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Original Research

C-reactive protein-to-albumin ratio is an independent poor prognostic factor in newly diagnosed chronic lymphocytic leukaemia: A clinical analysis of 322 cases

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ABSTRACT

Chronic lymphocytic leukaemia is one of the most common types of adult leukaemia. Cancer-related systemic inflammation response has been characterized to correlate with therapeutic outcome in patients with cancer. The C-reactive protein-to-albumin (CRP/ALB) ratio (CAR), which is an inflammatory marker, has been reported as a novel prognostic factor in several cancers. The aim of our study was to evaluate the prognostic value of the CAR in patients with chronic lymphocytic leukaemia (CLL). We retrospectively reviewed the clinical characteristics of 322 newly diagnosed CLL patients, investigated the correlations among pretreatment CAR, treatment-free survival (TFS) and overall survival (OS), assessed the prognostic effect of the CAR to compare with other inflammation-related prognostic index by the area under the curve (AUC), and combined CAR and CLL-international prognostic index (CLL-IPI) together to improve the current prognostic system. The results showed that CAR was an independent prognostic factor for OS. Furthermore, the predictive and discriminatory capacity of CLL-IPI together with CAR level was superior to that of CLL-IPI alone for OS. In conclusion, serum CRP and ALB levels are both simple and easily accessible parameters, whose ratio CAR may be good candidates for predicting prognosis in the future clinical practice of CLL.

Introduction

Chronic lymphocytic leukaemia (CLL), the most common type of adult leukaemia in the Western world, is a cause of death worldwide. Despite the wide application of new generations of targeted inhibitors, the current overall response rate ranges between 75% and 90%, and the complete response rate ranges between 22% and 45% [1].

The Rai and Binet systems were established and widely used in the last century to evaluate prognosis of CLL [2, 3]. To predict the clinical outcome of CLL more precisely, the CLL international prognostic index (CLL-IPI), which includes age, clinical stage, serum β-2 microglobulin (β2-MG) concentration, tumour protein 53 (*TP53*) status and immunoglobulin heavy variable-region gene (*IGHV*) mutation status, has been applied in the new era; this model stratifies patients into four risk groups (low, intermediate, high, and very high) [4]. In addition, a variety of other biomarkers and gene signatures, such as *SF3B1, NOTCH1, BIRC3*, and *MYD88,* have been identified to characterize the biological mechanism and predict the prognostic risk in CLL, although the precise examination of molecular markers is very expensive [5-9]. Hence, a simple and convenient marker could be added to the criteria of the scoring system to more accurately discriminate groups with notably distinct outcomes.

Inflammatory factors have long been known to play critical roles in initiation and progression in tumorigenesis, and increasing evidence has validates that cancer-associated systemic inflammation and malnutrition have exact prognostic impacts on the majority of patients with malignancies [10-12], such as small-cell lung cancer [13], breast cancer [14], cervical cancer [15], hepatocellular carcinoma [16], colorectal cancer [17] and cerebral cancers [18]. Abundant circulating inflammatory and nutritive indicators, such as C-reactive protein (CRP), albumin (ALB), and fibrinogen, and the Glasgow Prognostic Score (GPS) and modified Glasgow Prognostic Score (mGPS), have been proposed as prognostic indicators for malignant B-cell tumours, including CLL

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[19-24]. The novel inflammatory indicators that consider CRP and ALB, GPS and mGPS reflect both the systematic inflammatory response and nutritional status. The CRP-to-ALB ratio (CAR) has been identified as another serum-based inflammatory indicator. Previous studies reported that CAR has significant prognostic value in various types of cancers [13,16-18,25]. However, the association between CAR and the prognosis of CLL patients has not yet been elucidated. Therefore, the aims of this study were to investigate the relationship of CAR with CLL survival and to analyze any change in predictive value when adding CAR to the CLL-IPI.

Materials and methods

Ethics

The study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University. All aspects of the study, including the assessments of CRP and ALB levels and other clinical and laboratory tests, were performed according to the principles of the Declaration of Helsinki.

Patients

In total, 322 untreated CLL patients diagnosed in the First Affiliated Hospital of Nanjing Medical University between December 2007 and May 2018 were enrolled in this retrospective study. The diagnosis of CLL was made according to the International Workshop on CLL-National Cancer Institute criteria. The exclusion criteria were as follows: (1) patients with acute infection or chronic inflammatory disease; (2) patients with active rheumatic diseases; (3) patients recruited after May 2018 (to avoid bias in treatment-free survival (TFS) and overall survival (OS) caused by short follow-up); and (4) patients with particularly incomplete follow-up data.

Data collection

Baseline clinical characteristics, including age, sex, Rai stage, Binet stage and B symptoms, were collected from medical records. Additionally, laboratory data such as lymphocyte count (ALC), platelet count (PLT), haemoglobin (Hb), lactate dehydrogenase (LDH), β2-MG, CRP and ALB levels were assessed via the hospital-based laboratory service within 24 h after the first admission. During the study period, CRP (mg/L) and ALB (g/L) were measured consistently by the Department of Clinical Laboratory (normal ranges: 0–10 mg/L for CRP and 35–50 g/L for ALB).

Detection of *TP53* and *IGHV* mutation status was performed as previously described [5]. The 98% cut-off of germline homology was used to dichotomize *IGHV* mutational status.

Fluorescence *in situ* hybridization was carried out to detect 17p deletion according to procedures described previously [26]. CD38 and ZAP-70 were detected via flow cytometry, and the cut-off values for positivity were 30% and 20%, respectively.

Statistical analysis

TFS was calculated as the period from diagnosis to first-time treatment. OS was defined as the period from diagnosis to death due to any reason or last follow-up time. The optimal cut-off values for CAR were determined using X-tile software (version 3.6.1, Yale University, CT, USA). The data were analyzed and graphs were made with IBM SPSS statistical software (version 24.0, IBM Inc, NY, USA) and GraphPad Prism (version 7.0, GraphPad Software Inc, CA, USA). Characteristics between groups were compared by the chi-square test or by Fisher's exact test. Survival curves were constructed by the Kaplan-Meier method, and the survival times of different groups were compared by the log-rank test. Furthermore, factors that were deemed significant for survival by univariate analysis were included in the Cox proportional hazards multivariate model to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). Receiver operator characteristic (ROC) curves were constructed and the corresponding areas under the curve (AUCs) were calculated to assess the predictive accuracy of the CLL-IPI and the new risk models via MedCalc (version 19.0.4, MedCalc software, Ostend, Belgium). The Hosmer-Lemeshow goodness-of-fit test was applied to test the calibration of the risk models. The calibration plots were drawn with the observed events/total events and the corresponding expected events/total events as the *X* axis and *Y* axis, respectively. The results were evaluated with 95% CIs, and the significance level was set at two-sided $P<0.05$.

Results

Clinical characteristics of CLL patients

Three hundred and twenty-two newly diagnosed Chinese CLL patients, including 210 (65.2%) males and 112 (34.8%) females with a median age of 59 years (range 16–86 years), were enrolled in the study. There were 100 patients with Binet stage A disease (31.1%) and 222 patients with Binet stage B or C disease (68.9%). The numbers of patients with *TP53* disruption and unmutated *IGHV* were 65 (20.4%) and 127 (39.4%), respectively. The median follow-up time was 65 months (0–225 months). In total, 232 patients (72.0%) received treatment; the treatments included immunochemotherapy (206/232, 88.8%), ibrutinib (9/232, 3.8%) and unknown treatments (17/232, 7.3%).

The means for CRP and ALB were 11.89 ± 1.626 mg/L and 41.067 ± 0.288 g/L, respectively. The median value of CAR at diagnosis was 0.0831 (0.0604–15.7142), and the cut-off point for CAR according to X-tile analysis was 0.6166, which yielded the highest difference in OS. We applied the cut-off values to divide the primary cohort into two groups: 35 (10.9%) patients with a high CAR (H-CAR, >0.6166) and 287 (89.1%) with a low CAR (L-CAR, ≤0.6166). The numbers of patients who received treatments in H-CAR group and L-CAR group were 29 and 203, respectively. Patients' characteristics are listed in Table 1.

Correlations between CAR and other factors

In terms of clinical parameters, a significant dominant pattern was identified: patients who were more than 65 years old ($P=0.003$) and had advanced stage (Binet B or C) disease ($P=0.008$) and B symptoms ($P<0.001$) were more likely to develop H-CAR. Regarding laboratorial findings, low Hb ($P<0.001$), low PLT ($P=0.023$), elevated LDH (greater than the upper limit of normal (ULN)) ($P=0.003$) and elevated β2-MG (>3.5 mg/L) ($P=0.001$) were evidently related to H-CAR status (Table 1). Kaplan-Meier analysis validated the association of high CRP and low ALB levels with shorter OS and TFS, although the correlation between TFS and low ALB was not significant ($P=0.097$) (Fig. 1A–1D). Then, we generated Kaplan-Meier survival curves of patients stratified by CAR. The median OS times for patients with H-CAR and L-CAR were 38 months and not reached (NR). The 3-year and 5-year OS rates were 85.9±2.1% and 76.0±2.6%, respectively, in the L-CAR group vs. 59.4 ± 8.4% and 36.3 ± 8.5%, respectively, in the H-CAR group, which indicated that H-CAR status was related to significantly shorter OS ($P<0.001$) (Fig. 1F). Similarly, patients with H-CAR status had inferior TFS ($P=0.018$). The median TFS of patients with H-CAR and L-CAR was 1 month and 12 months, respectively. The 1- and 3-year TFS rates were 49.7% and 36.2%, respectively, for L-CAR patients vs. 31.0% and 18.1%, respectively, for H-CAR patients (Fig. 1E).

The results of the univariate and multivariate Cox proportional hazards regression analyses are summarized in Table 2 and Table 3. In the univariate analysis, male sex ($P=0.042$), Binet stage B/C ($P<0.001$), B symptoms ($P<0.001$), ALC $>50\times10^9$/L ($P<0.001$), PLT $<100\times10^9$/L ($P<0.001$), Hb <100 g/L ($P<0.001$), LDH >ULN ($P<0.001$), β2-MG >3.5 mg/L ($P<0.001$), *TP53* disruption ($P=0.001$), unmutated *IGHV*

Table 1
Baseline characteristics of untreated 322 chronic lymphocytic leukaemia patients.

Parameters	No. of cases (%)	CAR<0.6166(%) *n*=287	CAR>0.6166(%) *n*=35	*P*-value
Gender				
Male	210 (65.2)	186(64.8)	24 (68.6)	**0.659**
Female	112 (34.8)	101(35.2)	11 (31.4)	
Age				
≤ 65 years	218 (67.7)	202 (70.4)	16 (45.7)	**0.003**
> 65 years	104 (32.3)	85 (29.6)	19 (54.3)	
Binet Stage				
A	100 (31.1)	96 (33.4)	4 (11.4)	**0.008**
B or C	222 (68.9)	191 (66.6)	31 (88.6)	
Symptoms				
No B symptoms	240 (74.5)	223 (77.7)	17 (48.6)	**<0.001**
B symptoms	82 (25.5)	64 (22.3)	18 (51.4)	
Lymphocytes				
≤ 50×10^9/L	250 (77.6)	225 (78.4)	25(71.4)	**0.350**
> 50×10^9/L	72 (22.4)	62 (21.6)	10 (28.6)	
Hemoglobin				
≥ 100 g/L	239 (74.2)	230 (80.1)	9 (25.7)	**<0.001**
< 100 g/L	83 (25.8)	57 (19.9)	26 (74.3)	
Platelets				
≥ 100×10^9/L	220 (68.3)	202 (70.4)	18 (51.4)	**0.023**
< 100×10^9/L	102 (31.7)	85 (29.6)	17 (48.6)	
LDH				
≤ULN	248 (77.0)	228 (79.4)	20 (57.1)	**0.003**
>ULN	74 (23.0)	59 (20.6)	15 (42.8)	
β2-MG				
≤3.5 mg/L	171 (53.9)	162 (57.2)	9 (26.5)	**0.001**
>3.5 mg/L	146 (46.1)	121 (42.8)	25 (73.5)	
TP53 disruption				
Negative	253 (79.6)	228 (80.6)	25 (71.4)	**0.206**
Positive	65 (20.4)	55 (19.4)	10 (28.6)	
IGHV mutation				
M	195 (60.6)	176 (61.3)	19 (54.3)	**0.421**
UM	127 (39.4)	111 (38.7)	16 (45.7)	
CD38 (≥30%)				
Negative	212 (43.0)	192 (77.4)	20 (69.0)	**0.309**
Positive	65 (57)	56 (22.6)	9(31.0)	
ZAP-70 (≥20%)				
Negative	136 (43.0)	118 (49.2)	18 (66.7)	**0.085**
Positive	131 (57)	122 (50.8)	9 (33.3)	

The tests used in Table 1 were all Chi-Square test or Fisher's exact test.
Abbreviations: CAR, C-reactive protein-to-albumin (CRP-to-ALB) ratio; *IGHV*, immunoglobulin heavy variable-region gene; LDH, lactate dehydrogenase; M, mutated; UM, unmutated; β2-MG, β2-microglobulin; *TP*53, tumor protein 53; ULN, upper limit of normal.

Table 2
Univariate and Multivariate Cox regression analyses of TFS.

	Univariate analyses (TFS)		Multivariate analyses (TFS)	
Characteristics	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Male	1.335 (1.011–1.765)	**0.042**	1.211 (0.895–1.638)	0.214
Age >65 years	0.948 (0.719–1.250)	0.707	–	–
Binet Stage B or C	3.023 (2.176–4.200)	**<0.001**	1.972 (1.360–2.858)	**<0.001**
B symptoms	2.687 (2.017–3.579)	**<0.001**	1.674 (1.205–2.325)	**0.002**
Lymphocytes>50×10^9/L	1.806 (1.349–2.418)	**<0.001**	1.222 (0.892–1.676)	0.212
Hemoglobin<100 g/L	1.942 (1.468–2.569)	**<0.001**	0.960 (0.676–1.362)	0.818
Platelets<100×10^9/L	2.221 (1.693-2.914)	**<0.001**	1.353 (0.979–1.869)	0.067
LDH >ULN	1.929 (1.444–2.576)	**<0.001**	1.057 (0.757–1.477)	0.473
β2-MG >3.5 mg/L	2.581 (1.971–3.382)	**<0.001**	1.476 (1.067–2.042)	**0.019**
TP53 disruption	1.715 (1.263–2.329)	**0.001**	1.007 (0.715–1.419)	0.968
IGHV unmutated	2.071 (1.590–2.699)	**<0.001**	1.542 (1.143–2.079)	**0.005**
CD38 (≥30%)	1.359 (0.987–1.870)	0.060	–	–
ZAP-70 (≥20%)	0.971 (0.732–1.299)	0.975	–	–
CAR	1.523 (1.030–2.253)	**0.035**	0.904 (0.582–1.403)	0.652

Abbreviations: TFS, treatment-free survival; HR, hazard ratio; 95% CI, 95% confidence interval; LDH, lactate dehydrogenase; β2-MG, β2-microglobulin; ULN, upper limit of normal; *IGHV*, immunoglobulin heavy variable-region gene; *TP*53, tumor protein 53; CAR, C-reactive protein-to-albumin (CRP-to-ALB) ratio.

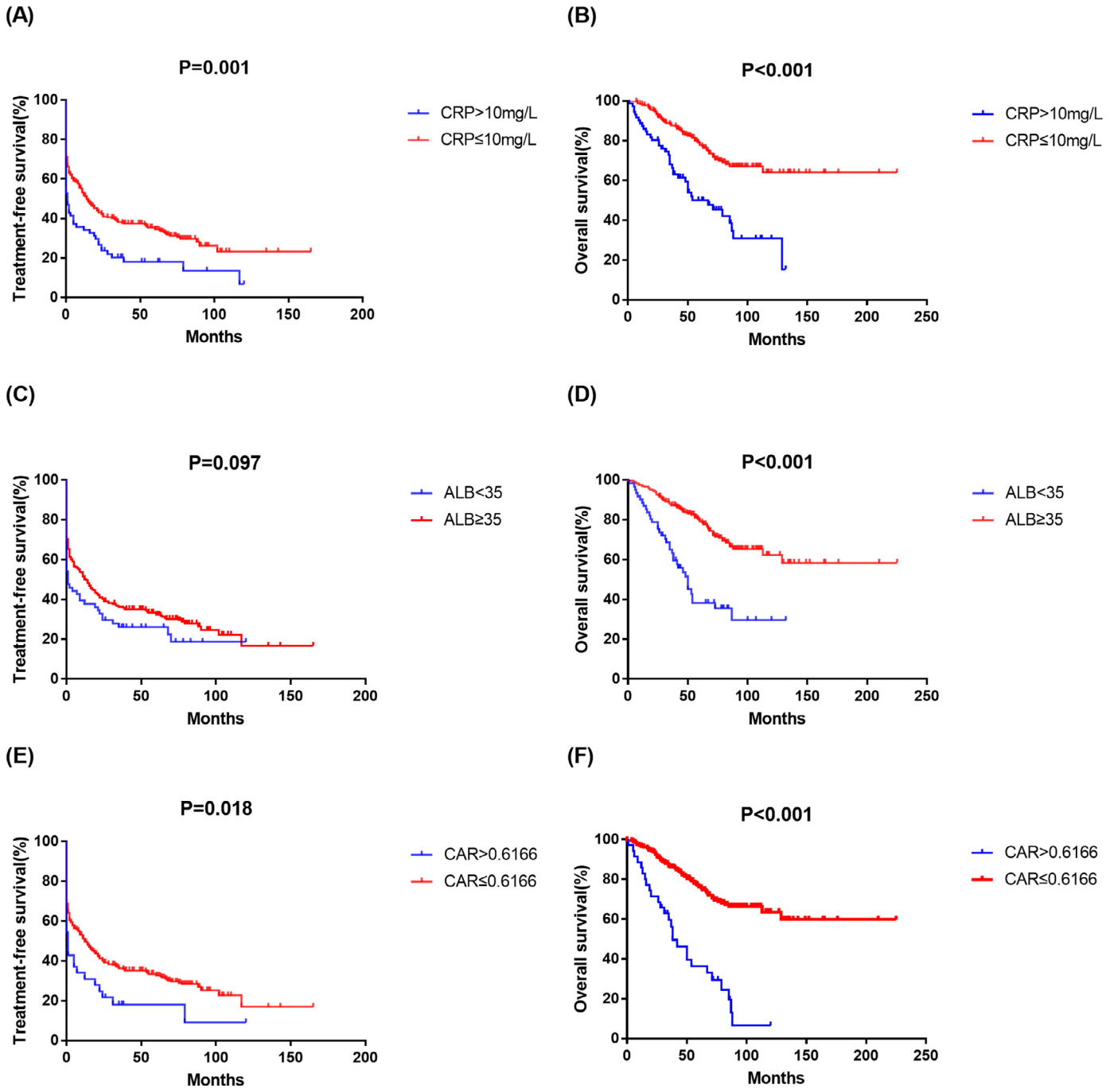


Fig. 1. Kapan–Meier analysis curves of treatment-free survival and overall survival for different CRP (A-B), ALB (C-D) and CAR (E-F) levels. Abbreviations: CRP, C-reaction protein; ALB, albumin; CAR, C-reactive protein-to-albumin ratio.

(P<0.001), and H-CAR status (P=0.035) had adverse impacts on TFS, and male sex (P=0.001), age >65 years (P=0.006), Binet stage B/C (P<0.001), B symptoms (P<0.001), ALC >50×10^9/L (P=0.008), PLT <100×10^9/L (P<0.001), Hb <100 g/L (P<0.001), LDH >ULN (P<0.001), β2-MG >3.5 mg/L (P<0.001), *TP53* disruption (P<0.001), unmutated *IGHV* (P<0.001), and H-CAR status (P<0.001) had adverse impacts on OS. The multivariate Cox regression model revealed that only Binet stage B/C (P<0.001), B symptoms (P=0.002), β2-MG >3.5 mg/L (P=0.019) and unmutated *IGHV* (P=0.005) were independent risk factors for TFS, and male sex (P<0.001), age >65 years (P=0.038), Hb <100 g/L (P=0.030), unmutated *IGHV* (P=0.001), and H-CAR status (P=0.008) were independently associated with inferior OS.

Subgroup analysis of the CAR in CLL patients

In the subgroup analysis, we separated the patients into different subgroups according to age, stage, β2-MG concentration, *IGHV* mutation status, and *TP53* status and analyzed the prognostic impact of CAR in these subgroups (Fig. 2). Worse OS was observed in H-CAR patients in subgroups such as the age ≤65 years old (P<0.001), age >65 years old (P<0.001), Binet stage A (P=0.007), Binet stage B/C (P<0.001), β2-MG ≤3.5 mg/L (P<0.001), β2-MG >3.5 mg/L (P<0.001), mutated *IGHV* (P<0.001), unmutated *IGHV* (P<0.001), normal *TP53* (P<0.001), and *TP53* disruption (P=0.020) subgroups.

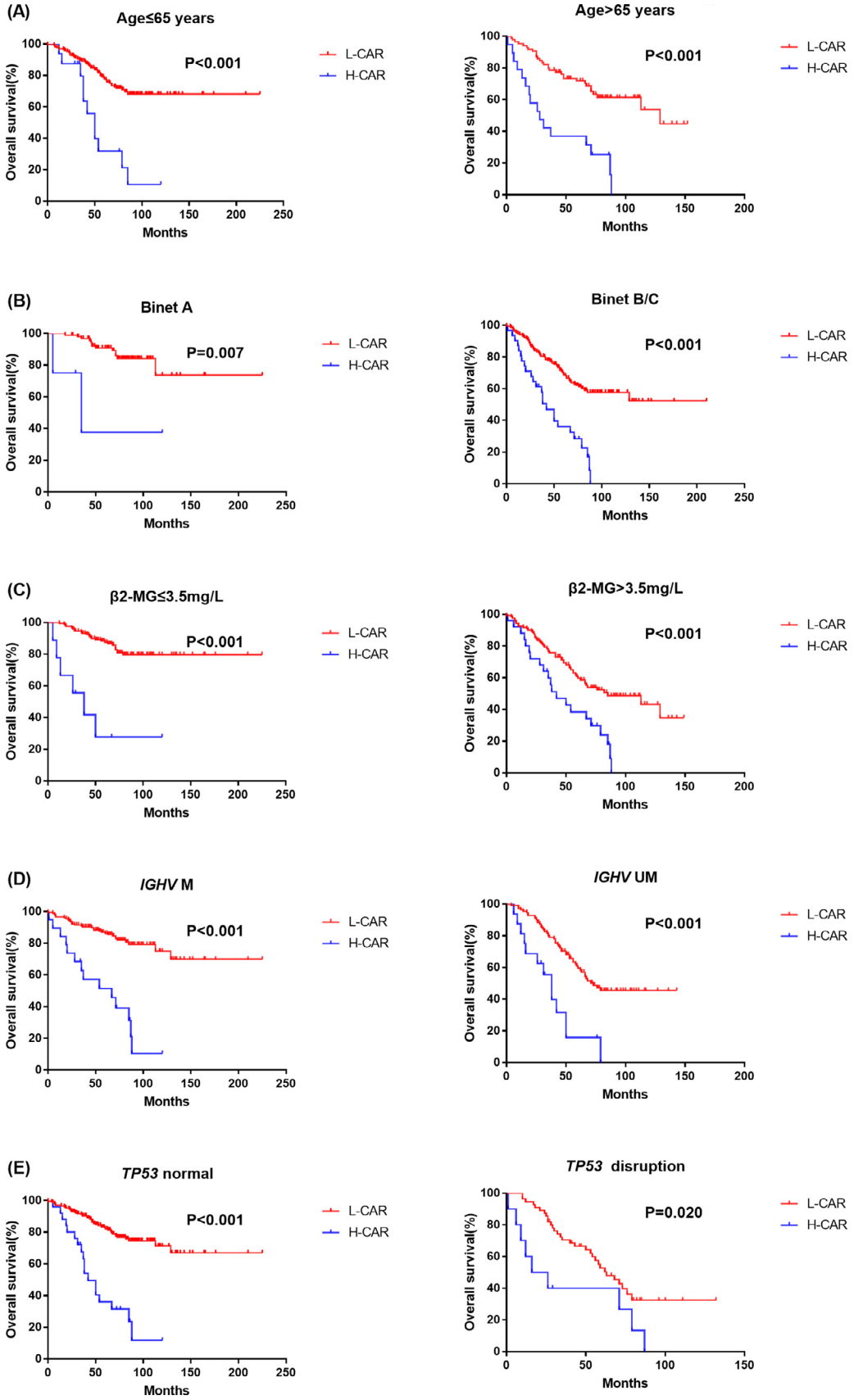


Fig. 2. Kaplan-Meier curves of overall survival for different levels of CAR stratified by age (A), stage (B), serum β2-MG concentration (C), *IGHV* mutation status (D), and *TP53* status (E). Abbreviations: CAR, C-reactive protein to albumin ratio; H-CAR, high-CAR; L-CAR, low-CAR; β2-MG, β2-microglobulin; *IGHV*, immunoglobulin heavy variable region gene; M, mutated; *TP53*, tumor protein 53; UM, unmutated.

Table 3
Univariate and multivariate Cox regression analyses of OS.

	Univariate analyses (OS)		Multivariate analyses (OS)	
Characteristics	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Male	2.206 (1.402–3.470)	**0.001**	2.425 (1.489–3.951)	**<0.001**
Age >65 years	1.715 (1.175–2.502)	**0.006**	1.560 (1.025–2.373)	**0.038**
Binet Stage B or C	3.390 (1.966–5.846)	**<0.001**	1.594 (0.858–2.961)	0.140
B symptoms	2.437 (1.662–3.573)	**<0.001**	1.527 (0.987–2.362)	0.057
Lymphocytes>50×10^9/L	1.727 (1.156–2.581)	**0.008**	0.970 (0.623–1.511)	0.894
Hemoglobin<100 g/L	3.656 (2.511–5.323)	**<0.001**	1.748 (1.054–2.897)	**0.030**
Platelets<100×10^9/L	2.161(1.486-3.143)	**<0.001**	0.851 (0.534–1.358)	0.500
LDH >ULN	2.721 (1.853–3.996)	**<0.001**	1.309 (0.817–2.097)	0.263
β2-MG >3.5 mg/L	3.378 (2.843–5.076)	**<0.001**	1.285 (0.792–2.086)	0.310
TP53 disruption	3.105 (2.094–4.603)	**<0.001**	1.532 (0.984–2.385)	0.059
IGHV unmutated	2.759 (1.882–4.043)	**<0.001**	2.231 (1.417–3.512)	**0.001**
CD38 (≥30%)	1.073 (0.672-1.714)	0.768	–	–
ZAP-70 (≥20%)	0.971 (0.642-1.468)	0.889	–	–
CAR	4.088 (2.640–6.330)	**<0.001**	2.071 (1.211–3.541)	**0.008**

Abbreviations: OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; LDH, lactate dehydrogenase; β2-MG, β2-microglobulin; ULN, upper limit of normal; *IGHV*, immunoglobulin heavy variable-region gene; *TP*53, tumor protein 53; CAR, C-reactive protein-to-albumin (CRP-to-ALB) ratio.

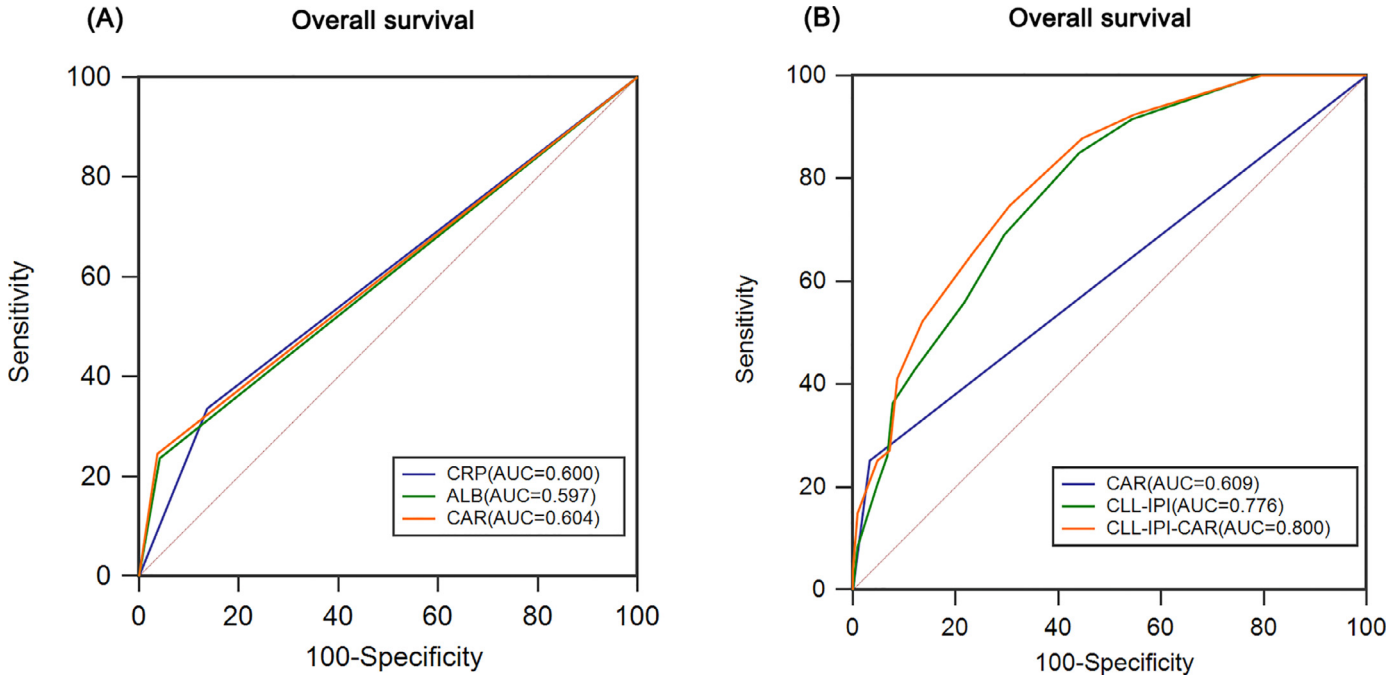
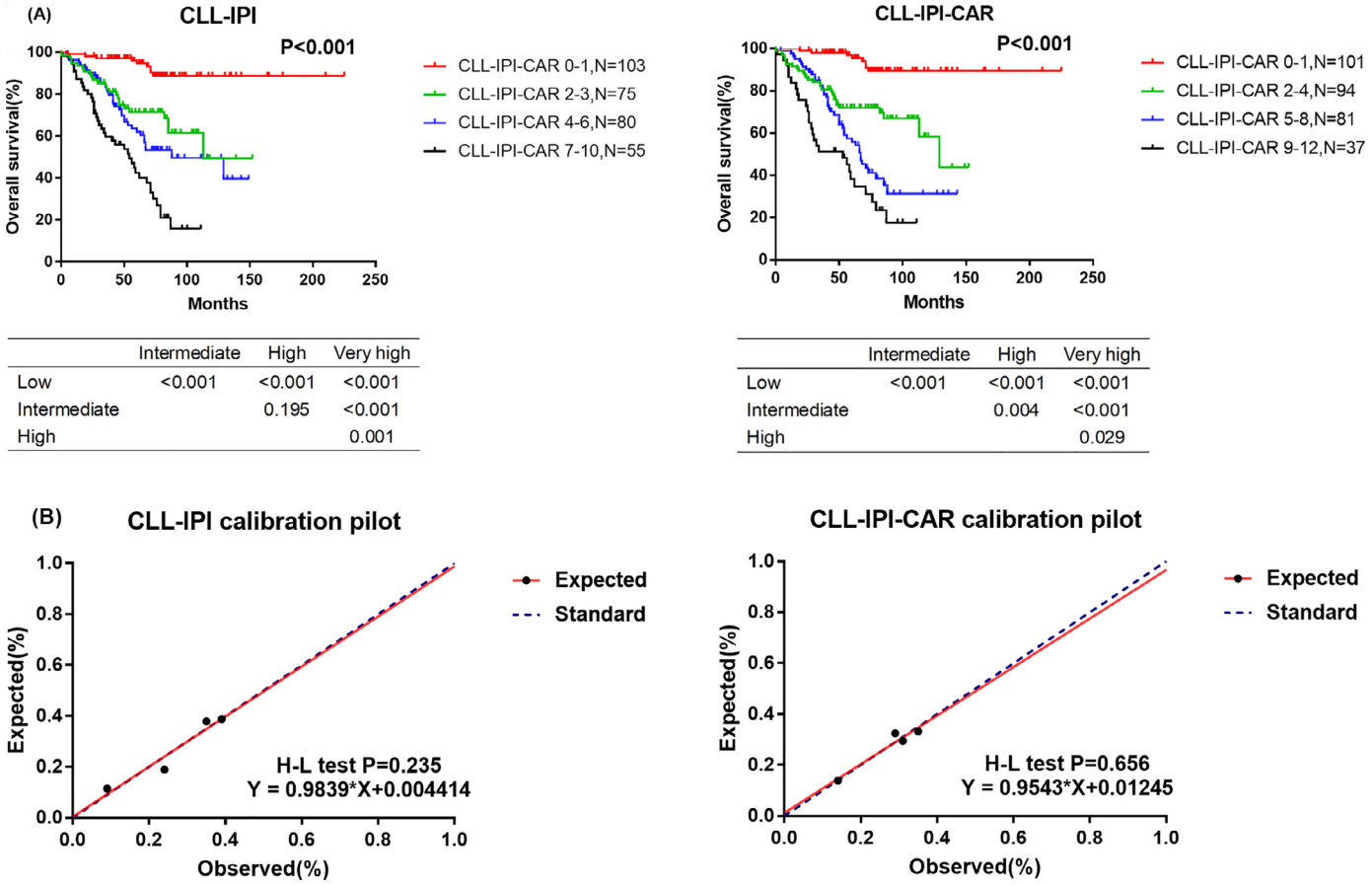


Fig. 3. Comparison of prognostic significance of the CRP, ALB with CAR (A) and the CAR, CLL-IPI with CLL-IPI-CAR (B) by ROC curves. Abbreviations: ROC, receiver-operator characteristic; AUC, areas under the curve; CRP, C-reaction protein; ALB, albumin; CAR, C-reactive protein to albumin ratio; CLL-IPI, chronic lymphocytic leukaemia-international prognostic index.

A better risk model based on the CLL-IPI and CAR

ROC curves were generated to evaluate the discrimination ability of CAR, CRP, and ALB by comparison of AUCs (Fig. 3A). The area under the curve (AUC) value for OS was 0.604 (95% CI: 0.548–0.659) for the CAR, which was higher than that for CRP (AUC =0.600 95% CI: 0.544–0.654) and ALB (AUC =0.597, 95% CI: 0.541–0.651). These data indicate that the OS-predictive power of the CAR was higher than that of CRP and ALB n CLL patients. Furthermore, we combined the CAR and CLL-IPI to develop a novel prognostic index that might provide better predictive accuracy than the CLL-IPI alone. The CAR was allocated as a risk factor with two points because the HR was similar to that of the *IGHV* mutation status in the multivariate analysis (Table 4). ROC curves were used to evaluate its specificity and sensitivity for predicting OS. The AUC of the CAR for predicting OS was 0.609 (95% CI: 0.553–0.664). The AUC of the CLL-IPI for predicting OS was 0.776 (95% CI: 0.726–0.821) for OS. The AUC of the CLL-IPI-CAR model for predicting OS was 0.800 (95% CI: 0.751–0.842). The CLL-IPI-CAR model was demonstrated to have superior prognostic value over the CLL-IPI (*P*=0.0008) (Fig. 3B).

We further validated the potency of the CLL-IPI-CAR model (low-risk 0–1; intermediate-risk 2–4; high-risk 5–8; very high-risk 9–12) and the CLL-IPI (low-risk 0–1; intermediate-risk 2–3; high-risk 4–6; very high-risk 7–10) in predicting OS in Chinese CLL patients (Table 4). Similar to the CLL-IPI model, the CLL-IPI-CAR model was also able to significantly separate Chinese CLL patients into 4 groups (*P*<0.001), and the CLL-IPI-CAR model could more precisely discriminate between the intermediate-risk group and high-risk group (*P*=0.004). The median OS of low-, intermediate-, high-, and very high-risk patients was NR, 113, 88, and 54 months, respectively, for the CLL-IPI model, and NR, 129, 67, and 53 months, respectively, for the CLL-IPI-CAR model (Fig. 4A).



	Intermediate	High	Very high
Low	<0.001	<0.001	<0.001
Intermediate		0.195	<0.001
High			0.001

	Intermediate	High	Very high
Low	<0.001	<0.001	<0.001
Intermediate		0.004	<0.001
High			0.029

Fig. 4. Kaplan-Meier curves of overall survival stratified by four CLL-IPI (A) and CLL-IPI-CAR (B) risk grades and P values between the overall survival of each two risk grades in CLL-IPI (A) and CLL-IPI-CAR (B) risk models. Calibration plot of CLL-IPI (D) and CLL-IPI-CAR (E). Abbreviations: CAR, C-reactive protein to albumin ratio; CLL-IPI, chronic lymphocytic leukaemia-international prognostic index.

Table 4
Risk models for OS.

Model	Variable	Score	Risk stratification	Total score
CLL-IPI	*TP53* disruption	4	Low	0–1
	IGHV unmutated	2	Intermediate	2–3
	β2-MG >3.5 mg/L	2	High	4–6
	Rai I-IV or Binet B/C	1	Very high	7–10
	Age >65 years	1		
CLL-IPI-CAR	*TP53* disruption	4	Low	0–1
	IGHV unmutated	2	Intermediate	2–4
	β2-MG >3.5 mg/L	2	High	5–8
	Rai I-IV or Binet B/C	1	Very high	9–12
	Age >65 years	1		
	H-CAR	2		

Abbreviations: OS, overall survival; CLL-IPI, chronic lymphocytic leukaemia-international prognostic index; *IGHV*, immunoglobulin heavy variable-region gene; TP53, tumor protein 53; β2-MG, β2-microglobulin; CAR, C-reactive protein-to-albumin (CRP-to-ALB) ratio; H-CAR, high-CAR.

The P values of the Hosmer-Lemeshow test were 0.235 and 0.656 for the CLL-IPI and the CLL-IPI-CAR model, respectively (Fig. 4B).

Discussion

Previous studies have validated that the systemic inflammatory response and nutrient consumption are significantly associated with poor clinical outcomes in cancer patients due to the altered tumour microenvironment, which is a vital factor in the development of CLL [11,27-29]. Proteins such as CRP and ALB are indicators of inflammation and nutrition status and may be useful markers for predicting the survival of CLL patients. The CAR was developed by Fairclough, E et al primarily to identify patients with severe illness in an acute medical ward [30]. Recently, several studies have explored its prognostic function in cancers, but whether CAR has similar value in CLL remains to be demonstrated [13, 16].

In this study, we retrospectively analyzed the clinical factors and prognosis of 322 eligible CLL patients with different CAR values at our center. To our knowledge, this is the first study to analyze the CAR in patients with CLL. Patients who were more than 65 years old and had advanced stage and B symptoms were more inclined to have H-CAR status. In addition, high concentrations of LDH or β2-MG led to H-CAR status because both of these variables can reflect inflammation levels, which are related to CRP to some extent [31, 32]. In addition, patients with high levels of LDH and β2-MG usually had a poor prognosis, and malnutrition, which is related to albumin, greatly affected their survival.

The results demonstrated that the baseline CAR at the time of diagnosis of CLL was an adverse prognostic indicator for OS. We found that compared to L-CAR status, H-CAR status was significantly associated with inferior OS in both the univariate and multivariate Cox regression analysis models. There were significant differences in terms of OS between the H-CAR and L-CAR subgroups, which indicated that the CAR could predict OS independent of the CLL-IPI and that the CAR level could possibly be incorporated into the prognostic stratification to optimize the CLL-IPI. On this basis, we combined the CAR and CLL-IPI to build a novel prognostic index. Consequently, the CLL-IPI-CAR model was demonstrated to have a superior power for OS prediction than the CLL-IPI alone, as indicated by a significant difference in the ROC curve

analysis. Moreover, the CLL-IPI-CAR model could distinguish more accurately between the intermediate-risk group and the high-risk group than the CLL-IPI when the calibration of the CLL-IPI-CAR model was fairly satisfactory. On account of the clinical advantages of CRP and ALB assessment, such as reproducibility, well-standardized methodology, and inexpensiveness, CAR has terrific potential in CLL prognosis prediction.

However, this model was built on a small cohort of Chinese patients and could only stratify patients in terms of OS. The cut-off point of CAR in this study was calculated according to the OS, not to the TFS, and the retrospective and single-center data of TFS had higher possibility to be biased due to other factors such as the economic conditions of patients. These reasons may account for that CAR was not an independent prognostic factor for TFS. Other analyses through prospective observation or interventional studies in a large cohort are recommended to confirm the repeatability and feasibility of this model. Due to the short follow-up of the patients received treatments of some novel nonchemotherapy-based drugs, most enrolled patients received chemotherapy, which is another deficiency of our study. New pharmacologic therapies such as ibrutinib have been proved to strongly associated with inflammation in CLL and this new risk model still needs further validation among patients receiving these novel agents [33].

The increases in the CAR might be explained as follows. Increased serum interleukin 6 levels have been previously proven to be correlated with a high risk of death in CLL, and CRP is mostly under transcriptional control by this inflammatory cytokine [34, 35]. Additionally, albumin levels decline when patients are undernourished. Adverse prognostic factors, such as tumour necrosis factor α, could also reduce the synthesis of albumin [36, 37]. There have been studies using anti-inflammatory drugs or nutritional supplements to alter the inflammatory and nutritional status of patients with cancer, and these therapies improved their immune function and reduced the risk of cancer [38-40]. Since CAR is related to not only inflammation-based indexes but also nutrition-based indexes, it would probably be an appropriate index to evaluate and predict the effectiveness of anti-inflammatory and nutrition improvement treatments in CLL patients in clinical practice.

In conclusion, we analyzed the CAR in 322 newly diagnosed Chinese CLL patients. Compared to L-CAR status, H-CAR status was significantly associated with worse TFS and OS, and it was an independent prognostic factor for OS. The addition of the H-CAR status criterion evidently improved the prognostic capacity of the CLL-IPI for predicting the OS of CLL patients. The retrospective nature of this study and limited number of subjects are the major limitations. Additional prospective multicentre studies are needed to further understand the role and clinical potency of the CAR.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Han-Ning Tang: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization. **Bi-Hui Pan:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization. **Li Wang:** Resources, Data curation. **Hua-Yuan Zhu:** Resources, Data curation. **Lei Fan:** Resources, Data curation. **Wei Xu:** Conceptualization, Investigation, Data curation, Validation, Writing - review & editing, Supervision. **Jian-Yong Li:** Conceptualization, Methodology, Investigation, Data curation, Validation, Writing - review & editing, Supervision.

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Authors' Contributions

HNT, BHP and JYL designed the study. LW, HYZ, and LF organized the clinical materials. HNT, BHP, WX and JYL performed the data analysis and wrote the paper. All authors contributed to the interpretation of the data, critically revised the article throughout development for intellectual content, approved the final version and are accountable for the accuracy and integrity of the work.

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