Int J Clin Exp Med 2018;11(3):2223-2231
www.ijcem.com /ISSN:1940-5901/IJCEM0061535

Original Article

Serum uric acid level is a prognostic indicator and improves the predictive ability of the IPI score in diffuse large B-cell lymphoma

Yiwei Li, Pengfei Shi, Yaping Xie, Shenxian Qian

Department of Hematology, Hangzhou First People's Hospital, Hangzhou 310006, China

Received July 15, 2017; Accepted November 1, 2017; Epub March 15, 2018; Published March 30, 2018

Abstract: Background: High levels of serum uric acid (SUA) have been shown to associate with negative clinical outcome in various malignancies. This study investigates whether SUA, at the time of diagnosis, has a prognostic significance in patients with diffuse large B-cell lymphoma (DLBCL). Methods: We retrospectively evaluated 167 Chinese patients with newly diagnosed DLBCL under rituximab (R)-CHOP or CHOP-like immune-chemotherapy from January 2008 to July 2016. The optimal cutoff value of SUA was determined by applying receiver operating curve (ROC) analysis. The prognostic influence of SUA and other factors were studied by Kaplan-Meier curve as well as univariate and multivariate Cox proportional analysis. The influence of SUA on the predictive accuracy of IPI score was subsequently calculated using the Harrell's concordance index (c-index). Results: ROC analysis showed the cutoff value of SUA with best sensitivity and specificity was 6.4 mg dl^{-1}. Increased SUA level shown by Kaplan-Meier curve had a shorter progression free and overall survival (PFS and OS, $p<0.001$, respectively). In multivariate analysis, an independent significant association between elevated SUA levels and poor clinical outcome for PFS (HR=3.851; 95% CI 1.816-8.167, $p<0.001$) and OS (HR=4.007; 95% CI 1.884-8.523, $p<0.001$) was identified. The estimated concordance index, using IPI stratification measures (0.777), improved to 0.837 when SUA was integrated in. Conclusions: In the present study, we concluded that increased SUA level at diagnosis is an independent predictor for worse clinical outcome in DLBCL patients. Integrating SUA to the IPI score might improve the survival prediction and risk stratification.

Keywords: Diffuse large b-cell lymphoma, serum uric acid, prognosis, new risk model

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype. It is a heterogeneous neoplasm with clinical, biologic and pathologic diversity [1]. A reliable prediction tool for patient's stratification paves the way for successful individualized treatments. The International Prognostic Index (IPI) has been the most commonly used risk stratification model for patients with aggressive lymphomas for extended period of time [2]. However, the discriminative capacity of the IPI weakened with the advancement in therapeutic regimen, especially among higher risk patients in the rituximab (R) era [3]. This promoted the introduction of revised IPI (R-IPI). In contrast to the conventional IPI targeted at DLBCL patients treated with standard immune-chemotherapy, Zhou *et al.* [4] further improved IPI by refining categorization of age, normalizing serum lactate dehydrogenase (LDH) and revising qualification of extranodal diseases by drawing data from National Comprehensive Cancer Network (NCCN) database. NCCN-IPI classifies patients into four risk groups, thereby enhancing discrimination for patients in the low- and high-risk subgroups. Nevertheless, a proportion of patients died of relapse or refractory disease remained poorly characterized [5]. Assessment of molecular marker is technically complicated, expensive and not broadly available. Therefore, the search for widely obtainable parameters remains valuable in discriminating among risk groups.

Serum uric acid (SUA) is produced by xanthine oxidase when purine nucleotides degrades and indicates a turnover of nucleic acid in cell [6]. Historically, elevated SUA is associated with

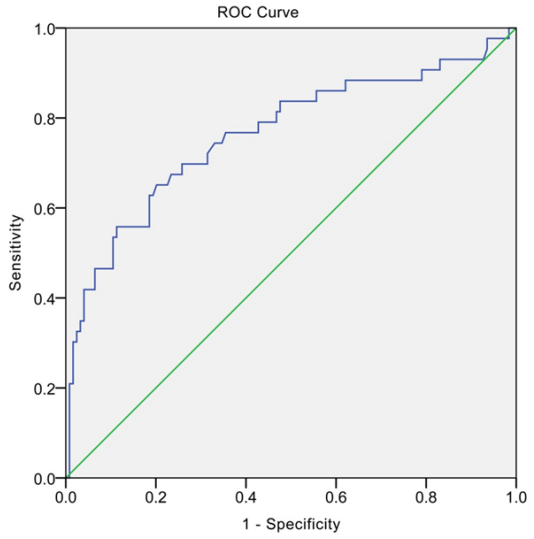

Figure 1. The cutoff value for SUA via the ROC analysis in this study was 6.4 mg dl^{-1} (sensitivity 65.1% and specificity 20.2%; AUC values 0.765, 95% CI 0.672-0.857, p<0.001). SUA, serum uric acid; ROC, receiver operating characteristic curve; AUC, area under the curve.

hypertension, cardiovascular, metabolic syndrome or kidney disease [7]. While some studies have demonstrated that SUA levels can be positively correlated with cancer development and progression [8-14], contradictory findings have been reported regarding the role of elevated SUA level in cancer prevalence as well as mortality and prognoses [15, 16]. The underlying cause of the paradox remains largely unknown. In the current retrospective analysis, we aim to show the prognostic value of pretreatment SUA in Chinese DLBCL patients, and compare the predictive ability of the existing IPI score to its SUA integrated variation.

Materials and methods

Subjects

167 consecutive patients with newly diagnosed DLBCL at Hangzhou Hospital Affiliated to Nanjing Medical University from January 2008 to July 2016 were enrolled in this retrospective study. The diagnosis was established based on tissue biopsy and the World Health Organization tumor classification criteria [17]. All patients received standard R-CHOP or CHOP-like immune-chemotherapy. Given their short follow-up time, 24 patients collected were excluded to reduce the bias in progression free survival (PFS) and overall survival (OS). 3 patients with a history of gout or renal failure were removed as well. In addition, patients who had missing laboratory parameters at the diagnosis, or who were positive for human immunodeficiency virus, primary central nervous system lymphoma and transformed Non-Hodgkin lymphoma (NHL) were excluded from subsequent analyses. Patients who failed to follow-up were excluded.

A number of clinical and pathologic factors were extracted from medical charts including: age, gender, presence of B symptoms and bone marrow involvement, the number of extranodal locations, clinical stage; laboratory data included SUA, LDH, serum creatinine and β2microglobulin. These clinical data were used to review and reassess the IPI and NCCN-IPI. All laboratory parameters were routinely assessed before the start of chemotherapy. This study has been approved by the Institutional Review Board of the Nanjing Medical University.

Statistical analysis

The optimal cutoff value of uric acid was 6.4 mg dl^{-1}, determined by applying receiver operating curve (ROC) analysis. Patients were subdivided into low- and high-SUA groups in accordance with the value. The association between uric acid levels and clinical characteristics was evaluated by non-parametric tests (Pearson chi-square test, Fisher's exact test). PFS was defined as time from first diagnosis to the first documentation of progressive disease or death from any cause. OS was calculated as time from first diagnosis to death from any cause. The Kaplan-Meier curve was used to determine correlation between SUA levels with OS and PFS and the comparison were assessed by the log-rank test. Furthermore, univariate Cox proportional analysis was calculated to identify independent prognostic factors for PFS and OS, followed by multivariate Cox analysis. The final multivariate model was chosen on the basis of the stepwise procedure as well as consideration of the clinical importance of variables in the model. Hazard ratios (HRs) estimated from the Cox analysis were reported as relative risks with corresponding 95% confidence intervals (CIs). Influence of SUA on the predictive accuracy of the IPI score was calculated by Harrell's concordance index (c-index). C-index was calculated by R (The R Foundation for Statistical Computing, Vienna, Austria). All other data were

Table 1. Baseline characteristics of DLBCL patients

	Total (n=167) n (%)	SUA<6.4 mg dl^{-1} (n=114), n (%)	SUA≥6.4 mg dl^{-1} (n=53), n (%)	*p*-value
Gender				
Female	71 (42.5%)	55 (48.3%)	16 (30.2%)	0.030
Male	96 (57.5%)	59 (51.7%)	37 (69.8%)	
Age				
≤40 years	23 (13.8%)	14 (12.3%)	9 (17.0%)	<0.001
41-60 years	51 (30.5%)	43 (37.7%)	8 (15.1%)	
61-75 years	61 (36.5%)	44 (38.6%)	17 (32.1%)	
>75 years	32 (19.2%)	13 (11.4%)	19 (35.8%)	
Presence of B symptoms				
No	46 (27.5%)	25 (21.9%)	21 (39.6%)	0.025
Yes	121 (72.5%)	89 (78.1%)	32 (60.4%)	
Ann Arbor stage				
I-II	40 (24.0%)	32 (28.1%)	8 (15.1%)	0.081
III-IV	127 (76.0%)	82 (71.9%)	45 (84.9%)	
Number of extranodal site				
≤1	89 (53.3%)	67 (58.8%)	22 (41.5%)	0.046
>1	78 (46.7%)	47 (41.2%)	31 (58.5%)	
LDH level				
Normal	82 (49.1%)	67 (58.8%)	15 (28.3%)	<0.001
Elevated	85 (50.9%)	47 (41.2%)	38 (71.7%)	
Bone marrow involvement				
Absence	137 (82.0%)	97 (85.1%)	38 (71.7%)	0.256
Presence	25 (15.0%)	13 (11.1%)	12 (22.6%)	
Unknown	5 (3.0%)	2 (1.8%)	3 (5.7%)	
Serum creatinine level				
Normal	134 (80.2%)	103 (90.4%)	31 (58.5%)	<0.001
Elevated	33 (19.8%)	11 (9.6%)	22 (41.5%)	
β2microglobulin				
Normal	52 (31.1%)	39 (34.2%)	13 (24.5%)	0.281
Elevated	115 (68.9%)	75 (65.8%)	40 (75.5%)	
IPI scores				
0-1	43 (25.7%)	34 (29.8%)	9 (17.0%)	0.052
2-3	74 (44.3%)	52 (45.6%)	22 (41.5%)	
4-5	50 (29.9%)	28 (24.6%)	22 (41.5%)	
NCCN-IPI scores				
0-1	21 (12.6%)	17 (14.9%)	4 (7.5%)	0.006
2-3	58 (34.7%)	41 (36.0%)	17 (32.1%)	
4-5	59 (35.3%)	44 (38.6%)	15 (28.3%)	
≥6	29 (17.4%)	12 (10.5%)	17 (32.1%)	

DLBCL, diffuse large b-cell lymphoma; SUA, serum uric acid; LDH, lactate dehydrogenase; IPI, International Prognostic Index; NCCN-IPI, National Comprehensive Cancer Network-International Prognostic Index.

analyzed by SPSS statistical software (version 21.0 SPSS, Chicago, IL, USA) and GraphPad Prism (version6.0; Graphpad Software, Inc, La Jolla, CA, USA), and the data-entry was examined twice. A two-sided P<0.05 is considered statically significant.

Results

Association between SUA level and other clinical characteristics in DLBCL

A total of 96 (57.5%) male and 71 (42.5%) female patients with newly diagnosed DLBCL under standard R-CHOP or CHOP-like immune-chemotherapies were selected in this study cohort. The mean age at diagnoses was 60 years (range: 7-86 years), with 19.2% of the patients being over 75 years old at diagnosis. The Ann Arbor tumor stage was observed as stage I or II in 40 patients (24%), stage III in 65 patients (38.9%) and stage IV in 62 patients (37.1%). According to the IPI classifier, 43 patients (25.7%) had low risk; 74 patients (44.3%) had intermediate risk; and 50 patients (29.9%) had high risk. As for NCCN-IPI classifier, 21 patients (12.6%) had low risk; 58 patients (34.7%) had low-intermediate risk; 59 patients (35.3%) had high-intermediate risk; and 29 (17.4%) had high risk. By the end of the follow-up period, 56 patients (33.5%) deaths occurred, of which 38 patients (67.9%) were caused by lymphoma progression, 13 patients (23.2%) due to infectious disease, and the rest 5 patients (8.9%) with unknown reasons.

1(31.7%) patients had high SUA (≥6.4 mg dl^{-1}) while 114 (68.3%) had low SUA (<6.4 mg dl^{-1}). The area under the curve (AUC) was 0.765 (95% confidence interval [CI] =0.672-0.857), with

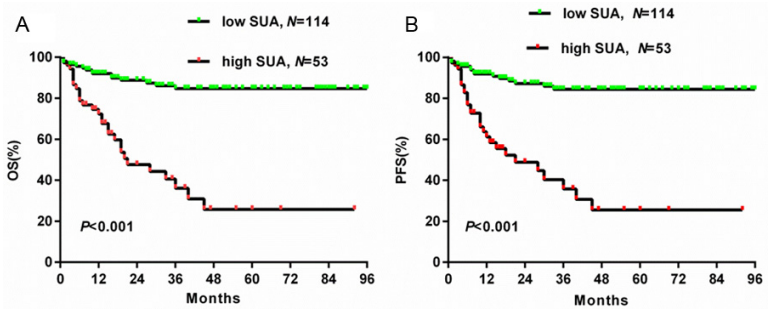

Figure 2. Kaplan-Meier curve for survival according to SUA level. A. Overall survival (Log-rank test, p<0.001). B. Progression-free survival (Log-rank test, p<0.001).

65.1% sensitivity and 20.2% specificity. (p<0.001, **Figure 1**).

The baseline characteristics according to cut-off point of pretreatment SUA were presented in **Table 1.** Males were more likely to develop high SUA level (p=0.030). High SUA level were significantly correlated with LDH and serum creatinine (p<0.001, p<0.001), age (p<0.001), B symptom (p=0.025), extranodal sites of disease (>1, p=0.046), and NCCN-IPI score (P=0.006). Additionally, SUA level was negative associated with Ann Arbor stage disease (III/IV, p=0.081), bone marrow involvement (p=0.256), β2microglobulin level (p=0.281) and IPI score (p=0.052).

High uric acid level correlates with inferior OS and PFS

Among patients with the median follow-up time of 21 (range, 1-95) months, the low uric acid group had a significantly higher OS than the high uric acid group as shown in **Figure 2A** (2-year OS, 62.3% vs 26.3%, respectively; P<0.001). A Similar correlation could be found in PFS between the two groups as revealed in **Figure 2B** (2-year PFS, 58.8% vs 22.6%, respectively; p<0.001).

Univariate and multivariate cox regression analysis for overall survival

Potential influences of OS and PFS in these patients were identified using univariate cox regression model (**Table 2**). Analysis of a high SUA level (p<0.001), Ann Arbor stage disease (III/IV, p=0.031), presence of B symptoms (p<0.001), extranodal involvement sites (>1, p<0.001),anelevatedLDH(p<0.001)andβ2microglobulin level (p=0.003), high serum creatinine (p=0.001), IPI score (≥2, p<0.001) and NCCN-IPI score (≥6, p<0.001) were identified as poor prognostic factors for PFS; similar results were found for OS in our study cohort. To determine the independent prognostic parameters in DLBCL, multivariate analyses of PFS and OS were performed. For PFS, we observed that three variables including LDH (HR=3.681; 95% CI 1.163-11.650, p=0.027), SUA (HR=3.851; 95% CI 1.816-8.167, p<0.001) and NCCN-IPI (≥6, HR=4.861; 95% CI 1.992-11.861, p=0.001) emerged as independent and significant predictors of increasing risk of cancer progression. For OS, similar findings were yielded (**Table 3**).

Adding UA level to IPI score improves risk stratification

To further investigate the value of SUA in DLBCL, we incorporated the baseline SUA level (SUA<6.4 mg dl^{-1}, 0 point; SUA≥6.4 mg dl^{-1}, 1 point) into the IPI score and preformed Harrell's C-statistics analysis. We identified SUA as a valuable prognostic factor; the c-index improved from 0.772 to 0.833 and 0.777 to 0.837 for OS and PFS respectively (**Table 4**). We also proved that the performance of new model surpassed the old one in both survival prediction and risk classification (**Figure 3**).

Discussion

Risk stratification models are crucial in the initial classification and overall management of patients due to disease heterogeneity. The conventional IPI has been a common prognostic model for more than 20 years [2]. Advancement in the treatment of DLBCL breeds new modifications on IPI, such as R-IPI and NCCN-IPI in the rituximab era. Other techniques including gene expression profiling (GEP), chromosomal aberration analysis and differential microRNA expression [18, 19] are precise but technically complicated, expensive and not broadly accessible. Thus, searching obtainable parameters to discriminate among risk groups remains important. SUA level is measured in routine laboratory tests and is readily available, sug-

Table 2. Univariate Cox Regression Analysis of OS and PFS.

	PFS		OS	
	HR (95% CI)	*p*-value	HR [95% CI]	*p*-value
Sex (male)	1.504 (0.803-2.816)	0.202	1.533 (0.818-2.871)	0.182
Age (>60 years)	1.659 (0.886-3.106)	0.114	1.650 (0.881-3.091)	0.118
B symptoms presence	4.941 (2.692-9.069)	<0.001	4.766 (2.597-8.746)	<0.001
Ann Arbor stage (III-IV)	2.785 (1.096-7.709)	0.031	2.657 (1.046-6.750)	0.04
Extranodal site (>1)	4.945 (2.474-9.882)	<0.001	4.775 (2.393-9.530)	<0.001
LDH (elevated)	8.620 (3.634-20.504)	<0.001	8.173 (3.438-19.429)	<0.001
Bone marrow presence	1.223 (0.566-2.641)	0.608	1.161 (0.538-2.504)	0.704
Serum creatinine (elevated)	2.974 (1.574-5.618)	0.001	3.083 (1.623-5.827)	<0.001
β2microglobulin (elevated)	4.053 (1.594-10.303)	0.003	3.930 (1.546-9.988)	0.004
IPI score (≥2)	4.298 (2.053-8.999)	<0.001	4.042 (1.993-9.988)	<0.001
NCCN-IPI score (≥6)	9.157 (4.867-17.230)	<0.001	8.785 (4.674-16.512)	<0.001
SUA (elevated)	6.170 (3.259-11.682)	<0.001	6.145 (3.248-11.625)	<0.001

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence internal; SUA, serum uric acid; LDH, lactate dehydrogenase; IPI, International Prognostic Index; NCCN-IPI, National Comprehensive Cancer Network-International Prognostic Index.

Table 3. Multivariate Cox Regression Analysis of OS and PFS.

	PFS		OS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Sex (male)	1.418 (0.714-2.818)	0.318	1.579 (0.793-3.144)	0.194
Age (>60 years)	0.459 (0.196-1.073)	0.072	0.498 (0.214-1.158)	0.105
Ann Arbor stage (>2)	1.105 (0.334-3.651)	0.870	1.136 (0.343-3.759)	0.835
LDH (elevated)	3.681 (1.163-11.650)	0.027	3.919 (1.233-12.459)	0.021
Serum creatinine (elevated)	0.929 (0.441-1.959)	0.847	0.814 (0.380-1.743)	0.596
IPI score (≥2)	1.720 (0.580-5.101)	0.328	1.516 (0.515-4.464)	0.450
NCCN-IPI score (≥6)	4.861 (1.992-11.861)	0.001	4.704 (1.909-11.587)	0.001
SUA (elevated)	3.851 (1.816-8.167)	<0.001	4.007 (1.884-8.523)	<0.001

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence internal; SUA, serum uric acid; LDH, lactate dehydrogenase; IPI, International Prognostic Index; NCCN-IPI, National Comprehensive Cancer Network-International Prognostic Index.

Table 4. Harrell's C-statistics analysis for discriminatory values on survival

	C-index for OS		C-index for PFS	
	HR	95% CI	HR	95% CI
IPI	0.772	0.683-0.861	0.777	0.688-0.866
IPI+SUA	0.833	0.743-0.923	0.837	0.745-0.928

IPI, International Prognostic Index; SUA, serum uric acid; OS, overall survival; PFS, progression-free survival.

gesting a clinically significant potential in prognostic value. There have been several studies investigating the association between SUA and caner in both healthy people and cancer patients. A large prospective study [20] on more than 28000 elderly Austrian women found an association between high SUA level (>5.41 ml/dl) and fatal cancer events (p<0.0001). Alexander Strasak and colleagues [21] confirmed similar findings in a male population across a wide age range. Further, he demonstrated a dose-response to baseline SUA, which was a time-dependent risk factor for cancer incidence.

These findings suggested that SUA derived from healthy people could be a pervasive parameter in the development of cancer. On the other hand, pretreatment SUA levels obtained from people with malignant tumor were also proven to be a prognostic marker in

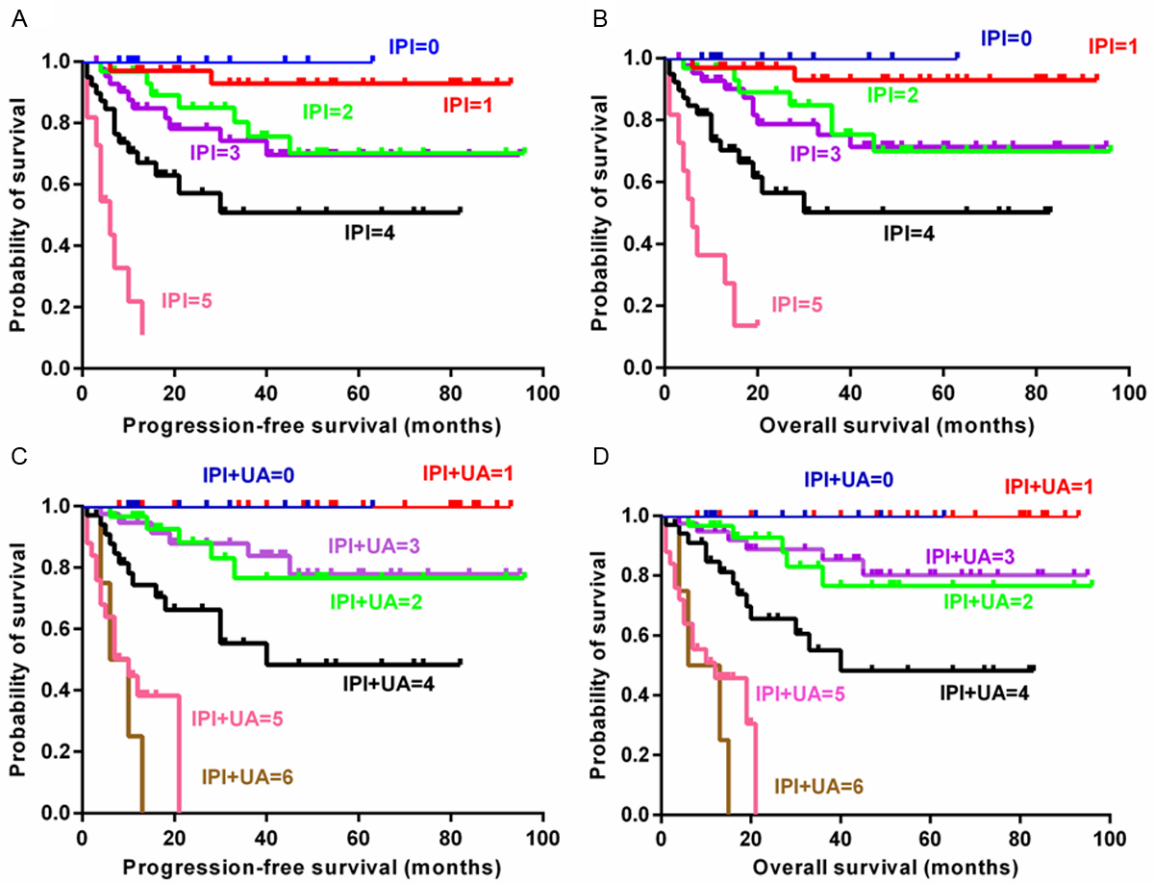

Figure 3. Kaplan-Meier curve of PFS (A, C) and OS (B, D) according to IPI and IPI+SUA.

various cancer types such as acute myeloid leukemia (AML) [8], pancreatic cancer [11], soft-tissue sarcoma [13], as well as other terminally ill cancers [14]. Further investigation reported that patients with higher SUA levels associated with endocrine and metabolic showed increased risk to develop metastases in solid cancers [9, 12]. Our study also suggested SUA level at diagnosis as a prognostic parameter in Chinese patients with DLBCL. However, positive associations between SUA level and survival in patients with certain cancer types (e.g., colorectal cancer and nasopharyngeal carcinoma) have also been reported [15, 16].

Such uncertainty in the prognostic use of SUA levels could be partially explained by the dual role theory of SUA. In one study, the presence of a molecular switch regulated by specific human organ microenvironment determined the role of SUA as an anti-oxidant or a pro-oxidant [22]. The anti-oxidant role of SUA among cancer patients was first explored by Ames [23] et al. showing that increased SUA level protected against initiation and progression of tumor by scavenging singlet oxygen and preventing lipid peroxidation. Similar results from a randomized, placebo-controlled double-blind study [24] further strengthened uric acid's anti-oxidant properties, in which reactive oxygen species (ROS) production was reduced, thereby inhibiting tumor cell proliferation and migration. In addition to the anti-oxidant aspect, the surveillance mechanism also helps to explain why SUA is protective against cancer. Degenerating/dying cells release SUA and antigens that the host is not tolerant. This process stimulates the immune system and generates responses against cancer cells [25].

On the other hand, SUA can increase the incidence of metabolic insulin resistance, hypertriglyceridemia and hepatic steatosis, which increases cancer incidence [26]. Increased SUA is also associated with chronic inflamma-

tion involving changes in adiponectin, C-reactive protein (CRP) and Leptin levels [6]. Accordingly, high SUA level reduces circulating adiponectin, which weakens bodily inhibition capacity against Wnt signaling, Akt activity and LKB1, thereby leads to increased cancer risk, recurrence and metastasis [6]. SUA level was positively correlated with CRP level, which increases risk for breast cancer (BC), gastric and renal cell cancers [27-29]. Elevated SUA level exhibits an increase in leptin, a dependent poor prognostic marker in breast, colon, prostate, and ovarian cancer [30, 31]. In addition, high level of SUA in cancer cells diminishes Xanthine Oxidoreductase (XOR) expression and activity, which contributes to tumor differentiation and metastasis [6]. Moreover, hyperuricemia predicts tumor lysis symptom (TLS) in patients with large tumor burden, especially hematologic malignancies [32]. TLS is characterized by massive destruction of rapid proliferating neoplastic cells, leading to metabolic dysfunction and organ failures. The pro-oxidative and pro-inflammation properties of SUA facilitate these organ injuries [32].

In the present study, we found that elevated SUA was associated with the presence of B symptom, higher counts of extranodal sites and higher level of LDH and serum creatinine. Therefore, the result coincides with previous publications that hyperuricemia reflects high tumor burden and rapid growth of tumor cells [33]. Furthermore, our study indicated that elevated SUA level was associated with worse OS and PFS in DLBCL patients. One explanation associated with serum creatinine is that elevated SUA caused by a reduction in renal excretion may indicate renal impairment. Patients with renal dysfunction tend to receive lower dosage on their initial chemotherapy. Insufficient concentration of drug in combination with a high tumor burden in these patients contributes to poor outcomes.

To the best of our knowledge, there is one retrospective analysis prior to ours concerned SUA level in BLDCL. Data from two Australian centers demonstrated similar findings with minor statistical discrepancies such as the cutoff value of SUA [34]. Nevertheless, different ethnic origins, population sample size and habits (e.g., diet) may be responsible for the different outcomes in the Australian study compared to ours. One weakness of the current study is the relatively small patient cohort (167 patients). In addition, patient follow-up remained limited in the present study. Nonetheless, while statistical analysis pointed SUA as an inexpensive and readily available parameter that improves risk stratification when integrated into the IPI score, further clinical research and external validation is needed.

Conclusion

In the present study, we suggested elevated SUA level at diagnosis as an independent predictor for worse clinical outcome in DLBCL patients under rituximab (R)-CHOP or CHOP-like immune-chemotherapy. Plus, by integrating SUA to the IPI score, we could improve the survival prediction and risk stratification of DLBCL patients.

Disclosure of conflict of interest

None.

Address correspondence to: Shenxian Qian, Department of Hematology, The Hangzhou Hospital Affiliated to Nanjing Medical University, 216 Huansha Road, Hangzhou 310006, P.R China. Tel: 008613750887628; E-mail: qsx_hzsy@163.com

References

[1] Xie Y, Pittaluga S and Jaffe ES. The histological classification of diffuse large B-cell lymphomas. Semin Hematol 2015; 52: 57-66.

[2] Hasenclever D and Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 1998; 339: 1506-1514.

[3] Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, Klasa R, Savage KJ, Shenkier T, Sutherland J, Gascoyne RD and Connors JM. 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 2007; 109: 1857-1861.

[4] 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 and Winter JN. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma

treated in the rituximab era. Blood 2014; 123: 837-842.
[5] 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, Ferme C and Tilly H. 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 2010; 116: 2040-2045.
[6] Fini MA, Elias A, Johnson RJ and Wright RM. Contribution of uric acid to cancer risk, recurrence, and mortality. Clin Transl Med 2012; 1: 16.
[7] Heinig M and Johnson RJ. Role of uric acid in hypertension, renal disease, and metabolic syndrome. Cleve Clin J Med 2006; 73: 1059-1064.
[8] Yamauchi T, Negoro E, Lee S, Takai M, Matsuda Y, Takagi K, Kishi S, Tai K, Hosono N, Tasaki T, Ikegaya S, Inai K, Yoshida A, Urasaki Y, Iwasaki H and Ueda T. A high serum uric acid level is associated with poor prognosis in patients with acute myeloid leukemia. Anticancer Res 2013; 33: 3947-3951.
[9] Rose DP, Haffner SM and Baillargeon J. Adiposity, the metabolic syndrome, and breast cancer in African-American and white American women. Endocr Rev 2007; 28: 763-777.
[10] Dhankhar R, Dahiya K, Sharma TK, Ghalaut VS, Atri R and Kaushal V. Diagnostic significance of adenosine deaminase, uric acid and C-reactive protein levels in patients of head and neck carcinoma. Clin Lab 2011; 57: 795-798.
[11] Stotz M, Szkandera J, Seidel J, Stojakovic T, Samonigg H, Reitz D, Gary T, Kornprat P, Schaberl-Moser R, Hoefler G, Gerger A and Pichler M. Evaluation of uric acid as a prognostic blood-based marker in a large cohort of pancreatic cancer patients. PLoS One 2014; 9: e104730.
[12] Tanriverdi O, Cokmert S, Oktay E, Pilanci KN, Menekse S, Kocar M, Sen CA, Avci N, Akman T, Ordu C, Goksel G and Meydan N. Prognostic significance of the baseline serum uric acid level in non-small cell lung cancer patients treated with first-line chemotherapy: a study of the Turkish Descriptive Oncological Researches Group. Med Oncol 2014; 31: 217.
[13] Szkandera J, Gerger A, Liegl-Atzwanger B, Stotz M, Samonigg H, Ploner F, Stojakovic T, Gary T, Leithner A and Pichler M. Uric acid levels in blood are associated with clinical outcome in soft-tissue sarcoma patients. Clin Chem Lab Med 2015; 53: 493-497.
[14] Shin HS, Lee HR, Lee DC, Shim JY, Cho KH and Suh SY. Uric acid as a prognostic factor for survival time: a prospective cohort study of terminally ill cancer patients. J Pain Symptom Manage 2006; 31: 493-501.
[15] Dziaman T, Banaszkiewicz Z, Roszkowski K, Gackowski D, Wisniewska E, Rozalski R, Foksinski M, Siomek A, Speina E, Winczura A, Marszalek A, Tudek B and Olinski R. 8-Oxo-7,8-dihydroguanine and uric acid as efficient predictors of survival in colon cancer patients. Int J Cancer 2014; 134: 376-383.
[16] Lin H, Lin HX, Ge N, Wang HZ, Sun R and Hu WH. Plasma uric acid and tumor volume are highly predictive of outcome in nasopharyngeal carcinoma patients receiving intensity modulated radiotherapy. Radiat Oncol 2013; 8: 121.
[17] Sabattini E, Bacci F, Sagramoso C and Pileri SA. WHO classification of tumours of haematopoietic and lymphoid tissues in 2008: an overview. Pathologica 2010; 102: 83-87.
[18] Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, Boldrick JC, Sabet H, Tran T, Yu X, Powell JI, Yang L, Marti GE, Moore T, Hudson J Jr, Lu L, Lewis DB, Tibshirani R, Sherlock G, Chan WC, Greiner TC, Weisenburger DD, Armitage JO, Warnke R, Levy R, Wilson W, Grever MR, Byrd JC, Botstein D, Brown PO and Staudt LM. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000; 403: 503-511.
[19] Shepshelovich D, Ram R, Uziel O, Kushnir M, Lithwick-Yanai G, Hoshen M, Feinmesser M, Bairey O and Lahav M. MicroRNA signature is indicative of long term prognosis in diffuse large B-cell lymphoma. Leuk Res 2015; 39: 632-637.
[20] Strasak AM, Rapp K, Hilbe W, Oberaigner W, Ruttmann E, Concin H, Diem G, Pfeiffer KP and Ulmer H. The role of serum uric acid as an antioxidant protecting against cancer: prospective study in more than 28 000 older Austrian women. Ann Oncol 2007; 18: 1893-1897.
[21] Strasak AM, Lang S, Kneib T, Brant LJ, Klenk J, Hilbe W, Oberaigner W, Ruttmann E, Kaltenbach L, Concin H, Diem G, Pfeiffer KP and Ulmer H. Use of penalized splines in extended Cox-type additive hazard regression to flexibly estimate the effect of time-varying serum uric acid on risk of cancer incidence: a prospective, population-based study in 78,850 men. Ann Epidemiol 2009; 19: 15-24.
[22] Kang DH and Ha SK. Uric acid puzzle: dual role as anti-oxidantand pro-oxidant. Electrolyte Blood Press 2014; 12: 1-6.
[23] Ames BN, Cathcart R, Schwiers E and Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci U S A 1981; 78: 6858-6862.

[24] Waring WS, Webb DJ and Maxwell SR. Systemic uric acid administration increases serum antioxidant capacity in healthy volunteers. J Cardiovasc Pharmacol 2001; 38: 365-371.
[25] Shi Y, Evans JE and Rock KL. Molecular identification of a danger signal that alerts the immune system to dying cells. Nature 2003; 425: 516-521.
[26] Viazzi F, Bonino B, Ratto E, Desideri G and Pontremoli R. [Hyperuricemia, diabetes and hypertension]. G Ital Nefrol 2015; 32: Suppl 62.
[27] Vona-Davis L, Howard-McNatt M and Rose DP. Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. Obes Rev 2007; 8: 395-408.
[28] Shimura T, Kitagawa M, Yamada T, Ebi M, Mizoshita T, Tanida S, Kataoka H, Kamiya T and Joh T. C-reactive protein is a potential prognostic factor for metastatic gastric cancer. Anticancer Res 2012; 32: 491-496.
[29] Saito K and Kihara K. Role of C-reactive protein as a biomarker for renal cell carcinoma. Expert Rev Anticancer Ther 2010; 10: 1979-1989.
[30] Jarde T, Perrier S, Vasson MP and Caldefie-Chezet F. Molecular mechanisms of leptin and adiponectin in breast cancer. Eur J Cancer 2011; 47: 33-43.
[31] Grossmann ME, Ray A, Nkhata KJ, Malakhov DA, Rogozina OP, Dogan S and Cleary MP. Obesity and breast cancer: status of leptin and adiponectin in pathological processes. Cancer Metastasis Rev 2010; 29: 641-653.
[32] Shimada M, Johnson RJ, May WS Jr, Lingegowda V, Sood P, Nakagawa T, Van QC, Dass B and Ejaz AA. A novel role for uric acid in acute kidney injury associated with tumour lysis syndrome. Nephrol Dial Transplant 2009; 24: 2960-2964.
[33] Sevinir B, Demirkaya M, Baytan B and Gunes AM. Hyperuricemia and tumor lysis syndrome in children with non-Hodgkin's lymphoma and acute lymphoblastic leukemia. Turk J Haematol 2011; 28: 52-59.
[34] Prochazka KT, Melchardt T, Posch F, Schlick K, Deutsch A, Beham-Schmid C, Weiss L, Gary T, Neureiter D, Klieser E, Greil R, Neumeister P, Egle A and Pichler M. NCCN-IPI score-independent prognostic potential of pretreatment uric acid levels for clinical outcome of diffuse large B-cell lymphoma patients. Br J Cancer 2016; 115: 1264-1272.