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Impact of MRI Findings and Clinical Parameters on Predicting Tumor-Infiltrating Lymphocytes in Hepatocellular Carcinoma Patients

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Abstract

Background: The preoperative identification of tumor-infiltrating lymphocyte (TIL) status in hepatocellular carcinoma (HCC) is clinically important, but the ability of magnetic resonance imaging (MRI) features combined with clinical parameters to predict TIL levels remains unclear. The present study aimed to investigate whether MRI features and clinical parameters can predict TIL levels in patients with HCC undergoing surgical resection.

Method: A retrospective study of 156 HCC patients categorized TILs into; group 0 (low TIL, 0%–10%), group 1 (intermediate TIL, 11%–59%), and group 2 (high TIL, ≥60%). Continuous and categorical variables were compared using appropriate tests. Logistic regression identified predictors of TILs.

Results: Of 131 included patients, 37.9% were included in group 0, 12.2% in group 1, and 50.4% in group 2. Group 0 was significantly associated with ≥60 years of age, grade III, microvascular invasion, alpha-fetoprotein (AFP) >400 ng/ml, satellite nodules, unclear tumor boundaries, irregular shapes, non-smooth margins, absence of tumor capsule, and larger size ($P < 0.05$ for all). AFP level (odds ratio (OR) 0.19; 95% confidence interval (CI) 0.08-0.75, $P = 0.03$), tumor shape (OR 6.31; 95% CI 2.44-40.31, $P = 0.01$), margin (OR 0.13; 95% CI 0.05-0.6, $P = 0.03$), and tumor size on MRI (OR 0.99; 95% CI 1.06-1.49, $P = 0.04$) were independent predictors of TIL levels.

Conclusion: Preoperative MRI features, including tumor morphology, margin characteristics, and tumor size, together with serum AFP levels, showed a significant value in predicting TIL density in HCC patients undergoing surgical resection. These findings highlight MRI as a non-invasive tool for preoperative assessment and risk stratification.

Keywords: Hepatocellularcarcinoma, Tumor-infiltrating lymphocytes, Magnetic resonance imaging

Introduction

Hepatocellular carcinoma (HCC) is a very aggressive form of liver malignancy that typically arises in people with cirrhosis or chronic liver disease. Its global incidence is steadily increasing and is expected to continue rising through 2030. The high prevalence of hepatitis either B and/ or C infections in Africa and Asia contributes substantially to the burden of HCC, as these infections promote chronic liver affection with subsequent malignant transformation.[1]

Despite the availability of screening programs, a significant number of HCC cases are detected at advanced stages, which is associated with poor survival outcomes.[2]Treatment options that can cure the condition are restricted for patients who are not eligible for surgical resection or orthotopic liver transplantation.[3] Even among patients who undergo resection, recurrence remains a major challenge, with up to 75% experiencing the development of new HCC lesions or local recurrence within five years.[4]

Several clinical and pathological factors have been shown to influence HCC prognosis, including elevated alpha-fetoprotein (AFP), tumor histological grade, the extent of liver fibrosis, and tumor-infiltrating lymphocytes (TILs).[5,6] TILs are immune cells present both within the tumor mass and in the surrounding tissue, and their presence has been linked to improved survival outcomes across numerous cancer types.[7]

HCC can often be diagnosed without tissue sampling when nodules of 1 cm or larger exhibit the characteristic imaging pattern of arterial phase hyper enhancement followed by venous phase washout on computed tomography (CT) or magnetic resonance imaging (MRI).[8] MRI has been shown to outperform CT in detecting small HCC lesions, providing a more precise evaluation of tumor characteristics.[9]

Although MRI is well-established as a diagnostic tool for HCC, its potential to provide prognostic information, particularly in predicting immune cell infiltration, has not been fully explored. Therefore, the present study aimed to investigate the relationship between MRI features, clinical parameters, and TIL levels in patients with HCC undergoing surgical resection.

Patients and Methods

Ethical approval

We obtained clearance for this retrospective analysis from the Institutional Review Board (IRB) of Zagazig University Hospital (ethics code: ZU-IRB#497 /11). Due to the retrospective design of the study, the requirement for informed consent was waived.

Study design and patient selection

This retrospective analysis included patients with HCC who were diagnosed and treated at the Departments of Medical Oncology, Pathology, Radiology, and Surgery, Faculty of Medicine, Zagazig University, between January 2017 and December 2022. Clinical and radiological data were obtained through chart review and the hospital's Picture Archiving and Communication System (PACS).

The inclusion criteria were: age ≥18 years, resectable, operable, and MRI findings consistent with HCC obtained within two weeks prior to surgery. Patients were excluded if they had received any preoperative systemic or local therapy directed to the tumors, or if clinical, pathological, or radiological data were incomplete. For patients with multifocal tumors, the lesion with the largest diameter

was selected for analysis. A flow diagram of patient selection is presented in Figure 1.

Data collection

Clinical and pathological parameters

Collected clinical data included age, sex, liver function tests, AFP levels, and hepatitis virus status. Pathological variables included tumor size, histologic grade, and the presence of microvascular invasion (MVI).

MRI features

MRI was reviewed by our radiodiagnosis consultant. MRI assessment concentrated on multiple morphologic and structural tumor features, including necrotic components, the presence of satellite lesions, capsular appearance, lesion boundary definition, margin characteristics, overall tumor configuration, and the largest tumor dimension. The examinations were performed on 1.5 T and 3.0 T clinical scanners. A standardized liver MRI protocol included axial T1-weighted GRE, axial T2-weighted FSE with and without fat suppression, and diffusion-weighted imaging (b-values 0–800 s/mm²). Dynamic contrast-enhanced imaging was performed following intravenous administration of a gadolinium-based contrast agent (0.1 mmol/kg at 2–3 mL/s with saline flush). Three dynamic phases were acquired: arterial (~20 s), portal venous (~60–70 s), and late venous (~3–4 min) post-injection, with sequence parameters optimized for high spatial resolution. Additional hepatobiliary phase imaging at 20 min was included when hepatocyte-specific contrast agents were used. This protocol allowed a comprehensive evaluation of lesion morphology, enhancement patterns, and ancillary features. Necrosis was identified as intratumoral areas lacking post-contrast enhancement and exhibiting high signal intensity on T2-weighted sequences. Satellite nodules were defined as discrete lesions detected within a 2-cm radius of the primary tumor. Capsular formation was recognized by the appearance of a hyperintense peripheral rim during the venous or equilibrium contrast phases. Lesion boundaries were evaluated as either clearly demarcated or indistinct, while tumor margins were classified as smooth or irregular. Tumor morphology was categorized as round or non-round, and tumor size was determined by measuring the greatest transverse diameter on axial MRI images (Figure 2).

Histopathological assessment

The resected specimens were reviewed by our pathologist. The specimens were fixed in paraffin, and immunohistochemistry was performed to evaluate TILs. TIL density and percentage were calculated according to International Working Group criteria:[10]

- **Group 0:** low infiltration (0%–10%)
- **Group 1:** moderate infiltration (11%–59%)
- **Group 2:** high infiltration (≥ 60%)

Representative immunohistochemistry images illustrating each group are provided in Figure 3.

Statistical analysis

The study used the Mann-Whitney U test, independent samples t-test, and chi-squared test to analyze continuous and categorical variables. Univariate and multivariate logistic regression analyses were conducted to examine the clinical variables and MRI parameters associated with TILs. Continuous variables were presented as mean ± standard deviation or median (interquartile range) values and compared using independent-samples t-tests or the Mann-Whitney U test. Categorical variables were presented as numbers (percentages) and compared using the chi-square test. Univariate analysis was conducted to identify potentially significant variables. Variables with significant differences (P<0.05) in the univariate analysis were included in multivariate analysis to identify independent predictors of TILs. Statistical analyses were carried out using SPSS 22.0 for Windows (IBM, Inc.,

Chicago, IL, USA) and MedCalc for Windows (MedCalc Software bvba, Ostend, Belgium).

Results

Out of 156 initially identified patients, 25 were excluded due to incomplete MRI data, leaving 131 eligible patients. The cohort included 94 men, with a mean age of 61.3 ± 8.7 years. Tumor distribution among TIL groups was: 49 patients (37.9%) in group 0, 16 (12.2%) in group 1, and 66 (50.4%) in group 2. Fourteen patients had multifocal tumors; in these cases, the largest lesion was analyzed. Table 1 provides a summary of the key clinical and pathological features.

Associations between TILs and clinical/MRI features

Group 0 (TILs 0%–10%) was associated with several unfavorable features, including age ≥ 60 years, grade III tumors, presence of MVI, AFP > 400 ng/mL, presence of satellite nodules, unclear tumor boundary, irregular (non-rounded) tumor shape, non-smooth tumor margin, absence of a tumor capsule, and larger tumor size (P< 0.05 for all) (Table 2).

Independent predictors of TILs

Logistic regression analysis identified AFP level (odds ratio (OR) 0.19; 95% confidence interval (CI) 0.08–0.75; P= 0.03), tumor shape (OR 6.31; 95% CI 2.44–40.31; P= 0.01), tumor margin (OR 0.13; 95% CI 0.05–0.60; P= 0.03), and tumor size on MRI (OR 0.99; 95% CI 1.06–1.49; P= 0.04) as statistically significant independent predictors of TILs (Table 3).

Discussion

The present study investigated how clinical data and MRI characteristics can help estimate the level of TILs in HCC patients undergoing resection. We found that tumors with low TIL density (0%–10%) were consistently associated with more aggressive histopathological, laboratory, and imaging characteristics. Notably, serum AFP level and MRI features including tumor size, morphology, and margin features emerged as independent determinants of TILs density.

HCC displays substantial immune involvement, as the tumor microenvironment contains a wide array of interacting inflammatory and immune cell populations.[11] Immune activity can both impede and support tumor development on one hand, eliminating malignant cells, and on the other enabling survival of more resistant clones or fostering conditions that permit tumor expansion. The prognostic effect of TILs may reflect their ability to counterbalance immunosuppressive components within the tumor milieu.[12]

Prior research has established the relevance of TILs across several cancer types, where their presence has been linked to treatment response and overall outcome.[13-17] A meta-analysis by Gooden et al. highlighted the prognostic value of TILs in a range of solid tumors, including HCC.[18] Similarly, the work of Gao et al. demonstrated that higher TIL levels correlate with improved survival in resectable HCC,[19] and findings from a larger pooled analysis also supported this association.[20]

In our cohort, several MRI features differed notably between patients with high and low TIL infiltration. Tumor contour, boundary definition, presence of a capsule, and lesion shape showed clear variation. Tumor shape, margin, and size retained independent predictive value even after adjustment for other variables. These observations partially parallel the results of Du et al., who also reported that lower TIL levels were associated with larger tumors, absence of a capsule, and inferior survival outcomes.[5]

MVI remains a pivotal factor in recurrence and metastatic potential. Patients with greater lymphocytic infiltration appear to develop MVI less frequently, although the

mechanisms underlying this trend require additional clarification.[21]

While multiple studies support the prognostic role of TILs, imaging-based assessment of immune infiltration remains an emerging field. Prior work, including studies by Liao et al. and Chen et al., suggests that radiologic features and radiomic signatures may reflect the degree of lymphocytic infiltration.[22-23]The ability of contrast-enhanced MRI to characterize tumor structure, vascular behavior, and tissue composition makes it well suited for such evaluations.[24]

Integrating clinical variables with imaging findings and pathological information can help refine individualized treatment strategies and may guide decisions regarding surgical management and systemic or immunotherapeutic interventions.

This study is subject to certain limitations, including its retrospective design, relatively small sample size, and single-center setting, which may limit the generalizability of the findings. In patients with multifocal disease, only the largest lesion was evaluated, potentially underrepresenting intratumoral and intertumoral heterogeneity. Furthermore, variability in MRI acquisition parameters and scanner platforms may have introduced imaging protocol heterogeneity, which could have influenced image interpretation and quantitative analysis.

Conclusion

Low TIL density (0–10%) was associated with several adverse features, including older age (≥60 years), higher tumor grade, MVI, AFP > 400 ng/mL, and MRI findings such as satellite nodules, irregular tumor contours, non-smooth margins, loss of capsule integrity, and larger tumor size. AFP level, tumor shape, tumor margin, and MRI-based tumor size were identified as independent predictors of TIL levels. These results highlight the potential role of TIL assessment in treatment planning and support the need for larger prospective studies to determine how immune infiltration may influence the selection of adjuvant or neoadjuvant therapies.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request and the IRB approval.

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Authors' Contribution

Amrallah Mohammed, Yaser Arafat, Ahmad BarakatWaley, BasmaSoliman, Amira Hanna, Marwa EL- Mosely, Mohamed Bayomi, Basant SH, and DoaaMandour: idea, data collection, interpretation, and discussion.

All authors contributed to study design, data collection and analysis, drafted and revised the manuscript, and approved the final version

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Conflict of Interest

None declared.

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Table 1. The main clinicopathological characteristics of the study population (n = 131)

Features	Number (131)	%	Features	Number	%
Age			**Satellite nodules**		
<60 years	73	55.73	Present	30	22.90
≥ 60 years	58	44.27	Absent	101	77.10
Sex			**Tumor boundary**		
Male	94	71.76	Clear	106	80.91
Female	37	28.24	Unclear	25	19.01
Grade			**Tumor shape**		
I	20	15.30	Rounded	85	64.88
II	54	41.22	Unrounded	46	35.12
III	57	43.48			
MVI			**Tumor margin**		
Present	63	48.10	Smooth	79	60.31
Absent	68	51.90	Non-smooth	52	39.69
Necrosis			**Tumor capsule**		
Present	70	53.43	Present	93	70.99
Absent	61	46.57	Absent	38	29.01
HCV	119	90.84	**Tumor size by MRI**		
Non-HVC	12	9.16	T1	34	25.95
			T2	55	41.98
			T3	42	32.07
Previous antivirus therapy			**Tumor size on pathology**		
Yes	103	78.63	T1	17	12.97
No	28	21.37	T2	65	49.62
			T3	49	37.41
TILs			**AFP (ng/mL)**		
Group 0	49	37.40	<400	58	44.27
Group 1	16	12.21	≥400	73	55.72
Group 2	66	50.39			

AFP: Alpha-fetoprotein; MRI: Magnetic resonance imaging; MVI: Microvascular invasion; HCV: Hepatitis C virus; TILs: Tumor infiltrating lymphocytes; n: Number; Group 0 = low TILs (0%-10%); Group 1= (11%-59%); Group 2 (≥ 60%)

Table 2. The distribution of TILs among hepatocellular carcinoma patients included in the study (n = 131)

Features	TILs			
	Group 0 N=49 (%)	**Group 1** N=16 (%)	**Group 2** N=66 (%)	***P*-value**
Age				
<60 years	15 (20.5)	13 (17.8)	45 (61.7)	0.03
≥ 60 years	34 (58.6)	3 (5.2)	21(36.2)	
Sex				
Male	25 (26.6)	11(11.7)	58 (61.7)	0.61
Female	24 (64.9)	5 (13.5)	8 (21.6)	
Grade				
I	4 (20)	5 (25)	11 (55)	
II	14 (25.9)	2 (3.7)	38 (70.4)	0.04
III	31(54.4)	9 (15.8)	17 (29.8)	
MVI				
Present	33 (52.4)	4 (12.1)	26 (35.5)	0.01
Absent	16 (23.6)	12 (17.6)	40 (48.8)	
Necrosis				
Present	33 (47.1)	8 (11.4)	29 (41.5)	0.82
Absent	16	8	37	
HCV	47 (39.5)	12 (10.1)	60 (50.4)	
Non-HCV	2 (16.7)	4 (33.3)	6 (50)	0.07
Previous anti-virus therapy				
Yes	42 (40.8)	8 (7.8)	51 (51.4)	0.12
No	5 (17.9)	8 (28.6)	15 (53.5)	
AFP (ng/mL)				
<400	6 (10.3)	9 (15.5)	43 (74.2)	<0.001
≥400	43 (58.9)	7 (9.6)	23 (31.5)	
Satellite nodules				
Present	19 (63.3)	5 (16.7)	6 (20)	<0.00
Absent	30 (29.7)	11(10.9)	60 (59.4)	
Tumor boundary				
Clear	37 (34.9)	10 (9.4)	59 (55.7)	
Unclear	12 (48)	6 (24)	7 (28)	0.02
Tumor shape				
Rounded	22 (25.9)	11 (12.9)	52 (61.2)	0.04
Unrounded	27 (58.7)	5 (10.9)	14 (30.4)	
Tumor margin				
Smooth	22 (27.8)	9 (11.4)	48 (60.8)	<0.001
Non-smooth	27 (51.9)	7 (13.5)	18 (34.6)	
Tumor capsule				
Present	28 (28.6)	12 (12.9)	53 (58.5)	<0.001
Absent	21 (55.3)	4 (10.5)	13 (34.2)	
Tumor size by MRI				
T1	5 (14.7)	11 (32.4)	18 (52.9)	
T2	27 (49.1)	3 (5.5)	25 (45.4)	0.01
T3	17 (40.5)	2 (4.8)	23 (54.7)	
Tumor size on pathology				
T1	2 (11.8)	5 (29.4)	10 (58.8)	0.03
T2	9 (13.8)	5 (7.7)	51 (78.5)	
T3	38 (77.6)	6 (12.2)	5 (10.2)	

Non-rounded morphology was defined as a lobulated or irregular but still well-demarcated expansile mass; AFP: Alpha-fetoprotein; MRI: Magnetic resonance imaging; MVI: Microvascular invasion; HCV: Hepatitis C virus; TILs: Tumor infiltrating lymphocytes; n: Number; *P*- value<0.05 is considered a significant; Group 0 = low TILs (0%-10%); Group 1= (11%-59%); Group 2 (≥ 60%)

Table 3. Cox proportional hazards regression analyses (univariate and multivariate) for the prediction of TILs in hepatocellular carcinoma patients

Features	Univariate		Multivariate	
	OR (95%CI)	***P*-value**	**OR (95%CI)**	***P*-value**
Age	0.99 (0.96-1.00)	0.07	--	--
Sex	2.31 (0.96-5.70)	0.91	--	--
Grade	1.12(0.45-2.76)	0.42	--	--
Necrosis	1.90 (0.86-4.20)	0.13	--	--
HCV vs non-HCV	0.58(0.18-1.81)	0.42	--	--
Previous antivirus therapy	1.53 (0.67-3.51)	0.71	--	--
AFP (ng/ml)	0.13 (0.06-0.50)	0.01	0.19 (0.08-0.75)	0.03
Satellite nodules	4.91 (0.93-17.32)	0.03	--	--
Tumor boundary	0.34 (0.09-0.98)	0.14	0.27 (0.09-0.57)	0.42
Tumor shape	8.46 (3.54-22.71)	<0.001	6.31 (2.44-40.31)	0.01
Tumor margin	0.15 (0.06-0.67)	0.002	0.13 (0.05-0.6)	0.03
Tumor capsule	0.56 (0.16-1.98)	0.02	--	--
Tumor size by MRI	1.54 (2.06-2.21)	0.001	0.99 (1.06-1.49)	0.04

AFP: Alpha-fetoprotein; MRI: Magnetic resonance imaging; MVI: Microvascular invasion; HCV: Hepatitis C virus; TILs: Tumor infiltrating lymphocytes; OR: Odds ratio; CI: Confidence interval; *P*- value<0.05 is considered a significant.

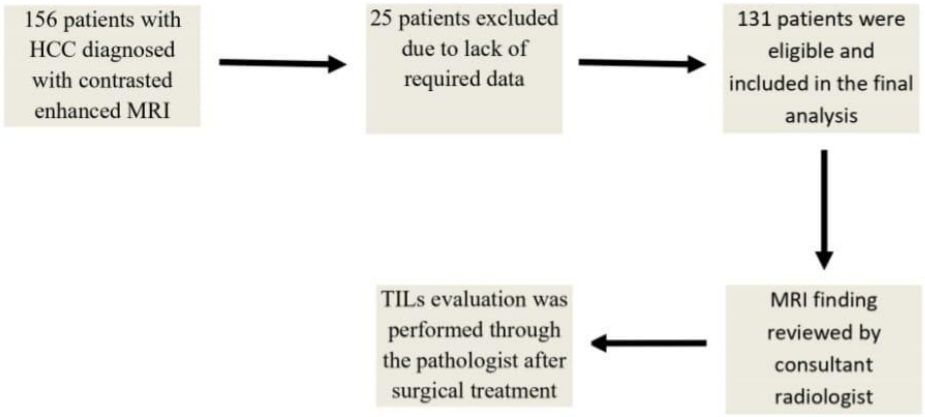

Figure 1. This figure illustrates the flow chart of patient selection and inclusion in the study. It shows the total number of patients initially assessed for eligibility, the number of patients excluded with reasons for exclusion, and the final number of HCC patients included in the analysis.
TILs: Tumor infiltrating lymphocytes; MRI: Magnetic resonance imaging; HCC: Hepatocellular carcinoma

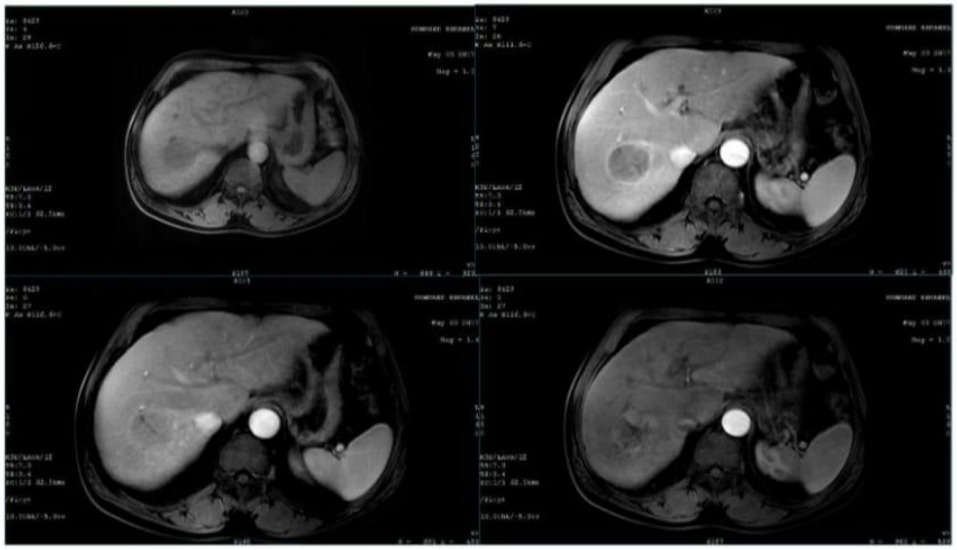

Figure2A

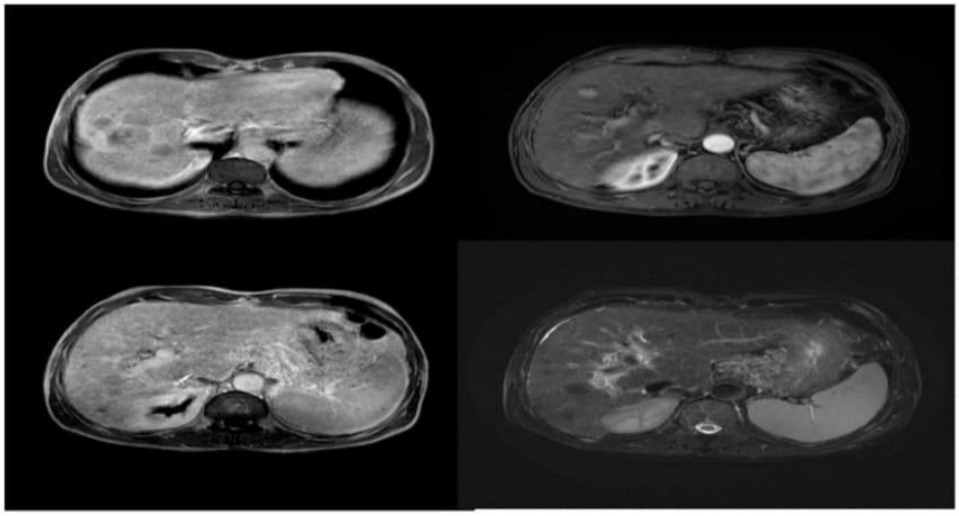

Figure2B

Figure 2. This figure demonstrates representative MRI findings in HCC patients according to the level of TILs, Figure 2A shows MRI features of an HCC lesion in a patient with high TILs, whereas Figure 2B shows MRI characteristics of an HCC lesion in a patient with low TILs.
MRI: Magnetic resonance imaging; HCC: Hepatocellular carcinoma; TILs: Tumor-infiltrating lymphocytes

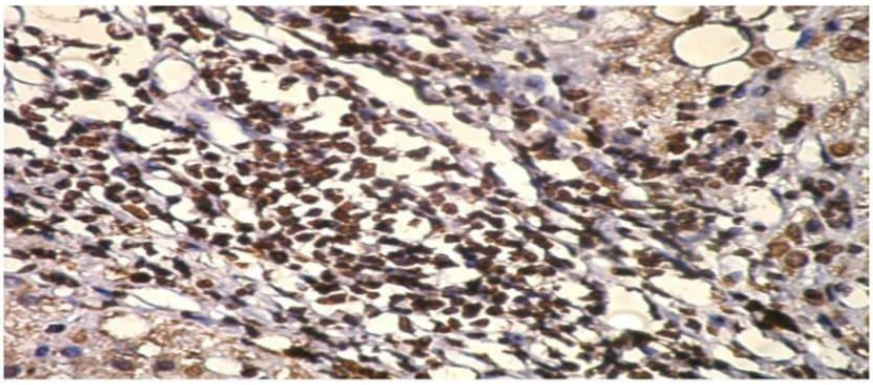

Figure3A

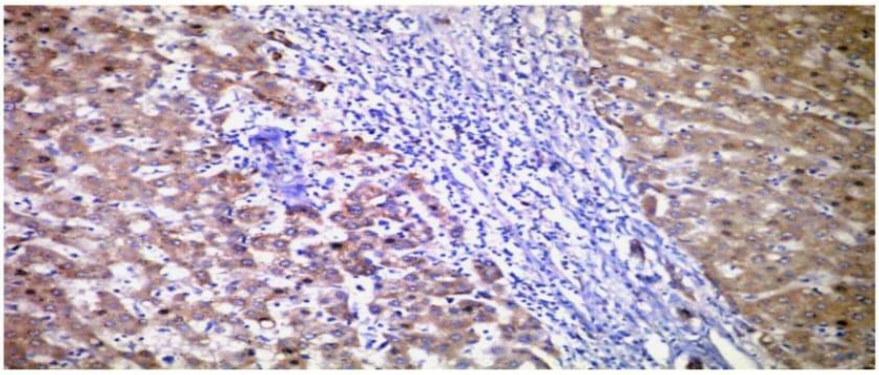

Figure3B

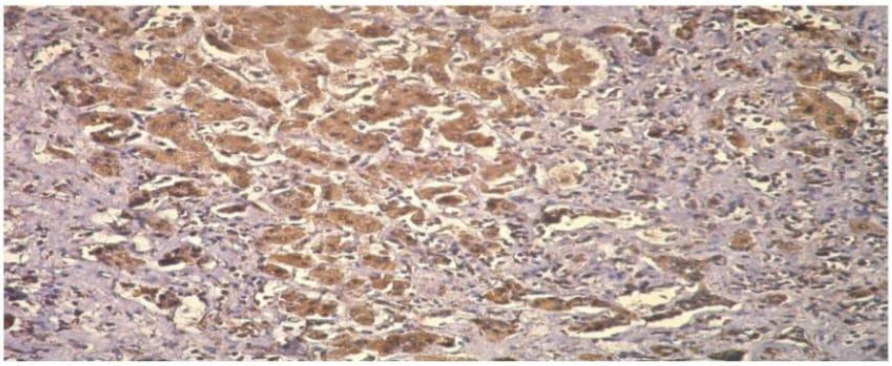

Figure3C

Figure 3. This figure shows hematoxylin and eosin (H&E) staining of TILs in hepatocellular carcinoma tissue sections at ×400 magnification, Figure 3A demonstrates a tumor with high TILs infiltration (≥ 60%), Figure 3B shows moderate TILs infiltration (11%–59%), and Figure 3C illustrates low TILs infiltration (0%–10%).

TILs: Tumor-infiltrating lymphocytes