Observational Study

Medicine®

OPEN

Monoclonal gammopathies regardless of subtypes are associated with poor prognosis of diffuse large B-cell lymphoma

A STROBE-compliant article

Yian Zhang, MD, Zheng Wei, MD, Jing Li, MD, Rupan Gao, MD, Peng Liu, MD, PhD*

Abstract

Monoclonal gammopathy (MG), a positive result of serum immunofixation electrophoresis (SIFE), has been reported in cases of diffuse large B-cell lymphoma (DLBCL). We performed this study to further investigate the prognostic value of MG in DLBCL.

We retrospectively reviewed patients diagnosed with DLBCL between January 2007 and December 2014, and identified 37 patients with MG. The clinical characteristics of these patients were then reviewed. A 1:2 case-control analysis was conducted on 74 matched controls, who were patients with DLBCL and without MG. Both cases and controls were age-matched and were diagnosed within the same year.

Among 37 DLBCL patients with MG, the monoclonal component of IgM was the most frequent compared to the other subtypes. Laboratory tests showed that the presence of MG was correlated with a decreased platelet-to-lymphocyte ratio (PLR). Survival analysis showed that MG-secreting DLBCL patients had an inferior overall survival (OS) and progression-free survival (PFS), compared with MG-nonsecreting patients, regardless of MG subtype. However, treatment response analysis showed that MG was not a good indicator for tumor relapse. When patients with DLBCL were grouped by immunophenotype, we found that MG was associated with poor prognosis in the non-germinal center B-cell-like (GCB) type, rather than GCB type in OS analysis. Meanwhile, there was no statistical significance upon PFS analysis in both immunophenotypes. Furthermore, our study found that the appearance of MG during treatment did make prognostic sense compared to nonsecretors.

Overall, MG can serve as a prognostic factor for DLBCL. We hypothesize that its presence in DLBCL may reflect the immune microenvironment in tumor progression and warrants further study to unveil the underlying molecular pathogenesis.

Abbreviations: CR = complete remission, DLBCL = diffuse large B-cell lymphoma, FLC = free light chain, GCB = germinal center B-cell-like, IPI = international prognostic index, LMR = lymphocyte-to-monocyte ratio, MG = monoclonal gammopathies, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, PCD = plasma cell diseases, PFS = progression-free survival, PLR = platelet-to-lymphocyte ratio, PR = partial remission, SIFE = serum immunofixation electrophoresis.

Keywords: diffuse large B-cell lymphoma, monoclonal gammopathy, prognosis, serum immunofixation electrophoresis

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common pathologic type of high-grade non-Hodgkin lymphoma among adults, with an estimated annual incidence of 7 to 8 cases per 100,000 people every year.[1,2] Standard treatment for DLBCL includes a combination of biological therapy consisting of rituximab and anthracycline-based chemotherapy regimens, usually comprising cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Owing to the use of rituximab, progression-free survival (PFS) and overall survival (OS) rates in DLBCL have improved.[3] However, the International Prognostic Index (IPI), which was developed in the era of chemotherapy treatment for aggressive lymphoma, has proven to be less powerful in the rituximab era. To better distinguish tumor prognosis, several models[4,5] and algorithms[6,7] have been developed. In addition, several markers have been discovered in DLBCL, to better identify patients who will likely have a poor therapeutic response.[8] Despite the rise of interests in these areas, there is still a strong need to discover more prognostic factors based on tumor phenotypes that will probably improve risk-adapted treatment approaches.

Serum immunofixation electrophoresis (SIFE) technology is used to identify monoclonal or polyclonal gammopathies.[9] Compared to serum free light chain (FLC) testing, which is becoming a mainstream screening test for plasma cell diseases (PCD), SIFE remains a lower-cost test, and is more widely used in clinical practice. Usually, a positive SIFE result refers to the discovery of serum monoclonal gammopathies (MG), and such results are mainly observed in patients with multiple myeloma

Editor: Weimin Guo.

YZ and ZW contributed equally to this article.

This work was supported by the National Natural Science Foundation of China (81570123), the National Key New Drug Creation Special Programs (2017ZX09304-021), Academic Pacesetters Program of Shanghai Healthcare System (2017BR033), Foundation of Science and Technology Commission of Shanghai (16ZR1405800), and Research project of Shanghai Municipal Commission of Health and Family Planning (201440390).

The authors report no conflicts of interest.

Supplemental Digital Content is available for this article.

Department of Hematology, Zhongshan Hospital, Fudan University, Shanghai, China.

* Correspondence: Peng Liu, Department of Hematology, Zhongshan Hospital, Fudan University, Shanghai, China, 180 Fenglin Road, Zhongshan Hospital, Fudan University, Shanghai 200032, China (e-mail: liu.peng@zs-hospital.sh.cn).

Medicine (2018) 97:30(e11719)

Received: 5 December 2017 / Accepted: 5 July 2018

http://dx.doi.org/10.1097/MD.0000000000011719

(MM), monoclonal gammopathies of undetermined significance (MGUS), *etc*. Besides these PCDs, there are approximately 17% of lymphoma patients of various subtypes reported to present with positive SIFE results.[10] We observed that patients with DLBCL, who had positive SIFE results, also known as MG-secreting DLBCL, shared poor prognosis after receiving immunochemotherapy. The relationship between the presence of MG and biological tumor behavior, however, remains obscure. To ascertain as to whether our observation was a meaningful finding, we conducted a retrospective case-control study to elucidate the significance of the presence of MG as a prognostic factor for DLBCL. In addition, the potential molecular pathogenesis of DLBCL with MG was also discussed.

2. Methods

This study was designed as a retrospective 1:2 case-control study.

2.1. Study subjects and selection criteria

This case-control study evaluated the incidence of patients with MG-secreting DLBCL, compared to a group of MG-nonsecreting controls. Clinicopathological features, treatment response, and survival were compared between the 2 groups. The study was approved by the Ethics Review Committee, Zhongshan Hospital of Fudan University, Shanghai, China. All patients provided written consent for the use of their clinical data, including laboratory test results. These results were retrospectively collected and obtained from corresponding medical records.

Thirty-seven patients were diagnosed with MG-secreting DLBCL between January 2007 and December 2014, according to the World Health Organization criteria. They were analyzed for SIFE throughout disease onset, middle of the treatment, and follow-up. As controls, a set of 74 MG-nonsecreting patients with DLBCL (1:2) were selected under the same diagnostic criteria. An eligible control was matched to a case by age (±5 years) and within the same year of diagnosis. Usually, >2 patients met the matching criteria, in which case we selected 2 matched individuals with similar Ann Arbor stage, and IPI score. Lastly, if >2 patients met the matching criteria, 2 matched individuals were selected randomly.

2.2. Immunohistochemistry

Cell of origin was assessed by immunohistochemistry according to the Hans algorithm.[11] Based on the 3 markers, CD10 (56C6, Novacastra/Leica microsystems, Wetzler, Germany), BCL6 (PG-B6p, DAKO, Glostrup, Denmark) and MUM1(MUM1p, DAKO, Glostrup, Denmark), according to the Hans classifier, the subgroups are as follows: GCB type ($CD10^+$; $CD10^-$ $BCL6^+$ $MUM1^-$), nonGCB type ($CD10^-$ $BCL6^+$ $MUM1^+$; $CD10^-$ $BCL6^-$). All biopsies were reviewed by 3 pathologists. The conditions for all the antibodies and their evaluation followed the guidelines recommended by the Lunenburg Lymphoma Biomarker Consortium.[12]

2.3. Treatment, treatment response evaluation, and survival time

All patients enrolled in the study received 6 to 8 cycles of R-CHOP every 21 days (375 mg/m^2 rituximab on day 0, 50 mg/m^2 doxorubicin on day 1, 750 mg/m^2 cyclophosphamide on day 1, 1.4 mg/m^2 vincristine on day 1 and 100 mg prednisolone on days 1–5). Patients with bone marrow, genital organ, glands or craniofacial site involvement, or with involvement of >2 extra nodal sites, received 4 to 6 injections of 12-mg methotrexate for intrathecal prophylaxis. The International Workshop Criteria for non-Hodgkin lymphoma was used to evaluate the patients' response to treatment and the incidence of relapse.[13] These patients also received physical examinations, blood tests, and computed tomography (CT) or positron emission tomography-CT scans to monitor their disease status during follow-up. The PFS was calculated as the length of time from diagnosis to disease progression, relapse, or death of any cause. The OS was calculated as the time from diagnosis to death because of any cause. Patients without an event or death were censored at the time of last known follow-up.

2.4. Statistical analysis

All values were expressed as mean ± standard deviation (SD). Categorical data were compared using χ^2 test or Fisher exact test and 2-sided P value. Student t test and independent t test were used for comparison between groups. Paired sample t test was used to evaluate the blood cell counts grouped by SIFE results. The actuarial survival analysis was carried out according to the method described by Kaplan Meier and the curves compared by the log-rank test. $P < .05$ was considered as statistically significant. Statistical analyses were conducted by IBM SPSS Statistics 19 (SPSS Inc. Chicago, IL)

3. Results

3.1. Baseline characteristics of participants

The final dataset consisted of 37 DLBCL patients with serum MG and 74 controls that were patients with MG-nonsecreting DLBCL. Clinicopathological features of the 37 cases are shown in Table S1 (see Supplemental Content, http://links.lww.com/MD/C369). Baseline clinical characteristics in 37 MG-secreting DLBCL cases and 74 nonsecreting controls were matched (Table 1). Among these 37 cases, 73% presented with stages III-IV. More than half of the patients harbored the germinal center B-cell-like (GCB) phenotype (56.8%). There were 12 cases (32.4%) with IgG subtype (IgG-κ:7, IgG-λ:5), 6 cases (16.2%) with IgA (IgA-κ: 3, IgA-λ:3) and 19 cases (51.4%) with IgM (IgM-κ: 9, IgM-λ: 10) (Table 2). Cases of MG-secreting DLBCL were further subgrouped into two groups, one of which includes patients that were SIFE-positive before treatment (24 cases), and the other one includes patients that were initially SIFE-negative before treatment and then became positive during the treatment (13 cases). No statistical differences in the baseline characteristics were found between these 2 groups (Table S2, http://links.lww.com/MD/C369).

3.2. Association between blood tests and SIFE results

The blood cell counts, the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) were evaluated and compared for any correlation with SIFE results. No significant differences were identified between MG-secreting and nonsecreting groups (Fig. 1A and Table S3, http://links.lww.com/MD/C369). Furthermore, the difference between the MG-secreting subgroups did not reach statistical significance (Table S4, http://links.lww.com/MD/C369). Among the 37 cases, 13 patients were initially SIFE-negative; interestingly

Table 1

Comparison of baseline clinical characteristics in MG-secreting (case) and nonsecreting(control) DLBCL patients (1:2 matched).

	Case (N = 37) N (%)	Control (N = 74) N (%)	OR (95% CI)	*P*
Sex (male vs. female)	24 (64.9)	36 (45.9)	2.172 (0.961–4.908)	.06
Age (≥60 vs.<60)	21 (56.8)	52 (70.3)	1.801 (0.794–4.087)	.157
Ann Arbor (I-II vs.III-IV)	10 (27)	32 (43.2)	0.4876 (0.206–1.148)	.097
B symptom*	18 (48.6)	35 (47.2)	0.947 (0.430–2.087)	.893
GCB vs. nonGCB	21 (56.8)	44 (62)	0.805 (0.359–1.807)	.599
IPI score (0–1 vs. 2–5)	8 (21.6)	24 (32.4)	0.575 (0.229–1.445)	.236

CI = confidence interval, GCB = germinal center B-cell like, IPI = international prognostic index, N = number, non-GCB = non-germinal center B-cell like, OR = odds ratio.
* Systemic symptoms of fever, night sweats, and weight loss.

Table 2

Subtypes of monoclonal gammopathies in 37 DLBCL cases.

Subtype	N	PCT (%)
IgG	12	32.4
IgG-λ	5	13.5
IgG-κ	7	18.9
IgA	6	16.2
IgA-λ	3	8.1
IgA-κ	3	8.1
IgM	19	51.4
IgM-λ	10	27.0
IgM-κ	9	24.4

DLBCL = diffuse large B-cell lymphoma, N = number, PCT = percentage.

these patients then became SIFE-positive during the treatment, whereas 6 patients who were initially SIFE-positive became negative during the treatment. These 19 patients matched with themselves in pairs according to SIFE status, and were further evaluated for NLR, LMR, and PLR. We found that the levels of PLR were associated with the change of SIFE results (Fig. 1B). Those SIFE-positive patients with DLBCL tend to have low PLR. When SIFE results indicated that it was negative, the level of PLR increased accordingly (P =.016).

3.3. MGs as a prognostic factor for DLBCL

Median follow-up was close to 12 months for the MG-secreting patients with DLBCL (range 2–84 months). As shown in Figure 2, the median OS was 60 months (95% CI 17.32–102.67) in the MG-secreting DLBCL group compared to 86.54 months (95% CI 66.67–107.33) in the MG-nonsecreting group (P =.008). Three-year OS rates were 60.5% (95% CI 51–70) in the MG-secreting DLBCL group, and 84.8% (95% CI 79.3–90.3) in the nonsecreting group (P =.001). The median PFS for secreting group was 44.89 months (95% CI 31.08–58.71) compared to 84 months (95% CI 62.72–93.26 months) in the nonsecreting group (P =.001). At 3 years, the PFS rate was 52.3% (95% CI 41.8–62.8) in the MG-secreting group and 76.4% (95% CI 70–82.8) in the nonsecreting group (P =.01). Differences in the OS and PFS among the various MG subtypes did not reach statistical significance (P =.953 and P =.952 respectively for median OS and PFS). Moreover, having a positive SIFE present during the treatment did make prognostic sense as compared to the nonsecreting ones (median OS 42.6 vs. 86.54 months, P =.004;

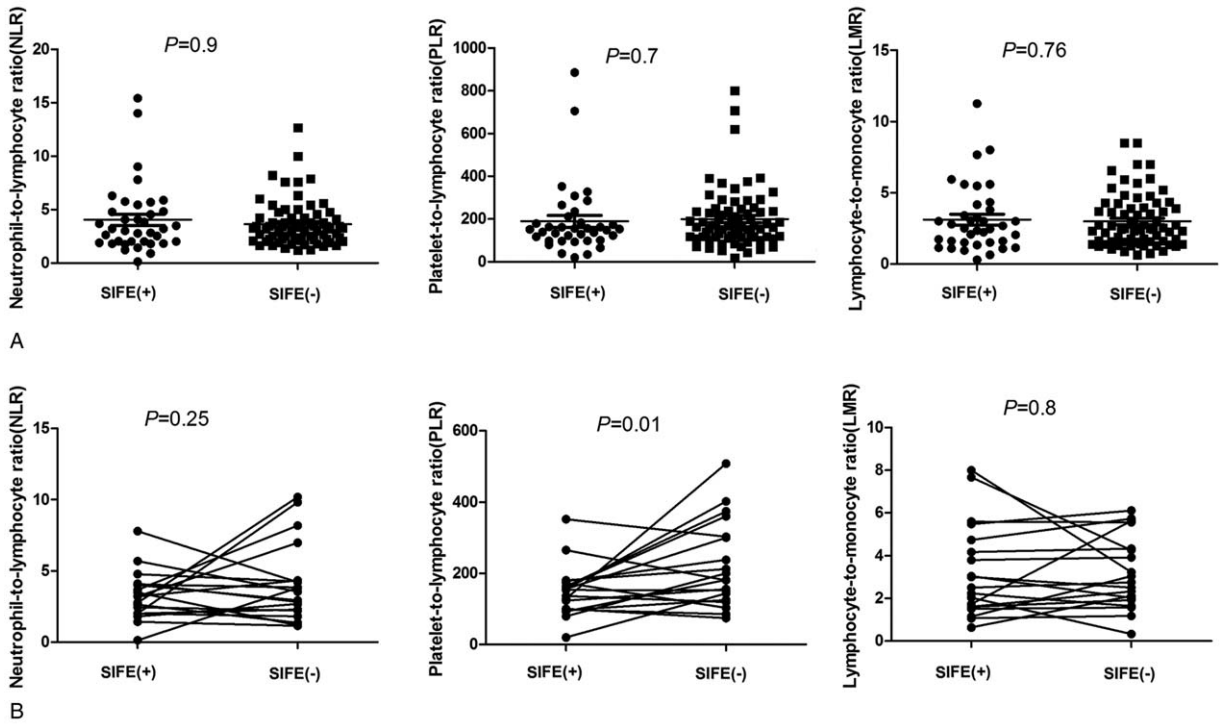

Figure 1. Ratios of different kinds of peripheral blood cells and SIFE results. (A) NLR, PLR, and LMR are grouped by secreting and nonsecreting DLBCL. The bars represent the mean ± standard deviation. (B) Among 37 MG-secreting DLBCL, 13 initially SIFE-negative patients became positive and 6 initially SIFE-positive patients became negative during the treatment. These 19 patients were further evaluated for NLR, LMR, and PLR by compared *t* test according to SIFE results. SIFE = serum immunofixation electrophoresis, NLR = neutrophil-to-lymphocyte ratio, LMR = lymphocyte-to-monocyte ratio, PLR = platelet-to-lymphocyte ratio.

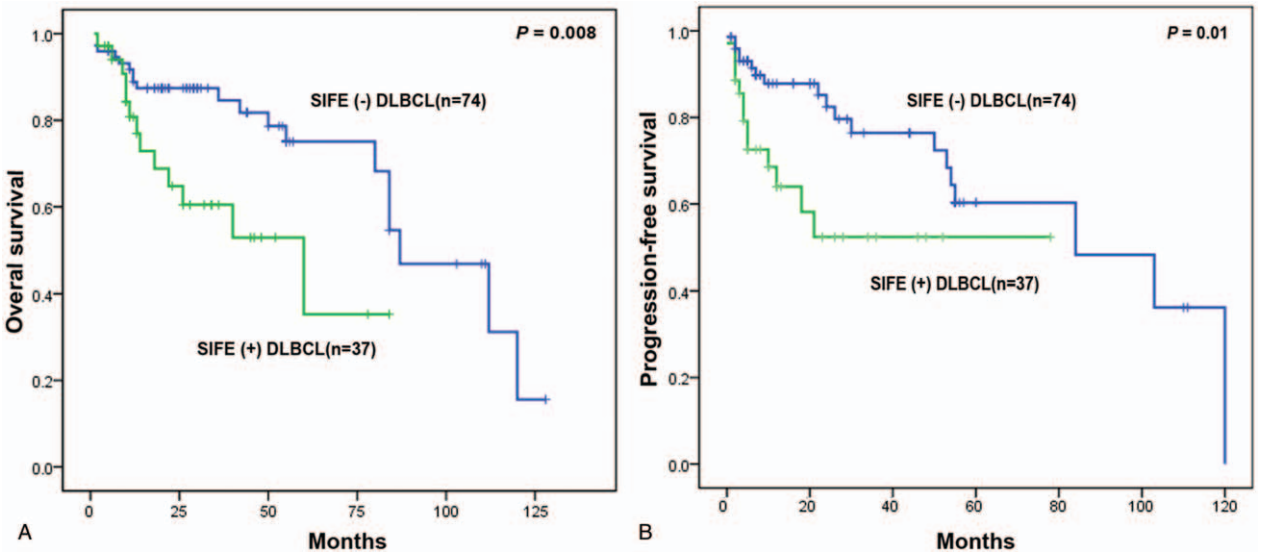

Figure 2. Overall survival (A) and progression-free survival (B) analysis between MG-secreting and nonsecreting DLBCL patients. DLBCL = diffuse large B-cell lymphoma, SIFE = serum immunofixation electrophoresis.

median PFS of 30.67 vs. 84 months, $P = .008$). However, the prognostic value of MG had its limitations in distinguishing survival outcomes between 2 MG-secreting subgroups ($P > .05$). When patients were grouped by immunophenotype, our results further showed that MG was associated with poor prognosis in the nonGCB type, rather than GCB type for OS analysis (Fig. 3A and B). Although PFS analysis showed that nonsecreting DLBCL patients had longer OS and PFS time than secreting ones in both GCB and nonGCB types, the differences did not reach statistical significance (Fig. 4A and B).

In terms of treatment response, among the 37 patients with MG-secreting DLBCL that were evaluated, 10 patients (27.0%) progressed after 3 cycles of first-line treatment, and a total of 23 patients (62.2%) achieved complete remission (CR) or partial remission (PR) (13 patients reached CR and 10 reached PR). As for the 74 patients with nonsecreting DLBCL, 19 patients (25.7%) progressed after 3 cycles R-CHOP treatment. The number of people who reached CR or PR was 44 (59.5%). No significant difference was identified between the MG-secreting and nonsecreting groups for treatment response rate.

4. Discussion

William et al previously reported that FLC abnormalities were present in 13% of 208 patients with lymphoma, and the prevalence of abnormal κ:λ FLC ratio in DLBCL was about 8%.[14] However, limited data have been reported on the exact prevalence of MG in different pathologic types of lymphoma, and there are few studies focusing on the molecular pathogenesis behind. We conducted a retrospective case-control study

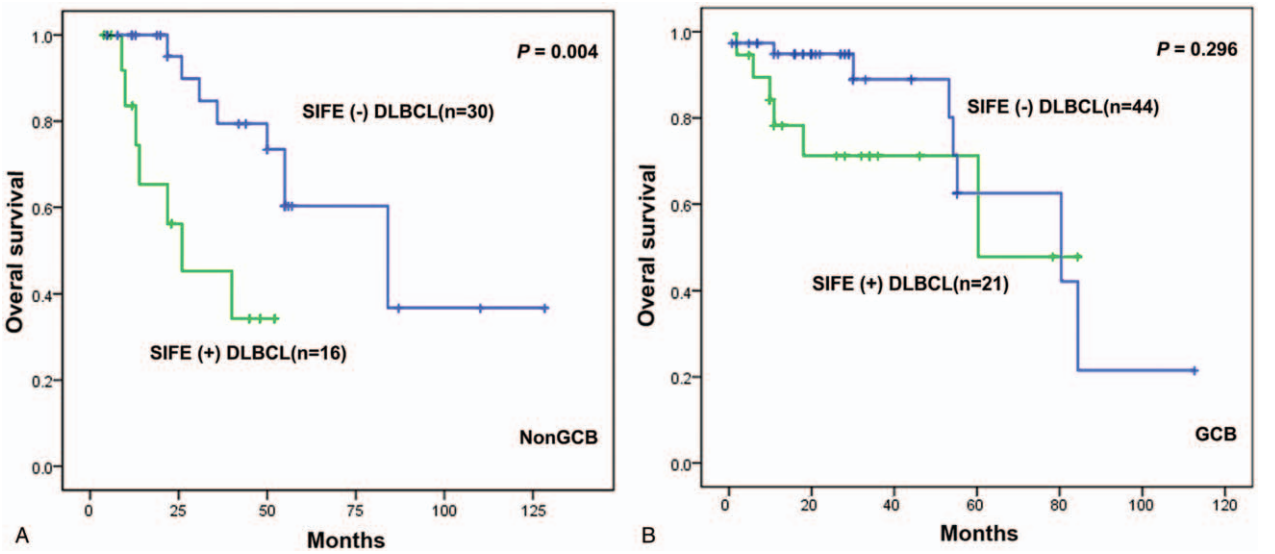

Figure 3. Overall survival analysis between MG-secreting and nonsecreting DLBCL patients who were grouped by non-GCB (A) and GCB (B) types. DLBCL = diffuse large B-cell lymphoma, GCB = germinal center B-cell-like, SIFE = serum immunofixation electrophoresis.

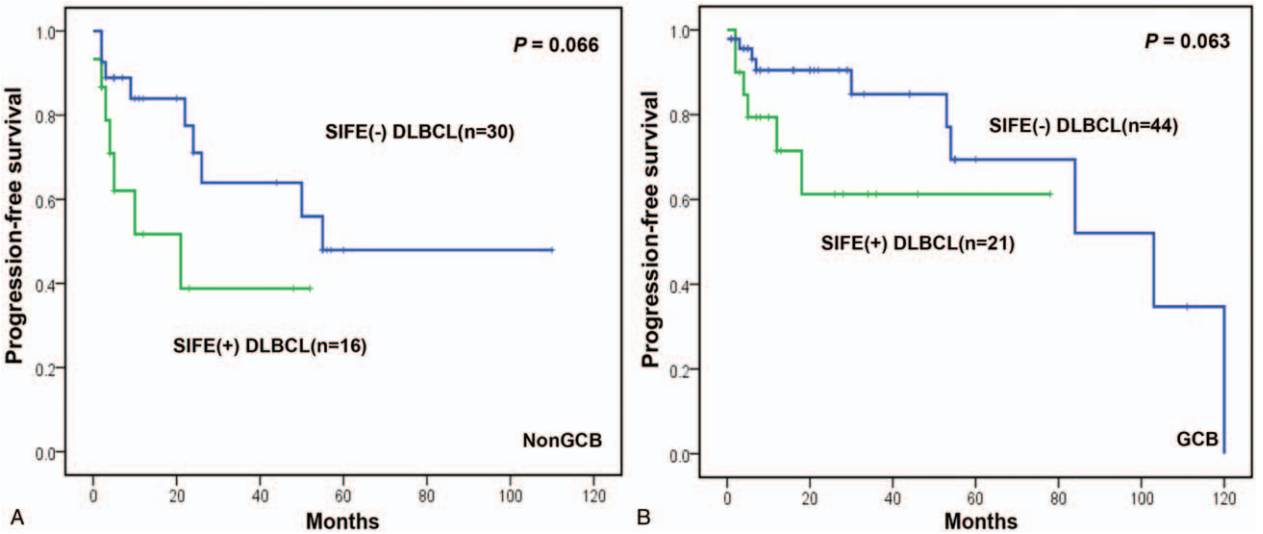

Figure 4. Progression-free survival analysis between MG-secreting and nonsecreting DLBCL patients who were grouped by non-GCB (A) and GCB (B) types. GCB = germinal center B-cell-like. DLBCL = diffuse large B-cell lymphoma, GCB = germinal center B-cell-like, SIFE = serum immunofixation electrophoresis.

including 37 DLBCL patients with positive SIFE. Regarding the subtypes of MG, the monoclonal component of IgM was more frequent compared to other subtypes (51.4%) among these 37 patients. Contrary to our study results, Economopoulos et al reported that IgM-MG was more frequent in cases with low-risk NHL, such as that of mucosa-associated lymphoid tissue lymphoma, follicular lymphoma, among others, whereas IgG was more frequent in cases with aggressive NHL such as DLBCL, Burkitt lymphoma, and so on.[10] This discrepancy may be because of the limited number of patients in both studies. Further studies with larger sample size should be conducted in the future to find out whether MG subtypes correlate with lymphoma pathologic types.

Another study by Cox et al found that after 1 to 3 cycles of R-CHOP, the monoclonal IgM component disappeared in all SIFE-positive patients. Some patients were persistently negative for IgM either during continuous CR or after recurrence (75% patients), whereas some underwent the reappearance of a monoclonal IgM preceding disease relapse.[15] In our study, among the 37 patients with MG-secreting DLBCL, the total number of people who reached CR or PR after 3 cycles of R-CHOP was 23 (62%). Among the 24 patients who were initially SIFE-positive, 6 became negative during treatment. Half of these 6 patients experienced disease progressions. Meanwhile, up to half of the patients who were initially SIFE-negative became positive while reaching persistent CR. As a result, the findings of both Cox et al, and our own findings reveal that MG, although has prognostic value, it might not serve as a proper monitor for tumor relapse or for treatment response.

Previous studies found that MG does not influence the survival of indolent lymphomas, but probably represents a negative prognostic factor in highly aggressive lymphomas[10] of both high-risk and low-risk patients (regardless of the IPI score).[14] Our survival analysis showed that, compared with non-secretors, patients with MG-secreting DLBCL of various MG subtypes have similar poor outcomes. Moreover, we found that according to the molecular classification of DLBCL, MG was associated with poor prognosis in nonGCB type for OS analysis, rather than GCB type (Fig. 3). In addition, PFS analysis showed that nonsecreting DLBCL patients had longer median PFS time than secreting ones in both GCB and nonGCB types; however, the differences were not statistically significant. These results were partly consistent with those of the study by Kim et al.[16] The lack of statistical significance for PFS may be because of the limited sample size.

As to the question why MG is evident in lymphoma, previously, it was hypothesized that MG may represent a malfunction of B-cells causing the predisposition to NHL.[17,18] However, according to the observation of Voigtlaender et al, the co-existence of MGUS and CD5 – monoclonal B-cell lymphocytosis did not progress to lymphoma with time. Therefore, they concluded that rather than polyclonal gammopathies which are regarded as a reaction of the anti-tumor response, MG may be attributed to disease-related immune stimulation.[19] Recent studies have introduced ratios of different kinds of peripheral blood cells to be used to predict prognosis of lymphoma. Watanabe et al revealed that LMR can reflect host systemic immunity and estimate clinical effects of R-CHOP treatments for DLBCL patients.[20] Wang et al[21] found that a decreased LMR led to a weak anti-tumor immunity and could be used as a poor prognostic biomarker of DLBCL. Meanwhile, PLR was reported as a potential predictive factor for several malignancies[22,23] and cardiovascular diseases.[24] A lower PLR was reported to be associated with poor prognosis in a few types of lymphoma.[23,25] In our study, we found that DLBCL patients who were SIFE-positive tend to have lower PLR. We suspected that the relationship of the low PLR and positive SIFE may be associated with the lymphoma immune environment and worth further investigation.

5. Conclusion

Overall, a variety of laboratory tests, including serum protein electrophoresis (SPEP), urine protein electrophoresis, SIFE, and serum FLC assays, can be performed to detect MG. It was reported that the presence of M-protein, discovered by SPEP or serum FLC, is associated with poor prognosis in patients with DLBCL.[26,27] Previously, IFE was regarded as being specific but not sensitive.[28] As a result, there is a possibility that we may potentially have missed some patients who have low-grade MG, which may partly explain the negative SIFE results before

treatment, which then subsequently became positive. Owing to the limited number of cases reported, further studies with a larger number of participants and longer follow-up are needed to clarify this observation. Finally, we conclude that MG, regardless of subtypes, could serve as a potential prognostic marker for DLBCL, and the molecular pathogenesis behind worth the effort to unveil it.

Author contributions

Conceptualization: Yian Zhang, Zheng Wei.
Data curation: Yian Zhang, Jing Li.
Formal analysis: Yian Zhang.
Funding acquisition: Zheng Wei, Peng Liu.
Investigation: Rupan Gao.
Methodology: Rupan Gao.
Writing – original draft: Yian Zhang.
Writing – review & editing: Zheng Wei, Peng Liu.

References

[1] Smith A, Howell D, Patmore R, et al. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. Br J Cancer 2011;105:1684–92.
[2] Morton LM, Wang SS, Devesa SS, et al. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood 2006;107:265–76.
[3] Fu K, Weisenburger DD, Choi WW, et al. Addition of rituximab to standard chemotherapy improves the survival of both the germinal center B-cell-like and non-germinal center B-cell-like subtypes of diffuse large B-cell lymphoma. J Clin Oncol 2008;26:4587–94.
[4] Hwang HS, Yoon DH, Suh C, et al. A new extranodal scoring system based on the prognostically relevant extranodal sites in diffuse large B-cell lymphoma, not otherwise specified treated with chemoimmunotherapy. Ann Hematol 2016;95:1249–58.
[5] Tomita N, Suzuki T, Miyashita K, et al. The SIL index is a simple and objective prognostic indicator in diffuse large B-cell lymphoma. Leuk Lymphoma 2016;57:2763–70.
[6] Ho CL, Lu CS, Chen JH, et al. Neutrophil/Lymphocyte Ratio, Lymphocyte/Monocyte Ratio, and Absolute Lymphocyte Count/Absolute Monocyte Count Prognostic Score in Diffuse Large B-Cell Lymphoma: Useful Prognostic Tools in the Rituximab Era. Medicine (Baltimore) 2015;94:e993.
[7] Seo JY, Hong J, Chun K, et al. Prognostic significance of PCR-based molecular staging in patients with diffuse large B-cell lymphoma treated with R-CHOP immunochemotherapy. Leuk Lymphoma 2017;58:357–65.
[8] Vaidya R, Witzig TE. Prognostic factors for diffuse large B-cell lymphoma in the R(X)CHOP era. Ann Oncol 2014;25:2124–33.
[9] Alper CA, Johnson AM. Immunofixation electrophoresis: a technique for the study of protein polymorphism. Vox Sang 1969;17:445–52.
[10] Economopoulos T, Papageorgiou S, Pappa V, et al. Monoclonal gammopathies in B-cell non-Hodgkin's lymphomas. Leuk Res 2003;27:505–8.
[11] Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004;103:275–82.
[12] de Jong D, Rosenwald A, Chhanabhai M, et al. Immunohistochemical prognostic markers in diffuse large B-cell lymphoma: validation of tissue microarray as a prerequisite for broad clinical applications–a study from the Lunenburg Lymphoma Biomarker Consortium. J Clin Oncol 2007;25:805–12.
[13] Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999;17:1244.
[14] Martin W, Abraham R, Shanafelt T, et al. Serum-free light chain-a new biomarker for patients with B-cell non-Hodgkin lymphoma and chronic lymphocytic leukemia. Transl Res 2007;149:231–5.
[15] Cox MC, Di Napoli A, Scarpino S, et al. Clinicopathologic characterization of diffuse-large-B-cell lymphoma with an associated serum monoclonal IgM component. PLoS One 2014;9:e93903.
[16] Kim YR, Kim SJ, Cheong JW, et al. Monoclonal and polyclonal gammopathy measured by serum free light chain and immunofixation subdivide the clinical outcomes of diffuse large B-cell lymphoma according to molecular classification. Ann Hematol 2014;93:1867–77.
[17] Landgren O, Kyle RA. Multiple myeloma, chronic lymphocytic leukaemia and associated precursor diseases. Br J Haematol 2007; 139:717–23.
[18] Vogt RF, Marti GE. Overview of monoclonal gammopathies of undetermined significance. Br J Haematol 2007;139:687–9.
[19] Voigtlaender M, Vogler B, Trepel M, et al. Hospital population screening reveals overrepresentation of CD5(-) monoclonal B-cell lymphocytosis and monoclonal gammopathy of undetermined significance of IgM type. Ann Hematol 2015;94:1559–65.
[20] Watanabe R, Tomita N, Itabashi M, et al. Peripheral blood absolute lymphocyte/monocyte ratio as a useful prognostic factor in diffuse large B-cell lymphoma in the rituximab era. Eur J Haematol 2014;92:204–10.
[21] Wang J, Gao K, Lei W, et al. Lymphocyte-to-monocyte ratio is associated with prognosis of diffuse large B-cell lymphoma: correlation with CD163 positive M2 type tumor-associated macrophages, not PD-1 positive tumor-infiltrating lymphocytes. Oncotarget 2017;8:5414–25.
[22] Kokcu A, Kurtoglu E, Celik H, et al. May the platelet to lymphocyte ratio be a prognostic factor for epithelial ovarian cancer? Asian Pac J Cancer Prev 2014;15:9781–4.
[23] Seo J, Kim WS, Kim JS, et al. Platelet to lymphocyte ratio (PLR) retains independent prognostic significance in advanced stage marginal zone lymphoma patients treated with rituximab, cyclophosphamide, vincristine, and prednisone combination chemotherapy (R-CVP): Consortium for Improving Survival of Lymphoma trial. Blood Res 2017;52:200–6.
[24] Akkaya E, Gul M, Ugur M. Platelet to lymphocyte ratio: a simple and valuable prognostic marker for acute coronary syndrome. Int J Cardiol 2014;177:597–8.
[25] Wang KF, Chang BY, Chen XQ, et al. A prognostic model based on pretreatment platelet lymphocyte ratio for stage IE/IIE upper aerodigestive tract extranodal NK/T cell lymphoma, nasal type. Med Oncol 2014;31:318.
[26] Hideaki Nitta , Yasuhito Terui , Masahiro Yokoyama , et al. The presence of M protein is strongly associated with very poor prognosis in patients with extranodal diffuse large B-cell lymphoma. Blood 2015;126:5638–68.
[27] Witzig TE, Maurer MJ, Stenson MJ, et al. Elevated serum monoclonal and polyclonal free light chains and interferon inducible protein-10 predicts inferior prognosis in untreated diffuse large B-cell lymphoma. Am J Hematol 2014;89:417–22.
[28] Alexanian R. Monoclonal gammopathy in lymphoma. Arch Intern Med 1975;135:62–6.