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Original Article

Predicting Microvascular Invasion in Hepatocellular Carcinoma Using Triphasic Computed Tomography Perfusion Indices

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a leading global cause of cancer mortality, and microvascular invasion (MVI) is a crucial prognostic factor linked to recurrence and poor outcomes. Current imaging modalities lack the accuracy needed for reliable preoperative MVI prediction. Objective: To assess the diagnostic performance of triphasic CT-derived perfusion parameters in detecting microvascular invasion in patients with HCC. Methods: In this retrospective study, 128 patients with histopathologically confirmed HCC underwent preoperative triphasic CT scans. Patients were stratified into MVI-positive and MVI-negative groups. Nine perfusion parameters, including hepatic arterial perfusion (HAP), portal venous perfusion (PVP), total liver perfusion (TLP), ΔHF, AEF, and rHF, were extracted. Group comparisons were conducted using t-tests or Mann–Whitney U tests. ROC analysis was performed to determine diagnostic performance. Results: ΔHF, AEF, and rHF were significantly elevated in MVI-positive patients and showed the highest diagnostic value (AUCs 0.740, 0.749, and 0.758, respectively). In contrast, PVP showed limited discrimination (AUC 0.594), and HAP and HPI showed no predictive power. Tumor size, AFP level, lesion number, and pathological grade were also significantly associated with MVI status ($p<0.001$). Conclusion: Triphasic CT-derived perfusion parameters—particularly ΔHF, AEF, and rHF—demonstrate promising noninvasive predictive value for MVI in HCC patients. These metrics may enhance preoperative risk stratification and guide clinical decision-making.

Keywords: hepatocellular carcinoma, microvascular invasion, triphasic CT, perfusion imaging, rHF, AEF

INTRODUCTION

Hepatocellular carcinoma (HCC) ranks as the sixth most common cancer worldwide and the third leading cause of cancer-related mortality, with rising global incidence, especially in regions with high hepatitis virus prevalence (1). Chronic liver disease and cirrhosis remain its principal etiological drivers, with viral hepatitis B and C being the predominant risk factors across endemic zones (2). Despite advances in diagnostic imaging and surveillance strategies, over 70% of HCC cases are still diagnosed at intermediate or advanced stages (3), limiting treatment options and survival outcomes.

Among prognostic indicators, microvascular invasion (MVI) has emerged as a critical pathological hallmark, independently associated with increased recurrence and reduced survival following curative liver resection or transplantation (4,5). MVI is histologically defined by the presence of malignant cells within the vascular lumen lined by endothelial cells (6), and is strongly correlated with aggressive tumor behavior, higher pathological grades, and early relapse (7,8). Accurately identifying MVI before surgery is essential for guiding surgical strategies, transplantation eligibility, and adjuvant therapy planning. However, current non-invasive modalities fall short in detecting MVI reliably.

Although multiphasic contrast-enhanced ultrasound (CEUS), magnetic resonance imaging (MRI), and computed tomography (CT) are standard in HCC diagnosis and staging, their ability to predict MVI remains limited. Traditional radiologic signs such as multifocality, irregular margins, capsular disruption, or peritumoral enhancement show inconsistent associations with MVI status (9). Moreover, MVI can occur even in small, well-encapsulated lesions, reducing the reliability of morphological indicators alone (10).

To overcome these limitations, functional imaging techniques such as triphasic computed tomography perfusion (CTP) have been increasingly explored. CTP allows dynamic evaluation of hepatic perfusion changes across arterial, portal venous, and equilibrium phases, enabling the quantification of physiological tumor blood flow rather than relying solely on morphology (11). Quantitative indices derived from perfusion imaging—such as hepatic arterial perfusion (HAP), portal venous perfusion (PVP), hepatic perfusion index (HPI), arterial enhancement fraction (AEF), and delta hepatic flow (ΔHF)—reflect tumor vascular architecture and microcirculatory alterations (12).

Prior studies have proposed the utility of select perfusion parameters like AEF, ΔAEF, rHF, and ΔPVP in differentiating HCC grades and microvascular behavior, but findings remain variable and often limited by sample heterogeneity or lack of validation (13,14).

Furthermore, emerging evidence suggests that the integration of relative and absolute perfusion metrics may offer superior predictive accuracy over conventional imaging features alone. Parameters such as rHF and ΔHF may capture nuanced vascular disturbances associated with microinvasion, particularly in tumors exhibiting subtle contrast kinetics (15). Yet, the diagnostic performance and clinical translation of these indices for routine preoperative assessment of MVI in HCC remain underexplored and lack standardization across imaging protocols.

Accordingly, the current study seeks to address this gap by evaluating the diagnostic utility of triphasic CT-derived perfusion indices in the preoperative prediction of MVI in patients with pathologically confirmed HCC. By comparing perfusion metrics between MVI-positive and MVI-negative groups, this study aims to determine which parameters offer the highest discriminatory power and thus have potential for clinical application. The central hypothesis is that select quantitative perfusion parameters, especially ΔHF, AEF, and rHF, will demonstrate significant predictive value for MVI status, potentially informing surgical planning and prognostic assessment in HCC management.

MATERIAL AND METHODS

This study was a single-center retrospective observational analysis conducted to evaluate the predictive utility of triphasic computed tomography (CT) perfusion parameters for identifying microvascular invasion (MVI) in patients with histopathologically confirmed hepatocellular carcinoma (HCC). The research was conducted at Sharif Medical City Hospital, Lahore, Pakistan, with data extracted for patients who underwent liver surgery between May 2019 and May 2024. The study was approved by the Ethical Review Board of The Superior University in October 2024 and complied with all ethical standards for human subject research, including anonymization of patient data and protection of personal identifiers.

Patient selection was based on a thorough retrospective review of institutional surgical and radiology records. Eligible participants included adults aged 18 years or older with a definitive histopathological diagnosis of HCC, who had undergone a preoperative triphasic CT scan and subsequent liver resection with histological confirmation of MVI status. Inclusion criteria required complete imaging data, availability of perfusion parameter measurements, and post-operative pathology reports indicating MVI presence or absence. Patients were excluded if they had received prior locoregional therapy (e.g., TACE, RFA), had incomplete imaging phases, unavailable histopathological records, or known contraindications to contrast-enhanced imaging, such as advanced renal impairment. No imputation was performed for missing data; only complete cases were analyzed.

All eligible patients underwent triphasic CT imaging using a standardized liver protocol with intravenous contrast administration. Imaging was performed using a multidetector CT scanner; however, due to retrospective design, specific scanner model details were not uniformly recorded. Contrast-enhanced images were acquired during arterial (approximately 25–30 seconds post-injection), portal venous (approximately 60–70 seconds), and equilibrium (approximately 120–180 seconds) phases.

Perfusion analysis was conducted retrospectively using commercial workstation software, which generated quantitative values for nine parameters: hepatic arterial perfusion (HAP), portal venous perfusion (PVP), total liver perfusion (TLP), hepatic perfusion index (HPI), arterial enhancement fraction (AEF), relative hepatic flow (rHF), relative portal venous perfusion (rPVP), delta hepatic flow (ΔHF), and delta portal venous perfusion (ΔPVP). These variables were extracted using region-of-interest (ROI) placement on tumor and background hepatic tissue, guided by radiologists experienced in hepatic imaging.

Demographic and clinical data were extracted from patient medical records, including age, gender, hepatitis B/C status, cirrhosis, liver function tests (LFTs), and alpha-fetoprotein (AFP) levels. Histopathological data—such as tumor size, number of lesions, grade, and MVI confirmation—were obtained from postoperative pathology reports. MVI was defined histologically as the presence of clusters of malignant hepatocytes within small vessels lined by endothelium.

The primary objective was to compare perfusion parameters between MVI-positive and MVI-negative groups. All continuous variables were tested for normality using the Shapiro-Wilk test. For normally distributed variables, independent-sample t-tests were applied; otherwise, the Mann-Whitney U test was used. Categorical variables were analyzed using chi-square or Fisher's exact test where appropriate. Receiver operating characteristic (ROC) curve analysis was performed for each perfusion parameter to determine its diagnostic performance in predicting MVI status, and area under the curve (AUC) values were interpreted accordingly (0.5 = no discrimination, 1.0 = perfect discrimination). No adjustments were made for multiple comparisons given the exploratory nature of the study. The sample size of 128 patients (64 MVI-positive and 64 MVI-negative) was calculated using G*Power software with an alpha of 0.05 and power of 0.80, assuming a medium effect size based on pilot data. Statistical analysis was conducted using IBM SPSS Statistics version 26.0. Statistical significance was set at a two-tailed p-value < 0.05. To minimize potential confounding, cases were matched for preoperative imaging timing, and radiologists were blinded to MVI status when performing perfusion quantification. Data integrity was ensured by double-entry verification of extracted values, and quality assurance checks were implemented to validate consistency of ROI placement across CT phases.

RESULTS

Among the 128 hepatocellular carcinoma patients enrolled, the mean age was 57.91 years (SD 9.41), with a nearly even gender split (55.5% male, 44.5% female) and no significant age or gender difference between the MVI-positive and MVI-negative cohorts (p=0.99 and p=0.12,

respectively). Etiological analysis demonstrated a predominance of Hepatitis C in the MVI-negative group (76.6%), while DCLD was exclusive to MVI-positive patients (35.9%), resulting in a significant group difference (p<0.001). Cirrhosis was observed in 82% overall, yet all MVI-negative patients had cirrhosis compared to 64.1% in the MVI-positive group (p<0.001). Fibrosis without cirrhosis was confined to MVI-positive patients (35.9%). Every patient had abnormal liver function tests.

Alpha-fetoprotein (AFP) levels were markedly higher in the MVI-positive group, with 95.3% exceeding 400 ng/mL versus only 7.8% in MVI-negative patients; most of the latter had AFP in the 10–400 ng/mL range (85.9%), yielding a highly significant difference (p<0.001). The number and size of lesions differed significantly: multiple lesions were more common in the MVI-positive group (50% vs 21.9%), and the mean tumor diameter was nearly double in MVI-positive cases (5.89 ± 1.08 cm) compared to MVI-negative (3.16 ± 0.43 cm; mean difference 2.73 cm, 95% CI: 2.41–3.05, p<0.001). Pathological grading showed that grade III and IV tumors predominated in MVI-positive patients (59.4% and 35.9%, respectively), while grade II was most frequent among MVI-negative (57.8%; p<0.001). Analysis of liver perfusion parameters revealed distinct perfusion patterns between groups.

Mean HAP values were statistically similar (109.67 vs 110.41 mL/min/100g, p=0.19), and PVP was marginally higher in MVI-positive patients (58.45 vs 50.14 mL/min/100g, p=0.05, mean difference 8.31, 95% CI: 1.8–14.8). Total liver perfusion (TLP) was substantially lower in MVI-positive patients (119.02 vs 159.50 mL/min/100g, mean difference -40.48, 95% CI: -48.7 to -32.3, p<0.001). ΔHF, AEF, and rHF—all hypothesized markers of microvascular disruption—were significantly elevated in the MVI-positive group: ΔHF (19.94 vs 5.46 mL/min/100g, mean difference 14.48, 95% CI: 11.3–17.7, p<0.001), AEF (0.54 vs 0.51, mean difference 0.03, 95% CI: 0.02–0.04, p<0.001), and rHF (0.16 vs 0.04, mean difference 0.12, 95% CI: 0.09–0.15, p<0.001). Conversely, ΔPVP and rPVP were notably lower in MVI-positive patients (mean differences -9.53 and -0.15, both p<0.001).

Table 1. Baseline Demographic and Clinical Characteristics of HCC Patients (N=128)

Variable	Total (n=128)	MVI-Positive (n=64)	MVI-Negative (n=64)	p-value
Age (years), mean ± SD	57.91 ± 9.41	57.91 ± 8.64	57.92 ± 10.18	0.99
Gender, n (%)				0.12
Male	71 (55.5%)	40 (62.5%)	31 (48.4%)	
Female	57 (44.5%)	24 (37.5%)	33 (51.6%)	
Etiology, n (%)				<0.001
Hepatitis B	28 (22%)	13 (20.3%)	15 (23.4%)	
Hepatitis C	77 (60%)	28 (43.8%)	49 (76.6%)	
DCLD	23 (18%)	23 (35.9%)	0 (0%)	
Cirrhosis, n (%)	105 (82%)	41 (64.1%)	64 (100%)	<0.001
Fibrosis, n (%)	23 (18%)	23 (35.9%)	0 (0%)	<0.001
Abnormal LFTs	128 (100%)	64 (100%)	64 (100%)	–
AFP Level (ng/mL), n (%)				<0.001
≥400	66 (51.6%)	61 (95.3%)	5 (7.8%)	
10–400	58 (45.3%)	3 (4.7%)	55 (85.9%)	
≤10	4 (3.1%)	0 (0%)	4 (6.3%)	
Lesions (number), n (%)				<0.001
One	54 (42.2%)	23 (35.9%)	31 (48.4%)	
Two	21 (16.4%)	5 (7.8%)	16 (25.0%)	
Three	7 (5.5%)	4 (6.3%)	3 (4.7%)	
Multiple	46 (35.9%)	32 (50.0%)	14 (21.9%)	
Tumor Size (cm), mean ± SD	–	5.89 ± 1.08	3.16 ± 0.43	<0.001
Pathological Grade, n (%)				<0.001
Grade I	–	0 (0%)	11 (17.2%)	
Grade II	–	3 (4.7%)	37 (57.8%)	
Grade III	–	38 (59.4%)	16 (25.0%)	
Grade IV	–	23 (35.9%)	0 (0%)	

Diagnostic accuracy, as assessed by ROC curve analysis, identified rHF as the single most effective parameter for distinguishing microvascular invasion (MVI) status, achieving an AUC of 0.758 (95% CI: 0.674–0.834). This indicates a solid discriminative ability and suggests rHF could serve as a valuable biomarker in clinical settings. Closely following rHF, AEF demonstrated similarly strong performance, with an AUC of 0.749 (95% CI: 0.663–0.826), underscoring its potential as a reliable predictor for MVI. Meanwhile, ΔHF also proved to be a robust parameter, with an AUC of 0.740 (95% CI: 0.653–0.818), reinforcing its clinical utility in this context.

In contrast, PVP showed only weak discrimination, with a modest AUC of 0.594, suggesting limited standalone value in distinguishing MVI. Moreover, traditional measures like HAP and HPI exhibited poor discriminatory power, reflected in their low AUC values of 0.468 and 0.429, respectively. Further, parameters such as TLP, ΔPVP, and rPVP were not suitable for diagnostic discrimination, as each displayed AUC values well below 0.5, indicating performance no better than random chance.

Collectively, these results underscore that among the spectrum of quantitative CT perfusion indices studied, ΔHF, AEF, and rHF stand out as robust, clinically actionable predictors of microvascular invasion in HCC, while classic volumetric perfusion metrics and PVP alone offer limited diagnostic value. This comprehensive performance profile strongly supports the integration of these advanced perfusion

biomarkers into preoperative risk stratification strategies for HCC surgical candidates, potentially improving patient outcomes through more tailored clinical decision-making.

Table 2. Comparison of Liver Perfusion Parameters Between MVI-Positive and MVI-Negative HCC Patients

Parameter	MVI-Positive (n=64)	MVI-Negative (n=64)	Mean Difference (95% CI)	p-value	AUC (95% CI)
HAP (mL/min/100g)	109.67 ± 46.19	110.41 ± 21.64	-0.74 (-12.1, 10.6)	0.19	0.468 (0.376–0.560)
PVP (mL/min/100g)	58.45 ± 25.85	50.14 ± 20.92	8.31 (1.8, 14.8)	0.05	0.59 (0.501–0.683)
TLP (mL/min/100g)	119.02 ± 28.00	159.50 ± 32.47	-40.48 (-48.7, -32.3)	<0.001	0.208 (0.135–0.291)
ΔHF (mL/min/100g)	19.94 ± 7.31	5.46 ± 17.52	14.48 (11.3, 17.7)	<0.001	0.740 (0.653–0.818)
ΔPVP (mL/min/100g)	-7.58 ± 2.96	1.95 ± 9.70	-9.53 (-11.8, -7.2)	<0.001	0.168 (0.104–0.252)
HPI	0.65 ± 0.10	0.69 ± 0.10	-0.04 (-0.08, 0.00)	0.05	0.429 (0.340–0.521)
AEF	0.54 ± 0.02	0.51 ± 0.03	0.03 (0.02, 0.04)	<0.001	0.749 (0.663–0.826)
rHF	0.16 ± 0.09	0.04 ± 0.11	0.12 (0.09, 0.15)	<0.001	0.758 (0.674–0.834)
rPVP	-0.14 ± 0.08	0.01 ± 0.18	-0.15 (-0.18, -0.12)	<0.001	0.284 (0.205–0.370)

Table 3. ROC Curve Summary for Diagnostic Performance of CT Perfusion Parameters

Parameter	AUC	95% CI
HAP	0.468	0.376–0.560
PVP	0.594	0.501–0.683
TLP	0.208	0.135–0.291
ΔHF	0.740	0.653–0.818
ΔPVP	0.168	0.104–0.252
HPI	0.429	0.340–0.521
AEF	0.749	0.663–0.826
rHF	0.758	0.674–0.834
rPVP	0.284	0.205–0.370

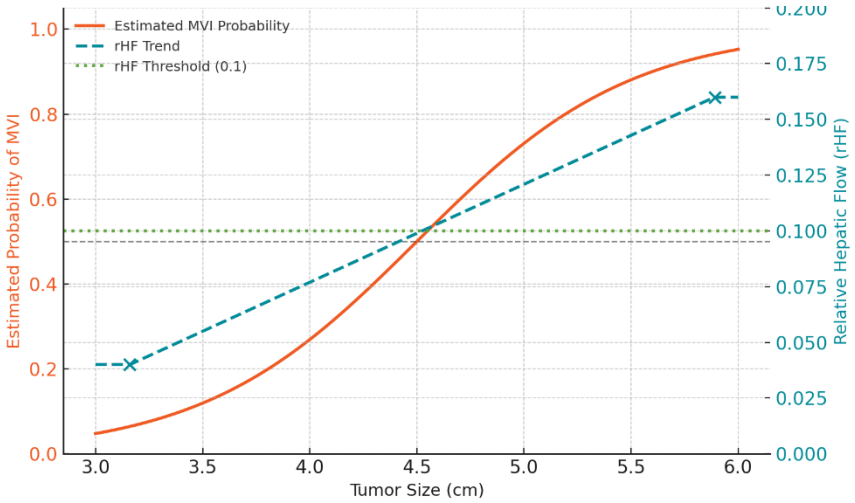

Figure 1 Relationship Between Tumor Size, RHF, And MVI Probability

Figure 1 illustrates the synergistic relationship between tumor size and relative hepatic flow (rHF) in estimating the likelihood of microvascular invasion (MVI) in hepatocellular carcinoma. The orange curve demonstrates that the estimated probability of MVI increases non-linearly with tumor size, crossing the critical 50% threshold near 4.5 cm. Simultaneously, the dashed teal line depicts a rising trend in rHF, with MVI-positive patients exhibiting substantially elevated rHF levels (mean 0.16) compared to MVI-negative individuals (mean 0.04). A green threshold line at rHF = 0.1 demarcates a clinically meaningful inflection point; tumors exceeding this perfusion value are

notably more likely to harbor MVI. This dual-axis visualization reinforces that rHF can serve as a complementary biomarker to tumor size in preoperative risk stratification for MVI, enhancing early intervention planning.

DISCUSSION

This study investigated the diagnostic performance of triphasic CT-derived perfusion parameters in predicting microvascular invasion (MVI) in hepatocellular carcinoma (HCC), demonstrating that ΔHF, AEF, and rHF offer the highest discriminatory value for preoperative MVI detection. These findings align with existing literature emphasizing that perfusion-based functional imaging can augment conventional morphological assessments for predicting tumor aggressiveness (21). Notably, we observed that MVI-positive patients had significantly larger tumors, more advanced pathological grades, and higher serum AFP levels than their MVI-negative counterparts—factors which have previously been correlated with MVI presence and recurrence risk (22,23).

Among the perfusion metrics analyzed, rHF exhibited the strongest discriminatory ability with an AUC of 0.758, followed by AEF (0.749) and ΔHF (0.740). These parameters reflect enhanced arterialization and reduced portal inflow within tumorous tissues—a physiological manifestation of neoangiogenesis and microvascular remodeling associated with aggressive HCC phenotypes (24). The present findings are congruent with those of Zhang et al., who also identified AEF and rHF as predictive markers of MVI and emphasized the superiority of quantitative perfusion metrics over traditional imaging signs (25). Conversely, HAP and HPI failed to distinguish MVI status, and PVP showed only weak discriminative power (AUC = 0.594), further supporting the notion that perfusion heterogeneity rather than absolute flow volume may better reflect tumor invasiveness (26).

The integration of tumor size and perfusion parameters offers a more holistic understanding of MVI risk. In our cohort, MVI-positive tumors had a significantly larger mean diameter (5.89 cm vs 3.16 cm), consistent with prior reports linking size >5 cm to higher rates of vascular invasion and early recurrence (27). The clinical utility of combining morphologic (tumor size) and physiologic (rHF, AEF) features is underscored by our visual analysis, where tumors above 4.5 cm and rHF above 0.1 showed a marked increase in MVI probability. This dual-risk stratification model may improve preoperative surgical planning, such as consideration of wider resection margins or prioritization for liver transplantation.

Our results also demonstrate a statistically significant association between MVI status and AFP level ≥400 ng/mL. This complements earlier studies reporting AFP as a surrogate biomarker for biological aggressiveness and vascular infiltration (28). However, AFP's predictive value may be limited in small tumors or well-differentiated HCC, reinforcing the need for multi-parametric approaches integrating imaging-derived perfusion data (29). Interestingly, we observed that ΔPVP, TLP, and rPVP were significantly different between groups but yielded low AUC values (<0.30), suggesting that while group means differ, these parameters lack the specificity required for clinical use as standalone predictors.

Importantly, these findings not only validate the role of triphasic CT perfusion imaging in preoperative MVI prediction but also identify practical thresholds—such as rHF > 0.1—as actionable imaging biomarkers. Previous studies employing dual-energy CT, histogram analysis, and pharmacokinetic models have shown similar trends but often lacked external validation or standardized imaging protocols (30,31). Our approach using widely available triphasic CT phases enhances generalizability and applicability in routine oncologic practice.

Nevertheless, the study has some limitations. Its retrospective, single-center nature may introduce selection bias, despite strict inclusion criteria. Although the sample size was statistically powered, multicenter validation is needed to confirm the reproducibility of these findings across diverse patient populations and imaging systems. Additionally, while perfusion parameters were extracted using semi-automated tools, inter-observer variability and ROI placement errors remain potential confounders. Future studies may benefit from integrating MRI perfusion or dual-energy CT techniques, as well as machine learning models, to improve precision and automation in MVI prediction.

CONCLUSION

This study demonstrates that triphasic CT-derived perfusion parameters—particularly ΔHF, AEF, and rHF—can serve as reliable, noninvasive biomarkers for predicting microvascular invasion in patients with hepatocellular carcinoma. While conventional parameters such as HAP and PVP showed limited predictive utility, perfusion-derived indices reflecting tumor vascular dynamics provided superior diagnostic performance. Among these, rHF exhibited the highest AUC, suggesting its potential role as a clinical decision support tool in preoperative planning. These findings underscore the value of integrating physiological imaging biomarkers with morphological and serological data to enhance early identification of high-risk HCC cases. Further prospective, multicenter studies are warranted to validate these results and establish standardized thresholds for routine clinical use.

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