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Development and Validation of Novel Clinicopathological Risk Models for Mantle Cell Lymphoma in the Era of Modern Immunochemotherapy

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Abstract

Individuals diagnosed with mantle cell lymphoma (MCL) demonstrate substantial diversity in both their clinical manifestations and long-term prognosis. Nevertheless, the prognostic tools currently in widespread use are outdated and fail to meet the requirements of modern multidisciplinary care for this malignancy. The current investigation aims to characterize the clinical and pathological features of MCL in the context of immunochemotherapy and to develop enhanced prognostic tools that more reliably predict patient outcomes. The North American Mantle Cell Lymphoma Project constitutes a collaborative effort across 23 institutions in North America dedicated to assessing and optimizing prognostic factors for initial treatment. This analysis encompasses 586 cases of MCL diagnosed from 2000 to 2012. An extensive retrospective review examined clinicopathological characteristics, therapeutic interventions, and survival endpoints. Novel prognostic models were formulated following detailed evaluation of pretreatment variables and were subsequently tested for validity in a separate, independent group of MCL patients. In frontline treatment regimens, hematopoietic stem cell transplantation was the predominant determinant of clinical endpoints, exerting highly significant effects on both overall survival (OS, $P < 0.0001$) and progression-free survival (PFS, $P < 0.0001$). Among pathological markers, p53 expression emerged as the strongest predictor of unfavorable prognosis ($P < 0.0001$ for OS and $P = 0.0021$ for PFS). Using baseline risk profiles, we constructed several prognostic models that combine clinical, laboratory, and pathological features, each designed for a specific clinical context. These models demonstrated excellent discrimination in the independent validation set and produced risk groupings that closely mirrored those in the derivation cohort. Survival rates among patients with MCL have improved considerably during the last twenty years, and continued progress is expected as therapeutic approaches advance. The newly proposed prognostic models presented here represent a useful resource for tailoring treatment selection to individual patients with MCL.

Keywords: Immunochemotherapy, Mantle cell lymphoma, Clinical manifestations, Long-term prognosis, Pathological features

Introduction

Mantle cell lymphoma (MCL) represents 3–10% of all non-Hodgkin lymphomas and is a mature B-cell neoplasm distinguished by the presence of cyclin D1 rearrangement. The disease typically arises in lymph nodes and commonly extends to extranodal sites, with the majority of patients exhibiting advanced-stage illness upon initial presentation [1, 2]. MCL possesses distinctive biological properties; although frequently responsive to initial therapy, it is often refractory to subsequent therapies, and disease progression ultimately develops in most cases after standard treatment. In recent decades, the integration of immunochemotherapy, hematopoietic stem cell transplantation (HSCT), and

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targeted small-molecule agents has substantially enhanced patient outcomes [3]. Because of the marked heterogeneity in presentation and disease trajectory, multiple risk assessment systems have been proposed to forecast prognosis in MCL. The most frequently used instrument remains the Mantle Cell Lymphoma International Prognostic Index (MIPI) [4], along with its refined version, MIPI-c [5]. However, real-world application of this framework has uncovered important shortcomings, leading to variable performance in independent validation efforts [6].

First, the original MIPI was constructed during the pre-immunotherapy chemotherapy period. Although its relevance has been confirmed in immunochemotherapy-treated populations [7, 8], models derived from more recent patient series may achieve superior accuracy. Second, the MIPI relied entirely on clinical and laboratory data and did not incorporate histopathological information. Although MIPI-c includes the Ki-67 proliferation index, other pathological factors—especially p53 overexpression, which has been linked to worse survival—should be systematically evaluated. Integrative models that simultaneously consider major clinical, laboratory, and pathological features could therefore deliver more complete risk stratification. Third, the MIPI was designed to predict overall survival (OS). Yet, contemporary practice increasingly requires accurate anticipation of relapse after initial therapy, particularly as Bruton tyrosine kinase (BTK) inhibitors and chimeric antigen receptor T-cell (CAR-T) therapy gain prominence. A model centered on progression-free survival (PFS) would therefore be more useful for guiding therapeutic decisions.

The North American Mantle Cell Lymphoma Project (NAMCLP) was initiated to improve clinical care for patients with MCL. This study presents a comprehensive analysis of clinicopathological data from a large patient cohort. It introduces a new collection of prognostic models demonstrating high predictive strength, applicable across the entire population and within age-specific subgroups (< 65 years and ≥ 65 years).

Materials and Methods

Patients

The primary analysis included 586 patients with MCL diagnosed from January 2000 through December 2012, drawn from 23 collaborating centers across North America. A separate validation set consisted of 185 cases diagnosed between January 2000 and December 2017, sourced from the University of Nebraska Medical Center (UNMC), Roswell Park Comprehensive Cancer Center, and the University of Calgary. Inclusion required sufficient documentation of clinical presentation and therapeutic management. The protocol received ethical approval from the institutional review boards at each participating site. Comprehensive clinical data were collected for all patients, and histopathologic review was performed for those with accessible tissue samples.

Pathologic assessment

For the main cohort, three hematopathologists with extensive expertise jointly assessed histologic features, including architectural growth pattern, cytologic morphology, immunoglobulin light chain restriction (ILCR), and immunohistochemical markers such as CD5, CD23, Ki-67, and p53. Diffuse architecture was recorded only when it occupied the entire evaluated specimen—cytologic classification distinguished classical from blastoid or pleomorphic variants. Core needle biopsies were omitted from detailed morphologic categorization because of limited sampling. Uniform p53 immunohistochemistry (clone DO-7, Ventana, USA) was centralized at UNMC. The Ki-67 labeling index threshold was applied at 30% in accordance with established benchmarks [6, 9]. Evaluation of p53 followed a previously validated semi-quantitative approach [10]. Nuclear staining intensity (scored 0 for absent, 1 for weak, 2 for moderate, and 3 for strong) was multiplied by the fraction of positively stained tumor cells, and the products were aggregated to yield an overall score. Cases with a final score of ≥ 0.9 were classified as p53-positive.

Statistical methods

Performance of the MIPI and MIPI-c indices was assessed by constructing Kaplan–Meier estimates for overall survival (OS, time from diagnosis until death from any cause) and progression-free survival (PFS, time from diagnosis until relapse or death from any cause) across risk strata, with intergroup differences tested by the log-rank method. Potential predictors were initially screened through univariate Cox regression analyses for both OS and PFS. Backward elimination in multivariable Cox modeling was then used to select the optimal set of independent variables and derive the definitive model. Model assumptions were evaluated via scaled Schoenfeld residuals [11, 12]. Predictors that violated the

proportional hazards assumption or contained large amounts of missing data in the multivariable setting were removed. Risk categories were formed by partitioning the prognostic index scores generated from the final model. Optimal thresholds—two for the full cohort and one within each age stratum—were determined using the minimal P-value technique to achieve maximal separation by the log-rank test [13]. Multiple-comparison adjustments were made using the Bonferroni correction. Model stability was examined through internal validation of log-rank statistics and Harrell's concordance index employing Efron's refined bootstrap procedure [14]. All analyses were conducted using R statistical software, version 4.1.1.

Results and Discussion

Clinical, laboratory, and pathological characteristics

This patient series showed a male-to-female ratio of 3.6:1, and 89% of participants were of Caucasian ancestry. Median age at diagnosis was 64 years (range 24–104 years). Patients were stratified by age using a 65-year cutoff into younger (< 65 years) and older (≥ 65 years) subgroups. At the time of diagnosis, 93% had an ECOG performance status below 2, 24% exhibited B symptoms, 73% demonstrated extranodal disease, and 89% presented with stage III or IV involvement. Laboratory findings at baseline included leukocytosis in 22%, raised lactate dehydrogenase (LDH) levels in 40%, anemia in 35%, thrombocytopenia in 15%, and circulating tumor cells detected by flow cytometry in 39% of cases. Pathology review was performed centrally on 315 specimens. In this subset, a purely diffuse growth pattern was noted in 41% and blastoid/pleomorphic morphology in 17%. Expression of CD5 was detected in 90% of the reviewed cases, and CD23 in 13%. A p53 score of ≥ 0.9 was present in 28%, while 33% showed Ki-67 proliferation ≥ 30%. Complete baseline features are detailed in **Table 1**.

Table 1 Baseline clinical and treatment features in the analytic cohort of MCL patients (n = 586)

Characteristic	Value	N	%	Characteristic	Value	N	%
Age ≥ 65 years	354	578	61.2	Lymphocyte count (>5 × 10³/μL)	93	457	20.4
Male sex	455	581	78.3	Anemia	176	508	34.7
White/Caucasian ethnicity	452	507	89.2	Platelet count (≤100 k/μL)	78	510	15.3
ECOG performance status <2	502	538	93.3	Circulating tumor cells detected	134	345	38.8
Presence of B symptoms	131	538	24.3	Largest tumor diameter (≥3 cm)	230	444	51.8
Disease limited to lymph nodes	151	550	27.5	Blastoid/Pleomorphic morphology	38	222	17.1
Extranodal disease sites				Diffuse histologic growth pattern	91	223	40.8
Tonsil	37	395	9.4	CD5 positivity	252	279	90.3
Colon	72	490	14.7	CD23 positivity	25	186	13.4
Liver	22	490	4.5	Kappa light-chain restriction	59	139	42.4
Small intestine	50	490	10.2	p53 (≥0.9 points)	77	273	28.2
Spleen	134	490	27.3	Ki-67 (≥30%)	100	306	32.7
Stomach	24	490	4.9	SOX11 (≥10%)	181	202	89.6
Digestive tract	98	490	20.0	**Chemotherapy regimen**			
Single extranodal site only	29	527	5.5	Cytarabine-containing regimen	159	503	31.6
AAS stage III–IV	488	548	89.1	Anthracycline-containing regimen	244	503	48.5
Elevated LDH	179	453	39.5	Purine analog-containing regimen	69	503	13.7
Elevated Beta-MG	93	159	58.5	Other treatment regimens	31	503	6.2
Clonal Ig	23	105	21.9	Rituximab maintenance therapy	96	485	19.8
WBC count (>11 × 10³/μL)	116	523	22.0	HSCT	167	511	32.7
Neutrophil count (>10 × 10³/μL)	7	455	1.5	Autologous SCT vs. Allogeneic SCT	133/33	166	80.1/19.9

Note: AAS Ann Arbor stage; Beta-MG beta-2 microglobulin; LDH lactate dehydrogenase; SCT stem cell transplantation; WBC white blood cell

For the complete study population, five-year overall survival (OS) reached 64% (95% CI: 59–68) and progression-free survival (PFS) reached 37% (95% CI: 32–42). In the older patient group, these rates were 48% (95% CI: 42–55) for OS and 20% (95% CI: 15–27) for PFS. In the younger patient group, the rates were 78% (95% CI: 73–83) for OS and 51% (95% CI: 45–58) for PFS **(Figure 1)**. Treatment details were available for 551

patients, of whom 512 underwent active therapy, and 39 were followed with observation alone. The most frequently employed frontline chemotherapy regimens were R-CHOP (45%) and R-hyperCVAD (30%). Patients were classified into four chemotherapy categories: anthracycline-containing, cytarabine-containing, purine analog-containing, and other regimens.

In the overall analysis, cytarabine-based regimens were linked to significantly better survival than anthracycline-based regimens ($P = 0.0028$ for OS; $P < 0.0001$ for PFS). This apparent advantage was largely confounded by the fact that 53% of patients receiving cytarabine-based therapy also underwent hematopoietic stem cell transplantation (HSCT), compared with only 27% of those on other regimens. Once HSCT was accounted for, the OS benefit associated with cytarabine-based chemotherapy was eliminated **(Figure 2)**. Cytarabine-based treatment nevertheless continued to demonstrate value in postponing disease progression, especially when paired with HSCT, yielding clear gains in PFS. This effect was most evident in younger individuals, who typically withstand intensive approaches more effectively **(Figure 2)**.

HSCT was utilized in 33% of patients, including autologous stem cell transplantation (auto-SCT) in 80% and allogeneic stem cell transplantation (allo-SCT) in 20%. Across every analyzed population, HSCT represented the most powerful treatment variable influencing clinical endpoints (full cohort: $P < 0.0001$ for OS and PFS; older cohort: $P = 0.0005$ for OS and $P = 0.0018$ for PFS; younger cohort: $P = 0.0015$ for OS and $P = 0.0003$ for PFS). Similar strong effects were observed in the blastoid/pleomorphic subgroup ($P = 0.01$ for OS and $P = 0.0114$ for PFS). In patients whose tumors expressed p53, auto-SCT conferred markedly improved survival relative to no transplantation ($P = 0.008$ for OS and $P = 0.024$ for PFS); **(Figure 3)**. Rituximab maintenance, given to 20% of the cohort, correlated with better PFS and OS in the overall group and older patients, but offered no meaningful benefit in the younger group.

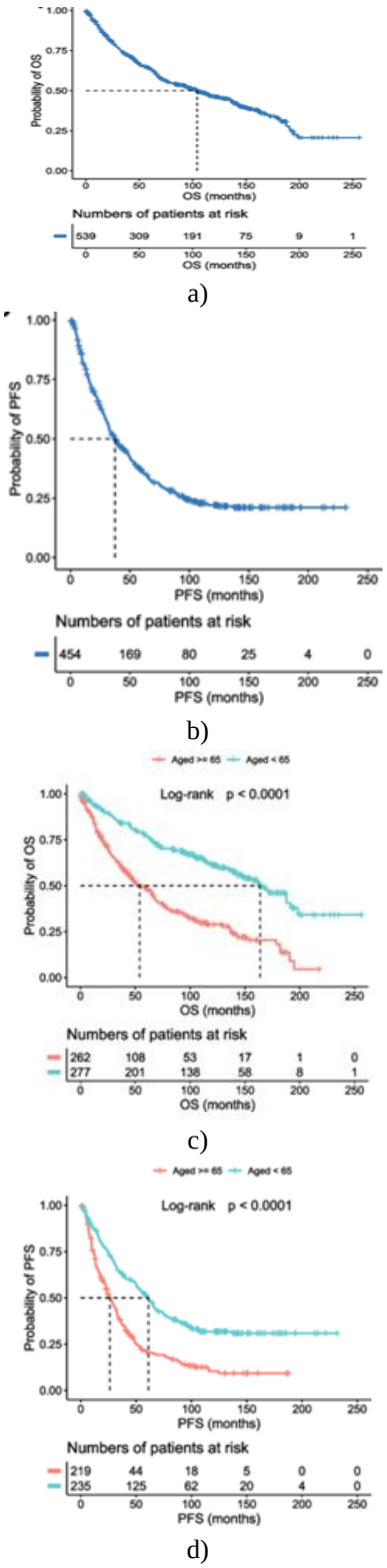
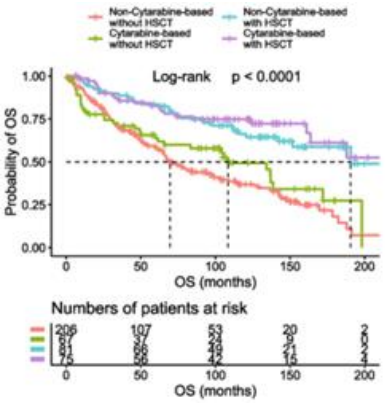


Figure 1. Survival curves for the analytic cohort. OS and PFS are illustrated for the full population (a and b) and according to age category (c and d).



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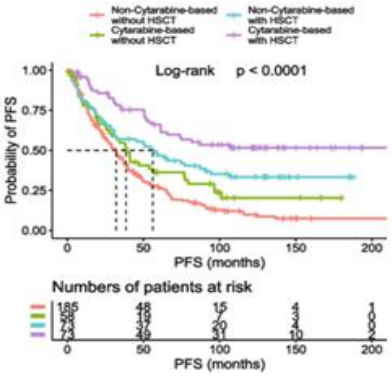

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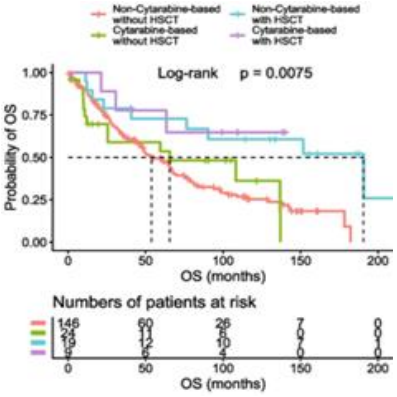

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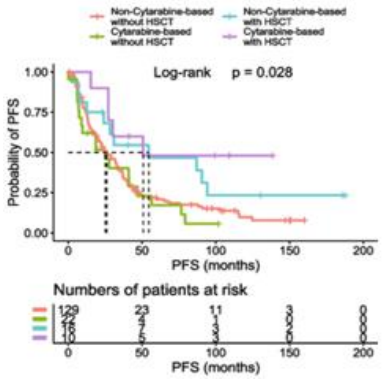

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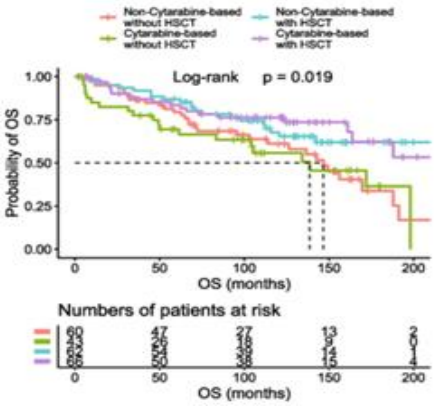

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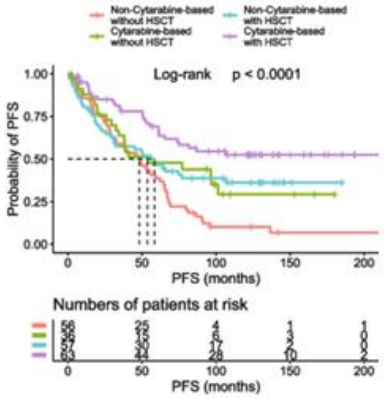

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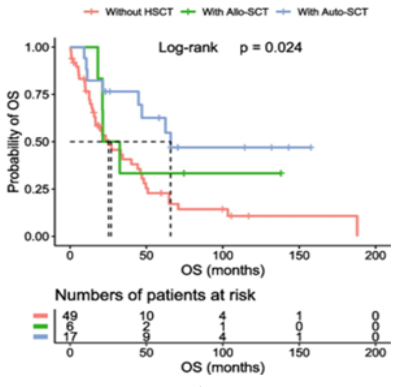
Figure 2. Influence of treatment approach on survival.

Four treatment groups were defined: cytarabine-based chemotherapy with or without HSCT, and non-cytarabine-based chemotherapy with or without HSCT. OS and PFS curves are shown for the entire cohort (a and b), older patients (c and d), and younger patients (e and f).



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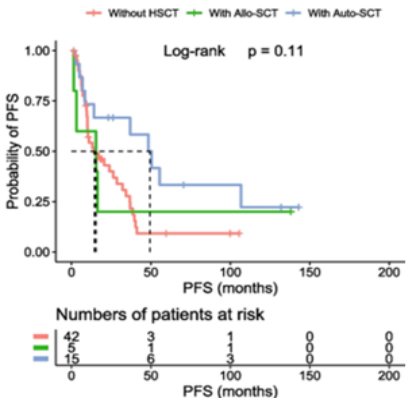

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Figure 3. Role of HSCT in patients showing p53 positivity. Comparison of OS (a) and PFS (b) among those receiving auto-SCT, allo-SCT, or no HSCT.

Univariate analysis of baseline characteristics

Key clinical and laboratory features most strongly tied to both OS and PFS in the full cohort included advancing age, ECOG performance status ≥ 2, B symptoms, and anemia. Additional adverse factors comprised splenic involvement, thrombocytopenia, circulating tumor cells, Ann Arbor stage ≥ III, elevated LDH levels, and multifocal disease. In contrast, colonic involvement was associated with favorable OS. Age-stratified evaluation indicated that ECOG status and anemia carried particular weight in older patients, while B symptoms were the leading predictor in younger patients. When treated as a continuous variable, age strongly predicted outcome in the overall and older cohorts but not in the younger cohort.

Virtually all pathological markers, except CD5, carried prognostic information, with p53 immunohistochemical positivity leading the way. In the entire cohort, p53 positivity, increased Ki-67 index, diffuse architectural pattern, and SOX11 positivity were significantly related to reduced OS and PFS. Immunoglobulin light chain restriction, histologic subtype, and CD23 expression showed associations limited to OS. In older patients, only diffuse growth pattern and p53 positivity maintained clear prognostic impact for both endpoints, with other features losing or weakening significance. In younger patients, p53 positivity, CD23 expression, Ki-67 index, SOX11 positivity, and morphologic variant retained importance for OS, yet no pathological parameter significantly predicted PFS.

MIPI and MIPI-c stratification

MIPI and MIPI-c scores could be calculated for 109 patients. Under MIPI classification, 11% were high risk, 52% intermediate risk, and 37% low risk. MIPI-c classification distributed patients as follows: 11% high risk, 29% high-intermediate risk, 27% low-intermediate risk, and 33% low risk. Both indices achieved highly significant risk separation ($P < 0.0001$) and performed best at isolating the low-risk category. Discrimination between intermediate- and high-risk groups was less pronounced. When applied to PFS, the stratification power of both MIPI and MIPI-c diminished considerably.

Multivariate analysis and prognostic regression model

Multivariable Cox regression was used to develop updated prognostic models for overall survival (OS) and progression-free survival (PFS). For OS, 203 cases with fully complete datasets satisfied inclusion criteria for model construction. In this group, p53 expression by immunohistochemistry represented the dominant independent predictor following backward stepwise selection, followed in importance by ECOG performance status, age (using a 60-year threshold that outperformed the conventional 65-year cutoff), B symptoms, and Ann Arbor stage. The resulting prognostic index is expressed as:

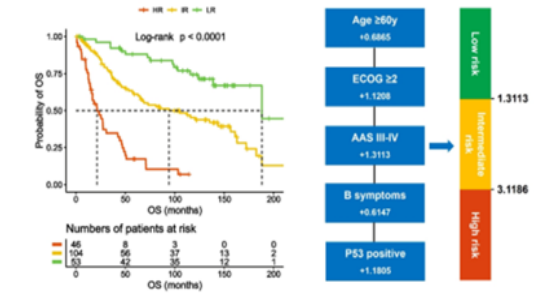
0.6865 (if age ≥ 60y) + 1.1208 (if ECOG ≥ 2) + 1.3113 (if AAS III-IV) + 0.6147 (if B symptoms present) + 1.1805 (if p53 positive).

Application of this index permitted division of patients into low-risk (26.1%, score ≤ 1.3113), intermediate-risk (51.2%, 1.3113 < score ≤ 3.1186), and high-risk (22.7%, score > 3.1186) categories, which exhibited clearly divergent OS curves ($p < 0.0001$), **(Figure 4a)**. External validation was performed in a distinct cohort of 185 patients, yielding survival distributions comparable to the derivation set. Notably, management in the validation group better represented modern standards, including bendamustine in 41% and BTK inhibitors in 23% of cases. Despite these variations in therapy, the model produced highly reproducible risk group proportions (25.9% low-risk, 51.9% intermediate-risk, and 22.2% high-risk) and consistent separation of outcomes **(Figure 4b)**.

For PFS, 193 cases provided sufficient data for modeling. Backward selection retained B symptoms, p53 positivity, platelet count (≤ 100 k/μL), Ann Arbor stage, and age. The corresponding index was computed as:

0.2782 (if age ≥ 60y) + 0.7561 (if AAS III-IV) + 0.6148 (if B symptoms present) + 0.7916 (if platelets ≤ 100 k/μL) + 0.6409 (if p53 positive).

This formula stratified patients into low-risk (25.4%, score ≤ 0.7561), intermediate-risk (62.2%, 0.7561 < score ≤ 2.0118), and high-risk (12.4%, score > 2.0118) groups with statistically significant differences in PFS (P < 0.0001), **(Figure 4c)**. The model retained excellent discriminatory capacity and closely replicated risk distributions in the validation cohort (24.7% low-risk, 62.9% intermediate-risk, and 12.4% high-risk), **(Figure 4d)**.



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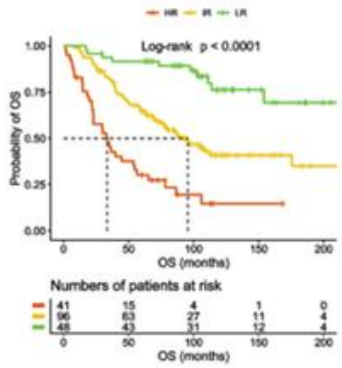

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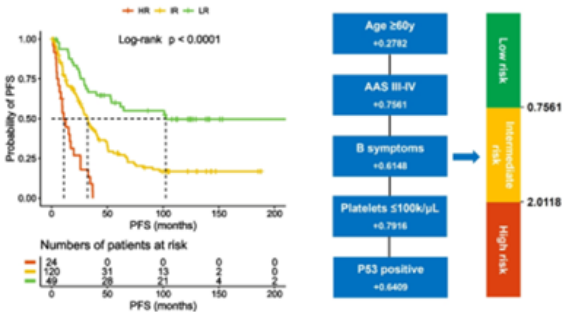

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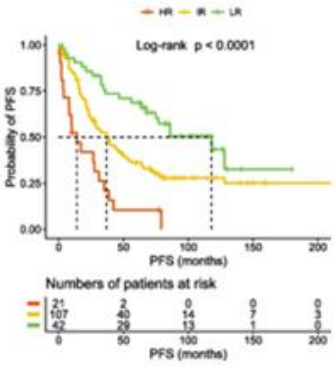
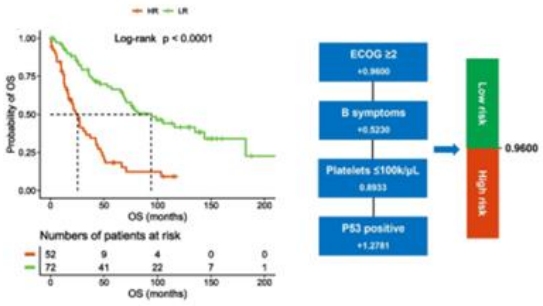


d)

Figure 4. Construction of novel comprehensive prognostic models. OS model derivation in the training cohort (a) and performance in validation (b). PFS model derivation in the training cohort (c) and performance in validation (d).

Although age is retained as a component in these models, similar to established indices, current clinical practice and trial designs frequently employ age-based stratification. To accommodate this trend, separate prognostic tools were created for patients aged ≥ 65 years and < 65 years, applying the same analytic framework. In the older group (≥ 65 years), the index was defined as: 0.9600 (if ECOG ≥ 2) + 0.5230 (if B symptoms present) + 0.8933 (if platelets ≤ 100 k/μL) + 1.2781 (if p53 positive), with low-risk assigned to scores ≤ 0.9600 (58.1% training, 60.3% validation) and high-risk to scores > 0.9600 (41.9% training, 39.7% validation) **(Figures 5a and 5b)**. In the younger group (< 65y), the index was:

0.6190 (if WBC > 11 k/μL) + 0.9356 (if B symptoms present) + 1.3314 (if p53 positive), with low-risk assigned to scores ≤ 0.6190 (61.5% training, 60.4% validation) and high-risk to scores > 0.6190 (38.5% training, 39.6% validation) **(Figures 5c and 5d)**.



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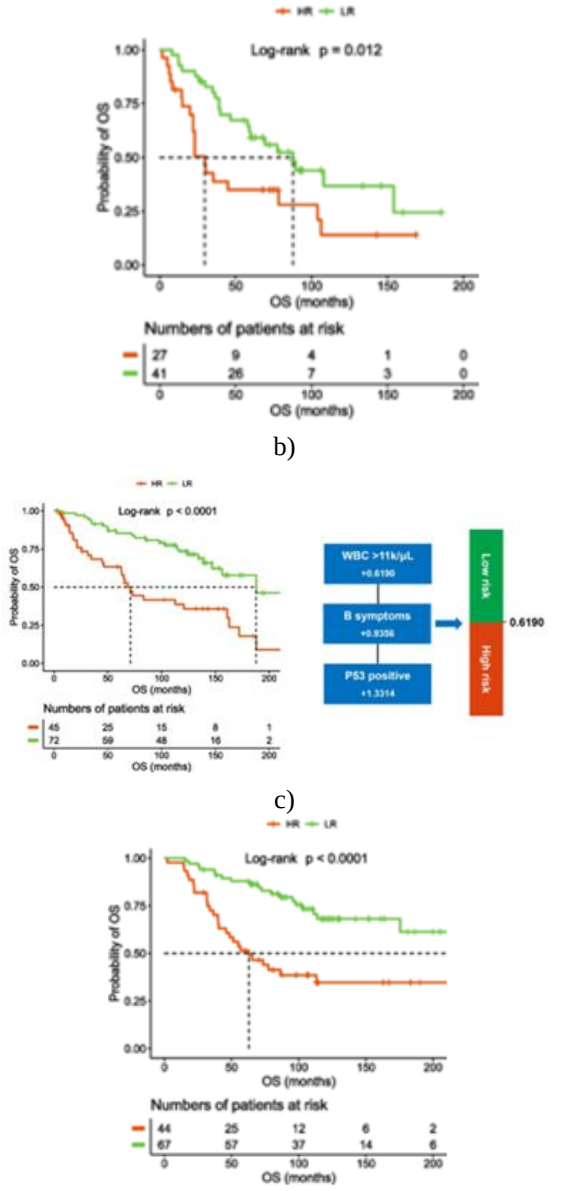

Figure 5. Construction of novel age-stratified prognostic models. Older patient model (≥ 65y) derivation in training (a) and validation (b); younger patient model (< 65y) derivation in training (c) and validation (d).

These stratification systems are hereafter referred to as the North American MCL Prognostic Indexes (NAMPIs) to distinguish them from previous approaches. They may be accessed via the following link: https://unmcredcap.unmc.edu/redcap/surveys/?s=WNFCJWACLMDC9WKN.

The present investigation conducted a retrospective examination of a substantial series of mantle cell lymphoma (MCL) cases managed during the immunochemotherapy period. Survival outcomes in this population exceeded those reported in earlier groups treated exclusively with conventional chemotherapy [15, 16], indicating that widespread incorporation of rituximab has contributed to genuine improvements in patient prognosis under real-world conditions. In addition, hematopoietic stem cell transplantation (HSCT) provided substantial clinical benefit, yielding markedly superior results compared with immunochemotherapy alone and emerging as a particularly useful strategy for the blastoid/pleomorphic subtype. Regarding chemotherapeutic choices, cytarabine-containing protocols combined with HSCT produced notable gains in progression-free survival among younger individuals, consistent with prior recommendations favoring this sequence for fit young patients [17, 18]. Although no clear overall survival advantage was observed—suggesting comparable relapse rates to non-cytarabine induction regimens—a favorable tendency toward cytarabine-based induction plus HSCT as initial treatment remains apparent. These findings highlight the importance of developing more effective post-remission strategies to optimize long-term results with this approach.

Despite this progress, MCL remains incurable for most affected individuals. Contemporary practice offers multiple frontline therapeutic options, while incorporating established second-line agents—including BTK inhibitors, bortezomib, and lenalidomide—into initial regimens holds considerable potential for further advancement. Optimal treatment selection depends on precise risk assessment. The current study therefore sought to create updated risk stratification tools that integrate key clinicopathological variables relevant to present-day management. Univariate evaluation in this cohort largely confirmed previously identified clinical and laboratory risk factors [4, 6, 19], while also revealing novel associations: thrombocytopenia and circulating tumor cells (CTCs) with adverse prognosis, and colonic involvement with more favorable outcomes. It should be noted that CTCs are characteristic of leukemic non-nodal MCL, a recently recognized indolent entity typically associated with minimal or no disease progression. Because this variant had not yet been formally defined at the time of diagnosis for the present cases, a sensitivity analysis restricted to patients with nodal disease was performed; CTCs retained their prognostic relevance in this subgroup. The association observed with colonic

involvement may reflect selection bias, as individuals with highly aggressive disease or compromised performance status are less likely to undergo colonoscopic evaluation. Supporting this interpretation, colonic involvement showed no significant prognostic effect in the younger subgroup, where colonoscopy is performed more routinely. Further dedicated investigations will be required to clarify this relationship.

With respect to histopathological parameters, beyond the well-established Ki-67 proliferation index, particular attention was directed toward p53 status. Multiple reports have shown that TP53 mutations are common in MCL and correlate with therapeutic resistance and poorer survival [20-23]. Immunohistochemical detection of p53 protein demonstrates strong sensitivity and specificity for identifying missense mutations and functions as an independent prognostic marker, even when accounting for MIPI and Ki-67 [21, 24]. In the present analysis, rather than relying solely on the percentage of stained cells, a semi-quantitative scoring system integrating staining intensity and extent was utilized. This approach showed excellent agreement (> 90%) with the 30% positivity threshold in our dataset and reduced inter-observer variability in cases with substantial weak staining. Notably, p53 expression proved a more powerful predictor of clinical outcome than the Ki-67 index. Furthermore, p53 positivity was the only pathological variable consistently retained across all multivariable Cox models, emphasizing its central role in disease behavior and treatment response when baseline features are considered together. A limitation of this study is the reliance on p53 protein expression rather than TP53 genetic status. Prior work indicates discordance rates of approximately 10–20% between expression and mutational analysis [21, 25], with sequencing regarded as the reference standard. Nevertheless, given the complex spectrum of p53 alterations in MCL, immunohistochemical assessment remains clinically relevant because it directly reflects the protein's functional status. Accumulating data continue to support a robust link between p53 expression and prognosis [26, 27]. Moreover, IHC is a widely accessible technique suitable for routine diagnostic laboratories and offers particular utility in resource-limited settings.

When considering additional histopathological characteristics, the diffuse architectural pattern was strongly associated with worse overall survival (OS) and progression-free survival (PFS) across the complete study population and among older individuals. Blastoid/pleomorphic morphology, immunoglobulin light chain restriction (ILCR), and CD23 expression likewise showed links to poorer prognosis, whereas CD5 positivity lacked any meaningful association across the subgroups examined. The adverse impact of blastoid/pleomorphic cytology has been consistently documented in earlier investigations [5, 28, 29]. Importantly, the current analysis demonstrated that HSCT substantially enhanced survival in patients with this aggressive histologic variant, supporting its preferential use in such cases. In contrast to some prior reports linking CD23 positivity to a more favorable prognosis [30, 31], the present study observed an association with inferior survival. This difference may stem from the relatively low frequency of CD23 expression observed in MCL. None of these histopathological variables were retained in the final multivariable Cox models, suggesting considerable overlap with other prognostic elements.

In contrast to many existing prognostic systems, the NAMPIs incorporate a dedicated PFS-based model to better support therapeutic decision-making. One possible implementation strategy is as follows: patients classified as low risk by the PFS model may be appropriately managed with milder regimens, such as bendamustine plus rituximab. Conversely, high-risk patients—particularly those identified as high-risk by both OS and PFS models—should be strongly considered for HSCT, enrollment in clinical trials, and rituximab maintenance therapy. Furthermore, the incorporation of BTK inhibitors, potentially in the frontline setting, represents a promising strategy for these individuals and aligns with current evolving standards of care in MCL. Two large recent cohort studies have provided support for this approach [23, 32]. For patients in the intermediate-risk category, a measured strategy is advisable, balancing the advantages and drawbacks of standard versus intensified therapies while accounting for comorbidities and other individual factors. Age-specific models were additionally constructed for patients aged 65 years and older and for those younger than 65 years. This development responds to the growing emphasis on age-stratified research and the development of tailored therapies for distinct age groups. All proposed models were successfully validated in an independent patient series. Of note, the validation cohort included a greater proportion of individuals treated with R-bendamustine or BTK inhibitors. Nevertheless, the models achieved highly consistent risk stratification compared with the

training set, indicating robustness across diverse therapeutic backgrounds and potential utility in guiding contemporary MCL management. Although the NAMPI systems are grounded in clinical and pathological variables, future refinement through integration of advanced molecular markers, such as the MCL35 assay [33], could facilitate more refined, multi-dimensional risk classification and enable increasingly personalized treatment strategies.

Conclusion

In summary, this multi-institutional collaborative effort across North America examined prognostic factors in MCL during the immunochemotherapy era. It developed new risk-stratification models applicable to the overall population and age-defined subgroups. Additional research will be required to incorporate molecular genetic features into risk assessment frameworks, particularly to optimize the use of second-line and emerging therapeutic options.

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