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ROLE OF EARLY ARTERIAL PHASE IMAGING IN ACCURATELY DIFFERENTIATING HEPATOCELLULAR CARCINOMA FROM DYSPLASTIC NODULES IN CIRRHOTIC PATIENTS

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ABSTRACT

Objective: To determine the diagnostic accuracy of early arterial phase contrast-enhanced CT imaging in distinguishing hepatocellular carcinoma (HCC) from dysplastic nodules (DN) in cirrhotic patients.

Study Design: Cross-sectional observational study conducted at a tertiary care hospital's radiology department in Lahore.

Methods: A total of 73 cirrhotic patients with focal liver lesions detected on screening were recruited using convenience sampling. Multi-phase contrast-enhanced CT scans were performed, with special focus on the early arterial phase (~30–35 seconds post-contrast injection). Imaging features assessed included lesion size, enhancement pattern, presence of washout, and stromal invasion. Lesions were categorized as HCC or DN based on imaging criteria and clinical/pathologic correlation. Chi-square analysis was used to evaluate associations between imaging features and lesion type, and diagnostic performance (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV]) of early arterial phase imaging was calculated against the reference standard diagnosis.

Results: The mean age of patients was 29±6 years, with 72.6% male. All patients had chronic liver disease (commonly hepatitis-related or alcohol-related cirrhosis). Early arterial phase CT revealed that both HCC and DN lesions predominantly showed heterogeneous enhancement (>75% of lesions). However, hallmark features distinguishing HCC from DN were identified. Arterial-phase washout was observed in 61.6% of HCCs versus only 17.8% of DNs. Similarly, stromal invasion was evident in 82.2% of HCCs compared to 23.3% of DNs. These differences were statistically significant ($p < 0.001$). Early arterial phase imaging correctly identified HCC with a sensitivity of 91.6% and specificity of 72.7%, while for DNs the sensitivity was 87.5% and specificity 72.7%. The PPV for HCC was 88% and NPV 80%, indicating high accuracy in confirming HCC and a reasonable ability to rule it out.

Conclusion: Early arterial phase CT imaging provides high diagnostic sensitivity for HCC in cirrhotic patients and significantly aids in differentiating HCC from dysplastic nodules. Characteristic arterial-phase findings such as contrast washout and stromal invasion are much more frequent in HCC than in DN, improving confidence in non-invasive diagnosis. Incorporating an early arterial phase in routine liver imaging protocols is recommended to enhance early detection and proper characterization of HCC in at-risk cirrhotic populations.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and represents a major global health concern. It is the sixth most common cancer worldwide and the third leading cause of cancer-related death. HCC typically arises in the context of chronic liver disease and cirrhosis, with hepatitis B virus, hepatitis C virus, alcoholic liver disease, and non-alcoholic fatty liver disease being the predominant etiologic factors. The pathogenesis of HCC often follows a multistep progression: regenerative nodules in a cirrhotic liver can evolve into low-grade dysplastic nodules (DN), progress to high-grade dysplastic nodules (which are considered premalignant lesions), and eventually transform into early HCC. High-grade dysplastic nodules carry a substantial risk of malignant transformation, with cumulative HCC development rates reported as high as 46–61% at 3 years. Distinguishing dysplastic nodules from early HCC is therefore a critical challenge, as early detection of HCC greatly expands therapeutic options and improves survival outcomes. Imaging plays a pivotal role in HCC surveillance and diagnosis in cirrhotic patients. In particular, multi-phase contrast-enhanced imaging of the liver – typically including arterial, portal venous, and delayed phases – is central to non-invasive diagnostic criteria for HCC in guidelines such as AASLD and LI-RADS. The biological basis for imaging diagnosis lies in the vascular alterations that accompany hepatocarcinogenesis. As benign or dysplastic nodules progress toward malignancy, they gradually lose portal vein blood supply and develop unpaired arteries through neoangiogenesis. Consequently, HCCs characteristically show arterial phase hyperenhancement (APHE) – i.e. they avidly enhance in the early arterial phase of contrast imaging – followed by washout in later phases, appearing hypoattenuating relative to the liver on portal/delayed phase images. Dysplastic nodules, in contrast, usually lack such pronounced arterial neovascularization. While some high-grade dysplastic nodules may exhibit mild arterial uptake, they often do not demonstrate clear washout on portal venous phase. These imaging features (APHE and washout) form the cornerstone of HCC diagnosis on CT and MRI. However, *overlap in appearance can occur:* for instance, a sizable dysplastic nodule could enhance heterogeneously, potentially mimicking an early HCC, whereas a very early HCC might be small or show atypical enhancement patterns. Thus, there is a need to optimize imaging techniques and phases to improve the differentiation of HCC from dysplastic nodules. The early arterial phase (also known as the hepatic arterial phase, approximately 20–35 seconds after contrast injection) is when hepatic arteries maximally enhance the tumor before substantial portal venous filling occurs. This phase can be crucial for detecting hypervascular lesions like HCC that might be missed or appear less conspicuous in later phases. Prior research has suggested that including an early arterial phase may increase sensitivity for small HCCs, by capturing transient arterial hyperenhancement before contrast equilibrium. We postulated that early arterial phase imaging could also better characterize lesions as HCC vs DN by accentuating differences in vascularity and allowing earlier visualization of washout. This study was therefore designed to evaluate the role of early arterial phase CT imaging in accurately differentiating HCC from dysplastic nodules in cirrhotic patients. We aimed to compare the early arterial phase imaging characteristics of confirmed HCCs and dysplastic nodules, and to determine the diagnostic performance of early arterial phase imaging in distinguishing between these two entities. We also discuss our findings in the context of existing literature and provide recommendations for integrating early arterial phase imaging into routine liver imaging protocols

Material and Methods:

This study was a cross-sectional observational analysis of diagnostic imaging, carried out at the Radiology Department of Lahore General Hospital, Pakistan. The study was conducted over a 4-month period following institutional review board approval and patient consent. A total of 73 patients with known liver cirrhosis and at least one focal liver lesion on screening ultrasound were enrolled. The sample size was calculated using Cochran's formula for an expected HCC prevalence of ~5% in the at-risk population, yielding a minimum of 73 subjects for 95% confidence and 5% margin of error. Patients were selected by non-probability convenience sampling. **Inclusion criteria** were adults with alcoholic or non-alcoholic cirrhosis (any etiology) undergoing

routine HCC surveillance who had one or more liver lesions detected on ultrasound or prior imaging. **Exclusion criteria** included children under 5 years old, patients with contraindications to contrast (e.g. prior severe contrast allergy or renal failure), and pregnant women. All participants provided written informed consent for the CT examination and inclusion of their data. All patients underwent multi-phase contrast-enhanced CT of the liver on a 64-slice CT scanner (Toshiba Aquilion CX). Intravenous iodinated contrast was administered (at ~1.5 mL/kg, 3–4 mL/s). Scans were obtained in: (1) **Early arterial phase** (~30 seconds post-injection), achieved by bolus-tracking or fixed delay to capture the hepatic arterial inflow; (2) **Portal venous phase** (~70 seconds post-injection); and (3) **Delayed phase** (~180 seconds) if needed for lesion characterization. The early arterial phase was defined operationally as the phase in which hepatic arteries are opacified but hepatic veins are not yet filled. Patients were scanned during a single breath-hold per phase. Thin-slice images were reconstructed and reviewed on PACS. Two experienced radiologists independently reviewed the early arterial phase images (with reference to other phases as needed) while blinded to clinical information. For each detected lesion, the following features were recorded: **size** (maximum diameter, and categorized as 0.5–1.0 cm, >1.0–1.5 cm, or >1.5–2.0 cm for analysis); **enhancement pattern** in arterial phase (homogeneous vs heterogeneous); presence of **washout** (relative hypoattenuation of lesion on portal venous phase); and presence of **stromal invasion or capsule invasion** (inferred from irregular margins, capsule disruption or satellite lesions suggesting microscopic vascular invasion) Lesions were provisionally categorized as "HCC" if they demonstrated arterial hyperenhancement with washout and/or invasive features, versus "DN" if they lacked those malignant hallmarks (for example, arterial iso- or hypoenhancement, or benign appearance). In cases of disagreement or indeterminate features on imaging, the final diagnosis was established by a combination of clinical follow-up, tumor markers (alpha-fetoprotein), and biopsy when available. For patients with multiple lesions, the largest or most suspicious lesion was considered the index lesion for analysis. Patient demographics and clinical history (etiology of cirrhosis, prior HCC treatment) were recorded. Continuous data are presented as mean ± standard deviation. Categorical data (e.g. frequency of each imaging feature in HCC vs DN) were tabulated as counts and percentages. A chi-square test was used to assess the association between lesion type (HCC or DN) and each imaging feature (enhancement pattern, washout, stromal invasion). A p-value < 0.05 (two-tailed) was considered statistically significant. Diagnostic performance of early arterial phase imaging was evaluated by calculating sensitivity, specificity, PPV, and NPV for identifying HCC versus DN, using the final diagnosis as the reference. These metrics were derived from the contingency of imaging-based diagnoses (HCC or DN) against the reference standard classifications. All statistical analyses were performed using SPSS version 29.

Results

Patient Demographics: A total of 73 patients were analyzed (53 males and 20 females; mean age ~29 years, range 20–40 years). The majority (86.3%) had chronic liver disease related to hepatitis B, hepatitis C, or alcohol abuse, and 82.2% had established cirrhosis on imaging or biopsy. Notably, 61.6% of patients had a prior history of liver malignancy or treatment, reflecting a cohort under surveillance for HCC recurrence. All patients underwent triple-phase CT scanning successfully with no adverse contrast reactions.

Table 4.1 *Demographics & past history of patients.*

Demographics		Frequency(n)	Percentage %
Age (years)	20-25	22	30.1
	25-30	21	28.8
	30-35	17	23.3
	35-40	13	17.8
	Total	73	100.0
Gender	male	53	72.6
	female	20	27.4

	Total	73	100.0
Chronic liver disease	yes	63	86.3
	no	10	13.7
	Total	73	100.0
Type of Cirrhosis	alcoholic	18	24.7
	non-alcoholic	55	75.3
	Total	73	100.0
Diagnosis of Cirrhosis	yes	60	82.2
	no	13	17.8
	Total	73	100.0
Previous history of malignancy	yes	45	61.6
	no	28	38.4
	Total	73	100.0

Imaging Findings – Early Arterial Phase: A total of 73 focal lesions were characterized (one per patient). Based on the composite reference standard, 48 of these lesions were confirmed as HCC and 25 as dysplastic nodules. Table 1 summarizes the early arterial phase imaging features observed in each group. Lesion size ranged from 0.5 to 2.0 cm for most lesions, with HCCs tending to be in the 1.0–1.5 cm range more often than DNs (47.9% of HCCs vs 30.1% of DNs were 1.0–1.5 cm). DNs were slightly more likely to be very small (<1 cm) or to exceed 1.5 cm, but size distribution alone did not significantly differentiate the groups (p=0.18)
Most lesions in **both** categories exhibited heterogeneous enhancement in the early arterial phase (79.5% of HCCs and 75.3% of DNs). Homogeneous enhancement was relatively uncommon overall, seen in ~20% of lesions in each group. Thus, enhancement pattern by itself was not a reliable discriminator between HCC and DN (p=0.58).

Figure 4.1 Age of patients

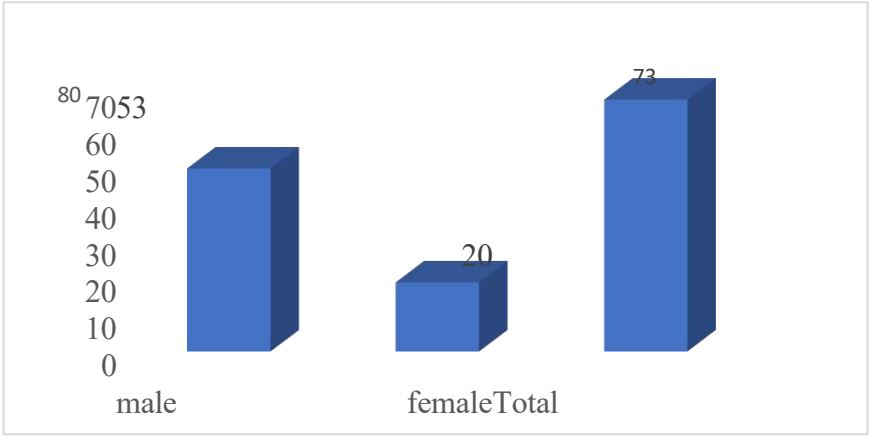

Figure 4.2 Gender of patients

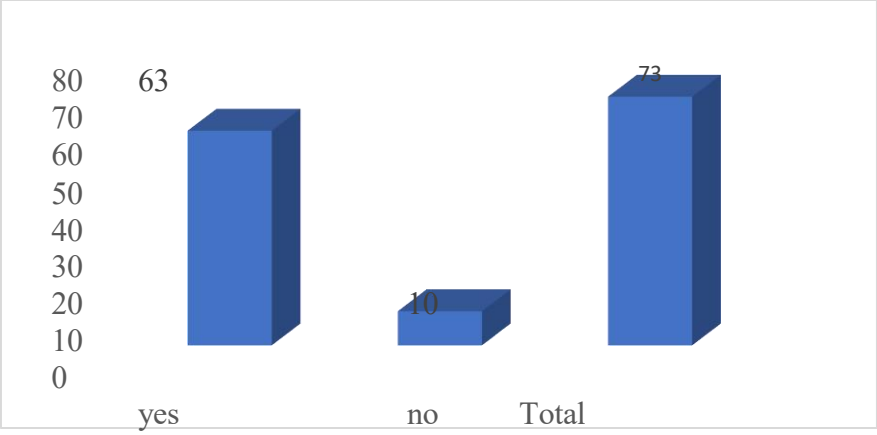

Figure 4.3 chronic liver disease of patients

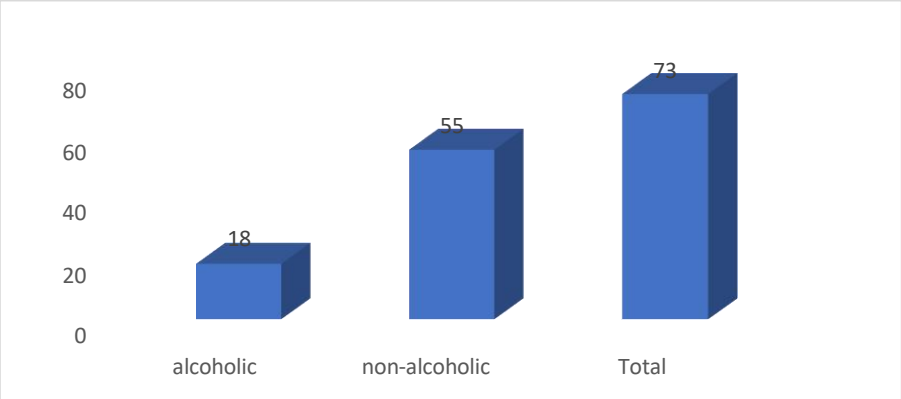

Figure 4.5 type of cirrhosis

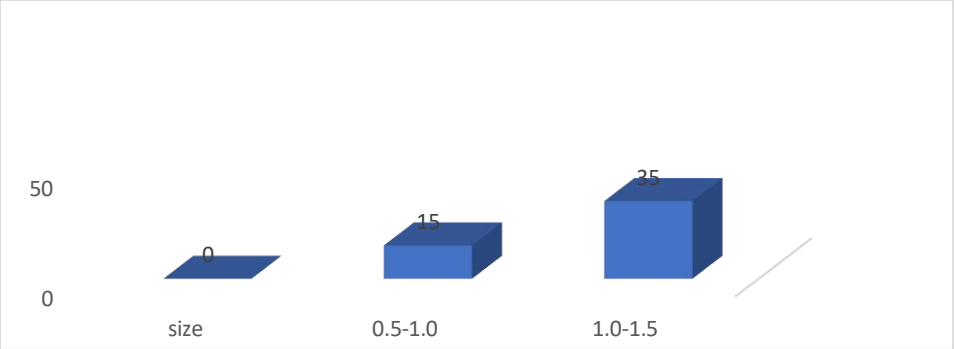

Figure 4.6 Previous history of Malignancy

Early arterial phase imaging is observed in HCC and DN. Upon different imaging features HCC and DN were differentiated. The size, enhancement pattern, washout phenomenon and stromal invasion were observed. The frequency distribution of these features in HCC and DN is given below in table 4.2.

TABLE 4.2 *Frequency of imaging features of early arterial phase of HCC and DN*

variables		HCC (f)	DN (f)
size	0.5-1.0	15 (20.5%)	23 (31.5%)
	1.0-1.5	35 (47.9%)	22 (30.1%)
	1.5-2.0	23 (31.5%)	28 (38.4%)
	Total	73 (100.0%)	73 (100.0%)
Enhancement pattern	homogeneous	15 (20.5%)	18 (24.7%)
	heterogeneous	58 (79.5%)	55 (75.3%)
	Total	73 (100.0%)	73 (100.0%)
Washout phenomenon	present	45 (61.6%)	13 (17.8%)
	absent	28 (38.4%)	60 (82.2%)

	Total	73 (100.0%)	73 (100.0%)
Stromal Invasion	yes	60 (82.2%)	17 (23.3%)
	no	13 (17.8%)	56 (76.7%)
	Total	73 (100.0%)	73 (100.0%)

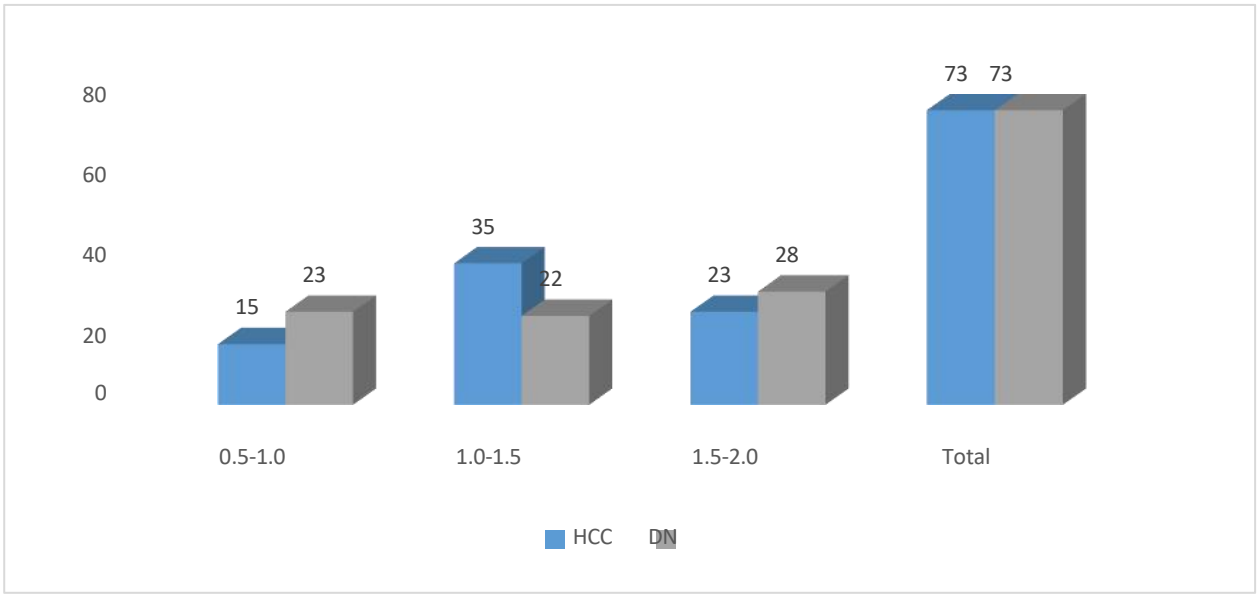

Figure 4.7 Graphical representation of size of HCC and DN

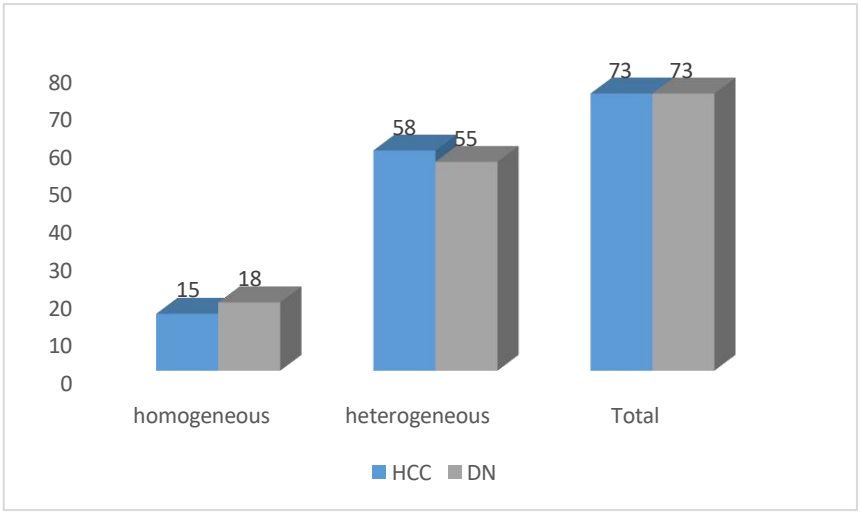

Figure 4.8 Graphical representation of enhancement pattern of HCC and DN

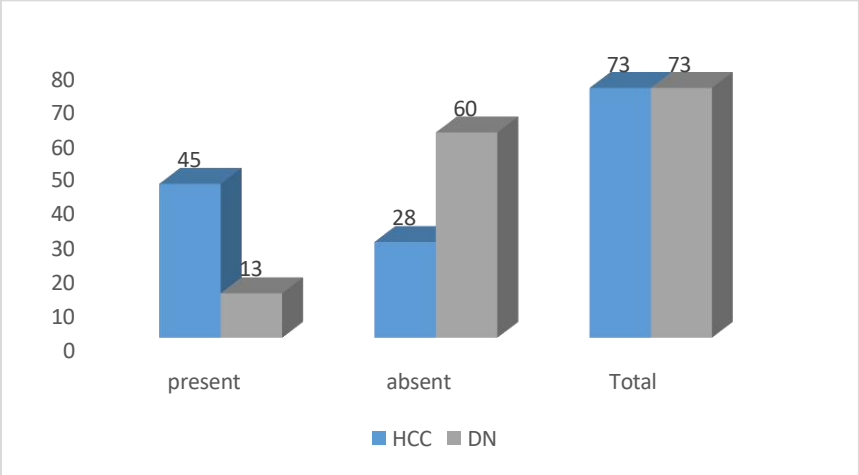

Figure 4.9 Graphical representation of washout pheomenon of HCC and DN

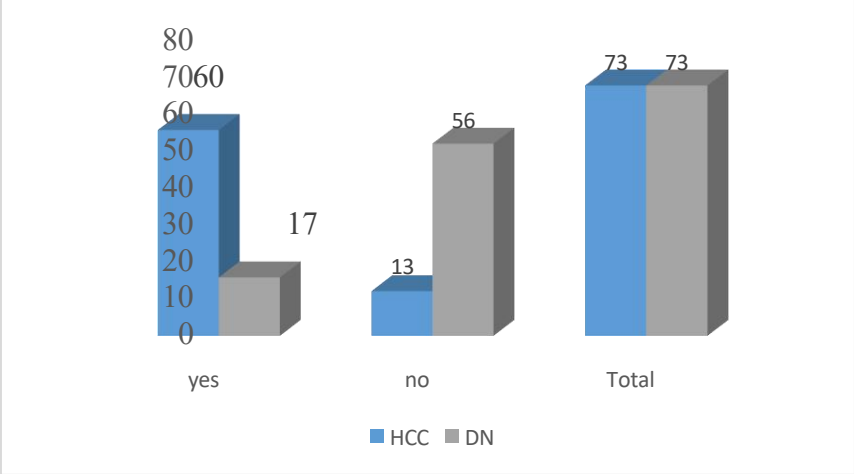

Figure 4.10 Graphical representation of stromal invasion of HCC and DN

The cross tabulation between early arterial phase imaging and enhancement pattern for HCC and DN is given below in table 4.3. After that chi square test was appllied and and the p-value obtained is < 0.001 which showed that results are significant.

Table 4.3 *Cross tabulation showing association between early arterial phase imaging and enhancement pattern of HCC & DN*

	Early arterial phase imaging					Total
	Homogenous		hetrogenous	Non Suggestive	Not Visualized	
Enhancement pattern	HCC	12	36	2	0	50
	DN	04	16	2	1	23
Total	73					

Chi-Square Tests		
	x^2	p value
Pearson Chi-Square	18.489[a]	<.001
Likelihood Ratio	18.794	<.001
Linear-by-Linear Association	14.675	<.001
N of Valid Cases	90	

Table 4.4 representing total number of true positive, true negative, false positive and false negative cases of HCC and DN in early arterial phase imaging. Out of 73 cases 03 were non suggestive. In 70 patients 44 for HCC and 42 for DN are in the category of true positive cases, 16 for HCC and 16 for DN were in true negative. And the false positive cases were 6 for HCC and 06 for DN and the 04 cases of HCC and 06 of DN were false negative.

Table 4.4 ***sensitivity, specificity, PPV and NPV value of HCC and DN by USG.***

Detectable cases	HCC	DN
True positive	44	42
False positive	06	06
True negative	16	16
False negative	04	06
Non suggestive	03	03
Total	73	73

a. 4 cells (50.0%) have expected count less than 5. The minimum expected count is .34.

Sensitivity = (True Positives) / (True Positives + False Negatives)
Sensitivity= 91.6 % for HCC. Sensitivity = 87.5% for DN

Specificity = (True Negatives) / (True Negatives + False Positives).
Specificity = 72.7% for HCC Specificity = 72.7% for DN

Positive predictive value (PPV), it can be calculated using this formula: PPV = True Positives / (True Positives + False Positives).
PPV= 88% for HCC PPV = 87.5% for DN
NPV = True Negatives / (True Negatives + False Negatives)
NPV= 80% for HCC NPV= 72.7% for DN.
Diagnostic Performance: Using the above imaging criteria, early arterial phase CT correctly identified 44 of 48 HCCs (true positives) and correctly recognized 16 of 25 DNs as benign (true negatives). There were 4 HCCs misclassified as DNs (false negatives) and 6 DNs misclassified as HCC (false positives). Three lesions were deemed indeterminate (non-suggestive on imaging) and excluded from performance calculations. This yielded a sensitivity of **91.6%** for HCC detection and specificity of **72.7%**, with a positive predictive value of **88%** and negative predictive value of **80%** for HCC diagnosis. For identifying dysplastic nodules, the test sensitivity was **87.5%** (i.e.

87.5% of actual DNs were correctly identified) and specificity **72.7%** (since specificity is symmetric in this two-group context). The diagnostic accuracy (overall agreement) of early arterial phase imaging in distinguishing HCC vs DN in this series was approximately 82%. These results indicate that incorporating the early arterial phase leads to a high detection rate for HCC, albeit with some trade-off in specificity (about 6 out of 25 DNs were erroneously labeled as HCC). Notably, all misclassified DNs in our study were high-grade nodules that exhibited partial arterial enhancement but lacked frank washout; this underscores that while early arterial phase improves detection of hypervascular lesions, a small fraction of premalignant nodules can share some enhancement characteristics with HCC.

CONCLUSION

Early arterial phase imaging plays a critical role in the accurate differentiation of hepatocellular carcinoma from dysplastic nodules in cirrhotic patients. In our study, the inclusion of an early arterial phase markedly improved the detection of HCC, yielding a sensitivity over 90%. Key distinguishing features – notably the presence of contrast washout and signs of stromal invasion – were significantly more frequent in HCC than in dysplastic nodules (which rarely exhibited these findings). These results underscore that the hemodynamic changes of hepatocarcinogenesis (arterial neoangiogenesis and portal flow loss) are best captured in the early arterial window. By visualizing these changes, radiologists can confidently differentiate early HCC from benign regenerating nodules without invasive procedures.

Implementing early arterial phase imaging in routine liver CT protocols for cirrhotic patients has the potential to **enhance diagnostic confidence**, reduce reliance on biopsy, and enable earlier intervention for malignant lesions. We recommend that multiphase liver CT (or MRI) always include an appropriately timed arterial phase. Radiologists should focus on identifying arterial hyperenhancement followed by washout, as this combination is highly specific for HCC in the cirrhotic liver. While a small proportion of high-grade dysplastic nodules may show some arterial enhancement, they typically lack washout and invasive features, helping to avoid false positives.

In conclusion, early arterial phase imaging should be considered an essential component in the evaluation of cirrhotic patients with liver nodules. Its use can improve non-invasive discrimination of HCC from dysplastic nodules, thereby facilitating prompt curative treatment for HCC and vigilant monitoring for premalignant nodules. Future large-scale studies and advancements in imaging (including functional imaging and AI-based analysis) will further refine this diagnostic approach, but our findings strongly support the routine use of early arterial phase imaging in current clinical practice to optimize outcomes for patients at risk of hepatocellular carcinoma

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