The Value of C-Reactive Protein, C-Reactive Protein Kinetics and C-reactive Protein to Albumin Ratio on Prognosis in Newly Diagnosed Indolent B-cell Non-Hodgkin Lymphoma

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Research

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Abstract

Objective: This study aimed to determine prognostic significance of C-reactive protein (CRP), CRP kinetics and CRP to albumin ratio (CAR) in indolent B-cell non-Hodgkin lymphoma (B-iNHL) patients.

Methods: The association among these blood makers and overall survival (OS), disease-free survival (DFS), progression-free survival (PFS) were analyzed in 243 B-iNHL patients. OS, DFS and PFS were determined by Kaplan–Meier curves. Cox proportional analysis was performed to examine the prognostic significance of clinicopathological variables.

Results: Multivariate analyses identified that elevated pretreatment CRP (HR: 5.110, 95% CI: 1.904-13.717, $p=0.001$), post-treatment CRP (HR: 5.826, 95% CI: 1.659-20.458, $p=0.006$), continuously elevated CRP (HR: 6.461, 95% CI: 2.620-15.930, $p<0.001$) and elevated CAR (HR: 3.768, 95% CI: 1.415-10.034, $p=0.008$) had association with worse OS. Likewise, elevated pretreatment CRP (HR: 3.767, 95% CI: 1.777-7.984, $p=0.001$), post-treatment CRP (HR: 2.384, 95% CI: 1.027-5.534, $p=0.043$), ever-elevated CRP (HR: 2.425, 95% CI: 1.105-5.322, $p=0.027$), continuously elevated CRP (HR: 4.748, 95% CI: 2.114-10.660, $p<0.001$) and elevated CAR (HR: 2.824, 95% CI: 1.336-5.971, $p=0.007$) were in independent significance with worse DFS. Elevated pretreatment CRP (HR: 2.606, 95% CI: 1.338-5.076, $p=0.005$), ever-elevated CRP (HR: 2.086, 95% CI: 1.040-4.188, $p=0.039$), continuously elevated CRP (HR: 3.296, 95% CI: 1.594-6.818, $p=0.001$) and elevated CAR (HR: 1.991, 95% CI: 1.021-3.882, $p=0.043$) were determined in independent significance with poor PFS. The effect was statistically significant in both follicular lymphoma (FL) and chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/ SLL) patients.

Conclusions: In conclusion, we demonstrate that CRP level, CRP kinetics and CAR could be potential prognostic indicators with independent significance in patients with B-iNHL, also in FL and CLL/ SLL subgroups. CRP and CAR make an implementation for prognostic evaluation more easily and effectively in B-iNHL patients.

Introduction

Indolent B-cell non-Hodgkin lymphoma (B-iNHL) are collection of malignancies, which are characterized by slow growth that can be alleviated with treatment but cannot be cured [1]. The main subtypes include follicular lymphoma (FL), marginal zone lymphoma (MZL), chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/ SLL) and lymphoplasmacytic lymphoma/ Waldenstroms macroglobulinemia (LPL/ WM). Disease progress or relapse is never desirable, but progress, relapse and retreatment occur on some B-iNHL patients. Early identification of these patients is of great significance for their treatment. However, limitations of existing risk stratification tools in routine clinical use exist, it is urgent to find new prognostic predictors. Thus, a series of studies had been carried out to search for effective alternative prognostic biomarkers [2–5].

The association between inflammation and tumors has been early presented [6]. C-reactive protein (CRP), a biomarker compounded in hepatic cells induced by pro-inflammatory cytokines, is the most commonly used clinical indicator of inflammation [7–9]. According to previous research, high CRP level is considered a dangerous factor for cardiovascular diseases, diabetes and chronic hepatitis B virus (HBV) inflammatory [10–14]. A number of previous studies have shown that elevated CRP level was associated with poor outcome in rectal cancer, hepatocellular carcinoma, lung carcinoma, melanoma, bone neoplasms, breast cancer, ovarian cancer, esophageal carcinoma and other solid tumors [15–23]. Regarding to hematological cancers, elevated CRP level has been reported as a poor prognostic predictor in diffuse large B-cell lymphoma, angioimmunoblastic T-cell lymphoma and CLL [24–26]. In addition, the prognostic value of CRP kinetics, dynamic change of CRP level throughout treatment, has been confirmed in metastatic nasopharyngeal carcinoma and renal cell carcinoma [27–29]. Furthermore, a novel prognostic markers involving inflammation and nutrition, CRP to albumin ratio (CAR), has been evaluated in colorectal cancer, liver cell carcinoma, lung cancer, and other solid tumors [30–34]. The prognostic significance of CRP level, CRP kinetics and CAR in B-iNHL are unclear.

This study aimed to investigate whether CRP level, CRP kinetics and CAR were potential prognostic indicators in B-iNHL patients. We studied the association among pretreatment CRP level, CRP level during treatment, post-treatment CRP level, CRP kinetics, pretreatment CAR and overall survival (OS), disease-free survival (DFS), progression-free survival (PFS). Furthermore, prognostic significance of CRP level, CRP kinetics and CAR in the different subgroups diseases also were investigated.

Materials And Methods

Patients

Patients who were diagnosed with B-iNHL according to the 2008 WHO classification and 2016 WHO classification between January 2012 and December 2019 at the Shandong provincial hospital in China were involved in this study [35-36]. The following types of disease were included in our analysis: FL, MZL, CLL/ SLL and LPL/ WM. Patients who were diagnosed with grade 3b FL, non-newly diagnosed, with other hematological cancers combined and had not any CRP or albumin record were excluded.

Clinical data

All clinicopathological data were obtained from medical records. Clinicopathological parameters included histologically confirmed B-iNHL, gender, age, clinical stage, international prognostic index (IPI) and treatment plan. Rai staging system was used for the clinical stage of CLL/ SLL and Ann Arbor staging system was used for FL, MZL and LPL/ WM. Laboratory data, including hemoglobin (Hb), platelet count (PLT), lactate dehydrogenase (LDH) and β 2-microglobulin (β 2-MG), were obtained ahead of treatment.

Follow-up

Patients were followed up each month during complete chemotherapy cycle, every 3 months after treatment first 2 years and semiyearly thereafter. Information of death or relapse were known by referring to clinical cases or calling to their relatives for ask. OS referred to the time (in months) from diagnosis to death from any cause. DFS referred to the time (in months) from diagnosis to the palindromia of the disease being confirmed histologically or death due to disease. PFS referred to the time (in months) from diagnosis to the progression of the disease or death due to disease. This study was approved by the Biomedical Research Ethic Committee of Shandong province hospital (NO. SWYX2020-027) and informed consent was exempted based on medical records involved in this study obtained in previous clinical diagnosis and treatment.

CRP level, CRP kinetics and albumin

Serum level of CRP were obtained at baseline (pretreatment CRP level), ahead of each chemotherapy (CRP level during treatment) and after all consecutive chemotherapy (post-treatment CRP level). The data were considered missing if the patient was suffering acute infection or acute episode of chronic infection. Furthermore, patients were divided into 3 cohorts based on CRP kinetics: i) continuously normal cohort: patients' CRP level were normal all the time, ii) ever-elevated cohort: patients' CRP level were ever elevated regardless any time point, iii) continuously elevated cohort: patients' CRP level were elevated all the time. In addition, serum level of albumin was obtained ahead of treatment.

Statistical analyses

First of all, receiver operating curve (ROC) analysis was used to determine the optimal cutoff value for pretreatment CRP level and CAR to distinguish between living and dead. The association between CRP level, CRP kinetics, CAR and clinicopathological parameters were evaluated by chi-square test. The association between CRP level, CRP kinetics, CAR and OS, DFS or PFS were determined by Kaplan–Meier curves and log-rank test. The significance of clinicopathological variables were confirmed by Cox proportional analysis in univariate and multivariate analyses. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were reported as relative risks. All statistical analyses were performed using IBM SPSS Statistics, Version 26. A two-sided $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Overall, a total of 377 B-iNHL patients, including FL, MZL, CLL/ SLL and LPL/WM, were diagnosed and treated during the January 2012 and December 2019 at our center. Patients who were diagnosed with grade 3b FL ($n=9$), non-newly diagnosed ($n=44$), with other hematological cancers combined ($n=3$) and had not any CRP or albumin record ($n=78$) were excluded. Finally, 243 patients, including FL ($n=77$), MZL ($n=46$), CLL/ SLL ($n=91$) and LPL/ WM ($n=29$), were found to meet study criteria and were involved in the analysis. The median age at diagnosis was 59 (range 19–85) years, with 133 (54.7%) males, and 110 (45.3%) females. The median follow-up time was 23 (range, 1–83) months. 31 (12.8%) patients died, 45 (18.5%) patients had disease recurrence or died due to disease and 51 (21.3%) patients suffered disease progression or died due to disease by their most recent follow-up visit. (Table 1).

Serum CRP level and CAR cutoff selection

An optimal pretreatment CRP level cutoff value was determined by ROC analysis (area under the curve: 0.747, 95% CI: 0.631–0.894, specificity: 0.739, sensitivity: 0.739, $p < 0.001$) (Figure 1A). This cutoff was 5.84 mg/L, also used in other time CRP level cohorts. Similarly, the optimal cutoff value of pretreatment CAR was 0.117 (area under the curve: 0.753, 95% CI: 0.634–0.872, specificity: 0.687, sensitivity: 0.783, $p < 0.001$) (Figure 1B).

Association of CRP level, CRP kinetics and CAR with clinicopathological features

Pretreatment elevated CRP level was significantly correlated with clinical stage, reduced Hb level, high LDH level, elevated β 2-MG level, disease types, IPI and treatment plan ($p < 0.05$). The correlation between post-treatment elevated CRP level and age, reduced Hb level and disease types were observed ($p < 0.05$). CRP kinetics was significantly correlated with age, clinical stage, reduced Hb level, elevated β 2-MG level, disease types, IPI and treatment plan ($p < 0.05$). Likewise, the correlation between CAR and clinical stage, reduced Hb level, elevated β 2-MG level, disease types, IPI and treatment plan were observed ($p < 0.05$). (Table1).

Prognostic value of pretreatment CRP level

Within the cohort of 243 patients, 222 had pretreatment CRP level record. Poor five-year OS (94.3% vs. 56.7%, $p < 0.001$, log-rank test), DFS (88.0% vs. 33.9%, $p < 0.001$, log-rank test) and PFS (78.3% vs. 40.6%, $p < 0.001$, log-rank test) could be determined among patients whose pretreatment CRP level

were elevated (Figure 2A-C).

Univariate Cox proportional analysis identified that pretreatment elevated CRP level was prognosticator for patients' worse OS (HR: 6.546, 95% CI: 2.543-16.853, $p<0.001$), DFS (HR: 4.704, 95% CI: 2.305-9.601, $p<0.001$) and PFS (HR: 3.177, 95% CI: 1.694-5.961, $p<0.001$). For the multivariate analyses, in line with the recommended ratio of $\geq 5-9$ events per variable, four variables, including pretreatment CRP level, clinical stage, PLT and $\beta 2$ -MG, was performed [37]. Since these four variables showed larger HR in the univariate model. We identified pretreatment elevated CRP level (HR: 5.110, 95% CI: 1.904-13.717, $p=0.001$) and reduced PLT (HR: 3.994, 95% CI: 1.635-9.754, $p=0.002$) as independent predictors for OS. Simultaneously, we also identified pretreatment elevated CRP level (HR: 3.767, 95% CI: 1.777-7.984, $p=0.001$), and reduced PLT (HR: 2.320, 95% CI: 1.071-5.023, $p=0.033$) were independent prognostic predictors for DFS. As well as, increased pretreatment elevated CRP level (HR: 2.606, 95% CI: 1.338-5.076, $p=0.005$) was proved predicting independently patients' poor PFS. (Table 2).

Prognostic value of CRP level during treatment

In our study, elevated CRP level during treatment was not associated with five-year OS (89.7% vs. 82.4%, $p=0.924$, log-rank test), DFS (81.7% vs. 56.6%, $p=0.378$, log-rank test) and PFS (69.4% vs. 55.5%, $p=0.586$, log-rank test) (Figure 2D-F). Thus, univariate and multivariate Cox proportional analyses were not carried out among these patients.

Prognostic value of post-treatment CRP level

To evaluate the prognostic significance of post-treatment CRP level, 64 of 243 patients who had post-treatment CRP level record were involved in the analysis. Negative prognostic value of post-treatment elevated CRP level for five-year OS (81.7% vs. 39.4%, $p<0.001$, log-rank test) (Figure 2G) and DFS (56.4% vs. 35.7%, $p=0.020$, log-rank test) (Figure 2H) could also be found. However, elevated post-treatment CRP level was not associated with five-year PFS (49.8% vs. 38.8%, $p=0.058$, log-rank test) (Figure 2I). So we just carried out univariate and multivariate Cox regression analyses of the main prognostic factors for OS and DFS in post-treatment CRP level subgroup.

Univariate Cox proportional analysis identified post-treatment elevated CRP level were associated with patients' worse OS (HR: 6.728, 95% CI: 2.015-22.465, $p=0.002$) and DFS (HR: 2.601, 95% CI: 1.126-6.008, $p=0.025$). As post-treatment CRP level, PLT and $\beta 2$ -MG showed the larger HR in the univariate model, they were involved in the multivariate analyses. We found post-treatment elevated CRP level (HR: 5.826, 95% CI: 1.659-20.458, $p=0.006$) and reduced PLT (HR: 8.532, 95% CI: 2.065-35.241, $p=0.003$) independently predicted patients' poor OS. In addition, we identified post-treatment elevated CRP level (HR: 2.384, 95% CI: 1.027-5.534, $p=0.043$) was independent predictor for DFS. (Table 3).

Prognostic value of CRP kinetics

Among 243 patients, highly significant association between CRP kinetics and poor five-year OS (80.0% vs. 82.8% vs. 47.1%, $p<0.001$, log-rank test), DFS (80.2% vs. 62.9% vs. 35.3%, $p<0.001$, log-rank test) and PFS (72.4% vs. 61.9% vs. 41.9%, $p<0.001$, log-rank test) could be found (Figure 2J-L).

Univariate Cox proportional analysis identified continuously elevated CRP level as prognosticator for patients' worse OS (HR: 6.661, 95% CI: 2.775-15.988, $p<0.001$). Ever-elevated CRP level (HR: 3.483, 95% CI: 1.615-7.511, $p=0.001$ for DFS and HR: 2.638, 95% CI: 1.346-5.173, $p=0.005$ for PFS) and continuously elevated CRP level (HR: 5.232, 95% CI: 2.356-11.622, $p<0.001$ for DFS and HR: 3.663, 95% CI: 1.790-7.496, $p<0.001$ for PFS) were significantly associated with patients' poor DFS and PFS. Multivariate analyses, including CRP kinetics, clinical stage, PLT and $\beta 2$ -MG were performed. We identified continuously elevated CRP level (HR: 6.461, 95% CI: 2.620-15.930, $p<0.001$) and reduced PLT (HR: 4.025, 95% CI: 1.791-9.049, $p=0.001$) could independently predict patients' poor OS. What's more, ever-elevated CRP level (HR: 2.425, 95% CI: 1.105-5.322, $p=0.027$), continuously elevated CRP level (HR: 4.748, 95% CI: 2.114-10.660, $p<0.001$) and elevated $\beta 2$ -MG level (HR: 2.100, 95% CI: 1.036-4.255, $p=0.039$) were found as independent predictors for DFS. Ever-elevated CRP level (HR: 2.086, 95% CI: 1.040-4.188, $p=0.039$) and continuously elevated CRP level (HR: 3.296, 95% CI: 1.594-6.818, $p=0.001$) also were found as independent predictors for PFS. (Table 4).

Prognostic value of pretreatment CAR

Within the cohort of 243 patients, 221 patients had pretreatment CAR record. Poor five-year OS (93.1% vs. 61.9%, $p<0.001$, log-rank test), DFS (87.3% vs. 42.8%, $p<0.001$, log-rank test) and PFS (77.2% vs. 48.8%, $p=0.002$, log-rank test) could be determined among these patients whose CAR were high (Figure 2M-O).

Univariate Cox proportional analysis identified pretreatment CAR were associated with patients' poor OS (HR: 5.426, 95% CI: 2.018-13.962, $p<0.001$), DFS (HR: 3.856, 95% CI: 1.888-7.874, $p<0.001$) and PFS (HR: 2.591, 95% CI: 1.381-4.858, $p=0.003$). For the multivariate analyses, four variables, including pretreatment CAR, clinical stage, PLT and $\beta 2$ -MG, were performed. We identified pretreatment CAR (HR: 3.768, 95% CI: 1.415-10.034, $p=0.008$) and reduced PLT (HR: 3.475, 95% CI: 1.439-8.394, $p=0.006$) independently predicted poor OS. Simultaneously, pretreatment CAR (HR: 2.824, 95% CI: 1.336-5.971, $p=0.007$ for DFS and HR: 1.991, 95% CI: 1.021-3.882, $p=0.043$ for PFS) also was independent predictors for DFS and PFS. (Table 5).

Prognostic significance of CRP level, CRP kinetics and pretreatment CAR in the different diseases subgroups

Highly significant association between CRP level, CRP kinetics, CAR and poor OS, DFS, PFS ($p < 0.05$, log-rank test) could be determined in CLL/ SLL subgroup. In FL cohort, a negative prognostic value of pretreatment elevated CRP level, CRP kinetics and CAR for OS, DFS, PFS ($p < 0.05$, log-rank test) could be identified. However, elevated post-treatment CRP level was not associated with OS and DFS in FL cohorts. Furthermore, elevated CRP level, CRP kinetics and CAR were not associated with OS, DFS and PFS in MZL and LPL/ WM subgroups. (Table 6).

Discussion

The present study is the first research to investigate the prognostic value of CRP level, CRP kinetics and CAR in B-iNHL patients.

The reason for elevated CRP level associated with worse prognosis among cancer patients remains unknown. Previous studies had shown that inflammatory may contribute directly to tumor progression [38-39]. Zhao Sun et al. demonstrated that tumors cause inflammation, and inflammatory tumor microenvironments recruit mesenchymal stem cells (MSCs) [40]. These MSCs promote tumor growth, progression, and metastasis, leading to the formation of a vicious cycle. Inflammation has also been reported promoting development and progression of cholangiocarcinoma and hepatocellular carcinoma [41-43]. IL-6, as the main inducers of CRP synthesis, was proved promote the progression of cholangiocarcinoma and other cancers [44-47]. Moreover, Yang et al. confirmed that CRP promoted myeloma cell proliferation under stress and protected cancer cells from being damaged by chemotherapy drugs [48]. What's more, Shengchao Xu et al. demonstrated that inflammasome inhibitors are helpful in the treatment of inflammation-related tumors [49]. Clearly, the mechanisms of CRP regarding the progression of B-iNHL need to be clarified in further investigations.

Fairclough et al. firstly presented the conception of CAR in 2009 [50]. Because of too much energy expenditure, cancer patients often suffer malnutrition. Because of increased catabolism and the reduce of hepatic synthesis, albumin is oppositely associated with inflammatory [51]. CAR is a novel and superior prognostic factor involving inflammatory and nutritional factors in various cancers, which was also confirmed in B-iNHL patients. CRP and albumin are routinely tested in most hospital, which make an implementation for prognostic evaluation more easily and effectively in B-iNHL patients.

In the stratified analyses, post-treatment elevated CRP level was considered to be not associated with PFS. This may be due to the fact that fewer patients have a record of post-treatment CRP and the cutoff value was no best distinction between progressive and non-progressive patients. In addition, post-treatment elevated CRP level was considered to be not associated with OS and DFS in FL cohort. This may be attributed to a reduced level of positive events. Besides, negative results were reported in MZL and LPL/ WM cohorts. The reason may be related to the small number of patients included in these cohorts.

Our study has some limitations. Patients with B-iNHL were recruited from a same hospital and might not be representative of the general B-iNHL. CRP is a non-specific biomarker of inflammation. It is possible that patient's infection status was not recorded in the case, which affected the exclusion of data. Other potential cofounders of CRP level, including body mass index, smoking and systemic treatment variables, were not included in our study.

Conclusions

We demonstrated pretreatment and post-treatment elevated CRP level can independently predict poor clinical outcomes in patients with B-iNHL. The study of CRP kinetics shows that ever and continuously and ever elevated CRP level indicate unfavorable prognosis for B-iNHL. Furthermore, pretreatment CAR as independent poor prognostic factor for clinical outcomes also were confirmed. Further investigations including large prospective studies were required to determine optimal CRP level and CAR value and to improve body inflammatory response to the malignancies.

Abbreviations

CRP C-reactive protein

CAR C-reactive protein to albumin ratio

B-iNHL indolent B-cell non-Hodgkin lymphoma

OS overall survival

DFS disease-free survival

PFS progression-free survival

FL follicular lymphoma

MZL marginal zone lymphoma

CLL/ SLL chronic lymphocytic leukemia/ small lymphocytic lymphoma

LPL/ WM lymphoplasmacytic lymphoma/ Waldenstroms macroglobulinemia

HBV hepatitis B virus

IPI international prognostic index

Hb hemoglobin

PLT platelet count

LDH lactate dehydrogenase

β2-MG β2-microglobulin

ROC receiver operating curve

HR Hazard ratio

CI confidence interval

MSCs mesenchymal stem cells

R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

R-FC rituximab, fludarabine and cyclophosphamide

Declarations

Ethics approval and consent to participate

This study was approved by the Biomedical Research Ethic Committee of Shandong province hospital (NO. SWYX2020-027) and informed consent was exempted based on medical records involved in this study obtained in previous clinical diagnosis and treatment.

Consent for publication

All of the authors review the manuscript and consent for publication.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Huimin Zhang, investigation, data curation, statistic analysis, writing-original draft preparation; Xiangxiang Zhou, Xiang Sun, Yang Han, Xinting Hu and Xiaoya Yun, investigation, data curation; Ya Zhang, funding acquisition, writing-review and editing; Xin Wang, project administration, funding acquisition, writing-review and editing.

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Tables

Table 1. Patient characteristics and association of CRP level, CRP kinetics and CAR with clinicopathological features.										
Characteristics	N(%)	Pretreatment CRP level, mg/L		Post-treatment CRP level, mg/L		CRP kinetics, mg/L			CAR	
		>5.84 N(%)	p- value	>5.84 N(%)	p- value	ever >5.84 N(%)	Continuously >5.84	p- value	>0.117 N(%)	p- value
Female	110(45.3%)	28(27.7%)	0.323	10(34.5%)	0.445	31(28.2%)	15(13.6%)	0.135	35(34.7%)	0.756
Male	133(54.7%)	41(33.9%)		9(25.7%)		42(31.6%)	29(21.8%)		44(36.7%)	
Age<60years	131(53.9%)	31(26.1%)	0.082	6(17.6%)	0.025	42(32.1%)	15(11.5%)	0.014	38(31.9%)	0.201
>=60years	112(46.1%)	38(36.9%)		13(43.3%)		31(27.7%)	29(25.9%)		41(40.2%)	
Clinical stage I-II (0-II for CLL/ SLL)	69(28.4%)	10(15.6%)	0.002	2(33.3%)	1.000	6(8.7%)	11(15.9%)	<0.001	13(20.3%)	0.002
III-IV	174(71.6%)	59(37.3%)		17(29.3%)		67(38.5%)	33(19.0%)		66(42.0%)	
Hb>=120g/L	143(58.8%)	22(16.4%)	<0.001	6(16.2%)	0.006	39(27.3%)	15(10.5%)	<0.001	25(18.7%)	<0.001
<120g/L	100(41.2%)	47(53.4%)		13(48.1%)		34(34.0%)	29(29.0%)		54(62.1%)	
PLT>=100*10 ⁹ /L	203(83.5%)	56(29.9%)	0.399	14(25.9%)	0.249	60(29.6%)	35(17.2%)	0.594	64(34.4%)	0.339
<100*10 ⁹ /L	40(16.5%)	13(37.1%)		5(50.0%)		13(32.5%)	9(22.5%)		15(42.9%)	
LDH<=250U/L	177(72.8%)	45(27.3%)	0.045	15(33.3%)	0.455	48(21.7%)	31(17.5%)	0.084	53(32.3%)	0.117
>250U/L	54(22.2%)	20(42.6%)		4(23.5%)		23(42.6%)	9(16.7%)		21(44.7%)	
β2-MG<=3mg/L	133(54.7%)	18(15.1%)	<0.001	10(28.6%)	0.759	37(27.8%)	12(9.0%)	<0.001	21(17.6%)	<0.001
>3mg/L	109(44.9%)	51(50.0%)		9(32.1%)		36(33.0%)	32(29.4%)		57(56.4%)	
Disease		<0.001		0.038		<0.001			<0.001	
FL	77(31.7%)	15(20.5%)		5(16.1%)		31(40.3%)	7(9.1%)		19(26.0%)	
MZL	46(18.9%)	15(33.3%)		3(33.3%)		16(34.8%)	8(17.4%)		15(33.3%)	
CLL/SLL	91(37.4%)	20(26.3%)		5(33.3%)		17(18.7%)	17(18.7%)		23(30.3%)	
LPL/WM	29(11.9%)	19(67.9%)		6(66.7%)		9(30.0%)	12(41.4%)		22(81.5%)	
Hypertension	56(23.0%)	17(33.3%)	0.629	4(33.3%)	1.000	18(32.1%)	11(19.6%)	0.841	19(37.3%)	0.798
Diabetes	21(8.6%)	6(33.3%)	0.829	4(57.1%)	0.184	9(42.9%)	4(19.0%)	0.358	10(55.6%)	0.067
Cardiovascular disease	17(7.0%)	7(43.8%)	0.392	1(50.0%)	0.516	3(17.6%)	7(41.2%)	0.063	7(43.8%)	0.488
HBV infection	15(6.2%)	5(35.7%)	0.929	2(50.0%)	0.578	8(53.3%)	2(13.3%)	0.153	5(35.7%)	0.998
IPI		0.001		0.986		<0.001			<0.001	
Low-risk	78(32.1%)	13(19.7%)		5(29.4%)		13(16.7%)	9(11.5%)		15(22.7%)	
Middle-risk	104(42.8%)	27(27.3%)		8(30.8%)		38(36.5%)	15(14.4%)		31(31.3%)	
High-risk	61(25.1%)	29(50.9%)		6(28.6%)		22(36.1%)	20(32.8%)		33(58.9%)	
Treatment plan		0.001		0.282		<0.001			0.007	
Non-chemotherapy	56(23.0%)	8(14.3%)		-		1(1.8%)	7(12.5%)		11(19.6%)	
R-CHOP or CHOP-like	102(42.0%)	31(32.0%)		10(23.3%)		51(50.0%)	12(11.8%)		35(36.1%)	
R-FC or FC-like	32(13.2%)	7(38.9%)		5(41.7%)		13(40.6%)	6(18.8%)		7(38.9%)	
Ibrutinib	9(3.7%)	1(11.1%)		-		1(11.1%)	1(11.1%)		3(33.3%)	
Other chemotherapy	24(9.9%)	13(59.1%)		4(50.0%)		7(29.2%)	9(37.5%)		14(66.7%)	
Untreated	20(8.2%)	9(45.0%)		-		0(0.0%)	9(45.0%)		9(45.0%)	

CRP C-reactive protein, *CAR* C-reactive protein to albumin ratio, *Hb* hemoglobin, *PLT* platelet count, *LDH* lactate dehydrogenase, *β2-MG* β2-microglobulin, *FL* follicular lymphoma, *CLL/ SLL* chronic lymphocytic leukemia/ small lymphocytic lymphoma, *MZL* marginal zone lymphoma, *LPL/ WM* lymphoplasmacytic lymphoma/ Waldenstroms macroglobulinemia, *HBV* hepatitis B virus, *IPI* international prognostic index, *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, *R-FC* rituximab, fludarabine and cyclophosphamide.

Table 2. Univariate and multivariate Cox regression analyses in pretreatment CRP level subgroup.

	OS		DFS		PFS	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Univariate analyses						
Elevated pretreatment CRP level	6.546 (2.543, 16.853)	<0.001	4.704 (2.305, 9.601)	<0.001	3.177 (1.694, 5.961)	<0.001
Age≥60years	1.502 (0.649, 3.480)	0.342	1.439 (0.724, 2.858)	0.299	1.147 (0.616, 2.314)	0.666
Clinical stage III and IV	10.230 (1.374, 76.183)	0.023	4.924 (1.499, 16.177)	0.009	2.472 (1.088, 5.621)	0.031
Hb < 120g/L	3.798 (1.545, 9.335)	0.004	3.010 (1.478, 6.128)	0.002	1.911 (1.024, 3.565)	0.042
PLT < 100*10 ⁹ /L	5.390 (2.327, 12.485)	<0.001	3.129 (1.516, 6.458)	0.002	2.409 (1.198, 4.841)	0.014
LDH >250U/L	2.495 (1.029, 6.049)	0.043	2.044 (0.962, 4.344)	0.063	1.857 (0.915, 3.768)	0.087
β2-MG >3mg/L	5.544 (1.876, 16.383)	0.002	4.021 (1.812, 8.922)	0.001	2.922 (1.479, 5.773)	0.002
Disease type	1.696 (1.098, 2.618)	0.017	1.318 (0.937, 1.856)	0.113	1.181 (0.865, 1.611)	0.295
IPI	2.211 (1.221, 4.004)	0.009	1.909 (1.192, 3.059)	0.007	1.598 (1.041, 2.453)	0.032
Treatment plan	1.820 (1.434, 2.312)	<0.001	1.478 (1.226, 1.781)	<0.001	1.367 (1.151, 1.624)	<0.001
Multivariate analyses						
Elevated pretreatment CRP level	5.110 (1.904, 13.717)	0.001	3.767 (1.777, 7.984)	0.001	2.606 (1.338, 5.076)	0.005
Clinical stage III and IV	3.469 (0.435, 27.698)	0.241	2.275 (0.651, 7.955)	0.198	1.425 (0.587, 3.458)	0.434
PLT < 100*10 ⁹ /L	3.994 (1.635, 9.754)	0.002	2.320 (1.071, 5.023)	0.033	1.849 (0.873, 3.917)	0.109
β2-MG >3mg/L	2.287 (0.725, 7.214)	0.158	2.204 (0.945, 5.143)	0.068	1.921 (0.924, 3.995)	0.080
<i>OS</i> overall survival, <i>DFS</i> disease-free survival, <i>PFS</i> progression-free survival, <i>HR</i> hazard ratios, <i>CI</i> confidence interval, <i>CRP</i> C-reactive protein, <i>Hb</i> hemoglobin, <i>PLT</i> platelet count, <i>LDH</i> lactate dehydrogenase, <i>β2-MG</i> β2-microglobulin, <i>IPI</i> international prognostic index.						

Table 3. Univariate and multivariate Cox regression analyses in post-treatment CRP level subgroup.				
	OS		DFS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Univariate analyses				
Elevated post-treatment CRP level	6.728 (2.015, 22.465)	0.002	2.601 (1.126, 6.008)	0.025
Age≥60years	1.880 (0.886, 3.987)	0.100	1.583 (0.862, 2.906)	0.138
Clinical stage III and IV	3.102 (1.072, 8.976)	0.037	3.157 (1.324, 7.530)	0.010
Hb < 120g/L	3.212 (1.490, 6.926)	0.003	2.578 (1.394, 4.768)	0.003
PLT < 100*10 ⁹ /L	4.729 (2.232, 10.021)	<0.001	2.871 (1.480, 5.568)	0.002
LDH >250U/L	2.971 (1.386, 6.368)	0.005	2.161 (1.119, 4.172)	0.022
β2-MG >3mg/L	3.478 (1.538, 7.866)	0.003	2.953 (1.553, 5.615)	0.001
Disease type	1.646 (1.107, 2.449)	0.014	1.265 (0.928, 1.723)	0.136
IPI	2.127 (1.285, 3.520)	0.003	1.877 (1.248, 2.822)	0.002
Treatment plan	1.685 (1.363, 2.083)	<0.001	1.441 (1.211, 1.715)	<0.001
Multivariate analyses				
Elevated post-treatment CRP level	5.826 (1.659, 20.458)	0.006	2.384 (1.027, 5.534)	0.043
PLT < 100*10 ⁹ /L	8.532 (2.065, 35.241)	0.003	2.727 (0.997, 7.455)	0.051
β2-MG >3mg/L	1.474 (0.382, 5.682)	0.573	1.648 (0.672, 4.043)	0.275
OS overall survival, DFS disease-free survival, HR hazard ratios, CI confidence interval, CRP C-reactive protein, Hb hemoglobin, PLT platelet count, LDH lactate dehydrogenase, β2-MG β2-microglobulin, IPI international prognostic index.				

Table 4. Univariate and multivariate Cox regression analyses in CRP kinetics subgroup.						
	OS		DFS		PFS	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Univariate analysis						
Ever elevated CRP level	1.763 (0.661, 4.707)	0.257	3.483 (1.615, 7.511)	0.001	2.638 (1.346, 5.173)	0.005
Continuously elevated CRP level	6.661 (2.775, 15.988)	<0.001	5.232 (2.356, 11.622)	<0.001	3.663 (1.790, 7.496)	<0.001
Age≥60years	2.316 (1.096, 4.893)	0.028	1.724 (0.946, 3.142)	0.075	1.259 (0.726, 2.184)	0.412
Clinical stage III and IV	3.463 (1.205, 9.950)	0.021	3.664 (1.534, 8.750)	0.003	2.180 (1.0850, 4.380)	0.029
Hb < 120g/L	3.144 (1.502, 6.580)	0.002	2.832 (1.534, 5.230)	0.001	1.895 (1.090, 3.297)	0.024
PLT < 100*10 ⁹ /L	4.985 (2.349, 10.581)	<0.001	3.015 (1.554, 5.851)	0.001	2.264 (1.194, 4.294)	0.012
LDH >250U/L	2.316 (1.107, 4.845)	0.026	2.220 (1.172, 4.206)	0.014	2.074 (1.128, 3.816)	0.019
β2-MG >3mg/L	4.224 (1.862, 9.580)	0.001	3.153 (1.670, 5.953)	<0.001	2.354 (1.324, 4.186)	0.004
Disease type	1.602 (1.093, 2.348)	0.016	1.290 (0.956, 1.741)	0.095	1.173 (0.885, 1.554)	0.268
IPI	2.248 (1.361, 3.713)	0.002	1.973 (1.316, 2.959)	0.001	1.618 (1.114, 2.351)	0.011
Treatment plan	1.722 (1.393, 2.130)	<0.001	1.453 (1.219, 1.731)	<0.001	1.347 (1.146, 1.584)	<0.001
Multivariate analyses						
Ever elevated CRP level	1.149 (0.422, 3.128)	0.785	2.425 (1.105, 5.322)	0.027	2.086 (1.040, 4.188)	0.039
Continuously elevated CRP level	6.461 (2.620, 15.930)	<0.001	4.748 (2.114, 10.660)	<0.001	3.296 (1.594, 6.818)	0.001
Clinical stage III and IV	2.267 (0.699, 7.350)	0.173	2.469 (0.964, 6.323)	0.060	1.449 (0.682, 3.081)	0.335
PLT < 100*10 ⁹ /L	4.025 (1.791, 9.049)	0.001	1.984 (0.977, 4.028)	0.058	1.633 (0.816, 3.271)	0.166
β2-MG >3mg/L	2.392 (0.960, 5.962)	0.061	2.100 (1.036, 4.255)	0.039	1.791 (0.963, 3.331)	0.065
OS overall survival, DFS disease-free survival, PFS progression-free survival, HR hazard ratios, CI confidence interval, CRP C-reactive protein, Hb hemoglobin, PLT platelet count, LDH lactate dehydrogenase, β2-MG β2-microglobulin, IPI international prognostic index.						

Table 5. Univariate and multivariate Cox regression analyses in CAR subgroup.						
	OS		DFS		PFS	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Univariate analysis						
Elevated CAR	5.426 (2.018, 13.962)	<0.001	3.856 (1.888, 7.874)	<0.001	2.591 (1.381, 4.858)	0.003
Age>=60years	1.513 (0.653, 3.503)	0.334	1.446 (0.728, 2.874)	0.292	1.259 (0.726, 2.184)	0.412
Clinical stage III and IV	10.102 (1.356, 75.237)	0.024	4.844 (1.474, 15.918)	0.009	2.180 (1.085, 4.380)	0.029
Hb < 120g/L	3.828 (1.558, 9.408)	0.003	3.029 (1.488, 6.167)	0.002	1.895 (1.090, 3.297)	0.024
PLT < 100*10 ⁹ /L	5.371 (2.319, 12.440)	<0.001	3.120 (1.512, 6.439)	0.002	2.264 (1.194, 4.294)	0.012
LDH >250U/L	2.484 (1.024, 6.023)	0.044	2.036 (0.958, 4.329)	0.065	2.074 (1.128, 3.816)	0.019
β2-MG >3mg/L	5.583 (1.889, 16.498)	0.002	4.043 (1.822, 8.970)	0.001	2.354 (1.324, 4.186)	0.004
Disease type	1.711 (1.106, 2.646)	0.016	1.326 (0.941, 1.868)	0.107	1.173 (0.885, 1.554)	0.268
IPI	2.228 (1.230, 4.038)	0.008	1.921 (1.199, 3.078)	0.007	1.618 (1.114, 2.351)	0.011
Treatment plan	1.823 (1.437, 2.314)	<0.001	1.481 (1.229, 1.784)	<0.001	1.347 (1.146, 1.584)	<0.001
Multivariate analyses						
Elevated CAR	3.768 (1.415, 10.034)	0.008	2.824 (1.336, 5.971)	0.007	1.991 (1.021, 3.882)	0.043
Clinical stage III and IV	3.766 (0.474, 29.941)	0.210	2.441 (0.702, 8.494)	0.161	1.512 (0.625, 3.658)	0.359
PLT < 100*10 ⁹ /L	3.475 (1.439, 8.394)	0.006	2.051 (0.954, 4.407)	0.066	1.691 (0.802, 3.564)	0.168
β2-MG >3mg/L	2.475 (1.439, 8.394)	0.125	2.275 (0.973, 5.320)	0.058	2.002 (0.959, 4.178)	0.064
OS overall survival, DFS disease-free survival, PFS progression-free survival, HR hazard ratios, CI confidence interval, CRP C-reactive protein, CAR C-reactive protein to albumin ratio, Hb hemoglobin, PLT platelet count, LDH lactate dehydrogenase, β2-MG β2-microglobulin, IPI international prognostic index.						

Table 6. Prognostic significance of CRP level, CRP kinetics and CAR in the different disease subgroups.											
	Pretreatment CRP level			Post-treatment CRP level		CRP kinetics			CAR		
	OS	DFS	PFS	OS	DFS	OS	DFS	PFS	OS	DFS	PFS
	<i>p</i> -value	<i>p</i> -value	<i>p</i> -value	<i>p</i> -value	<i>p</i> -value	<i>p</i> -value	<i>p</i> -value	<i>p</i> -value	<i>p</i> -value	<i>p</i> -value	<i>p</i> -value
FL	0.006	<0.001	0.004	0.317	0.600	0.034	0.040	0.023	0.019	0.002	0.022
MZL	0.488	0.515	0.579	0.075	0.937	0.355	0.168	0.181	0.488	0.515	0.579
CLL/SLL	<0.001	<0.001	<0.001	0.006	0.033	<0.001	<0.001	0.001	0.001	<0.001	<0.001
WM	0.500	0.399	0.399	0.295	0.295	0.399	0.392	0.392	0.998	0.998	0.998
OS overall survival, DFS disease-free survival, PFS progression-free survival, CRP C-reactive protein, CAR C-reactive protein to albumin ratio, FL follicular lymphoma, MZL marginal zone lymphoma, CLL/ SLL chronic lymphocytic leukemia/ small lymphocytic lymphoma, LPL/WM lymphoplasmacytic lymphoma/Waldenstroms macroglobulinemia.											

Figures

Figure 1

Figure 1

Receiver operating characteristic curve analysis determination of cutoff score. (A) For pretreatment serum C-reactive protein level. (B) For C-reactive protein to albumin ratio.

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Receiver operating characteristic curve analysis determination of cutoff score. (A) For pretreatment serum C-reactive protein level. (B) For C-reactive protein to albumin ratio.

Figure 2

Figure 2

Kaplan-Meier analysis. (A) Overall survival according to pretreatment C-reactive protein level. (B) Disease-free survival according to pretreatment C-reactive protein level. (C) Progression-free survival according to pretreatment C-reactive protein level. (D) Overall survival according to C-reactive protein level during treatment. (E) Disease-free survival according to C-reactive protein level during treatment. (F) Progression-free survival according to C-reactive protein level during treatment. (G) Overall survival according to post-treatment C-reactive protein level. (H) Disease-free survival according to post-treatment C-reactive protein level. (I) Progression-free survival according to post-treatment C-reactive protein level. (J) Overall survival according to C-reactive protein kinetics. (K) Disease-free survival according to C-reactive protein kinetics. (L) Progression-free survival according to C-reactive protein kinetics. (M) Overall survival according to C-reactive protein to albumin ratio. (N) Disease-free survival according to C-reactive protein to albumin ratio. (O) Progression-free survival according to C-reactive protein to albumin ratio.

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Kaplan-Meier analysis. (A) Overall survival according to pretreatment C-reactive protein level. (B) Disease-free survival according to pretreatment C-reactive protein level. (C) Progression-free survival according to pretreatment C-reactive protein level. (D) Overall survival according to C-reactive protein level during treatment. (E) Disease-free survival according to C-reactive protein level during treatment. (F) Progression-free survival according to C-reactive protein level during treatment. (G) Overall survival according to post-treatment C-reactive protein level. (H) Disease-free survival according to post-treatment C-reactive protein level. (I) Progression-free survival according to post-treatment C-reactive protein level. (J) Overall survival according to C-reactive protein kinetics. (K) Disease-free survival according to C-reactive protein kinetics. (L) Progression-free survival according to C-reactive protein kinetics. (M) Overall survival according to C-reactive protein to albumin ratio. (N) Disease-free survival according to C-reactive protein to albumin ratio. (O) Progression-free survival according to C-reactive protein to albumin ratio.