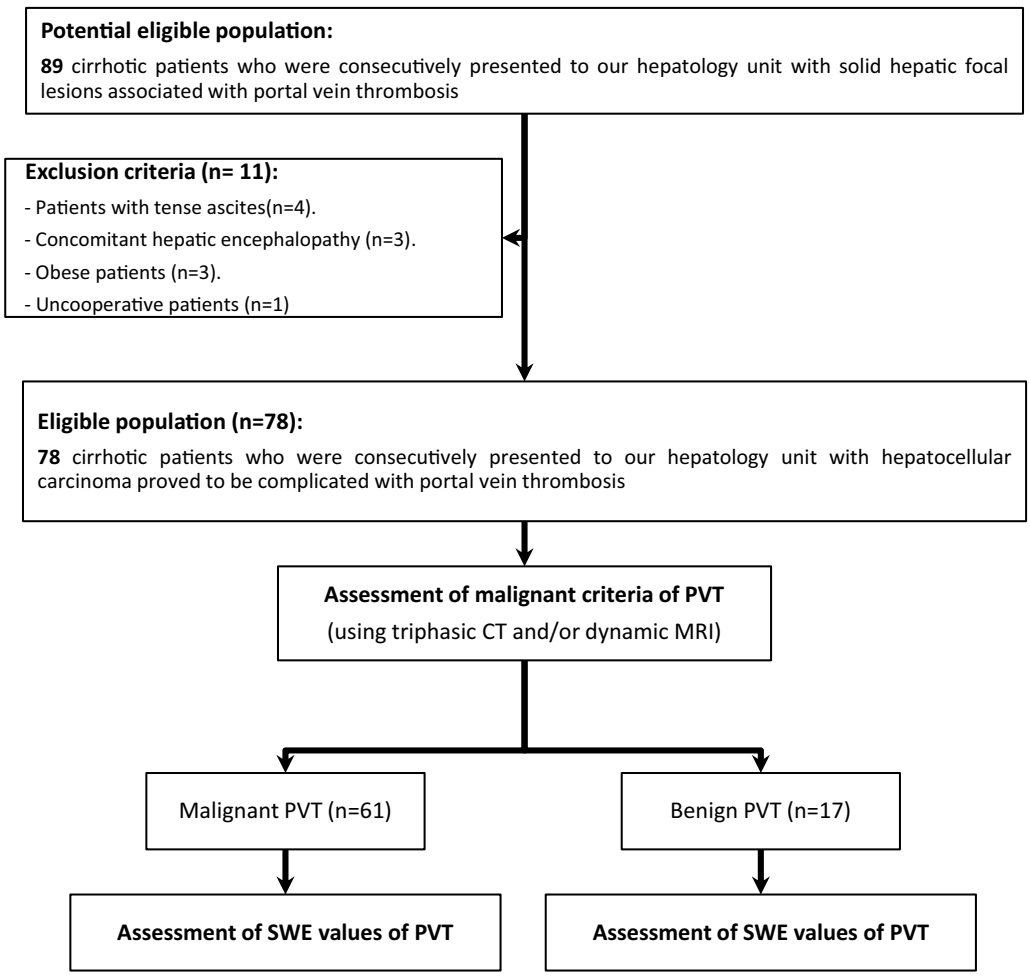

Fig. 1 Study participant's flowchart

collected data. The median with (IQR) was calculated for all our quantitative data (abnormally distributed), all our qualitative data were tabulated as frequency and relative frequency. We used Mann–Whitney U test for two group comparisons of our quantitative data. Chi-Square test was performed to conduct group comparisons for categorical data. The logistic regression analysis was performed for our candidate predictors; participants' demographic criteria (age and sex), laboratory criteria (AST, ALT, Child–Pugh scores, platelets count, hemoglobin levels, white blood cells, serum creatinine, and AFP), imaging criteria related to HCC (HCC size and focality) and PVT-related criteria (PVD and SWE). Univariate logistic regression analysis was done first for each predictor to identify the significant predictors, and then the most independent significant predictors were identified using the multivariable logistic regression analysis by entering all the previously identified significant predictors simultaneously with a stepwise backward strategy. Receiver operating characteristics (ROC) were calculated for SWE values of PVT, and area under the ROC curve (AUC) was computed. Two cutoff values of SWE were calculated; the 1st cutoff point was selected to rule in malignant PVT with the highest specificity and highest LR+, the 2nd cutoff point was selected to rule out the malignant PVT with the highest sensitivity and lowest LR-. P-values less than 0.05 were considered statistically significant (Fig. 4).

Results

Table 1 of our results illustrates the demographic criteria (age and gender) of our study participants, their laboratory parameters (ALT, AST, serum albumin, serum bilirubin, INR, Child–Pugh grade, hemoglobin, white blood cells, platelets, serum creatinine and AFP) and the imaging criteria (HCC focality, HCC size, PVD as well as PVT nature). The malignant portal vein invasion (PVI) was present in most of our participants (78.2%), while 21.8% of our participants were complicated with non-tumoral

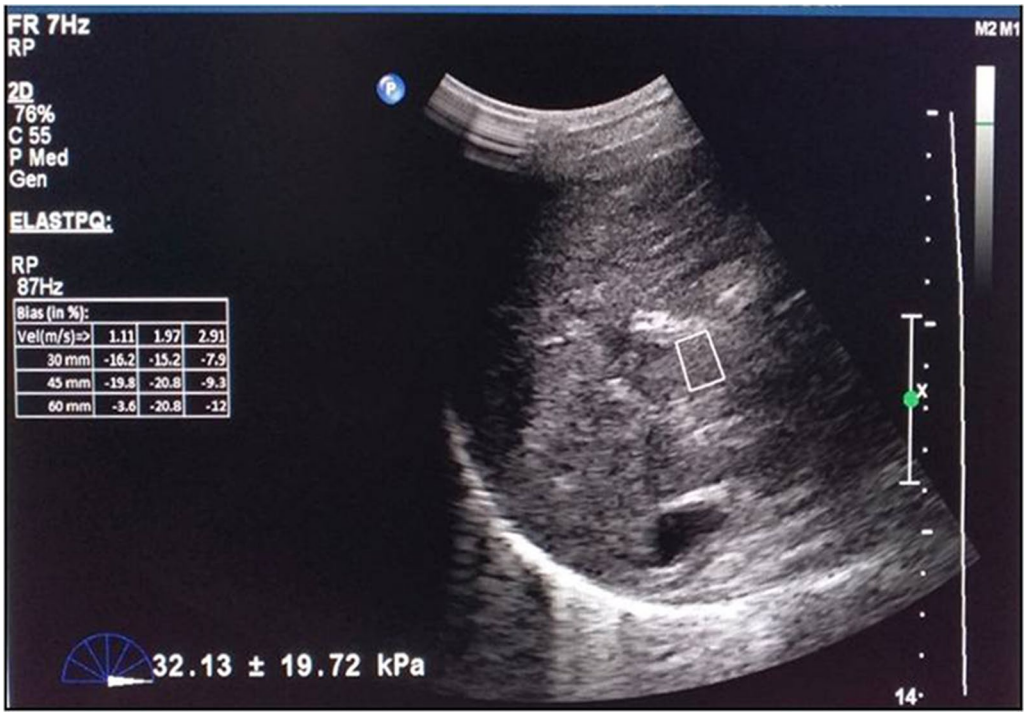

Fig. 2 p-SWE of the liver with ROI on a malignant portal vein thrombus (mean ± SD = 32.13 ± 19.72 kPa)

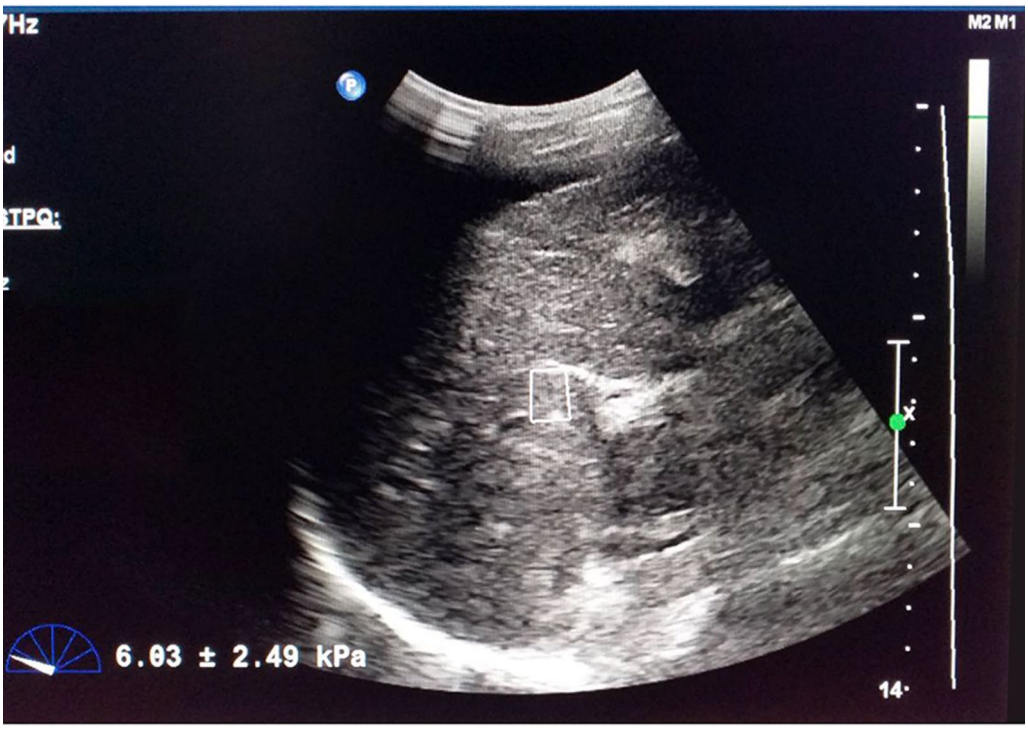

Fig. 3 p-SWE of the liver with ROI on a benign portal vein thrombus (mean ± SD = 6.03 ± 2.49 kPa)

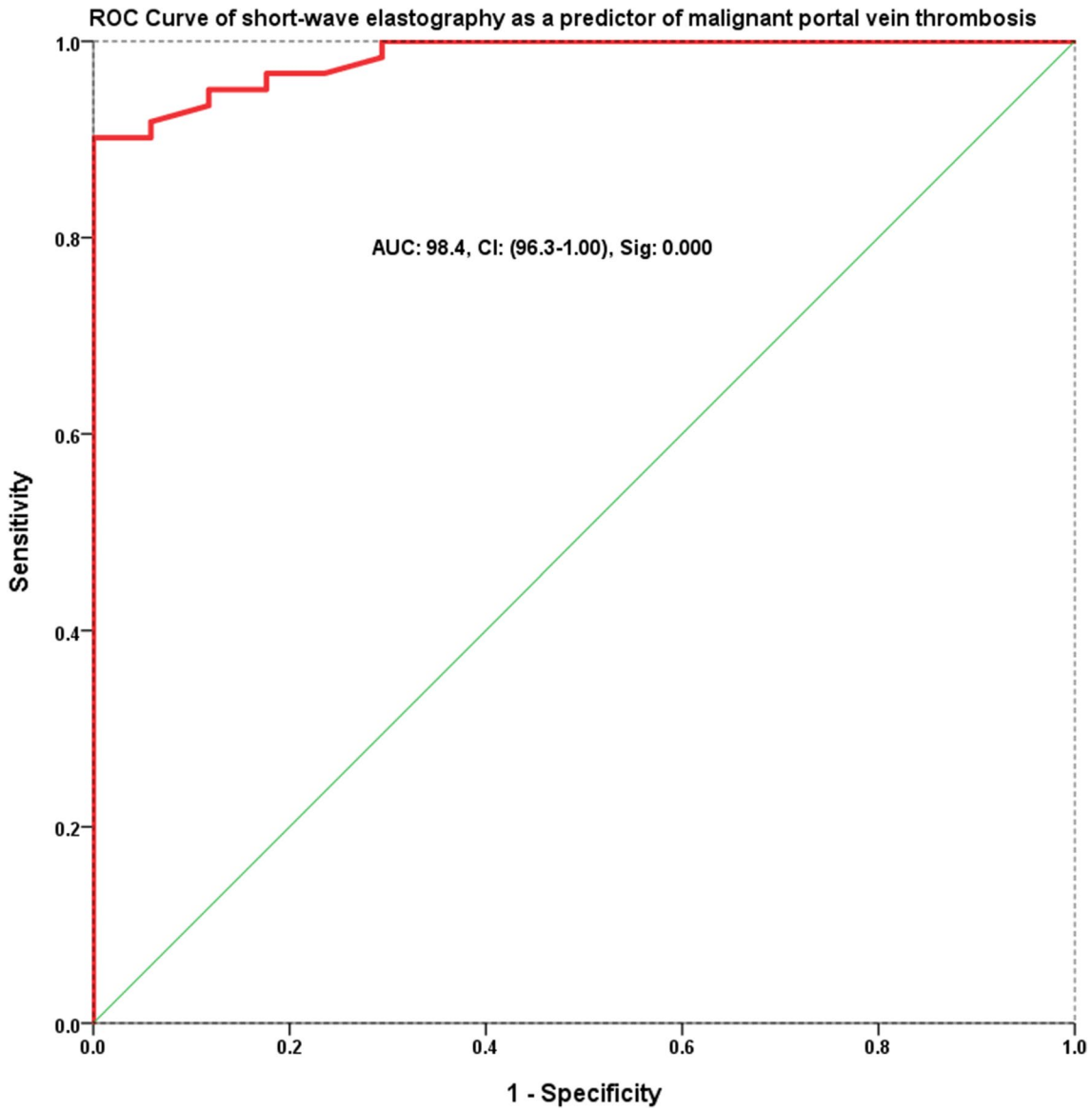

Fig. 4 ROC curve of short wave elastography as a predictor of malignant portal vein thrombosis

PVT. There were significant differences between malignant portal vein invasion and benign non-tumoral PVT as regards SWE, AFP, HCC size, HCC focality, and PVD as a surrogate indicator for underlying malignant expansion. All other studied parameters showed non-significant difference between the malignant and benign non-tumoral nature of PVT.

All our evaluated predictor factors were evaluated by logistic regression analysis at first separately, to identify the significant factors in prediction of malignant PVI that were SWE, AFP, HCC size, HCC multi-focality, and PVD. Then, all these significant factors were analyzed simultaneously using multivariate logistic regression that identified the most independent significant factors in our sample that were SWE and PVD (sig.: 0.012 and 0.045 respectively) as illustrated in Table 2 of our results.

The Receiver Operating Characteristics (ROC) was calculated for SWE values and their area under the ROC curve (AUC) was computed (AUC: 0.984; sig.: 0.000). Two cutoff points were calculated for SWE values; the 1st cutoff value was selected to rule in malignant portal vein invasion ($\geq$ 13 kPa) while the 2nd cutoff value was selected to rule out malignant portal vein invasion ($\leq$ 9 kPa), the sensitivity, specificity and likelihood ratios for both cutoff

Table 1 The Main evaluated participants' demographic, laboratory and imaging criteria

Participants' criteria		All participants $n=78$ (100%)		Malignant PVT $n=61$ (78.2%)		Benign PVT $n=17$ (21.8%)		Sig
Demographic criteria								
Age (ys)	Median (IQR)	60	(12)	60	(12)	62	(16)	0.716
Sex								
Male	Count (%)	45	(57.7%)	34	(55.7%)	11	(64.7%)	0.508
Female	Count (%)	33	(42.3%)	27	(44.3%)	6	(35.3%)	
Liver functions								
ALT (IU/L)	Median (IQR)	41	(17)	41	(17)	40	(12)	0.611
AST (IU/L)	Median (IQR)	46	(16)	48	(14)	43	(13)	0.085
Serum albumin (gm/dl)	Median (IQR)	2.9	(0.6)	2.9	(0.7)	2.7	(0.5)	0.468
Serum bilirubin (mg/dl)	Median (IQR)	1.9	(0.5)	1.8	(0.6)	1.9	(0.6)	0.258
INR	Median (IQR)	1.8	(0.2)	1.8	(0.2)	1.9	(0.4)	0.201
Child–Pugh grade								
A	Count (%)	8	(10.3%)	7	(11.5%)	1	(5.9%)	0.128
B	Count (%)	52	(66.7%)	43	(70.5%)	9	(52.9%)	
C	Count (%)	18	(23.1%)	11	(18%)	7	(41.2%)	
Other laboratory parameters								
Hemoglobin (g/dl)	Median (IQR)	11.7	(1.6)	11.7	(1.7)	11.6	(1.4)	0.904
White blood cells ($\times 10^3/mm^3$)	Median (IQR)	6.4	(3.7)	5.9	(3.2)	7.9	(4.6)	0.145
Platelets ($\times 10^3/mm^3$)	Median (IQR)	123	(35)	123	(33)	115	(59)	0.712
Serum creatinine (mg/dl)	Median (IQR)	1.0	(0.2)	1.1	(0.1)	1	(0.2)	0.236
Criteria related to HCC								
HCC focality								
Multifocal	Count (%)	45	(57.7%)	39	(63.9%)	6	(35.3%)	0.035
Unifocal	Count (%)	33	(42.3%)	22	(36.1%)	11	(64.7%)	
HCC size (cm)	Median (IQR)	5.4	(2.1)	5.6	(2.4)	4.5	(1.3)	0.000
AFP (ngm/ml)	Median (IQR)	215	(521)	323	(630)	21	(60)	0.000
Criteria related PVT								
PVD (mm)	Median (IQR)	18	(5)	19	(5)	14	(3)	0.000
SWE (kps)	Median (IQR)	20.8	(13.7)	22.7	(9.1)	8.2	(3.5)	0.000

ALT Alanin aminotransferase, *AST* Aspartate aminotransferase, *INR* International normalized ratio, *PVT* Portal vein thrombosis, *PVD* Portal vein diameter, *KPa* Kilopascal, *SWE* Shear wave elastography

values were calculated as identified in Table 3 and Fig. 2 of our results.

Discussion

Liver cirrhosis may be complicated by HCC that may coexist with malignant PVI passively affecting patients' morbidity and prognosis [12, 13]. However, liver cirrhosis especially advanced stages may be associated with non-tumoral PVT [5]. For this reason, it is critical to differentiate between the tumoral and non-tumoral PVT at the time of HCC diagnosis and staging as it affects the clinical decision of selecting the most appropriate treatment option [14]. In our study, we tried to evaluate the diagnostic performance of SWE as a novel, non-invasive, easy and rapid modality to differentiate between both tumoral PVI and non-tumoral PVT in cirrhotic patients with HCC.

Our results identified that about 21.8% of our HCC patients complicated with non-tumoral PVT. Most of those patients were either Child–Pugh grade B or C. Previous reports estimated the prevalence of PVT to be as low as 1% in compensated cirrhosis. This prevalence may be increased to be as high as 8.1–15.8% in decompensated cirrhosis waiting liver transplantation [5, 15–17]. This finding indicates that not all PVT associated with HCC are tumoral PVI, for this reason, the accurate differentiation between malignant and benign PVT has a critical importance before HCC management especially for curative modalities.

In our study, we identified that the malignant PVI was significantly related to increased tumor burden in the form of larger HCC lesions, HCC multifocality and higher values of AFP. These results are confirmed by shabana et al. (2018) who concluded that macrovascular

Table 2 The logistic regression analysis for the evaluated predictor factors of malignant portal vein invasion

Participants' criteria	*B*	Wald	Sig	EXP(*B*)	95% CI
Univariate regression analysis					
Age (ys)	0.027	0.678	0.410	1.027	(0.963–1.096)
Sex (male)	−0.376	0.435	0.509	0.687	(0.225–2.096)
ALT (IU/L)	0.014	0.361	0.548	1.014	(0.969–1.060)
AST (IU/L)	0.039	2.371	0.124	1.040	(0.989–1.094)
Child–Pugh score	−0.244	1.280	0.258	0.783	(0.513–1.196)
Hemoglobin (g/dl)	0.073	0.116	0.733	1.076	(0.707–1.638)
White blood cells ($\times 10^3/mm^3$)	−0.187	2.134	0.144	0.829	(0.645–1.066)
Platelets ($\times 10^3/mm^3$)	−−0.008	0.757	0.384	0.992	(0.974–1.010)
Serum creatinine (mg/dl)	1.810	1.029	0.310	6.109	(0.185–2.015)
PVD (mm)	0.724	12.261	0.000	2.063	(1.397–3.045)
SWE (kpa)	0.802	9.740	0.002	2.230	(1.348–3.689)
HCC multi-focality	1.179	4.227	0.040	3.250	(1.057–9.997)
HCC size (cm)	0.962	9.362	0.002	2.616	(1.413–4.845)
AFP (ngm/ml)	0.006	6.529	0.011	1.006	(1.001–1.010)
Multivariate regression analysis					
SWE (kps)	0.817	6.334	0.012	2.264	(1.198–4.279)
PVD (mm)	0.926	4.003	0.045	2.525	(1.019–6.256)
Constant	−24.559				

ALT Alanin aminotransferase, *AST* Aspartate aminotransferase, *INR* International normalized ratio, *PVT* Portal vein thrombosis, *PVD* Portal vein diameter, *KPa* Kilopascal, *SWE* Shear wave elastography

Table 3 Receiver operating characteristics of short wave elastography in prediction of malignant portal vein invasion

Predictor	Rule	Cutoff	Sensitivity (%)	Specificity (%)	LR+	LR−	AUC	(95%CI)	Sig
SWE (kps)	Rule in	≥ 13	90	94	15.33	0.10	0.984	(0.963–1.000)	0.000
	Rule out	≤ 9	98.8	71	3.34	0.02			

PVT Portal vein thrombosis, *SWE* Shear wave elastography, *LR* Likelihood ratio, *AUC* Area under the curve, *CI* Confidence interval

malignant invasion of HCC significantly associated with severity of liver impairment and tumor burden [18]. Similarly our results showed that PVD significantly related to malignant PVI, we could explain this result by the progressive malignant expansion of HCC that leads to progressive increase of PVD after malignant PVI.

Ultrasound-based transient elastography is known to be a simple and reliable non-invasive tool that used in quantitative measurement of liver stiffness and stratification of different stages of liver fibrosis, although it doesn't provide two-dimensional images and it difficult to be used in ascites [19, 20]. Interestingly, SWE provide a more accurate quantification and scoring of liver stiffness using normal B-mode ultrasound real time and at the same time it could facilitate the prediction of HCC in liver cirrhosis [21, 22]. As the pathological tissues tend to be less elastic than the surrounding healthy tissue, the quantification of tissue elasticity could allow a proper diagnosis of intrinsic tissue properties [9, 10].

Based on this concept in combined with the capability of B-mode ultrasound real-time-based elastography quantification, SWE may be a valuable tool to discriminate between malignant and non malignant tissue within the portal vein specifically in decompensated cirrhosis with HCC. In our results, SWE was evaluated versus the criteria of PVT and we found that malignant PVI have significant higher SWE values than benign non-tumoral PVT (sig: 0.012). Upto our knowledge, this is the first time using SWE in differentiating malignant PVI from non-tumoral portal invasion.

Two cutoff points were calculated for SWE values using ROC curve; the 1st cutoff value was selected to rule in malignant portal vein invasion for values equal or more than 13 kPa, while the 2nd cutoff value was selected to rule out malignant PVI for values equal or less than 9 kPa with a significant discriminatory performance (AUC: 0.984; sig: 0.000). We could explain this result as the malignant tissue may be harder and less elastic than

the non-tumoral thrombus. This concept was used as our study rationale to use SWE as a novel non-invasive modality to diagnose malignant PVI and rule out the non-tumoral PVT even in critically decompensated cirrhotic patients with HCC.

There are some potential limitations in our study, firstly, the single operator that may affect the reliability of our results; however the high experience of the operator in this field may mitigate this limitation. Secondly, the study was a uni-centric that may lead to selection bias. Third, SWE technique is not widely available except in highly experienced centers.

Conclusions

SWE may be used as a novel fast and non-invasive indicator of malignant portal vein invasion in cirrhotic patients with HCC especially for values ≥ 13 kPa and particularly if coexists with larger values of portal vein diameter and AFP.

Abbreviations

AFP: Alpha fetoprotein; ALT: Aspartate aminotransferase; AST: Alanine aminotransferase; AUC: Area under the curve; CT: Computed tomography; HCC: Hepatocellular carcinoma; INR: International normalized ratio; kPa: Kilopascal; LR: Likelihood ratio; OR: Odds ratio; PLT: Platelets; PVD: Portal vein diameter; PVI: Portal vein invasion; PVT: Portal vein thrombosis; Sig: Significance; STARD: Standards for Reporting of Diagnostic Accuracy Studies; SWE: Shear wave elastography.

Acknowledgements

We would like to thank all staff members in hepatology unit of internal medicine department and hepatoma unit of diagnostic and interventional radiology department at our university hospitals who assisted us in this study.

Author contributions

All authors read and approved the final manuscript, according to the following respective roles of each author: AFA shared in study conception and design, data collection, and data interpretation. AAE shared in study conception and design, data collection, data analysis, data interpretation and as a corresponding author. HMO shared in study conception and design, data collection and data interpretation. MHA and MTG shared in study conception and design, data collection and data interpretation and final revision of the manuscript.

Funding

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the ethics committee of our Faculty of Medicine (33410/10/19). All patients provided written informed consent. The results of the research were used only in scientific purposes and not in any other aims.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 28 February 2022 Accepted: 11 August 2022
Published online: 23 August 2022

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