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Research Paper

High preoperative serum globulin in hepatocellular carcinoma is a risk factor for poor survival

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Abstract

Background: Serum globulin (GLB), albumin (ALB) and albumin/globulin ratio (AGR) have been reported as prognosis related factors for certain malignancies; however, the prognostic value of globulin (GLB) in hepatocellular carcinoma (HCC) has rarely been studied. This study was performed to evaluate whether GLB analysis could be applied for the prediction of the prognosis of patients received liver resection.

Methods: A training cohort study involving 210 HCC patients undergoing curative liver resection between January 2007 and December 2012, and a validation cohort involving 100 HCC patients contemporaneously undergoing curative liver resection in another set were recruited. The survival curves were graphed and log-rank test was performed to analyze the differences between the curves. The cutoff value was selected by X-title program.

Results: Univariate and multivariate analysis indicated that high serum GLB level is a risk factor for poor cancer-specific survival (CSS) ($P < 0.05$). Conversely, high ALB level is a prediction for favor CSS ($P = 0.010$).

Conclusions: We identified the preoperative high GLB level as a prognostic risk factor for patients after treatment of liver cancer resection. This easily obtained variable may act as an available clinical biomarker to predict the prognosis of such patients.

Key words: HCC, globulin, albumin, survival

Introduction

Hepatocellular carcinoma (HCC) ranks 5th (men) and 9th (women) in frequency and is globally third leading cause of cancer-related death [1]. Although most cases of HCC occur in Africa and Eastern Asia, trends in HCC have shown considerable increases in low-incidence areas such as the United States and Canada [2]. Chronic hepatitis B or C virus (HBV or HCV) infections are the major risk factors for HCC [3]. The increasing level of diagnosis in high-risk populations, such as ultrasonography and computed tomographic scanning, has led to the identification of increasing numbers of patients with HCC. Although the survival benefit of surgical techniques and preoperative management in HCC has been well made, its prognosis remains dismal [4, 5]. Actually, serum alpha-fetoprotein (AFP) was widely recognized and utilized as a diagnostic and prognostic marker of HCC [6, 7].However, AFP was increased in 211-58% of patients with chronic hepatitis or cirrhosis without HCC, and 30-40% of HCC patients were AFP negative [6, 8, 9]. Moreover, AFP was also reported to have no prognostic role in small

hepatocellular carcinoma patients with well-compensated cirrhosis [10]. Thus, identifying simple and reliable biological markers to predict patient who are at high-risk for early death and recurrence would be important.

Albumin (ALB) and globulin (GLB), the two major constituents of serum proteins, are routinely measured by biochemical examinations. Both of them are considered to play a pivotal role in the inflammatory process. Serum ALB level, as well as albumin/globulin ratio (AGR), has been known as a prognostic indicator in several types of cancer, including gastric cancer, colorectal cancer, breast cancer, ovarian cancer and nasopharyngeal carcinoma [11-13]. In contrast to the considerable amount of researches on ALB and AGR, however, whether the impact of the GLB and A/G ratio is associated with outcome in patients with HCC has not yet been elucidated. Therefore, the purpose of this study was to assess whether preoperative globulin and A/G ratio had a prognostic value in patients with HCC.

Methods

Study population

Data involved was collected from patients suffering HCC and receiving liver resection in the First Affiliated Hospital of Nanjing Medical University (NJMU) and Nanjing Drum Tower Hospital, Nanjing, China between January 2007 and December 2012. The latest detection of serum ALB level, GLB level and albumin/globulin ratio (AGR) was recorded before liver resection operation. Patients aged between 18 and 85 years at diagnosis, undergoing partial liver resection with pathologically confirmed HCC as primary tumor were included. Patients who had preexisting diseases of immune system, received immunosuppressive therapies involving recent exposure of steroid or other immunity medicine before operation, and those died within 30 days after surgery were excluded from this study. Meanwhile, patients with incomplete clinical information including vascular invasion, tumor multiplicity, tumor size, Edmondson grade, or without follow up were excluded.

The study was approved by the Institutional Ethics Committee of the First Affiliated Hospital of NJMU. And our research was performed according to the Helsinki Declaration and government policies. Written informed consent was obtained from all patients.

Statistical analysis

Basic information about patients, and data of clinicopathological and laboratory examination was retrieved from the medical recording system of the first affiliated hospital of NJMU. Patients' clinical features including sex, age, level of HbsAg, ALT (U/L), AFP (ng/ml), GLB (g/L), ALB (g/L), cirrhosis or not, pathological features about vascular invasion, tumor multiplicity, tumor size, Edmondson grade and information on follow up was obtained. Serum level of GLB, ALB as well as HbsAg, ALT and AFP was detected by an automatic biochemical analyzer (Hitachi 7600). All the patients were further divided into two groups based on criterion as follows: (1) sex: male or female; (2) age: ≤ 60 years (young group) or > 60 years (old group); (3) serum HbsAg: negative (normal) or positive (abnormal); (4) ALT level: ≤ 45 U/L (normal) or >45 U/L (abnormal); (5) AFP level: ≤ 13.6 U/L (normal) or >13.6 U/L (abnormal); (6) cirrhosis in liver tissues: absent or present; (7) tumor vascular invasion: absent or present; (8) tumor multiplicity: solitary or multiple; (9) tumor size: ≤ 5 cm or >5 cm; (10) Edmondson grade: I-II or III-IV. The AGR value was calculated, [AGR = Albumin/(Total protein - Albumin)]. The cutoff value was selected by X-title program and set as follows: GLB, 32.70 g/L; ALB, 40.60 g/L; AGR, 1.40. CSS, calculated from the date of diagnosis to the date of cancer specific death was selected as the primary endpoint of the study. Deaths were set as events and deaths attributed to other causes were set as censored observation. Kaplan-Meier estimates were applied to graph the survival curves, and log-rank test was performed to analyze the differences between the curves. Risk factors for survival outcomes in HCC patients were analyzed using Multivariable Cox regression models. Chi-square test was performed for categorical variables. 5-year CSS was evaluated from Kaplan-Meier curves. SPSS 17.0 for Windows (IBM Corp, Armonk, NY, USA) was used to perform all the statistical analyses. $P < 0.05$ (two-tailed test) was considered statistical significant.

Results

Patients

210 patients in total initially diagnosed as HCC and receiving liver resection in the first affiliated hospital of NJMU from 2007 to 2012 were involved in this study as a training cohort (Table 1). Among them, 173 are male (82.4%) and 37 (17.6) are female. The average age of the patients was 55 years (range, 47-75 years). Of these 184 (87.6%) were chronic hepatitis B patients, and 160 (76.2%) were diagnosed as liver cirrhosis. During follow-up, 107 patients experienced HCC recurrence and 75 patients developed tumor metastasis. By the end of follow-up, 153/210 patients (72.9%) died of HCC.

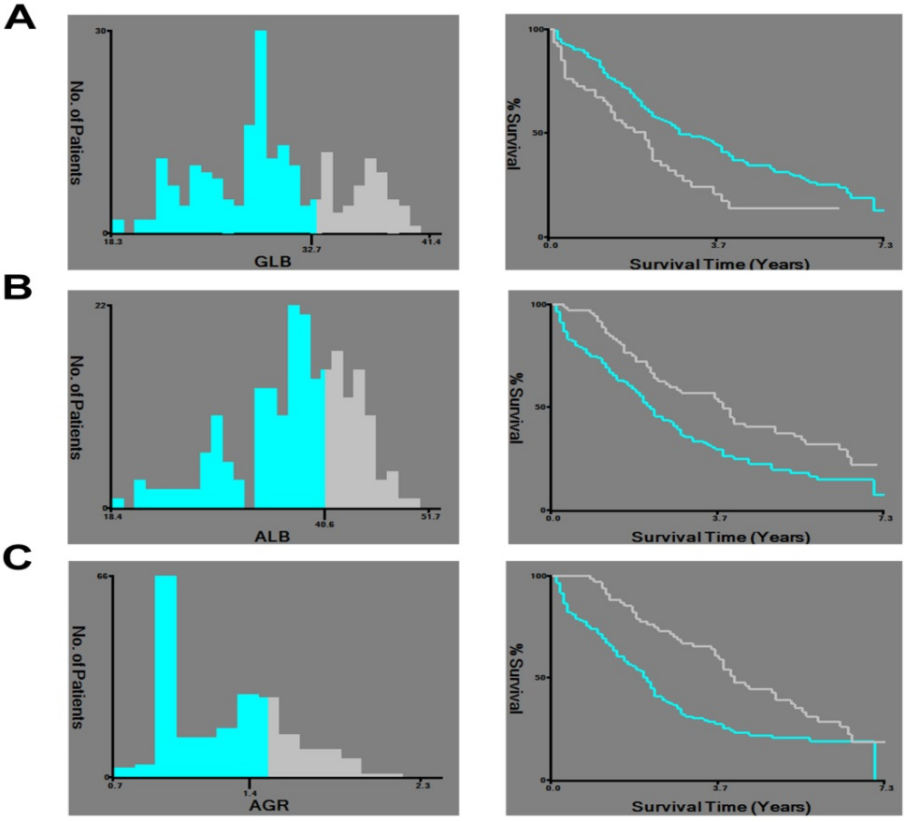

Figure 1. X-tile analysis of survival data of HCC patients. X-tile analysis was done on patient data from our center, equally divided into training and validation sets. X-tile plots of the training sets are shown in the *left panels*, with plots of matched validation sets shown in the *smaller inset*. The optimal cut-point highlighted by the *black circle* in the *left panels* is shown on a histogram of the entire cohort (*middle panels*), and a Kaplan-Meier plot (*right panels*). *P* values were determined using the cutoff point defined in the training set and applying it to the validation set. A: Shows the optimal cutoff point for the GLB (32.70, $\chi 2$ = 10.625, P = 0.001). B: Shows the optimal cutoff point for the ALB (40.60, $\chi 2$ = 10.038, P = 0.002). C: Shows the optimal cutoff point for the AGR (1.40, $\chi 2$ = 13.172, P < 0.001).

Table 1. Clinical features of patients with HCC in the training cohort

	n=210	%
Age (year)	55(47-75)	
Sex		
male	173	82.4%
female	37	17.6%
HbsAg		
negative	26	12.4%
positive	184	87.6%
ALT (U/L)		
≤45	159	75.7%
>45	51	24.3%
AFP (ng/ml)		
≤13.6	79	37.6%
>13.6	131	62.4%
Cirrhosis		
absent	50	23.8%
present	160	76.2%
Vascular invasion		
absent	52	24.8%
present	158	75.2%
Tumor multiplicity		
solitary	157	74.8%
multiple	53	25.2%
Tumor size (cm)		
≤5	125	59.5%
>5	85	40.5%
Edmondson grade		
I-II	118	56.2%
III-IV	92	43.8%

Identification of optimal cut-off value for GLB, ALB, and AGR

The mean value of GLB and ALB involved were 29.88 g/L (range, 18.30-41.40 g/L) and 37.71 g/L (range, 18.40- 51.70 g/L), respectively. And the mean value of AGR involved was 1.30 (range, 0.70-2.30). X-tile program was applied to set the optimal cut-off points for GLB, ALB and AGR. The GLB cutoff value for CSS was 32.70 g/L with maximum $\chi 2$ log-rank value of 10.625 (P= 0.001), and all patients were divided into either high (>32.70 g/L) or low (≤32.70 g/L) GLB groups. Similarly, an ALB cutoff point of 40.60 g/L and an AGR cutoff point of 1.40 were selected as the optimal cutoff value for survival analyses ($\chi 2$ = 10.038, P = 0.002, and $\chi 2$ = 13.172, P < 0.001, respectively) to divide the patients involved into low and high risk subsets in terms of CSS (Figure. 1).

Association of ALB and GLB with the clinicopathological features of HCC

On the basis of the optimal cutoff value, 138/210 patients (65.7 %) had a low ALB level and 149/210 patients (71.0 %) had a low GLB level. When stratified by the test results of serum level of AFP and

pathological results of cirrhosis, tumor size and Edmondson grade, the patient distribution of the GLB level differed significantly. Comparing with patients in higher GLB group (12/61, 19.7%), more patients were with low AFP level in the low GLB group (67/149, 43.0%) (P=0.001). Conversely, significantly more patients had basic liver cirrhosis in high GLB group (52/61, 85.2 %) than in low GLB group (108/149, 72.5 %) (P=0.049). Moreover, there were higher percentage of patients with tumor size of ≤5 in the low GLB (104/149, 69.8%) group than patients in higher GLB group (21/61, 34.4%) (P=0.001). More patients were classified as Edmondson grade I-II in high GLB group (29/122, 23.8 %) than in low GLB group (7/64, 10.9 %) (P=0.025).

The patient distribution of ALB level showed significant difference when stratified by the test results of HbsAg, ALT, AFP and pathological results of cirrhosis and Edmondson grade. Significantly more patients were with low HbsAg level in the high ALB group (24/72, 33.3%) than in the low ALB group (2/138, 1.4%) (P<0.001). More patients were in high level of ALT in the high ALB group (61/72, 84.7%) than in the low ALB group (98/138, 71.0%) (P=0.028). And there were higher percentage of patients with a higher serum value of AFP in the high ALB group (43/72, 59.7%) than in the low ALB group (36/138, 26.1%) (P<0.001). In addition, comparing with patients in low ALB group (25/138, 18.1%), more patients had basic liver cirrhosis in the high ALB group (25/72, 34.7%) (P=0.007). More patients were classified as Edmondson grade I-II in high ALB group (56/72, 77.8%) than in low ALB group (62/138, 44.9%) (P<0.001) (Table 2).

Prognostic value of ALB, GLB, and AGR

As the results of univariate analysis indicated, the high serum of AFP (P=0.005) and GLB (P=0.001), low serum level of ALB (P=0.002), low AGR value (P<0.001) and other clinicopathological factors involving tumor vascular invasion (P=0.012), tumor multiplicity (P=0.001), tumor size (P<0.001) and Edmondson grade (P<0.001) were significant risk factors for poor survival of HCC patients suffering liver resection (Table 3).

Various prognostic factors were adjusted with the performance of multivariate Cox regression analysis. In accordance with the results of univariate analysis, the high serum level of GLB (hazard ratio [HR] 1.865; 95 % confidence interval [CI] 1.089-3.194, P= 0.023), low serum level of ALB (HR 0.658; 95 % CI 0.436-0.993, P=0.046), tumor vascular invasion (HR 1.847; 95 % CI 1.221-2.795, P=0.004), tumor multiplicity (HR 0.361; 95 % CI 0.230-0.567, P<0.001), tumor size (HR 2.308; 95 % CI 1.588-3.354, P<0.001) and Edmondson grade (HR 2.784; 95 % CI 1.694-4.573, P<0.001) were suggested as independent predictive factors for HCC. A serum value of higher GLB and low ALB demonstrated a negative effect on CSS. However, the serum level of AFP and AGR score were not significant predictive factors in multivariate analysis (Table 3).

Table 2. Association among GLB, ALB and the clinical features in HCC patients.

Variable	GLB level(g/L)		P	ALB level(g/L)		P
	low	high		*low*	high	
Sex			0.617			0.100
Male	124	49		118	55	
Female	25	12		20	17	
Age			0.812			0.614
≤60	110	46		101	55	
>60	39	15		37	17	
HbsAg			0.799			0.000
negative	19	7		2	24	
positive	130	54		136	48	
ALT (U/L)			0.948			0.028
≤45	113	46		98	61	
>45	36	15		40	11	
AFP (ng/ml)			0.001			0.000
≤13.6	67	12		36	43	
>13.6	82	49		102	29	
Cirrhosis			0.049			0.007
absent	41	9		25	25	
present	108	52		113	47	
Vascular invasion			0.148			0.954
absent	41	11		34	18	
present	108	50		104	54	
Tumor multiplicity			0.107			0.782
solitary	116	41		104	53	
multiple	33	20		34	19	
Tumor size (mm)			0.000			0.526
≤5	104	45		80	45	
>5	21	40		58	27	
Edmondson grade			0.000			0.000
I-II	109	9		62	56	
III-IV	31	61		76	16	

Validation of the prognostic value of GLB

To verify the prognostic value of GLB in HCC patients, we recruited validation cohort involving 100 HCC patients from the other cohort. Clinical information of patients was listed in Table. S1. According the cut-off we identified in Figure 1, patients were divided into two groups. As expected, high serum level of GLB (hazard ratio [HR] 1.376; 95 % confidence interval [CI] 1.049-2.795, P= 0.032), low serum level of ALB (HR 0.622; 95 % CI 0.439-0.972, P=0.039) were associated with poor outcome of HCC (Figure 2 and Table S2).

Discussion

As a kind of malignant tumor with high morbidity and motility, HCC is always characterized by delayed diagnosis and poor prognosis.[14] Treatments for HCC include open surgical operation, radiotherapy, radiofrequency ablation and

chemotherapy.[15-17] For HCC patients at early stages without distant metastasis, surgical resection is the best choice.[18, 19] The reported five-year cancer specific survival (CSS) for HCC patients receiving liver resection is about 20~40 %, which is far from satisfactory. [20] The prognosis of HCC may be decided by many factors, such as age, gender, tumor size, tumor stage, vascular invasion, tumor multiplicity and so forth. [21, 22] These factors may act as predicators for the prognosis of patients after HCC resection. However, sole factor is not sufficient to make an accurate prediction, as many host and tumor related factors must be considered.

Table 3. Univariate and multivariate survival analyses evaluating GLB, ALB, and AGR influencing CSS in HCC of the training cohort.

		Univariate analysis		Multivariate analysis	
Variable	5-year CCS	Log rank χ^2 test	P	HR(95%CI)	P
Sex		0.463	0.496		NI
Male	26.5%				
Female	29.1%				
Age		0.059	0.808		NI
≤60	26.6%				
>60	27.4%				
HbsAg		0.027	0.870		NI
negative	28.8%				
positive	28.0%				
ALT (U/L)		0.873	0.350		NI
≤45	28.2%				
>45	22.1%				
AFP (ng/ml)		7.727	0.005		0.288
≤13.6	36.5%			Reference	
>13.6	20.7%			1.221 (0.845-1.764)	
Cirrhosis		3.400	0.065		NI
absent	30.5%				
present	25.9%				
Vascular invasion		6.255	0.012		0.004
absent	27.6%			Reference	
present	25.1%			1.847 (1.221-2.795)	
Tumor multiplicity		11.811	0.001		0.000
solitary	18.2%			Reference	
multiple	46.2%			0.361 (0.230-0.567)	
Tumor size (mm)		34.515	0.000		0.000
≤ 5	34.7%			Reference	
> 5	14.5%			2.308 (1.588-3.354)	
Edmondson grade		27.857	0.000		0.000
I-II	36.6%			Reference	
III-IV	11.4%			2.784 (1.694-4.573)	
GLB (g/L)		10.625	0.001		0.023
≤ 32.7	31.3%			Reference	
> 32.7	14.2%			1.865 (1.089-3.194)	
ALB (g/L)		10.038	0.002		0.046
≤ 40.6	20.1%			Reference	
> 40.6	37.7%			0.658 (0.436-0.993)	
AGR		13.172	0.000		0.358
≤ 1.4	20.7%			Reference	
> 1.4	39.4%			0.811 (0.519-1.267)	

NI: not included in multivariate survival analysis. HR: hazard ratio, CI: confidence interval, GLB: globulin, ALB: albumin, AGR: albumin/globulin ratio.

Globulin, including the gamma globulins or antibodies and glycoprotein, is one the most important groups of blood proteins. [23] GLB may act as a regulator in the circulatory system by assisting the blood in clotting, transporting proteins through the lipoproteins, indicating antibody levels, and so forth. High globulin levels may be attributed to chronic inflammatory diseases such as chronic viral or bacterial infection, liver disease, auto-immune status, ulcerative colitis, kidney disease and so on. [24-28] Chronic inflammation is a common cause of multiple tumors. HCC is an inflammation related carcinoma and mounting evidence suggested that persistent chronic inflammation status is associated with poor prognosis of HCC patients. [29-31] Inflammation based prognostic factors involving serum C-reactive protein and the neutrophils to lymphocyte ratio have been demonstrated as potential predictors of the CSS of liver cancer. [32-34]

ALB is produced in the liver and forms about 50% of all plasma protein. Its main function is to regulate the colloidal osmotic pressure of blood thus

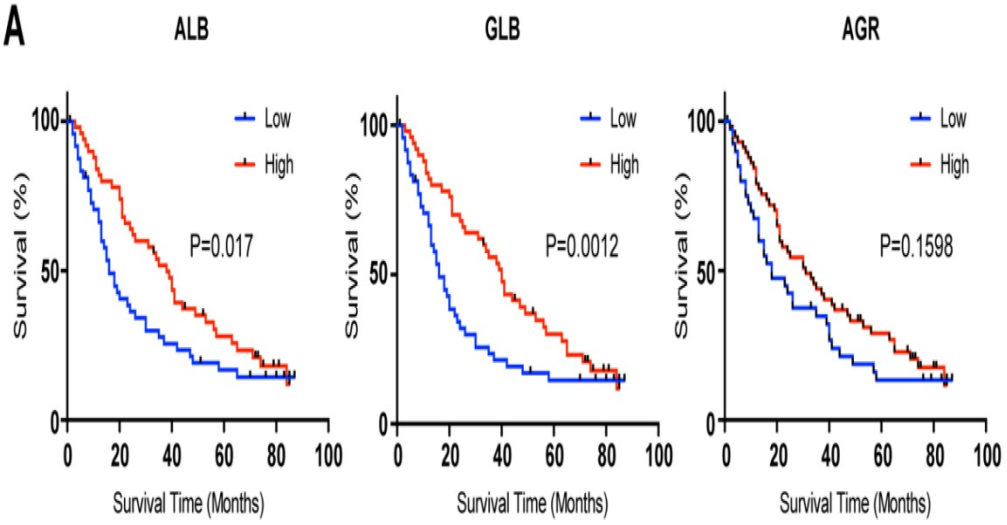

Figure 2. Kaplan-Meier analysis of CSS for ALB, GLB and AGR in the validation cohort. A: ALB B: GLB C: AGR.

maintain the volume of whole blood. It also serves as carriers for molecules of low water solubility, such as bile salts, unconjugated bilirubin, free fatty acids and so forth. Low albumin may be caused by liver disease, nephrotic syndrome, malnutrition and malignancy. [35-37] ALB is also suggested as a potential predictor of the CSS of liver cancer. [37]

Our study found that serum GLB and ALB level were promising predictors of CSS in patients treated with HCC resection. We firstly found that high GLB level was significantly related to high AFP value, the existence of cirrhosis, major tumor size and high Edmondson grade and low ALB value was markedly associated with positive HbsAg, high ALT and AFP level, the existence of cirrhosis, and high Edmondson grade. Then with the application of univariate analysis, GLB, ALB and AGR was suggested to be related to 5-year CSS, however after adjustment for AFP value, and the clinical characteristics with multivariate analysis, only the predicative GLB and ALB remained significant. An absolute improvement of 7.1% in 5-year CSS if ≤ 32.70 g/L GLB level comparing to > 32.70 g/L ($P<0.05$). And there was a 17.6% improvement in 5-year CSS if >40.6 g/L ALB level rather than ≤ 40.6 g/L ($P<0.05$). As the completed mechanisms shared by cancers and inflammation, markers of inflammatory reaction may serve as indicators of cancer diagnosis and predictors of prognosis, nevertheless, the significance of the markers was ignored to a great extent and few such markers were identified. The present study, for the first time, utilized two different cohorts to identify and confirm the cut-off of GLB and ALB, then focused on the association of serum GLB and ALB level with prognosis as well as clinicopathological parameters in HCC treated with liver section.

As a matter of fact, there exist some limitations in this study, of which, the major one would be that relevant measurements of several specific cytokines and C-reactive protein levels were missing, so consequently, we could not analyze the relationship among GLB, ALB with such inflammatory factors. Besides, this research was performed with relatively small sample, which may cause some small sample bias and limit the statistical power. Future large-scale studies involving more people with prospective designs are urgently desired.

Despite these limitations, our informative study is the first to identify the preoperative high GLB level as a prognostic risk factor for patients after curative liver resection. Furthermore, we also demonstrated ALB as an independent predictor for the prognosis according to our study population. Serum GLB and ALB value, moreover, can be obtained directly from routine medical laboratories, thus can act as available clinical biomarkers to predict the prognosis of HCC undergoing liver section.

Supplementary Material

Supplementary tables.
http://www.jcancer.org/v10p3494s1.pdf

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Ethics approval and consent to participate

Written and publication consent was obtained from each patient, and the study was approved by Institutional Ethics Committee of the First Affiliated Hospital, Nanjing Medical University. The study was performed in accordance with the Declaration of Helsinki.

Authors' contributions

WJZ and BCS: Conceptualization, methodology, validation, investigation, writing–original draft, writing–review and editing, and visualization. WJZ, GYZY and BCS: Data curation and writing–review and editing. WJZ, HTZ and WWY: Formal analysis, investigation, and writing–review and editing. FW and YL: Investigation, resources, writing–original draft, and writing–review and editing. WJZ and BCS: Formal analysis, writing–original draft, writing–review and editing, visualization, and supervision. HTZ and GYZY: Investigation, resources, writing–original draft, and writing–review and editing. JCW, WWY and YL: Formal analysis, investigation, resources, and writing–review and editing. KPJ, ZKX and BCS: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, and supervision.

Competing Interests

The authors have declared that no competing interest exists.

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