IPI-Independent Prognostic Gene Expression Signatures in DLBCL

Global and LymphGen Subtype-Specific Analysis

Data Source: Wang et al. 2026 Cancer Cell

Bulk RNA-seq (562 samples, 234 with survival)

Analysis: Cox Proportional Hazards Regression

with IPI Adjustment

Rationale & Background

The Challenge:

- IPI (International Prognostic Index) is the standard clinical risk tool
- However, IPI misses molecular heterogeneity within risk groups
- Patients with same IPI can have vastly different outcomes

Hypothesis:

- Gene expression profiles capture biology not reflected in IPI
- These profiles may stratify patients within IPI risk groups
- Different LymphGen subtypes may have distinct prognostic genes

Goal:

- Identify gene signatures predicting survival INDEPENDENT of IPI
- Build both global and subtype-specific signatures
- Validate in multivariate models adjusting for clinical factors

Data Overview

RNA-seq Data

562 DLBCL samples

25,066 genes

Z-score normalized

Clinical Data

234 with survival

98 deaths (42%)

IPI, COO, LymphGen

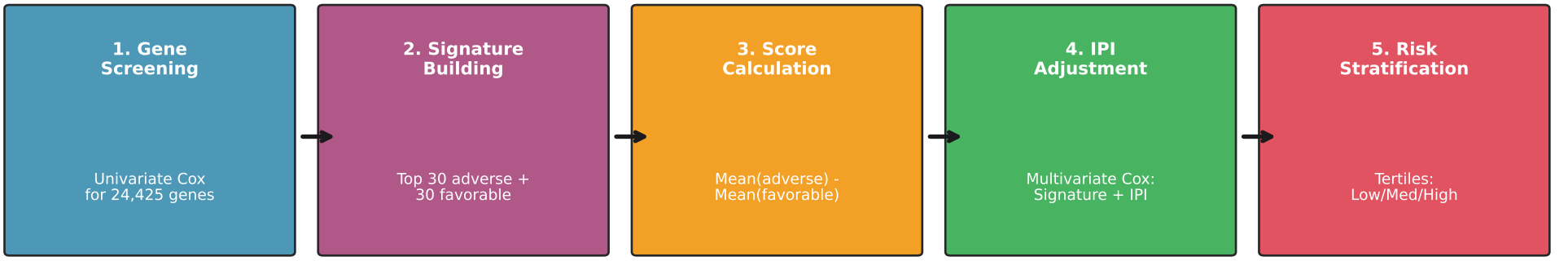
LymphGen Subtype Distribution:

Other	EZB	BN2	MCD	N1
n=117	n=50	n=42	n=19	n=6

Analysis Cohort

104 samples with complete OS + IPI data (38 events)

Analysis Pipeline



Repeated for Each LymphGen Subtype:

Key Methods

- Cox Proportional Hazards: HR per SD increase in expression
- Multiple Testing Correction: Benjamini-Hochberg FDR
- Composite Score: Weighted combination of gene z-scores

Global Signature Results

KEY FINDING: Signature is IPI-INDEPENDENT

Multivariate HR = 1.74 (95% CI: 1.33-2.29), p = 0.0001

Cox Regression Model Comparison

Model	HR	95% CI	p-value
Signature only	1.82	1.42-2.33	<0.0001
IPI only	1.84	1.47-2.31	<0.0001
Signature + IPI	**1.74**	**1.33-2.29**	**0.0001**
IPI (adjusted)	1.71	1.36-2.16	<0.0001

Risk Group Stratification

Low Risk

n=78, 14 deaths

Mortality: 17.9%

Medium Risk

n=78, 31 deaths

Mortality: 39.7%

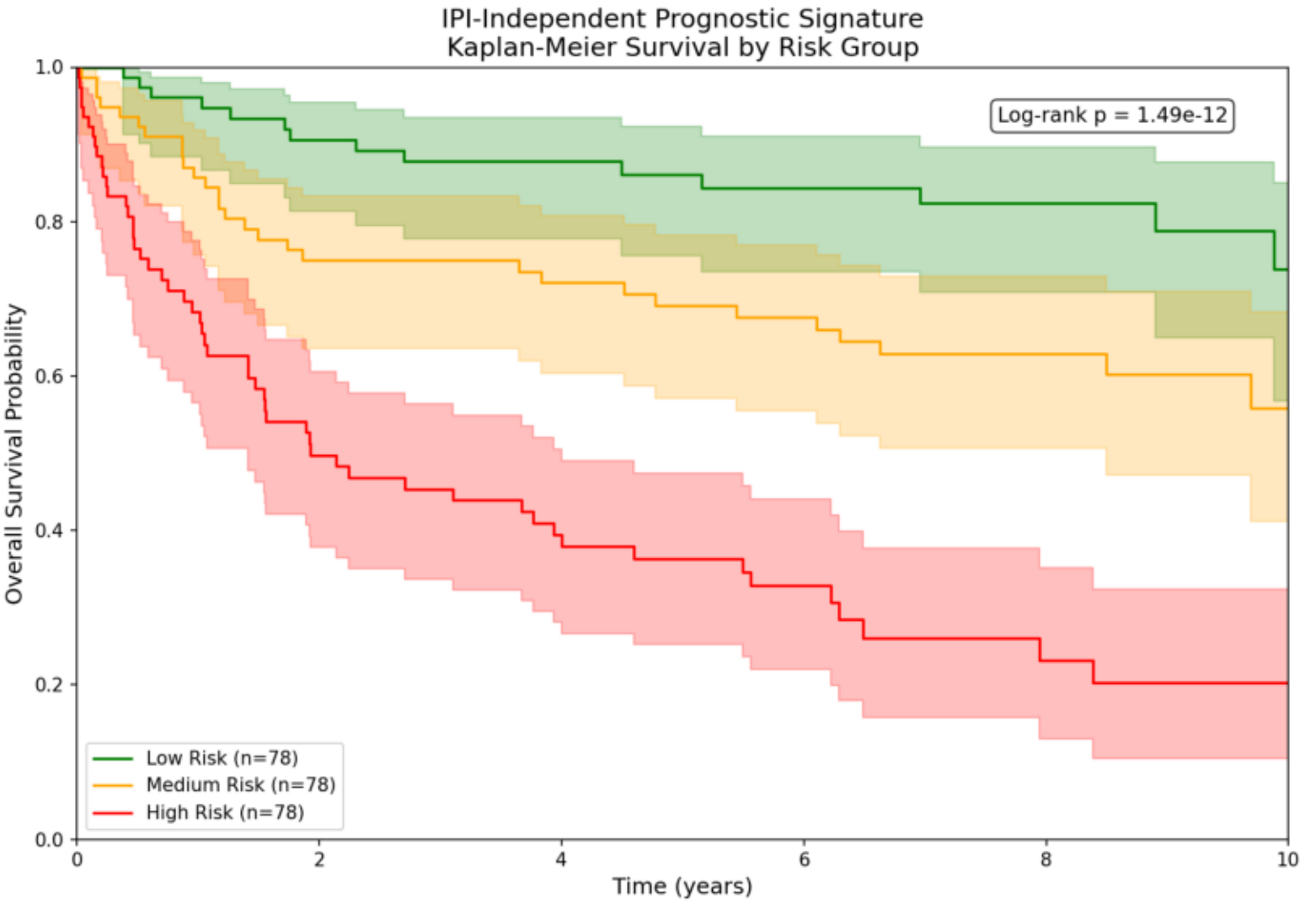
High Risk

n=78, 53 deaths

Mortality: 67.9%

Log-rank test (Low vs High): $p = 1.49 \times 10^{-12}$

Survival Analysis by Risk Group



LymphGen Subtype-Specific Signatures

Composite signatures work across all subtypes; individual gene FDR varies by power

Subtype	N	Events	FDR<0.05	HR (uni)	p-value	HR (+IPI)	p (+IPI)
Other	117	43	**16 ★**	2.11	<0.0001	2.24	0.0003
EZB	50	21	0	8.26	<0.0001	8.70	0.0038
BN2	42	15	0	8.15	<0.0001	22.63	0.021
MCD	19	15	0	5.48	0.0002	N/A	—

Key Findings:

Other

16 genes at FDR<0.05
(only powered subtype)

EZB/BN2

Composite signature
works (p<0.05)

MCD

High mortality (79%)
needs larger cohort

EZB Subtype Analysis

Cohort: n=50, 21 deaths (42%)

0 genes pass FDR < 0.05

Univariate HR = 8.26

IPI-adjusted HR = 8.70 (p=0.0038)

Individual genes exploratory (underpowered for FDR control)

ADVERSE PROGNOSIS

• **MYC**	HR=2.18	Oncogene - KEY DRIVER
• **AKAP1**	HR=2.27	Kinase anchor protein
• **B3GNTL1**	HR=2.22	Glycosyltransferase
• **FLJ41603**	HR=2.15	Uncharacterized

FAVORABLE PROGNOSIS

• **ZNF396**	HR=0.42	Zinc finger TF
• **ZNF626**	HR=0.45	Zinc finger TF
• **CIB2**	HR=0.56	Calcium binding
• **RBBP9**	HR=0.41	Retinoblastoma binding

Biological Insight

EZB includes double-hit lymphomas with MYC/BCL2 translocations.

MYC expression (HR=2.18) confirms proliferative biology drives poor outcome.

Multiple zinc finger TFs favorable - may represent differentiation state.

BN2 Subtype Analysis

Cohort: n=42, 15 deaths (36%)

0 genes pass FDR < 0.05

Univariate HR = 8.15

IPI-adjusted HR = 22.63 (p=0.021)

Individual genes exploratory (underpowered for FDR control)

ADVERSE PROGNOSIS

• **DRAP1**	HR=3.38	DR1-associated protein
• **C9orf23**	HR=3.95	Chromosome 9 ORF
• **C6orf108**	HR=4.18	Chromosome 6 ORF
• **PRCP**	HR=4.71	Prolylcarboxypeptidase

FAVORABLE PROGNOSIS

• **IFT81**	HR=0.19	Intraflagellar transport
• **PIKFYVE**	HR=0.25	Phosphoinositide kinase
• **CYP46A1**	HR=0.23	Cytochrome P450
• **SLC41A1**	HR=0.38	Magnesium transporter

Biological Insight

BN2 is characterized by BCL6 fusions and NOTCH2 mutations.

DRAP1 (transcription co-repressor) and PRCP (peptidase) adverse.

Phosphoinositide signaling (PIKFYVE) favorable - potential target.

Other/Unclassified Subtype Analysis

Cohort: n=117, 43 deaths (37%)

16 genes pass FDR < 0.05

Univariate HR = 2.11

IPI-adjusted HR = 2.24 (p=0.0003)

★ Only subtype with sufficient power for FDR-controlled gene discovery

ADVERSE (FDR < 0.05)

• **CHPT1**	HR=2.02	FDR=0.042	Choline phosphotransferase

(Only 1 adverse gene passed strict criteria)

FAVORABLE (FDR < 0.05)

• **C3**	HR=0.49	FDR=0.035	Complement
• **DNM1**	HR=0.49	FDR=0.035	Dynamin
• **ADC**	HR=0.47	FDR=0.035	Decarboxylase
• **APBA2**	HR=0.43	FDR=0.035	Adaptor protein

Biological Insight

C3 (complement) suggests tumor immune microenvironment influences survival.

CHPT1 (choline metabolism) - lipid pathway may drive aggressive phenotype.

15 favorable genes vs 1 adverse: favorable biology more detectable.

MCD Subtype Analysis

Cohort: n=19, 15 deaths (79%)

0 genes pass FDR < 0.05

Univariate HR = 5.48 (p=0.0002)

IPI-adjusted: N/A (small n)

Severely underpowered - exploratory only

ADVERSE PROGNOSIS

• **FGFR1OP**	HR=4.77	FGFR1 oncogene partner
• **MUSK**	HR=2.88	Muscle kinase
• **CFP**	HR=5.06	Complement factor P
• **C14orf133**	HR=2.19	Uncharacterized

FAVORABLE PROGNOSIS

• **ZNF189**	HR=0.19	Zinc finger protein
• **CEBPG**	HR=0.25	C/EBP gamma TF
• **LIN54**	HR=0.29	Lin-54 homolog
• **THAP9**	HR=0.13	THAP domain protein

Biological Insight

MCD has MYD88/CD79B mutations with very poor prognosis (79% mortality).

Small sample size (n=19) limits multivariate analysis power.

CEBPG (favorable) - transcription factor involved in stress response.

Key Prognostic Genes (Global Signature)

ADVERSE PROGNOSIS

(Higher expression → Worse survival)

• **ALDH3A1**	HR=1.78	Aldehyde dehydrogenase
• **UGT2B7**	HR=1.96	Glucuronosyltransferase
• **ATP1B3**	HR=1.54	Na+/K+ ATPase
• **MYC (EZB)**	HR=2.18	Oncogene
• **METTL7B**	HR=1.65	Methyltransferase

FAVORABLE PROGNOSIS

(Higher expression → Better survival)

• **LMO2**	HR=0.60	GCB marker, TF
• **SSBP3**	HR=0.53	DNA binding
• **ITPKB**	HR=0.61	Inositol kinase
• **C3**	HR=0.49	Complement
• **MMP9**	HR=0.58	Metalloproteinase

Biological Interpretation

- LMO2 is a validated GCB marker - favorable GCB biology confirmed
- MYC drives proliferation in EZB/double-hit lymphomas
- Complement (C3) suggests immune microenvironment contribution
- Metabolic enzymes (ALDH3A1, UGT2B7) may indicate drug resistance

Conclusions

1. Gene expression signatures provide prognostic information BEYOND IPI

2. Global 60-gene signature: HR=1.74 (p=0.0001) after IPI adjustment

3. All major LymphGen subtypes have distinct IPI-independent prognostic genes

4. Risk stratification: Low (18%) vs High (68%) mortality - striking separation

5. Key biological insights: LMO2, MYC, complement genes contribute to prognosis

Clinical Implication:

These signatures could identify high-risk patients within IPI groups