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MYC/BCL2 protein co-expression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program Study.

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Blood. 2013 May 16;121(20):4021-31

ΒΙΒΛΙΟΓΡΑΦΙΚΗ ΕΝΗΜΕΡΩΣΗ ΓΝΑ ΕΥΑΓΓΕΛΙΣΜΟΣ Θ. ΚΑΝΕΛΛΟΠΟΥΛΟΥ

ΕΙΣΑΓΩΓΗ

Ταξινόμηση WHO 2008 - DLBCL

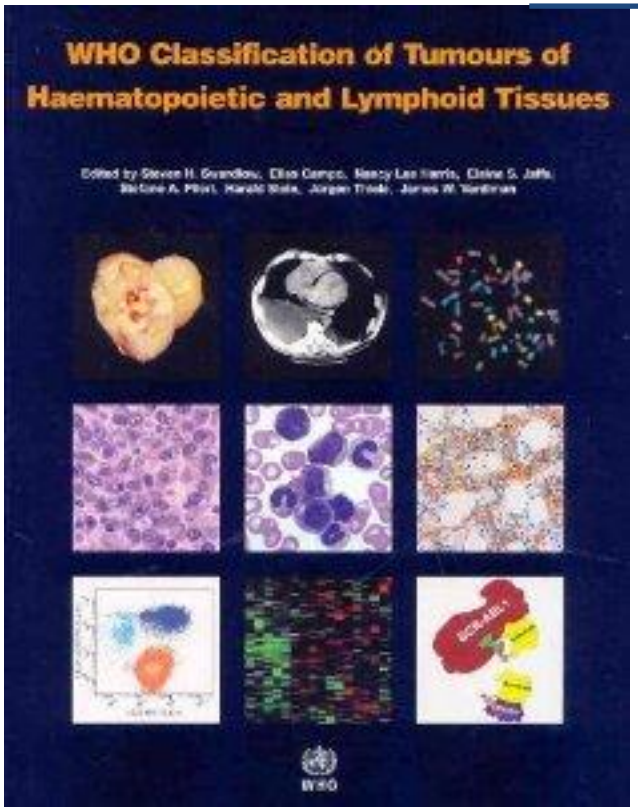


Table 10.14 Diffuse large B-cell lymphoma: variants, subgroups and subtypes/entities.

Diffuse large B-cell lymphoma, not otherwise specified (NOS)

- Common morphologic variants
  - Centroblastic
  - Immunoblastic
  - Anaplastic
- Rare morphologic variants
- Molecular subgroups
  - Germinal centre B-cell-like (GCB)
  - Activated B-cell-like (ABC)
- Immunohistochemical subgroups
  - CD5-positive DLBCL
  - Germinal centre B-cell-like (GCB)
  - Non-germinal centre B-cell-like (non-GCB)

Diffuse large B-cell lymphoma subtypes

- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV positive DLBCL of the elderly

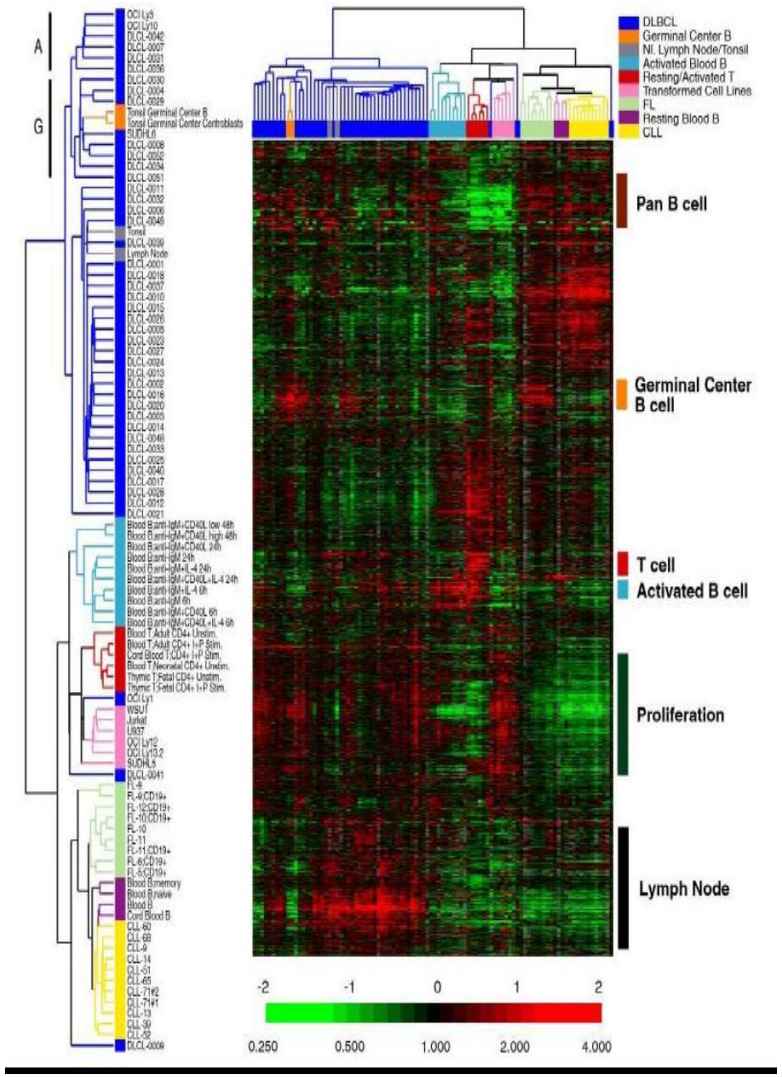
Other lymphomas of large B cells

- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- ALK-positive LBCL
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma

Borderline cases

- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

Gene-expression profiles



DLBCL – NOS

- Τύπος βλαστικού κέντρου (GCB)
  - *CD10, BCL6*
- Τύπος ενεργοποιημένου β-λεμφοκυττάρου (ABC)
  - *MYC, BCL2, MUM1, CD44 FLIP, cyclinD2*
  - Ενεργοποίηση NF-κB
  - Χειρότερη πρόγνωση

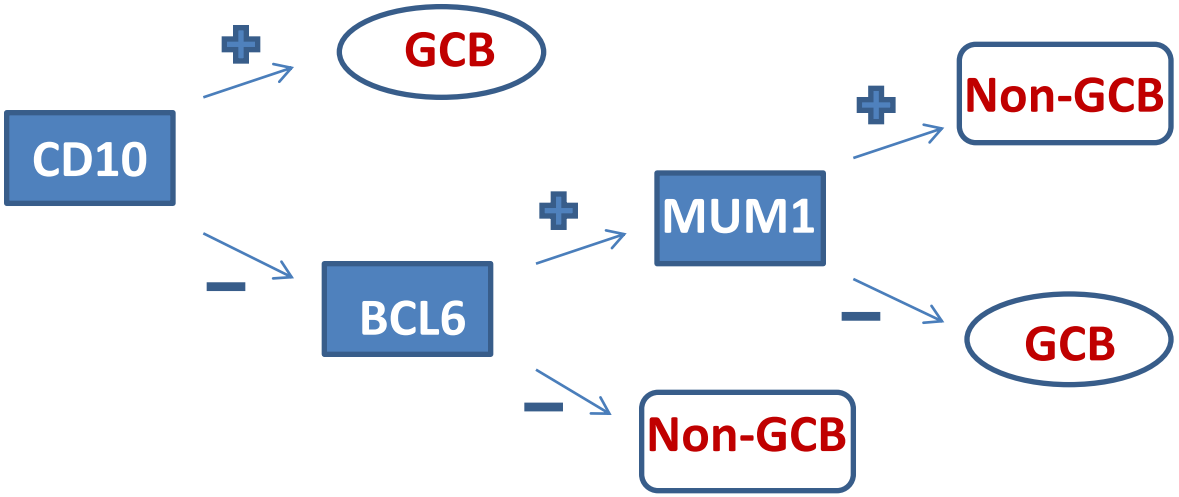
Gene-expression profiles

- **Περιορισμοί …**
  - Η τεχνολογία GEP δεν είναι διαθέσιμη στην καθημερινή κλινική πράξη
  - Αναπαραγωγιμότητα;;;
  - Παραμένει άγνωστο ποια γονιδιακά προϊόντα συμβάλλουν στη χειρότερη πρόγνωση των ασθενών με ABC-DLBCL

Εναλλακτικές λύσεις ;;;

Ανοσοϊστοχημεία

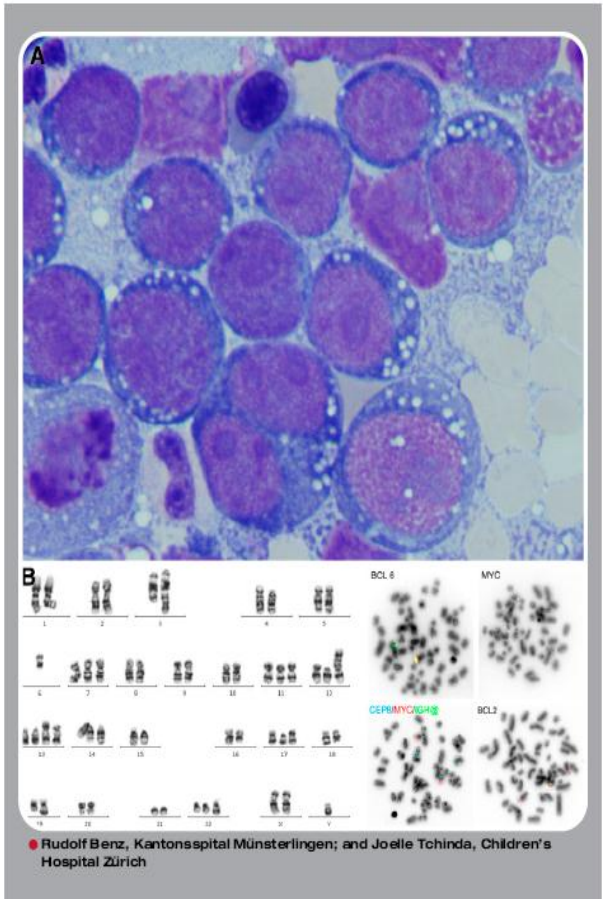
- Αλγόριθμος του Hans



Hans CP, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood. 2004 Jan 1;103(1):275-82

- Συμφωνία με GEP 80%

“Double-Hit”



- Λεμφώματα με επαναλαμβανόμενες μεταλλαγές που ενεργοποιούν πολλαπλά ογκογονίδια

- Επιθετική κλινική πορεία και αντοχή στη θεραπεία

- *BCL2+/MYC+ , BCL6+/MYC+, BCL3+/MYC+*

- Συνήθως GCB φαινότυπος
  - CD10+, BCL6+, MUM1/IRF4-

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Νεότερα βιβλιογραφικά δεδομένα

- Ασθενείς με DLBCL με συνέκφραση BCL2/MYC με ή χωρίς αναδιατάξεις MYC ή BCL2 έχουν χειρότερη πρόγνωση

  - *Johnson NA, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2012 Oct 1;30(28):3452-9*

  - *Green TM, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2012 Oct 1;30(28):3460-7*

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Blood. 2013 Feb 28. [Epub ahead of print]

AMERICAN SOCIETY OF HEMATOLOGY ®

ΥΛΙΚΑ & ΜΕΘΟΔΟΙ

Ασθενείς

International DLBCL R-CHOP Consortium Program Study

893 ασθενείς
De novo DLBCL
MYC+/BCL2+
(ανοσοϊστοχημικά)
R-CHOP

Χαμηλής κακοήθειας B-NHL
HIV
DLBCL δέρματος/ΚΝΣ
EBV (+) DLBCL

466 training set

234 validation set #1

193 validation set #2

GEP σε 451 ασθενείς

9% αταξινόμητα

ΑΠΟΤΕΛΕΣΜΑΤΑ

Χαρακτηριστικά ασθενών

	Overall			DP	Non-DP	
	N (%)	OS (p-value)	PFS (p-value)	N (%)	N (%)	p-value
Patients	466 (100%)			157 (100%)	309 (100%)	
Gender						
Male	272 (58%)	0.7477	0.4730	90 (57%)	182 (59%)	0.7445
Female	194 (42%)			67 (43%)	127 (41%)	
Age						
≤60	194 (42%)	0.0004	0.0016	49 (31%)	145 (47%)	0.0011
>60	272 (58%)			108 (69%)	164 (53%)	
B symptoms*						
Absence	276 (68%)	0.0015	0.0014	88 (62%)	188 (72%)	0.0541
Presence	127 (32%)			53 (38%)	74 (28%)	
ECOG performance status*						
<2	350 (88%)	<0.0001	<0.0001	111 (83%)	239 (90%)	0.0453
≥2	50 (12%)			23 (17%)	27 (10%)	
Stage*						
I-II	219 (49%)	<0.0001	<0.0001	50 (33%)	169 (57%)	<0.0001
III-IV	228 (51%)			100 (67%)	128 (43%)	
Extranodal Sites*						
<2	346 (78%)	<0.0001	<0.0001	106 (72%)	240 (82%)	0.0160
≥2	96 (22%)			42 (28%)	54 (18%)	
LDH*						
Normal	168 (40%)	0.0003	<0.0001	51 (36%)	117 (42%)	0.2908
Elevated	252 (60%)			89 (64%)	163 (58%)	
IPI risk group*						
0-2	263 (64%)	<0.0001	<0.0001	70 (51%)	193 (70%)	0.0001
3-5	148 (36%)			67 (49%)	81 (30%)	
Tumor size (cm)*						
<7.5	253 (77%)	0.0100	0.0172	81 (73%)	172 (79%)	0.2587
≥7.5	77 (23%)			30 (27%)	47 (21%)	
Treatment response						
CR	354 (76%)	<0.0001	<0.0001	103 (66%)	251 (84%)	<0.0001
Others	112 (24%)			54 (34%)	48 (16%)	
COO Classification						
GCB	241 (52%)	0.0080	0.0075	53 (34%)	188 (61%)	<0.0001
ABC	225 (48%)			104 (66%)	121 (39%)	
KI-67*						
<70%	158 (34%)	0.2998	0.3434	41 (26%)	117 (38%)	0.0086
≥70%	304 (66%)			116 (74%)	188 (62%)	
TP53 mutations						
Absence	357 (77%)	0.0005	0.0004	117 (75%)	240 (78%)	0.4480
Presence	109 (23%)			40 (25%)	69 (22%)	

Χαρακτηριστικά ασθενών

Table 2. Multivariate analysis of clinicopathological parameters in DLBCLs treated with R-CHOP

	OS			PFS		
	HR	95% CI	*P*	HR	95% CI	*P*
B symptoms	1.47	1.04-2.09	.0310	1.45	1.03-2.03	.0314
Tumor size, ≥7.5 cm	1.22	0.87-1.71	.2467	1.21	0.86-1.69	.2708
IPI risk, >2	2.38	1.67-3.38	<.0001	2.22	1.59-3.11	<.0001
COO classification, ABC	1.17	0.79-1.72	.4329	1.18	0.82-1.71	.3750
TP53 mutation	1.72	1.17-2.52	.0057	1.63	1.12-2.37	.0105
MYC/BCL2 coexpression	2.52	1.73-3.67	<.0001	2.45	1.71-3.51	<.0001

CI, confidence interval; HR, hazard ratio.

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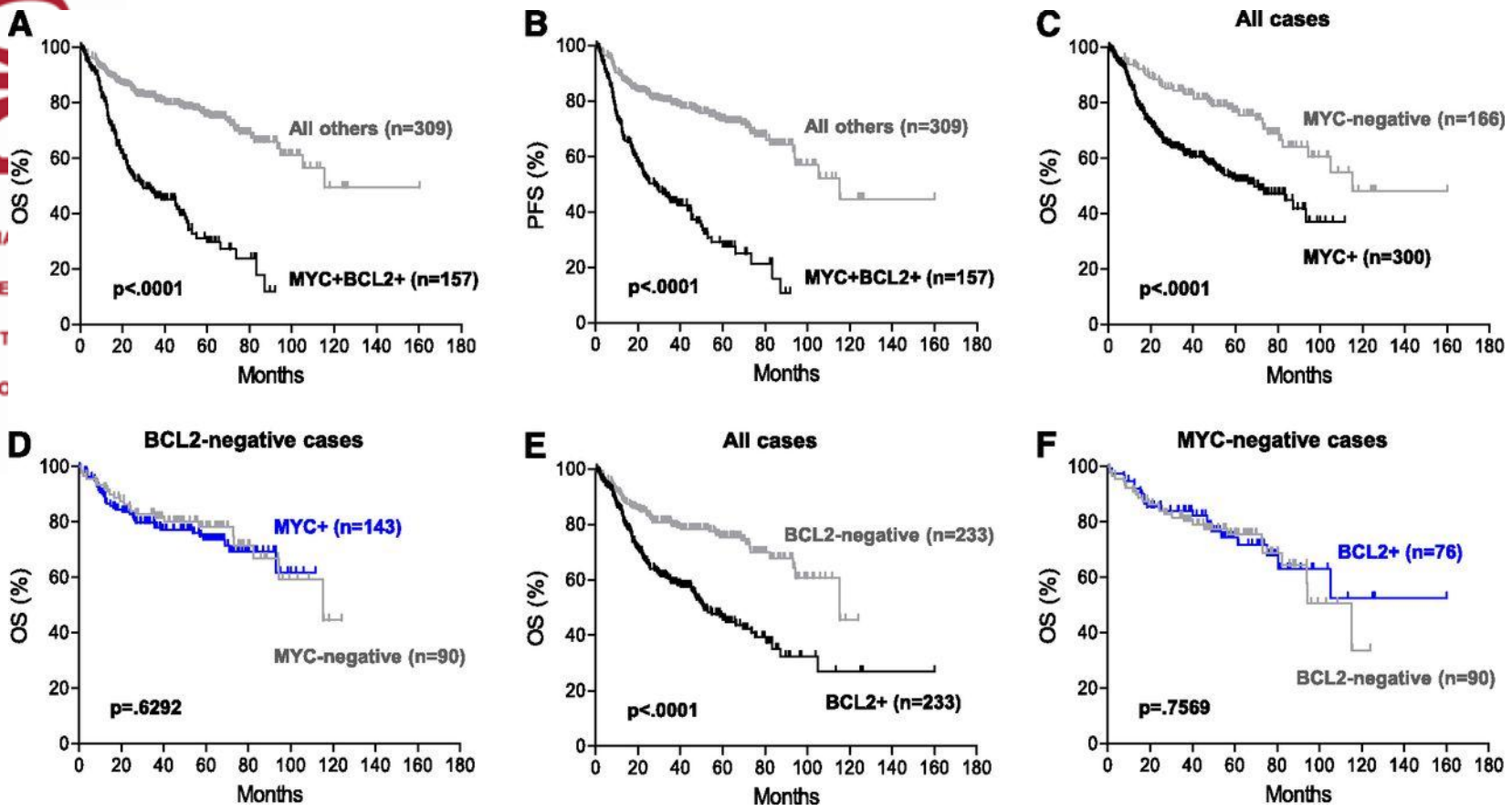
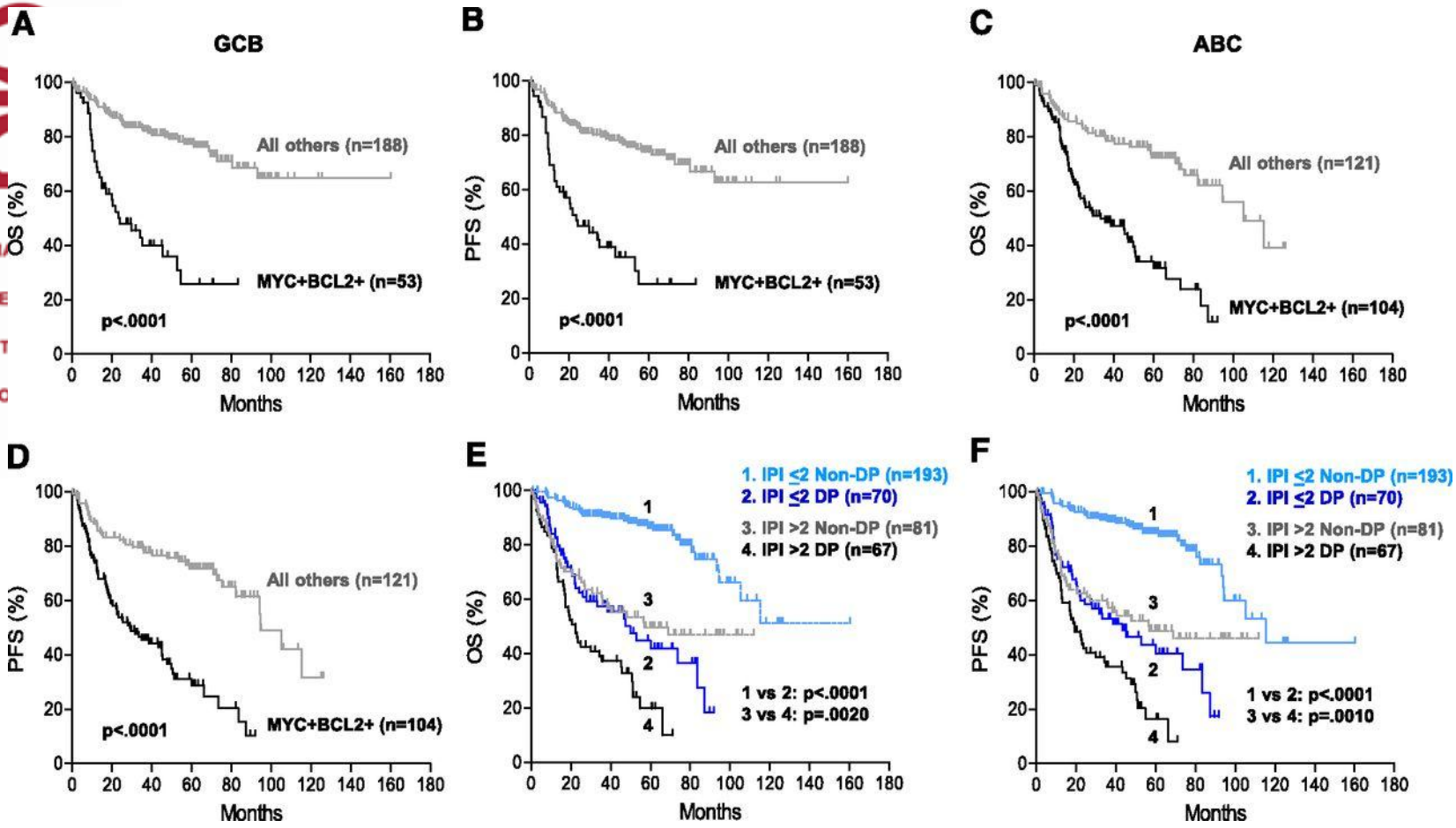
Prognostic impact of MYC/BCL2 coexpression in DLBCL. (A-B) OS (A) and PFS (B) of patients with DLBCL with MYC/BCL2 coexpression (MYC+BCL2+) in the training set.



Hu S et al. Blood 2013;121:4021-4031

Prognostic impact of MYC/BCL2 coexpression in DLBCL risk-stratified according to clinicopathologic parameters.



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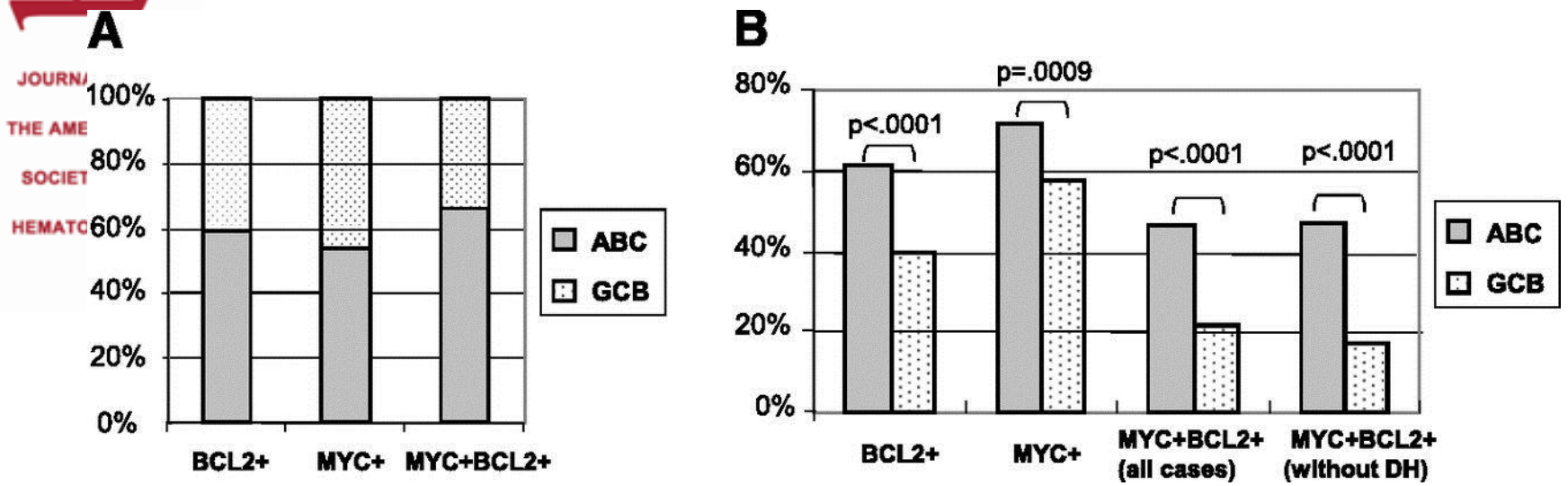
Frequency of BCL2 and MYC expression in COO subtypes of DLBCL. (A) Relative frequency of the ABC vs GCB subtype in DLBCL positive for BCL2 expression, MYC expression, or MYC/BCL2 coexpression in the training set.



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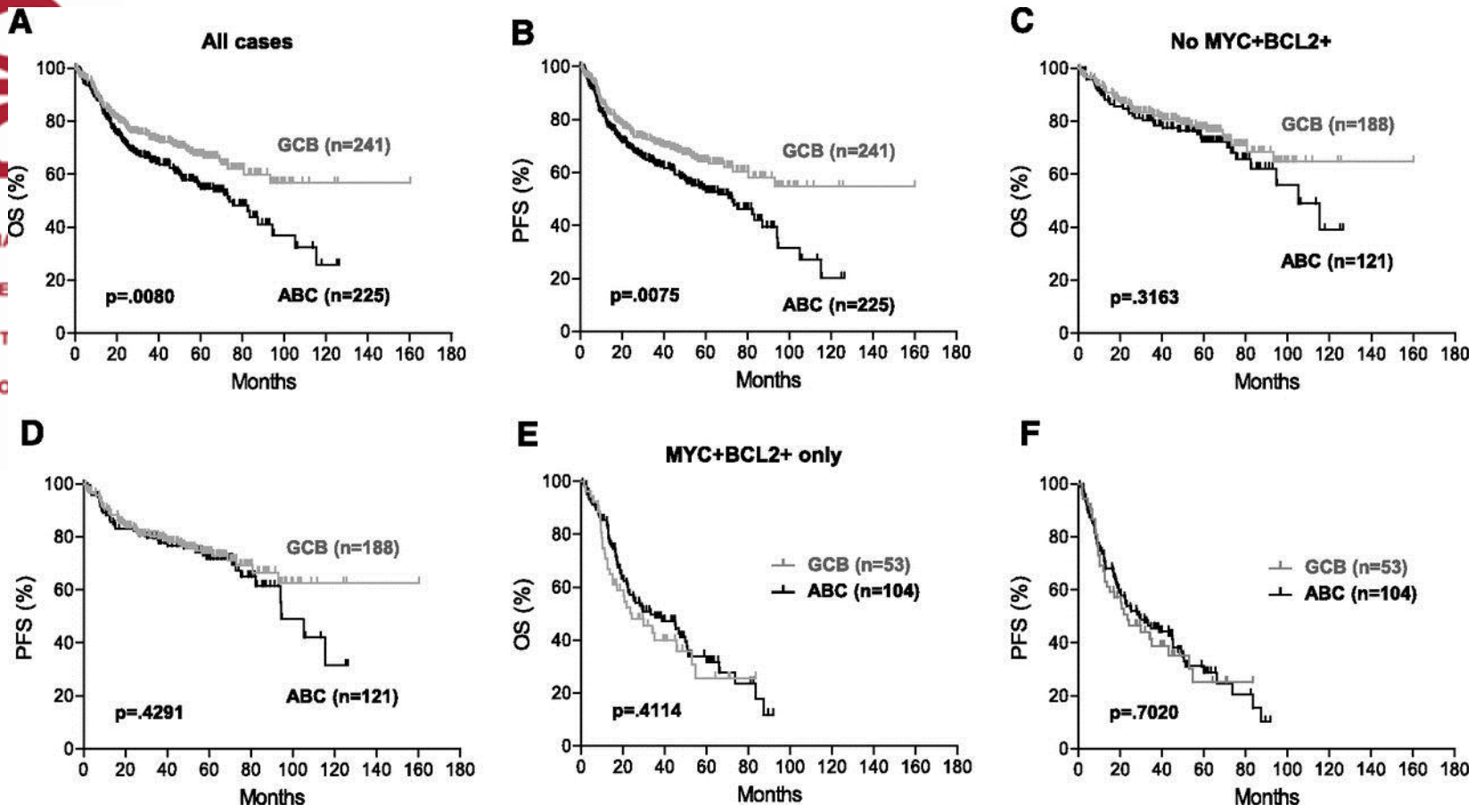
MYC/BCL2 coexpression contributes to the inferior prognosis of ABC-DLBCL.



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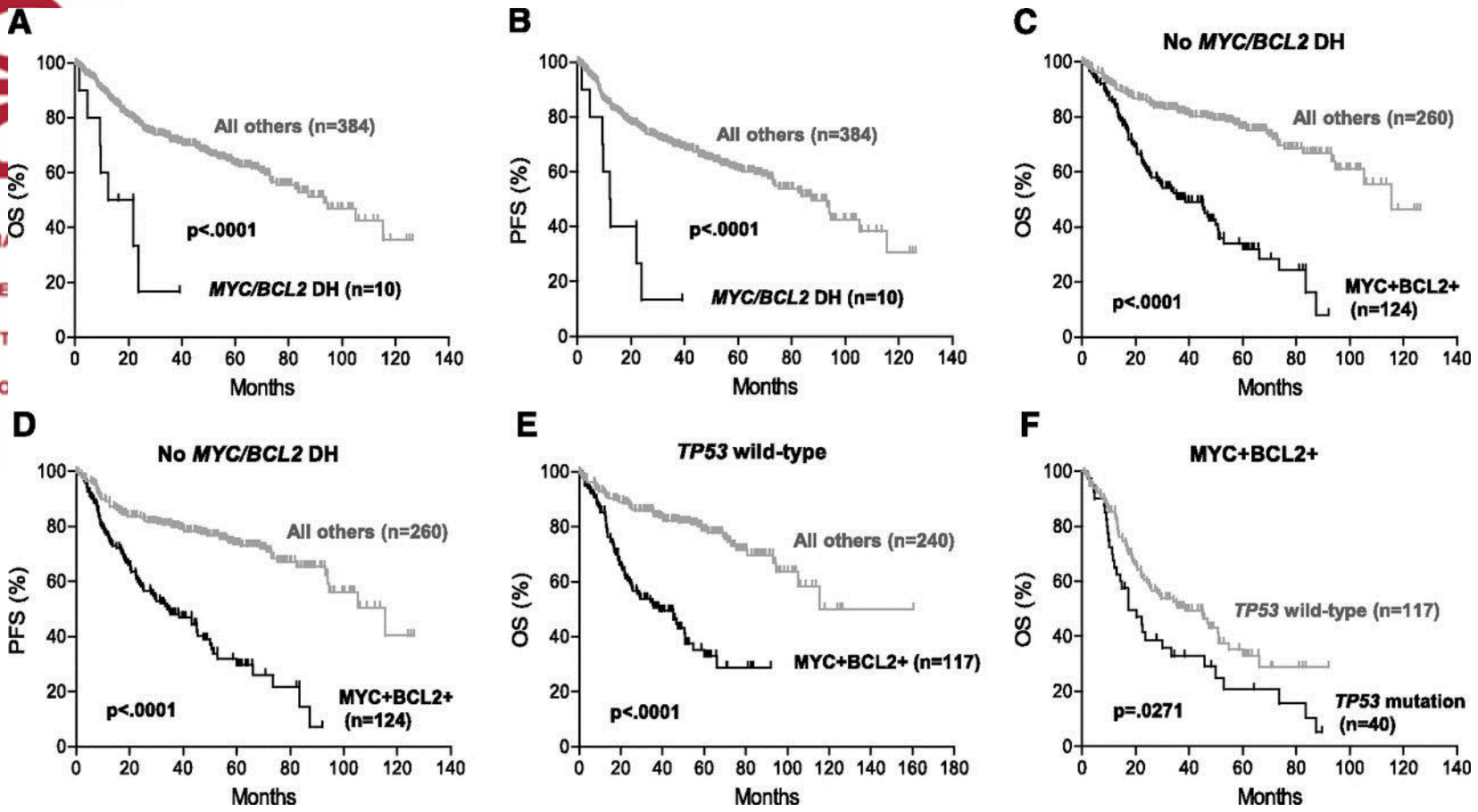
Prognostic impact of MYC/BCL2 coexpression in DLBCL is independent of MYC/BCL2 corearrangement and TP53 mutation status.



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MYC/BCL2 coexpression contributes to the different gene expression profiles between GCB and ABC subtypes of DLBCL.

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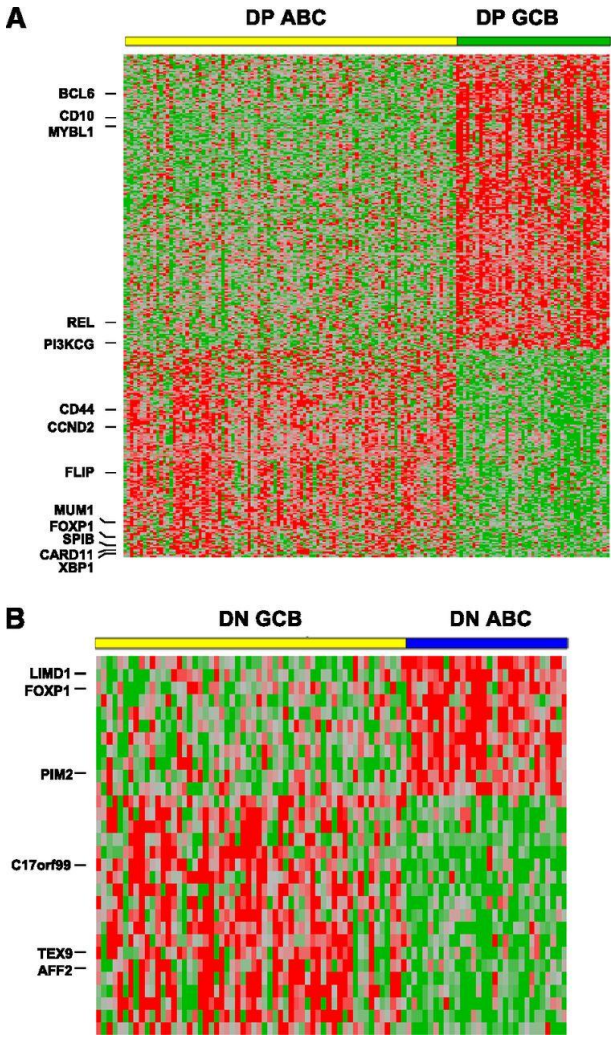

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Gene expression signature of DLBCL with MYC/BCL2 coexpression.

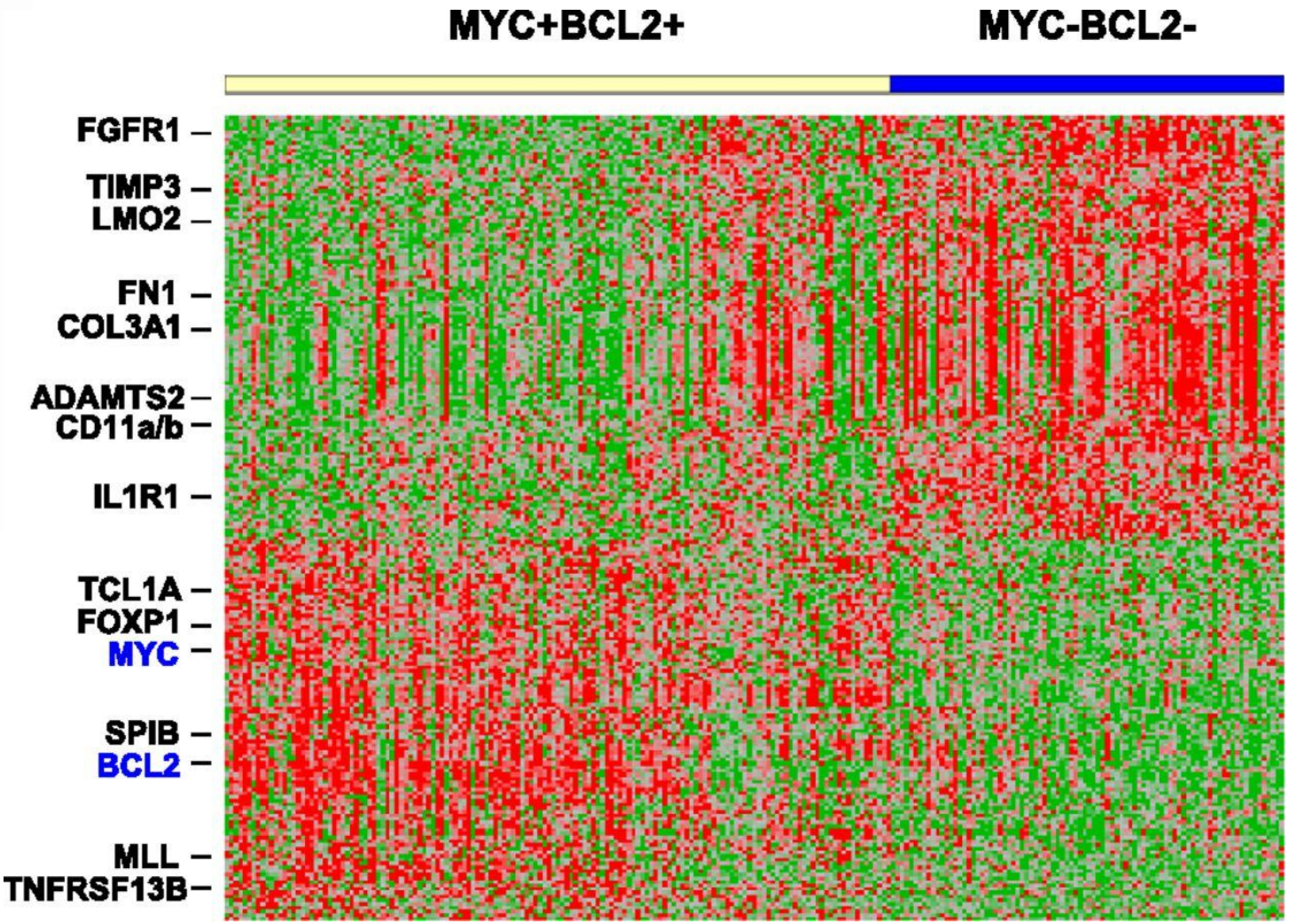

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Table 3. Differentially expressed genes in $MYC^{+}BCL2^{+}$ de novo DLBCL

Gene functional categories	No. of genes	Representative genes
Downregulated genes		
ECM, ECM production and remodeling	33	*COL3A1, VCAN, TNS1, FN1, THBS2, TIMP3, SPARC, SULF1, SPINK2, MMP2, ADAM12, FGFR1, FAP*
Cell adhesion and cytoskeletal organization	21	*CD11A/CD11B, CD58, THY1, RFTN1, ANTXR1, RHOB, MICAL2*
Cell growth regulation	16	*LM02, TRAF1, CDK14, SGK1, RGS1, NBL, PDE4D*
Others, including unknown	18	*PSAP, LYZ, LOC115110, ZNF662*
Upregulated genes		
Cell proliferation	20	*MYC, BCL2, TCL1A, MLL, FOXP1, SPIB, TCF4, TNFRSF13B, PMDAIP1, GAB1, PLOR3G*
Cell metabolism	5	*DCTPP1, CYB5R2, HK2, TMEM97, CYB5R2*
Miscellaneous cell functions	13	*PPIL1, PIGW, FUT8, SPINK5*
Unknown	27	*KIAA0664, C9orf91, ZNF107*

ΣΥΖΗΤΗΣΗ

Συζήτηση

- Ασθενείς με DLBCL και συνέκφραση MYC/BCL2 έχουν κακή πρόγνωση με 5ετή επιβίωση <30% ανεξαρτήτως αν πρόκειται για GCB ή ABC φαινότυπο

- 30% των ασθενών με DLBCL έχουν συνέκφραση MYC/BCL2 ενώ μόνο το 3% αντιπροσωπεύει DH λέμφωμα που αναδεικνύει ότι η επιθετικότητα των παραπάνω λεμφωμάτων είναι πέρα από το γενετικό επίπεδο

- Ασθενείς με MYC-/BCL2- έχουν μη στατιστικά σημαντική διαφορά στην επιβίωση ανεξαρτήτως GCB ή ABC φαινοτύπου

- Η συνέκφραση MYC/BCL2 παρατηρείται πιο συχνά στον ABC φαινότυπο που πιθανόν να ευθύνεται για την χειρότερη πρόγνωση αυτής της κατηγορίας ασθενών

CME Article

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Disclosures

The authors, Associate Editor A. Keith Stewart, and CME questions author Charles P. Vega, Associate Professor and Residency Director, Department of Family Medicine, University of California-Irvine, declare no competing financial interests.

Learning objectives

Upon completion of this activity, participants will be able to:

1. Assess genetic abnormalities associated with diffuse large B-cell lymphoma (DLBCL).
2. Analyze the prevalence and survival impact of MYC and BCL2 co-expression in the current study.
3. Distinguish the relationship between MYC/BCL2 co-expression and other negative prognostic variables in the current study.
4. Evaluate the relative effect of MYC/BCL2 co-expression on survival in the context of DLBCL subtypes.

Release date: May 16, 2013; Expiration date: May 16, 2014