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ORIGINAL PAPER

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Simplified Molecular International Prognostic Index as an eligibility criterion for clinical trials: Analysis of the Turkish Lymphoma Study Group's large B-cell lymphoma cohort

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Summary

Comparative first-line trials in large B-cell lymphoma (LBCL) have mostly failed over the last decade. Failures were commonly attributed to overestimation of the progression risk for the control arms, bringing the precision of the international prognostic index (IPI) into scrutiny. Simplified molecular IPI (smIPI), introduced at American Society of Hematology 2023, was developed to address the shortcomings of IPI. This study investigated smIPI and its potential implications as trial eligibility criteria among a multicentre LBCL cohort of 1439 patients. Patients diagnosed between 2012 and 2024 were included. Data were collected from institutional archives. The primary end-point was risk stratification for progression-free survival (PFS). Kaplan–Meier and Cox regression methods were used for survival analyses. The smIPI reclassified 38.2% and 5.3% of patients to higher and lower risk groups from IPI, respectively. Patients reclassified to higher risk groups by smIPI had an increased risk of progression than the rest of the group (hazard ratio = 1.34, $p = 0.003$). High-risk groups classified by IPI and smIPI had similar outcomes (3-year PFS 54.9%

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vs. 56.3%); however, the high-risk group size was expanded by 35.2% when defined by smIPI. The smIPI is easily applicable and more sensitive than IPI in identifying patients under high risk of progression who are ideal candidates to participate in clinical research.

KEYWORDS
BCL-2, clinical trials, lymphomas, non-Hodgkin lymphoma, prognostic factors

INTRODUCTION

International prognostic index (IPI) has been used to prognostically classify large B-cell lymphoma (LBCL) patients for decades.[1] It relies on parameters that reflect two main domains. One is the patient's overall physical condition reflected by age and Eastern Cooperative Oncology Group performance score. The second is the tumour burden represented by lactate dehydrogenase, stage, and number of extra-medullary sites. Despite the development of multiple risk-assessment models derived from IPI (age-adjusted IPI, National Comprehensive Cancer Network (NCCN)-IPI, international metabolic prognostic index [IMPI], etc.),[1–3] the original IPI has maintained its place as an eligibility criterion for major clinical trials. One recent example is the ground-breaking POLARIX trial, where patients with an IPI score of 2 or more were enrolled, changing the standard of care for this population.[4]

The German Lymphoma Alliance (GLA/DSHNHL) and the French Lymphoma Study Association (LYSA) collaborated to improve the risk-stratification power in LBCL.[5] The main starting point was the idea that some of the largest trials (ROBUST, PYRAMID, etc.) failed due to the inclusion of a high number of low-risk patients, which blunted the advantages demonstrated for high-risk patients.[6,7] This was mainly attributed to the lack of precision with the IPI in stratifying patients in the intermediate categories. The simplified molecular IPI (smIPI) was developed in this context and presented at the 2023 American Society of Hematology (ASH) Congress.[5] Data of 548 patients from Germany who were enrolled in LBCL trials (training cohort) were analysed, singling out B-cell lymphoma gene 2 (BCL2) expression in tumour tissue as an independent prognostic factor. The smIPI was generated based on this revelation and validated among 657 trial patients from France as well as 628 real-life patients from Canada in the same study.[5] The criterion for the involvement of two or more extra-medullary sites was replaced by BCL2 expression in tumour tissue as the only modification from IPI to smIPI, making it appealing by expanding the scope of IPI with a feature concerning tumour biology while maintaining the same number of parameters. The study concluded that the smIPI stratifies risk groups with a wider spread of survival curves compared to IPI, better identifying patients with truly unmet needs for research.[5]

The improvements in prognostic models over the previous decade by the inclusion of parameters concerning tumour biology in other haematological malignancies have changed the landscape of trial designs.[8–11] The incorporation of a biological variable as proposed by the major scientific consortia from Germany and France is a step forward in this regard for LBCL.[5] A unique advantage of smIPI is its practicality. It does not necessitate additional testing or infrastructural revisions since BCL2 expression is routinely reported in LBCL diagnostic samples. We conducted this study to further investigate the potential implications of smIPI in a large real-world cohort, as well as to promote biological risk stratification in LBCL. The paper presents the selected features of the cohort, analyses survival outcomes based on prognostic indices and explores the implications of smIPI as a possible eligibility criterion in clinical trials.

MATERIALS AND METHODS

This LBCL cohort was generated through an initiative of the Turkish Lymphoma Study Group with the collaboration of nine centres from four regions of Türkiye. Patients diagnosed with LBCL between 2012 and 2024 and treated outside of clinical trials for first-line therapy were included. Data were collected through archives and institutional records by researchers from each institution.

Patients with primary central nervous system (CNS) lymphoma and cases with unavailable data regarding IPI and BCL2 expression, or with data necessary to calculate time-to-event outcomes were excluded from the total cohort. Histological subtype for LBCL was categorized as diffuse large B-cell lymphoma—not otherwise specified (DLBCL-NOS), transformed LBCL, high-grade LBCL, primary mediastinal B-cell lymphoma (PMBCL), T-cell/histiocyte-rich B-cell lymphoma and others. BCL2 and MYC expressions were determined based on the local haematopathologist's interpretation of positivity in the pathology report. In cases lacking a clear statement regarding BCL2 status in the report, expression levels above 50% were considered positive.[12] First-line therapy was categorized as 'RCHOP full dose', 'RCHOP reduced intensity', 'R-miniCHOP', 'DA-R-EPOCH' and 'others'. RCHOP with reduced intensity was defined as more than 21 days of total delay during first-line therapy or a reduction in dose of any of the five drugs by 20% for at least two cycles.

Progression-free survival (PFS) was defined as the time between diagnosis and the demonstration of disease progression, relapse, death, or demonstration of active disease after first-line therapy. Patients without a progression event

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were censored at the time of their last clinical evaluation for PFS. Overall survival (OS) was defined as the time between diagnosis and death. Living patients were censored at the time they were last documented to be alive for OS. Survival analyses were performed with the Kaplan–Meier method, and Cox regression analysis was used to determine the hazard ratio (HR) for progression or death with 95% confidence intervals (CIs). The risk groups for smIPI were derived from the traditional IPI (0, 1: low risk; 2: low intermediate; 3: high intermediate; 4, 5: high risk) as was also used by Ziepert et al.[5] For categorical data in contingency tables, statistical analyses were assessed by the Fisher's exact test with 95% CI.

Comparing different prognostic scores is not straightforward and does not have a universal code.[13] Each risk-stratification tool may have advantages for a particular purpose. Therefore, we confined the comparison of IPI and smIPI to their utility as eligibility criteria for clinical trials and possible implications when either would be used to generate trial populations. Other ramifications of prognostic estimation were considered beyond the scope of this study. The primary end-point was risk stratification for PFS. PFS was preferred over OS, reflecting the recent trends of primary end-points in LBCL trial designs as the key variable for sample size calculations.[4,6,7,14,15] Secondary end-points were defined as response rates and OS according to smIPI and IPI. Exploratory end-points were comparisons of pooled patient groups based on IPI and smIPI for patient numbers and the risk of progression.

The study was approved by the Non-Interventional Research Committee of the Institutional Review Board of Kocaeli University on 16 January 2025 with an approval number of 2025/27.

RESULTS

The LBCL cohort was composed of 1439 consecutive entries of cases from nine centres. The cohort size was reduced to 1117 for the primary end-point analysis after exclusions. The most common reasons for exclusion were unavailability of the data for the IPI score and/or BCL2 expression status (*n*: 184) and missing dates for diagnosis or relapse (*n*: 82). Other important reasons were diagnosis earlier than 2012 (*n*: 29) and primary CNS disease (*n*: 22).

The selected features regarding the smIPI analysis cohort of 1117 patients are presented in Tables 1 and 2. The median age was 59 years with an interquartile range (IQR) from 46 to 69. The most common histological subtype was DLBCL-NOS (79.5% of cases) and the cell of origin determined by immunohistochemistry was of the non-germinal centre B-cell type in almost half of cases. BCL2 expression in tumour tissue was observed in 64.1% of the cohort and was distributed evenly between IPI risk groups. Higher MYC expression rates were associated with higher IPI scores (Table S1). Regarding IPI, 41.2% and 15.1% of cases were among low-risk and high-risk groups respectively (Table 1). Full-dose RCHOP treatment was intended for the majority (73.6%) of the cohort; however, 10.6% had significant reductions in RCHOP intensity. The median age of patients receiving R-miniCHOP (8% of all cases) was 78 years. DA-R-EPOCH was mainly administered to PMBCL patients and those classified as high-grade B lymphomas. Occasional DLBCL-NOS patients (4.9% of cases), most with the 'double expressor' profile, also received this intensive therapy. CNS prophylaxis was administered to 21.2% of patients, with 82.7% of these being intrathecal only (Table 2). The median follow-up was 38 months (IQR = 15–67 months); 351 PFS events and 221 OS events were documented. More than 80% of patients censored for survival analyses had their last clinical evaluation within the last 12 months of data cut-off, with 7.4% censored before 2021.

The smIPI score reclassified 38.2% of patients to one higher risk group, whereas 5.4% of patients were reclassified to one lower risk group compared to their IPI stratification (Figure 1).

TABLE 1 Frequency of selected features among 1117 LBCL patients analysed for smIPI at the time of diagnosis.

Age	
Median/range	59 (17–91)
Histological subtype	
DLBCL-NOS	79.5% (*n* = 872)
Transformed LBCL	6.6% (*n* = 72)
High-grade LBCL	5.6% (*n* = 61)
TCHRBCL	1.6% (*n* = 18)
PMBCL	2.9% (*n* = 32)
Cell of origin	
Non-GCB	49.9%
GCB-like	45.4%
BCL2 positive	64.0%
LDH elevated	54.1%
Age >70	21.8%
Gender	
Female/male	47.5%/52.5%
IPI/smIPI score	
0	14.9%/6.5%
1	26.3%/19.2%
2	24.3%/27.7%
3	19.5%/26.1%
4, 5	15.1%/20.5%
Stage	
1–2	40.7%
3–4	59.3%
Extra-nodal disease	32.2%
Breast	4.7%
Testicle	1.8%

Abbreviations: BCL2, B-cell lymphoma gene 2; DLBCL-NOS, diffuse large B-cell lymphoma—not otherwise specified; GCB, germinal centre B-cell; IPI, international prognostic index; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; PMBCL, primary mediastinal B-cell lymphoma; smIPI, simplified molecular IPI; TCHRBCL, T-cell/histiocyte-rich B-cell lymphoma.

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TABLE 2 Frequency of selected features regarding treatment and follow-up.

First line ($n=1117$)		Failed first-line treatment ($n=351$)	
First-line treatment		Second-line treatment	
R-CHOP	73.6% ($n=822$)	R-ICE	21.9%
R-miniCHOP	8.0% ($n=89$)	R-DHAP/DHAOx	12.6%
DA-R-EPOCH	7.1% ($n=79$)	R-GDP	12.6%
Other regimens[a]	11.4% ($n=127$)	R-bendamustine	9.1%
CNS prophylaxis	21.2% ($n=237$)	Other regimens[c]	19.3%
Frontline ASCT/RT	1.6%/15%	No further treatment	25.4%
Response to first line[b]		Response to second line	
CR/PR	76.5%/5.4%	CR/PR	26.9%/11.8%
First-line failure	29.1%	Subsequent treatments	
Primary progressive	9.5%	ASCT	29.2%
Late relapse	8.8%	Third line	33.2%
Median follow-up (months)	38	Median follow-up (months)	9
3-year PFS	70.9%	Median PFS (months)	5
3-year OS	82.2%	Median OS (months)	13.5

Abbreviations: ASCT, autologous stem cell transplantation; CNS, central nervous system; CR, complete remission; OS, overall survival; PFS, progression-free survival; PR, partial remission; RT, radiotherapy.

[a]Include R-CEOP (*n*: 6), O-CHOP (*n*: 4), R-lenalidomide (*n*: 7), rituximab monotherapy (*n*: 13), R-CHOEP (*n*: 5), Pola-R-CHP (*n*: 4), R-CVP (*n*: 17), R-gemcitabine + CVP (*n*: 5), platinum based (*n*: 9), R-bendamustine (*n*: 5), frontline ASCT (*n*: 2), hyperCVAD (*n*: 2) and more than one protocol for at least two cycles each (*n*: 18).

[b]Include R-ESHAP (*n*: 7), O-ICE (*n*: 3), DA-R-EPOCH (*n*: 6), R-GEMOX (*n*: 7), ibrutinib (*n*: 4), R-lenalidomide (*n*: 4), HyperCVAD (*n*: 3) and bispecifics (*n*: 5).

[c]Overall response rate was 81.9%, 9.5% of patients had primary progressive disease, 4.7% died before a response evaluation, 1.7% had stable disease and 2.1% had not been evaluated for response at the time of data cut-off.

Table 3 summarizes response rates and time-to-event outcomes for each IPI and smIPI risk group. PFS and OS estimates based on IPI and smIPI risk groups are summarized in Figure 2. HR calculated with Cox regression analysis is presented below the survival curves and demonstrates a numerically wider spread between risk groups with smIPI stratification compared to IPI.

Regarding the primary end-point of the study, PFS was significantly shorter for patients who were reclassified to one higher risk group by smIPI (Figure 1—curves flowing downwards, $n=427$) compared to the rest of the cohort who either remained in the same risk category ($n=630$) or were reclassified to one lower risk group ($n=60$) than their initial IPI. The PFS estimate at 3 years for patients reclassified to one higher risk category was 65.2%, significantly lower compared to the 74.1% for the rest of the group, demonstrating smIPI's superior sensitivity over IPI in identifying patients with a higher risk of progression through the entire range of risk groups (Figure 3A, HR = 1.34, 95% CI: 1.1–1.7, $p<0.01$). The differences in patient numbers, complete remission rates and 3-year PFS per IPI and smIPI risk group are presented in more detail on a confusion matrix in the Table S2.

The estimated 3-year PFS was below 60% for patients with scores of 3, 4 and 5 with both IPI and smIPI, identifying groups with truly unmet needs (Table 3). The IPI and smIPI classified 34.6% ($n=386$) and 46.6% ($n=520$) of the entire LBCL cohort to these high-risk groups respectively. Figure 3B shows the lack of difference between PFS curves for the IPI and smIPI high-risk groups with similar estimates for 3-year PFS of 56.3% and 54.9% respectively (HR = 1.07, 95% CI: 0.88–1.3 $p=0.47$). The smIPI was able to increase the number of LBCL patients grouped as high risk by 35.2% without a discernible change in the risk of progression. The estimated 3-year PFS was 53.9%, 60.9% and 83.6% for patients defined as high risk (score 3–5) by both IPI and smIPI, high risk by smIPI only and low risk by both IPI and smIPI respectively (Figure S1).

As an exploratory end-point, we tested two possible trial eligibility criteria in our cohort. The first criterion was defined as smIPI 3 or more (smIPI 3–5 group) and the other as IPI 2 or more (IPI 2–5 group). The IPI 2–5 was the comparator since it was the inclusion criterion for most of the recent first-line trials, including POLARIX, ROBUST, GUIDANCE-01 and E1412.[4,6,15,16] The smIPI 3–5 group was composed of 520 patients and the IPI 2–5 group covered all the 520 patients from the smIPI 3–5 group, plus an additional 137 patients (Figure 1). These 137 additional patients in the IPI 2–5 group demonstrated a significantly lower risk of progression than smIPI 3–5 patients with an estimated 3-year PFS of 76.5% and 56.3% respectively (Figure 4A, HR = 0.49, 95% CI: 0.35–0.71, $p<0.0001$). Therefore, expanding the eligibility spectrum from smIPI 3–5 to IPI 2–5 resulted in the inclusion of a large group without truly unmet needs. This effect was also demonstrable when 271 patients classified as IPI 2 were reclassified to smIPI 1–2 ($n=113$) or to smIPI 3 ($n=158$) with estimated 3-year PFS rates of 78.3% and 61.3% respectively (Figure 4B, HR = 1.67, 95% CI: 1.06–2.6, $p=0.026$). These findings highlight the presence of a substantial number of patients within the IPI 2 risk group with a distinctly lower risk of progression. This subgroup can result in significantly fewer numbers of events than initially anticipated and expose study objectives to the risk of failure.

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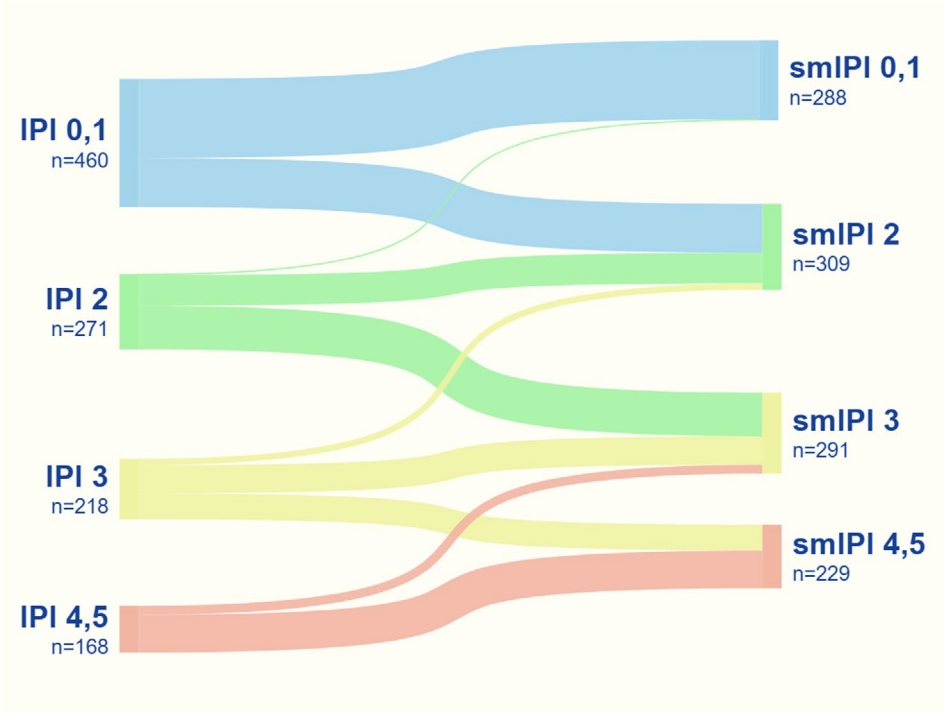


FIGURE 1 Sankey diagram of 1117 LBCL patients classified to IPI risk groups on the left and their reclassification to smIPI risk groups towards right. Overall, 427 patients were reclassified to one higher risk group (curves flowing downwards from IPI to smIPI) and 60 patients were reclassified to one lower risk group (thin curves flowing sharply upwards from IPI to smIPI) by smIPI from their initial IPI risk groups. The remaining 630 patients (thick curves flowing slightly upwards from IPI to smIPI) were stratified to the same risk group by both IPI and smIPI. IPI, international prognostic index, LBCL, large B-cell lymphoma; smIPI, simplified molecular IPI.

TABLE 3 Three-year PFS and five-year OS estimates for each IPI and smIPI risk group.

Risk groups	*n*	CR rate (%)	3-Year PFS (95% CI)	5-Year OS (95% CI)
Low risk				
IPI 0, 1	460	91.4	85.4% (82.8–89)	90.5% (87.4–93.5)
smIPI 0, 1	288	95.6	92.5% (89.4–95.7)	93.8% (90.3–97.2)
Low-intermediate risk				
IPI 2	271	80.5	69.1% (63.1–75.1)	80.7% (75.2–86.2)
smIPI 2	309	83.2	72.9% (68–77.9)	82.6% (78.7–87.6)
High-intermediate risk				
IPI 3	218	72.4	59.8% (52.6–67)	66.8% (58.8–74.7)
smIPI 3	291	73.8	58.8% (52.6–64.9)	70.2% (64–76.3)
High risk				
IPI 4, 5	168	69.7	51.7% (43.6–59.7)	50.1% (40.3–60.4)
smIPI 4, 5	229	72.9	53.6% (46.7–60.5)	51.9% (43.6–60.1)

Abbreviations: CI, confidence interval; CR, complete remission; IPI, international prognostic index; OS, overall survival; PFS, progression-free survival; smIPI, simplified molecular IPI.

The analyses described above were repeated in a subpopulation of 668 patients restricted in diagnosis and therapy to DLBCL-NOS and RCHOP respectively (Figures S2–S5). This exploratory analysis was performed to exclude the influence of IPI on the choice of therapy, which may have blunted the differences in outcomes between risk groups. DLBCL-NOS patients treated with RCHOP who were reclassified to one higher smIPI risk group from their initial IPI score ($n = 246$) had a higher risk of progression compared to the rest of the group (HR = 1.6, 95% CI: 1.17–2.19) and patients classified as high-risk (scores 3–5) were increased by 45.3% when grouped by smIPI ($n = 250$) over IPI ($n = 172$), without a difference in progression risk between the high-risk groups of the two indices (HR = 0.98, 95% CI: 0.71–1.36). We categorized induction treatment into three groups: 'less intensive', 'RCHOP' and 'more intensive' (Table S3) to explore if IPI-driven therapy alterations were present. We found no association between the frequency of more intensive therapies and IPI risk category (8.6% vs. 10.9%, $p = 0.24$). Less intensive therapies were more commonly administered to patients in the high IPI risk category (6.8% vs. 27.7%, $p < 0.001$). The association between these three treatment groups and risk categories was similar when performed using smIPI (Supporting Information). The strongest association for less intensive therapy was age over 60 (26.5% vs. 2.1%, $p < 0.0001$). The strongest association with more intensive therapy was histological subtype of high-grade LBCL or PMBCL (37.6% vs. 6.9%, $p < 0.0001$).

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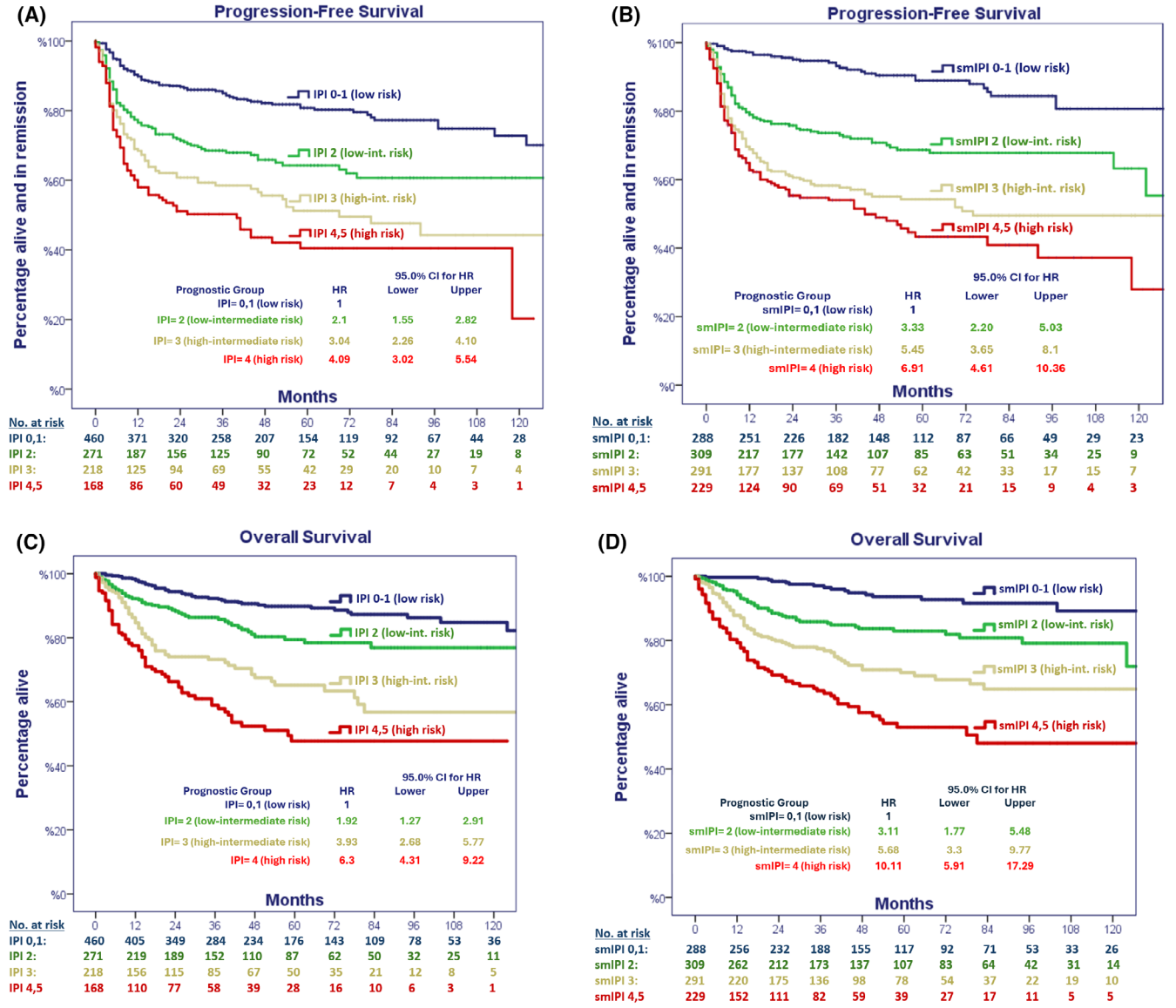


FIGURE 2 Kaplan–Meier survival analysis for PFS (A, B) and OS (C, D) of patients in each IPI (A, C) and smIPI (B, D) risk groups. HR and CIs for each risk group calculated with Cox regression analysis are presented below the curves. CI, confidence interval; HR, hazard ratio; IPI, international prognostic index; OS, overall survival; PFS, progression-free survival; smIPI, simplified molecular IPI.

DISCUSSION

The smIPI, proposed by GLA/DSHNHL and LYSA as a novel and practical risk-stratification tool, was evaluated in this study. Analysing a large real-world cohort, we found encouraging results validating the usefulness of this novel index. The standout findings were that the smIPI is easily applicable, stratifies patients into clearly distinct categories for both PFS and OS with a relatively linear escalation of HR along with the index (Figure 2). The smIPI was more sensitive than IPI in identifying patients under increased risk of progression, a particularly convenient feature as trial eligibility criteria.

There is a constant tension between three considerations in trial designs. First is the will to represent a large proportion of subjects affected by the disease. Second is keeping the sample size and recruitment rate feasible. The third is an acceptable budget. Inclusion of patients with low risk of events, while satisfying the first consideration, is detrimental to the other two since the sample size depends on the frequency of progression events. Furthermore, low-risk patients are less likely to benefit from experimental approaches, and their exposure to uncharted risks of clinical research may not be appropriate. Including only high-risk patients keeps the sample size and budget reasonable; however, it risks slow recruitment and narrows the scope of the study, conflicting with the first consideration. This is where precision in prognostic stratification must come in to set the right balance and resolve the dilemma. Whether IPI has been the right tool is under scrutiny.

To elaborate on the relevance of considerations in trial design mentioned above for LBCL, three major first-line trials

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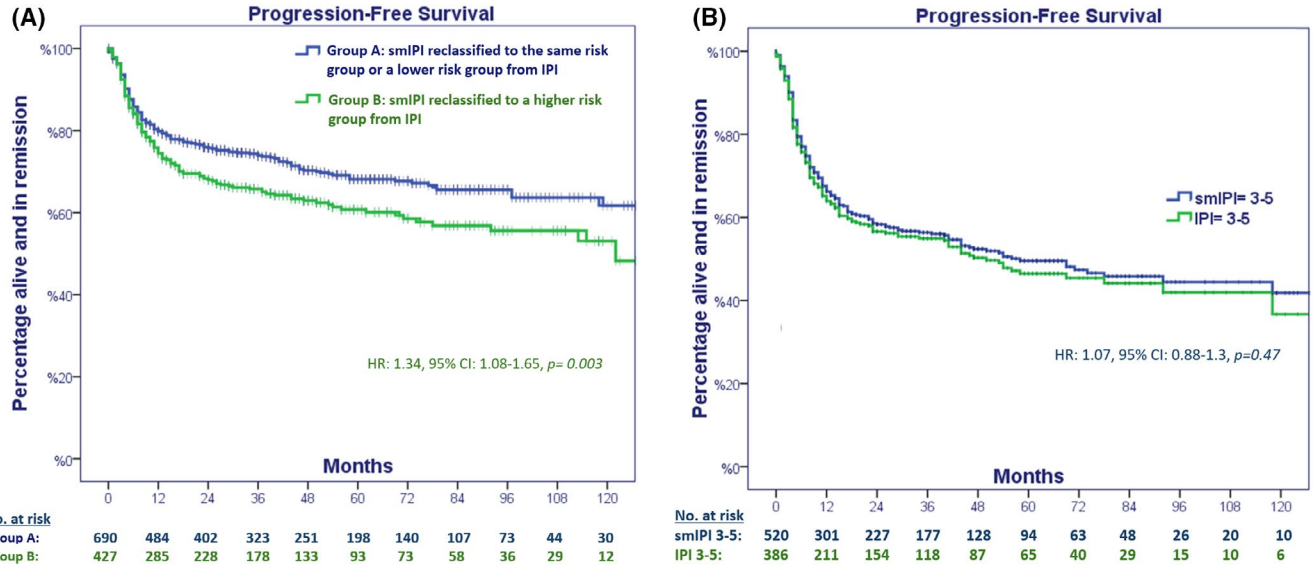


FIGURE 3 The green curve in (A) represents patients who were reclassified to a higher smIPI risk group than their initial IPI risk group (Group B, *n*: 427). The blue curve (Group A) represents the combined group of patients who were reclassified to the same smIPI risk group with their initial IPI risk group (*n*: 630) and those reclassified to an smIPI risk group lower than their initial IPI risk group (*n*: 60). (B) Shows Kaplan–Meier survival curves comparing high-risk groups (score 3–5) defined by smIPI (*n*: 520) and IPI (*n*: 386) with 361 patients overlapping between groups. HR and CIs calculated with Cox regression analysis are presented below the curves. CI, confidence interval; HR, hazard ratio; IPI, international prognostic index; smIPI, simplified molecular IPI.

over the last decade will be examined below. The POLARIX trial was designed to demonstrate the PFS superiority of the experimental therapy over RCHOP. POLARIX met its primary end-point for the experimental arm. On subgroup analysis, the advantage of the experimental therapy was pronounced with an HR of 0.72 among patients with IPI 3–5. The advantage was not clear for IPI 2 patients (HR = 0.91, 95% CI: 0.61–1.36) who constituted 38% of the trial population, almost jeopardizing the primary objective.[4,17] This happened for the ROBUST and PYRAMID trials conducted with similar designs where the experimental arms were associated with HRs of 0.74 and 0.66 for progression in the high-risk groups (IPI 3–5) over RCHOP respectively. These potentially promising data were blunted by the markedly fewer number of events and higher HRs (1.2 and 1.13 respectively) in patients with lower IPIs (constituting 42%, 53% of the trial populations respectively), which may have contributed to the failure of these large trials.[6,18]

A fundamental limitation of IPI is its association with patient fitness and tumour burden. Patients with lower IPI scores are much more likely to be otherwise eligible for clinical trials due to younger age, better performance and organ function. Thus, when the trial design allows patients with lower IPIs to be enrolled, these 'low-risk' patients tend to be overrepresented, PFS event rates drop beyond initial estimates and the risks of trial failure escalate. This overrepresentation was visible in the trials mentioned above, with IPI 2 patients constituting approximately 40% of trial populations,[4–7,14] whereas in real-world studies, including in our cohort, this rate is specified at approximately 25%.[2,5,19] Exclusion of IPI 2 in earlier trials may have been considered unpractical since higher IPI risk groups constitute only one-third of LBCL cases, which narrows the scope and impedes effective recruitment. The key advantage of smIPI over IPI to guide enrolment in trials, as emphasized in this study, is the expansion of the 'high-risk' group. The number of patients classified to high-risk groups increased by 35.2% and 41.2% when smIPI was used over IPI in this cohort and in the report by Ziepert et al. respectively.[5] The risk of progression was no different for the IPI 'high-risk' group compared to the smIPI 'high-risk' group in this study, despite significantly increased size with the latter. Therefore, the smIPI has the potential to confine trial populations to true 'high-risk' groups while not being as restrictive as IPI regarding the scope of the study and recruitment rate.

The International Metabolic Prognostic Index (IMPI) proposed in 2022 uses age and stage as continuous variables, and tumour burden is measured precisely by metabolic tumour volume (MTV) offering a personalized prognostic estimation. The 3-year PFS was 46.3% for IMPI high-risk cases, classifying only 10% of patients to this risk group,[3] compared to smIPI, which categorized 46.6% of our cohort to high risk, with a 3-year PFS of 56.3%. IMPI may be a more specific tool to identify very high-risk patients, whereas smIPI may be more sensitive. Due to its novelty, MTV data are less likely to be widely available, as it is yet to be standardized, compared to BCL2 expression, which has been commonly included in pathology reports for decades. A subsequent study by our group in collaboration with nuclear medicine to evaluate various metabolic positron emission tomography parameters in this cohort is under way.

This study had limitations inherent to any real-world study. Particularly significant were the unavailability of data

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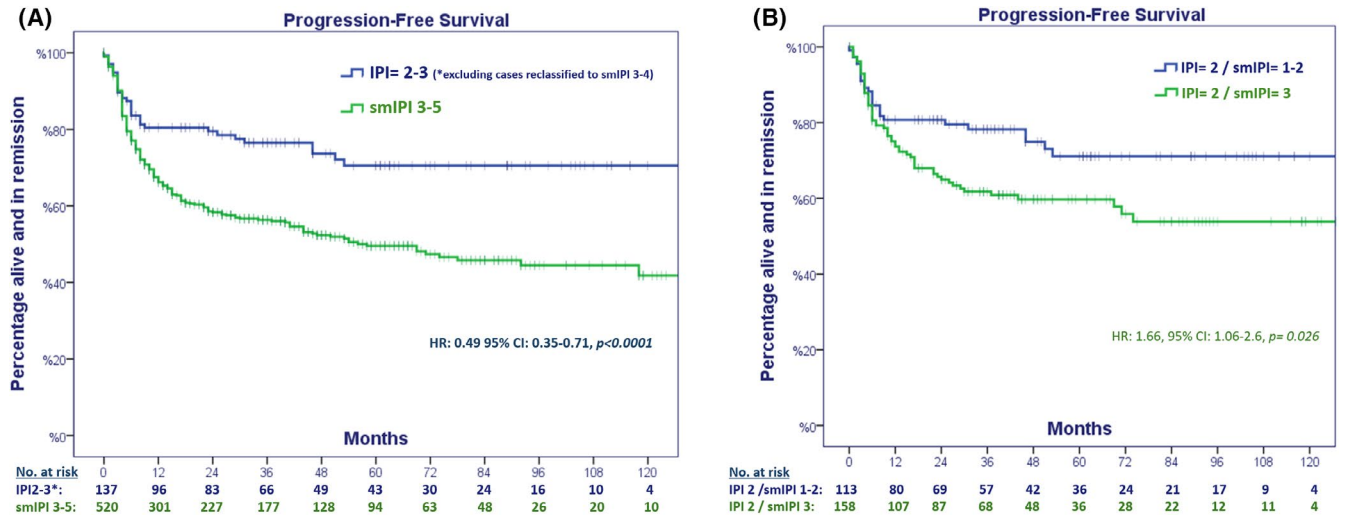


FIGURE 4 The blue curve in (A) represents patients with an IPI score of 2 or 3 who have been reclassified to smIPI ≤2 (non-overlapping patients between IPI 2–5 and smIPI 3–5). The PFS of these 137 cases are compared with those who have an smIPI of 3–5 represented by the green curve. Panel (B) is restricted to patients with an IPI score of 2. The blue curve in (B) represents patients who were reclassified from IPI 2 to smIPI 1 or 2, whereas the green curve represents patients who were reclassified from IPI 2 to smIPI 3. HR and confidence intervals calculated with Cox regression analysis are presented below the curves. CI, confidence interval; HR, hazard ratio; IPI, international prognostic index; smIPI, simplified molecular IPI.

for immunohistochemical stains and time-to-event analyses in a proportion of patients that may potentially lead to selection bias. Furthermore, the non-uniform BCL2 testing and reporting, which was highlighted as a limitation for immunohistochemical biomarkers in earlier publications, necessitates caution.[12,20–22] The limitations were partially offset by the large sample size restricted to a contemporary period, predetermined end-points previously studied in training and validation cohorts as well as clear correlations with *p* values being consistently lower than 0.01 for all major end-points analysed, along with narrow CIs throughout various correlations. Concerns for the reproducibility of BCL2 expression status, although well founded, are also alleviated to a degree by consistent BCL2 expression rates (60%–70%) across the four independent cohorts from different countries (two trial, two real world), each exceeding 600 patients that were analysed to investigate smIPI. The heterogeneity of the LBCL cohort for histological subtypes and treatments as a potential limitation was addressed with analysis among the homogeneous subgroup of 668 DLBCL-NOS patients treated with RCHOP, reproducing complementary findings. The differences in treatment intensity were not directly associated with IPI, and the interference of possible IPI-driven therapy modifications with the correlations presented in this study was negligible.

In this large LBCL cohort, the high-risk groups defined by IPI and smIPI had remarkably similar PFS estimates. Classification by smIPI expanded the number of patients in the high-risk group by 35.2% over classification by IPI (Figures 1 and 3B), demonstrating superior sensitivity for smIPI in identifying patients with an increased risk of progression. Furthermore, lower risk patients who have been overrepresented in previous trials were better identified by smIPI, potentially reducing the probability of trial failure (Figure 4B). Opting for smIPI ≥3 for eligibility in first-line LBCL trials instead of IPI ≥3 or IPI ≥2 may be the key adjustment in LBCL study designs to balance the necessity to enrol patients at a higher risk of progression while not being too restrictive to interfere with recruitment. Based on the promising data presented at ASH 2023 and further explorations with this study, the smIPI deserves widespread acknowledgement and repeated validations in other cohorts, and is a compelling candidate to replace IPI as an eligibility criterion in future research.

AUTHOR CONTRIBUTIONS

UY was involved in the design of the study, analysed data, and wrote the paper. ETD was involved in the design of the study and data collection. FKK was involved in data collection. UH was involved in data collection. MUM was involved in the design of the study and data collection. EP was involved in data collection. TT was involved in data collection. ENK was involved in data collection. MM was involved in data collection. AD was involved in data collection. MAK was involved in data collection. MÖ was involved in the design of the study, data collection and critical revision of the manuscript. TE was involved in data collection. AFY was involved in the design of the study and data collection. DG was involved in the design of the study and data collection. TT was involved in data collection. TU was involved in data collection. ÖM was involved in the design of the study, critical revision of the manuscript and data collection. MSD was involved in data collection. OMA was involved in data collection. MCA was involved in data collection and critical revision of the manuscript. GS was involved in data collection. FA was involved in data collection. EBA was involved in the design of the study and critical revision of the manuscript. BF conceptualised the study and was involved in the design, data collection, manuscript preparation and critical revision of the manuscript.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest declared.

DATA AVAILABILITY STATEMENT

Data are not publicly available due to local regulations; however, raw data can be shared with peers upon reasonable request.

ETHICS APPROVAL STATEMENT

The study was approved by the Non-Interventional Research Committee of the Institutional Review Board of Kocaeli University on 16 January 2025 with an approval number of 2025/27. All researchers complied with good clinical practice in accordance with the Declaration of Helsinki. All authors have approved the final version of this manuscript.

PATIENT CONSENT STATEMENT

Due to the retrospective nature of this non-interventional study spanning back to 2012, individual consent was not deemed necessary by the ethical board. All patient data were anonymized before analysis. No patient photo or radiologic image were collected, and no individual identifier of any sort has been included in the manuscript.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

No material from other sources has been used in this manuscript.

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