



# Prognostic impact of concordant and discordant bone marrow involvement on diffuse large B-cell lymphoma

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**Background:** In diffuse large B-cell lymphoma (DLBCL), bone marrow (BM) involvement includes two types that are concordant involvement and discordant involvement. It has been reported that concordant BM involvement has a worse prognosis than discordant involvement in previous studies. However, the prognostic effects of concordant or discordant BM involvement on DLBCL still need further research. In this work, DLBCL cases with BM involvement were collected and analyzed to better reflect the prognostic implications of concordant and discordant BM involvement.

**Methods:** We reviewed the cases with newly diagnosed DLBCL and BM involvement from April 2018 to April 2022 in Northern Jiangsu People's Hospital. Overall survival (OS) and progression-free survival (PFS) were assessed by the Kaplan-Meier method and compared between groups by the log-rank test. A multivariate regression analysis based on Cox proportional hazard model was used to test the independent effect of each variable on survival.

**Results:** In total, 32 patients were included and 15 (46.9%) patients had concordant BM involvement and 17 (53.1%) patients had discordant BM involvement. Compared with the discordant group, the concordant group tended to be older and had elevated lactate dehydrogenase level. The outcome of patients with concordant BM involvement was worse than the discordant subset, including OS (P=0.04) and PFS (P=0.03). Furthermore, the discordant BM involvement was excluded to acquire a BM-adjusted International Prognostic Index (IPI) score. The significance of BM-adjusted IPI scores to predict OS was improved greatly compared with the previous IPI scores (P=0.053 *vs.* P=0.16). Multivariate analysis showed that the BM-adjusted IPI was an independent predictor for OS [hazard ratio =3.406; 95% confidence interval (CI): 1.145–10.127; P=0.03].

**Conclusions:** These results highlight the requirement for identifying BM infiltration type accurately and then adjusting the IPI score by excluding discordant BM involvement since concordant involvement can partly predict a poor prognosis of DLBCL with BM involvement other than discordant involvement.

**Keywords:** Diffuse large B-cell lymphoma (DLBCL); concordant bone marrow involvement; discordant bone marrow involvement; prognosis; International Prognostic Index (IPI)

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## Introduction

Diffuse large B-cell lymphoma (DLBCL), an aggressive disease, is the most common subtype of non-Hodgkin's lymphoma and accounts for approximately 30% of all lymphomas (1). DLBCL is heterogeneous in prognosis though the combination of rituximab with standard cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy (R-CHOP) has dramatically improved its outcome (2). Various prognostic markers are introduced such as International Prognostic Index (IPI), gene expression profiling and tumor microenvironment (3). Thereinto, IPI, the typical one proposed firstly in 1993, remains a useful tool for risk stratification in DLBCL and consists of five parameters, which are age, performance status, stage, serum lactate dehydrogenase (LDH) level, and number of extranodal sites (4).

Bone marrow (BM) involvement in lymphoma is clinically recognized as a poor prognostic factor because it implicates stage IV and contributes to a higher IPI score. Approximately 11–17% of patients have BM involvement at initial diagnosis (5). Interestingly, BM involvement includes two types that are concordant BM involvement characterized by large B cells and discordant BM involvement infiltrated with small lymphoid cells (6–9). The mechanism for the discordant involvement remains unclear. It is speculated that the two distinct lymphomas are

independent, or alternatively DLBCL may be transformed from a small B-cell lymphoma.

Some studies have demonstrated that concordant BM involvement displays a worse outcome than the discordant (6–8). However, the clinical significance of concordant or discordant BM involvement still needs further research. In this retrospective study, we collected the DLBCL cases with BM involvement at initial diagnosis and analyzed the prognostic features to better reflect the prognostic effects of concordant and discordant BM involvement. We present this article in accordance with the STROBE reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-24-238/rc>).

## Methods

### *Patient population*

A total of 326 patients were newly diagnosed with DLBCL between April 1, 2018 and April 30, 2022 at the Northern Jiangsu People's Hospital, of whom 36 had BM involvement with an incidence of 11%. Of these, 32 patients (17 patients with discordant BM involvement and 15 patients with concordant involvement) were included in this study since they had complete clinical data for analysis. All patients met the following prerequisites: they were older than eighteen years of age, diagnosed as DLBCL based on biopsy according to the 2016 World Health Organization (WHO) criteria; their BM was involved confirmed by a pre-treatment BM biopsy. The patients were excluded if they had any of the following conditions: central nervous system involvement at diagnosis; primary cutaneous, mediastinal, breast, or testicular DLBCL; a past history of lymphoma; human immunodeficiency virus (HIV) infection; another uncontrolled malignancy. Disease staging was assessed by the Ann Arbor system. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Northern Jiangsu People's Hospital (No. 2023ky274) and the requirement for informed consent was waived because of the retrospective study.

### *Determination of BM involvement*

BM biopsies from DLBCL patients were centrally reviewed by two haematopathologists for the positive or negative BM involvement and discordant or concordant involvement. The criteria for identifying lymphomatous

### Highlight box

#### Key findings

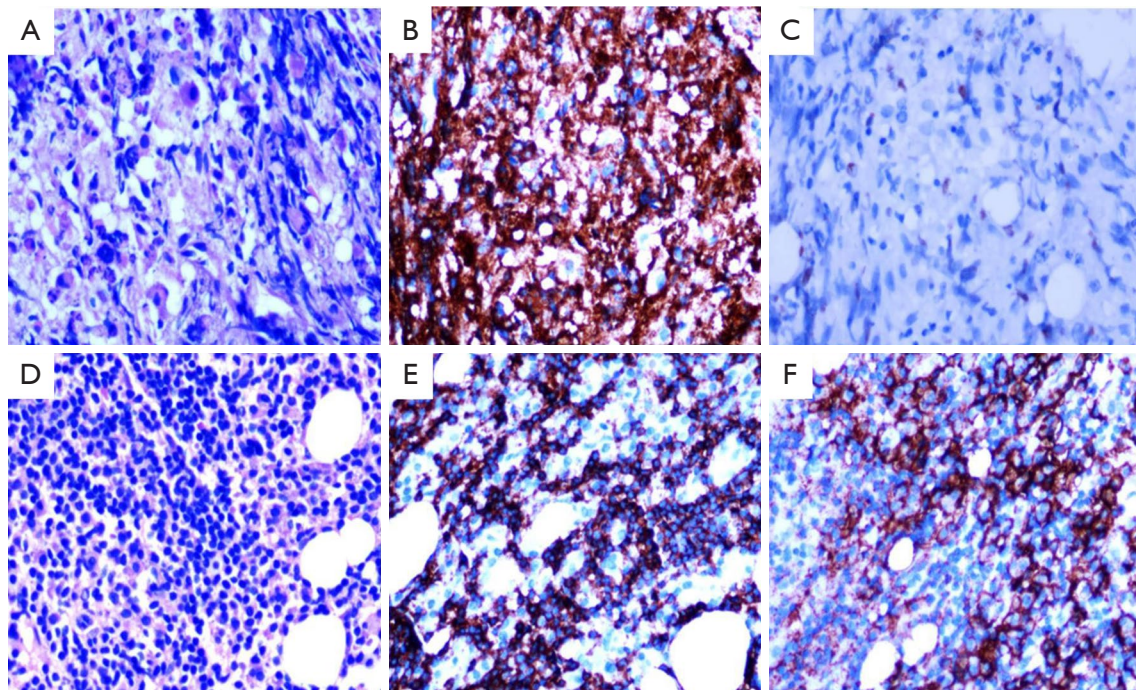
- Concordant bone marrow (BM) involvement predicts a poor prognosis of diffuse large B-cell lymphoma (DLBCL) with BM involvement. BM-adjusted International Prognostic Index (IPI) by excluding discordant BM involvement was an independent predictor for overall survival (OS).

#### What is known and what is new?

- BM involvement in DLBCL includes two types that are concordant involvement and discordant involvement. Concordant BM involvement has a worse prognosis than discordant involvement.
- The significance of BM-adjusted IPI scores by excluding discordant BM involvement to predict OS was improved greatly compared with the previous IPI scores. BM-adjusted IPI was an independent predictor for OS.

#### What is the implication, and what should change now?

- Concordant BM involvement predicts a poor prognosis of DLBCL and the IPI score should be adjusted by excluding discordant BM involvement.



**Figure 1** Images of bone marrow biopsies for diffuse large B-cell lymphoma with bone marrow involvement. One case for concordant involvement with hematoxylin and eosin staining (A), CD20 staining (B), and Ki-67 staining (C); one case for discordant involvement diagnosed as Waldenstrom's macroglobulinemia with hematoxylin and eosin staining (D), CD20 staining (E), and CD138 staining (F). Magnification for all images:  $\times 400$ .

involvement or benign lymphoid infiltration have been described in detail elsewhere (8). The type of BM involvement was distinguished through morphology and immunohistochemical staining. Concordant BM involvement was characterized by large DLBCL cells while discordant BM involvement was defined by small low-grade lymphoma cells in the involved BM area.

### Statistical analysis

Response was evaluated by the 2014 Lugano Classification lymphoma response criteria (10). Overall survival (OS) was defined as the time from initial diagnosis to the date of death (regardless of the cause) or last follow-up. Progression-free survival (PFS) was defined as the time from initial diagnosis to progression, relapse, or death due to any cause. The  $\chi^2$  test for categorical variables was utilized to compare clinical features between the two groups. OS and PFS were accessed by the Kaplan-Meier method and compared between groups by the log-rank test. Patients were censored if they were still alive when the last

contact. A multivariate regression analysis based on Cox proportional hazard model was used to test the independent effect of each variable on survival. Multivariable Cox regression analysis was performed for the variables with a univariate P value  $< 0.2$ . Data were analyzed using the SPSS software (V 22.0). A two-sided P value  $< 0.05$  was considered to be statistically significant.

## Results

### Patient characteristics

A total of 32 patients with DLBCL and BM involvement had complete data, of which 15 (46.9%) patients were with concordant involvement and 17 (53.1%) cases were with discordant involvement. Representative images of concordant and discordant BM biopsies are exhibited in *Figure 1*. According to the status of BM, clinical features for the two types are summarized in *Table 1*. The median age was 62.5 (range, 37 to 84) years in the entire cohort. There was no significant difference in all listed clinical characteristics, including sex, age, B symptoms, LDH

**Table 1** Clinical features in the concordant BM involvement and discordant BM involvement groups

Clinical features	Concordant BM involvement, n=15, n (%)	Discordant BM involvement, n=17, n (%)	$\chi^2$	P
Sex			0.473	0.49
Male	7 (46.7)	10 (58.8)		
Female	8 (53.3)	7 (41.2)		
Age (years)			3.689	0.055
≤60	3 (20.0)	9 (52.9)		
>60	12 (80.0)	8 (47.1)		
B symptoms			0.000	0.98
No	8 (53.3)	9 (52.9)		
Yes	7 (46.7)	8 (47.1)		
Extranodal sites, excluding BM			2.169	0.14
0–1	10 (66.7)	15 (88.2)		
≥2	5 (33.3)	2 (11.8)		
LDH			3.821	0.051
Normal	1 (6.7)	6 (35.3)		
Elevated	14 (93.3)	11 (64.7)		
ECOG score			0.098	0.76
0–1	7 (46.7)	7 (41.2)		
2–4	8 (53.3)	10 (58.8)		
IPI score			1.671	0.48
0–1	0 (0)	1 (5.9)		
2–3	6 (40.0)	9 (52.9)		
4–5	9 (60.0)	7 (41.2)		
COO			2.611	0.11
GCB	4 (26.7)	1 (5.9)		
Non-GCB	11 (73.3)	16 (94.1)		

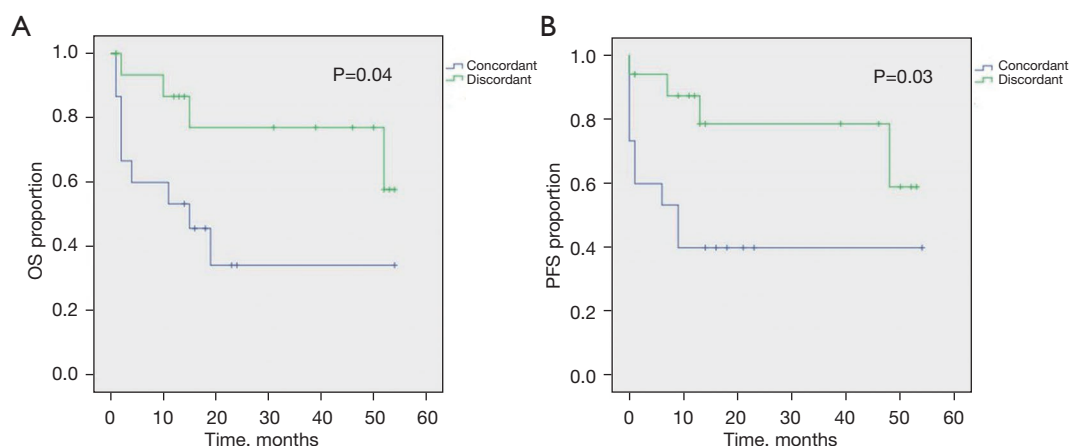
BM, bone marrow; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; COO, cell of origin; GCB, germinal center B cell.

level, extranodal sites (excluding BM involvement), Eastern Cooperative Oncology Group (ECOG) performance status, International Prognostic Index (IPI) score, and subtypes classified by the Hans algorithm between these two groups. Some variables, such as age, LDH, extranodal sites and IPI, had no statistical differences probably due to the small sample. However, patients with concordant BM involvement tended to be older (>60 years, 80.0%; mean, 61.8 years; range, 42–74 years) than those with discordant BM involvement (>60 years, 47.1%;  $P=0.055$ ). In addition,

elevated LDH levels were more often founded in the concordant BM involvement group than the discordant BM involvement group ( $P=0.051$ ).

#### *Prognostic significance of BM involvement*

The median follow-up was 31 (range, 1 to 55) months at the time of analysis. Thirteen (40.6%) patients had died of lymphoma, of which 4 patients (30.8%) were with discordant BM involvement and 9 cases (69.2%) were with



**Figure 2** Kaplan-Meier curves for OS (A) and PFS (B) comparing the concordant and discordant bone marrow involvement groups. OS, overall survival; PFS, progression-free survival.

concordant BM involvement. The mean survivals for the concordant group and discordant group were  $23.4 \pm 6.4$ ,  $43.5 \pm 5.2$  months, respectively. The median survival was  $15.0 \pm 7.6$  months for the patients with concordant BM involvement, while the median survival for the discordant subset was not reached during the follow-up. The OS for patients with concordant BM involvement was significantly worse than the patients with discordant BM involvement (OS,  $\chi^2=4.373$ ,  $P=0.04$ ; 1-year OS: 53% vs. 87%,  $P<0.001$ ) (Figure 2A). In regard to the PFS, the concordant subset had a likewise significantly worse outcome compared with the discordant subset (PFS,  $\chi^2=4.915$ ,  $P=0.03$ ) and 1-year PFS were 37% vs. 73% ( $P<0.001$ ) (Figure 2B).

Based on the clinical features of all patients with concordant or discordant BM involvement at diagnosis, the univariate analysis demonstrated that age  $>60$  years ( $P=0.02$ ) and concordant BM involvement ( $P=0.04$ ) had adverse effects on OS, whereas IPI score did not ( $P=0.16$ ). Considering that patients with BM involvement tended to have a higher IPI score due to the advanced stage and more involved extranodal sites, a BM-adjusted IPI score was constructed by excluding the discordant BM involvement to illustrate the prognostic impact of concordant BM involvement. Ann Arbor stage IV was recognized when patients had concordant BM involvement. For DLBCL cases with discordant BM involvement, BM involvement was excluded, and the stage was reevaluated based on the other involved sites. Additionally, the number of extranodal sites for patients with discordant BM involvement was reduced, as discordant BM involvement could not be considered an extranodal site. Consequently, the BM-adjusted IPI was

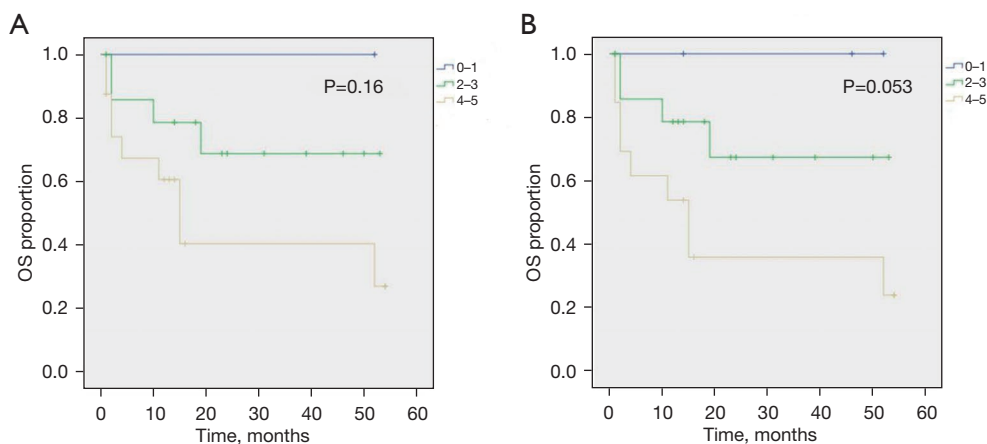
acquired to predict OS, with low [0–1], intermediate [2–3], and high [4–5] risk groups. The significance of the BM-adjusted IPI on OS was improved greatly compared with the previous IPI ( $P=0.053$  vs.  $P=0.16$ ) (Figure 3).

Multivariate analysis was carried out to clarify the independent prognostic significance of BM involvement types. A Cox model for OS was established incorporating the age, ECOG, BM-adjusted IPI score and BM status as covariates. Concordant BM involvement was not an independent predictor of OS based on this analysis, while the BM-adjusted IPI was an independent predictor [hazard ratio =3.406; 95% confidence interval (CI): 1.145–10.127;  $P=0.03$ ].

## Discussion

Nowadays, DLBCL is regarded as a potentially curable disease and approximately 60–70% of patients can be cured following immunochemotherapy with rituximab (11). It has been demonstrated that the subsequent overall survival of patients who acquire event-free survival at 24 months from diagnosis is similar to that of age-matched population. However, despite initial response, 30–40% of patients remain progressed or relapsed, which will dramatically shorten their lifespan and result in a poor outcome (12,13). Therefore, early identification of patients with poor prognoses is essential for exploring a more personalized treatment strategy as an alternative first-line approach.

Generally, BM involvement, contributing to a high IPI score through the increased extranodal sites and advanced stage, has been associated with a poor prognosis



**Figure 3** Kaplan-Meier survival curves for OS stratified by IPI scores (A) and bone marrow-adjusted IPI scores (B). OS, overall survival; IPI, International Prognostic Index.

in DLBCL and affects approximately 11–17% of cases at de novo diagnosis (5,14). In our hospital, the incidence of BM involvement was about 11%, consistent with references. Currently, BM biopsy and positron emission tomography with computed tomography (PET-CT) are widely performed to evaluate BM infiltration (15). PET-CT is a non-invasive imaging technique that has shown high sensitivity in detecting BM involvement in aggressive lymphomas (16). Nevertheless, some cases could be false positive in PET but negative by BM biopsy. Furthermore, BM involvement by PET-CT at DLBCL diagnosis has not survival implication, compared with BM biopsy (17). In lymphoma, BM biopsy is still recognized as the gold standard for BM involvement diagnosis (5). Therefore, BM biopsy was performed in all patients at diagnosis. Regrettably, several patients did not undergo PET-CT examination. Consequently, the correlation between PET-CT and BM biopsy could not be analyzed, nor the prognostic impact on DLBCL.

In prior studies, two types of BM infiltration were observed in patients diagnosed with DLBCL, namely discordant and concordant involvement. Although the concordant involvement appears to be associated with an unfavorable prognosis of patients with or without R-CHOP treatment (6-8), whether discordant or concordant infiltration influences the prognosis of DLBCL is still controversial. In this study, 32 patients with BM involvement were included and 46.9% of them were with concordant BM involvement, which was slightly inferior to previous reports (7-9). In the rituximab era, the outcome of DLBCL has been improved greatly, but the prognoses

of concordant and discordant BM involvement have not been altered (18). Retrospective analysis revealed that the concordant group still had a worse outcome, including OS and PFS, than the patients without BM involvement or with discordant BM involvement (7,8). In our study, the patients with concordant BM involvement tended to be older than the discordant subset, and they also had a poor OS and PFS. Because the aged is too frail to tolerate intensive chemotherapy, some novel targeted therapies should be considered. For elderly patients, polatuzumab, an antibody-drug conjugate, is recommended in frontline. The new pola-R-CHP regimen with polatuzumab replaced vincristine in R-CHOP demonstrated a 2-year PFS of 76.7%, better than standard R-CHOP (19). Additionally, a “chemo-free” treatment is an emerging approach for those unfit/frail patients, based on some small molecules and novel antibodies. The CD3×CD20 bispecific antibodies, such as mosunetuzumab and epcoritamab, showed encouraging efficacy as first-line treatment in the elderly with a manageable safety profile (20). Bruton tyrosine kinase inhibitors combined with rituximab and lenalidomide also showed encouraging efficacy and safety in newly diagnosed DLBCL elderly patients (21,22).

In previous studies, concordant BM involvement was indicated as a risk factor of OS independent of both the five IPI components and the IPI score (6,9), but the multivariate analysis in our study did not show the consistent result. A further study with enlarged sizes is still needed because of the limited cases enrolled. The IPI is a vital prognostic tool for aggressive non-Hodgkin’s lymphomas in recent several decades. The IPI, comprising age, performance

status, LDH, stage, and extranodal sites, stratifies four risk categories: low [0–1], low-intermediate [2], high-intermediate [3], and high [4–5] (23). In DLBCL, the patients assigned to the high risk group (score 4 or 5) only have a 5-year OS of 26% before the rituximab introduction (24). Given that the typical IPI remains a powerful prognostic indicator for predicting survival of patients with DLBCL, we analyzed the effects of IPI scores of on OS. Before adjustment, IPI score did not significantly correlate with OS according to the univariate analysis. Afterwards, IPI score was adjusted and recalculated in the patients with discordant BM involvement. Discordant BM involvement was excluded in the extranodal sites and Ann Arbor stage. The significance of the BM-adjusted IPI on OS was improved markedly compared with the previous IPI. These findings suggest that concordant BM involvement, rather than discordant BM involvement, impairs patient outcomes in DLBCL and the IPI scores should be adjusted by excluding discordant BM involvement.

## Conclusions

In summary, this retrospective study analyzed the significance of concordant and discordant BM involvement in patients diagnosed as DLBCL. Concordant BM involvement contributed to a worse outcome of DLBCL, including OS and PFS, than discordant BM involvement. These results highlight the requirement for identifying BM infiltration type accurately since concordant involvement can predict a poor prognosis of DLBCL with BM involvement to a certain extent. It is necessary to adjust the IPI score when it is discordant involvement and explore more targeted therapies for concordant involvement.

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## Footnote

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-24-238/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Northern Jiangsu People's Hospital (No. 2023ky274) and individual consent for this retrospective analysis was waived.

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