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ORIGINAL ARTICLE

Validity of predictive score model for microvascular invasion in Hepatocellular carcinoma.

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ABSTRACT... Objective: To validate a risk score model to predict MVI using Total tumor volume (TTV) and AFP. **Study Design:** Cross-sectional. **Setting:** Department of Gastroenterology, Liaquat National Hospital, Karachi, Pakistan. **Period:** June 2022 to December, 2023. **Methods:** Patients of either gender, older than 18 years and above with confirmed diagnosis of HCC were enrolled. When there were several HCC tumors, the largest tumor's axis was measured and used as the representative HCC diameter. When microscopic tumor invasion was detected in the portal, hepatic vein, or biliary vein of the surrounding liver tissue that was adjacent to the tumor, it was referred to as micro vascular invasion. **Results:** Total 302 patients were studied with mean age of 62.1 ± 9.2 years. Majority of patients were males (64.2%). Around one-fifth patients had more than one tumor (19.9%). Out of 302 patients, MVI was seen in 30.1% patients. In multivariable analysis number of tumors (aOR=220.65, 95% CI: 128.91-922.67), tumor volume (aOR=1.01, 95% CI: 1.01-1.02), and AFP (aOR=1.01, 95% CI: 1-1.02) were found to be significant predictors of MVI. **Conclusion:** This study validated a prediction model for forecasting of MVI in HCC patients with highly significant variables including number of tumors, tumor volume and alpha feto protein. Timely decision making could be done using this model.

Key words: Hepatic Disorders, Hepatocellular Carcinoma, Liver Disease, Microvascular Invasion, Tumor.

INTRODUCTION

Between 75 and 85 percent of cases of liver malignancy are led by hepatocellular carcinoma (HCC), the sixth most frequent type of malignancy.[1] One of the main risk factors is cirrhosis, which is brought on by damaged and inflamed liver tissue. With a 5-year survival rate of <15%, HCC has poor results and is resistant to most therapy.[2] Well-known risk factors that can lead to the HCC development include long-term alcohol or aflatoxin exposure, non-alcoholic fatty liver disease and chronic hepatitis B or C virus infection. The two most significant predictive markers of tumor histological features are histopathologic grade of differentiation and micro-vascular invasion (MVI), which have a significant influence on both tumor recurrence and patient survival.[3]

There are two types of vascular invasion, microscopic and macroscopic. While the histological examination of the tumor and adjacent hepatic tissue determines the microvascular invasion, the macroscopic invasion is assessed by radiography or gross tissue evaluation. Microvascular invasion (MVI) is characterized as a microscopic cancer cell nest in endothelial-lined arteries. It is typically seen in the hepatic artery, bile duct, and lymphatic veins, as well as in the small branches of the portal vein in surrounding liver tissues.[4] The existence of micrometastatic HCC emboli in the liver's vascular system is a crucial factor in determining the quick recurrence and HCC survival. Tumor cells can proliferate and spread to produce a portal vein tumor thrombus, numerous lesions, or distant metastases in the liver when MVI is present.[4] High grade big tumor size and raised blood AFP are two undesirable biological markers that are closely correlated with MVI, which is commonly found in HCC patients.

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According to reports, MVI can affect individuals with HCC at a rate of 15% to 57%. For certain individuals, hepatectomy and liver transplantation are the most successful managements and offer a chance for recovery.[5]

Serum alpha-fetoprotein (AFP) is the most extensively recognized HCC biomarker and can be utilized in the HCC surveillance and diagnosis in individuals with chronic liver disease because its serum concentration increases in most cases.[6,7] A plasma AFP concentration of more than 400 ng/ml is typically regarded as reliable evidence to support the diagnosis of HCC, as AFP is secreted by about 50% of HCCs.[8] Certain medical professionals have stated that smaller tumors appear to release less AFP into the bloodstream, and that elevated serum AFP levels are linked with larger tumor sizes.[9] Numerous tumors, huge tumor size, microvascular invasion, and high alpha fetoprotein (AFP) levels have all been linked to a considerable risk of either an early or late HCC recurrence.[9,10]

If these patients with an elevated tumor recurrence are identified early, a rigorous surveillance program may be implemented, potentially improving survival.[10] Another prognostic indicator for tumor burden is total tumor volume (TTV), which combines the size and quantity of tumor nodules into a single calculation to reliably forecast the result.[10] Pretreatment detection of MVI is frequently challenging, even with the use of sophisticated imaging modalities used for staging assessment. Consequently, before beginning any curative therapy, it is critical to accurately and as soon as possible forecast whether MVI will be present.[11] An efficient risk score model can be validated by using the findings of prior research, which shown that TTV and AFP levels are determinants of MVI. Before providing any curative treatment, our goal is to establish a risk score model for predicting MVI using TTV and AFP. This way, the treatment strategy for HCC may be modified based on the risk of MVI to maximize survival results.[12]

METHODS

This cross-sectional study was performed in Gastroenterology Department during June 2022 to December, 2023 after obtaining formal permission from hospital ethics committee (IRB: App#0778-2022-LNH-ERC). Patients of either gender, older than 18 years and above with confirmed diagnosis of HCC were enrolled. Patients with other malignancies, receiving radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE) or radiotherapy and pregnant females were excluded from this study.

Frequency of MVI in HCC patients was 46.3% in previously reported study.[4] Therefore at 95% confidence interval and 6% precision, a sample of total 300 patients is required. Sample size calculation is performed on Open-Epi sample size calculator. A written consent form was taken from all patients prior to their enrolment into the study.

When there were several HCC tumors, the largest tumor's axis was measured and used as the representative HCC diameter. Tumor size was characterized by the longest axis and evaluated using ultrasound or CT scan.[8] The volume of each tumor added together is known as the total tumor volume (TTV), and it can be computed as follows: length $\times$ width $\times$ width $\times$ 0.52.[4] Thirty, sixty, and three hundred cm^3 will be the TTV cut-off thresholds.[10] When microscopic tumor invasion was detected in the portal, hepatic vein, or biliary vein of the surrounding liver tissue that was adjacent to the tumor, it was referred to as micro vascular invasion.[9]

The gathered data was entered in SPSS version 27 for statistical analysis. Frequencies and percentages were computed from categorical variables. Numerical variables were summarized as mean $\pm$ standard deviation when normally distributed otherwise expressed as median with inter-quartile range. Binary logistic regression was applied to determine association of tumor size, tumor volume and AFP. Univariate and adjusted odds ratio were computed with their 95% confidence interval. Variables with $p<0.25$ in univariate analysis were used to compute adjusted odds ratio. P-value at 5% level of significance was considered as significant on final regression analysis.

RESULTS

Total 302 patients were enrolled into the study with mean age of 62.1 ± 9.2 years. Majority of patients were males (64.2%), were belonging to urban areas (79.5%), and enrolled from in-patient department. Patients had comorbidity of hypertension (39.1%), diabetes (27.2%) and asthma (1.3%). Majority had disease etiology of HCV (72.8%). Around one-fifth patients had more than one tumor (19.9%). Table-I displays summary of patients' socio-demographic and clinical features.

Variables	Groups	Frequency	Per-centage
Gender	Male	194	64.2
	Female	108	35.8
Residence	Rural	62	20.5
	Urban	240	79.5
Visit type	OPD	62	20.5
	IPD	240	79.5
Hypertension	Yes	118	39.1
	No	184	60.9
Diabetes	Yes	82	27.2
	No	220	72.8
Asthma	Yes	4	1.3
	No	298	98.7
CLD etiology	HBV	26	8.6
	HCV	220	72.8
	Others	56	18.5
Hepatic encephalopathy	Yes	30	9.9
	No	272	90.1
Ascites	Yes	164	54.3
	No	138	45.7
Ascites grading	mild	76	46.3
	moderate	70	42.7
	severe	18	11.0
Child-Pugh classification	Class A	106	35.1
	Class B	148	49.0
	Class C	48	15.9

Table-I. Summary of patients' socio-demographic and clinical features

OPD: out-patient department, IPD: in-patient department, CLD: chronic liver disease, HBV: hepatitis B virus, HCV: hepatitis C virus.

Median level of HB, RBC, platelet count, PT/INR, albumin, AFP, total bilirubin, , ALT, ALKPO4, GGT and AST were 1.3 (IQR=1.2-1.4), 2.9 (IQR=2.6-3.2), 322.5 (IQR=67.3-1305.5), 1.4 (IQR=0.8-2.7), 41 (IQR=23-76), 149 (IQR=85-233), 89 (IQR=45-175) and 61 (IQR=35-120) respectively. Out of 302 patients, MVI was seen in 30.1% patients.

Table-II shows comparison of patients' features among those with and without microvascular invasion and their univariate association. In univariate analysis, gender, hypertension, CLD etiology, number of tumors, tumor volume, Child-Pugh class and AFP were found to be associated with MVI.

Table-III presents multivariable association of patients' features with microvascular invasion. In multivariable analysis, gender, number of tumors, tumor volume, Child-Pugh class, albumin and AFP were found to be associated with MVI.

DISCUSSION

Globally, HCC is frequent and considered as one of the most deadly malignancies.[13] MVI reflects a substantial risk contributor for metastasis and survival following resection among HCC cases.[14] Multiple retrospective investigations indicate that MVI hold a crucial attention in prompt recurrence within 24 hours of surgical procedure. Moreover, multiple scholars prognosis pattern is variable when HCC patients with MVI are managed with different treatment modalities.[15,16] Nevertheless, existing criteria for to establish MVI diagnosis is based on post-operative pathological assessment of specimen, which is not supportive approach for developing treatment plan prior to surgery.[17] Therefore we developed a model for overcoming problem. The formulation of this model would be beneficial for establishing a mechanism for prompt and ongoing surveillance.

MVI is prevalent in HCC and indicates the tumor's strong potential for early invasion and metastasis.[18] Still up for dispute, nonetheless, is the predictive importance of MVI after curative surgery.[19,20] MVI burden in HCC varies from 30% to 50%, presumably as a result of various MVI diagnostic criteria and specimen sampling techniques used in various investigations. MVI incidence remains more than 20%, even in tiny HCCs (< 3 cm).[21,22] In agreement to the existing literature, we found burden of MVI in 30.1% of our patients.

Variables	Groups	Microvascular Invasion		OR (95% CI)	P-Value
		Yes	No		
Age (in years)	-	62(55-66)	65(54-70)	0.99 (0.96-1.01)	0.451
Gender	Male	70(36.1)	124(63.9)	2.34 (1.34-4.09)	**0.003
	Female	21(19.4)	87(80.6)	Reference category	
Residence	Rural	21(33.9)	41(66.1)	1.24 (0.68-2.25)	0.472
	Urban	70(29.2)	170(70.8)	Reference category	
Hypertension	Yes	26(22)	92(78)	0.52 (0.32-0.88)	*0.015
	No	65(35.3)	119(64.7)	Reference category	
Diabetes	Yes	19(23.2)	63(76.8)	0.62 (0.34-1.11)	0.109
	No	72(32.7)	148(67.3)	Reference category	
Asthma	Yes	0(0)	4(100)	-	-
	No	91(30.5)	207(69.5)	-	-
CLD etiology	1.00	8(30.8)	18(69.2)	2.04 (0.69-6.01)	0.193
	2.00	73(33.2)	147(66.8)	2.28 (1.09-4.78)	*0.028
	3.00	10(17.9)	46(82.1)	Reference category	
No. of tumors	1	58(96.7)	2(3.3)	183.66 (42.79-788.19)	**<0.001
	>1	33(13.6)	209(86.4)	Reference category	
Tumor volume	-			1.01 (1.01-1.02)	**<0.001
Hepatic encephalopathy	Yes	5(16.7)	25(83.3)	0.43 (0.16-1.16)	0.098
	No	86(31.6)	186(68.4)	Reference category	
Ascites	Yes	44(26.8)	120(73.2)	0.71 (0.43-1.16)	0.173
	No	47(34.1)	91(65.9)	Reference category	
Child-pugh class	Class A	32(30.2)	74(69.8)	0.61 (0.29-1.22)	0.165
	Class B	39(26.4)	109(73.6)	0.50 (0.25-0.98)	0.046
	Class C	20(41.7)	28(58.3)	Reference category	
Hemoglobin	-	10.5(9.1-11.8)	10.4(8.9-12.2)	0.98 (0.88-1.09)	0.753
Total leukocyte count	-	6.9(5.8-9.3)	6.3(4.6-9.2)	1 (1-1)	0.800
Platelet count	-	130(80-182)	106(71-165)	1 (0.99-1.01)	0.268
Total bilirubin	-			1.02 (0.97-1.08)	0.324
ALT	-	48(26-90)	39(22-62)	1.01 (0.99-1.01)	0.147
$ALKPO_4$	-	165(85-365)	144(85-214)	1 (1-1.01)	0.058
GGT	-	109(49-175)	80(39-177)	1 (0.99-1.01)	0.690
AST	-	75(43-150)	55(35-99)	1 (0.99-1.01)	0.487
Albumin	-	2.9(2.6-3.1)	2.6(2.6-3.2)	0.73 (0.47-1.12)	0.154
PT/INR	-	1.3(1.2-1.4)	1.3(1.2-1.5)	0.64 (0.20-2.02)	0.449
Child-Pugh clas	Class A	32(30.2)	74(69.8)	0.61 (0.30-1.22)	0.165
	Class B	39(26.4)	109(73.6)	0.50 (0.25-0.98)	*0.046
	Class C	20(41.7)	28(58.3)	Reference category	
AFP	-	800(241-3625)	197(56-644)	1.01 (1-1.02)	*0.015

Table-II. Comparison of patients' features among those with and without microvascular invasion and their univariate association

CI: Confidence interval, OR: Odds ratio, *Significant at $p<0.05$

The higher frequency of MVI may be due to unclear tumor borders, which frequently imply incomplete capsules, invasive abilities, poorer differentiation, and are more favorable to the development of microscopic tumor thrombi.

Tumor thrombus, satellite nodules, and capsular invasion may be linked to greater tumor sizes.[23] Through the use of clinical, laboratory, and imaging criteria, the authors of various previous studies have attempted to preoperatively foresee MVI.[21,24] Tumor size was examined in this study as one of the most reliable indicators of MVI. Numerous studies have formerly demonstrated that tumor size is a prognostic determinant

Variables	Groups	aOR (95% CI)	P-Value
Gender	Male	18.41 (3.91-86.81)	**<0.001
	Female	Reference category	
Hypertension	Yes	0.43 (0.15-1.24)	0.119
	No	Reference category	
Diabetes	Yes	0.23 (0.34-1.11)	0.061
	No	Reference category	
CLD etiology	1.00	1.35 (0.16-11.42)	0.778
	2.00	2.29 (0.55-9.54)	0.253
	3.00	Reference category	
No. of tumors	1	220.65 (128.91-922.67)	**<0.001
	>1	Reference category	
Tumor volume	-	1.01 (1.01-1.02)	**<0.002
Hepatic encephalopathy	Yes	0.54 (0.11-2.82)	0.463
	No	Reference category	
Ascites	Yes	0.44 (0.07-2.75)	0.383
	No	Reference category	
Child-pugh class	Class A	0.16 (0.013-1.22)	0.169
	Class B	0.12 (0.02-0.56)	*0.046
	Class C	Reference category	
ALT	-	1.01 (0.99-1.01)	0.997
$ALKPO_4$	-	1 (1-1.01)	0.375
Albumin	-	0.19 (0.04-0.85)	*0.030
AFP	-	1.01 (1-1.02)	*0.043

Table-III. Multivariable association of patients' features with microvascular invasion
CI: Confidence interval, aOR: Adjusted odds ratio, *Significant at p<0.05

in individuals with HCC.[21,25] When adjuvant medication is administered to HCC patients with positive MVI, tumor size also significantly affects the prognosis.[26]

A powerful predictor of HCC recurrence following liver transplantation or resection is tumor volume, which is a mix of number of tumors and their size to indicate the burden.[27] This study confirmed the current literature's findings by finding a positive correlation between tumor volume and MVI. Patients with tumors >5cm in diameter have demonstrated to benefit greatly from anatomic hepatectomy in terms of long-term survival.[28,29] This shows that tumors with greater diameters are also more prone to cause MVI.

Indeed, there are still certain limitations our investigation. First off, all of the study's data were studied from a single institution; further data from other centers are required to confirm the model's trustworthiness.

CONCLUSION

This study validated a prediction model for forecasting of MVI in HCC patients with highly significant variables including number of tumors, tumor volume and alpha feto protein. Timely decision making could be done using this model.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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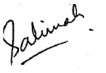
1	Salimah Anwar Jussa	Conceptualized the study, Designed the study protocol initial manuscript writing, Data collection, Manuscript revision.	
2	Mansoor Ul Haq	Designed the study protocol, Critical review & revision of initial manuscript draft.	
3	Adeel Rahat	Designed the study protocol statistical analysis, Initial manuscript writing.