



OPEN POD24-Based prognostic signature enables personalized risk stratification in mantle cell lymphoma

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Mantle cell lymphoma (MCL) exhibits significant biological and clinical heterogeneity, necessitating a refined prognostic model. According to the drawbacks of existing models which do not truly define the complexity of the disease, we used the clinical and molecular data from nine medical centers of China to validate the predictive utility of progression of disease within 24 months (POD24), and also established a novel prognostic risk model to predict the survival outcome of MCL patients. POD24 occurred in 37.7% of evaluable patients, with the median over survival being 21 months (vs. 122 months for those without POD24, $P < 0.0001$). The POD24-based risk model had the highest sensitivity to predict survival with the most satisfying AUC value for risk score (AUC = 0.869). In conclusion, we confirm the obviously predictive performance of POD24 and established a novel risk model combined POD24 and clinical factors. Our new prognostic model might be helpful in effectively classify MCL patients with high-risk groups in terms of survival rate, which may help in selecting high-risk MCL patients for more intensive treatment at time of relapse.

Keywords Mantle cell lymphoma, Progression of disease within 24 months, Prognostic, Clinical factor

Mantle cell lymphoma (MCL) is a unique subcategory of B cell malignancy disease accounting for 6–7% of non-Hodgkin lymphomas (NHL), which is characterized by the overexpression of the cell cycle regulatory protein cyclin D1^{1–3}. This lymphoma subtype is considered an incurable disease showing a generally aggressive, albeit heterogeneous and clinical course³. The prognosis of MCL after relapse is generally poor, and there is no standard of treatment guidance, with a median survival time of approximately 5 years². MCL is a disease of older individuals with the median age at diagnosis being 70 years, and is more common in male than female (male/female ratio, 3:1)⁴. Additionally, MCL has a heterogeneous clinical course, including a subgroup of patients with long survival in different treatment but without a striking unfavorable effect on their outcomes⁵. The majority of patients are diagnosed with widespread disease and are characterized by frequent recurrences⁶. Most of MCL patients respond to the current standard of care but often relapse or refractory due to drug resistance⁷. At time

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of relapse, no standard of treatment guidance exists and the prognosis after relapse is generally poor despite the increasing novel treatment options, such as BTK inhibitors⁸.

Well-established prognostic factors such as the MCL International Prognostic Index (MIPI) and the proliferative activity (Ki-67), classify MCL patients into different risk groups, but have not been useful in predicting the prognosis of identifying indolent disease patients^{9,10}. Other relevant factors such as karyotypic complexity, genetic aberrations and DNA methylation are well verified as independent prognostic factors for MCL outcome⁸. Moreover, in the era of newer therapies such as proteasome inhibitors, immunomodulatory drugs, tyrosine kinase inhibitors and Chimeric Antigen Receptor T (CAR-T) cells, the relevance of these prognostic factors is largely inefficient for the accurate definition of expected response and survival rates for relapsed or refractory (R/R) MCL patients^{8,11}. Therefore, there is an urgent necessity to develop innovative biomarkers for individual prognosis and risk stratification, enabling a precise estimation of survival outcomes.

POD within 2 years (POD24) of diagnosis has been identified as a robust predictor of poor survival in lymphoma disease, although the specific diagnosis or induction regimen administered is unknown^{12–14}. POD24 can assist in selecting second line treatments in relapsed patients, which defines high-risk groups of patients in whom further study is warranted in both directed prospective clinical trials of biology and treatment¹⁵. Likewise, the observation that patients with relapse over two years have prolonged survival expectation in the novel treatment era seems of great importance in the clinical management of MCL patients^{13,15}.

Due to its rarity and the great diversity in clinical behavior of MCL, it has been difficult to predict the prognosis and the heterogeneity of clinical of MCL¹⁶. The aim of this study was to describe the clinical features and clinical outcomes of MCL patients in China from nine cancer centers, while confirming the prognostic impact of progression of disease within 24 months (POD24) and highlighting the relevance of other clinical biomarkers in predicting the survival of MCL patients. More importantly, a first-ever prognostic model based on POD24 and clinical factors has been provided to stratify MCL patients into different survival outcomes, which might be helpful for allowing individualized, risk-adapted treatment decisions in patients with advanced stage of MCL.

Results

Clinical features and characteristics

Of 979 total patients with MCL, 369 patients were in POD \leq 24 months group and 610 patients in POD $>$ 24 months (Non-POD24) group. Clinical features and characteristics for different POD groups were shown in Table 1.

In the POD24 cohort, 283 (77%) were male. In POD 24 patients with quantifiable MIPI, 218 (66%) and 110 (34%) had low/intermediate and high-risk MIPI respectively. In the Non-POD24 cohort, 464 (76%) were male. In Non-POD24 patients with quantifiable MIPI, 482 (82%) and 103 (18%) had low/intermediate and high-risk MIPI respectively. POD24 patients were more likely to have B symptoms ($p=0.003$), elevated LDH ($p<0.0001$), splenomegaly ($p<0.0001$), Ki67 expression ($p<0.0001$), Anti-CD20 with induction ($p<0.0001$), novel agent with induction ($p=0.042$), post-induction rituximab maintenance ($p<0.0001$) and autologous transplant ($p=0.037$) and as expected, were more likely to have a worse performance status ($p=0.005$).

Patient outcomes

Follow-up time was available for all patients with a median follow-up of 31 months, with ranging from 1 to 210 months. The median PFS was 30 months (95% CI: 26.73–33.28, range: 1–194 months), and the median OS was 75 months (95%CI: 66.17–85.83, range: 1–210 months). The 5-year PFS and OS estimates for all patients were 30.5% and 56.1%, respectively (Fig. 1A and B).

RCS models showed an approximately linear association between month to disease progression and risk of death, while it became flat thereafter, with a point of inflection located around 24 months. The hazard ratio for death decreased rapidly with POD during the 24–36 months (Fig. 1C). Subsequently, the ROC curve analysis also confirmed POD24 presented a good performance in survival prediction with the highly reliable AUC being 0.797, and the AUC for POD12 was 0.754 (Fig. 1D). Thus, 24 months seemed a reasonable cut-off which showed the most significant prognostic effects in predicting OS.

Risk prognostic factors associated with overall survival in patients with MCL were presented in Fig. 2. There were significant differences in median OS between POD24 groups and Non-POD24 groups. The median OS for Non-POD24 patients (mOS: 122 months) was significantly longer compared with those of POD24 patients (mOS: 24 months) ($P<0.0001$, Fig. 2G). In the time-dependent Cox model, POD24 was associated with poor subsequent OS (HR = 2.345; 95% CI, 1.678–3.276; $P<0.001$). These data demonstrated that POD24 was significantly associated with inferior survival of MCL patients.

Univariate analysis and multivariate analysis

In a univariate analysis of all patients, sex, disease stage, extranodal sites and HBV infection were not associated with OS. The identified prognostic factors included age, ECOG performance status, LDH level, MIPI score, B symptoms, splenomegaly, Ki67 expression, ASCT, Anti-CD20 with induction, post-induction rituximab maintenance and POD24 (Table 2).

Variables factors included in the multivariate analysis were those clinically relevant or statistically significant in univariate analysis. Among these factors, age, LDH level, MIPI score, splenomegaly, Ki67 expression, ASCT and POD24 remained significant for OS in multivariate analysis (Table 2). These results indicated that those clinical factors and POD24 were significantly related with the prognosis of MCL patients.

Features	POD24 (n = 369)	Non-POD24(n = 610)	P- value
Age(y)			0.066
≥ 60	202	297	
< 60	167	313	
Sex			0.823
Male	283	464	
Female	86	146	
B symptom			0.003
Yes	132	167	
No	225	433	
LDH			0.000
Elevated	164	166	
Normal	188	428	
ECOG			0.005
≥ 2	276	73	
< 2	66	511	
Extranodal sites			0.171
≥ 2	66	89	
< 2	303	521	
HBsAg			0.96
Positive	38	62	
Negative	311	513	
Ann Arbor Stage			0.076
I or II	32	76	
III or IV	329	528	
MIPI scores			0.000
≥ 6	110	103	
< 6	218	482	
Splenomegaly			0.000
Yes	193	249	
No	163	349	
Ki67			0.000
≤ 30%	291	112	
> 30%	212	162	
NA	107	95	
Anti-CD20 with induction			0.000
Yes	460	229	
No	99	120	
Novel agent with induction			0.042
Yes	127	57	
No	472	301	
Post-induction rituximab maintenance			0.000
Yes	179	56	
No	421	306	
ASCT			0.037
Yes	68	26	
No	540	340	

Table 1. Clinical features of 979 patients with MCL according to POD24 status. MCL: Mantle cell lymphoma; POD24: Progression of disease within 24 months; LDH: Lactate dehydrogenase; ECOG: Eastern Cooperative Oncology Group; MIPI: Mantle cell lymphoma international prognostic index; NA: not available; ASCT: autologous stem cell transplantation; Novel agents: BTK inhibitors, lenalidomide or bortezomib.

Construction of the prognostic nomogram

In an exploratory analysis, we developed a nomogram to quantitatively evaluate the impact of progression of disease within 24 months (POD24) alongside other overall survival (OS)-related clinical factors within a predictive model for Mantle Cell Lymphoma (MCL) patient survival. Utilizing multivariate Cox regression

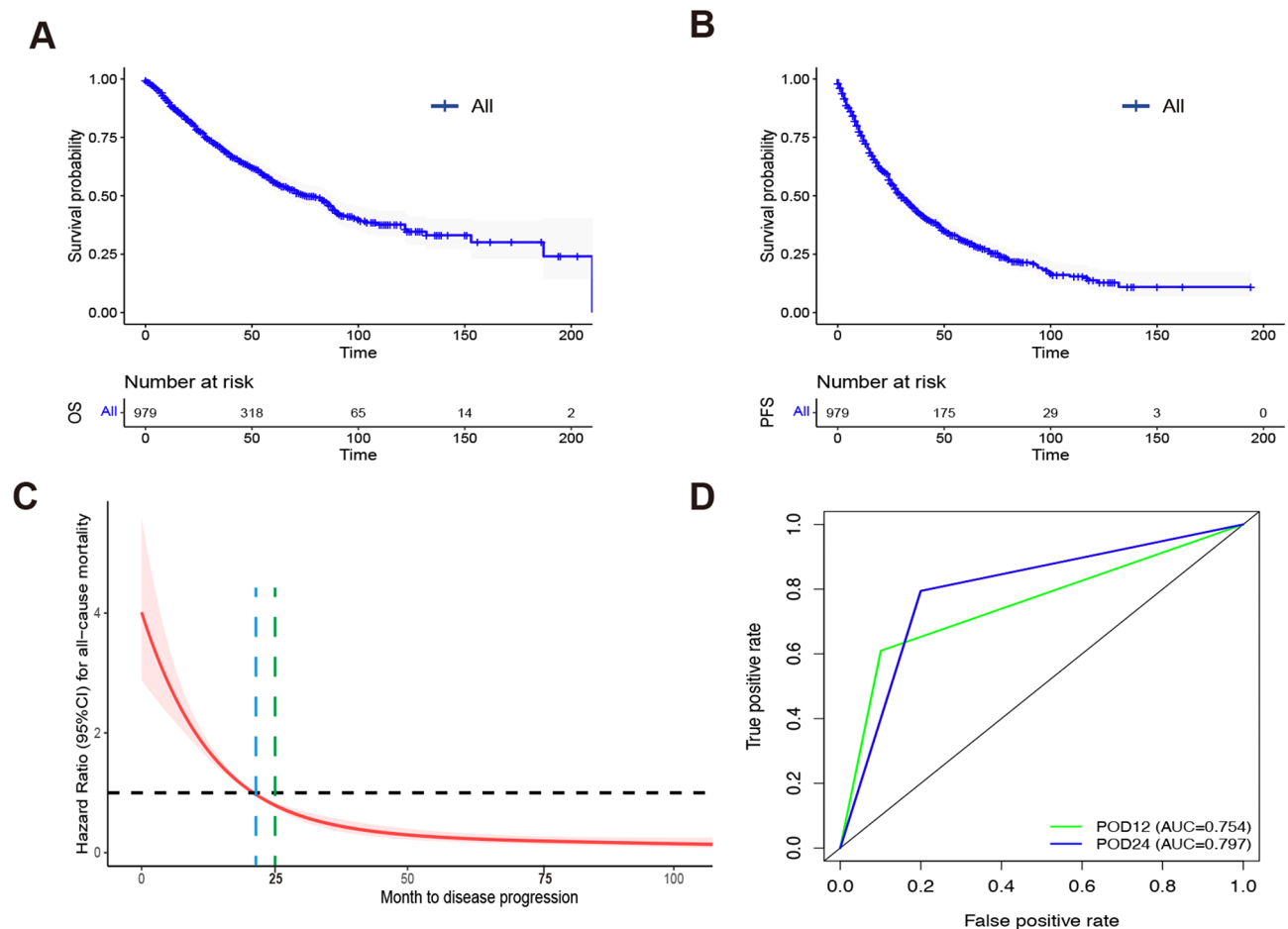


Fig. 1. Overview the survival outcome of all patients and confirm POD24 as a prognostic marker for outcome. Kaplan-Meier analysis of (A) overall survival and (B) progression-free survival of all patients with mantle cell lymphoma. (C) Spline curve showing the predicted hazard ratio of time to POD from start of frontline treatment as a prognostic marker. (D) Time-dependent receiver operating characteristic (ROC) curve for predicting 3-years survival of POD12 and POD24. POD24: Progression of disease within 24 months; POD12: Progression of disease within 12 months.

analysis, we allocated scores to each factor on the nomogram scale, ascertained the individual contribution of each variable, and computed the aggregate risk score for each patient, thereby enhancing the precision of survival prediction. The total score was normalized to a distribution ranging from 0 to 100 and used to calculate the 3- and 5-year estimated OS rates of MCL patients (Fig. 3A). Calibration curves of observed versus predicted probabilities of 3- and 5-year OS demonstrated excellent concordance between the predicted survival rate and the actual survival rate (Fig. 3B). Patients with higher score indicated a poor outcome and POD24 combined with clinical factors contributed most to the survival. These results suggested that the nomogram might reliably predict MCL patient prognoses in clinical practice.

Validation of the POD24 combined with clinical prognostic factors signature

To compare the predictive power of compound nomogram and POD24 or clinical risk factors separately, we then used multivariable ROC to compare the predictive accuracy between nomogram model and individual predictors. The AUC of the POD24 was 0.797 for predicting 3-year OS, which also showed a good predictive effect, but was significantly lower than the POD24-model (AUC 0.797 vs. 0.869, $p < 0.001$, Fig. 4A). Similar results were also observed in predicting 5-year survival (Fig. 4B). To sum up, although POD24 showed an obviously predictive performance, our POD24-clinical nomogram combining the POD24 and clinical risk factors demonstrated high prognostic predictive efficiency than their separation.

Discussion

MCL is a rare subtype of hematological malignant disease that comprised 2.5–6% of non-Hodgkin's lymphomas. The incidence of MCL has been increasing over the years, especially among elderly patients¹⁷. Moreover, the complexity of its clinical presentations, variety in disease pathophysiology and the high incidence of disease progression/recurrence pose a major challenge to developing personalized precise therapeutic strategy^{8,17}. Although various of chemotherapeutic regimens show significant activity in MCL patients, no regimen has

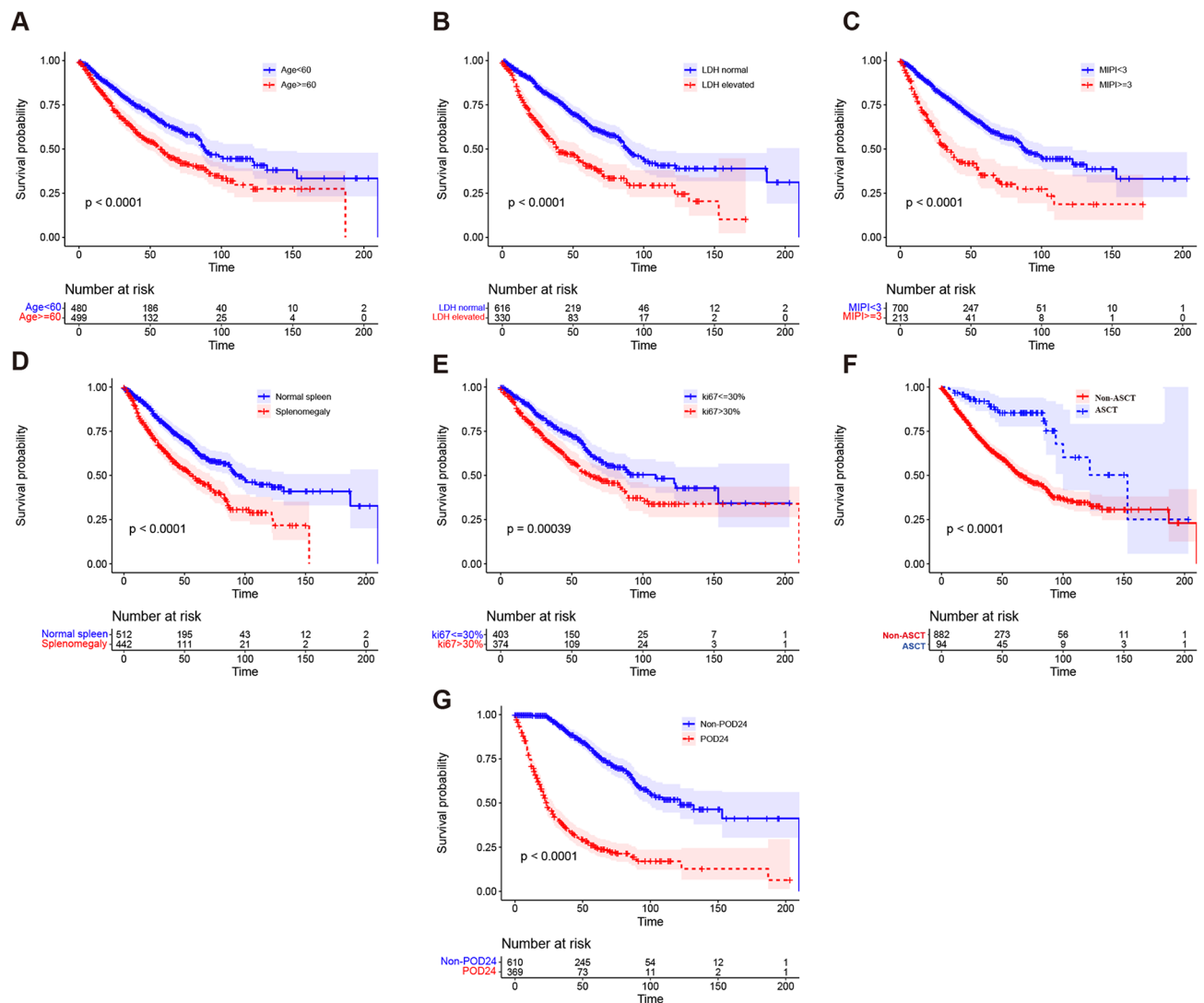


Fig. 2. Risk prognostic factors associated with overall survival in patients with MCL. Kaplan-Meier curves of OS for MCL patients according to (A) the age, (B) the LDH, and (C) the MIPI score, (D) the Splenomegaly, (E) the Ki67, (F) the MIPI score and (G) the POD24. MCL: Mantle cell lymphoma; POD24: Progression of disease within 24 months; LDH: Lactate dehydrogenase; MIPI: mantle cell lymphoma international prognostic index, Ki67: cell proliferation marker, POD24: Progression of disease within 24 months.

been found to be superior, and no standard treatment has been identified for^{4,18}. Over the years, the therapeutic options have been gradually evolving from combination chemotherapy to combination novel treatment options⁴. A number of targeted therapies are approved for R/R MCL patients in a surprisingly short time, including immunomodulatory agents, proteasome inhibitors and Bruton kinase inhibitors^{11,19,20}. Despite currently available therapies show significant activity in MCL patients, prognosis remains poor after progression on these novel agents²¹. Treating aggressive variants of this disease is a serious challenge for clinicians and researchers¹⁸. Therefore, there is an urgent need to identify new prognostic and risk-stratified biomarkers to distinguish MCL prognostic subsets and guide therapeutic decisions.

In this study, we summarized 979 cases of MCL from nine medical centers of China, which is the a largest retrospective study on MCL in China. The present study presents similar clinical outcome as those reported in previous reports^{13,15}. The proportion POD-24 patients with Low/intermediate MIPI were significantly lower (66% vs. 82%), and the POD-24 patients more likely to have a worse performance status. Also, POD24 could be used as a prognostic predictor of MCL patients, as has been proposed by previous works^{13,15}. Consistent with these results, our study demonstrated that the median OS for Non-POD24 patients was significantly longer than those of POD24 patients (122 months vs. 24 months), which demonstrates that POD24 was significantly associated with inferior survival of MCL patients. Additionally, there was nonlinear dose-response relationship between POD and survival outcome of MCL, with POD was highly prognostic with a cut-off around 24 months. POD24 was associated with markedly reduced OS with a hazard ratio (HR) of 5.373 (95% CI, 3.984-7.247) in multivariable cox regression analysis and POD24 was most powerful factor associated with an elevated risk of

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex	1.131	0.885–1.445	0.326			
Age (> 60 vs. ≤60 years)	1.638	1.333–2.012	0.000	1.340	1.002–1.790	0.048
ECOG (>= 2 vs. <2)	1.854	1.424–2.415	0.000	1.037	0.675–1.592	0.869
Stage (III/IV vs. I/II)	1.311	0.936–1.835	0.115			
LDH (Elevated vs. Normal)	2.132	1.733–2.624	0.000	1.407	1.033–1.917	0.030
Extranodal sites (>= 2 vs. <2)	0.995	0.750–1.320	0.973			
MIPI(>= 3 vs. <3)	2.412	1.919–3.031	0.000	1.581	1.063–2.355	0.024
B symptom (Yes vs. No)	1.639	1.325–2.028	0.000	1.194	0.884–1.614	0.248
HBsAg (Positive vs. Negative)	1.17	0.855–1.601	0.326			
Splenomegaly (Yes vs. No)	1.802	1.463–2.221	0.000	1.383	1.024–1.870	0.035
Ki67 (> 30% vs. ≤3%)	1.537	1.208–1.954	0.000	1.460	1.096–1.939	0.010
ASCT (Yes vs. No)	0.324	0.199–0.527	0.000	0.408	0.203–0.823	0.012
Anti-CD20 with induction (Yes vs. No)	0.535	0.429–0.667	0.000	0.908	0.672–1.228	0.531
Novel agent with induction (Yes vs. No)	0.977	0.732–1.304	0.876			
Post-induction rituximab maintenance (Yes vs. No)	0.533	0.402–0.707	0.000	0.743	0.503–1.097	0.135
POD24 (Yes vs. No)	5.966	4.785–7.439	0.000	5.373	3.984–7.247	0.000

Table 2. Factors associated with improved overall survival in MCL patients on univariate and multivariate analysis. MCL: Mantle cell lymphoma; POD24: Progression of disease within 24 months; LDH: Lactate dehydrogenase; ECOG: Eastern Cooperative Oncology Group; MIPI: Mantle cell lymphoma international prognostic index; ASCT: autologous stem cell transplantation; Novel agents: BTK inhibitors, lenalidomide or bortezomib.

death, more powerful than age, LDH level, MIPI score, splenomegaly, Ki67 expression and ASCT. These results indicated that POD24 was related to worse prognosis outcome for MCL patients.

MCL patient risk stratification and prognosis remain a challenge for clinicians. Mantle cell lymphoma international prognostic index (MIPI) score was established as the first prognostic stratification tool to identify clinical prognostic factors and patient with different risk groups²². The MIPI discriminated three groups of low, intermediate and high risk groups and has been validated by numerous studies^{10,22,23}. However, the MIPI was derived from patients with advanced stage disease primarily in the pre-rituximab era and therefore presumably does not represent the general patient population of a new era¹⁰. Several studies have demonstrated that Ki-67 proliferation index is a strong biologic prognostic factor independent of MIPI score^{24,25}. Thus, a combined biologic index (MIPI-b) that integrated MIPI and the Ki-67 proliferation index was developed and confirmed the prognostic value for patients with MCL¹⁰. MIPI-b model discriminates the high-risk group well, but a small low-risk group that overlapping with the intermediate-risk group in overall survival curves¹⁰. Therefore, MIPI-b does not adequately reflect the heterogeneity clinical outcome of MCL¹³. Similarly, our results also confirmed that MIPI and Ki67 do not show a promising performance in 3-years survival prediction with the AUC was 0.626 and 0.572, respectively. Therefore, new risk assessment strategies with relevant biomarkers are crucial for developing precision medicine.

Various of prognostic factors are markedly associated with survival outcome in MCL patients, including TP53 mutation, epigenetic profile variance, SOX11 gene expression profile and POD24^{4,11,26}. Several prognostic tools currently allow for risk stratification at diagnosis, but do not truly define the complexity of the heterogeneity of MCL disease^{12,13}. Our findings are consistent with some results of the previously studies from western countries, which have confirmed the impact of POD24 as a prognostic and predictive marker both at diagnosis and at time of relapse in the 2 prospective Nordic MCL trials¹³. Notably, by using a time-dependent Cox regression model, this study overcame the time-dependency bias commonly found in traditional survival analyses, offering a more precise evaluation of the dynamic impact of POD24. Furthermore, we constructed an encompassed prognostic nomogram combining POD24 with OS-related clinical factors. This nomogram (AUC=0.869) was superior to the POD24 single factor and other clinical factors. This model significantly improves prognostic accuracy and can be used to personalize patient survival outcomes, with potential for future clinical application.

Additionally, the level of healthcare resources and available treatments in China vary from one country/region to another^{27–29}. While some areas may have only basic access to oncology care, some highly urbanized areas may have world-class expertise and newer therapies, some areas may have only basic treatments after being diagnosed with MCL²⁷. Additionally, many Chinese patients commonly have different comorbidities, for example hepatitis B virus or tuberculosis infection. Although, our results did not found the clinically relevant or statistically significant of active hepatitis B virus infection in univariate analysis, chemotherapy may increase threat with hepatitis B virus reactivation and the spread of tuberculosis. Therefore, these should be considered as a serious consideration for the treatment of MCL patients in China²⁷.

While our study has several limitations including its limited quality of the captured data and a heterogeneous patient population, making it difficult to generalize the findings to a broader population. Second, treatment response was not centrally reviewed due to the retrospective design of this study. Third, genetic testing for

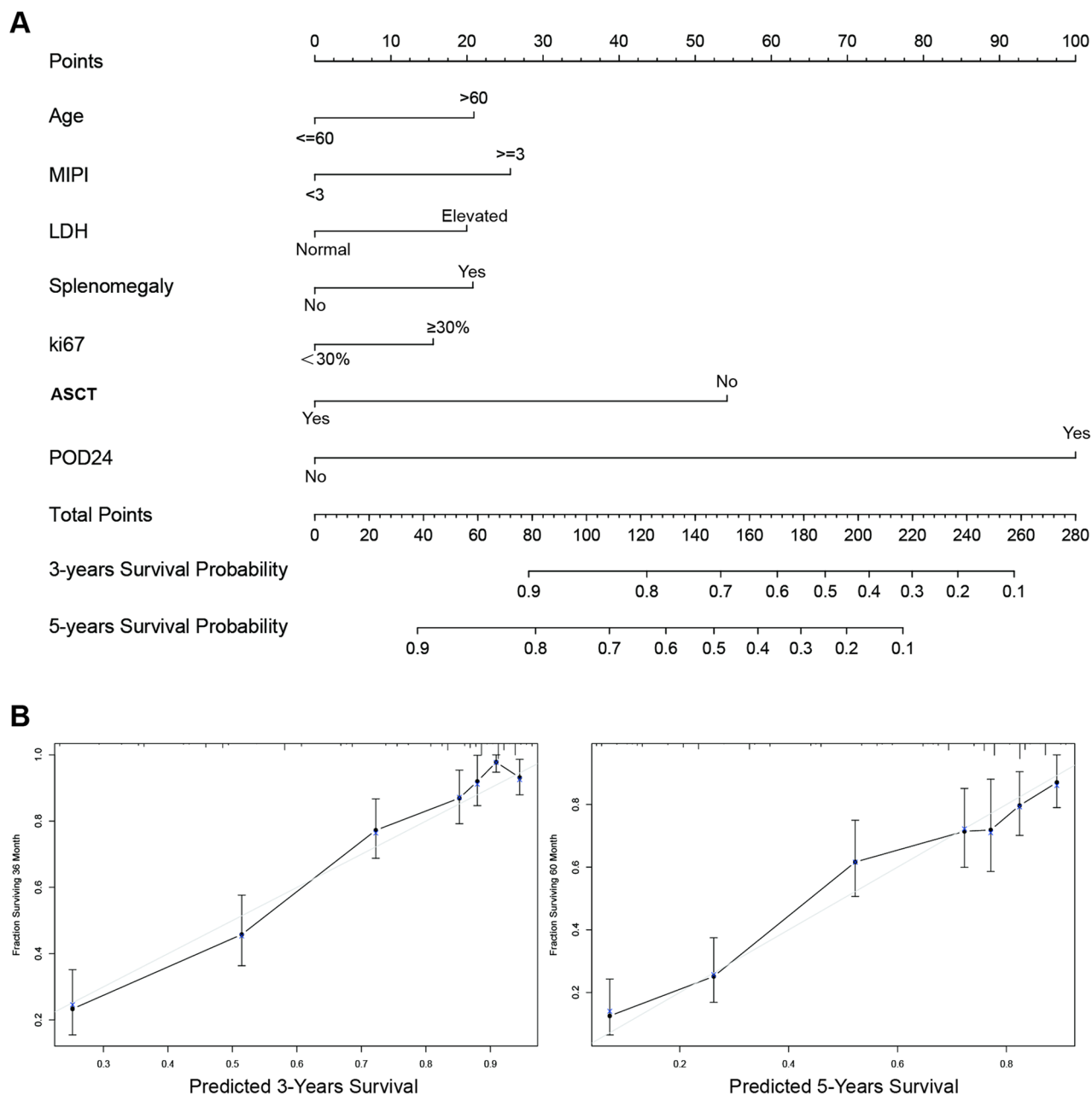


Fig. 3. A nomogram based on the POD24 combined with clinical factors signature. **(A)** Construction of a nomogram to forecast 3- and 5-years survival by the model. **(B)** The calibration chart shows that the predicted survival rate is consistent with the actual survival rate for 3-years and 5-years.

specific mutations or deletions, such as TP53, was not routinely performed in our clinical practice and therefore was not included in the data analysis. Lastly, it truly reflects a real-world experience in Chinese patients, further validation in different ethnic and geographical contexts is needed.

In summary, we confirm the prognostic impact of the POD24 and highlight the relevance of other known prognostic biomarkers in a retrospective analysis of a real-world cohort in Chinese patients, including a nomogram model of POD24-Clinical that was established. Our study is the first to identify and validate a POD24-based prognostic model with clinical factors in MCL patients, which could serve as a stratification tool to guide patient counseling, treatment decisions, and follow-up scheduling.

Methods

Patients

We conducted a retrospective cohort study of 979 patients diagnosed with MCL from nine medical centers of China between January 17, 2020 and February 1, 2020. All patients received at least one chemotherapeutic regimen of MCL. All patients had biopsy-proven MCL disease and were age 18 or older at time of evaluation at

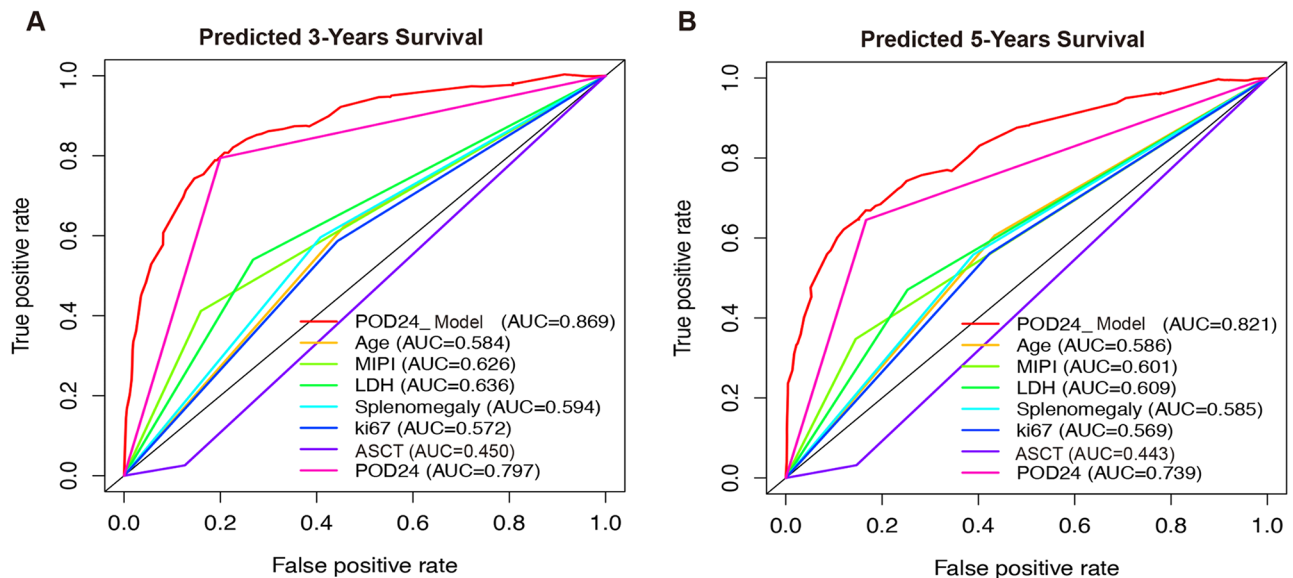


Fig. 4. Estimate the prognostic accuracy of the POD24 combined with clinical factors signature-based nomogram to predict 3- and 5-years survival in mantle cell lymphoma patients. Time-dependent receiver operating characteristic curve analysis for clinical risk factors only, the POD24, and POD24 combined with clinical risk factors for prediction 3- (A) and 5-years (B) survival of patients.

each center. The following data were collected: age, gender, ECOG performance status, stage of disease, serum LDH, extranodal disease, MIPI score, presence of B symptoms, splenomegaly, hepatitis B virus (HBV) infection, initial date of diagnosis, Ki67 expression and use of ASCT. Response to induction treatment was assessed by each participating center through clinical examination, standard biological parameters, computed tomography scan and, when available, bone marrow aspiration/biopsy and positron emission tomography scan. The outcomes were updated in August 2023. The study was approved by the institutional review board of The Affiliated Tumor Hospital of Xiangya Medical School. All procedures were carried out in accordance with the principles of the Helsinki Declaration. The requirement for written informed consent was waived for the retrospective data by institutional review board of The Affiliated Tumor Hospital of Xiangya Medical School.

Statistics

The primary objective of this work was to describe clinical characteristics and survival outcomes of disease progression in MCL patients with POD24 and 24 months after detection, and secondarily to assess prognostic and predictive biomarkers of survival across different groups. We reported differences in baseline characteristics, MIPI score, and prognostic markers between POD groups (≤ 24 and >24 months) using Fisher Exact and Chi-Square tests as appropriate. Individual risk factors were compared using the χ^2 test. Cox proportional hazards regression was used to estimate each hazard ratio (HR) and build the multivariate model. Cox regression analysis was performed, treating POD24 as a time-dependent covariate, to assess the relationship between POD24 and subsequent overall survival (OS).

Overall survival (OS) was calculated from the time of diagnosis to the date of last follow-up or date of death. Progression-free survival (PFS) was defined as the time from the date of diagnosis to either the date of first relapse or first sign of progression after initial treatment. The Kaplan-Meier test was used to analyze the OS and PFS of MCL patients and each subgroup was performed by using a log-rank test.

To evaluate the prognostic impact of POD24, restricted cubic spline (RCS) were applied to detect the possible nonlinear dependency of the relationship between time to POD and risk of death, using 4 knots at prespecified locations according to the percentiles of the distribution of POD.

The descriptive statistics were represented using the proportion and median. $P < 0.05$ was considered statistically significant. All Statistical analysis were performed using Statistical Package for the Social Sciences (SPSS) 17.0 software (Chicago, IL, USA).

Construction and validation of the prognostic nomogram

Univariate and multivariate analysis of conventional clinical risk factors and POD24 was performed to identify independent prognostic factor of OS in MCL patients. A prognostic nomogram encompassing POD24 and OS-related clinical factors was assessed by “rms” R package. Calibration curves and concordance index (C-index) were used to calculate the accuracy abilities of nomogram between predicted survival and actual survival. Time-dependent receptor operating characteristic (ROC) analysis was conducted by “survival ROC” R package to evaluate the predictive accuracy of the POD24-clinical prognostic model. The Delong test was used to evaluate the difference in AUC between the two different models.

Data availability

The datasets generated during the current study are available from the corresponding author on reasonable request.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical statements

According to ethical policies of the Affiliated Tumor Hospital of Xiangya Medical School Ethics Committee, clinical data can be analyzed and used under the precondition of without revealing the identity of patients.

Additional information

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