ORIGINAL RESEARCH

Tumor Markers for Hepatocellular Carcinoma; A predictive model analysis

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ABSTRACT

Objective: We retrospectively evaluated the levels of pre-diagnostic blood indicators in patients with HCC in order to develop a non-invasive predictive model that can precisely anticipate the onset of HCC and possibly enhance early clinical identification and prognostic assessment. **Methodology:** Between June 2021 and December 2022, total of150 HCC patients were admitted toHospital, 70 of whom had complete prognostic data. Twenty five factors that could indicate whether or not HCC would develop early were retrieved. Propensity score matching, ROC curve, logistic regression, and decision curve analyses were performed using R (version 3.6.1) software. All the tests were two sided and p value less than 0.05 was considered as for statistical significance. **Results:** The scoring model included two common patient characteristics (age and gender) as well as five independent predictor variables for the start of HCC. With an area under the curve (AUC) of 0.890 (95% CI 0.856-0.925). When compared to single variables or other score systems, the score model had greater predictive performance in discriminating and clinical net benefit, according to ROC analysis. The score model, however, exhibited strong predictive values for patients with early tumour stages (AJCC stage I) or small tumours (2 cm), according to stratified study. Additionally, the HCC patient's score started to rise 30 months before the clinical diagnosis and peaked at 6 months. **Conclusion:** By adopting this model, we may be able to make early adjustments to the current risk categorization system and take into account more extensive surveillance programmes for high-risk individuals. Additionally, it can assist doctors in evaluating the prognosis and development of HCC patients.

Keywords:

INTRODUCTION

Hepatocellular carcinoma (HCC), one of the deadliest malignant tumours (8.2%), is the third most frequent cause of cancer-related death worldwide [1]. According to the Global Cancer Statistics 2018, the worldwide incidence and mortality rates of HCC were 841000 (4.7%) and 782000 (8.2%)respectively [2]. More than 70% of patients acquire their initial diagnoses at intermediate-to-advanced stages as a result of the HCC's cunning beginning [3]. The prognosis for people with HCC remains poor; the 5-year survival rate is about 11.7–14.1%, in spite of major advances in medical technology in recent years [4]. However, the 5-year survival rates of individuals with early-stage hepatocellular carcinoma who underwent curative surgical therapy ranged from 69.0 to 86.2% [5]. A scientific screening method for early detection and rapid treatment is crucial to improving the prognosis of HCC patients. As a result, full therapeutic responses are more typical in HCC patients. Early detection of cancer recurrence opens the door for the prospective reapplication of curative treatment modalities.

Abdominal ultrasound scan and detection of serum alpha-fetoprotein are the most effective clinical screening techniques for early HCC diagnosis [6]. The abdominal ultrasound scan provide 39-65% sensitivity for tiny liver tumours (less than 2 cm), the accuracy of the data from the US is, however, significantly impacted by the image observer's skills, the

instrumentation's conditions, and the patient's characteristics (such as obesity, liver texture) [7]. Although there is a strong correlation between AFP, a test commonly used to detect HCC, and tumour size, it is negative in 15–30% of HCC patients [8]. Additionally, a number of clinical disorders, such as chronic liver disease, germ cell tumours, and stomach cancer, were associated with significantly higher AFP levels [9][10] .AFP-L3 and protein induced by vitamin K deficiency or antagonist-II (PIVKA-II) have high specificities for the diagnosis of HCC (92.9% and 89%, respectively), despite the fact that the sensitivity of each of these individual blood markers for the early diagnosis of HCC is below average [11][12]. Additional combination markers that can be used to predict the prognosis and onset of HCC include gamma-glutamyl transpeptidase to platelet ratio (GPR) [14], neutrophil-lymphocyte ratio (NLR)[13], and gamma-glutamyl transpeptidase to lymphocyte ratio (GLR)[15] . The development of score models based on a variety of variables, including gender, age, AFP levels, and pathological data, has boosted the accuracy of early HCC detection in several studies. The models' application is also limited by the difficulty in gathering some of their input variables. A model that could accurately predict HCC and make it simple for doctors to make an early HCC diagnosis was therefore urgently needed. We retrospectively evaluated the levels of pre-diagnostic blood indicators in patients with HCC in order to develop a non-invasive predictive model that can precisely anticipate the onset of HCC and possibly enhance early clinical identification and prognostic assessment.

METHODOLOGY

Between June 2021 and December 2022, total of150 HCC patients were admitted toHospital, 70 of whom had complete prognostic data. We reviewed their clinical data. The following criteria have to be met in order to be included in our study: patients having complete record of blood marker concentrations, general characteristics, and period of follow-up; HCC patients lacked any new malignant tumours of any kind. As controls, 750 patients with chronic hepatitis or liver cirrhosis were recruited.

The variables that were employed in the study were as follows: All patients' ages, genders, and medical histories were gathered as general clinical data; the PubMed database was exhaustively searched for any blood variables or combined signs that would point to the onset of HCC.Then, 25 factors that could indicate whether or not HCC would develop early were retrieved, including AFP, AFP-L3, PIVKA-II, Alanine transaminase (ALT), Aspartate transaminase (AST) levels, Albumin (ALB), Total Protein (TP), Total bilirubin (TB), Apolipoprotein I, Antithrombin III, Fibrinogen, Neutrophil to lymphocyte ratio (NLR), Gammaglutamyl transpeptidase (GGT) to platelet ratio (GPR), GGT to lymphocyte ratio (GLR), platelet to lymphocyte ratio (PLR), and bilirubin to albumin ratio (TB/ALB) [17].

STATISTICAL ANALYSIS

For statistical analysis, IBM SPSS software (version 22) was used. The mean and standard deviation of continuous measurement data with a normal distribution were used to compare the two groups. On the other hand, we used a non-parametric U-test (Mann-Whitney U test) to compare the two sets of parameters and reported the continuous measurement data with a non-normal distribution as the median (interquartile range). Categorical variables were expressed as percentages, and the chi-square test was used to compare the variations. Propensity score matching, and ROC curve analyses were performed using R (version 3.6.1) software. All the tests were two sided and p value less than 0.05 was considered as for statistical significance.

RESULTS

A total of 950 patients who matched the eligibility requirements were enrolled in the current trial, including 800 patients with chronic hepatitis or liver cirrhosis and 150 patients with HCC (HCC group). The results of the baseline analysis showed that the age and gender of the patients in the two groups differed significantly (Table 1). The general characteristics of the two groups—age, gender, and duration of surveillance—were considerably balanced ($p > 0.01$), indicating that the PSM analysis enhanced the groups' capacity to be compared. The matched data's statistical analysis, however, showed that there were still variations in some serum variables between the two groups, including AFP, AFP-L3, PIVKAII, etc. ($p < 0.01$).

Table 1: Characteristics of included participants

Variables	Before propensity score			After propensity score		
	Control group (N=800)	HCC group (N=150)	p-value	Control group (N= 150)	HCC group (N=150)	p-value
Age in mean	55.4 ± 13.2	58.6 ± 9.7	<0.001	52.7 ± 11.5	58.7 ± 9.5	0.48
Gender			<0.001			0.73
Male (%)	500	120		115	115	
Female (%)	300	30		18	15	
Positive HBsAg (%)	400	110	<0.001	80	100	<0.001
Surveillance time in	151.8 ± 8.7	121 ± 14.7	0.52	128.5 ±	123.1 ±	0.89

days				27.9	16.2	
Positive HBeAg (%)	135	8	<0.001	25	7	<0.001

*Table 2 Univariate logistic regression analysis was utilized to identify risk factors for the prediction of HCC, and ROC curve analysis was conducted to assess the predictive effectiveness of the serum indicators. utilizing, respectively, the criteria of AUC > 0.55 and p< 0.25.

Table 2: Comparison of liver functions and blood count ratio by using propensity score

Variables	Before propensity score			After propensity score		
	Control group	HCC group	p-value	Control group	HCC group	p-value
Liver Function						
Alanine transaminase, U/L	84 (28 to 285)	31.8 (19.68 to 51)	0.00	58.1 (27 to 245)	31.12 (19.85 to 51)	0.000
Albumin, g/L	38.2 (33.7 to 42.7)	39.8 (34.9 to 43.7)	0.034	37.8 (33.2 to 41.3)	40.7 (35.7 to 44.2)	0.0007
Aspartate aminotransferase (U/L)	65 (32 to 169)	37.5 (24.3 to 60.5)	0.00	54 (28 to 148)	35 (22 to 61)	<0.001
Gamma-glutamyl transferase, (U/L	99.7 (46.2 to 208)	67 (33.4 to 155.8)	<0.001	116 (47.1 to 207)	66.3 (32 to 154.12)	<0.001
Alkaline phosphate, U/L	108 (82 to 155)	109 (80 to 156.5)	0.79	114 (83 to 155)	106 (79.9 to 153.1)	0.68
Prothrombin time	13.7 (12.5 to 15.5)	13.7 (13.1 to 14.7)	0.45	13.7 (12.8 to 15.9)	13.7 (12.5 to 15.5)	0.68
Total protein, g/L	68.1 (63.2 to 74.5)	67.9 (64.3 to 73.5)	0.64	67.6 (61.9 to 75.8)	68.2 (63.8 to 75)	0.28
Total bilirubin, umpl/L	18.5 (13.4 to 34.2)	16.9 (12.6 to 24.9)	0.038	18.4 (13.5 to 38.1)	17.1 (12.59 to 25)	0.08
Blood routine						
Neutrophill, 10^9/L	2.6 (1.87 to 3.8)	3.12 (2.29 to 3.98)	0.02	2.86 (2.09 to 3.85)	3.05 (2.36 to 3.89)	0.34
Platelet 10^9/L	149.9 (91 to 205.2)	141 (92 to 196)	0.019	134.9 (90 to 199)	136 (91 to191.5)	0.28
Lymphocyte, 10^9/L	1.42 (1.04 to 1.89)	1.27 (0.89 to 1.75)	0.000	1.33 (0.95 to 1.79	1.25 (0.86 to 1.73)	0.05
Platelet volume distribution (%)	14.3 (1.04 to 1.98)	14.1 (12.3 to 15.9)	0.14	14.8 (12.1 to 16.9)	13.8 (12.4 to15.7)	0.08
Mean platelet volume (%)	11.9 (10.5 to 12)	11.7 (10.9 to 12.1)	0.09	11.7 (9.8 to 12.4)	11.4 (10.1 to 12)	0.034
White blood cells 10^9/L	4.61 (3.5 to 6.29)	4.99 (3.98 to 6.2)	0.59	4.88 (3.8 to 6.37)	4.86 (3.39 to 6.23)	0.78

Patients in the HCC group were older (58.6 ± 9.7 and 55.4 ± 13.1, p< 0.001) than those in the control group, and a larger percentage of men were present (83.4% versus 62.5%, p <0.001).We used the closest neighbor method to perform PSM analysis with a 1:1 ratio and a caliper of 0.05 in order to lessen the impact of these potential confounding variables. The majority of the HCC patients in this study were early stage (AJCC TNM Stage I-IV, 48.7%, 19.48%, 17.53%, and 14.29%, respectively), with 154 patients in each group after PSM.(Table 3)

Table 3: Comparison of tumor stage and tumor markersy using propensity score

Variables	Before propensity score			After propensity score		
	Control group	HCC group	p-value	Control group	HCC group	p-value
Tumor stage n(%)						
Stage 1	Not mentioned	75	-	Not mentioned	70	-
Stage 2	Not mentioned	30	-	Not mentioned	28	-
Stage 3	Not mentioned	25	-	Not mentioned	24	-
Stage 4	Not mentioned	21	-	Not mentioned	18	-
Tumor markers						
Alpha-fetoprotein, ng/ml	3.4 (1.8 to 11.9)	22 (3.89 to 548.9)	0.0000	4.3 (2.1 to 17.3)	20.9 (3 to 605)	0.000
Lensculinaris agglutinin-reactive fraction of AFP(AFP-L3), %	0.5 (0.51 to 6.1)	10.7 (0.5 to 45.8)	0.0000	0.5 (0.51 to 6.1)	10.7 (0.5 to 45.5)	0.000
PIVKAII, mAU/ml	15 (11 to 21)	117 (23.8 to 3889	0.0000	16 (12 to 21)	125 (23.8 to 3889)	0.000

When compared to single variables or other score systems, the score model had greater predictive performance in discriminating and clinical net benefit, according to ROC analysis. There were found to be 15 variables that could predict the beginning of HCC. AFP-L3, ALB, ALT, the presence or absence of HBsAg, and the presence or absence of HBeAg were all identified as independent risk factors for the development of HCC by multivariate logistic regression analysis. (Table 4)

Table 4: ROC ANALYSIS

	Sensitivity (%)	Specificity (%)	Area under the curve	Cut-off
Age	54	51	0.5	58.5
Gender	16.9	85	0.5	Female
HBsAg	81	48	0.63	Positive
HBeAg	95	19	0.55	Negative
Alanine transaminase, U/L	92.9	42.2	0.67	94.9
Albumin, g/L	33	83	0.57	42.9
Aspartate aminotransferase (U/L)	71.4	55.2	0.63	51.3
Gamma-glutamyl transferase, (U/L	57.8	65.6	0.6	71.3
Total bilirubin, umpl/L	78	37	0.54	26.9
Alpha-fetoprotein, ng/ml	47.4	85.1	0.64	28.9
Lensculinaris agglutinin-reactive fraction of AFP(AFP-L3)	46	95	0.45	0.71

DISCUSSION

The prognosis for the HCC patient is dire because of the disease's covert onset [18]. The prognosis of HCC patients could be considerably improved by effective early detection methods and curative treatments [19]. However, there are a number of drawbacks with the current methods and biomarkers for detecting early-stage HCC, including low adherence, a lack of sensitivity, and time requirements. Early on, patients are not closely monitored [20]. On the other hand, non-invasive biomarkers that can accurately and quickly detect HCC are still needed in the clinical setting. We examined serum pre-diagnostic biomarkers for the formation of HCC in this work, and we developed a non-invasive risk score model for the early identification of HCC. The discriminant function of this scoring model worked admirably (AUC: 0.890, sensitivity: 89.4%, specificity: 71.4%). The model's HCC onset prediction value was found to be equivalent in a separate group (AUC: 0.799). The clinical performance of the risk model's predictive efficacy was shown by the Kaplan-Meier curve, decision curve analysis, and clinical impact curve analysis. Notably, utilizing the risk score technique, patients with early-stage (AJCC Stage I) or small tumors (2 cm) nevertheless shown satisfactory prediction ability. On the basis of this model, we could assess the prognosis of HCC patients and enhance patient risk categorization in the early stages.

This paradigm consists of five pre-diagnostic blood indicators, which can be categorized into three groups as follows: (1) host variables include age, gender, and ALB; (2) HBsAg, HBeAg, and ALT variables connected to viral activity; (3) AFP-L3linked to the growth of malignant hepatocytes. In comparison to the GALAD model, the indicators of viral activity-related parameters were included. Hepatitis B virus (HBV) infection is a substantial risk factor for the etiology of HCC, especially in eastern Asia and sub-Saharan Africa [21]. A history of HBV infection was present in between 36% and 74% of HCC patients in India [22].There are a number of potential routes by which the Hepatitis B virus develops into HCC [23].HBeAg positivity nevertheless demonstrated that the HBV virus was actively reproducing [24]. Several case-control studies suggested that HBeAg was a more reliable predictive marker for HCC brought on by HBV [25]. Alpha-fetoprotein (AFP) and Lens culinaris agglutinin-reactive fraction of AFP(AFP-L3) are the blood markers that are most frequently used to identify HCC. Blood AFP levels in patients with HCC increased as their condition worsened and were linked to the growth of tumours, according to studies [26]; with sensitivity and specificity of 45.3-62% and 87-93% for detecting HCC at an early stage, respectively [27].AFP isoform L3 (AFP-L3), a glycoprotein with a primary origin in hepatocellular cancer cells, was a marker unrelated to AFP. The levels of AFP-L3 were significantly associated with the development of HCC, with a sensitivity of 45.9–50.7% and specificity of 92.9% [11]. Recent studies suggest that the serum AFP-L3 may be present in about 35% of those with mild HCC [28]. The blood level of ALB, a crucial nutritional indicator, also reflects the capacity to govern the immune system and antioxidant response to carcinogenesis [29][30]. People with HCC who have abnormal levels of ALB may have a worse prognosis, according to multiple studies. The growth and prognosis of the cancer are linked by these signals, which are a component of our score model. Therefore, the scoring model we created may be used to fulfil a number of HCC aims, such as risk assessment, post-treatment care, and prognosis prediction.

There are still some limitations of this study. First off, there are not enough HCC patients in our study as a whole. Second, there were gaps in the follow-up information for all patients based on hospital records, particularly for those with early-stage HCC (AJCC stages I and II). Finally, the virus genotypes were not taken into account by the score model. Therefore, in order to further validate the clinical values of the risk model, we will expand the patient cohort, conduct long-term follow-up, and conduct multi-center investigations in the future.

CONCLUSION

In conclusion, the scoring model developed in this study possessed the virtues of high accuracy, dependability, and usability. By adopting this model, we may be able to make early adjustments to the current risk categorization system and take into account more extensive surveillance programmes for high-risk individuals. Additionally, it can assist doctors in evaluating the prognosis and development of HCC patients.

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