ACTA ABP BIOCHIMICA POLONICA

Vol. 70, No 4/2023
767–776
https://doi.org/10.18388/abp.2020_6171

Regular paper

Prognostic value of serum albumin level in patients with diffuse large B cell lymphoma

Liyan Chen[1], Lili Pan[2] and Tingbo Liu[3]

[1]Department of Breast Surgery, Zhuhai Maternity and Child Health Hospital, Zhuhai, China; Fujian Medical University Union Hospital, Fujian, China; [2]Pediatric Hematology Department, Fujian Medical University Union Hospital, Fujian, China; [3]Hematology Department, Fujian Medical University Union Hospital, Fujian, China

Objective: To investigate the prognostic value of serum albumin (SA) levels before chemotherapy in patients with diffuse large B-cell lymphoma (DLBCL) after receiving chemotherapy. Methods: This is a retrospective study, and 127 patients with DLBCL including 71 males (55.9%) and 56 females (44.1%) were included. Patients' gender, age, Ann Arbor staging, eastern cooperative oncology group (ECOG) score, treatment options, international prognostic index, response rate, overall survival (OS), and progression-free survival (PFS) were obtained for statistical analysis. Results: Univariate analysis showed that SA≤34 g/L, Ann Arbor III-IV, B symptoms, ECOG≥2, and bone marrow involvement suggest a poor prognosis in patients with DLBCL. Patients with persistent SA>34 g/L had significantly longer OS than patients with persistent SA≤34 g/L (*P*=0.020). Multivariate analysis showed that SA≤34 g/L (HR=0.48, 95% CI=0.26-0.90, *P*=0.022) and R-CHOP-like treatment regimen (HR=0.43, 95% CI=0.24-0.76, *P*=0.004) are independent factors that could affect the prognosis of patients with DLBCL. Conclusion: SA can be used as an indicator of prognosis in patients with DLBCL before the first chemotherapy. DLBCL patients with SA≤34 g/L are associated with short OS and poor prognosis, which may potentially provide guidance for the clinician to pay more attention to this population before the first chemotherapy.

Keywords: diffuse large B-cell lymphoma, serum albumin, chemotherapy, prognosis, IPI

Received: 22 January, 2022; revised: 08 April, 2022; accepted: 15 November, 2023; available on-line: 05 December, 2023

e-mail: tb_liu19@sina.com

Abbreviations: aaIPI, Age adjusted international Prognostic index; ADM, Adriamycin; CR, Complete remission; CTX, Cyclophosphamide; DLBCL, Diffuse large b cell lymphoma; ECOG, Eastern cooperative oncology group; EFS, Event free survival; EPB, Epirubicin; GCB, Germinal center b cell like; IPI, International prognostic index; LDH, Serum lactate dehydrogenase level; NCCN-IPI, An enhanced international Prognostic index; NHL, Non-hodgkin's lymphoma; Non, GCB, Non-germinal center b cell like; NRR, No reminssion; ORR, Overall responserate; OS, Overall survival; PD, Progressive disease; PFS, Progression free survival; PR, Partial remission; Pred, Prednisone; R, Rituximab; SA, Serum albumin; SD, Stable disease; VCR, Vincristine; VDS, Vindesine

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common pathological subtype of non-Hodgkin's lymphoma (NHL), and its incidence rate is 6.3% with an estimated more than 25 thousand new cases in the United States in 2016 (Li *et al.*, 2018). The heterogeneities of DLBCL in clinical manifestations and histomorphology lead to differences in treatment response and prognosis.

The international prognostic index (IPI) is currently the common risk stratification criteria for lymphoma, which includes age, Ann Arbor disease stage, serum lactate dehydrogenase (LDH) level, extranodal involvement and eastern cooperative oncology group (ECOG) score (Ziepert *et al.*, 2010). Afterwards, the age-adjusted international prognostic (aaIPI) can be used to assess the long-term prognosis of patients aged ≤60 years (Sehn *et al.*, 2007).

The National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI) followed the five clinical features of IPI, and the LDH and age factors were more subdivided, and their evaluation was better than IPI (1993). The R-CHOP regimen is effective in the treatment of patients with DLBCL, and its overall survival (OS) and event-free survival (EFS) are superior to the CHOP-like regimen (Coiffier *et al.*, 2002; Coiffier *et al.*, 2010; Pfreundschuh *et al.*, 2006)

BCL-2, MYC, and BCL-6 molecular biological indicators have made significant progress in assessing prognosis (Miyaoka *et al.*, 2018), though the examination is expensive. Serum albumin (SA) results show that patients with low SA have lower OS (Dalia *et al.*, 2014), and SA can predict the prognosis of patients with DLBCL (Eatrides *et al.*, 2015), but it is excluded from the IPI prognosis approach due to insufficient data (1993). In this study, we aimed to investigate the prognostic value of SA levels before chemotherapy in patients with DLBCL after receiving chemotherapy. After determining the optimal threshold of SA level in DLBCL patients, the patients were divided into high and low cut-off SA groups. The OS and progression-free survival (PFS) were analyzed to assess the effectiveness of NCCN-IPI in DLBCL patients, especially those under 60 years of age. This retrospective analysis of DLBCL patients with different SA levels might provide more clinically relevant guidance for clinicians to assess the prognostic outcomes of patients before the first chemotherapy.

OBJECTIVES AND METHODS

Object selection

This retrospective study was approved by the Ethics Committee of Fujian Medical University Union Hospital (the approval number: 2019KY029) in Fuzhou City, Fujian Province, China in 2019. A total of 127 patients with DLBCL admitted to the Union Hospital of Fujian Medi-

Table 1A. The International Prognostic Index (IPI)

Index	0 Point	1 Point
Age (Year)	≤60	>60
ECOG	0 or 1	≥2
LDH	≤Normal Value	>Normal Value
Extranodal involvement	0 or 1	>1
Ann Arbor staging	I or II	III or IV

Low-risk group, 0–1 point; low-intermediate risk group, 2 points; high-intermediate risk group, 3 points; high-risk group, 4–5 points. ECOG, Eastern Cooperative Oncology Group; LDH, Lactate Dehydrogenase.

Table 1B. The age-adjusted international Prognostic Index (aaIPI)

Index	0 Point	1 Point
ECOG	< 2	≥2
LDH	≤Normal Value	>Normal Value
Ann Arbor staging	I or II	III or IV

Low-risk group, 0 points; low-intermediate risk group, 1 point; high-intermediate-risk group, 2 points; high-risk group, 3 points. ECOG, Eastern Cooperative Oncology Group; LDH, Lactate Dehydrogenase.

Table 1C. The National Comprehensive Cancer Network International Prognostic Index (NCCN-IP)

Index	Grouping	Point
Age	<41 Year	0
	41–60 Year	1
	61–75 Year	2
	>75 Year	3
ECOG	0 or 1	0
	≥2	1
LDH	<1 of Normal Value	0
	1–3 of Normal Value	1
	>3 of Normal Value	2
Extranodal involvement	No	0
	Yes	1
Ann Arbor staging	I or II	0
	III or IV	1

Low-risk group, 0-1 point; low-intermediate risk group, 2–3 points; high-intermediate risk group, 4–5 points; high-risk group, ≥6 points. ECOG, Eastern Cooperative Oncology Group; LDH, Lactate Dehydrogenase.

cal University from January 1, 2010 to December 31, 2014 were consecutively enrolled. Inclusion criteria were as follows: 1) initial treatment and age ≥18 years; 2) initial diagnosis of DLBCL; 3) pathological tissues were diagnosed according to WHO lymphoma typing (Fmedsci & Frs, 2015); 4) no severe heart, lung, liver, and kidney dysfunction; 5) patients were treated with rituximab and CHOP (R-CHOP) like regimen or CHOP-like regimen. Exclusion criteria were as follows: 1) initial treatment and age <18 years; 2) no chemotherapy in our hospital or incomplete data; 3) patients with history of heart, lung, liver, or kidney dysfunction; 4) patients were diagnosed with primary central nervous system diffuse large B-cell lymphoma, primary diffuse large B-cell lymphoma, primary mediastinal diffuse large B-cell lymphoma, original bone marrow diffuse large B-cell lymphoma, or Epstein-Barr virus (EBV)-positive elderly diffuse large B-cell lymphoma. The clinical data, including gender, age, germinal center B cell-like (GCB) subtypes (by the Hans algorithm (Hans *et al.*, 2004)), Ann Arbor staging (Sehn *et al.*, 2005), B symptoms, ECOG, extranodal involvement, LDH, SA, treatment regimen, and NCCN-IPI, were analyzed in this study. All patient details were de-identified and the identity of patients could not be ascertained from this study. Meanwhile, the reporting of this study conforms to the STROBE statement (von Elm *et al.*, 2007).

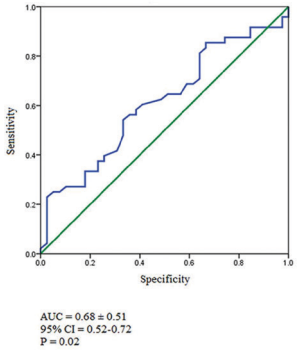

Figure 1. Receiver operating characteristic (ROC) curve of serum albumin.

Treatment

The patients' consent to treatment was obtained in this study. All patients received an R-CHOP-like regimen (rituximab (R) 375 mg/m^2 once, cyclophosphamide (CTX) 750 mg/m^2 once, vincristine (VCR) 1.4 mg/m^2 or vindesine (VDS) once, doxorubicin (Adriamycin, ADM) 50 mg/m^2 once and epirubicin (EPI) or prednisone (Pred) 40 mg/m^2 for 5 continuous days) repeated at 14-day intervals for 1-6 cycles, or CHOP-like regimen (CTX, VCR or VDS, ADM, EPI or Pred) for 1-6 cycles (Lamy *et al.*, 2018).

Table 2. Information of the Patients with DLBCL

Index		Patients No.	Ratio (%)	SA		*P*
				≤34 g/L (%)	>34 g/L (%)	
Sex						0.512
	Male	71	55.9	42 (59.2)	29 (40.8)	
	Female	56	44.1	29 (51.8)	27 (48.2)	
Age (Year)						0.257
	≤60	82	64.6	46 (56.1)	36 (43.9)	
	>60	45	35.4	25 (55.6)	20 (44.4)	
Ann Arbor staging						0.003
	I-II	41	32.3	18 (43.9)	23 (56.1)	
	III-IV	86	67.7	53 (61.6)	32 (37.2)	
B symptoms						0.007
	Yes	45	35.4	35 (77.8)	10 (22.2)	
	No	82	64.6	37 (45.1)	45 (54.9)	
ECOG score						0.004
	<2	105	82.7	52 (49.5)	54 (51.4)	
	≥2	22	17.3	19 (85.4)	3 (13.6)	
Extranodal involvement						0.301
	Yes	69	54.3	45 (65.2)	24 (34.8)	
	No	58	45.7	27 (46.6)	31 (53.4)	
Bone marrow involvement						0.038
	Yes	32	25.2	23 (71.9)	9 (28.1)	
	No	95	74.8	47 (49.5)	48 (50.5)	
LDH (U/L)						0.019
	>250	67	52.8	48 (71.6)	19 (28.4)	
	≤250	60	47.2	23 (38.3)	37 (61.7)	
Pathological type						0.389
	GCB	45	35.4	26 (57.8)	19 (42.2)	
	Non-GCB	81	63.8	44 (54.3)	37 (45.7)	
Treatment						0.002
	CHOP-like	54	42.5	35 (64.8)	19 (35.2)	
	R-CHOP like	69	54.3	35 (50.7)	34 (49.3)	
IPI/aaIPI						0.003
	Low-risk	34	26.8	14 (41.2)	20 (58.8)	
	Low-intermediate risk	34	26.8	17 (50)	17 (50)	
	High-intermediate risk	30	23.6	20 (66.7)	10 (33.3)	
	High-risk	29	22.8	21 (72.4)	8 (27.6)	
NCCN-IPI						0.000
	Low-risk	23	18.1	10 (43.5)	13 (56.5)	
	Low-intermediate risk	64	50.4	31 (48.4)	33 (51.6)	
	High-intermediate risk	32	25.2	24 (75)	8 (25)	
	High-risk	8	6.3	8 (100)	0 (0)	

DLBCL, diffuse large B-cell lymphoma; ECOG, eastern cooperative oncology group; LDH, lactate dehydrogenase; GCB, germinal center B cell-like; IPI, international prognostic index; aaIPI, age-adjusted international prognostic index; NCCN-IPI, the national comprehensive cancer network international prognostic index.

Prognostic assessment method

Patients were assessed by IPI, aaIPI and NCCN-IPI (Table 1A, B and C). NCCN-IPI assessment includes patients' age, ECOG score, serum lactate dehydrogenase level (LDH), extranodal involvement (involved distinct sites, such as bone marrow, CNS, gastrointestinal tract, liver or lung), and Ann Arbor stage. By using this assessment method, patients were divided into low-risk group (NCCN-IPI=0–1), low-intermediate risk group (NCCN-IPI=2–3), high-intermediate risk group (NCCN-IPI=4–5) and high-risk group (NCCN-IPI ≥6) (Table 1C).

SA grouping

The cut-off value of SA was obtained by analyzing the SA level- receiver operating characteristic (ROC) curve. Following this approach, the cut-off value of SA was 34 g/L. Therefore, in this study, the DLBCL patients were divided into low SA≤34 g/L and high SA>34 g/L groups (Fig. 1).

Efficacy criteria

The short-term efficacy evaluation was based on the Response Criteria for Malignant Lymphoma (Cheson *et al.*, 2007) by using CT or PET-CT imaging techniques after the first chemotherapy. Generally, the short-term efficacy was divided into four groups: complete remission (CR, defined as disappearance of all evidence of disease), partial remission (PR, defined as regression of measurable disease and no new sites), stable disease (SD, defined as failure to attain the CR/PR), Progressive disease (PD, defined as any new lesion or increase by 50% of previously involved sites from nadir). OS and PFS are followed up by inpatient medical records or by telephone. The deadline is the study endpoint December 31, 2017, to obtain 3-year and 3-year of OS and PFS data. OS: The primary endpoint was OS with 3 years (3-year OS), defined as the time from diagnosis to death from any cause, following the IPI criteria. PFS was defined as the time from DLBCL diagnosis until the disease recurrence, death-from-any-cause, or censoring (Cheson *et al.*, 2007).

Data processing method

All data were analyzed using SPSS 20.0. ROC curve analysis was performed to obtain the cut-off SA value. OS and PFS were assessed by using the Kaplan-Meier estimator. Univariate and multivariate analyses were performed using the Cox regression model, and short-term efficacy analysis was performed by using the chi-square test. $P<0.05$ was statistically significant.

RESULT

General clinical characteristics of patients with DLBCL

A total of 156 cases of DLBCL were diagnosed by pathology in our hospital from January 1, 2010 to December 31, 2014, while 26 cases were not treated with chemotherapy and 3 cases were combined with other tumors. Therefore, 127 patients were finally collected, including 71 males (55.9%) and 56 females (44.1%). Generally, the median age of patients was 56 (18–86) years, while 45 patients (35.4%) were aged >60 years. The ECOG<2 points were reported in 105 cases (82.7%), while ECOG≥2 points were reported in 22 cases (17.3%). There were 82 cases (64.6%) who had no B symptoms, and 45 cases (35.4%) were with B symptoms. The patients with normal LDH levels were found in 60 cases (47.2%), while 67 cases (52.8%) were shown with high LDH. The low SA (≤34 g/L) was observed in 70 cases (55.1%) and high SA (>34 g/L) was in 54 cases (42.5%). The other clinical characteristics of these patients are shown in Table 2.

Pathologically diagnosed with germinal center B cell-like (GCB) was found in 45 cases (35.4%) and non-GCB was in 81 cases (63.8%). Meanwhile, 41 cases (32.3%) were diagnosed with Ann Arbor staging I-II, while 86 cases (67.7%) were Ann Arbor staging III-IV. In addition, 58 cases (45.7%) were not found with extranodal involvement, while 69 cases (54.3%) were shown with extranodal involvement. According to the NCCN-IPI assessment, there were 23 cases (18.1%) in the low-risk group, 64 cases (50.4%) in the low-intermediate risk group, 32 cases (25.2%) in the high-intermediate risk group, and 8 cases (6.3%) in the high-risk group, with 3-year OS of 76.5%, 73.8%, 32.5%, 37.5 %, respectively. Meanwhile, 54 patients (42.5%) received CHOP-like regimens, 69 patients (54.3%) received R-CHOP-like regimens, and the other 4 patients received other chemotherapy (Table 2).

Survival and prognosis analysis

Up to the last follow-up date, the rate of loss to follow-up was 15.7%, while the mortality rate was 35.4%. The median follow-up time was 25 (0–66) months. The OS of 1 year, 3 years and 5 years were 70.3%, 61.0% and 50.5%, respectively. The PFS rates of 1 year, 3 years and 5 years were 56.7%, 41.2% and 32.0%, respectively (Fig. 2A and B).

Cox regression analysis of factors in association with OS of patients with DLBCL

By using univariate Cox analysis, it showed that Ann Arbor staging (P=0.008), B symptoms (P=0.008), ECOG score (P=0.004), bone marrow involvement (P=0.017), LDH levels (P=0.063), SA levels (P=0.002), and treatment regimens (P=0.003) were significantly associated with 3-year OS in patients with DLBCL (Table 3). However, when using the multivariate Cox regression model, it showed that Ann Arbor staging, B symptoms, ECOG score, bone marrow involvement, and LDH levels had no significant correlation with the prognostic values of DLBCL patients. On the contrary, SA levels (P=0.022) and treatment regimens (P=0.004) were an independent prognostic factor for patients with DLBCL (Table 4).

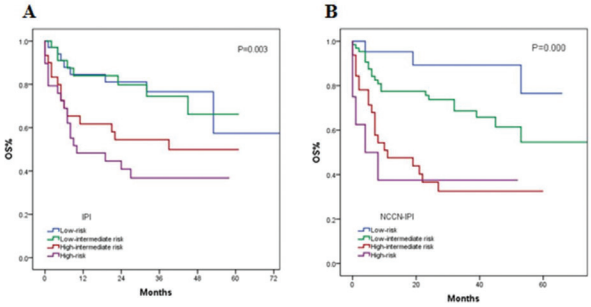

Figure 2. The 3-year overall survival of the low-risk group, the low-intermediate-risk group, the high-intermediate-risk group and the high-risk group of the IPI/aaIPI (A) and the NCCN-IPI (B).

Table 3. Results of univariate Cox regression model

Index	3-year OS		
	HR	95% CI	P
Sex (Male *vs* Female)	1.045	0.788-1.385	0.762
Age (≤60 years *vs* >60 years)	0.945	0.528-1.691	0.849
Ann Arbor staging (I-II *vs* III-IV)	2.689	1.302-5.553	0.008
B symptoms (Yes *vs* No)	0.469	0.267-0.823	0.008
ECOG Score (<2 *vs* ≥2)	2.55*	1.348-4.824	0.004
Extranodal involvement (Yes *vs* No)	0.972	0.732-1.290	0.842
Bone marrow involvement (Yes *vs* No)	0.701	0.524-0.938	0.017
LDH (Normal *vs* > Normal)	0.761	0.571-1.015	0.063
Low SA *vs* High SA	1.629	1.193-2.224	0.002
GCB *vs* non-GCB	1.151	0.647-2.045	0.633
CHOP- like *vs* R-CHOP-like	1.571	1.208-2.044	0.003
IPI	1.571	1.208-2.044	0.001
NCCN-IPI	2.131	1.522-2.984	0.000

*Example in this analysis: HR is obtained from the exponential regression coefficient, and gives the effect size of the predictors. In our example, the ECOG variable had an HR =2.55, meaning that the hazard (year OS) in patients with ECOG ≥2 is about 2.55 times higher than in the patients with ECOG <2. ECOG, Eastern Cooperative Oncology Group; LDH, Lactate Dehydrogenase; GCB, germinal center B cell-like; IPI, International Prognostic Index; SA, serum albumin; NCCN-IPI, the National Comprehensive Cancer Network International Prognostic Index; OS, overall survival; HR, hazard ratio; CI, confidence interval.

The association of SA concentration with short-term efficacy

In the SA of ≤34 g/L population (n=70), the overall response rate (ORR) was 58.6%, with 28 complete remission (CR) patients and 13 partial remission (PR) patients, while the non-remission rate (NRR) was 41.4%. In the SA>34 g/L population (n=54), the ORR was 90.7% (n=49), while the NRR was 9.3% (n=5). The short-term efficacy of patients with DLBCL between these two groups was statistically significant (P=0.033), indicating the low SH patient has a low CR rate after receiving chemotherapy (Table 5). In addition, the 3-year OS and PFS in the high SA group were 57.4% and 32.8%, which was significantly better than that in the low SA group (*P*=0.002 and *P*=0.022) (Fig. 3 and Table 6).

Prognostic value of SA level in association with other factors of patients with DLBCL

The 3-year OS in patients with a sustained SA of >34 g/L was significantly longer than those with a continuous SA of ≤34 g/L (*P*=0.02), whereas there was no significant difference in terms of PFS, suggesting that patients with SA>34 g/L before the initial chemotherapy have longer OS than that of patients with SA≤34 g/L, while the level of SA did not affect on PFS of patients with DLBCL (Fig. 4). The 3-year OS of high SA patients with NCCN-IPI stratified low-intermediate risk group was significantly higher than the 3-year OS of low SA (*P*=0.029), while there was no significant difference in 3-year OS between high and low SA levels in low-risk/high-intermediate group (*P*>0.05) (Fig. 5). The 3-year OS of patients with high SA with ECOG score of 0-1 was significantly higher than that of pa-

Table 4. Results of multivariate Cox regression model

Index	3-year OS		
	HR	95.0% CI	P
Ann Arbor staging (I-II *vs* III-IV)	1.67	0.74-3.79	0.219
B symptoms (Yes *vs* No)	0.73	0.37-1.42	0.350
ECOG score (2 *vs* ≥2)	1.58*	0.77-3.25	0.212
Bone marrow involvement (Yes *vs* No)	0.78	0.4-1.48	0.451
LDH (Normal *vs* > Normal)	1.14	0.60-2.18	0.685
Low SA *vs* High SA	0.48	0.26-0.90	0.022
CHOP-like *vs* R-CHOP -like	0.43	0.24-0.76	0.004

*Example in this analysis: HR is obtained from the exponential of regression coefficient, and gives the effect size of the predictors. In our example, the ECOG variable had an HR=1.58, meaning that the hazard (3-year OS) in patients with ECOG ≥2 is about 1.58 times higher than in the patients with ECOG <2. ECOG, Eastern Cooperative Oncology Group; LDH, Lactate Dehydrogenase; OS, overall survival; HR, hazard ratio; CI, confidence interval.

Table 5. Comparison of serum albumin levels and short-term efficacy

Serum albumin (g/L)	CR (%)	NRR (%)	ORR (%)
≤34 g/L (n=70)	28 (40)	29 (41.4)	41 (58.6)*
>34 g/L (n=54)	32 (59.3)	5 (9.3)	49 (90.7)*

*P=0.033; CR: complete remission; NRR, non-remission rate; ORR, overall response rate.

Table 6. Analysis of Serum albumin levels and 3-year OS/PFS by univariate Cox regression model

%	HR	95% CI	P
3-year OS ratio: low SA (43.6%) *vs* high SA (57.4%)	1.629	1.193-2.224	0.002
3-year PFS ratio: low SA (20%) *vs* high SA (32.8%)	0.607	0.392-0.938	0.022

OS, overall survival; PFS, progression-free survival; SA, serum albumin; HR, hazard ratio; CI, confidence interval.

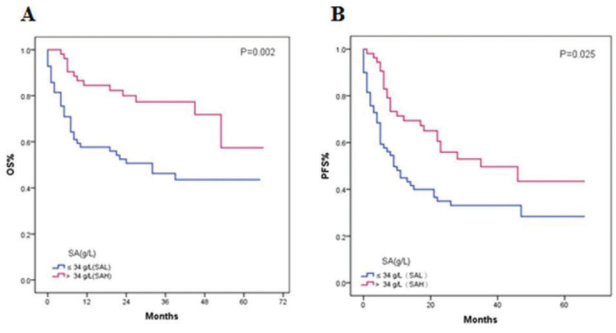

Figure 3. Analysis of 3-year OS (A) and PFS (B) in the low and high SA patients.

tients with low SA with ECOG score of 0-1 (HR=0.439, 95% CI=0.232–0.831, P=0.011) (Table 7). In the non-GCB group, the low SA patients survived for 47.9% in 3 years, and the 3-year survival rate of high SA patients was 78.3 %, which was statistically significant (*P*=0.004, Table 8). The 3-year OS of low SA patients in group III-IV was 33.2 %, which was significantly lower than 72 % in high SA patients (*P*=0.018) (Fig. 6 and Table 9).

Analysis of 3-year OS of treatment regime grouped SA group by univariate Cox regression model

The Kaplan–Meier test showed that in the CHOP-like treatment group, the 3-year OS ratio of patients in the high SA group was higher than that in the low SA group (62% *vs* 38%) (*P*=0.087, Fig. 7A). In the R-CHOP like treatment group, the 3-year OS ratio of patients in the high SA group was higher than that in the low SA group (87% *vs* 61% (*P*=0.101, Fig. 7B). Univariate Cox regression analysis showed that there were significantly different in the 3-year OS between low and high SA among the CHOP like (*P*=0.035) and R-CHOP like groups (*P*=0.04) (Table 10).

DISCUSSION

In this study, we retrospectively analyzed the 127 patients with DLBCL and found that the cut-off SA value of 34 g/L could be used as a prognostic predictor for DLBCL patients in the clinic. Similarly, Wei and others (Wei *et al.*, 2021) reported that the best cutoff value of SA for survival analysis of patients with DLBCL was 39.2 g/L, and also concluded that hypoalbuminemia can act as a simple and effective adverse prognostic factor in

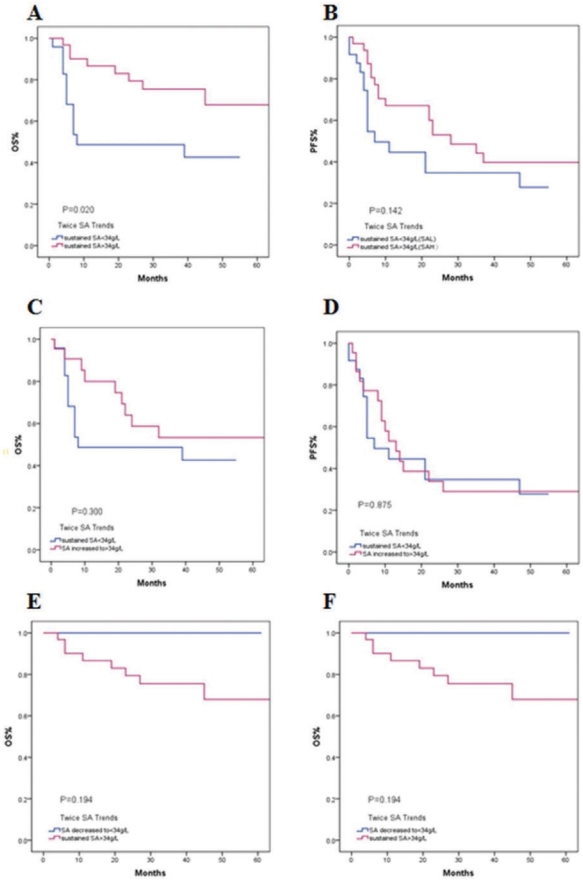

Figure 4. Analysis of 3-year OS and 3-year PFS in low and high SA patients before and after the chemotherapy.
3-years OS (**A**) and 3-year PFS (**B**) in patients with two SAs>34 g/L and two SAs ≤ 34 g/L before the first two chemotherapy. 3 years OS (**C**) and 3-year PFS (**D**) in patients with two SAs≤34 g/L and initial SA 34 g/L, second SA>34 g/L before the first two chemotherapy. 3-year OS (**E**) and 3-year PFS (**F**) in patients with two SAs>34 g/L and initial SA>34 g/L, second SA≤34 g/L before the first two chemotherapy.

these patients. In addition, Eatrides and others (Eatrides *et al.*, 2015) showed that SA <37g/L in patients treated with R-CHOP like had a lower OS and PFS. However, in this study, we divided the DLBCL patients into >34 g/L and SA≤34 g/L groups, and compared the prognostic outcomes of these patients in different subgroups, including NCCN-IPI risk grouping, before and after

Table 7. Analysis of 3-year OS of ECOG score stratified serum albumin levels by univariate Cox regression model

ECOG score	SA group	Patients No. (%)	3-year OS		
			HR	95% CI	*P*
0-1 point	Low SA	51/102 (50)	0.439	0.232-0.831	0.011
	High SA	51/102 (50)			
2-4 points	Low SA	19/22 (86.4)	0.034	0.000-12.697	0.263
	High SA	3/22 (13.6)			

OS, overall survival; ECOG, Eastern Cooperative Oncology Group; SA, serum albumin; HR, hazard ratio; CI, confidence interval.

Table 8. Analysis of 3-year OS of pathological grade-stratified serum albumin group by univariate Cox regression model

Pathological diagnosis	SA group	3-year OS ratio (%)	3-year OS		
			HR	95% CI	*P*
GCB	Low SA	35.6	0.441	0.176-1.109	0.082
	High SA	74.9			
non-GCB	Low SA	47.9	0.315	0.143-0.693	0.004
	High SA	78.3			

OS, overall survival; GCB, germinal center B cell like; SA, serum albumin; HR, hazard ratio; CI, confidence interval.

Table 9. Analysis of 3-year OS of Ann Arbor staging-stratified serum albumin group by univariate Cox regression model

Ann Arbor staging	SA group	3-year OS ratio (%)	3-year OS		
			HR	95% CI	*P*
I-II	Low SA	72.8	0.658	0.196-2.206	0.498
	High SA	85.2			
III-IV	Low SA	33.2	0.454	0.236-0.875	0.018
	High SA	72			

OS, overall survival; SA, serum albumin; HR, hazard ratio; CI, confidence interval.

Table 10. Analysis of 3-year OS of treatment regime grouped serum albumin group by univariate Cox regression model

Treatment regime	SA group	3-year OS ratio (%)	3-year OS ratio		
			HR	95% CI	*P*
CHOP -like	Low SA	29.7	0.427	0.194-0.940	0.035
	High SA	63			
R-CHOP -like	Low SA	83.7	0.375	0.147-0.957	0.04
	High SA	60.6			

OS, overall survival; SA, serum albumin; HR, hazard ratio; CI, confidence interval.

chemotherapy, Ann Arbor staging, ECOG score, treatment options, respectively. By evaluating SA concentration predictive efficacy in these subgroups, it showed that SA may serve as the prognostic predictor in DLBCL patients with specific clinical characteristics.

IPI/aaIPI/NCCN – IPI assessment

IPI/aaIPI has been used as a prognostic indicator for DLBCL. In this study, univariate Cox regression model analysis IPI/aaIPI showed significant differences in OS of different risk stratification, indicating that IPI/aaIPI may effectively assess the prognosis of patients. Ziepert et al reported that rituximab increases OS in patients with DLBCL, and IPI can effectively assess patient prognosis in both CHOP-like and R-CHOP like regimens (Ziepert *et al.*, 2010). In this study, patients with DLBCL who received an R-CHOP regimen had longer OS than patients with DLBCL who received a CHOP-like regimen, which is consistent with other studies. IPI was able to assess the prognosis of patients with DLBCL treated with the R-CHOP-like regimen but was unable to completely distinguish the four risk stratifications and the effectiveness of IPI in assessing the prognosis of such patients was limited (Salles *et al.*, 2011). Multivariate analysis showed that age ≥60 years, elevated LDH levels, low SA and Ann Arbor staging were independent prognostic risk factors (Ngo *et al.*, 2008). Zhou and others (Zhou *et al.*, 2014) studied patient data from seven clinical centers and proposed an NCCN-IPI prognostic assessment model to assess the prognosis of patients with DLBCL treated with the R-CHOP-like regimen.

NCCN-IPI is effective in assessing OS in patients treated with CHOP-like and R-CHOP-like regimens, and

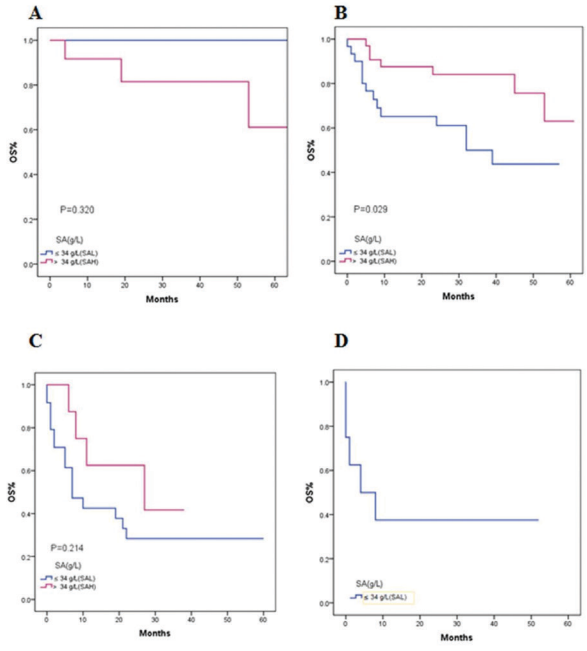

Figure 5. 3-year overall survival of patients with SA≤34 g/L and with SA>34 g/L in NCCN-IPI risk stratification grouping.
(**A**) low-risk group; (**B**) low-intermediate risk group, (**C**) high-intermediate risk group; (**D**) high-risk group.

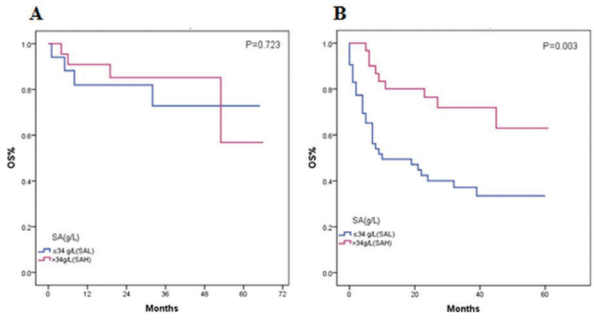

Figure 6. Comparison of OS between SA>34 g/L and SA≤34 g/L patients.
(**A**) Ann Arbor staging I-II group; (**B**) Ann Arbor staging III-IV group.

is more effective than IPI/aaIPI, in patients treated by R-CHOP-like (Salles *et al.*, 2011; Ngo *et al.*, 2008; Zhou *et al.*, 2014). However, Melchardt and others (Melchardt *et al.*, 2015) believe that the effectiveness of NCCN-IPI in evaluating the prognosis of patients treated with an R-CHOP-like regimen is still insufficient. Our study was stratified by age and the results showed that NCCN-IPI was able to effectively assess risk stratification in patients >60 years old and ≤60 years old.

SA levels

As an independent prognostic risk factor, SA has been confirmed in other hematological malignancies, including Hodgkin's lymphoma, myelodysplastic syndrome, acute myeloid leukemia, primary cutaneous T-cell lymphoma, spleen marginal lymphoma, and Primary mediastinal DLBCL (Huang *et al.*, 2015; Chihara *et al.*, 2009; Watanabe *et al.*, 2010; Zhu *et al.*, 2011; Arcaini *et al.*, 2006; Kharfan-Dabaja *et al.*, 2011; Komrokji *et al.*, 2012). The SA detection cycle is short, and the cost is

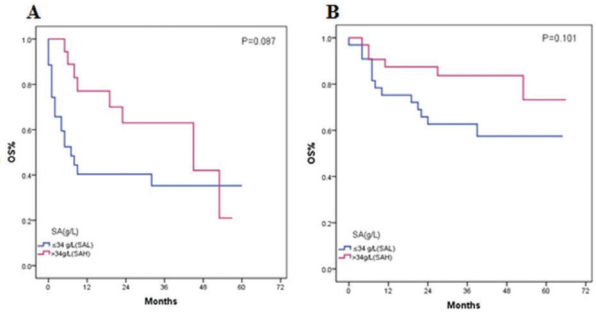

Figure 7. Comparison of 3-year OS between SA>34 g/L and SA≤34 g/L patients.
(**A**) CHOP-like treatment group; (**B**) R-CHOP like treatment group.

low, which can cover the population in remote areas. At the same time, SA is also a stable biomarker. A previous study showed that the 3-year OS in patients with SA levels >34g/L before chemotherapy was significantly higher than low SA (Eatrides *et al.*, 2015), which was consistent with our current finding. SA levels before chemotherapy are an independent prognostic risk factor for DLBCL. After chemotherapy, patients with low SA had shorter OS. CHOP like and R-CHOP-like treated patients with low SA had shorter OS than patients with high SA.

Evaluation of SA concentration predictive efficacy

The chi-square test showed a difference in CR between the two groups of SA that the short-term efficacy of low SA was poor. The long-term efficacy evaluation of COX regression showed that patients with low SA had significantly shorter PFS/OS than high SA patients. Patients with SA sustained >34 g/L before the second chemotherapy had longer OS than patients with SA sustained ≤ 34 g/L. Before the initial chemotherapy, patients with SA >34 g/L had higher OS than patients with SA≤34 g/L and were not affected by SA changes before the second chemotherapy.

Limitations

There were some limitations in this study. Firstly, this is a retrospective clinical analysis and should eliminate mutual interference between effective factors by using multivariate analysis. Secondly, as a limited case number was involved in this study, a comparsion of chemotherapy courses was not performed among these patients. Thirdly, the patients with the CHOP regimen had a very high population in this study, while the current chemotherapy is commonly applied with the R-CHOP regimen. Therefore, further investigations among DLBCL patients who received R-CHOP should be required to provide the guidance for the current clinical settings. Last but not least, as this is a single-center retrospective study, further studies with multi-center with larger sample size can help reinforce our current findings.

CONCLUSION

Before the initial chemotherapy, high SA patients had a longer 3-year OS than the low SA group. Pre-chemotherapy SA is an independent prognostic risk

factor for patients with DLBCL. This study indicates that the CR and NRR of SA≤34 g/L patients will be significantly lower than that of SA>34 g/L patients. In addition, the R-CHOP-like regimen may help improve low and high SA patients 3-year OS.

Declarations

Funding. None.

Conflict of Interest. The authors declare that they have no competing interests.

Authorship. LC and TL were involved in the guarantor of integrity of the entire study, study design and manuscript review; LC was dedicated to design concepts, definition of intellectual content, literature research, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation and manuscript editing, LP performed study design, manuscript editing and manuscript review. All authors have read and approved this article.

REFERENCES

Arcaini L, Lazzarino M, Colombo N, Burcheri S, Boveri E, Paulli M, Morra E, Gambacorta M, Cortelazzo S, Tucci A, Ungari M, Ambrosetti A, Menestrina F, Orsucci L, Novero D, Pulsoni A, Frezzato M, Gaidano G, Vallisa D, Minardi V, Tripodo C, Callea V, Baldini L, Merli F, Federico M, Franco V, Iannitto E, Integruppo Italiano Linfomi (2006) Splenic marginal zone lymphoma: a prognostic model for clinical use. *Blood* **107**: 4643–4649. https://doi.org/10.1182/blood-2005-11-4659

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V, International Harmonization Project on Lymphoma (2007) Revised response criteria for malignant lymphoma. *J Clin Oncol* **25**: 579–586. https://doi.org/10.1200/JCO.2006.09.2403

Chihara D, Oki Y, Ine S, Yamamoto K, Kato H, Taji H, Kagami Y, Yatabe Y, Nakamura S, Morishima Y (2009) Analysis of prognostic factors in peripheral T-cell lymphoma: prognostic value of serum albumin and mediastinal lymphadenopathy. *Leuk Lymphoma* **50**: 1999–2004. https://doi.org/10.3109/10428190903318311

Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P, Gisselbrecht C (2002) CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *New Engl J Med* **346**: 235–242. https://doi.org/10.1056/NEJMoa011795

Coiffier B, Thieblemont C, Van Den Neste E, Lepeu G, Plantier I, Castaigne S, Lefort S, Marit G, Macro M, Sebban C, Belhadj K, Bordessoule D, Fermé C, Tilly H (2010) Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood* **116**: 2040–2045. https://doi.org/10.1182/blood-2010-03-276246

Dalia S, Chavez J, Little B, Bello C, Fisher K, Lee JH, Chervenick P, Sokol L, Sotomayor E, Shah B (2014) Serum albumin retains independent prognostic significance in diffuse large B-cell lymphoma in the post-rituximab era. *Ann Hematol* **93**: 1305–1312. https://doi.org/10.1007/s00277-014-2031-2

Eatrides J, Thompson Z, Lee JH, Bello C, Dalia S (2015) Serum albumin as a stable predictor of prognosis during initial treatment in patients with diffuse large B cell lymphoma. *Ann Hematol* **94**: 357–358. https://doi.org/10.1007/s00277-014-2150-9

Fmedsci Avhmdfffd, Frs Drhmf (2015) 51. *WHO Classification: Tumours of the Haematopoietic and Lymphoid Tissues* (2008). John Wiley & Sons, Ltd

Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, Müller-Hermelink HK, Campo E, Braziel RM, Jaffe ES, Pan Z, Farinha P, Smith LM, Falini B, Banham AH, Rosenwald A, Staudt LM, Connors JM, Armitage JO, Chan WC (2004) Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood* **103**: 275–282. https://doi.org/10.1182/blood-2003-05-1545

Huang CE, Chen YY, Lu CH, Chen PT, Lee KD, Chen CC (2015) Validation of an enhanced International Prognostic Index (NCCN-IPI) in an Asian cohort of patients with diffuse large B cell lymphoma. *Ann Hematol* **94**: 1063–1065. https://doi.org/10.1007/s00277-014-2293-8

International Non-Hodgkin's Lymphoma Prognostic Factors Project (1993) A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* **329**: 987–994. https://doi.org/10.1056/NEJM199309303291402

Kharfan-Dabaja MA, Chavez JC, Yu D, Zhu W, Fernandez-Vertiz EI, Perkins J, Shapiro J, Bookout R, Perez L, Fernandez HF, Komrokji RS, Lancet J, Brand L, Field T, Ayala E, Janssen W, List AF, Anasetti C (2011) Severe hypoalbuminemia at day 90 predicts worse nonrelapse mortality and overall survival after allogeneic hematopoietic stem cell transplantation for acute myelogenous leukemia and myelodysplastic syndrome. *Biol Blood Marrow Tr* **17**: 384–393. https://doi.org/10.1016/j.bbmt.2010.07.011

Komrokji RS, Corrales-Yepez M, Kharfan-Dabaja MA, Al Ali NH, Padron E, Rollison DE, Pinilla-Ibarz J, Zhang L, Epling-Burnette PK, Lancet JE, List AF (2012) Hypoalbuminemia is an independent prognostic factor for overall survival in myelodysplastic syndromes. *Am J Hematol* **87**: 1006–1009. https://doi.org/10.1002/ajh.23303

Lamy T, Damaj G, Soubeyran P, Gyan E, Cartron G, Bouabdallah K, Gressin R, Cornillon J, Banos A, Le Du K, Benchalal M, Moles MP, Le Gouill S, Fleury J, Godmer P, Maisonneuve H, Deconinck E, Houot R, Laribi K, Marolleau JP, Tournilhac O, Branger B, Devillers A, Vuillez JP, Fest T, Colombat P, Costes V, Szablewski V, Béné MC, Delwail V, LYSA Group (2018) R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma. *Blood* **131**: 174–181. https://doi.org/10.1182/blood-2017-07-793984

Li S, Young KH, Medeiros LJ (2018) Diffuse large B-cell lymphoma. *Pathology* **50**: 74–87. https://doi.org/10.1016/j.pathol.2017.09.006

Melchardt T, Troppan K, Weiss L, Hufnagl C, Neureiter D, Tränkenschuh W, Hopfinger G, Magnes T, Deutsch A, Neumeister P, Hackl H, Greil R, Pichler M, Egle A (2015) A modified scoring of the NCCN-IPI is more accurate in the elderly and is improved by albumin and beta2-microglobulin. *British J Haematol* **168**: 239–245. https://doi.org/10.1111/bjh.13116

Miyaoka M, Kikuti YY, Carreras J, Ikoma H, Hiraiwa S, Ichiki A, Kojima M, Ando K, Yokose T, Sakai R, Hoshikawa M, Tomita N, Miura I, Takata K, Yoshino T, Takizawa J, Bea S, Campo E, Nakamura N (2018) Clinicopathological and genomic analysis of double-hit follicular lymphoma: comparison with high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements. *Mod Pathol* **31**: 313–326. https://doi.org/10.1038/modpathol.2017.134

Ngo L, Hee SW, Lim LC, Tao M, Quek R, Yap SP, Loong EL, Sng I, Hwan-Cheong TL, Ang MK, Ngeow J, Tham CK, Tan MH, Lim ST (2008) Prognostic factors in patients with diffuse large B cell lymphoma: Before and after the introduction of rituximab. *Leuk Lymphoma* **49**: 462–469. https://doi.org/10.1080/10428190701809156

Pfreundschuh M, Trümper L, Osterborg A, Pettengell R, Trneny M, Imrie K, Ma D, Gill D, Walewski J, Zinzani PL, Stahel R, Kvaloy S, Shpilberg O, Jaeger U, Hansen M, Lehtinen T, López-Guillermo A, Corrado C, Scheliga A, Milpied N, Mendila M, Rashford M, Kuhnt E, Loeffler M, MabThera International Trial Group (2006) CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol* **7**: 379–391. https://doi.org/10.1016/S1470-2045(06)70664-7

Salles G, De Jong D, Xie W, Rosenwald A, Chhanabhai M, Gaulard P, Klapper W, Calaminici M, Sander B, Thorns C, Campo E, Molina T, Lee A, Pfreundschuh M, Horning S, Lister A, Sehn LH, Raemaekers J, Hagenbeek A, Gascoyne RD, Weller E (2011) Prognostic significance of immunohistochemical biomarkers in diffuse large B-cell lymphoma: a study from the Lunenburg Lymphoma Biomarker Consortium. *Blood* **117**: 7070–7078. https://doi.org/10.1182/blood-2011-04-345256

Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, Klasa R, Savage KJ, Shenkier T, Sutherland J, Gascoyne RD, Connors JM (2007) The revised international prognostic index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood* **109**: 1857–1861. https://doi.org/10.1182/blood-2006-08-038257

Sehn LH, Donaldson J, Chhanabhai M, Fitzgerald C, Gill K, Klasa R, MacPherson N, O'Reilly S, Spinelli JJ, Sutherland J, Wilson KS, Gascoyne RD, Connors JM (2005) Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. *J Clin Oncol* **23**: 5027–5033. https://doi.org/10.1200/JCO.2005.09.137

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* **147**: 573–577. https://doi.org/10.7326/0003-4819-147-8-200710160-00010

Watanabe T, Kinoshita T, Itoh K, Yoshimura K, Ogura M, Kagami Y, Yamaguchi M, Kurosawa M, Tsukasaki K, Kasai M, Tobinai K,

Kaba H, Mukai K, Nakamura S, Ohshima K, Hotta T, Shimoyama M (2010) Pretreatment total serum protein is a significant prognostic factor for the outcome of patients with peripheral T/natural killer-cell lymphomas. *Leuk Lymphoma* **51**: 813–821. https://doi.org/10.3109/10428191003721359

Wei XL, Zheng JX, Zhang ZW, Liu QZ, Zhan ML, Huang WM, Chen JJ, Wei Q, Wei YQ, Feng R. (2021) Consecutive hypoalbuminemia predicts inferior outcome in patients with diffuse large B-cell lymphoma. *Front Oncol* **10**: 3167. https://doi.org/10.3389/fonc.2020.610681

Zhou Z, Sehn LH, Rademaker AW, Gordon LI, Lacasce AS, Crosby-Thompson A, Vanderplas A, Zelenetz AD, Abel GA, Rodriguez MA, Nademanee A, Kaminski MS, Czuczman MS, Millenson M, Niland J, Gascoyne RD, Connors JM, Friedberg JW, Winter JN (2014) An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood* **123**: 837–842. https://doi.org/10.1182/blood-2013-09-524108

Zhu YJ, Huang JJ, Xia Y, Zhao W, Jiang WQ, Lin TY, Huang HQ, Li ZM (2011) Primary mediastinal large B-cell lymphoma (PMLBCL) in Chinese patients: clinical characteristics and prognostic factors. *Int J Hematol* **94**: 178–184. https://doi.org/10.1007/s12185-011-0898-4

Ziepert M, Hasenclever D, Kuhnt E, Glass B, Schmitz N, Pfreundschuh M, Loeffler M (2010) Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. *J Clin Oncol* **28**: 2373–2380. https://doi.org/10.1200/JCO.2009.26.2493