Comparison of BCL2 Positivity and Ki67 Expression Rates and Clinical Prognostic Parameters in Diffuse Large B-cell Lymphoma with Germinal Center (GCB) and Activated B Cell (ABC-like) Immunophenotype

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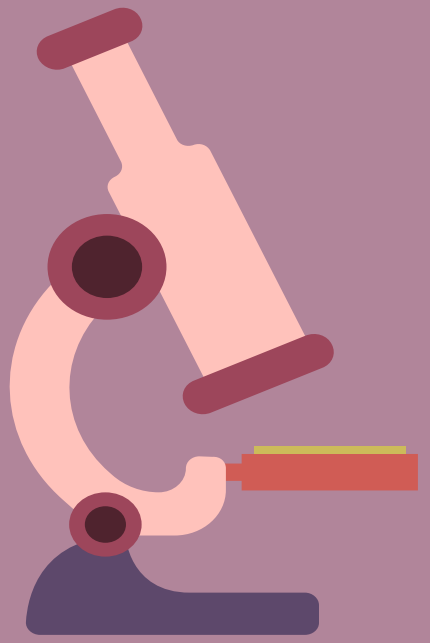

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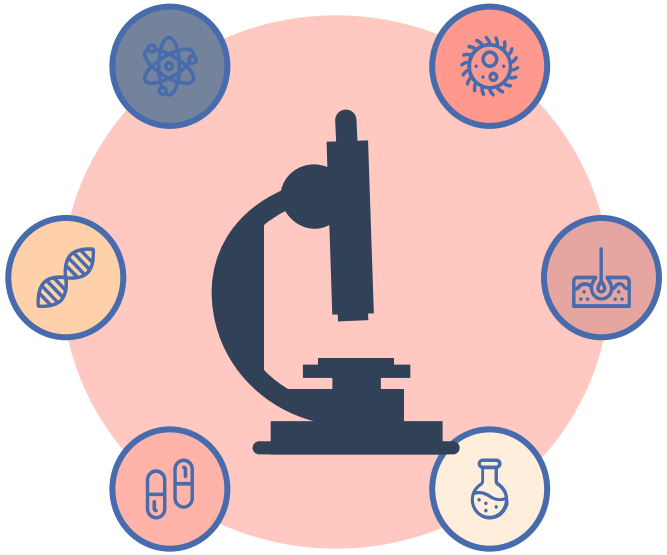
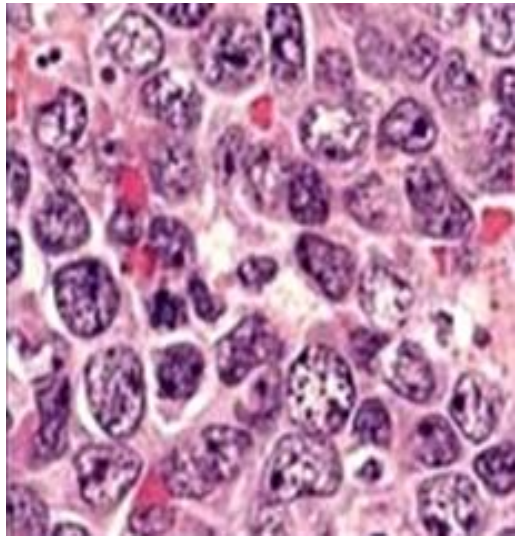
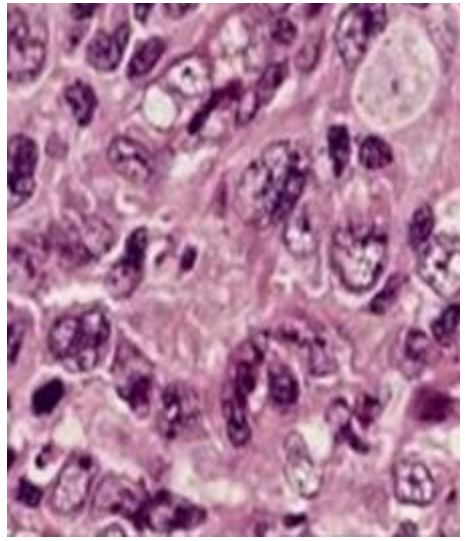


Diffuse Large B Cell Lymphoma

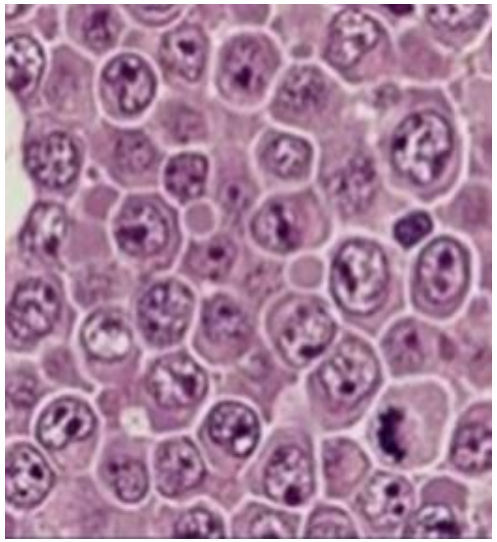
- Most common of adult lymphoma
- Aggressive course and diffuse growth pattern
- Pleomorphism and multiple mitoses



Centroblastic variant



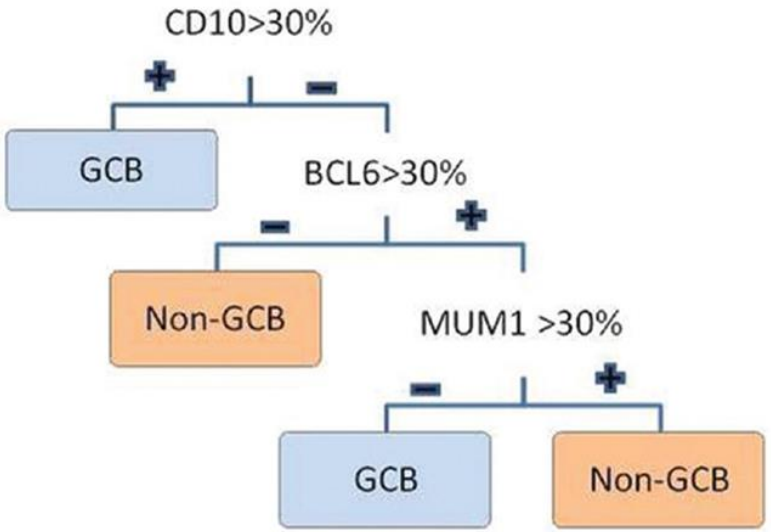
Anaplastic variant



Immunoblastic variant

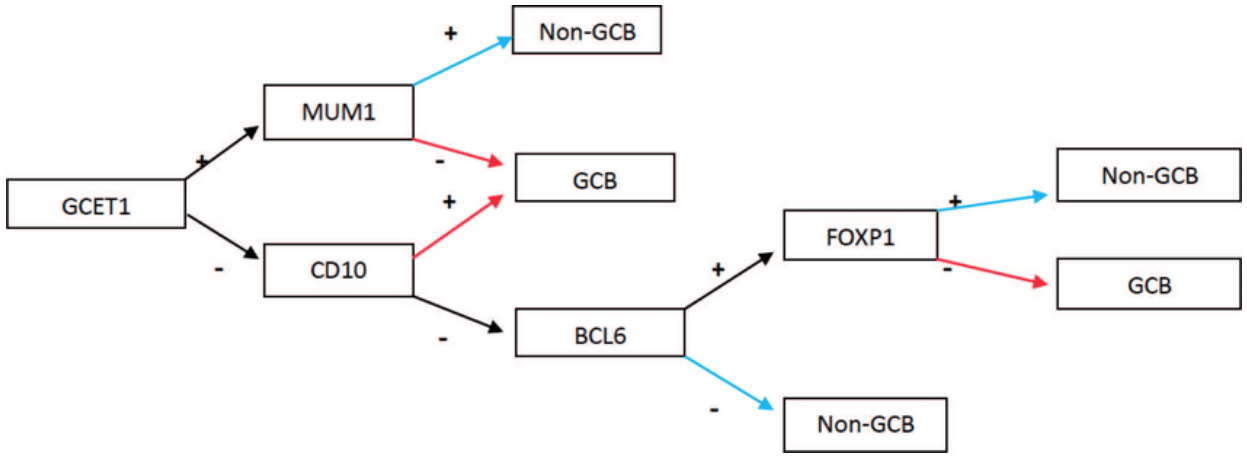
Hans algorithm

Hans et al., 2004 (3)



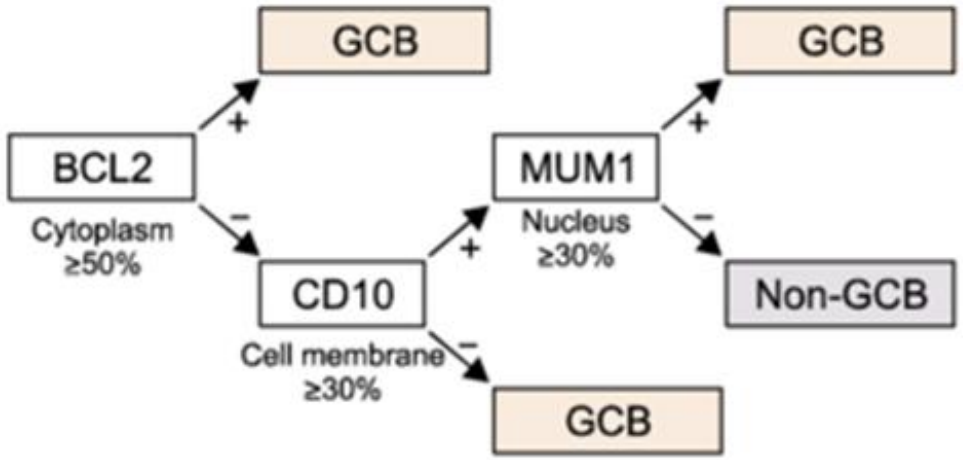
Choi algorithm

Choi et al., 2009 (4)



Muris algorithm

Hwang et al., 2013 (5)



Aims of the Study

To determine

the connection between pathological routines and clinical prognostic parametres.

To assess

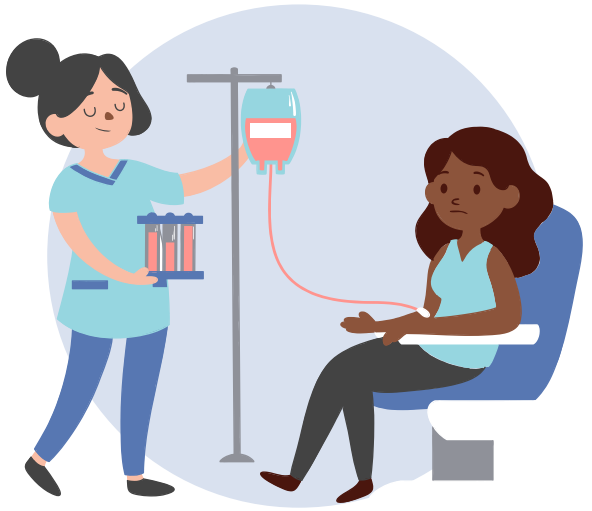
whether pathological routines have any relevance within themselves.

To contribute

the literature that Ki67 is a poor prognostic factor in terms of NCCN-IPI score and immunophenotyping.

Material & Method

n = 102



Pathology Department

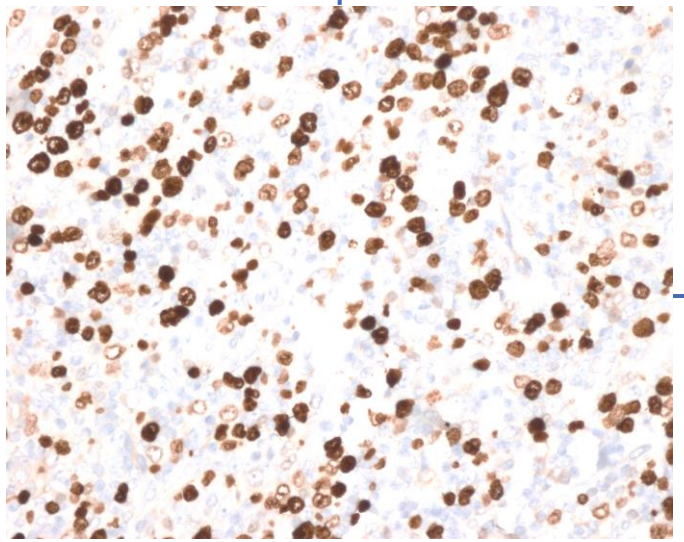
- January 2014 – February 2022
- Age 17 - 92
- Excisional biopsy
- Reports including: BCL2 posivity, Ki67 expression rates and immunophenotype markers

Hematology Department

- Age
- State (PET / CT Reports)
- Performance Status
- Extranodal Sites
- LDH Value

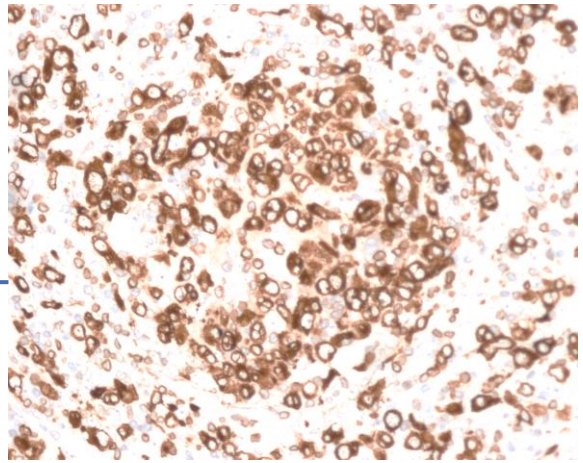
Proliferation index: Ki67

- A nuclear protein found in cell phases other than G0



Immunohistochemical BCL2 protein

- Anti-apoptotic expression



MAKROSKOPİK BULGULAR: Büyüğü 2,7x1,7x1,2 cm, küçüğü 1,1x1x0,2 cm ölçüde 2 adet yumuşak elastik kıvamda doku. Büyük dokunun kesit yüzü gri-pembe renkli, balık eti kıvamındadır 1-7. (Büyük doku): 7P7K/Y, 8. (Küçük doku): 1P1K/Y.

MİKROSKOPİK BULGULAR: Gönderilen biyopsi örneklerinde doğal lenf nodu çatısı izlenmemektedir. Fibroadipöz dokularda, yer yer ezilme artefaktının gözlendiği, difüz paternli atipik lenfoid infiltrasyon mevcuttur. Atipik lenfositler orta boyutlu, yuvarlak nüveli, veziküler kromatinli, irice tek ya da daha küçük birkaç nükleollü, dar sitoplazmalıdır. Mitotik figürler yer yer artış göstermektedir. Zeminde nekrobiyoz ve fokal nekroz odakları izlenmektedir. Atipik lenfositler immünhistokimyasal olarak CD20 (+), CD5 (-), CD10 (+), Bcl6 (+), Bcl2 (+), MUM1 (-), CD30 (-), HHV8 (-)'tir. C-myc ile > %90, orta şiddette nükleer boyanma izlenmiştir. CD21 ve CD23 ile infiltrasyon zemininde dendritik ağ organizasyonu saptanmamıştır. CD3 infiltrasyona eşlik eden reaktif T lenfositlerde pozitiftir. Ki67 proliferatif indeks heterojenite göstermekte olup yer yer %60-65'e ulaşmaktadır.

PATOLOJİK TANI:

Sağ aksiller lenf nodu; Eksizyonel biyopsi: Germinal merkez B hücre immünfenotipli agresif lenfoma infiltrasyonu.

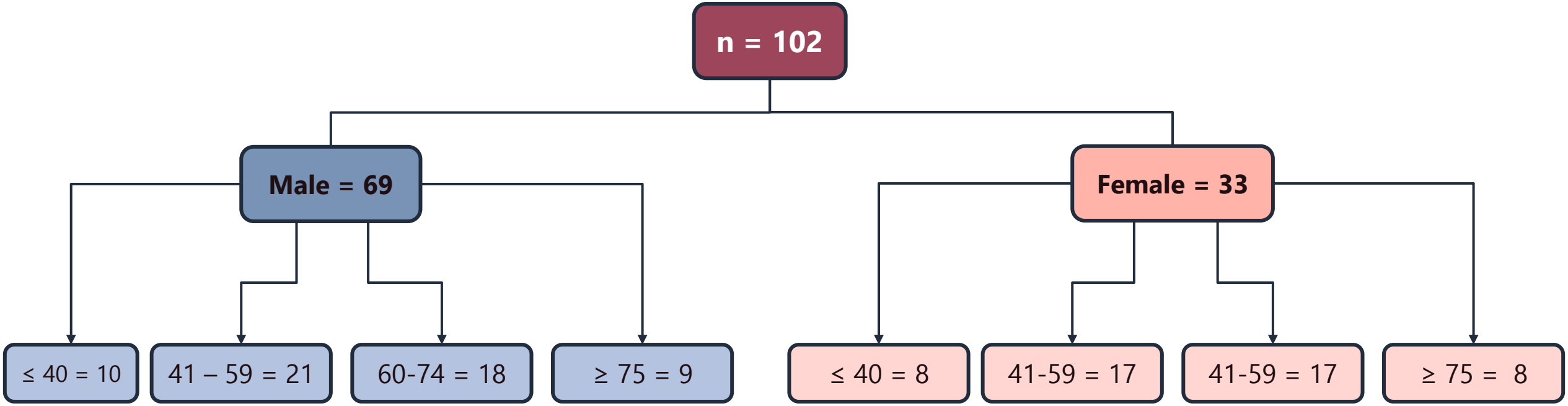
EPİKRİZ: Histopatolojik ve immünhistokimyasal özellikler ön planda difüz büyük B hücreli lenfoma, germinal merkez benzeri (GCB like) fenotip lehinde düşündürmektedir. Olguya ait inguinal lenf nodu tru-cut biyopsi örneğinde de benzer immünfenotipik özellikler gösteren ancak histopatolojik olarak indolan morfolojide atipik lenfoid infiltrasyon izlenmiştir. PET görüntüleme bulguları da göz önüne alınarak, iki biyopsi örneği birlikte değerlendirildiğinde, güncel eksizyon materyalinde izlenen agresif lenfoma, foliküler lenfomanın transformasyonu olabilir. İmmünhistokimyasal c-myc ile atipik hücrelerin çoğunda (> %90), orta şiddette nükleer boyanma saptanmıştır. Agresif B hücreli lenfoma (Double/Triple hit) ayırıcı tanısı açısından *Bcl2, Bcl6, c-myc* gen rearrangemanlerinin FISH ile değerlendirilmesi önerilir.

case number- patholc	patient name	age	gender	CD10	BCL6	MUM1	BCL2	C-myc	CD5	CD30	location	phenotyp	ki67
2866-19		55	M	focal+	postive	30%	positive	zyf/orta		positive	lymph node	GCB	%40-45
2296-19		73	M	negative	negative	zyf +	positive	negative	negative	seyrek hü	Tonsil	ABC	%40-50
1810-19		74	F	negative	>%30	positive	positive	>%30	negative	negative	brain/frontal	ABC	%80-90
379-19		76	F	positive	positive	negative	positive	%70-80	negative	negative	lymph node	GCB	%70-75
33038-18		65	F	positive	positive	negative	kısmi+	%20-30	negative	seyrek hü	lymph node	GCB	%75-85
32606-18		66	F	negative	seyrek bo	positive	zyf +	30%		kısmi+	lymph node	ABC	%70-80
31284-18		66	M	negative	positive	positive	negative	>%40	negative	negative	lymph node	ABC	>%95
28779-18		66	F	positive	fokal/zayı	Zyf+	zyf+	positive	positive	postive	lymph node	GCB	
26826-18		62	M	zyf	positive	positive	positive	40%	positive	negative	lymph node	ABC	%70-75
25951-18		33	M	postive	fokal/zayı	positive	positive			zyf +	lymph node	ABC	
24933-18		66	M	negative	fokal/zayı	positive	seyrek +		negative	positive	lymph node	ABC	
24703-18		52	M	negative	negative	positive	positive	60%	fokal+	fokal+	lymph node	ABC	%80-90
23004-18		70	M	negative	negative	positive	zyf/orta+	%20-30+	negative	positive	Tonsil	ABC	%70-75
21707-18		52	F	zyf/orta +	negative	positive	positive	<%40	negative	zyf +	Mediasten TRUCUT	GCB	%80-90
15161-18		92	F	zyf+	syrek zyf+	orta+	positive	%40+	positive	negative	lymph node	GCB	%75-85
15796-18		55	M	positive	positive	positive	positive	<%40	negative	negative	lymph node PUNCH	GCB	%70-80
14369-18		69	M	negative	positive	positive	positive	<%40	negative	negative	Tonsil	ABC	%50-60
13810-18		70	F	negative	positive	positive	negative	<%40	negative		stomach	ABC	%90-95
13712-18		42	M	positive	positive	negative	negative	>%40	negative	negative	lymph node	GCB	98
12631-18		76	F	positive	positive	negative	negative	%40 +	negatif		Retroperitoneal kitle	GCB	%70-80
11899-18		76	F	negative	<%30+	positive	positive	>%40	negatif	negatif	lymph node	ABC	%90-95
13019-18		40	M	negative	positive	positive	zyf +	<%40	zyf +	negatif	lynph node	ABC	%90-95
12311-18		45	M	fokal+	positive	positive	positive	>%40	positive	negative	lymph node	ABC	%85-90
8362-18		72	F	negative	seyrek bo	positive	negative	<%40	negative	kısmi+	Lung	ABC	%40-45

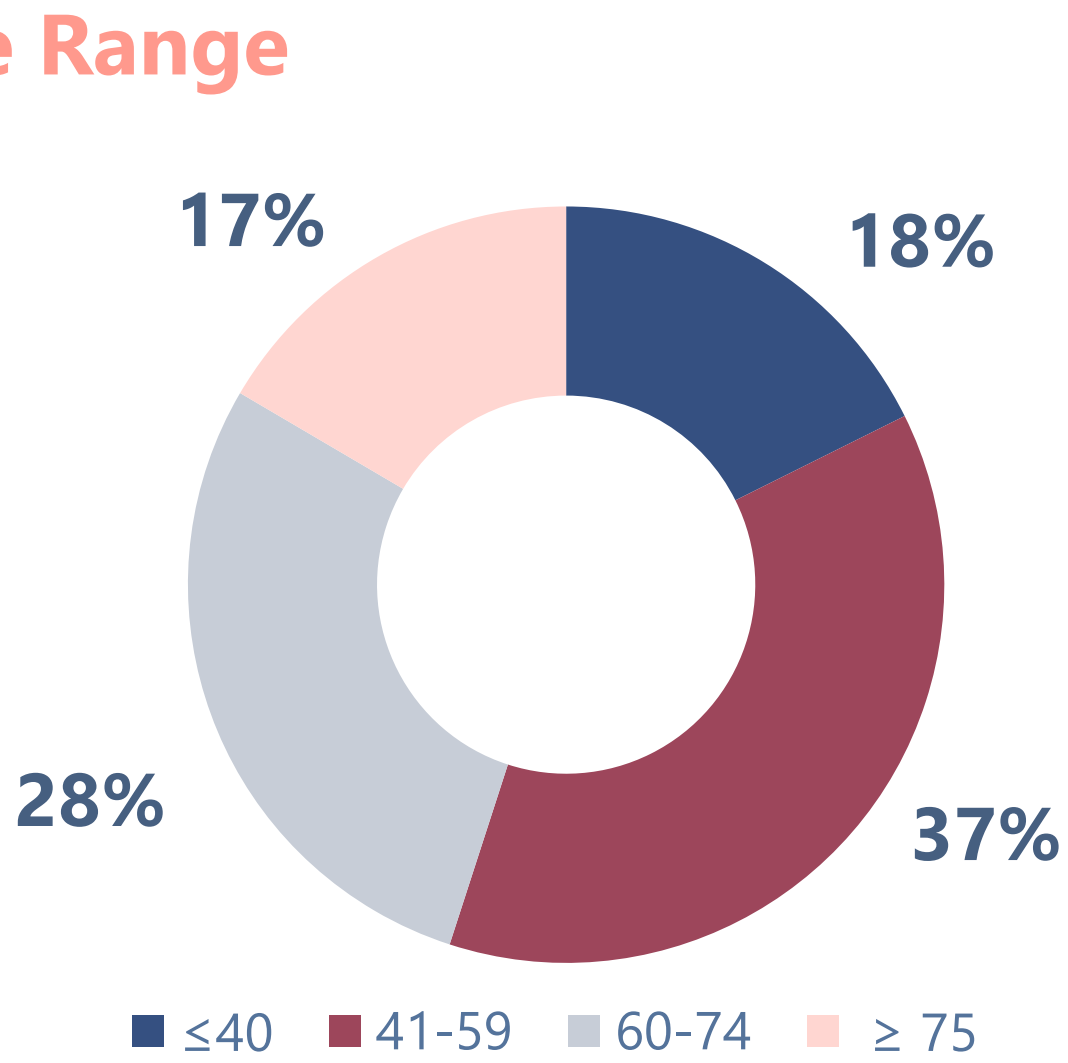
Gender	age	bcl2	bcl2 score	ki67	stage	stage modifi	ekstranodal	ecog	ldh	phenot	phenotype sc	IPI	age sco	eceog sco	ldh score	ekstranodal p	stage scor	NCCN-IPI	NCCN-IPI score
1	38	+	2	80-90%	3E	3	+	2	1349	ABC	2		0	1	2	0	1	4	3
1	68	+	2	40%	2	2	-	1	294	GCB	1		2	0	1	0	0	3	2
1	20	+	2	70-80%	2B	2	-	2	549	ABC	2		0	1	1	0	0	2	2
1	52	-	2	90%	3B	3	-	2	253	ABC	2		1	1	1	0	1	4	3
1	45	+	2	40%	3B	3	-	1	196	GCB	1		1	0	0	0	1	2	2
1	83	+	2	90%	4B	4	+	1	422	ABC	2		3	0	1	0	1	5	3
1	25	+	2	80%	1B	1	-	1	183	GCB	1		0	0	0	0	0	0	1
1	55	-	2	70%	4S	4	+	3	412	ABC	2		1	1	1	0	1	4	3
1	83	-	2	80%	4B	4	+	3	1012	ABC	2		3	1	2	0	1	7	4
1	42/46	+	2	%80-85	3	3	+	1	212	GCB	1		3	0	0	0	1	4	3
1	53	+	2	80%	3B	3	-	1	176	ABC	2		1	0	0	0	1	2	2
2	68	+	2	%80-85	4BS	4	+	2	442	ABC	2		2	1	1	0	1	5	3
2	80	-	2	%80-90	1A	1	-	1	228	GCB	1		3	0	1	0	0	4	3
1	21	-	2	90%	1E	1	+	1	122	ABC	2		0	0	0	0	0	0	1
1	80	+	2	%70-80	2	2	-	3	189	GCB	1		3	1	0	0	0	4	3
1	62	+	2	%60-65	4B	4	+	1	166	ABC	2		2	0	0	0	1	3	2
2	44	-	2	%75-85	3	3	+	3	337	GCB	1		1	1	1	0	1	4	3
2	64	+	2	%35-45	1E	1	+	1	410	GCB	1		2	0	1	0	0	3	2
1	61	-	2	%60-65	2B	2	+	2	348	GCB	1		1	1	1	0	0	3	2
2	65	+	2	%75-85	2	2	+	1	243	GCB	1		2	0	1	0	0	3	2
2	76	+	2	%70-75	3E	3	+	1	161	GCB	1		2	0	0	0	1	3	2
1	45	+	2	%85-90	3BS	3	+	2	209	ABC	2		1	1	0	0	1	3	2
1	57	+	2	%60-65	3E	3	+	0	272	ABC	2		1	0	1	0	1	3	2
2	57	+	2	%60-65	2	2	-	1	215	ABC	2		1	0	0	0	0	1	1

Scan Me!

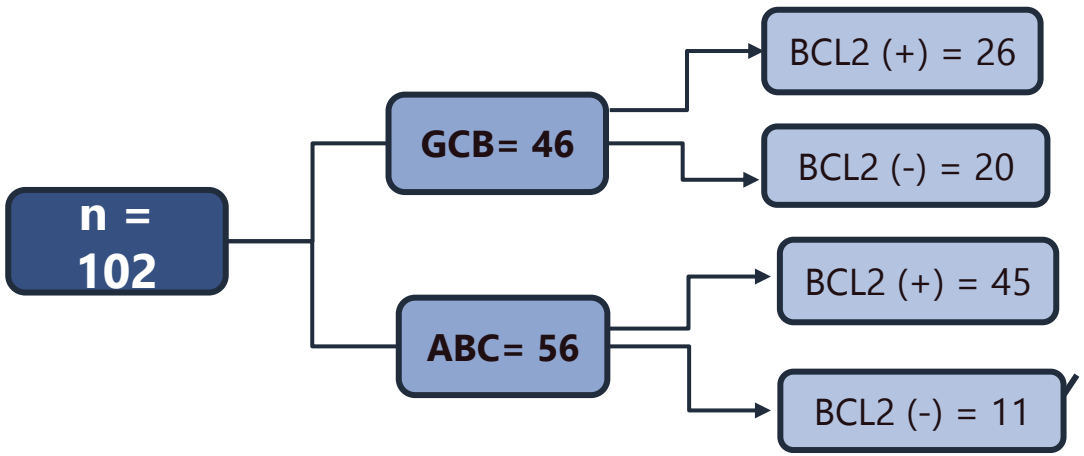
Results


n = 102
Male = 69
Female = 33
≤ 40 = 10
41 – 59 = 21
60-74 = 18
≥ 75 = 9
≤ 40 = 8
41-59 = 17
41-59 = 17
≥ 75 = 8

Results



BCL2 relation with immunophenotype



	Value	df	Asymptotic Significance(2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
Pearson Chi-Square	6,782	1	0,009	0,011	0,008	
Continuity Correction	5,702	1	0,017			
Likelihood Ratio	6,816	1	0,009	0,017	0,008	
Fisher's Exact Test				0,017	0,008	
Linear-by-Linear Association	6,716	1	0,01	0,011	0,008	0,006
N of Valid Cases	102					

Those with BCL2 negativity are more common in the GCB group as an immunophenotype

Ki 67 Range

40 – 60 %

- F/M = 9/13
- BCL2 (+) / (-) = 20/2
- GCB/ABC = 11/11

61 – 80 %

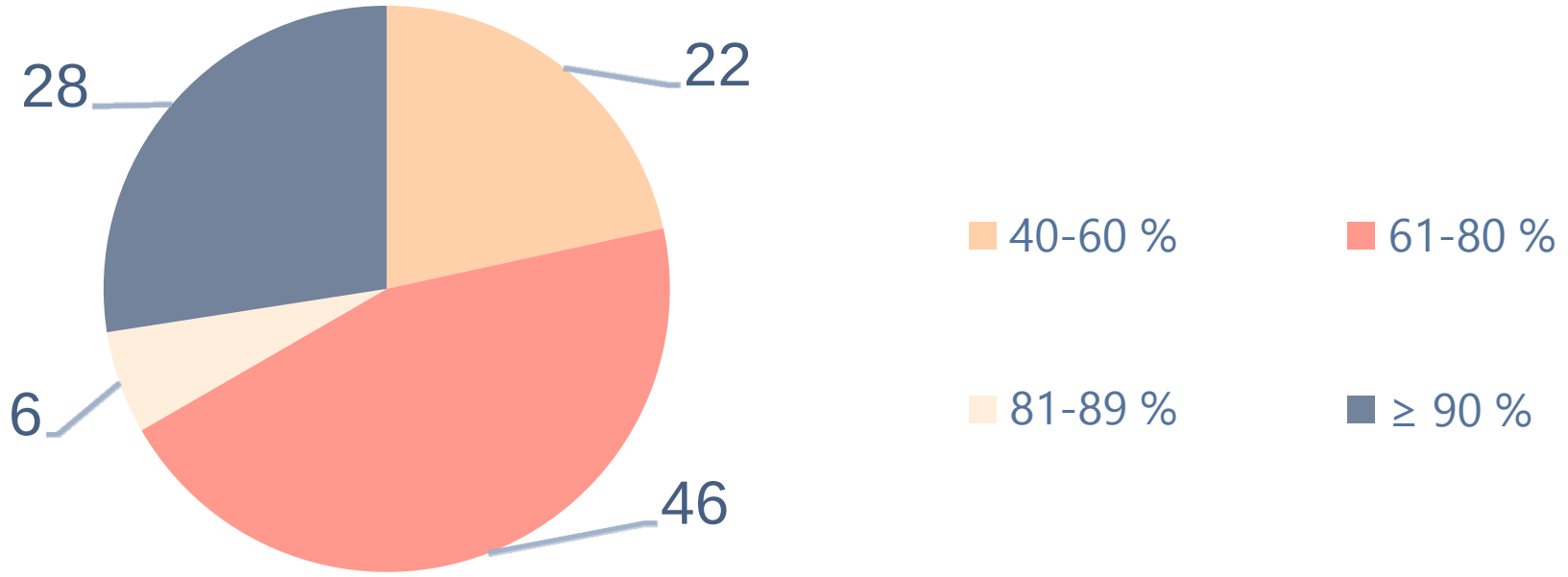
- F/M = 14/36
- BCL2 (+) / (-) = 35/11
- GCB/ABC = 20/26

81 – 89 %

- F/M = 1/5
- BCL2 (+) / (-) = 5/1
- GCB/ABC = 1/5

≥ 90 %

- F/M = 9/19
- BCL2 (+) / (-) = 11/17
- GCB/ABC = 14/14

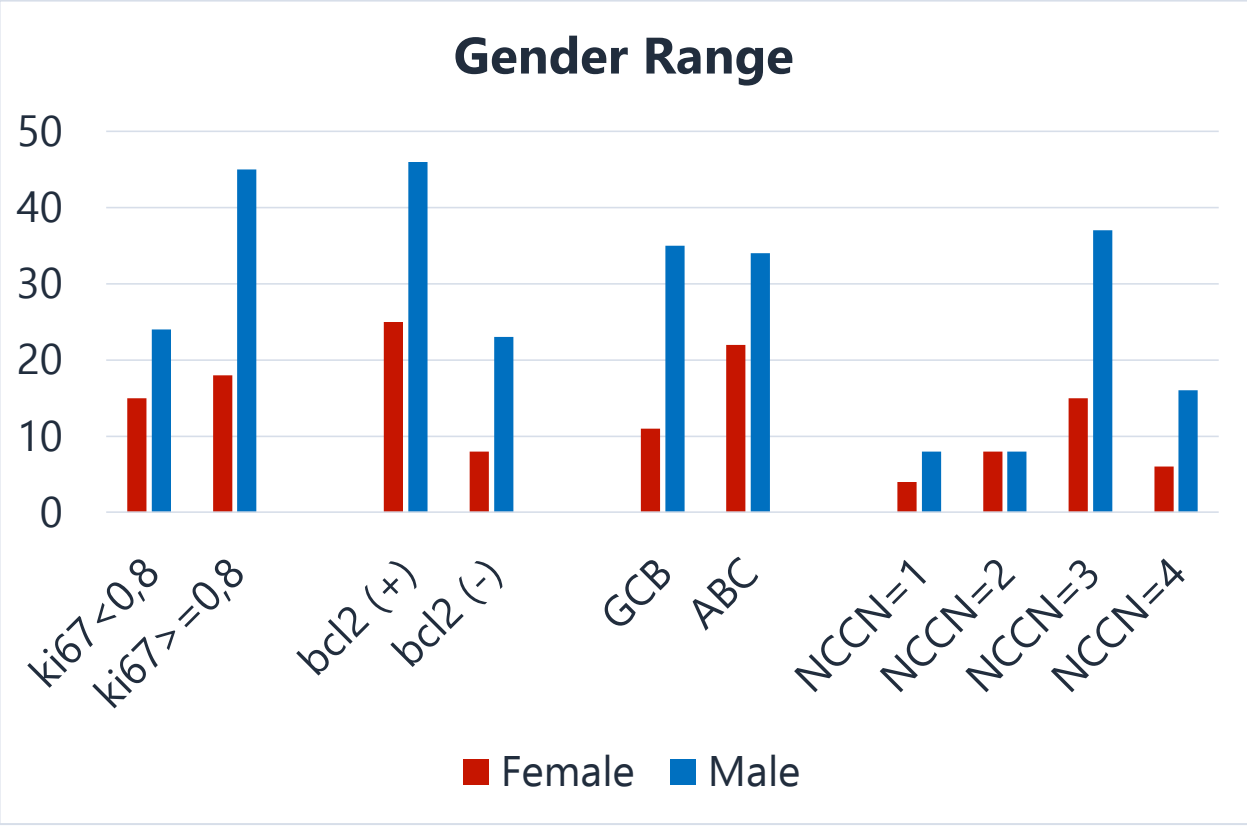


BCL2 relation with Ki67

	ki67
Mann-Whitney U	577,000
Wilcoxon W	3133,000
Z	-3,875
Asymp. Sig. (2 failed)	<0.001

It was observed that Ki67 expression rate was higher in which the antiapoptotic protein BCL2 was negative ($p<0.001$)

BCL2 relation with Ki67



No significant difference in BCL2 or Ki67 expression, immunophenotype or NCCN-IPI score was found between genders and age ranges.

Ki67 > %90

	Value	df	Asymptotic Significance(2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
Pearson Chi-Square	6,304	1	0,012	0,021	0,015	
Continuity Correction	4,582	1	0,032			
Likelihood Ratio	6,817	1	0,009	0,021	0,015	
Fisher's Exact Test				0,021	0,015	
Linear-by-Linear Association	6,242	1	0,01	0,021	0,015	0,014
N of Valid Cases	102					

	Value	df	Asymptotic Significance(2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
Pearson Chi-Square	13,382	1	0	0,001	0,001	
Continuity Correction	10,613	1	0,001			
Likelihood Ratio	12,455	1	0	0,001	0,001	
Fisher's Exact Test				0,001	0,001	
Linear-by-Linear Association	13,251	1	0	0,001	0,001	0,001
N of Valid Cases	102					

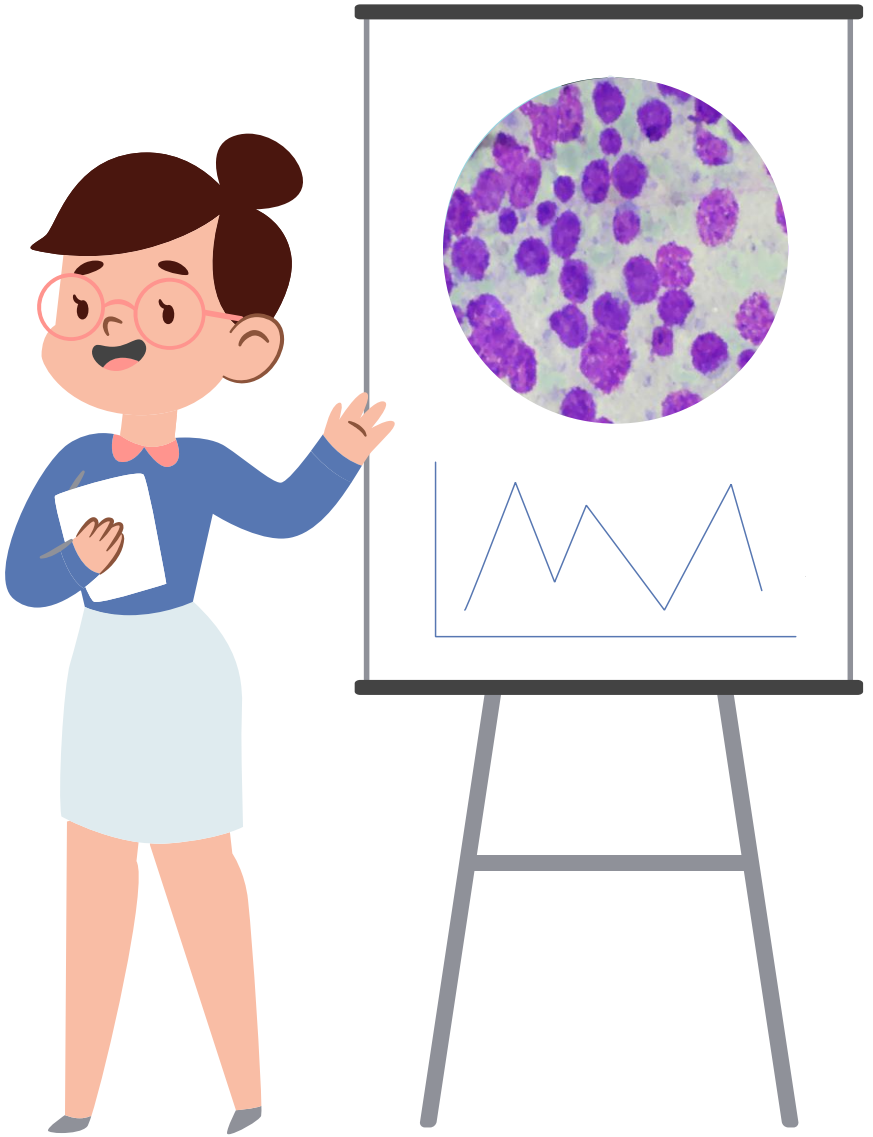
There was no correlation with the NCCN-IPI score in those with Ki67 expression rate above 90, but it was detected at higher rate in the BCL2 negative group and with the GCB phenotype (p= 0.001; p= 0.021).

- The difference between NCCN-IPI score and Bcl2, Ki67 and phenotype were found to be statistically insignificant

	NCCN-IPI SCORE	ki67	BCL2
Mann-Whitney U	914,500	1248,000	995,500
Wilcoxon W	1410,500	2329,000	1556,500
Z	-1,466	-0,274	-1,108
Asymp. Sig. (2 failed)	0,143	0,784	0,268

Limitations

- Single-centered study
- Accessing the clinical data of the patient list that organized from biopsy reports
- Not assesing the patients according to response of the therapy



Discussion

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Ki67 Proliferation Index in Germinal and Non-Germinal Subtypes of Diffuse Large B-Cell Lymphoma

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BCL2/Ki-67 index predict survival in germinal center B-cell-like diffuse large B-cell lymphoma

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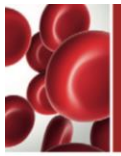

blood® Regular Article

CLINICAL TRIALS AND OBSERVATIONS

International prognostic indices in diffuse large B-cell lymphoma: a comparison of IPI, R-IPI, and NCCN-IPI

Amy S. Ruppert,[1] Jesse G. Dixon,[2] Gilles Salles,[3] Anna Wall,[2] David Cunningham,[4] Viola Poeschel,[5] Corinne Haioun,[6] Herve Tilly,[7] Herve Ghesquieres,[3] Marita Ziepert,[8] Jocelyne Flament,[9] Christopher Flowers,[10] Qian Shi,[2] and Norbert Schmitz[11]

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Conclusion

- Pathologically, BCL2, Ki67 expression rates and neoplastic cell origin (GCB/ABC) and clinically NCCN-IPI score alone were not sufficient to determine the clinical prognosis of DLBCL..
- Currently availabe prognostic markers are immunohistochemical and in situ hybridization evaluation pathologically and clinical data.
- However, according to these data there is no change in treatment.
- Molecular profiling of the tumor with NGS which allows us to make a more accurate prediction of prognosis and detecting the resistance of the current treatment.

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Thank you for Listening

Do you have any questions?

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