

A modified prognostic model in patients with diffuse large B-cell lymphoma treated with immunochemotherapy

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Abstract. In the era of immunochemotherapy, the traditional international prognostic index (IPI) has partially lost its predictive value in diffuse large B-cell lymphoma (DLBCL) and the National Comprehensive Cancer Network-IPI (NCCN-IPI) is unable to effectively identify high-risk patients. Thus, the present study aimed to develop a modified prognostic model (M-PM) to identify high-risk patients that require aggressive treatment. The present study included 169 patients with newly diagnosed DLBCL treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (RCHOP) or RCHOP-like regimens, between 2011-2017. The results demonstrated that the risk discrimination was improved in the NCCN-IPI compared with the IPI, and patients were divided into four risk groups with a 5-year overall survival rate of 93.8, 76.5, 54.3 and 39.4%, respectively. However, the NCCN-IPI failed to identify the high-risk DLBCL population. The newly developed M-PM presented here included four parameters: Age (≥ 65 years), an elevated lactate dehydrogenase level, Eastern Cooperative Oncology Group score ≥ 2 and total metabolic tumor volume ≥ 300 cm³. The M-PM also divided patients into four risk groups that comprised 40.8, 23.1, 26.0 and 10.1% of the patients, and the 5-year survival rates of these groups were 92.4, 70.6, 52.3 and 24.5%, respectively. Taken

together, the results of the present study demonstrated that the M-PM was more accurate compared with the IPI and the NCCN-IPI, which served as an effective tool for identifying patients with DLBCL at high risk of an adverse prognosis.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is one of the most common subtypes of Non-Hodgkin's lymphoma (NHL) in adults, accounting for ~30% of NHLs (1). DLBCL has significant heterogeneity in clinical manifestations, biological characteristics, and prognosis (2-4). Although >50% of patients with DLBCL may be cured by upfront chemoimmunotherapy (2), ~40-50% of patients relapse and/or the disease becomes refractory, and it is estimated that one third of patients will eventually die of the disease (5).

Given the notable heterogeneity within DLBCL, an accurate and reliable prediction tool is essential to optimize the treatment of patients. Since 1993, the international prognostic index (IPI) has become a major clinical predictive tool for the prognosis of patients with DLBCL (6). Based on the number of adverse prognostic factors, four independent risk groups were identified, and the 5-year overall survival (OS) rate was between 26-73% (6). However, as rituximab significantly improves the prognosis of patients with DLBCL, use of the IPI in identifying high-risk groups is questionable (7,8).

In 2014, Zhou *et al* (9) proposed the National Comprehensive Cancer Network (NCCN)-IPI based on IPI, which highlights the prognostic effects of age, lactate dehydrogenase (LDH) level and extranodal involvement site. Although previous studies have reported that the NCCN-IPI has better risk stratification than the IPI between low-risk and high-risk DLBCL (5-year OS, 96% vs. 33% for NCCN-IPI; 5-year OS 90% vs. 54% for IPI), NCCN-IPI fails to identify extremely high-risk populations (10-13). As was the case with its predecessor, the prognostic factors of NCCN-IPI mainly come from the clinical indicators of DLBCL (14). However, the model does not contain information obtained from standardized imaging techniques.

Positron Emission Tomography-Computed Tomography (PET/CT) has great value in the accurate staging, evaluation of efficacy, determination of prognosis and guidance for

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the subsequent treatment of malignant lymphoma (15-17). High fluorodeoxyglucose (FDG) uptake is a surrogate indicator of aggressive biological characteristics of malignant lymphoma (18). The total metabolic tumor volume (TMTV) assessed by PET/CT can be used as an index to measure tumor volume and invasiveness (18). Previous studies have demonstrated that TMTV has a greater prognostic value than Ann Arbor stage and can be used as a prognostic factor independent of IPI (19,20). High TMTV is associated with poor progression-free survival (PFS) (21). Analyses from the GOYA study revealed that higher TMTV is significantly associated with poor prognosis in patients independent of IPI (22). Notably, quantitative tumor imaging indicators, such as TMTV have the potential to replace traditional IPI factors that reflect tumor burden, such as extranodal diseases and Ann Arbor stage (19,20).

Thus, in the era of immunochemotherapy, the present study aimed to design a novel prognostic model of DLBCL composed of standardized imaging techniques and clinical parameters, and to assess its prognostic value in patients with DLBCL.

Patients and methods

Patients and data collection. This retrospective study included 169 patients treated at Tianjin Medical University Cancer Institute and Hospital between January 2011 and December 2017. The present study was approved by the Institutional Review Board of the Tianjin Medical University Cancer Institute and Hospital (Tianjin, China) and written informed consent was obtained from all the patients. The inclusion criteria were as follows: i) Age (>18 years), regardless of sex; ii) CD20 positive patients with DLBCL who had not received treatment in the past and iii) first-line treatment options were rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (RCHOP) or RCHOP-like regimens. Diagnosis of DLBCL was confirmed by Dr. Meng and Dr. Zhai from the Department of Pathology at The Tianjin Medical University Cancer Hospital (Tianjin, China). The immunohistochemical markers CD10, BCL-6 and multiple myeloma oncogene 1 were detected and patients were subsequently divided into germinal-center B-cell-like (GCB) or non-GCB subtypes, using Hans' algorithm (23). All patients were restaged according to the Lugano classification system (24). Bulky disease was defined as a measurable tumor mass ≥ 7.5 cm in diameter.

The IPI includes five risk factors: Age (>60 years), LDH above upper normal value, the involvement of extra-lymph node tissues or organs >1 , Eastern Cooperative Oncology Group (ECOG) score ≥ 2 and disease stage III/IV (6). According to the number of poor prognostic factors, IPI divided patients into four groups: Low-risk group, low-intermediate risk group, intermediate-high risk group and high-risk group. The NCCN-IPI relies on the same five poor prognostic indicators as the IPI, but the patient's age, elevated LDH levels and specific extranodal involvement are more heavily weighted (9). Patients were also divided into four groups by the NCCN-IPI (Table I).

PET imaging. All patients underwent FDG PET/CT scanning prior to chemotherapy. PET/CT studies were performed

according to protocols and manufacturer guidelines (25). A total of two experienced nuclear medicine experts calculated the quantitative parameters. The TMTV was obtained by summarizing the metabolic volume of all lymph nodes and extra-lymph node lesions. Bone marrow involvement was included in the volume measurement only in the presence of focal uptake. The spleen was involved if the focal or disseminated uptake was $>150\%$ of the liver background.

Statistical analysis. Statistical analysis was performed using SPSS 22 software (IBM Corp.). OS time refers to the time from random assignment to mortality for any reason (lost follow-up is the last follow-up time; patients who are still alive at the end of the study are the end date of follow-up) (26). PFS refers to the time from the start of randomization to the first tumor progression, relapse, mortality or last contact (26). The Kaplan-Meier method was used to calculate OS and PFS time, and the log-rank test was used to determine statistically significant differences between the two groups. Univariate and multivariate analyses were performed according to the Cox regression model to assess prognostic value. $P \leq 0.05$ was considered to indicate a statistically significant difference.

Results

Clinical characteristics of patients. The clinical characteristics of the 169 patients are presented in Table II. The patients' median follow-up time was 60 months. All patients received induction chemotherapy containing R-CHOP or RCHOP-like regimens, and 88.8 and 11.2% received RCHOP and R-mini-CHOP, respectively. A total of 49 patients (29.0%) were >65 years old and men have slightly more cases than women (53.3%). There were 25 patients (14.8%) with bulky disease (mass >7.5 cm). The involvement of bone marrow occurred in 23 cases (13.6%). A total of 52 patients (30.8%) were diagnosed at stage I-II, while the remaining 117 patients (69.2%) were diagnosed at stage III-IV. A total of 99 patients (58.6%) had elevated LDH levels, and 28 patients (16.6%) had an ECOG performance status ≥ 2 . Extranodal involvement was present in 43 patients (25.4%). According to the IPI, 56 patients (33.1%) and 35 patients (20.7%) had low or low-intermediate IPI scores, respectively, whereas 44 patients (26.1%) and 34 patients (20.1%) were categorized as intermediate-high or high risk, respectively. According to the NCCN-IPI, 42 cases (24.9%) were classified as low risk, 51 as low-intermediate risk, 48 as intermediate-high and 28 cases as high risk. Notably, fewer patients were classified as low risk by the NCCN-IPI compared with the traditional IPI.

TMTV. The median TMTV of the entire population was 291.4 cm^3 (50.3-1598.4 cm^3 ; Fig. 1). The receiver operating curve (ROC) analysis demonstrated that the best TMTV cut-off value for PFS and OS estimation was 300 cm^3 (data not shown). For PFS and OS, the area under the curve (AUC) values were 0.701 and 0.724, respectively (data not shown). The sensitivity and specificity of the 300 cm^3 cut-off for PFS were 75.1 and 67.3%, respectively, while the sensitivity and specificity for OS were 76.6 and 66.7%, respectively (data not shown).

The critical value of the ROC curve was used for Kaplan-Meier survival analysis. The results demonstrated

Table I. Characteristics and scoring of the different systems.

| Characteristic | IPI | Score | NCCN-IPI | Score | M-PM | Score |
|--|--------|-------|------------|-------|------|-------|
| Age, years | NA | 0 | >40 to ≤60 | 1 | NA | 0 |
| | >60 | 1 | >60 to ≤75 | 2 | ≥65 | 1 |
| | NA | 0 | >75 | 3 | NA | 0 |
| Ann Arbor stage | III-IV | 1 | III-IV | 1 | NA | 0 |
| LDH, normalized | >1 | 1 | >1 to ≤3 | 1 | >1 | 1 |
| | NA | 0 | >3 | 2 | NA | 0 |
| Extranodal disease | ≥2 | 1 | NA | 0 | NA | 0 |
| ^a Distinct extranodal disease | NA | 0 | Any | 1 | NA | 0 |
| Performance status | ≥2 | 1 | ≥2 | 1 | ≥2 | 1 |
| COO | NA | 0 | NA | 0 | NA | 0 |
| TMTV, cm ³ | NA | 0 | NA | 0 | ≥300 | 1 |
| Maximum score | NA | 5 | NA | 8 | NA | 4 |

^aExtranodal involvement of bone marrow, central nervous system, liver/gastrointestinal tract, or lung. IPI, international prognostic index; NCCN, National Comprehensive Cancer Network; M-PM, modified prognostic model; LDH, lactate dehydrogenase; COO, cell of origin; TMTV, total metabolic tumor volume; NA, not applicable.

that TMTV was a reliable predictor of OS at the univariable level (Table III). As presented in Fig. 2, the 5-year PFS rate of patients with high TMTV (≥300 cm³, n=94, 55.6%) was 38.3%, while that of patients with low TMTV (<300 cm³, n=75, 44.4%) was 72% (P<0.001). The 5-year OS rate of patients with high TMTV was 44.7%, while that of patients with low TMTV was 80% (P<0.001). In addition, significant differences were observed in OS between patients with TMTV values above and below 300 cm³ at the multivariate level [hazard ratio (HR), 4.21; 95% confidence interval (CI), 2.71-7.32; P<0.001; Table III].

Univariate and multivariate analyses. As presented in Table III, the following prognostic factors were assessed in the univariate and multivariable analyses: Age (<65 years vs. ≥65 years), disease stage (I-II vs. III-IV), ECOG performance status (0-1 vs. 2-4), B-symptoms (yes vs. no), LDH level (normal vs. elevated), the number of extranodal sites involved (0-1 vs. ≥2), cell of origin (GCB vs. Non-GCB), bulky disease (yes vs. no), bone marrow involvement (yes vs. no) and TMTV (≥300 cm³ vs. <300 cm³). Univariate analysis demonstrated that age ≥65 years (P<0.001), B-symptoms (P=0.019), elevated LDH levels (P<0.001), ECOG performance status 2-4 (P=0.011), advanced stage (P=0.015), number of extranodal sites >1 (P=0.013), bulky disease (P=0.033), bone marrow involvement (P=0.024) and TMTV ≥300 cm³ (P<0.001) were all associated with poor prognosis. However, multivariate analysis demonstrated that only age ≥65 years (HR, 2.14; 95% CI, 1.20-4.41; P=0.002), B-symptoms (HR, 2.24; 95% CI, 1.38-4.36; P=0.016), elevated serum LDH levels (HR, 4.21; 95% CI, 2.12-14.54; P<0.001), ECOG performance status 2-4 (HR, 3.32; 95% CI, 2.45-6.62; P=0.025) and TMTV ≥300 cm³ (HR, 4.21; 95% CI, 2.71-7.32; P<0.001) were considered independent prognostic factors.

Comparison of the M-PM with existing prognostic indexes. In the rituximab era, the M-PM model presented here combined metabolic parameters and clinical characteristics into a new

integrative prognostic factor (Table I). According to the number of IPI risk factors, patients were distributed into four different risk groups. However, the IPI failed to effectively differentiate between the intermediate-high group and the high-risk group. As presented in Fig. 3, the 5-year PFS rate of patients at high risk was 41.2% and the OS rate was 50.8%, whereas those at intermediate-high risk had a 5-year PFS rate of 52.3% and an OS rate of 60.4% (P=0.017 for PFS; P=0.028 for OS). The NCCN-IPI also divided patients into four different risk groups. Each group had significantly different 5-year OS and PFS rates, and the index had a better discriminative ability compared with IPI. According to the NCCN-IPI, the 5-year PFS rate of patients at intermediate-high risk was 45.8% and the 5-year OS rate was 54.3%, while the 5-year PFS rate of patients at high risk was 28.6% and the 5-year OS rate was 39.4% (P=0.004 for PFS; P=0.012 for OS) (Table IV and Fig. 3).

Patients were also divided into four different risk groups by the M-PM, namely the low risk, low-intermediate risk, intermediate-high risk and high risk groups. The groups had a median follow-up time of 61, 58, 59 and 60 months, respectively. As presented in Table IV, the 5-year PFS rates of the four groups were 81.2, 61.5, 43.2 and 23.5%, respectively, while the 5-year OS rates were 92.4, 70.6, 52.3 and 24.5%, respectively (P<0.001 for PFS and OS; Fig. 3). The M-PM identified a group with even worse outcomes, with a 5-year OS rate of only 24.5%, which neither the NCCN-IPI or the IPI identified. Thus, it was concluded that the predictive value of the M-PM was significantly stronger compared with the IPI and the NCCN-IPI for predicting high risk DLBCL (P<0.01). This high-risk group in the M-PM only represented a small number of patients (10.1%), which was lower than that identified by the NCCN-IPI (16.6%) and the IPI (20.1%) (Table IV).

Discussion

DLBCL is a disease with biological heterogeneity, which is reflected in the different curative effects and survival of

Table II. Clinical characteristics of patients (n=169).

| Characteristic | Number of patients, n (%) |
|------------------------|---------------------------|
| Age, years | |
| <65 | 120 (71.0) |
| ≥65 | 49 (29.0) |
| Sex | |
| Male | 90 (53.3) |
| Female | 79 (46.7) |
| Presence of B-symptoms | |
| No | 118 (69.8) |
| Yes | 51 (30.2) |
| Performance status | |
| 0-1 | 141 (83.4) |
| ≥2 | 28 (16.6) |
| Serum LDH | |
| Normal | 70 (41.4) |
| Elevated | 99 (58.6) |
| Stage | |
| I-II | 52 (30.8) |
| III-IV | 117 (69.2) |
| Extranodal involvement | |
| <2 | 126 (74.6) |
| ≥2 | 43 (25.4) |
| BM involvement | |
| Absent | 146 (86.4) |
| Present | 23 (13.6) |
| IPI | |
| Low, 0-1 | 56 (33.1) |
| Low-intermediate, 2 | 35 (20.7) |
| High-intermediate, 3 | 44 (26.1) |
| High, 4-5 | 34 (20.1) |
| Subtype | |
| GCB | 72 (42.6) |
| Non-GCB | 97 (57.4) |
| NCCN-IPI | |
| Low, 0-1 | 42 (24.9) |
| Low-intermediate, 2-3 | 51 (30.1) |
| High-intermediate, 4-5 | 48 (28.4) |
| High, ≥6 | 28 (16.6) |
| Therapy | |
| RCHOP | 150 (88.8) |
| RminiCHOP | 19 (11.2) |
| Bulky disease | |
| No | 144 (85.2) |
| Yes | 25 (14.8) |

ECOG; Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; BM, bone marrow; IPI, international prognostic index; GCB, germinal-center B-cell-like; NCCN, National Comprehensive Cancer Network; RCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

era, the cure rate of DLBCL has improved, and the value of IPI's prognostic risk stratification has weakened, particularly among intermediate-high risk and high-risk groups (8,27). In addition, NCCN-IPI and other prognostic evaluation systems cannot sufficiently distinguish high risk patients with a short survival time (28,29). Thus, it remains critical to develop a more accurate prognostic model for DLBCL.

Common prognostic indexes of lymphoma include age, ECOG score and increased LDH levels, which are associated with a short survival time in DLBCL (6). In the original IPI model, the age limit was set to 60 years, which represented the demarcation point for myeloablative therapy and stem cell transplantation at the time (30). Currently, this restriction is no longer in place (30). With the extensive application of growth factors and rituximab, an increasing number of elderly patients have received sufficient immunochemotherapy (30). Thus, in the novel prediction model presented here, the age limit was altered to 65 years. The results of the present study confirmed that age (≥65 years) is a key prognostic indicator. Notably, age (<65 years) is also commonly used as an age node for dose-intensified immunochemotherapy or hematopoietic stem cell transplantation in mantle cell lymphomas (30).

Disease stage is a crude substitute for total tumor burden, which is illustrated by bulky stage I disease vs. stage IV lesions, with extensive but small extranodal lesions (31). FDG-PET/CT uses quantitative indicators of metabolically active tissues, such as TMTV, as indicators of tumor volume (31). In previous studies, the prognosis of patients with DLBCL was often stratified based on interim PET-CT parameters, such as the Deauville score (32,33). The prognostic model presented here is based on baseline PET-CT parameters and clinical markers, and can predict the prognosis of patients earlier. The Maximum Standardized Uptake Value (SUVmax) is the most common metabolic parameter used in the clinic (34-37). However, measurement of SUVmax can only detect the most obvious metabolic activity of a tumor at a single site, and is unable to reflect the metabolic activity of the whole tumor, the size and volume of the tumor (34). Furthermore, several factors affect the accuracy of SUVmax, such as uptake interval, injection dose, injection leakage, tumor size and heterogeneity, blood sugar and hormone levels (34,35). Thus, the prognostic value of SUVmax in DLBCL remains controversial (36,37). TMTV and TLG reflect tumor volume and tumor activity (38). Our previous study demonstrated that TMTV is a more robust predictor of survival than TLG (39). Thus, TMTV was incorporated into the novel prognostic model presented here.

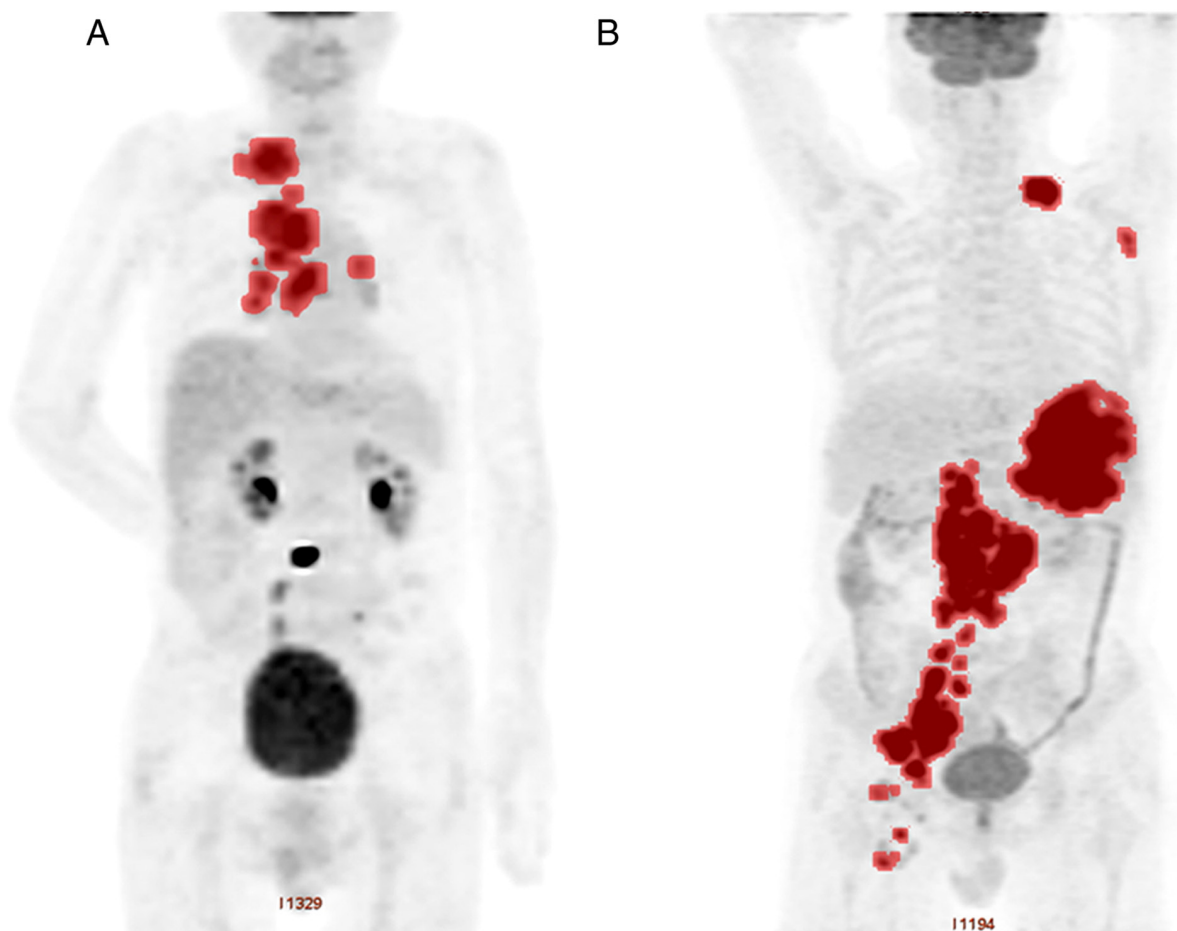
Previous studies have reported that TMTV has a strong predictive value for newly treated patients with DLBCL (40,41). Higher TMTV is significantly associated with worse PFS and OS in patients with DLBCL (19,20,42,43). Previous studies have also demonstrated that TMTV measured on 18F-FDG PET/CT can be used as an important index in determining the prognosis of DLBCL (19,43). However, there is still insufficient consensus on the calculation of TMTV. Currently, the two most common methods are based on the fixed threshold of SUV 2.5 (MTV 2.5) and the use of 41% SUVmax isocontour (MTV 41) (41,44). These methods are based on the principle of the fixed threshold to calculate the metabolism of local tumors (41,44). The European Association of Nuclear Medicine recommends a SUVmax threshold of 41%, which

patients (2-4). The IPI is the most recognized and widely used prognostic evaluation model in DLBCL (6). In the rituximab

Table III. Multivariate analysis of variables for overall survival.

| Variable (risk factor) | Univariate | | Multivariate | |
|--|------------------|---------|-------------------|---------|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age, years (65 vs. ≥ 65) | 3.32 (1.52-6.13) | <0.001 | 2.14 (1.20-4.41) | 0.002 |
| ^a B-symptoms, Yes vs. No | 1.54 (1.16-3.26) | 0.019 | 2.24 (1.38-4.36) | 0.016 |
| Cell of origin, GCB vs. Non-GCB | NS | | NS | |
| Serum LDH, normal vs. elevated | 3.29 (1.79-9.12) | <0.001 | 4.21 (2.12-14.54) | <0.001 |
| ECOG PS, 0-1 vs. 2-4 | 2.65 (2.16-5.72) | 0.011 | 3.32 (2.45-6.62) | 0.025 |
| Ann Arbor stage, I-II vs. III-IV | 3.11 (1.88-5.22) | 0.015 | NS | |
| Number of extranodal sites, 0-1 vs. ≥ 2 | 1.89 (1.16-5.51) | 0.013 | NS | |
| TMTV, cm ³ (≥ 300 vs. <300) | 3.13 (2.43-6.76) | <0.001 | 4.21 (2.71-7.32) | <0.001 |
| Bone marrow involvement, Yes vs. No | 2.37 (1.27-5.43) | 0.024 | NS | |
| ^b Bulky mass, Yes vs. No | 1.37 (1.19-4.21) | 0.033 | NS | |

^aB-symptoms were defined as night sweats, disease-related fevers, or weight loss $\geq 10\%$ of body weight. ^bTumor size of bulky mass was ≥ 7.5 cm. GCB, germinal-center B-cell-like; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; PS, performance status; TMTV, total metabolic tumor volume; HR, hazard ratio; CI, confidence interval; NS, no significance.

Figure 1. Patients with high and low TMTV. (A) TMTV was 213 cm³. (B) TMTV was 1,448 cm³. TMTV, total metabolic tumor volume.

has been used in patients with DLBCL with good interobserver repeatability (40). Given that the patients included in these studies had different ethnicities and research methods, different cut-off values were used (20,40,45). The results of

the present study demonstrated that TMTV ≥ 300 cm³ was significantly associated with poor prognosis.

High TMTV was significantly associated with advanced tumor stage and bulky disease (9,14,46). High TMTV often

Table IV. 5-year overall survival rates and distribution of patients in the risk groups using IPI, NCCN-IPI and M-PM scores.

| Risk level | IPI | | | NCCN-IPI | | | M-PM | | |
|-------------------|------------|---------------|--------------|------------|---------------|--------------|------------|---------------|--------------|
| | Score (%) | 5-year PFS, % | 5-year OS, % | Score (%) | 5-year PFS, % | 5-year OS, % | Score (%) | 5-year PFS, % | 5-year OS, % |
| Low | 0-1 (33.1) | 82.1 | 90.8 | 0-1 (24.9) | 83.3 | 93.8% | 0-1 (40.8) | 81.2 | 92.4 |
| Low-intermediate | 2 (20.7) | 71.4 | 78.4 | 2-3 (30.1) | 68.6 | 76.5% | 2 (23.1) | 61.5 | 70.6 |
| Intermediate-high | 3 (26.1) | 52.3 | 60.4 | 4-5 (28.4) | 45.8 | 54.3% | 3 (26.0) | 43.2 | 52.3 |
| High | 4-5 (20.1) | 41.2 | 50.8 | 6-8 (16.6) | 28.6 | 39.4% | 4 (10.1) | 23.5 | 24.5 |

IPI, international prognostic index; NCCN, National Comprehensive Cancer Network; M-PM, modified prognostic model; PFS, progression-free survival; OS, overall survival.

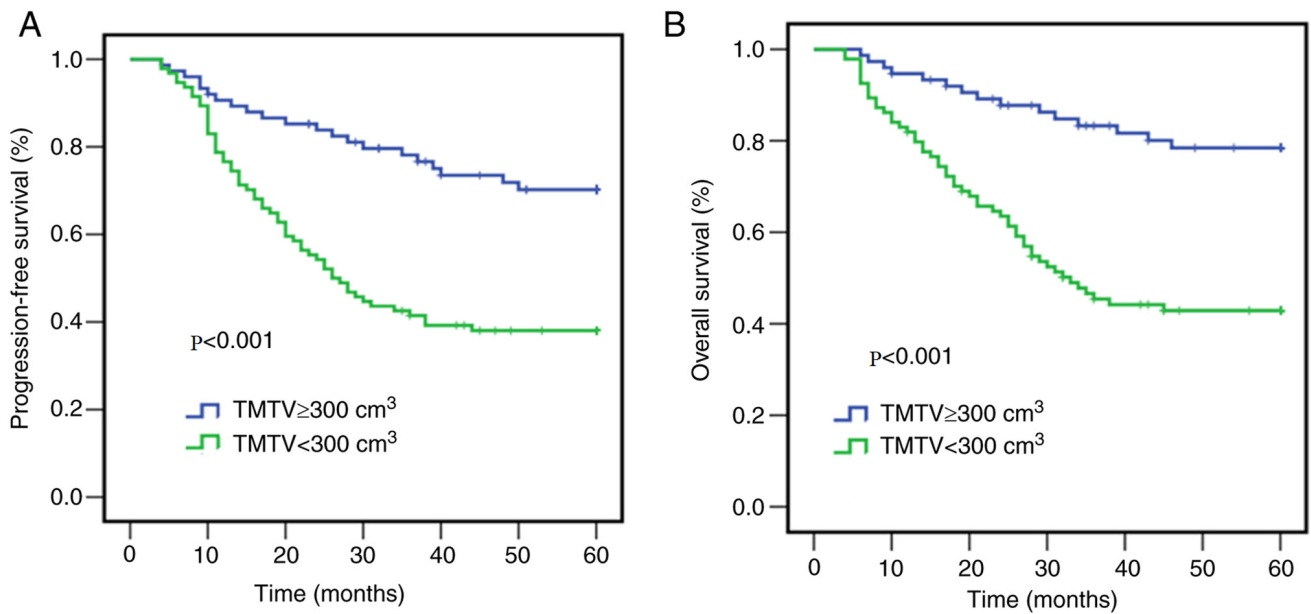


Figure 2. Kaplan-Meier analysis on (A) progression-free survival and (B) overall survival of patients based on TMTV. TMTV, total metabolic tumor volume.

represents a large tumor load and it may eventually replace the traditional IPI factors reflecting tumor load, such as extranodal diseases and Ann Arbor stage (9,14,46). Thus, it would be useful to add indicators associated with tumor metabolic characteristics to the current prognostic model in the form of quantitative PET indicators.

Some studies have included the functional parameters of PET into the prognostic evaluation model of DLBCL (32,47,48). However, most prognostic models are based on the results of interim PET-CT indicators (32,47). The present study predominantly used baseline TMTV and clinical indicators to predict the prognosis of DLBCL. To the best of our knowledge, the M-PM presented here is the first prognostic model to combine PET metabolic parameters and clinical characteristics in the rituximab era. According to the M-PM, there were 40.8, 33.1, 26.0 and 10.1% of patients with a low, low-intermediate, intermediate-high, and high risk, respectively.

Patients with low or intermediate risk can be cured by the RCHOP regimen (49); however, an unmet clinical requirement for patients at high risk remains. The M-PM can effectively

identify this group of exceedingly high-risk patients. Future clinical trials should aim to maximize disease control and survival in high risk patients and develop promising targeted drugs.

The present study was not without limitations. First, it was a single-center, retrospective study with a moderate sample size, so there may have been some statistical errors. Secondly, the calculation of TMTV is time-consuming and the current calculation method is not uniform. In addition, transplantation and CAR-T may also affect the overall survival of patients. In our studies, patients who relapsed or refractory did not receive CAR-T cell therapy and allogeneic hematopoietic stem cell transplantation. A total of four patients received autologous hematopoietic stem cell transplantation, of which two patients relapsed 2 years after transplantation. However, a small sample size will not affect the final outcome. In the context of modern treatment, the model presented here should be verified in prospective trials. Furthermore, the present study failed to predict time to next therapy using the novel model. Thus, further studies are required to confirm the results presented here.

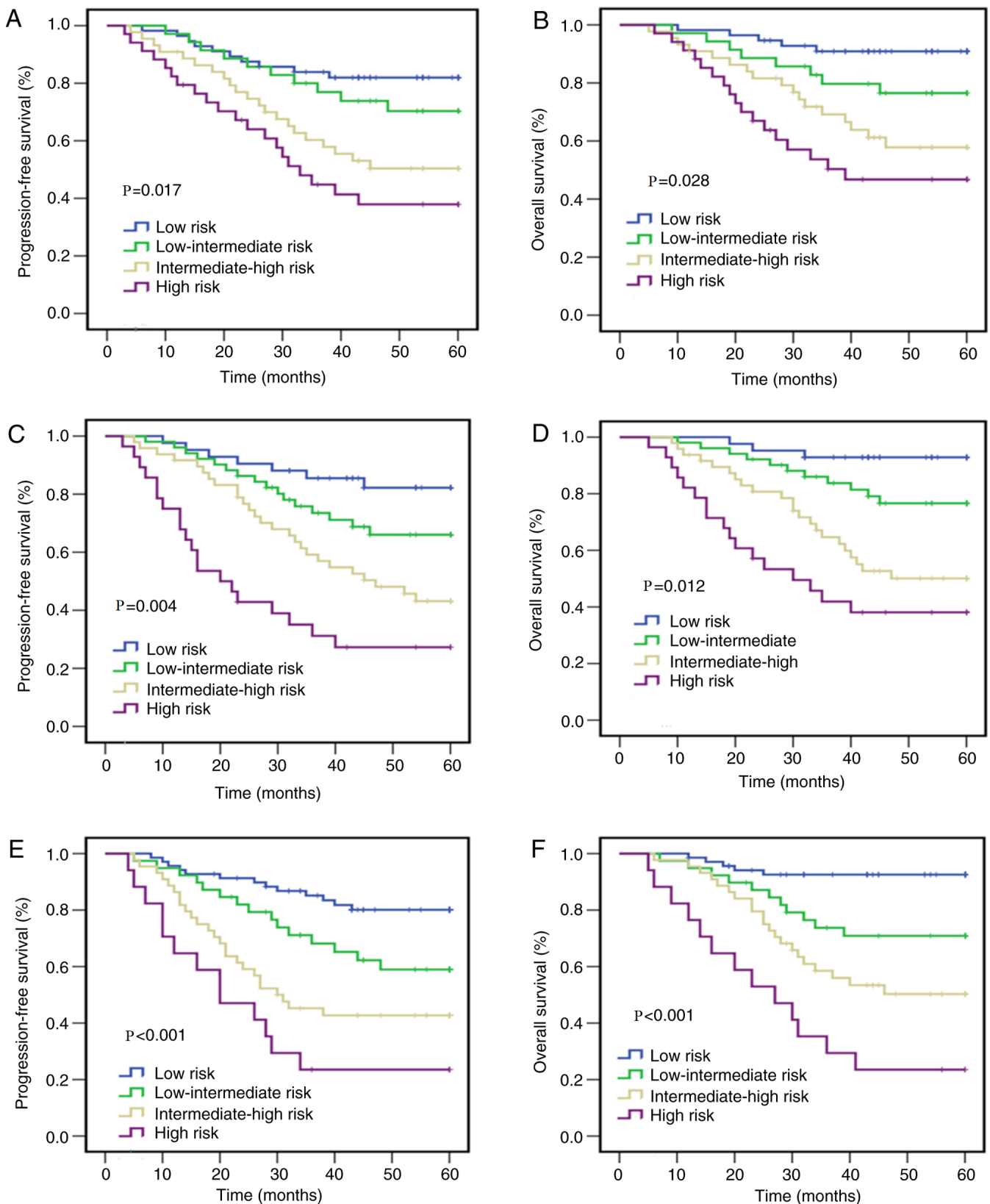


Figure 3. Kaplan-Meier analysis on progression-free survival and overall survival of patients with diffuse large B-cell lymphoma according to risk groups defined by the (A and B) IPI, (C and D) NCCN-IPI and (E and F) M-PM.

In conclusion, the present study proposed a novel modified prognostic model for newly diagnosed DLBCL, which consists of clinical parameters, biological parameters, and standardized imaging techniques. The results confirmed that in the

rituximab era, the predictive value of the M-PM is more accurate than that of the IPI and the NCCN-IPI, particularly in the high risk DLBCL group. Furthermore, the M-PM can identify the high-risk population with a 5-year OS rate <30%. Taken

together, these results suggest that M-PM may be applied to prospective clinical trials. The prognostic model presented here requires verification through large-scale and multi-center trials. In addition, whether M-PM will retain its strong risk stratification ability in the context of targeted treatment and novel biomarkers also warrants further investigation.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

HZ and WX designed the present study. PZ and LZ analyzed the experimental data and drafted the initial manuscript. LL, ZQ, LQ and SZ helped perform some experiments, obtained the data and revised the manuscript for important intellectual content. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of Tianjin Medical University Cancer Institute and Hospital (Tianjin, China). Written informed consent was obtained from all the patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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