Research article

MRI in differentiating malignant versus benign portal vein thrombosis in patients with hepatocellular carcinoma: Value of post contrast imaging with subtraction

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ABSTRACT

Purpose: To evaluate MR imaging parameters including quantitative multiphasic post-contrast enhancement with subtraction and qualitative diffusion weighted imaging (DWI) in differentiating benign versus malignant portal venous thrombosis (PVT) in patients with hepatocellular carcinoma (HCC).
Method: Radiology reports over a 6-year period ending February 2016 were searched for key words indicating presence of both HCC and PVT on abdominal MRI. 39 patients were identified with PVT characterized as benign or malignant based on pathologic data or serial imaging growth criteria. Image review was performed by two subspecialized radiologists blinded to the diagnosis and medical chart. Signal intensity for regions of interest were recorded within the portal vein thrombus as well as the portal vein on pre-contrast and dynamic post-contrast phases without and with subtraction. Qualitative parameters for DWI and presence of PV expansion were also evaluated.
Results: Percent enhancement generated high area under the curve (AUC) for both readers on all non-subtraction phases: arterial (0.95/0.98), portal venous (0.97/0.97) and delayed phase (0.96/0.99) and subtraction phases: arterial (0.91/0.96), portal venous (0.94/0.99) and delayed phases (0.96/0.97). Statistically significant differences were observed between benign and malignant PVT for both readers for PV expansion (p = < 0.001/0.006). No qualitative DWI parameter reached statistical significance for both readers.
Conclusions: Post-contrast and subtraction MRI can reliably distinguish malignant from benign PVT in patients with HCC using subtracted or non-subtracted images and at arterial, portal venous, or delayed phase timing.

1. Introduction

Malignant portal vein thrombosis (PVT) is a well-known frequent complication of hepatocellular carcinoma (HCC) with reported incidences of 36–44% [1–3]. Benign PVT also frequently occurs in this population, with estimated prevalence in cirrhotic patients of 0.6–26% [4–6]. Furthermore benign PVT can coexist with malignant PVT [7–9]. Malignant PVT is an absolute contraindication to liver transplant, and its presence drastically alters treatment options and worsens prognosis

[9,10]. On the other hand, benign PVT does not have the same high levels of morbidity and can potentially be treated with anticoagulation. The disparate pathophysiology of benign and malignant PVT can aid in the differentiation. Benign PVT is usually secondary to sluggish flow in patients with cirrhosis and HCC which leads to the development of thrombosis. Whereas in malignant PVT there is invasion of a branch of portal vein with tumor and the associated tumor neovascularity that potentially demonstrates contrast enhancement on MRI.

While PVT detection and characterization is critical to staging HCC,

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obtaining the gold standard of histopathologic diagnosis is rarely performed in clinical practice due largely to the risks of sampling the portal vein and the potential for false diagnosis in settings with coexistent benign and malignant thrombus [2,11]. An accurate noninvasive imaging based diagnosis is therefore highly desirable. Multiphasic MRI is frequently performed for diagnosis and follow-up of patients with HCC, and it therefore can potentially be used to detect and characterize PVT. Recent studies have shown usefulness of MRI in distinguishing benign versus malignant thrombosis [2,12,13]. However, the number of studies evaluating MRI for this determination remains limited [14], and prior studies have shown conflicting results on the value of some findings such as signal on diffusion-weighted imaging (DWI) and vessel expansion [2,12,13]. Further, while there is evidence that malignant PVT demonstrates increased enhancement [15], the threshold for determining enhancement and the effect of post-contrast phase timing on PVT enhancement for differentiating bland from malignant thrombus has not been rigorously examined. Prior studies have used qualitative factors [2] or arbitrary cutoffs without prior supporting evidence [12]. Further, subtraction images have not been assessed, and the method of determining enhancement has not been standardized in prior research reports or in clinical practice. The primary aim of this study is to determine the utility of multiphasic contrast enhanced MRI, including postcontrast subtraction images at various intensities and timepoints, in differentiating benign versus malignant portal vein thrombosis.

2. Material and methods

2.1. Study population

Institutional review board permission was obtained for the retrospective assessment of imaging and clinical data with a waiver of informed consent. All MRI reports at a single institution over a 6-year period ending February 2016 were searched for the current procedure terminology codes "primary malignant neoplasm of liver" and "portal venous thrombosis", yielding 1441 and 396 reports, respectively. 58 subjects were identified as having both CPT codes. Additional chart and imaging review of these patients was conducted to determine the final study population. Patients were included in the study only if they had a hepatocellular carcinoma diagnosis, cirrhosis and no diagnosis of other malignancy such as cholangiocarcinoma. All patients were required to have identifiable portal venous thrombosis on an abdominal MRI and adequate follow-up imaging or histopathological proof to confirm thrombus as benign or malignant. 19 subjects were excluded due to inadequate follow-up imaging or lack of any histologic reports to characterize the portal venous thrombus as benign or malignant. Ultimately 39 patients comprised the study population.

2.2. Reference standard

Thrombus was classified as benign or malignant according to prior published criteria [2]. Chart review was conducted to search for histologic diagnosis on biopsy or resection, yielding 2 patients with bland thrombus and 1 with malignant thrombus. The remaining diagnoses were confirmed using strict imaging follow-up criteria. Stability for at least 12 months was classified as benign thrombus. Malignant thrombus was classified in cases where there was substantial increase in thrombus size within 3 months despite anticoagulation therapy.

2.3. MRI technique

All patients underwent contrast enhanced MR imaging using a 1.5-T (Symphony or Avanto, Siemens Healthcare, Erlangen, Germany) or 3-T MRI (Trio, Siemens Healthcare, Erlangen, Germany) with a phased array body coil. The following imaging sequences were included in all protocols: breath-hold T1-weighted dual-echo (in-phase and opposed-phase) sequence, free-breathing fat-saturated T2-weighted turbo spin-

echo or BLADE sequence, T2-weighted HASTE coronal sequence, diffusion-weighted imaging (DWI), and transverse T1-weighted fat-suppressed 3D volumetric interpolated breath-hold sequences obtained before and after intravenous contrast injection. A dose of 0.1 ml/kg of IV gadobutrol (Gadavist, Bayer Healthcare Pharmaceuticals, Whippany, NJ) or gadoxetic acid (Eovist/Primovist; Bayer Healthcare, Pharmaceuticals, Whippany, NJ) was administered at a rate of 2 mL/s, using a power injector (Spectris Solaris, Medrad). There were 32 studies with gadobutrol and 7 studies with gadoxetic acid. Bolus tracking was performed to obtain axial post-contrast T1 images at late arterial phase, portal venous phase, and delayed (3 min) phase with coronal images obtained at 4 min after administration of contrast. Using scanner software (Siemens Healthcare, Erlangen, Germany), subtraction images were generated by subtracting the axial T1 post contrast images from pre-contrast axial T1 images. For DWI, b-values of 50 and 600 s/mm2 were used to calculate the ADC map monoexponentially. DWI images were not available in 2 patients.

2.4. Image evaluations

Two subspecialized abdominal radiologists with 8 and 11 years of experience interpreting abdominal MRI, blinded to subject clinical data and diagnosis, reviewed the MR images independently. The reviewers recorded the following quantitative parameters maximum diameter of PVT and presence of vessel expansion due to thrombus using previously defined criteria [12]. In addition, the signal intensities of the PVTs were recorded on T1 axial non-contrast, arterial, portal venous, and delayed phase images in non-subtracted and subtracted series by placing regions of interest (ROIs) (Figs. 1 and 2). Readers were instructed to carefully generate ROIs as large as possible while reviewing the slice above and below to ensure the target thrombus remains within the chosen ROI. The percent enhancement on each nonsubtracted imaging series was calculated using the formula: (contrast enhanced ROI thrombus – precontrast ROI thrombus)/(precontrast ROI thrombus) * 100. For the subtraction series, the percent enhancement was calculated using the formula (subtracted ROI thrombus / precontrast ROI thrombus) * 100. Subjective assessment was made on b 600 DWI and ADC maps, and the intensity of thrombus was determined as isointense, hypointense, or hyperintense relative to the liver for both sequences.

2.5. Statistical analysis

Results are expressed as number (percentage) or, when appropriate, as mean ± standard deviation. Comparisons between the two treatment groups were performed using the independent t-test and Fisher's Exact test as appropriate.

Receiver operating characteristic (ROC) curve and area-under-the-curve (AUC) analysis was used to assess the usefulness of conventional MRI findings and subtraction imaging measurements in detecting bland versus malignant PVT and were graphed and calculated using the "pROC" package in R (V 1.12.1). 95% confidence intervals (CI) for the AUCs were calculated using the "bootstrap" method with 2000 replications. Optimal cut-points were determined from "OptimalCutpoints" package in R (V 1.4) using the method of maximizing the product of the sensitivity and specificity.

The inter-rater reliability, or more specifically intra-class correlation (ICC) and their 95% CI were calculated using the "irr" package in R (V 0.84) based on a single-rating, absolute-agreement, 2-way random effects model. Inter-observer agreement on DWI and ADC of thrombus relative to tumor and liver were calculated using weighted Cohen's Kappa and 95% confidence intervals. Two-tailed p values less than 0.05 were considered statistically significant. Descriptive statistics, inter-observer agreement, and univariate analyses were performed either using SPSS software, version 19 (SPSS, Chicago, IL), or SAS 9.4 (SAS Institute Inc., Cary, NC).
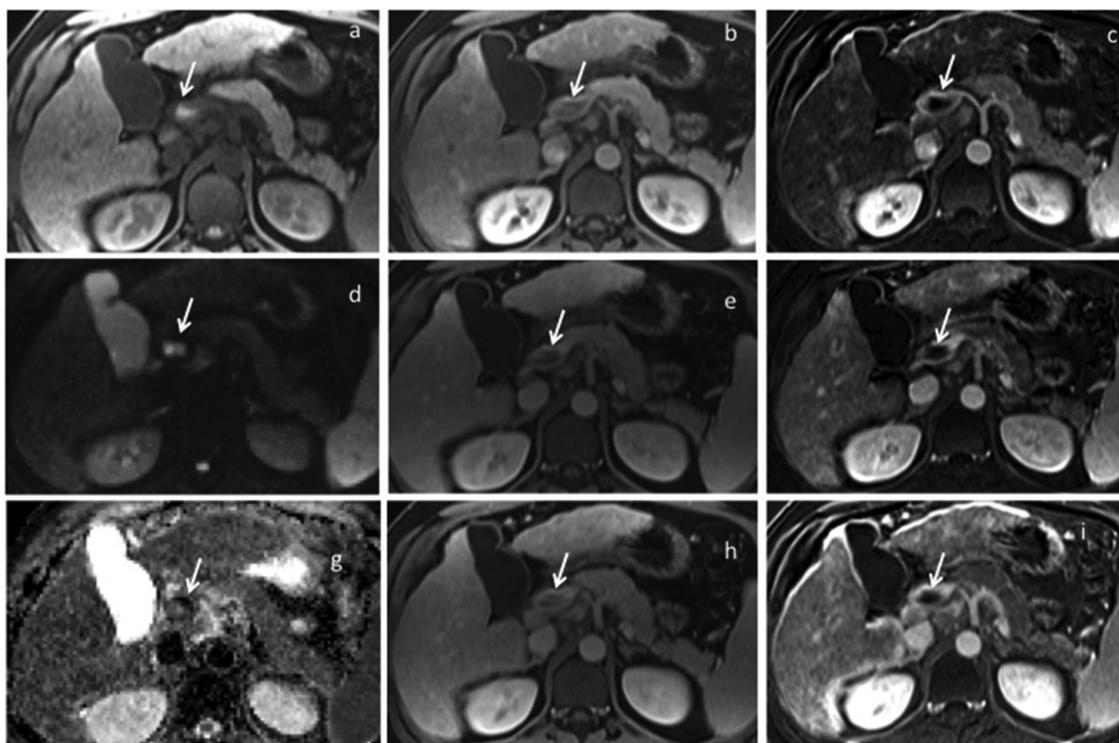
Fig. 1. Benign portal vein thrombosis in a patient with liver cirrhosis and HCC (not shown). Portal vein thrombus (white arrow) appears hyperintense on precontrast T1 images (a). The thrombus continues to appear mildly hyperintense on the post contrast arterial phase, AP (b), but does not show significant enhancement on the subtracted AP (c). Thrombus also shown on portal venous phase, PVP (e), subtracted PVP (f), delayed phase DP (h) and subtracted DP (i). The benign thrombus appears hyperintense on DWI (d) and heterogeneous on ADC maps (g) with restricted areas.

3. Results

3.1. Study population

Mean age of the cohort was 58.0 ± 7.0 years. There were 27 males and 12 females. There was no statistically significant difference in age ($p = 0.369$) or sex ($p = 0.457$) distribution between the patients with malignant PVT (mean age, 57.6 years; range, 40–76 years; 19 men and six women) and those with benign PVT (mean age, 59.0 years; range, 49.8–65.1 years; eight men and four women).

3.2. Evaluation of discriminating factors for benign and malignant thrombus

All quantitative measures of enhancement evaluated showed statistically significant differences between the bland and malignant thrombus groups (Table 1, Fig. 3). Sensitivity and specificity for detecting malignant thrombus for each reader is calculated at various threshold levels of percent enhancement for the subtracted and non-subtracted images (Table 2a and 2b). Statistically significant differences between the bland and malignant thrombus groups were observed for PV expansion for both readers (p = < 0.001/0.006) (Table 1). No subjective DWI parameters reached statistical significance for either reader (Table 1).

3.3. ROC analysis

Percent enhancement generated high AUC for both readers on all non-subtraction phases as detailed in Table 3. ROC curves are similar regardless of phase of contrast or use of subtraction (Fig. 4).

3.4. Inter-rater reliability (Table 4)

Excellent inter-rater reliability was found for subtraction percent

enhancement on all three phases (ICC range of 0.72-0.78). Moderate inter-rater reliability was found for non-subtraction percent enhancement on all three phases (ICC range 0.37-0.46).

Kappa statistics showed slight to poor correlation for DWI of thrombus relative to liver (kappa = 0.31) and ADC of thrombus relative to liver (kappa = .09). There was fair correlation for portal vein expansion (kappa = 0.46).

4. Discussion

This study confirms prior reports indicating the utility of post-contrast MRI sequences in differentiation of malignant PVT from benign, and further indicates that measuring this enhancement leads to high diagnostic accuracy at arterial, portal venous, and delayed phases as well as with subtracted post-contrast images. The use of increased vascular flow to differentiate these entities has been widely reported previously. Tublin et al [16] observed tumor neovascularity on CT to be 100% specific in their 58 patient retrospective study. They defined neovascularity as having characteristic morphologic appearance, though they did not quantitatively assess the degree of enhancement. This categorization limited the utility of contrast enhancement as over half the malignant thrombi did not have this characteristic. Similarly, the presence of confirmed hypervascular thrombus on ultrasound has been shown to be highly specific for HCC malignant thrombus, however using ultrasound up to 25% of the cases of malignant thrombus may be missed [17] Initial reports evaluating enhancement of tumor on MRI similarly appeared to show diminished sensitivity of enhancement alone in diagnosing malignant PVT. Sandrasegaran et al evaluated arterial enhancement on MRI and found an AUC of 0.73 for differentiating malignant from bland thrombus. However, they did not specify cutoff values and the threshold for enhancement leading to this determination is unclear [2]. This may account for our higher reported AUC. It is important to note that the threshold of enhancement for tumor thrombus in our study appears to be much lower than tumor in
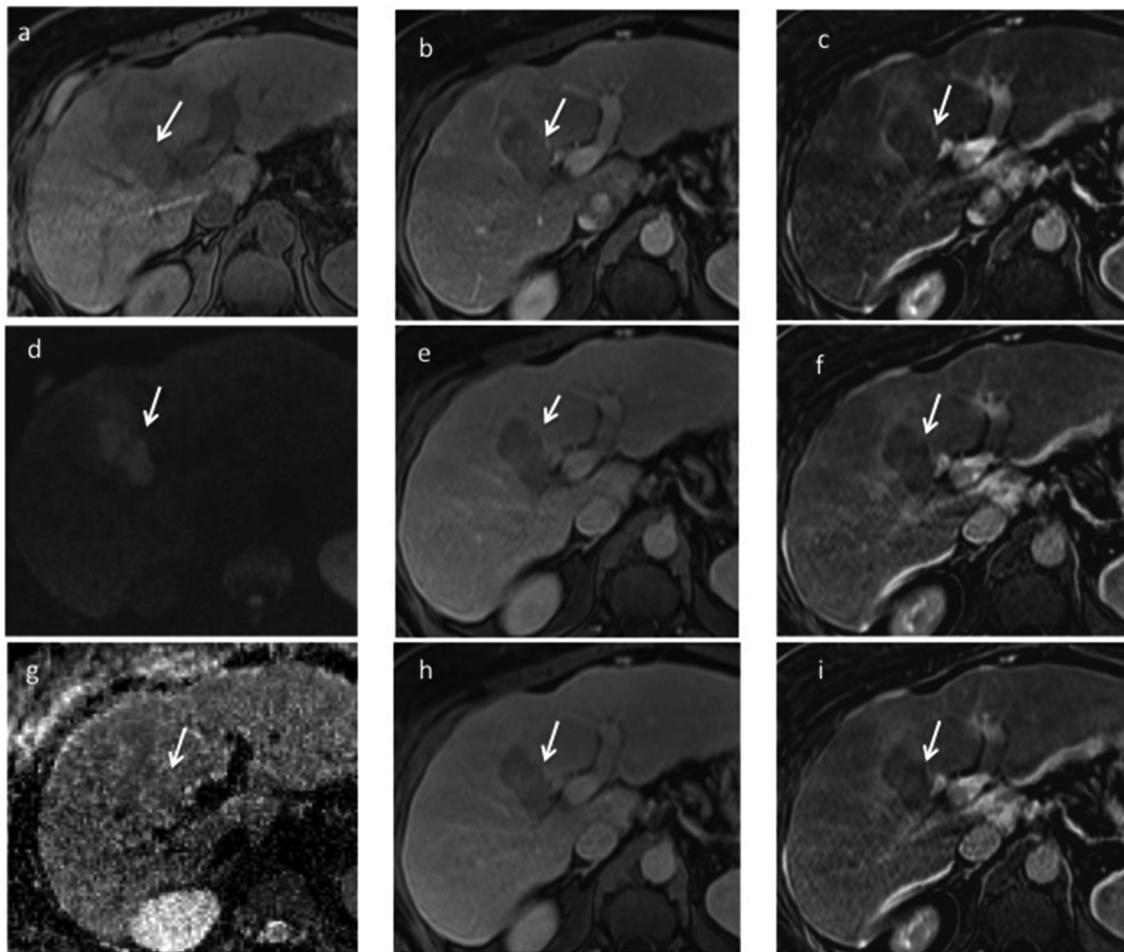
Fig. 2. Malignant portal vein thrombosis confirmed by growth criteria in a patient with liver cirrhosis and HCC in the right lobe. Portal vein tumor thrombus (white arrow) appears hypointense on precontrast T1 images (a). It demonstrates mild enhancement and remains hypointense on the post contrast arterial phase, AP (b), and mild enhancement is seen on the subtracted AP (c). Similar degree of enhancement is seen on the portal venous phase, PVP (e) and delayed phase DP (h) as well as the subtracted PVP (f), and subtracted DP (i). The tumor thrombus appears hyperintense on DWI (d) and isointense to the liver on ADC maps (g).

the liver parenchyma, and in our experience this is a point of frequent confusion in clinical practice. Although to our knowledge there is not clear published evidence of a threshold amount of enhancement that is indicative of tumor thrombus, at least one paper [13] applied a 15% threshold of enhancement at MRI as definitive evidence of malignant thrombus, a number extracted from prior work on renal cyst enhancement on MRI [18]. More recently, Kim et al demonstrated that enhancement of at least 15% detected 80–87% of thrombi, though the timing of post-contrast imaging was unclear in that study. Additionally, they had a false negative rate of 2–8% using that threshold [12]. Our results are in line with this prior work, while potentially providing more detail. Using the prior published 15% threshold at arterial, portal venous, and delayed timepoints, we find sensitivities of 0.88/0.92 (Reviewer1/2), 0.88/0.96 and 0.92/1.00 for non-subtraction images and 0.91/0.95, 0.91/1.0 and 0.91/1.0 for subtraction images; specificities are 0.85/0.77, 0.85/0.92 and 0.77/0.92 for non-subtraction images and 0.77/0.77, 0.85/0.77 and 0.77/0.85 for subtraction images respectively. In order to reach 100% specificity, the percent enhancement thresholds for non-subtracted arterial, portal venous, and delayed phases are 35%, 25% and 40% for reviewer 1 and 25%, 30% and 40% for reviewer 2.

Prior studies have investigated the role of DWI in differentiating benign vs malignant PVT. Catalano et al provided evidence that DWI signal and ADC values of malignant PVT were similar to that of HCC. They reported that ADC values of benign PVT were higher, with statistically significant differences between the two groups. This finding

was confirmed by Kim et al, though not confirmed in the study by Sandrasegaran et al. In our study we found no statistically significant differences between subjective assessment of benign and malignant PVT when evaluating DWI and ADC maps. It should be noted that our technique was different to prior approaches, relying on a qualitative evaluation and using slightly different b-values. We opted for a qualitative approach in this evaluation, as it may be more directly applicable to current clinical practice. Our results are in accordance with Sandrasegaran et al who found that signal intensity of PVT on DWI and ADC maps and PVT/Liver ADC ratios were not statistically significant between benign and malignant PVT. They found that conventional MRI yielded an AUC of 0.92 and 0.91 for diagnosis of PVT on ROC curve analysis, whereas ADC measurements yielded much lower AUCs of 0.69 and 0.64.

Our study found statistically significant differences between the benign and malignant groups regarding expansion of the vein. Our findings are in accordance with prior studies [2,16]. Sandrasegaran et al reported that maximum caliber of portal vein was not always significantly higher in patients with malignant thrombosis and optimal sensitivity of portal vein caliber in diagnosis of malignant PVT was 62%, similar to results obtained by Tublin et al on contrast enhanced CT.

Prior studies have incorporated a multi-factorial approach to demonstrate increased reported accuracies than enhancement alone. However, the multi-factorial approaches applied have been different across previous studies and interpretation is not straightforward. For

Table 1
Features evaluated to distinguish bland from malignant thrombus. (R1 indicates reader 1, R2 indicates reader 2). Note that two studies did not have diffusion-weighted images available for evaluation.*.

Variable	Category	Tumor Thrombus (N = 25)	Bland Thrombus (N = 13)	P-value
Maximum Diameter of PVT (mm)	Mean (SD) R1	15.25 (5.96)	16.05 (6.37)	0.748
	Mean (SD) R2	17.28 (6.52)	13.92 (4.46)	0.241
Venous Expansion by thrombus? (N with percentage)				
	Yes R1/R2	21 (84%)/ 18 (72%)	2 (15%)/ 3 (23%)	< 0.001/ 0.006
	No R1/R2	4 (16%)/ 7 (28%)	11 (84%)/ 10 (76%)	
DWI of thrombus relative to liver (N with percentage)		N = 23*	N = 13	
	Hyperintense R1/R2	22 (96%)/ 16 (70%)	10 (77%)/ 5 (38.46%)	0.236/ 0.144
	Isointense R1/R2	0/ 6 (26%)	2 (15%)/ 6 (46%)	
	Hypointense R1/R2	1 (4%)/ 1 (4%)	1 (8%)/ 2 (15%)	
ADC of thrombus relative to liver (N with percentage)		N = 23*	N = 13	
	Hyperintense R1/R2	0/0	2 (15%)/ 0	0.059/0.083
	Isointense R1/R2	2 (9%)/ 10 (43%)	3 (23%)/ 10 (77%)	
	Hypointense R1/R2	21 (91%)/ 13 (57%)	8 (61%)/ 3 (23%)	
Percentage of arterial enhancement Arterial phase	Mean (SD) R1	72.89 (83.45)	−2.12 (16.37)	< 0.001
	Mean (SD) R2	67.77 (47.11)	3.19 (10.13)	< 0.001
Percentage of portal enhancement Portal phase	Mean (SD) R1	83.06 (73.87)	−2.71 (16.66)	< 0.001
	Mean (SD) R2	73.14 (56.03)	−1.48 (13.22)	< 0.001
Percentage of delayed enhancement Delayed phase	Mean (SD) R1	75.04 (70.34)	−1.97 (18.30)	< 0.001
	Mean (SD) R2	76.88 (47.44)	−3.16 (17.39)	< 0.001
Percentage of arterial enhancement Subtraction arterial phase	Mean (SD) R1	226.0 (553.2)	1.05 (16.84)	< 0.001
	Mean (SD) R2	129.4 (168.9)	6.12 (9.60)	0.003
Percentage of portal enhancement Subtraction portal phase	Mean (SD) R1	235.7 (538.2)	6.65 (7.84)	< 0.001
	Mean (SD) R2	142.2 (144.7)	4.02 (14.07)	< 0.001
Percentage of delayed enhancement Subtraction delayed phase	Mean (SD) R1	207.1 (475.2)	4.79 (7.75)	< 0.001
	Mean (SD) R1	142.4 (134.0)	7.38 (22.83)	0.001

instance, Tublin et al demonstrated that CT neovascularity characteristics and expansion of the MPV to > 23 mm, were both diagnostic for malignant HCC and utilizing any one factor could improve overall sensitivity while maintaining specificity. It has been suggested that branch portal vein thrombus expansion can similarly allow differentiation of these entities. However, benign processes can also lead to expansion of these vessels, and at least one study suggests that established parameters are not specific for HCC, and vessel expansion must be used with caution [2,14]. To improve accuracy, Sandrasegaran et al suggest establishing the diagnosis in the presence of 2 of 3 factors (arterial enhancement, size of HCC > 5 cm, and thrombus within 2 cm of the HCC). While this improved statistical accuracy in their cohort, it

Percent Enhancement by Diagnosis and Type
Both Reviewers
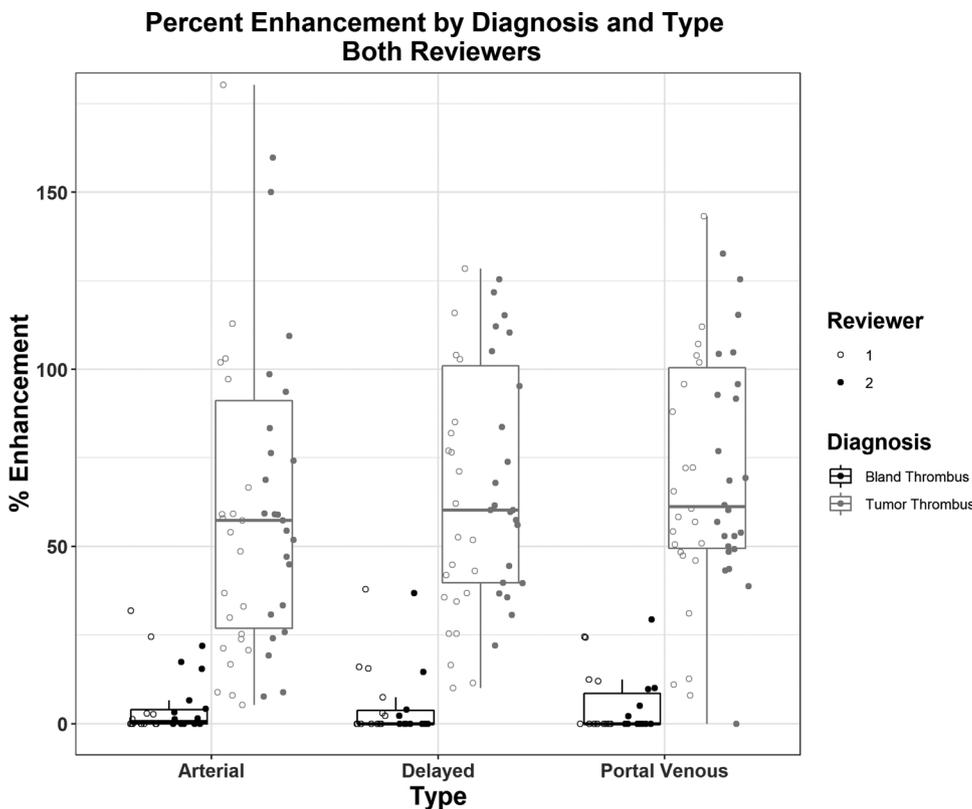
Fig. 3. Scatter plot showing data distribution between benign (black, left) and malignant (grey, right) groups on arterial phase, venous phase and delayed imaging for reviewer 1 (open dot) and 2 (solid dot). Outliers on the high end of the scale (n = 3 for each type for those with tumor thrombus) were removed to improve image scale and visibility.

Table 2a

Sensitivities and specificities for detection of malignant thrombus at various threshold percent enhancement for non-subtraction data for both readers. All results displayed as reader 1/reader 2. Optimal cut-point was determined based on maximizing the product of the sensitivity and specificity.

| | Non-subtraction | | | | | |
| | Arterial | | Portal venous | | Delayed | |
Enhancement (%)	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity
0	62 / 38	100 / 100	69 / 62	100 / 96	53 / 69	100 / 100
5	85 / 69	100 / 100	69 / 69	100 / 96	69 / 85	100 / 100
10	85 / 77	88 / 92	69 / 92	96 / 96	76 / 85	96 / 100
15	85 / 77	88 / 92	85 / 92	88 / 96	77 / 92	92 / 100
20	85 / 92	84 / 88	85 / 92	88 /96	92 / 92	88 / 100
25	92 / 100	72 / 84	100 / 92	88 / 96	92 / 92	88 /96
30	92 / 100	64 / 80	100 / 100	88 / 96	92 / 92	80 / 96
35	100 / 100	60 / 72	100 / 100	84 / 96	92 / 92	76 / 92
40	100 / 100	56 / 72	100 / 100	84 / 92	100 / 100	68 / 76
45	100 / 100	56 /68	100 / 100	84 / 84	100 / 100	56 / 72
"Optimal Cut-point"	5.30 / 24.0		31.0 / 38.7		16.5 / 22.1	

is less helpful in many patients who have had prior locoregional therapy. Further, there is no theoretical reason why patients with large tumors cannot have nearby benign thrombus. We did not exclude prior treatment in our cohort, and therefore many patients did not have large tumors and would therefore have been misdiagnosed using their criteria. In the largest cohort to date, Kim et al report an accuracy of up to 92–95% for differentiating benign from malignant PVT using a subjective approach incorporating enhancement, proximity to tumor, vessel expansion, diffusion restriction, and T2 signal intensity [19]. This indicates that this differentiation can be accurately achieved by experts, though the many factors they use without a clear guiding framework may make it much more difficult for all practicing radiologists to achieve this level of accuracy.

One such framework is the latest version of LI-RADS v2018, which states that malignant thrombus (LR-TIV) should be diagnosed in the presence of "unequivocal enhancement)" on CT or MRI, and additional findings such as diffusion restriction or contiguity of thrombus with the tumor are suggestive though do not establish the diagnosis [20]. Our results would support this conclusion, while perhaps providing more quantitative guidance on the optimal threshold for "unequivocal" enhancement as well as suggesting that timing of the postcontrast images is not critical in establishing enhancement. Benign thrombosis can have intrinsic high T1 signal on MRI and can be very heterogeneous on conventional sequences, potentially making the diagnosis of contrast enhancement difficult. Hence subtraction images are of potential value in identifying "unequivocal" enhancement of the thrombus in malignant PVT and increasing the confidence of the reader. We found that inter-rater reliability was excellent for subtraction images and ROC

Table 3

AUC and 95% CI of percent enhancement for differentiating benign and malignant thrombus.

Measure	Reviewer 1 (AUC 95% CI)	Reviewer 2 (AUC 95% CI)
Non-Subtraction		
Arterial	0.95 (0.86 – 1)	0.98 (0.93 - 1)
Portal venous	0.97 (0.91 - 1)	0.97 (0.91 - 1)
Delayed	0.96 (0.90 - 1)	0.99 (0.95 - 1)
Subtraction		
Arterial	0.91 (0.81 - 1)	0.96 (0.86 - 1)
Portal venous	0.94 (0.84 - 1)	0.99 (0.97 - 1)
Delayed	0.96 (0.88 - 1)	0.97 (0.91 - 1)

AUC was similar to non-subtracted evaluation, indicating they may be useful to guide radiologist interpretations. Arterial, venous and delayed phase images performed similarly for this differentiation without statistically significant differences. This is important in cases where multiphasic MRI has not been performed or some phases are difficult to interpret due to respiratory or motion artifacts, a frequent phenomenon in clinical practice.

Our study has several limitations. First, the study was a retrospective analysis. The sample size was low, but similar to prior studies on this topic. The imaging was performed on several different scanners, but from a single vendor. It remains to be seen if quantitative evaluation would yield similar results for other vendors. Also, we did not have direct histologic proof of malignant PVT due to the invasive nature of portal vein biopsy. However we confirmed the diagnosis using the best
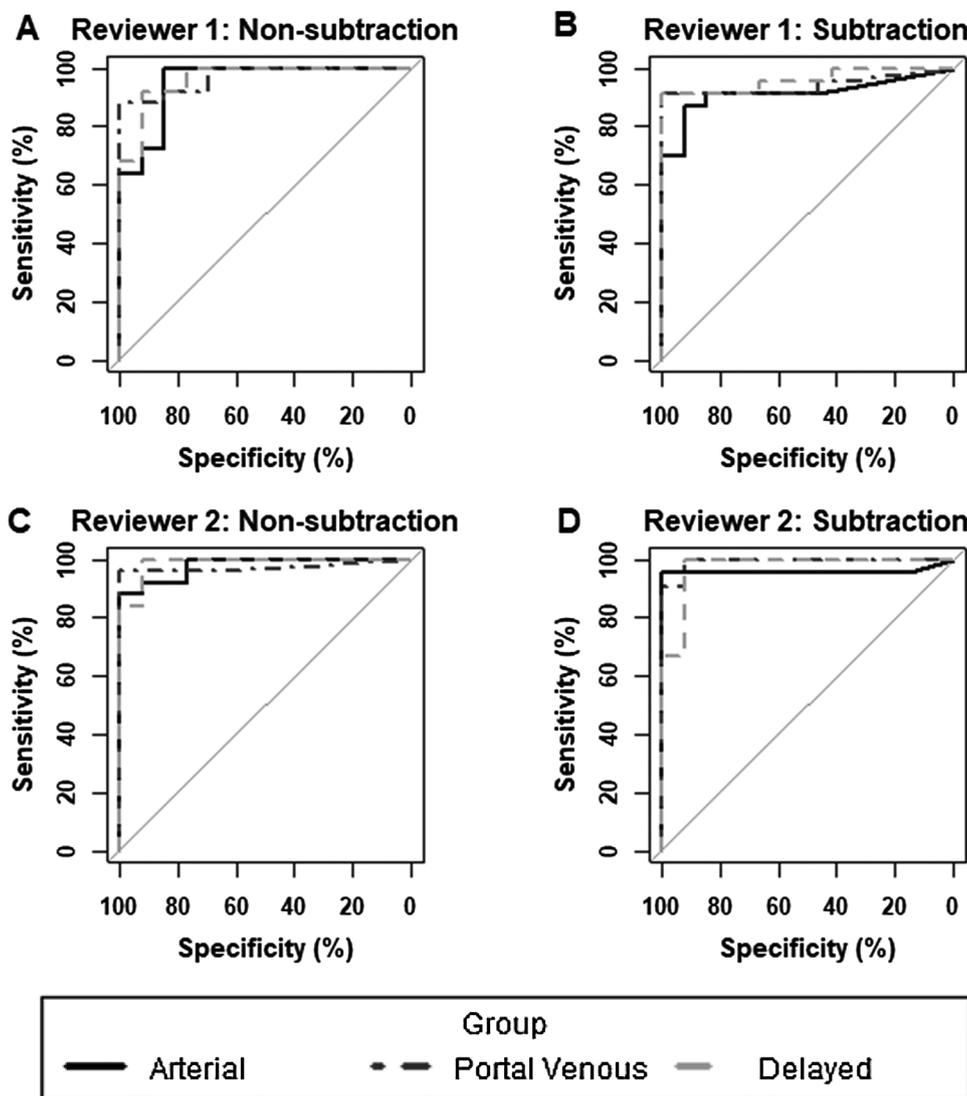
Table 2b

Sensitivities and specificities for detection of malignant thrombus at various threshold percent enhancement for subtraction data for both readers. All results displayed as reader 1/reader 2. Optimal cut-point was determined based on maximizing the product of the sensitivity and specificity.

| | Subtraction | | | | | |
| | Arterial | | Portal venous | | Delayed | |
Enhancement (%)	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity
0	46 / 15	91 / 95	38 / 54	96 / 100	42 / 38	100 / 100
5	69 / 46	91 / 95	62 / 69	91 / 100	67 / 69	96 / 100
10	77 / 77	91 / 95	69 / 69	91 / 100	83 / 85	91 / 100
15	77 / 77	91 / 95	85 / 77	91 / 100	92 / 85	91 / 100
20	92 / 92	83 / 95	92 / 92	91 / 100	100 / 92	91 / 100
25	92 / 100	74 / 95	92 / 92	91 / 95	100 / 92	87 / 100
30	100 / 100	70 / 81	100 / 92	91 / 90	100 / 92	87 / 100
35	100 / 100	61 / 76	100 / 100	78 / 90	100 / 92	83 / 95
40	100 / 100	61 /71	100 / 100	78 / 86	100 / 92	74 / 95
45	100 / 100	57 / 71	100 / 100	78 / 86	100 / 92	65 / 95
"Optimal Cut-point"	19.5 / 27.8		31.6 / 22.6		20.7 / 33.3	

Fig. 4. ROC curves for reviewer 1 (A and B) and reviewer 2 (C and D). Black solid line: percentage of arterial enhancement. Black dotted line: percentage of portal venous enhancement. Grey dashed line: percentage of delayed enhancement.

Table 4
Intra-class Correlation.

Variable	Inter-rater Reliability ICC (95% CI)
Percentage of arterial enhancement (arterial phase)	0.37 (0.09, 0.62)
Percentage of portal enhancement (portal phase)	0.46 (0.16, 0.68)
Percentage of delayed enhancement (delayed phase)	0.42 (0.11, 0.65)
Percentage arterial of enhancement (subtraction arterial phase)	0.77 (0.58, 0.88)
Percentage of portal enhancement (subtraction portal phase)	0.78 (0.60, 0.88)
Percentage of delayed enhancement (subtraction delayed phase)	0.72 (0.50, 0.85)

For continuous variables, ICC (intra-class correlation) is calculated as reliability: > 0.5 is large, 0.3-0.5, moderate; 0.1-0.3, small and < 0.1, trivial.

available previously established criteria of meticulous imaging follow up, and we avoided using other imaging modalities to establish the diagnosis.

5. Conclusion

We confirm that enhancement is a key factor in differentiating benign and malignant PVT. Definitive enhancement on any of the standard phases of post-contrast imaging by subtraction or non-subtracted images is indicative of malignant PVT.

IRB statement

The study was approved by Institutional Review Board.

References

[1] A. Pawarode, N. Voravud, V. Sriuranpong, P. Kullavanijaya, Y.Z. Patt, Natural history of untreated primary hepatocellular carcinoma: a retrospective study of 157 patients, Am. J. Clin. Oncol. 21 (1998) 386–391.

[2] K. Sandrasegaran, B. Tahir, K. Nutakki, F.M. Akisik, U. Bodanapally, M. Tann, N. Chalasani, Usefulness of conventional MRI sequences and diffusion-weighted imaging in differentiating malignant from benign portal vein thrombus in cirrhotic patients, AJR Am. J. Roentgenol. 201 (2013) 1211–1219, https://doi.org/10.2214/AJR.12.10171.

[3] M. Pirisi, C. Avellini, C. Fabris, C. Scott, P. Bardus, G. Soardo, C.A. Beltrami, E. Bartoli, Portal vein thrombosis in hepatocellular carcinoma: age and sex distribution in an autopsy study, J. Cancer Res. Clin. Oncol. 124 (1998) 397–400.

[4] S. Fujiyama, S. Saitoh, Y. Kawamura, H. Sezaki, T. Hosaka, N. Akuta, M. Kobayashi, Y. Suzuki, F. Suzuki, Y. Arase, K. Ikeda, H. Kumada, Portal vein thrombosis in liver cirrhosis: incidence, management, and outcome, BMC Gastroenterol. 17 (2017) 112, https://doi.org/10.1186/s12876-017-0668-8.

[5] J.C. Garcia-Pagan, D.-C. Valla, Portal vein thrombosis: a predictable milestone in cirrhosis? J. Hepatol. 51 (2009) 632–634, https://doi.org/10.1016/j.jhep.2009.06.009.

[6] D.J. Harding, M.T.P.R. Perera, F. Chen, S. Olliff, D. Tripathi, Portal vein thrombosis in cirrhosis: controversies and latest developments, World J. Gastroenterol. 21 (2015) 6769–6784, https://doi.org/10.3748/wjg.v21.i22.6769.

[7] S.A. Raza, H.-J. Jang, T.K. Kim, Differentiating malignant from benign thrombosis in hepatocellular carcinoma: contrast-enhanced ultrasound, Abdom. Imaging 39 (2014) 153–161, https://doi.org/10.1007/s00261-013-0034-4.

[8] M. Ogren, D. Bergqvist, M. Bjorck, S. Acosta, H. Eriksson, N.H. Sternby, Portal vein thrombosis: prevalence, patient characteristics and lifetime risk: a population study based on 23,796 consecutive autopsies, World J. Gastroenterol. 12 (2006) 2115–2119, https://doi.org/10.3748/wjg.v12.i13.2115.

[9] G.C. Sotiropoulos, A. Radtke, K.J. Schmitz, E.P. Molmenti, T. Schroeder, F.H. Saner, H.A. Baba, I. Fouzas, C.E. Broelsch, M. Malago, H. Lang, Liver transplantation in the setting of hepatocellular carcinoma and portal vein thrombosis: a challenging dilemma? Dig. Dis. Sci. 53 (2008) 1994–1999, https://doi.org/10.1007/s10620-007-0099-4.

[10] D. Takizawa, S. Kakizaki, N. Sohara, K. Sato, H. Takagi, H. Arai, K. Katakai, A. Kojima, Y. Matsuzaki, M. Mori, Hepatocellular carcinoma with portal vein tumor thrombosis: clinical characteristics, prognosis, and patient survival analysis, Dig. Dis. Sci. 52 (2007) 3290–3295, https://doi.org/10.1007/s10620-007-9808-2.

[11] L. Tarantino, G. Francica, I. Sordelli, F. Esposito, A. Giorgio, P. Sorrentino, G. de Stefano, A. Di Sarno, G. Ferraioli, P. Sperlongano, Diagnosis of benign and malignant portal vein thrombosis in cirrhotic patients with hepatocellular carcinoma: color Doppler US, contrast-enhanced US, and fine-needle biopsy, Abdom. Imaging 31 (2006) 537–544, https://doi.org/10.1007/s00261-005-0150-x.

[12] J.H. Kim, J.M. Lee, J.H. Yoon, D.H. Lee, K.B. Lee, J.K. Han, B.I. Choi, Portal Vein Thrombosis in Patients with Hepatocellular Carcinoma: Diagnostic Accuracy of Gadoxetic Acid-enhanced MR Imaging, Radiology 279 (2016) 773–783, https://doi.org/10.1148/radiol.2015150124.

[13] O.A. Catalano, G. Choy, A. Zhu, P.F. Hahn, D.V. Sahani, Differentiation of malignant thrombus from bland thrombus of the portal vein in patients with hepatocellular carcinoma: application of diffusion-weighted MR imaging, Radiology 254 (2010) 154–162, https://doi.org/10.1148/radiol.09090304.

[14] J.-Y. Choi, J.-M. Lee, C.B. Sirlin, CT and MR imaging diagnosis and staging of hepatocellular carcinoma: part I. Development, growth, and spread: key pathologic and imaging aspects, Radiology 272 (2014) 635–654, https://doi.org/10.1148/radiol.14132361.

[15] Z.K. Shah, M.G. McKernan, P.F. Hahn, D.V. Sahani, Enhancing and expansile portal vein thrombosis: value in the diagnosis of hepatocellular carcinoma in patients with multiple hepatic lesions, AJR Am. J. Roentgenol. 188 (2007) 1320–1323, https://doi.org/10.2214/AJR.06.0134.

[16] M.E. Tublin, G.D. Dodd 3rd, R.L. Baron, Benign and malignant portal vein thrombosis: differentiation by CT characteristics, AJR Am. J. Roentgenol. 168 (1997) 719–723, https://doi.org/10.2214/ajr.168.3.9057522.

[17] P. Sorrentino, L. Tarantino, S. D'Angelo, L. Terracciano, U. Ferbo, A. Bracigliano, L. Panico, G. De Chiara, M. Lepore, N. De Stefano, F. Fiorentino, R. Vecchione, Validation of an extension of the international non-invasive criteria for the diagnosis of hepatocellular carcinoma to the characterization of macroscopic portal vein thrombosis, J. Gastroenterol. Hepatol. 26 (2011) 669–677, https://doi.org/10.1111/j.1440-1746.2010.06564.x.

[18] V.B. Ho, S.F. Allen, M.N. Hood, P.L. Choyke, Renal masses: quantitative assessment of enhancement with dynamic MR imaging, Radiology. 224 (2002) 695–700, https://doi.org/10.1148/radiol.2243011048.

[19] S. Kim, L. Mannelli, C.H. Hajdu, J.S. Babb, T.W.I. Clark, E.M. Hecht, B. Taouli, Hepatocellular carcinoma: assessment of response to transarterial chemoembolization with image subtraction, J. Magn. Reson. Imaging 31 (2010) 348–355, https://doi.org/10.1002/jmri.22038.

[20] V. Chernyak, K.J. Fowler, A. Kamaya, A.Z. Kielar, K.M. Elsayes, M.R. Bashir, Y. Kono, R.K. Do, D.G. Mitchell, A.G. Singal, A. Tang, C.B. Sirlin, Liver imaging reporting and data system (LI-RADS) version 2018: imaging of hepatocellular carcinoma in At-Risk patients, Radiology. 289 (2018) 816–830, https://doi.org/10.1148/radiol.2018181494.