Supplementary Materials: The Incidence and Treatment Response of Double Expression of MYC and BCL2 in Patients with Diffuse Large B-Cell Lymphoma: A Systematic Review and Meta-Analysis

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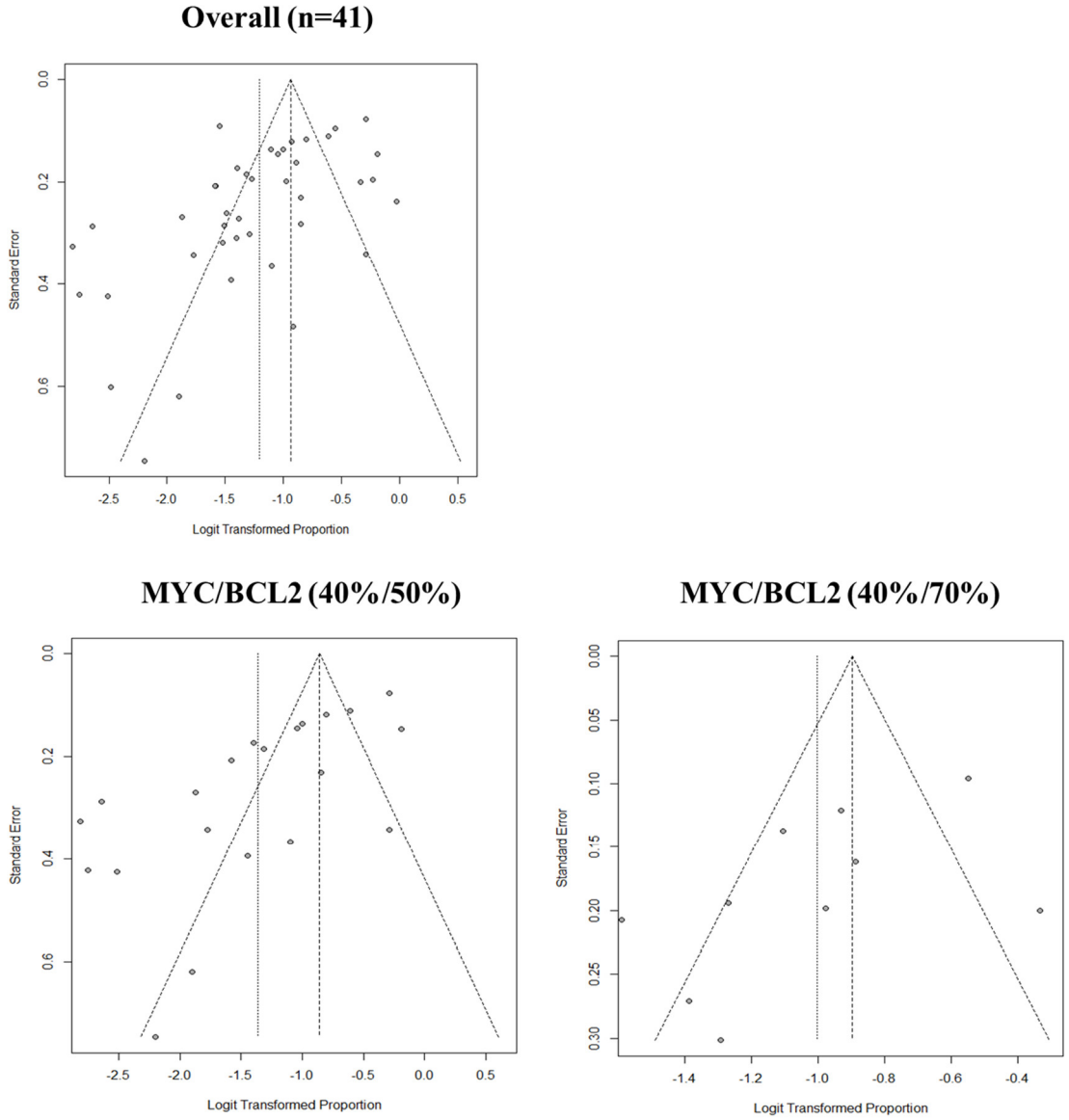

Figure S1. Funnel plots for pooled proportion of double protein expression of MYC and BCL2. Funnel plot and Egger's test revealed substantial publication bias in overall pooled proportion ($p < 0.001$) and subgroups using ≥40%/50% cutoffs ($p < 0.001$) and ≥40%/70% cutoffs ($p = 0.07$).

Table S1. Newcastle-Ottawa Quality Assessment Scale of included studies in the synthesis of double expressor status.

Reference	Design	Selection	Comparability	Outcome	Total Score
Abdulla et al. (2016)[1]	Cohort	4	0	2	6
Barraclough et al. (2019)[2]	Cohort	4	2	3	9
Birceanu Corobea et al. (2018)[3]	Cohort	4	0	3	7
Clark Schneider et al. (2016)[4]	Cohort	4	2	2	8
Fogliatto et al. (2019)[5]	Cohort	4	2	2	8
Friedberg et al. (2014)[6]	Secondary analysis	4	0	2	6
Green et al. (2012)[7]	Cohort	4	2	3	9
Hori et al. (2019)[8]	Cohort	4	0	3	7
Jesionek-Kupnicka et al. (2019)[9]	Cohort	4	2	1	7
Johnson et al. (2012)[10]	Cohort	4	2	2	8
Jovanovic et al. (2015)[11]	Cohort	4	0	2	6
Klanova et al. (2019)[12]	Secondary analysis	4	2	2	8
Li et al. (2018)[13]	Cohort	4	0	2	6
Li et al. (2017)[14]	Cohort	4	2	2	8
Liu et al. (2017)[15]	Cohort	4	2	2	8
Lu et al. (2015)[16]	Cohort	4	2	3	9
Ma et al. (2019)[17]	Cohort	4	2	2	8
Mohammed et al. (2019)[18]	Cohort	4	2	3	9
Molina et al. (2014)[19]	Secondary analysis	4	2	3	9
Na et al. (2019)[20]	Cohort	4	2	2	8
Pedersen et al. (2017)[21]	Cohort	4	2	2	8
Peroja et al. (2018)[22]	Cohort	4	2	2	8
Perry et al. (2014)[23]	Cohort	4	0	3	7
Petrella et al. (2017)[24]	Secondary analysis	4	2	2	8
Phang et al. (2019)[25]	Cohort	4	2	2	8
Rajnai et al. (2014)[26]	Cohort	4	2	3	9
Scott et al. (2015)[27]	Cohort	4	2	2	8
Sha et al. (2019)[28]	Secondary analysis	4	0	2	6
Staiger et al. (2017)[29]	Secondary analysis	4	2	2	8
Suresh et al. (2019)[30]	Cohort	4	0	2	6
Takahashi et al. (2016)[31]	Cohort	4	2	3	9
Teoh et al. (2018)[32]	Cohort	4	2	3	9
Tessier-Cloutier et al. (2019)[33]	Cohort	4	0	2	6
Ting et al. (2019)[34]	Cohort	4	2	2	8
Wang et al. (2017) *[35]	Cohort	4	2	3	9
Xia et al. (2015)[36]	Cohort	4	2	3	9
Xie et al. (2014)[37]	Cohort	4	0	3	7
Xu et al. (2017)[38]	Cohort	4	2	3	9
Yan et al. (2014)[39]	Cohort	4	2	2	8
Ye et al. (2016)[40]	Cohort	4	2	2	8
Zhang Y et al. (2018)[41]	Cohort	4	2	1	7
Wang et al. (2015)[42]	Cohort	3	0	2	5

Note–overall quality of a study: 8–9, very good; 6–7, good; 4–5, satisfactory; 0–3, unsatisfactory. * A study by Wang et al. selected patients whose outcome were already present at start of study. The study received five scores ("satisfactory" rating) and was excluded in the systematic review and meta-analyses.

Table S2. Patient characteristics of included studies in the synthesis of double expressor status.

First Author	IPI Category	Ann Arbor Stage	Elevated LDH	Treatment Arm
Abdulla M	† 0 (19%), 1(24%), 2 (38%), 3(8%)	1(21%), 2(15%), 3(18%), 4(37%)	61%	R-CHOP
Barraclough A	NA	1(57%), 2(43%)	31%	R-CHOP or R-CHOP-like regimens
Birceanu Corobea A	NA	1–2(37.5%), 3–4(62.5%)	NA	R-CHOP
Clark Schneider KM	0–2 (55%), 3–5 (35%)	1–2(45%), 3–4(51%)	NA	R-CHOP
Fogliatto L	‡ 0 (10%), 1–2 (61.4%), 3–5 (28.6%)	NA	50%	R-CHOP or R-CHOP-like regimens
Friedberg JW	0–1 (24%), 2 (32%), 3 (32%), 4–5 (12%)	2–4(100%)	NA	R-CHOP with Iodine-131 Tositumomab consolidation (radioimmunotherapy)
Green TM	3–5 (34%)	3–4(48%)	48%	R-CHOP
Hori Y	0–1 (48%), 2 (22%), 3 (22%), 4–5 (7%)	* I-II1 (48%), II2, IIE, and IV (52%)		CHOP-based regimen with or without rituximab
Jesion-ek-Kupnicka D	NA	NA	NA	NA
Johnson NA	0–1 (47%), 2 (27%), 3 (14%), 4–5 (12%)	>2 (50%)	40%	R-CHOP
Jovanovic MP	0–2 (51%), 3–5 (49%)	1–2 (29%), 3–4 (71%)	66%	R-CHOP or CHOP protocols
Klanova M	NA	NA	NA	G-CHOP or R-CHOP
Li L	0–2 (71.7%), 3–5 (26.4%)	1–2 (46.7%), 3–4 (47.2%)	43.90%	R-CHOP-like regimens
Li M	≥3 (65%)	3–4 (85%)	62%	CHOP or EPOCH plus rituximab or not
Liu Y	0–1 (50%), 2–5 (50%)	NA	NA	NA
Lu TX	NA	NA	NA	R-CHOP like regimens in 141 patients, NA in others
Ma Z	0–2 (54.08%), 3–5 (45.92%)	1–2 (31.63), 3–4 (68.37)	44.90%	R-CHOP or R-CHOP-like regimens
Mohammed AA	0–1(15.6%), 2(25.6%), 3(36.7%), 4–5(22.2%)	1(15.6%), 2(27.8%), 3(38.9%), 4(17.8%)	NA	R-CHOP
Molina TJ	NA	NA	NA	R-ACVBP vs. R-CHOP (LNH 03-2B trial)
Na HY	0–2 (63.5%), 3–5 (36.4%)	1–2 (54.8%), 3–4 (45.1%)	50.20%	R-CHOP, CHOP, other chemotherapy
Pedersen MO	†2 (78%), 3 (22%)	1 (1%), 2(5%), 3(42%), 4(50%)	96%	R-CHOP or R-CHOEP
Peroja P	0–1(38%), 2–3 (48%), 4–5 (11%)	3–4 (53%)	57%	R-CHOP like regimens
Perry AM	0–2(75%), 3–5(25%)	1–2(53%), 3–4(48%)	47%	Rituximab and CHOP or CHOP-like regimens
Petrella T	0(0%), 1(1%), 2(23%), 3(38%), 4(28%), 5(10%)	3–4(90%)		R-CHOP (LNH03-6B trial)
Phang KC	NA	NA	NA	NA
Rajnai H	0–2(58.5%), 3–5(17%)	1(68.2%), 2(9.7%), 4(21.9%)	NA	R-CHOP,CHOP,CHOP-like,unknown
Scott DW	0–1(35%), 2–3(46%), 4–5(19%)	1–2(49%), 3–4(51%)	52%	R-CHOP
Sha C	NA	NA	NA	R-CHOP and RB-CHOP (REMoDL-B trial)

Staiger AM	NA	NA	NA	CHOP-14 with or without rituximab (RICOVER-60 trial), CHOEP-14 or Mega-CHOEP-21 (R-MegaCHOEP trial)
Suresh B	NA	* IE (9.5%), IIE (66.7%),IV(23.8%)	NA	CHOP based chemotherapy +/− rituximab
Takahashi H	†2(47.5%), 3(52.5%)	1–2(0%), 3–4(100%)	97.50%	R-Double-CHOP regimen
Teoh CS	NA	NA	NA	R-CHOP
Tessier-Cloutier B	NA	NA	NA	NA
Ting CY	>2 (41.7%)	3–4(56.7%)	74.20%	Various (R-CHOP like, CHOP-like, MTX-based regimen, EPOCH)
Wang XJ	≥3 (56.3%)	3–4(65.9%)	57%	R-CHOP, R-EPOCH, R-hyper-CVAD/Ara-C/MTX
Xia B	0–2(83.3%), 3–5(16.6%)	*I-II2 (60%), IIE-IV (40%)	43.30%	R-CHOP-like regimen
Xie Y	0(20%), 1(26%),2(19%),3(13%),4(19%),5(4%)	1(21%), 2(26%), 3(12%), 4(41%)	53%	R-CHOP, R-CHOP-like regimen
Xu PP	NA	NA	NA	R-CHOP
Yan LX	0–1(51%), 2(25%), 3(18%), 4–5(7%)	3–4(46%)	38%	R-CHOP or CHOP
Ye Q	NA	NA	NA	R-CHOP
Zhang Y	NA	NA	NA	NA

† Age-adjusted IPI; ‡ Revised IPI; * Lugano staging system.

Table S3. IHC protocols.

Reference	Details of IHC Protocol			Reviewer of IHC Stains
	Platform	Antibody	Staining Conditions and Other Details	
Abdulla et al. (2016)[1]	1	1	0	P
Barraclough et al. (2019)[2]	0	0	0	0
Birceanu Corobea et al. (2018)[3]	0	1	1	P
Clark Schneider et al. (2016)[4]	1	1	1	P,HP
Fogliatto et al. (2019)[5]	0	1	0	P
Friedberg et al. (2014)[6]	0	1	0	0
Green et al. (2012)[7]	1	1	0	P
Hori et al. (2019)[8]	0	1	1	P
Jesionek-Kupnicka et al. (2019)[9]	1	1	0	0
Johnson et al. (2012)[10]	1	1	0	P
Jovanovic et al. (2015)[11]	0	1	0	HP
Klanova et al. (2019)[12]	1	1	0	0
Li et al. (2018)[13]	0	1	0	P
Li et al. (2017)[14]	1	1	1	P
Liu et al. (2017)[15]	1	1	0	P
Lu et al. (2015)[16]	0	1	0	0
Ma et al. (2019)[17]	0	1	1	HP
Mohammed et al. (2019)[18]	1	1	1	0
Molina et al. (2014)[19]	1	1	1	P
Na et al. (2019)[20]	1	1	1	HP
Pedersen et al. (2017)[21]	1	1	1	HP
Peroja et al. (2018)[22]	0	1	1	HP
Perry et al. (2014)[23]	1	1	1	HP
Petrella et al. (2017)[24]	1	1	1	0
Phang et al. (2019)[25]	0	1	1	HP
Rajnai et al. (2014)[26]	0	1	0	HP
Scott et al. (2015)[27]	1	1	1	HP
Sha et al. (2019)[28]	0	1	0	P
Staiger et al. (2017)[29]	0	1	1	HP
Suresh et al. (2019)[30]	0	1	0	0
Takahashi et al. (2016)[31]	0	1	0	HP
Teoh et al. (2018)[32]	0	1	0	P
Tessier-Cloutier et al. (2019)[33]	0	1	0	P
Ting et al. (2019)[34]	1	1	1	P
Wang et al. (2017)[35]	0	1	0	0
Xia et al. (2015)[36]	0	1	1	HP
Xie et al. (2014)[37]	1	1	1	P
Xu et al. (2017)[38]	0	1	1	0
Yan et al. (2014)[39]	1	1	1	P
Ye et al. (2016)[40]	0	1	0	0
Zhang Y et al. (2018)[41]	1	1	0	P

1 = Yes; 0 = not available; P = pathologist(s); HP = hematopathologist(s).

Table S4. Study and patient characteristics from articles reporting DHITsig status in DLBCL.

First Author	Publication Year	Patient Enrollment Period	Institution	Country	Design	Patients (N)	Age (Range)	Male to Female Ratio	Clinical Setting
Nguyen et al.[43]	2021	2000–2016	City of Hope National Medical Center and from the province of Manitoba/ CancerCare Manitoba	USA	NA	247	60	1.4:1	de novo DLBCL
Isaksen et al.[44]	2021	2000–2012	23 North American academic medical centers	North America	Secondary analysis (Clinical trial, Phase 2)	90	55 (22–65)	66:34	high-risk de novo DLBCL
Ennishi et al.[45]	2018	1985–2011	BC Cancer	Canada	NA	157	62 (35–79) in DHITsig-positive, 62 (19–92) in DHITsig-negative group	95:62	de novo GCB-DLBCL

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