Data Supplement

High-grade B-cell lymphoma, not otherwise specified: a multi-institutional retrospective study

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Table S1. Characteristics of HGBL, NOS according to cytomorphology.

Variable	Burkitt-like		Blastoid		Unspecified	
	N	%	*N*	%	*N*	%
All patients	72	100.0%	38	100.0%	50	100.0%
Age group						
<=50	25	34.7%	9	23.7%	8	16.0%
50-65	23	31.9%	11	28.9%	14	28.0%
65-75	14	19.4%	13	34.2%	16	32.0%
>75	10	13.9%	5	13.2%	12	24.0%
Sex						
Male	47	65.3%	26	68.4%	35	70.0%
Female	25	34.7%	12	31.6%	15	30.0%
ECOG performance status						
0-1	56	82.4%	28	73.7%	36	76.6%
2-4	12	17.6%	10	26.3%	11	23.4%
Stage						
1 or 2	24	33.8%	7	18.4%	17	35.4%
3 or 4	47	66.2%	31	81.6%	31	64.6%
>1 extranodal site						
No	47	65.3%	14	36.8%	33	66.0%
Yes	25	34.7%	24	63.2%	17	34.0%
Bone marrow involvement						
No	53	75.7%	22	59.5%	38	84.4%
Yes	17	24.3%	15	40.5%	7	15.6%
CNS involvement						
No	65	90.3%	34	89.5%	50	100.0%
Yes	7	9.7%	4	10.5%	0	0.0%
LDH > ULN						
No	22	33.3%	9	25.0%	7	15.2%
Yes	44	66.7%	27	75.0%	39	84.8%
LDH > 3xULN						
No	53	80.3%	24	66.7%	34	73.9%
Yes	13	19.7%	12	33.3%	12	26.1%
IPI						
Low	21	32.3%	5	13.9%	8	17.4%
Intermediate low	12	18.5%	4	11.1%	11	23.9%
Intermediate high	16	24.6%	12	33.3%	14	30.4%
High	16	24.6%	15	41.7%	13	28.3%
Cell of origin[1]						
GCB	61	85.9%	33	89.2%	37	74.0%
Non-GCB	10	14.1%	4	10.8%	13	26.0%
CD10						
Negative	12	16.7%	6	15.8%	19	38.0%
Positive	60	83.3%	32	84.2%	31	62.0%
BCL6 expression						
Negative	12	17.9%	9	26.5%	9	18.4%
Positive	55	82.1%	25	73.5%	40	81.6%
BCL2 expression						
Negative	32	44.4%	16	45.7%	23	48.9%
Positive	40	55.6%	19	54.3%	24	51.1%
MYC expression						
Negative	13	20.0%	12	37.5%	15	33.3%
Positive	52	80.0%	20	62.5%	30	66.7%
MUM1 expression						
Negative	34	58.6%	15	46.9%	23	54.8%
Positive	24	41.4%	17	53.1%	19	45.2%
Dual expressor						
Negative	34	52.3%	25	78.1%	29	67.4%
Positive	31	47.7%	7	21.9%	14	32.6%
CD10+BCL6+BCL2- phenotype						
No	42	62.7%	22	64.7%	36	76.6%
Yes	25	37.3%	12	35.3%	11	23.4%
CD5 expression						
Negative	65	97.0%	26	76.5%	31	75.6%
Positive	2	3.0%	8	23.5%	10	24.4%
MYC rearrangement						
No	45	62.5%	30	78.9%	41	82.0%
Yes	27	37.5%	8	21.1%	9	18.0%
BCL2 rearrangement						
No	55	94.8%	23	76.7%	39	84.8%
Yes	3	5.2%	7	23.3%	7	15.2%
BCL6 rearrangement						
No	51	91.1%	28	90.3%	40	85.1%
Yes	5	8.9%	3	9.7%	7	14.9%
First-line regimen						
DA-EPOCH-R	36	51.4%	16	42.1%	16	32.0%
R-CHOP	16	22.9%	11	28.9%	26	52.0%
R-CODOX-M/IVAC	5	7.1%	3	7.9%	3	6.0%
R-hyperCVAD/MA	4	5.7%	2	5.3%	0	0.0%
other	7	10.0%	5	13.2%	4	8.0%
untreated	2	2.9%	1	2.6%	1	2.0%

Note: table excludes observations with missing data

Table S2. Characteristics of HGBL, NOS according to cell of origin by Hans algorithm.

Variable	GCB		Non-GCB		*P* (exact)
	N	%	*N*	%	
All patients	131	100.0%	27	100.0%	
Age group					0.55
<=50	37	28.2%	4	14.8%	
50-65	41	31.3%	7	25.9%	
65-75	35	26.7%	8	29.6%	
>75	18	13.7%	8	29.6%	
Sex					0.82
Male	87	66.4%	19	70.4%	
Female	44	33.6%	8	29.6%	
ECOG performance status					0.11
0-1	102	81.6%	17	65.4%	
2-4	23	18.4%	9	34.6%	
Stage					0.99
1 or 2	40	31.0%	8	30.8%	
3 or 4	89	69.0%	18	69.2%	
>1 extranodal site					0.52
No	76	58.0%	18	66.7%	
Yes	55	42.0%	9	33.3%	
Bone marrow involvement					0.99
No	94	74.6%	18	75.0%	
Yes	32	25.4%	6	25.0%	
CNS involvement					0.99
No	122	93.1%	25	92.6%	
Yes	9	6.9%	2	7.4%	
LDH > ULN					0.13
No	34	27.9%	3	12.5%	
Yes	88	72.1%	21	87.5%	
LDH > 3xULN					0.61
No	93	76.2%	17	70.8%	
Yes	29	23.8%	7	29.2%	
IPI					0.22
Low	31	25.6%	3	12.5%	
Intermediate low	23	19.0%	4	16.7%	
Intermediate high	30	24.8%	11	45.8%	
High	37	30.6%	6	25.0%	
Cytomorphology					0.13
Burkitt-like	61	46.6%	10	37.0%	
Blastoid	33	25.2%	4	14.8%	
Unspecified	37	28.2%	13	48.1%	
CD10					<0.001
Negative	8	6.1%	27	100.0%	
Positive	123	93.9%	0	0.0%	
BCL6 expression					0.43
Negative	23	18.9%	7	25.9%	
Positive	99	81.1%	20	74.1%	
BCL2 expression					0.032
Negative	64	50.4%	7	26.9%	
Positive	63	49.6%	19	73.1%	
MYC expression					0.22
Negative	36	30.8%	4	16.7%	
Positive	81	69.2%	20	83.3%	
MUM1 expression					<0.001
Negative	70	66.0%	2	7.7%	
Positive	36	34.0%	24	92.3%	
Dual expressor					0.016
Negative	79	68.1%	9	39.1%	
Positive	37	31.9%	14	60.9%	
CD10+BCL6+BCL2- phenotype					<0.001
No	73	60.3%	26	100.0%	
Yes	48	39.7%	0	0.0%	
CD5 expression					0.13
Negative	102	87.9%	19	76.0%	
Positive	14	12.1%	6	24.0%	
MYC rearrangement					0.009
No	89	67.9%	25	92.6%	
Yes	42	32.1%	2	7.4%	
BCL2 rearrangement					0.13
No	97	85.1%	19	100.0%	
Yes	17	14.9%	0	0.0%	
BCL6 rearrangement					0.022
No	105	92.9%	14	73.7%	
Yes	8	7.1%	5	26.3%	
First-line regimen					0.93
DA-EPOCH-R	56	43.1%	11	42.3%	
R-CHOP	44	33.8%	9	34.6%	
R-CODOX-M/IVAC	9	6.9%	2	7.7%	
R-hyperCVAD/MA	5	3.8%	0	0.0%	
other	13	10.0%	3	11.5%	
untreated	3	2.3%	1	3.8%	

Note: table excludes observations with missing data

Table S3. Characteristics of cases which did or did not undergo additional expert local histology review.

Variable	No additional review		Local histology review		*P* (exact)
	N	%	*N*	%	
All patients	63	100.0%	97	100.0%	
Age group					0.78
<=50	15	23.8%	27	27.8%	
50-65	18	28.6%	30	30.9%	
65-75	17	27.0%	26	26.8%	
>75	13	20.6%	14	14.4%	
Sex					0.30
Male	46	73.0%	62	63.9%	
Female	17	27.0%	35	36.1%	
ECOG performance status					0.55
0-1	48	81.4%	72	76.6%	
2-4	11	18.6%	22	23.4%	
Stage					0.60
1 or 2	20	33.3%	28	28.9%	
3 or 4	40	66.7%	69	71.1%	
>1 extranodal site					0.99
No	37	58.7%	57	58.8%	
Yes	26	41.3%	40	41.2%	
Bone marrow involvement					0.99
No	42	73.7%	71	74.7%	
Yes	15	26.3%	24	25.3%	
CNS involvement					0.53
No	60	95.2%	89	91.8%	
Yes	3	4.8%	8	8.2%	
LDH > ULN					0.084
No	10	17.5%	28	30.8%	
Yes	47	82.5%	63	69.2%	
LDH > 3xULN					0.33
No	40	70.2%	71	78.0%	
Yes	17	29.8%	20	22.0%	
IPI					0.33
Low	14	24.6%	20	22.2%	
Intermediate low	10	17.5%	17	18.9%	
Intermediate high	12	21.1%	30	33.3%	
High	21	36.8%	23	25.6%	
Cytomorphology					0.20
Burkitt-like	28	44.4%	44	45.4%	
Blastoid	11	17.5%	27	27.8%	
Unspecified	24	38.1%	26	26.8%	
Cell of origin [1]					0.20
GCB	49	77.8%	82	86.3%	
Non-GCB	14	22.2%	13	13.7%	
CD10					0.70
Negative	16	25.4%	21	21.6%	
Positive	47	74.6%	76	78.4%	
BCL6 expression					0.84
Negative	11	18.6%	19	20.9%	
Positive	48	81.4%	72	79.1%	
BCL2 expression					0.32
Negative	31	51.7%	40	42.6%	
Positive	29	48.3%	54	57.4%	
MYC expression					0.13
Negative	12	21.1%	28	32.9%	
Positive	45	78.9%	57	67.1%	
MUM1 expression					0.072
Negative	22	44.0%	50	61.0%	
Positive	28	56.0%	32	39.0%	
Dual expressor					0.48
Negative	33	58.9%	55	65.5%	
Positive	23	41.1%	29	34.5%	
CD10+BCL6+BCL2- phenotype					0.86
No	40	69.0%	60	66.7%	
Yes	18	31.0%	30	33.3%	
CD5 expression					0.25
Negative	44	77.2%	78	91.8%	
Positive	13	22.8%	7	8.2%	
MYC rearrangement					0.21
No	42	66.7%	74	76.3%	
Yes	21	33.3%	23	23.7%	
BCL2 rearrangement					0.99
No	45	88.2%	72	86.7%	
Yes	6	11.8%	11	13.3%	
BCL6 rearrangement					0.57
No	43	86.0%	76	90.5%	
Yes	7	14.0%	8	9.5%	

Note: table excludes observations with missing data

Table S4. Characteristics of patients with HGBL, NOS receiving R-CHOP or DA-EPOCH-R as first-line therapy.

Variable	R-CHOP		DA-EPOCH-R		*P* (exact)
	N	%	*N*	%	
All patients	53	100.0%	68	100.0%	
Age group					0.47
<=50	6	11.3%	19	27.9%	
50-65	17	32.1%	26	38.2%	
65-75	20	37.7%	16	23.5%	
>75	10	18.9%	7	10.3%	
Sex					0.99
Male	36	67.9%	45	66.2%	
Female	17	32.1%	23	33.8%	
ECOG performance status					0.63
0-1	42	80.8%	55	84.6%	
2-4	10	19.2%	10	15.4%	
Stage					0.042
1 or 2	20	38.5%	14	20.9%	
3 or 4	32	61.5%	53	79.1%	
>1 extranodal site					0.19
No	36	67.9%	38	55.9%	
Yes	17	32.1%	30	44.1%	
Bone marrow involvement					0.28
No	40	80.0%	46	69.7%	
Yes	10	20.0%	20	30.3%	
CNS involvement					0.99
No	51	96.2%	66	97.1%	
Yes	2	3.8%	2	2.9%	
LDH > ULN					0.13
No	16	33.3%	13	20.3%	
Yes	32	66.7%	51	79.7%	
LDH > 3xULN					0.047
No	41	85.4%	44	68.8%	
Yes	7	14.6%	20	31.3%	
IPI					0.55
Low	12	24.5%	13	20.6%	
Intermediate low	13	26.5%	11	17.5%	
Intermediate high	12	24.5%	18	28.6%	
High	12	24.5%	21	33.3%	
Cytomorphology					0.010
Burkitt-like	16	30.2%	36	52.9%	
Blastoid	11	20.8%	16	23.5%	
Unspecified	26	49.1%	16	23.5%	
Cell of origin [1]					0.99
GCB	44	83.0%	56	83.6%	
Non-GCB	9	17.0%	11	16.4%	
CD10					0.83
Negative	13	24.5%	15	22.1%	
Positive	40	75.5%	53	77.9%	
BCL6 expression					0.48
Negative	8	15.7%	15	22.7%	
Positive	43	84.3%	51	77.3%	
BCL2 expression					0.71
Negative	23	46.9%	28	41.8%	
Positive	26	53.1%	39	58.2%	
MYC expression					0.35
Negative	13	27.7%	11	18.6%	
Positive	34	72.3%	48	81.4%	
MUM1 expression					0.69
Negative	25	54.3%	33	58.9%	
Positive	21	45.7%	23	41.1 %	
Dual expressor					0.32
Negative	29	64.4%	32	54.2%	
Positive	16	35.6%	27	45.8%	
CD10+BCL6+BCL2- phenotype					0.99
No	35	71.4%	46	69.7%	
Yes	14	28.6%	20	30.3%	
CD5 expression					0.76
Negative	37	90.2%	57	87.7%	
Positive	4	9.8%	8	12.3%	
MYC rearrangement					0.15
No	43	81.1%	47	69.1%	
Yes	10	18.9%	21	30.9%	
BCL2 rearrangement					0.17
No	39	79.6%	47	90.4%	
Yes	10	20.4%	5	9.6%	
BCL6 rearrangement					0.36
No	44	91.7%	45	84.9%	
Yes	4	8.3%	8	15.1%	

Note: table excludes observations with missing data

Table S5. Univariate associations between clinicopathologic characteristics in HGBL, NOS and PFS or OS.
Hazard ratios (HR) and 95% confidence intervals (95%CI) were derived from univariate proportional hazard models for PFS or OS conducted in a dataset augmented by multiple imputation using chained equations (except where indicated otherwise); *P* values from Wald test. Statistically significant associations are highlighted.

Variable	PFS			OS			*N* with non-missing data
	HR	95%CI	P	HR	95%CI	P	
Age (continuous)	**1.02**	**(1.00-1.03)**	**0.0193**	**1.02**	**(1.00-1.04)**	**0.0235**	160
Age > 40y	1.47	(0.78-2.80)	0.2353	1.47	(0.69-3.11)	0.3149	160
Age > 60y	1.33	(0.83-2.13)	0.2286	1.40	(0.81-2.41)	0.2278	160
Female sex	0.74	(0.45-1.23)	0.2489	0.73	(0.40-1.33)	0.3075	160
Poor performance status	**2.12**	**(1.26-3.55)**	**0.0045**	**2.68**	**(1.52-4.73)**	**0.0007**	160
Stage 3/4 (vs. 1/2)	**2.54**	**(1.4-4.62)**	**0.0022**	**2.78**	**(1.36-5.68)**	**0.0051**	160
>1 extranodal site	1.13	(0.71-1.79)	0.6037	1.29	(0.76-2.20)	0.3464	160
Bone marrow involvement	**2.05**	**(1.27-3.33)**	**0.0035**	**2.31**	**(1.32-4.04)**	**0.0034**	160
CNS involvement	1.38	(0.6-3.18)	0.4502	1.34	(0.54-3.37)	0.5294	160
LDH > ULN	**2.09**	**(1.12-3.91)**	**0.0202**	**2.24**	**(1.09-4.63)**	**0.029**	160
LDH > 3x ULN	**2.43**	**(1.47-4.02)**	**0.0006**	**2.74**	**(1.53-4.90)**	**0.0007**	160
IPI High/High-intermediate	**2.41**	**(1.44-4.02)**	**0.0008**	**2.66**	**(1.44-4.89)**	**0.0017**	160
Cytomorphology: Burkitt-like	0.76	(0.48-1.20)	0.2402	0.73	(0.42-1.25)	0.2444	160
Cytomorphology: blastoid	1.63	(0.98-2.69)	0.0573	**1.82**	**(1.02-3.25)**	**0.0423**	160
Non-GCB phenotype[1]	**1.92**	**(1.12-3.29)**	**0.0172**	1.63	(0.85-3.10)	0.1388	160
MYC expression (IHC)	1.34	(0.77-2.34)	0.2954	1.31	(0.68-2.51)	0.4232	160
BCL2 expression (IHC)	**1.91**	**(1.17-3.11)**	**0.0092**	1.69	(0.96-2.95)	0.0674	160
DEL (MYC and BCL2)	**1.81**	**(1.14-2.89)**	**0.0121**	1.63	(0.94-2.82)	0.0833	160
CD10+BCL6+BCL2-	**0.47**	**(0.27-0.82)**	**0.0075**	0.55	(0.29-1.03)	0.0601	160
CD5 expression	1.34	(0.70-2.56)	0.3823	1.17	(0.52-2.62)	0.6996	142 [a]
MYC rearrangement	1.27	(0.78-2.08)	0.3400	1.37	(0.78-2.41)	0.2726	160
BCL2 rearrangement	1.80	(0.94-3.47)	0.0779	1.76	(0.84-3.70)	0.1362	160
BCL6 rearrangement	1.52	(0.75-3.09)	0.2435	1.05	(0.42-2.66)	0.9162	160
TP53 alteration	**4.01**	**(1.34-11.96)**	**0.0128**	**3.52**	**(1.04-11.89)**	**0.0423**	26 [a]
Pathology review group	1.40	(0.86-2.29)	0.1712	1.56	(0.87-2.79)	0.1363	160

[a] variable not imputed due to lack of model convergence

Table S6. Performance characteristics of standard prognostic indices in HGBL, NOS: International Prognostic Index (IPI), age-adjusted IPI (aaIPI) and Burkitt lymphoma-IPI (BL-IPI).

Performance of the model was characterized by hazard ratios (HR) from a proportional hazard model, C-statistic, and Akaike Information Criterion (AIC). Confidence intervals (CI) for the C-statistic were obtained using a bootstrap with 1000 replications.

Index	Group	N (%)	PFS				OS			
			HR	95%CI	C-statistic (95%CI)	AIC	HR	95%CI	C-statistic (95%CI)	AIC
IPI	Low	34 (23.1%)	1		0.64	620.0	1		0.64	460.6
	Low intermediate	27 (18.4%)	4.03	(1.52-10.67)	(0.58-0.69)		2.85	(0.93-8.78)	(0.55-0.68)	
	High intermediate	42 (28.6%)	5.82	(2.40-14.11)			4.52	(1.68-12.17)		
	High	44 (29.9%)	4.21	(1.70-10.41)			4.42	(1.64-11.88)		
aaIPI	0	19 (13.2%)	1		0.66	608.2	1		0.68	441.9
	1	33 (22.9%)	1.58	(0.48-5.12)	(0.59-0.71)		1.38	(0.34-5.52)	(0.62-0.74)	
	2	70 (48.6%)	4.14	(1.48-11.60)			3.50	(1.06-11.59)		
	3	22 (15.3%)	5.87	(1.94-17.75)			7.95	(2.29-27.65)		
BL-IPI	Low	17 (11.8%)	1		0.66	607.4	1		0.68	442.3
	Intermediate	68 (47.2%)	1.97	(0.69-5.64)	(0.60-0.71)		1.57	(0.46-5.37)	(0.61-0.73)	
	High	59 (41.0%)	4.97	(1.76-13.98)			4.9	(1.49-16.11)		

IPI risk factors: age >60y, advanced stage, LDH >ULN, performance stage ECOG ≥2, >1 extranodal site.[2]
aaIPI risk factors: advanced state, LDH >ULN, performance stage ECOG ≥2.[2]
BL-IPI risk factors: age >40y, LDH >3xULN, performance stage ECOG ≥2, CNS involvement.[3]

References

1. Hans CP, Weisenburger DD, Greiner TC, et al: Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 103:275-82, 2004
2. The International Non-Hodgkin's Lymphoma Prognostic Factors Project: A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 329:987-94, 1993
3. Olszewski AJ, Jakobsen LH, Collins GP, et al: Burkitt Lymphoma International Prognostic Index. J Clin Oncol 39:1129-1138, 2021

Table S7. Multivariable models in the subset of patients with known *TP53* alteration status (*N*=26).

Variable	PFS			OS		
	HR	95% CI	P	HR	95% CI	P
TP53 alteration	4.08	(1.06-15.68)	0.040	2.99	(0.76-11.70)	0.11
Poor performance status	2.70	(0.39-18.64)	0.31	3.53	(0.58-21.40)	0.17
LDH > 3x ULN	1.04	(0.27-3.97)	0.95	1.75	(0.45-6.78)	0.42
DEL phenotype	6.82	(1.13-41.19)	0.036	3.59	(0.55-23.40)	0.18

CI: confidence interval; DEL: dual expresser lymphoma (MYC and BCL2); HR: hazard ratio; LDH: lactate dehydrogenase; PFS: progression-free survival; OS: overall survival; ULN: upper limit of normal

Table S8. Multivariable survival models evaluating the use of DA-EPOCH-R versus R-CHOP chemotherapy in HGBL, NOS (*N*=121)

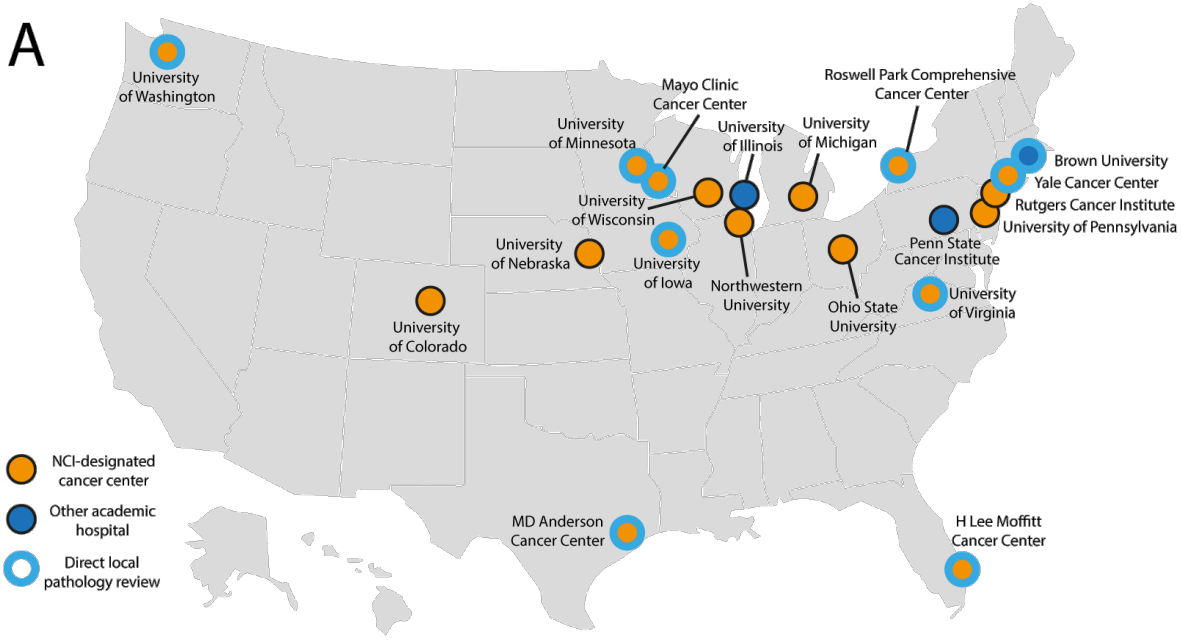
The model was deployed in a dataset augmented by multiple imputation using chained equations, as described in Methods. Model coefficients and standard errors were averaged across the imputed datasets using Rubin's rules. Age was modeled using a restricted cubic spine (RCS) to account for potential non-linear association (note: the RCS coefficients do not have a well-defined interpretation and are listed for reference only).

Variable	PFS			OS		
	HR	95% CI	P	HR	95% CI	P
R-CHOP	*Ref.*			*Ref.*		
DA-EPOCH-R	0.76	(0.41-1.41)	0.392	1.08	(0.51-2.27)	0.839
Age (RCS 1)	1.04	(0.95-1.15)	0.395	1.06	(0.93-1.21)	0.383
(RCS 2)	0.88	(0.67-1.16)	0.373	0.86	(0.61-1.23)	0.406
(RCS 3)	1.82	(0.33-10.11)	0.493	2.77	(0.3-25.37)	0.368
(RCS 4)	0.41	(0-65.67)	0.732	0.04	(0-39.53)	0.365
Poor performance status	1.23	(0.58-2.61)	0.588	2.07	(0.87-4.94)	0.101
Stage 3/4 (versus 1/2)	3.02	(1.24-7.34)	0.015	2.89	(0.95-8.84)	0.063
LDH: > ULN	1.17	(0.5-2.73)	0.724	1.03	(0.37-2.89)	0.949
> 3x ULN	2.55	(1.3-4.99)	0.006	2.43	(1.09-5.42)	0.031
MYC-R	0.79	(0.38-1.64)	0.525	0.78	(0.33-1.82)	0.569
Non-GCB phenotype	1.59	(0.73-3.46)	0.243	1.08	(0.4-2.96)	0.877
DEL phenotype	1.73	(0.93-3.22)	0.084	1.43	(0.67-3.06)	0.353

CI: confidence interval; DEL: dual expresser lymphoma (MYC and BCL2); GCB: Germinal center B-cell; HR: hazard ratio; LDH: lactate dehydrogenase; *MYC*-R: *MYC* rearrangement present; PFS: progression-free survival; OS: overall survival; ULN: upper limit of normal

Fig. S1. (A) Geographic distribution of participating hospitals; (B) case selection process in the study.

The direct local pathology review was conducted by expert lymphoma hematopathologists for cases submitted from 10 participating institutions (overall, 61% of cases). For the central pathology report review, the corresponding author reviewed de-identified pathology reports and the results of FISH testing, excluding cases: without known *MYC*-R status; with insufficient workup to rule out double-hit HGBL, blastoid mantle cell lymphoma, or lymphoblastic lymphoma; where the final HGBL, NOS diagnosis, or a compatible description of morphology was not evident. Overall, this review led to exclusion of 36 of 99 cases (36%), constituting between 0% and 88% of cases from each hospital.



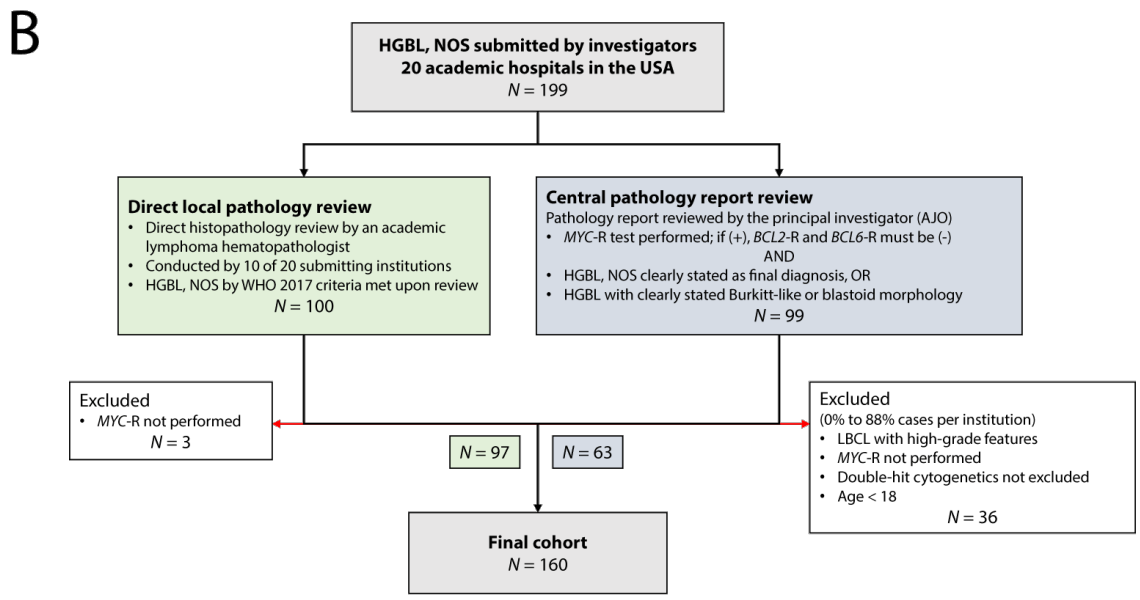


Fig. S2. Concordance in the assessment of HGBL morphology among expert hematopathologists.

Entire slides, stained with hematoxylin and eosin, were scanned using Aperio ScanScope Slide Scanner at 20x magnification, and examined by 6 academic hematopathologists (LJM, MG, AB, MAAL, MX, KNN), who assigned morphology (DLBCL-like, Burkitt-like, blastoid, or unable to determine due to artifact). The readers were blinded to the results of immunohistochemistry, molecular tests, or to the final clinicopathologic diagnosis.

Complete concordance was achieved in only 2 cases (marked with green asterisks), for an inter-rater reliability measured by Cohen's kappa of 0.27—consistent with "minimal" concordance.

In cases HGBL-1, HGBL-2, and HGBL-3, multiple slides from the same patient were examined, either from different biopsies, or from the same biopsy, illustrating variable morphology assignments from the same lymphoma. Furthermore, there was no concordance in 3 cases with final clinicopathologic diagnoses of DLBCL, NOS, Burkitt lymphoma, or B-lymphoblastic lymphoma.

The figure shows a heatmap of specific morphologic assignments. Note: rows do not correspond to a specific pathologist.

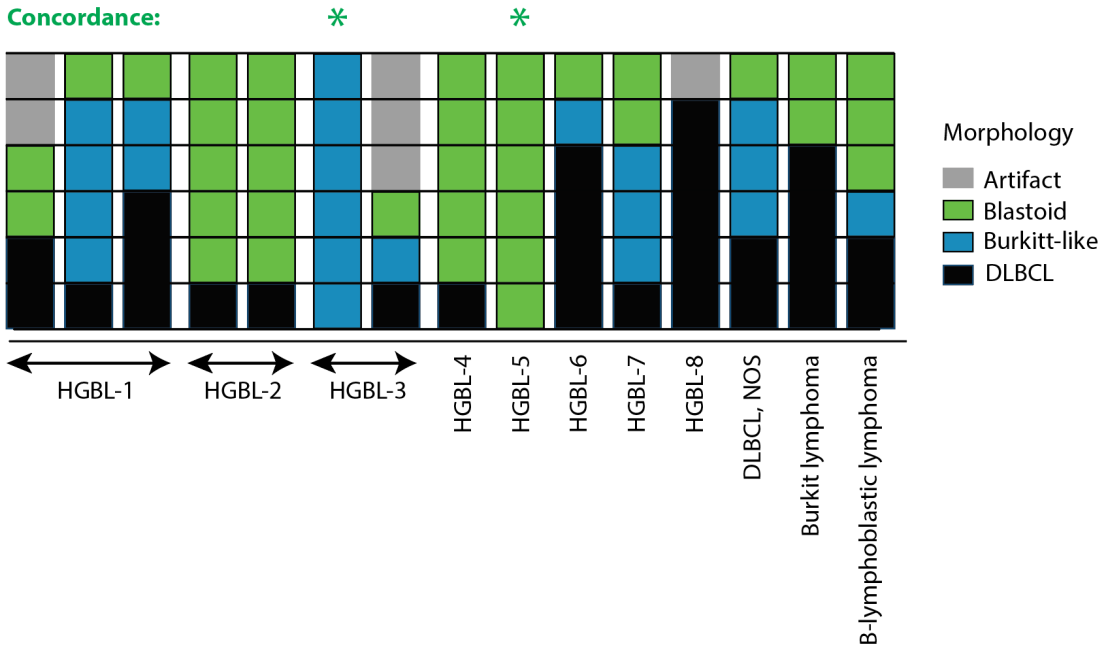


Fig. S3. Clinical prognostic factors in HGBL, NOS: progression-free survival (PFS) stratified by (A) age, (B) LDH, (C) stage, (D) bone marrow involvement, (E) International Prognostic Index (IPI), and (F) age-adjusted IPI. *P*-values are from log-rank tests (test for trend where indicated).

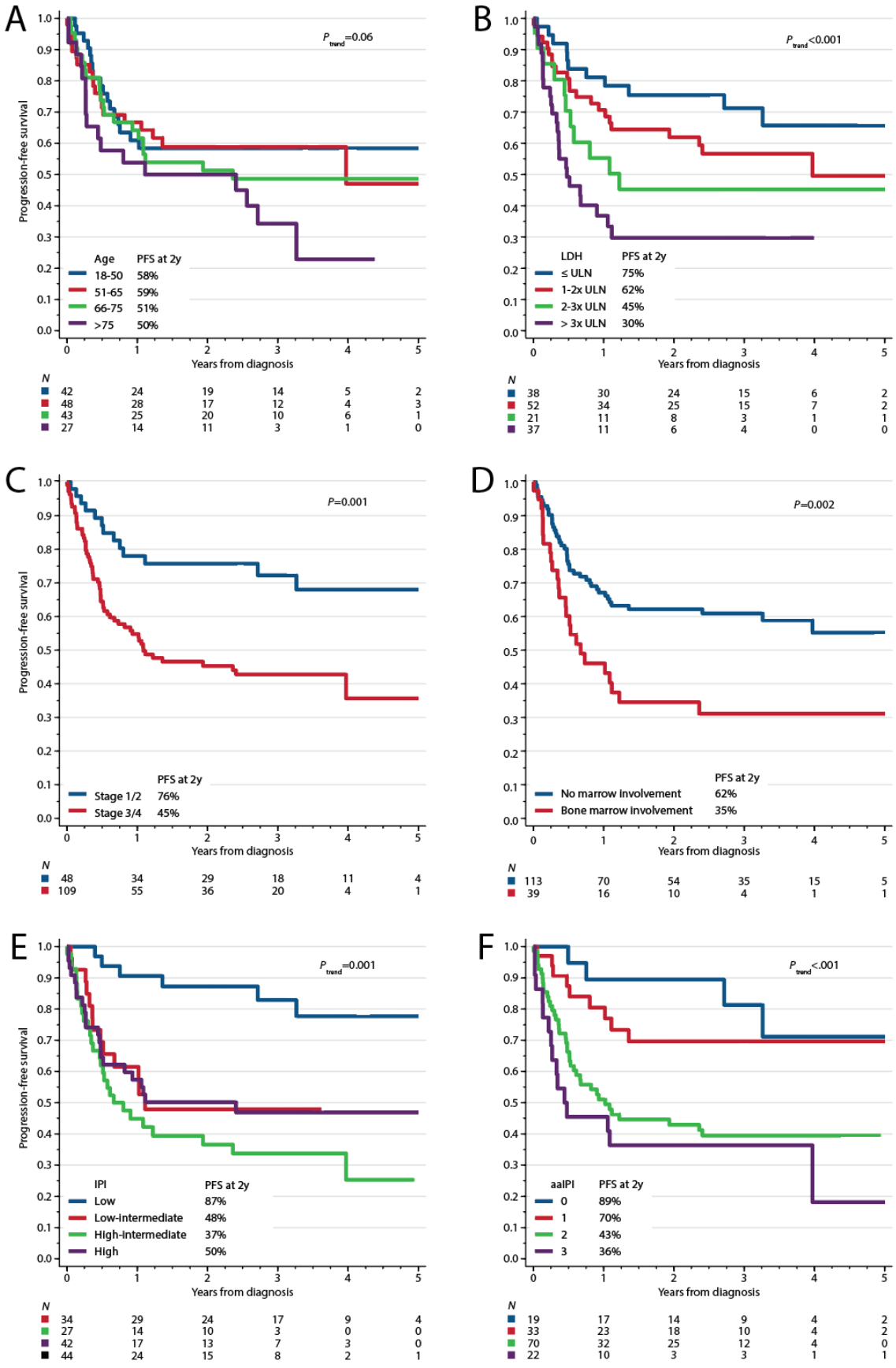


Fig. S4. Clinical prognostic factors in HGBL, NOS: overall survival (OS) stratified by (A) age, (B) LDH, (C) stage, (D) bone marrow involvement, (E) International Prognostic Index (IPI), and (F) age-adjusted IPI. *P*-values are from log-rank tests (test for trend where indicated).

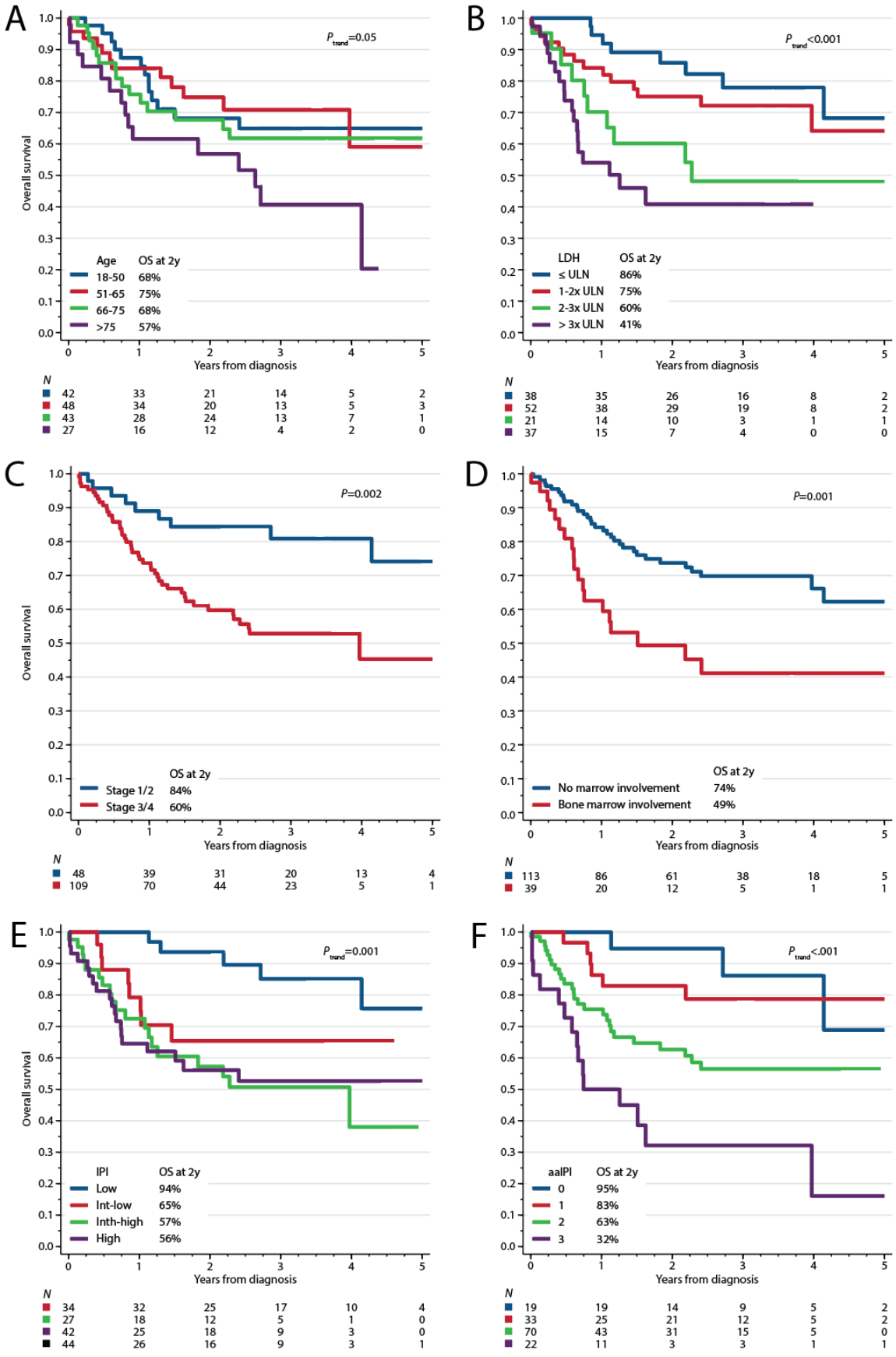


Fig. S5. Additional prognostic factors in HGBL, NOS: PFS stratified by (A) presence or absence of additional expert pathology review for the study, (B) MYC expression by immunohistochemistry (IHC), (C) BCL2 expression by IHC, (D) CD5 expression (by IHC or flow cytometry), (E) presence of *BCL2::IGH* rearrangement or *BCL2* extra copies (EC); (F) presence of *BCL6* rearrangement (*BCL6*-R) or *BCL6* EC; OS stratified by the same factors (G-L, respectively). *P*-values are from log-rank tests.

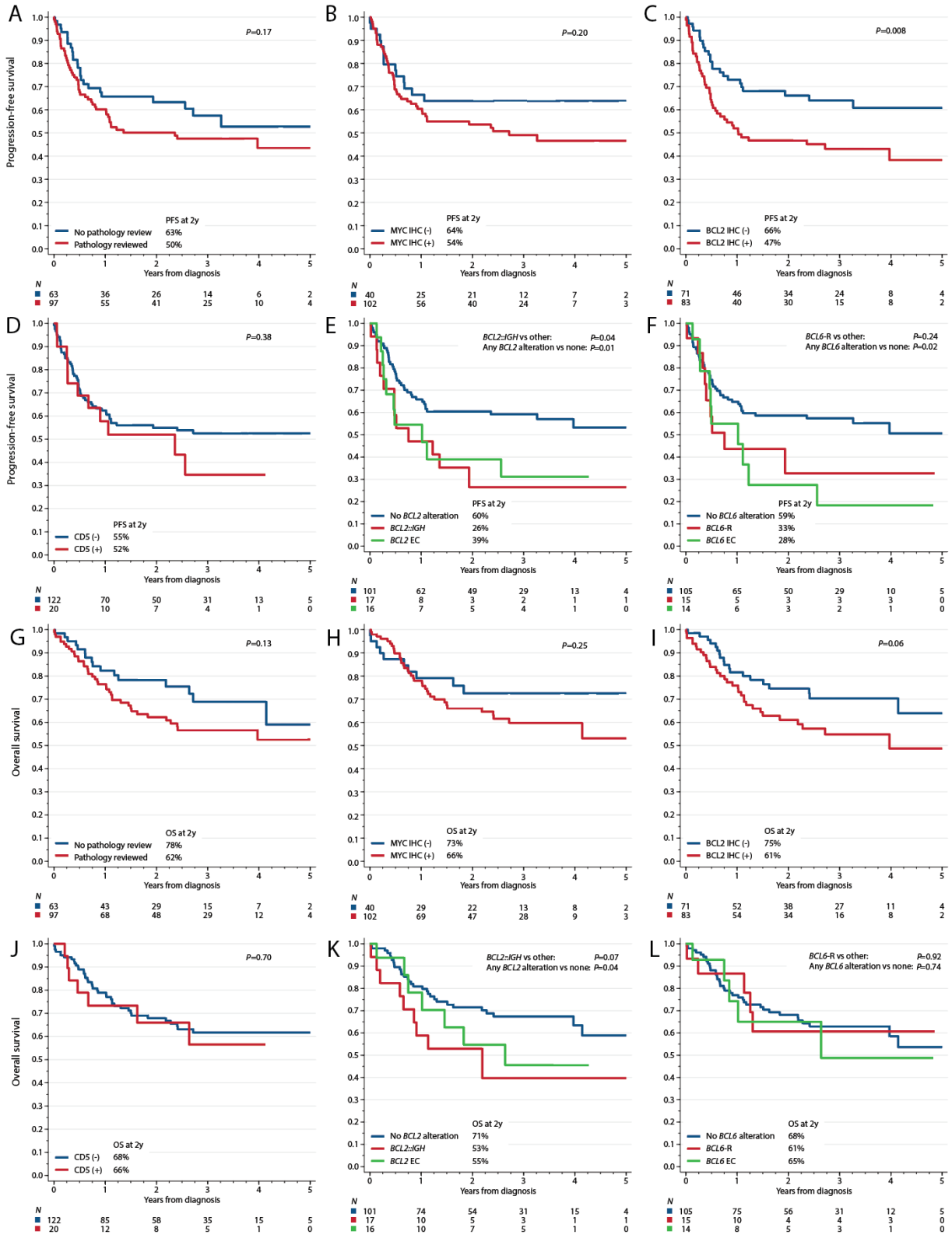


Fig. S6. (A) PFS and (B) OS of patients with HGBL, NOS treated with first-line R-CHOP or DA-EPOCH-R, stratified by age-adjusted International Prognostic Index (aaIPI); *P*-values are from log-rank tests stratified by aaIPI.