Involvement of soluble B7-H3 in combination with the serum inflammatory cytokines interleukin-17, -8 and -6 in the diagnosis of hepatocellular carcinoma

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Abstract. Previous studies have demonstrated that B7-H3, and the inflammatory cytokines interleukin (IL)-17, IL-8 and IL-6, are involved in the development of a variety of tumors. The objectives of the present study were: i) To investigate the association between soluble B7-H3 (sB7-H3) and cytokine levels of IL-17, IL-8 and IL-6 in the serum of patients with hepatocellular carcinoma (HCC); and ii) to determine their potential value for use in HCC diagnosis. Serum sB7-H3, IL-17, IL-8 and IL-6 levels in the HCC patients and healthy control subjects were measured using ELISA. The accuracy of each of these biomarkers in HCC diagnosis was compared using a receiver operating characteristic curve and the area under the curve (AUC). A logistic regression model was used to investigate the accuracy of diagnosing HCC when evaluated using combined determinations of sB7-H3, IL-17, IL-8 and IL-6 levels. The data demonstrated that serum levels of sB7-H3, IL-17, IL-8 and IL-6 were significantly increased in HCC patients compared with those in the healthy control group. Serum sB7-H3 levels were positively associated with serum IL-17, whereas serum IL-8 levels were negatively correlated with serum IL-17 levels. The AUC values for sB7-H3, IL-17, IL-8 and IL-6 were 83.2, 65.7, 95.3 and 97.0%, respectively, and indicated that all four biomarkers exhibited a statistically significant capacity for diagnosing HCC. Using the logistic regression model, the AUC value, sensitivity and specificity, as determined for the combination of the four biomarkers, were 99.2, 96.67 and 97.14%, respectively. This was significantly greater than that achieved when any single biomarker was used alone in the logistic regression model to assess their accuracy in HCC diagnosis. The optimum cutoff value of the predicted probability obtained by the combination of sB7-H3, IL-17, IL-8 and IL-6 in the regression model was 0.5745. To conclude, the present study revealed that there exists a positive association between serum sB7-H3 and IL-17 levels in HCC patients. Determinations involving the combination of serum sB7-H3, IL-17, IL-8 and IL-6 levels demonstrate great potential for use in HCC diagnosis.

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Introduction

Antitumor immune responses represent extremely complex biological processes involving a variety of immune cells, proteins and signaling molecules (1,2). The mechanisms underlying antitumor immune responses have been extensively investigated through *in vitro* and *in vivo* experiments as well as through clinical studies (3,4). It has been reported that co-stimulatory molecules contribute to T-cell activation and improve antitumor immunity, thereby playing an important role in tumor diagnosis and treatment (5-7). For example, B7-H3 (also known as CD276), a newly identified member of the B7 family of co-stimulatory molecules, is a type I transmembrane protein mainly expressed in activated T cells, B cells, monocytes and dendritic cells (8). In addition to the B7-H3 membrane protein, a serum soluble B7-H3 (sB7-H3) has also been identified. This sB7-H3 is involved in the regulation of immune responses and autoimmune diseases, but its role in the regulation of T-cell responses remains controversial (9). Our previous study revealed that the cancer tissue from hepatocellular carcinoma (HCC) patients exhibited significantly increased levels of B7-H3 (10). B7-H3 has also been reported to be involved in the development of a variety of other solid tumor tissue cancer types, including osteosarcoma, pancreatic cancer, glioma, bladder cancer and non-small cell lung cancer (11-15), as well as in the development of inflammatory diseases (16).

It has been well established that tumor development is closely associated with inflammatory reactions. Inflammatory cytokines, including interleukin (IL)-17, IL-8 and IL-6, not only induce inflammatory reactions by activating lymphocytes,

but also promote tumor cell proliferation and regulate tumor angiogenesis and development (17). IL-17, a recently discovered inflammatory cytokine, can induce the expression of other inflammatory cytokines [including IL-6 and tumor necrosis factor-α (TNF-α)] and chemotactic factors (18,19). In this way, IL-17 promotes neutrophil migration to sites of inflammation and mediates inflammatory responses to enhance the antitumor effects of the body (20). IL-8 is a chemotactic inflammatory factor that plays an important role in maintaining cancer cell self-renewal and resistance to chemotherapy drugs through its regulation of cancer stem cells (21-23). IL-6, as a multifunctional cytokine derived from activated lymphocytes, monocytes, macrophages, bone marrow cells and certain tumor cells, can induce the synthesis of infection- or injury-induced acute inflammatory proteins resulting from acute phase responses.

HCC is the most common type of primary liver cancer globally (24), and accurate clinical diagnosis and screening for HCC are critical for improving the survival rate and the quality of life of HCC patients. Serum markers, including α-fetoprotein (AFP), carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), are widely used in the diagnosis of HCC. However, their specificity and sensitivity are far from meeting the standards required for clinical evaluation, with the result being that there remains a high rate of misdiagnosis. Thus, a search for serum inflammatory factors that may be more specific and sensitive for HCC diagnosis has become the focus of numerous investigations. At present, the potential association between the co-stimulatory molecule sB7-H3 and the cytokines IL-17, IL-8 and IL-6 remains unknown, as does the value of combining sB7-H3 with IL-17, IL-8 and IL-6 for use in diagnosing HCC. Therefore, the purpose of the present study was to investigate the association between serum sB7-H3 levels and levels of IL-17, IL-8 and IL-6 in HCC patients. The results of the study demonstrate the potential value of combining sB7-H3 with IL-17, IL-8 and IL-6 for the diagnosis of HCC.

Patients and methods

Patients. A total of 63 hospitalized HCC patients (49 males and 14 females; age range, 34-74; mean ± standard deviation age, 56±10.9), whose diagnosis was confirmed with pathological tests, were selected from the Yuhuangding Hospital (Yantai, China) and the Binzhou Medical College Affiliated Hospital (Yantai, China), and were assessed between January and November in 2008. Another 50 healthy subjects (32 males and 18 females; age range, 26-75; mean ± standard deviation age, 52±11.5 years), also from the Yuhuangding Hospital and the Binzhou Medical College Affiliated Hospital, were assessed over the same time period and served as controls. The control subjects had no autoimmune diseases, no history of allergies and no recent infections, and were otherwise healthy, collected consecutively between January and November 2008. The sex and ages of the control group matched those of the HCC group, with no statistically significant differences being identified between the two groups. Relative clinical information (age, sex, clinical staging, distant metastasis and nodal metastasis) according to the 7th edition tumor-node-metastasis (TNM) classification of the American Joint Committee on Cancer Staging system (25) was provided by the Yuhuangding Hospital and the Binzhou Medical College Affiliated Hospital with informed consent from the patients. This project was approved by the Ethics Committee at Yuhuangding Hospital and the Binzhou Medical University Affiliated Hospital (Yantai, China) and written informed consent was obtained from each patient for specimen collection and participation in the study.

Sample collection. Fasting blood samples (3 ml) were drawn from the HCC patients and controls in the morning. Serum was immediately separated by centrifugation at 754 x g, 4˚C for 5 min and stored at -80˚C prior to being assayed for serum levels of sB7-H3, IL-17, IL-8 and IL-6.

sB7-H3, IL-17, IL-8 and IL-6 measurements. An sB7-H3 ELISA kit was developed by the Biotechnology Research Institute of Suzhou University (Suzhou, China) and was kindly gifted by Suzhou University for use in analyzing serum sB7-H3 levels in HCC patients and controls (26). IL-17, IL-8 and IL-6 ELISA kits (IL-17, cat. no. D1700; IL-8, cat. no. D8000C; IL-6, cat. no. D6050; R&D Systems, Inc., Minneapolis, MN, USA) were used for assaying serum IL-17, IL-8 and IL-6 levels according to the manufacturer's protocols.

Statistical analysis. Data were analyzed using SPSS15.0 software. Numeric data are expressed as the mean ± standard error of the mean (SEM). Comparisons between the two groups were performed using unpaired Student's t-tests. The accuracy of the test in distinguishing HCC patients from healthy patients was evaluated using receiver operating characteristic (ROC) curve analysis, with the area under curve (AUC) being used to measure predictive accuracy. The ROC was drawn using Medcalc software (version 15.0; Medcalc Software, Ostend, Belgium). The maximal Youden index (sensitivity + specificity-1) was used to calculate the cutoff point. Logistic regression analysis was used to analyze whether the biomarker levels predicted an HCC diagnosis. $P<0.05$ was required for results to be considered statistically significant.

Results

HCC patients exhibit elevated serum levels of sB7-H3, IL-17, IL-8 and IL-6. In line with our previous findings, which revealed increased B7-H3 levels in tumor tissues (10), the ELISA assay results from the present study demonstrated that the serum sB7-H3 levels of the HCC patients were significantly higher than those of the control subjects ($P<0.05$). In addition, the serum IL-17, IL-8 and IL-6 levels in the HCC patients were also significantly increased compared with those of the control group ($P<0.05$) (Fig. 1).

Association between sB7-H3, IL-17, IL-8 and IL-6 levels in HCC patients and their clinicopathological characteristics. Although our previous findings (10) revealed an association between tumor tissue B7-H3 levels and clinicopathological characteristics, the present study identified no significant association between sB7-H3 levels and certain clinicopathological characteristics, including age, sex and lymph node metastasis. However, sB7-H3 levels were found to differ

Table I. Association between serum inflammatory factors in hepatocellular carcinoma patients and their clinicopathological characteristics.

Group	n	sB7-H3, pg/ml	IL-17, pg/ml	IL-8, pg/ml	IL-6, pg/ml
Age, years					
<60	22	3,873.369±622.368	349.934±76.505	337.347±94.018	64.073±14.229
≥60	41	3,850.689±829.661	360.087±63.329	334.007±83.785	63.375±15.632
Sex					
Male	49	3,940.958±891.735	354.797±67.336	319.177±81.509	63.839±14.332
Female	14	3,650.267±819.650	350.698±86.772	385.828±97.451	64.535±16.088
Clinical staging					
I-II	39	3,588.798±690.508	340.565±83.387	326.112±87.642	65.556±13.411
III	24	4,353.536±556.423[a]	361.381±63.419	345.979±91.673	61.243±16.111
Distant metastasis					
Yes	14	4,205.617±704.864[b]	360.297±69.329	361.410±98.941	57.015±16.041
No	49	3,719.306±726.908	333.003±76.051	325.027±84.597	66.542±13.371
Nodal metastasis					
Yes	10	4,138.331±677.314	320.313±31.428	377.399±25.301	61.851±15.282
No	53	3,812.446±658.582	359.252±19.091	326.625±12.413	64.981±10.311

[a]P<0.01; [b]P<0.05. sB7-H3, soluble B7-H3; IL, interleukin.

significantly among the clinical stages examined, and were associated with distant metastasis. Specifically, sB7-H3 levels for stage III patients were significantly higher than those of the overall means at stages I and II (4,353.536±556.423 vs. 3,588.798±690.508 pg/ml; P<0.01), and patients with distant metastasis had significantly increased sB7-H3 levels compared with those without (4,205.617±704.864 vs. 3,719.306±726.908 pg/ml; P<0.05). In the present study, the association between serum levels of IL-17, IL-8 or IL-6 and clinicopathological characteristics, including age, sex, pathological stage and lymph node metastasis, was also analyzed. No significant differences for age and sex were identified among IL-17, IL-8 and IL-6 levels. Furthermore, while HCC patients with lymph node metastasis exhibited lower IL-17 and IL-6 and higher IL-8 levels compared with those without lymph node metastasis, these differences were not statistically significant (Table I).

Associations among sB7-H3, IL-17, IL-8 and IL-6 levels. Analysis of the associations between serum sB7-H3 and IL-17, IL-8 or IL-6 in HCC patients revealed that serum sB7-H3 levels were positively associated with IL-17 levels, but that no statistically significant associations were identified between IL-8 or IL-6 and sB7-H3 levels (Fig. 2). Analysis of the associations among these inflammatory cytokines revealed that while IL-17 was negatively associated with IL-8, there was no association with IL-6. Furthermore, no statistically significant association was exhibited between IL-8 and IL-6 levels (Fig. 3).

Analysis of accuracy in using sB7-H3, IL-17, IL-8 or IL-6 to diagnose HCC. Serum sB7-H3, IL-17, IL-8 and IL-6 levels of the healthy control subjects provided the reference levels for this study, with which an ROC curve was generated to evaluate the accuracy of using these biomarkers in HCC diagnosis. Results of this analysis revealed that AUC values for the diagnosis of HCC were 83.2% for sB7-H3 (P=0.0001), 65.7% for IL-17 (P=0.0066), 95.3% for IL-8 (P=0.0001) and 97.0% for IL-6 (P=0.0001) (Fig. 4; Table II). These findings suggest that each of these biomarkers may serve as valid and reliable markers for the clinical diagnosis of HCC.

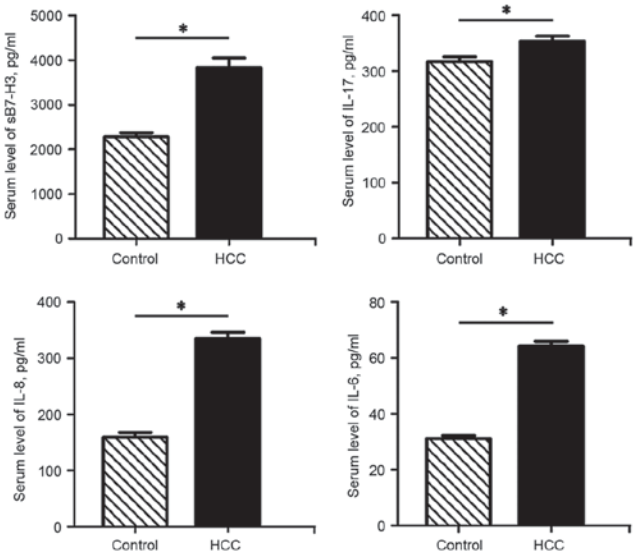

Figure 1. Serum levels of sB7-H3, IL-17, IL-8 and IL-6 in HCC patients vs. control subjects. *P<0.05. sB7-H3, soluble B7-H3; IL, interleukin; HCC, hepatocellular carcinoma.

Application of a logistic regression model with sB7-H3, IL-17, IL-8 and IL-6 in HCC diagnosis. A stepwise logistic regression model was used to evaluate the accuracy of using sB7-H3,

Table II. Serum sB7-H3, IL-17, IL-8 and IL-6 in diagnosing hepatocellular carcinoma, and their sensitivity, specificity and Youden index.

Biomarker	Sensitivity, %	Specificity, %	AUC, %	95% CI	P-value	Std	Youden index
sB7-H3	76.09	90.20	83.2	0.742-0.900	0.0001	0.0424	0.6629
IL-17	51.60	80.00	65.7	0.552-0.752	0.0066	0.0579	0.3160
IL-8	91.70	91.40	95.3	0.889-0.986	0.0001	0.0208	0.8310
IL-6	95.00	96.85	97.0	0.913-0.994	0.0001	0.0164	0.9185
PRE	96.67	97.14	99.2	0.947-1.000	0.0001	0.0084	0.9381

sB7-H3, soluble B7-H3; IL, interleukin; PRE, predicted probability; 95% CI, 95% confidence interval; Std, standard deviation.

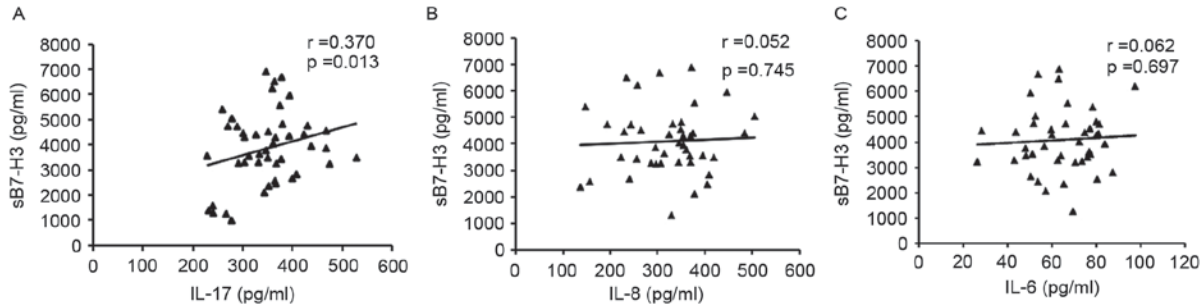

Figure 2. Associations between serum levels of sB7-H3 and IL-17, IL-8 or IL-6. Association between (A) sB7-H3 and IL-17, (B) sB7-H3 and IL-8, and (C) sB7-H3 and IL-6. sB7-H3, soluble B7-H3; IL, interleukin.

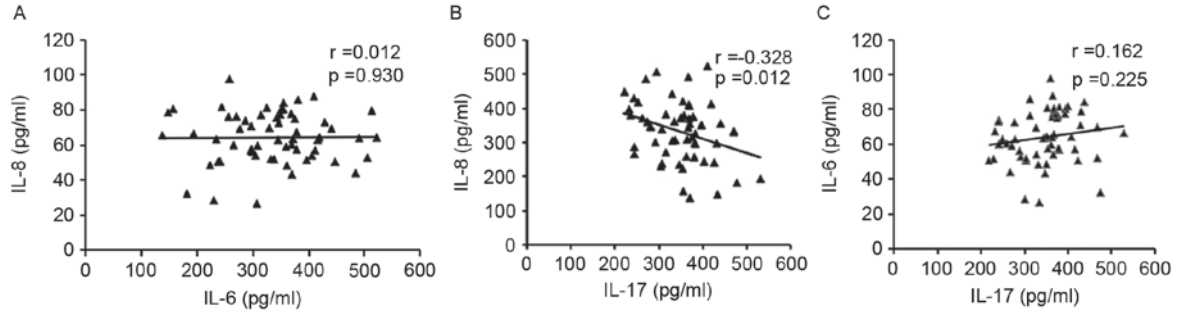

Figure 3. Associations between serum levels of IL-8, IL-6 and IL-17 in hepatocellular carcinoma patients. Associations between (A) IL-8 and IL-6, (B) IL-8 and IL-17, and (C) IL-6 and IL-17. IL, interleukin.

IL-17, IL-8 and IL-6 in HCC diagnosis. The significance level for entry into the model was 0.10, and the significance level for remaining in the model was 0.15. The regression equation was as follows: $P = 1/[1 + e^{-(-11.23 + 0.001x_1 - 0.018x_2 + 0.035x_3 + 0.191x_4)}]$, where x_1 represents sB7-H3, x_2 represents IL-17, x_3 represents IL-8 and x_4 represents IL-6. P was the predicted probability for the logistic model with a range of 0-1, and e was the natural logarithm (e≈2.718). These results demonstrated that patients with high levels of these parameters were at greater risk of HCC, with increases of 1.032 for IL-8 and 1.151 for IL-6 being observed (Table III). Using the predicted probability (PRE) as a test variable obtained by the combination of sB7-H3, IL-17, IL-8 and IL-6 in the regression model, the value for AUC was 99.2%, which was significantly greater than that observed when these inflammatory factors were used as individual variables: sB7-H3 (AUC, 83.2%), IL-17 (AUC, 65.7%), IL-8 (AUC, 95.3%) and IL-6 (AUC, 97.0%). The sensitivity of the model using all four biomarkers was 96.67%, which was significantly greater than the sensitivities of each inflammatory marker when used as a single predictor. Furthermore, the specificity of the model using all four biomarkers was 97.14%, which was significantly greater than the individual specificities of each when used as single predictors (Table II; Fig. 4). Additionally, there was a clear cutoff value for the PRE (0.5745) in the regression model obtained by the combination of sB7-H3, IL-17, IL-8 and IL-6.

Discussion

HCC is one of the most common malignant tumors, and is known to have a poor prognosis due to its invasive and metastatic properties. At present, AFP and CEA are two of the most common serum tumor markers used to diagnose liver cancer. However, neither of these are highly specific markers for liver cancer (27), and therefore, the attention of numerous researchers

Table III. Stepwise logistic regression model for diagnosing hepatocellular carcinoma (n=113).

Biomarker	β	P-value	OR value	95% CI
IL-8	0.032	0.009	1.032	1.008-1.057
IL-6	0.141	0.004	1.151	1.046-1.266
Constant	-12.9	<0.001		

IL, interleukin; OR, odds ratio; 95% CI, 95% confidence interval.

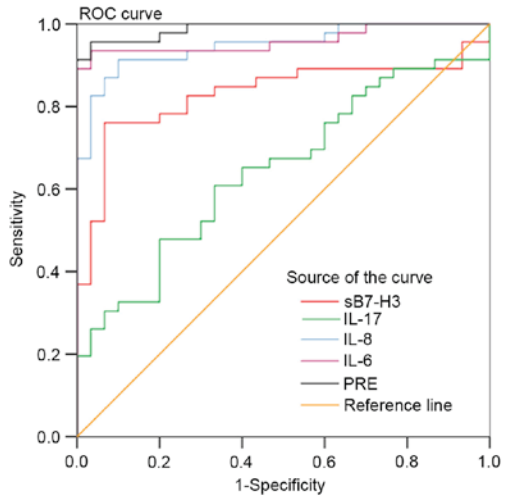

Figure 4. ROC curve of serum levels of sB7-H3, IL-17, IL-8, IL-6 and the combination of these four biomarkers for diagnosing hepatocellular carcinoma. ROC, receiver operating characteristic; sB7-H3, soluble B7-H3; IL, interleukin; PRE, predicted probability.

has turned toward finding a more specific diagnostic marker for liver cancer. Previously, we reported that B7-H3 levels were increased in the tumor tissue of HCC patients (10). In the present study, this investigation was extended to include serum levels of sB7-H3 and the cytokines IL-17, IL-8 and IL-6 in HCC patients, and the potential of combining these factors for use as diagnostic biomarkers of HCC was evaluated. The results revealed that serum levels of sB7-H3 in HCC patients were significantly increased compared with those of the healthy control group. In support of these findings are data on the serum levels of sB7-H3 in patients with non-small cell lung cancer, which were also significantly increased when compared with those of healthy controls (26). Taken together, these findings suggest that sB7-H3 could serve as a serum diagnostic biomarker for HCC.

The present study also observed that serum IL-17, IL-8 and IL-6 levels were increased in HCC patients compared with those in the healthy control group, but the design of this study did not provide an opportunity to determine the underlying mechanisms for such increases. However, it has been reported that increases in the number of Th17 cells in HCC patients, which occur concurrently with increases in serum IL-17 levels, are associated with decreases in overall survival and disease-free survival time (28,29). Additionally, Park *et al* (30) reported that anticancer drugs can induce IL-8 secretion and the expression of IL-8 receptors on liver cells. Furthermore, serum IL-8 levels were positively correlated with tumor size, whereas silencing of the IL-8 gene within hepatocytes significantly decreased tumor size. It has also been reported that IL-8 is involved in tumor angiogenesis, growth and metastasis (31), and can therefore serve as an important chemokine for blood vessel formation in HCC (32). In order to clarify the clinical effects and associations of IL-6, IL-27, TNF-α and vascular endothelial growth factor with signal transducer and activator of transcription proteins under different clinical and pathological stages of HCC, Kao *et al* (33) demonstrated that overexpression of IL-6 was closely associated with maintaining liver function and 6-month mortality rate in HCC while the elevated IL-27, TNF-α, or VEGF presented no significant correlation with 6-month mortality rate in HCC. In addition, determinations of preoperative IL-6 serum levels can serve as a potential biomarker for the early prediction of hepatitis B virus-related HCC relapse (34). Results from the present study revealed that serum levels of soluble IL-17 in HCC patients were significantly increased and positively associated with sB7-H3 levels, but that they were negatively associated with IL-8 levels. The level of IL-6 was also increased in the HCC patients, indicating that IL-6 participates in the development of HCC. Notably, no association was observed between serum levels of sB7-H3 and IL-8. Together, these data suggest that the immune regulation of sB7-H3 and cytokines in HCC involves a complex process. However, details regarding the mechanisms involved require further investigations.

Given our previous findings that B7-H3 was highly expressed in tumor tissue (10), and the results of the present study demonstrating increased serum levels of sB7-H3 and a positive correlation between serum sB7-H3 and IL-17 levels in HCC patients, efforts were directed toward assessing the accuracy of using sB7-H3, IL-17, IL-8 and IL-6 in HCC diagnosis using ROC analysis. The potential value of using sB7-H3, IL-17, IL-8 and IL-6 in HCC diagnosis was also evaluated using logistic regression analysis. Results from the ROC analyses indicated that levels of sB7-H3, IL-17, IL-8 and IL-6 all differed significantly between the HCC patients and the control group. Further logistic regression analysis revealed that combining the responses obtained from all four of these biomarkers significantly enhanced the potential for predicting HCC. An optimal cutoff value of 0.5745 for PRE was obtained by combining the four biomarkers in the regression model. The specificity and AUC achieved maximal values of 97.14 and 99.2%, respectively, for this combination of biomarkers, which were higher in comparison with the specificity and AUC observed when the four biomarkers were used individually. These findings suggest that this model has potential applications for the clinical diagnosis of HCC.

In the present study, combinations of serum sB7-H3, IL-17, IL-8 and IL-6 yielded a high AUC and were revealed to be highly specific and sensitive in diagnosing HCC. To the best of our knowledge, there exists no report proposing the combined use of sB7-H3 and cytokines for the diagnosis of HCC. However, one limitation of this study was the small sample size, which may have caused multicollinearity in the logistic regression model. Additionally, no comparison was made between the proposed model and the commonly used clinical serological markers, AFP and CEA, with regards to their relative efficacies in diagnosing HCC. Therefore, a future study would incorporate larger samples and a comparison between

the proposed model and AFP and CEA, in order to assess the relative effectiveness of this model.

To conclude, an accurate clinical diagnosis and screening tool for HCC is vital for improving the survival rate and quality of life of HCC patients. The present study investigated the association among sB7-H3 and cytokine levels of IL-17, IL-8 and IL-6 in HCC patients. Based on these findings, the combination of serum B7-H3, IL-17, IL-8 and IL-6 may provide a novel and effective protocol for use in HCC screening and diagnosis.

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