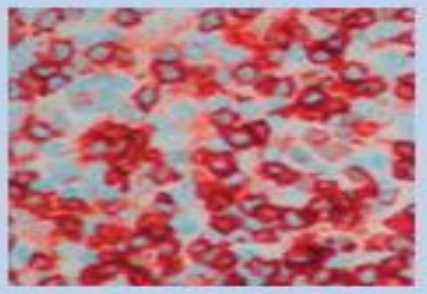
POLICLINICO DI SANT'ORSOLA

PROGNOSTIC FACTORS FOR PTCL



Francine Foss MD
Yale University School of Medicine
New Haven, CT USA

The History of Prognostic Indices for Aggressive T cell Lymphomas

	IPI[a]	PIT[b]	IPTCLP[c]	mPIT[d]
Age (≤60 versus >60)	X	X	X	X
ECOG (≤1 versus >1)	X	X	X	X
LDH (normal versus high)	X	X		X
Ann Arbor stage (I–II versus III–IV)	X			
Extranodal involvement (<2 versus ≥2 sites)	X			
BM involvement (negative versus positive)		X		
Platelet cell count (≤150 versus >150 × 10^9/l)			X	
Ki-67 (%) (≤75 versus >75)				X

- Clinical stage relevant in IPI
- PIT identified bone marrow involvement, extranodal involvement fell out
- mPIT drops Bone marrow for Ki-67 index
- IPTCLP based on AITL and PTCLu identified low platelets as important prognostic factor

A closer look at PIT results…

Table 3. Clinical and biologic characteristics of the patients

Characteristics	No. of patients	No. of patients available	%
Age, y		385	
60 or younger	234		60.8
Older than 60	151		39.2
Sex			
Men	249	385	64.7
Women	136		35.3
ECOG PS		383	
0-1	274		71.2
2-4	109		28.3
Ann Arbor stage		385	
I-II	92		23.9
III-IV	293		76.1
Systemic symptoms		385	
Yes	175		45.4
No	210		54.6

Table 4. Sites involved in 281 patients with extranodal involvement

Site	No. of cases	% of cases	% of all ENSs
BM	118	30.6	41.9
Spleen	95	24.6	33.8
Liver	50	12.9	17.7
Waldeyer ring	42	10.9	14.9
Skin	39	10.1	13.8
Lung + pleura	38	9.8	13.5
Gut	35	9.0	12.4
Bone	18	4.6	6.4
Soft tissues	5	1.2	1.7
Others	54	14.02	19.2

Table 5. Clinical parameters influencing survival in univariate analysis

Parameter	Cut-off value	P
Age, y	Older than 60	.0002
ECOG PS	2 or higher	< .0001
Stage	III or higher	.0001
LDH level	More than 1× normal value	< .0001
ENSs	2 or more	.0002
IPI	L, I-L, I-H, H	< .0001
BM	Infiltrated	.0001
Response to CT	CR vs PR vs NR	< .0001

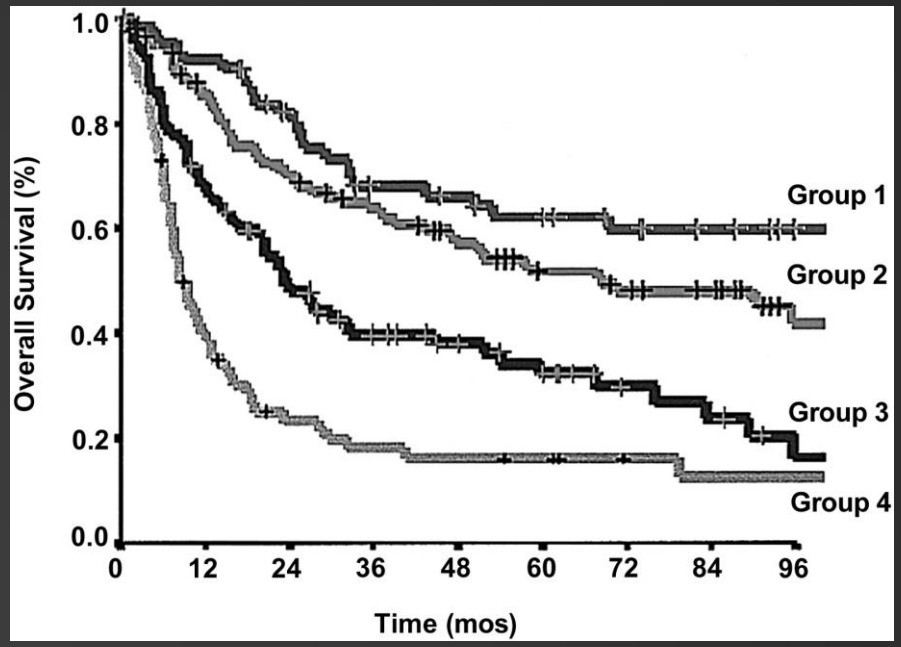
L indicates low; I-L, intermediate-low; I-H, intermediate-high; H, high.

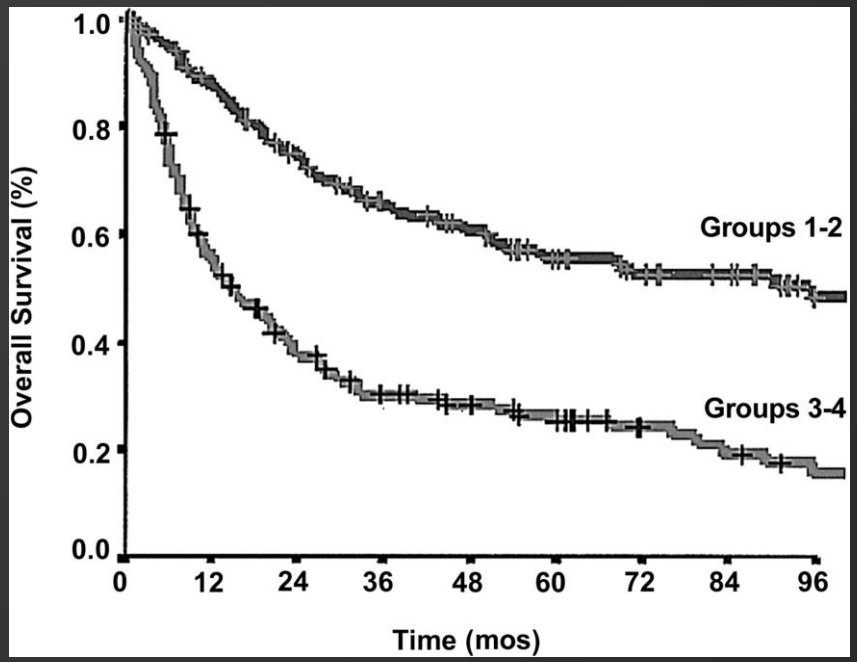
- Only included PTCLnos subtypes
- Retrospective group (1989-2001)
- Most patients were younger
- Overall most had good PS
- Bone marrow most common EN site, occurred in 41% of cases

Gallamini et al, Blood 2004

PIT outcomes- what we learned

- Treatment was anthracycline regimens in 78%, auto BMT in 12%
- Overall response rate to chemotherapy was 53%
- No difference in outcome with autoBMT (P=0.2)
- Slightly better than IPI to stratify patients
- Identified a low risk group





Swedish Registry Study

Clinical characteristics	All patients (N = 755)
Age (y), median (range)	67 (18-96)
Male	445 (59)
Female	310 (41)
B symptoms	444 (59)
Stage III-IV	490 (65)
BM	154 (20)
Extranodal involvement >1	110 (15)
WHO PS >1	267 (35)
Bulky disease (>10 cm)	81 (11)
LDH > ULN	441 (54)
IPI 0-1	170 (23)
IPI 2-3	386 (51)
IPI 4-5	139 (18)
5-y OS (%)	34.1
5-y PFS (%)	25.7

Ellin et al,Blood 2014

- 755 patients from more modern treatment era- 2000-2009
- Included EATL and NK-T
- Median age older
- Most had good PS
- 20% had bone marrow involvement
- 84% has CHOP like regimen
- Overall response 70%
- Auto BMT in 104 pts (14%)

Swedish Registry Results

Outcomes by Subtype of PTCL

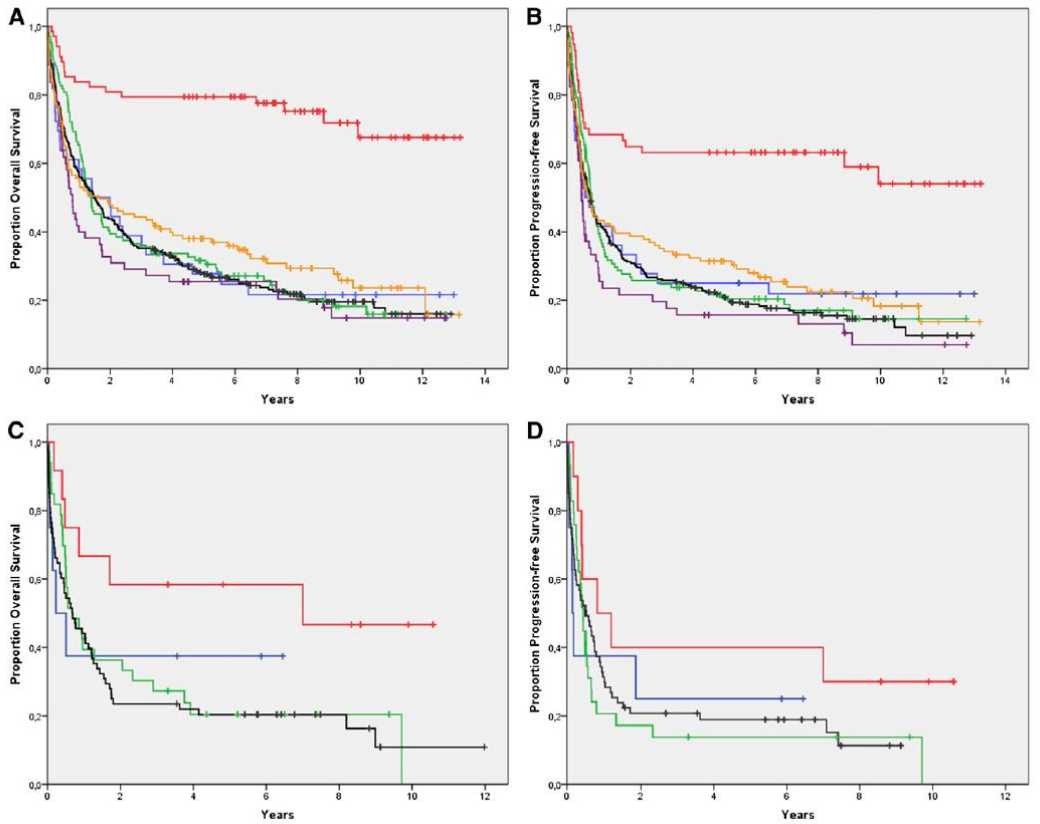
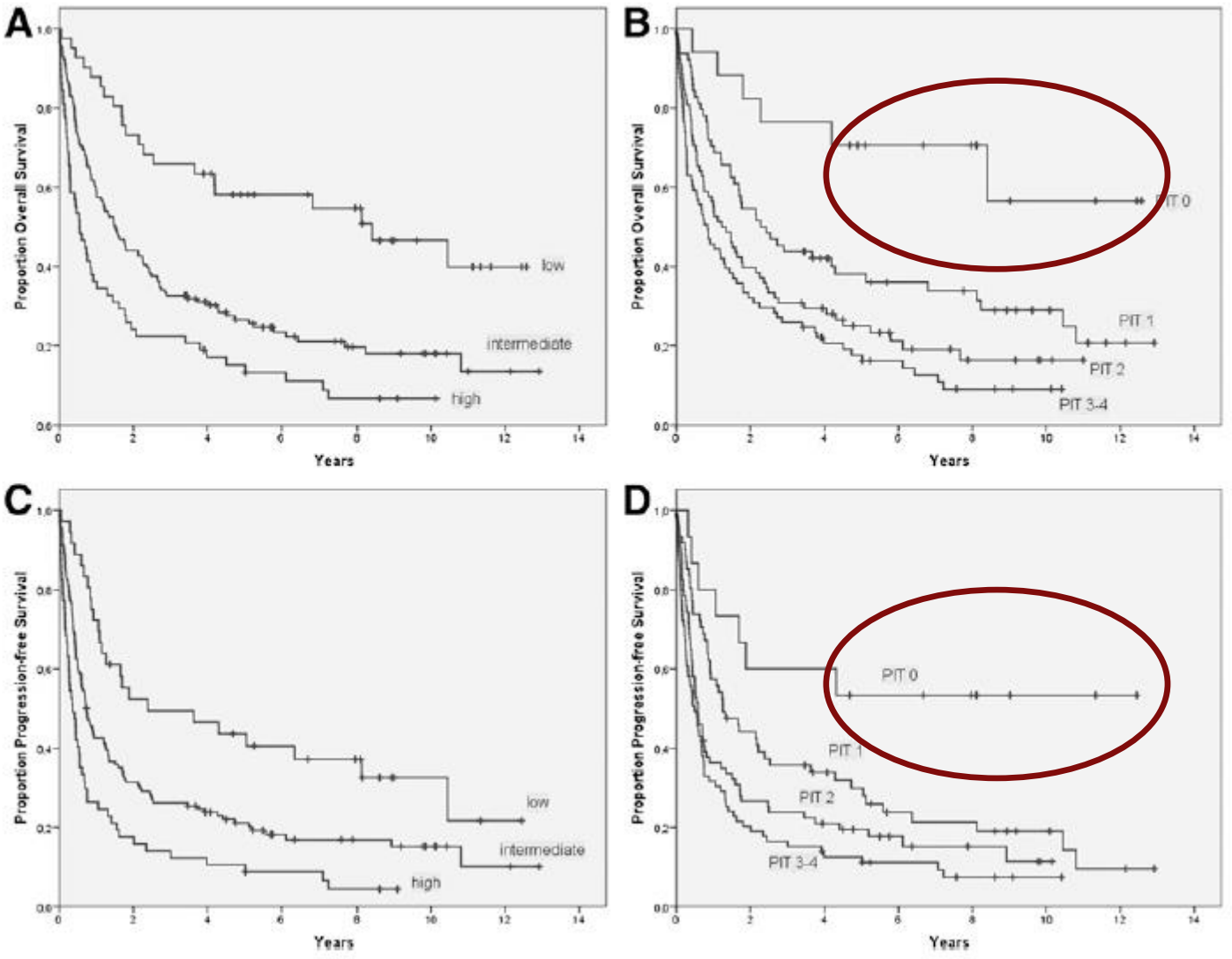


Figure 1. OS and PFS in 755 patients with PTCL. (A) OS among nodal subtypes: ALKpos ALCL (red line), ALKneg ALCL (orange line), ALKu ALCL (blue line), PTCL NOS (black line), AITL (green line), and TCL U (purple line). (B) PFS among nodal subtypes. (C) OS among extranodal subtypes: SPTCL (red line), HSTCL (blue line), NK/T, nt (green line), and EATL (black line). (D) PFS among extranodal subtypes.

	OS (n = 248)	
	HR (95% CI)	*P*
Age	1.003 (0.984-1.023)	.730
Male gender	1.60 (1.12-2.29)	.010
Ann Arbor III-IV	1.56 (1.03-2.31)	.028
Extranodal involvement >1	1.55 (1.03-2.35)	.037
WHO PS >0	1.78 (1.23-2.57)	.002
PTCL NOS	1.00	—
ALKneg ALCL	0.81 (0.50-1.25)	.307
AITL	0.90 (0.59-1.39)	.643
EATL	1.92 (1.18-3.14)	.009
TCL U	1.98 (0.96-4.09)	.066
Etoposide	0.81 (0.53-1.25)	.341
Auto-SCT ITT	0.58 (0.40-0.84)	.004

- Overall adverse prognostic factors in addition to IPI were male gender
- EATL and rare subtypes had worse outcome

Swedish study: PIT vs IPI



- PIT and IPI were both predictive for OS and PFS in PTCLnos
- PIT identified low risk group

Comparison of four prognostic scores in peripheral T-cell lymphoma

G. Gutiérrez-García[1], A. García-Herrera[2], T. Cardesa[2], A. Martínez[2], N. Villamor[2], G. Ghita[1], A. Martínez-Trillos[1], L. Colomo[2], X. Setoain[3], S. Rodríguez[4], E. Giné[1], E. Campo[2] & A. López-Guillermo[1]*

Departments of [1]Hematology; [2]Pathology; [3]Nuclear Medicine; [4]Radiology, Hospital Clínic, Institut de Recerca Biomèdica August Pi i Sunyer, Barcelona, Spain

Received 7 April 2010; revised 14 May 2010; accepted 19 May 2010

Age	
Median (range)	55 (17–84)
≤60 years	63 (63)
Gender, *n* (%)	
Female	36 (36)
Male, *n* (%)	64 (64)
Histology, *n* (%)	
PTCL-NOS	56 (56)
AILT	19 (19)
NK/T-cell lymphomas	15 (15)
HSTL	7 (7)
SPTCL	3 (3)
Ki-67 >75%[a], *n* (%)	8 (20)
Poor performance status (ECOG >1), *n* (%)	40 (40)
B symptoms, *n* (%)	52 (52)
Extranodal involvement ≥2 sites, *n* (%)	37 (37)
Bone marrow involvement, *n* (%)	39 (39)
Ann Arbor stage III–IV, *n* (%)	81 (81)
High serum LDH, *n* (%)	56 (56)
High serum β2-m[b], *n* (%)	56 (72)
Platelet cell count <150 × 10^9/l, *n* (%)	28 (28)
First-line treatment, *n* (%)	
<CHOP	9 (9)
CHOP	91 (91)
Response, *n* (%)	
Complete response	36 (36)
Partial response	20 (20)
Non response/progression	44 (44)

[a]Ki-67 count was available in 41 cases.
[b]β2-m levels was available in 78 cases.

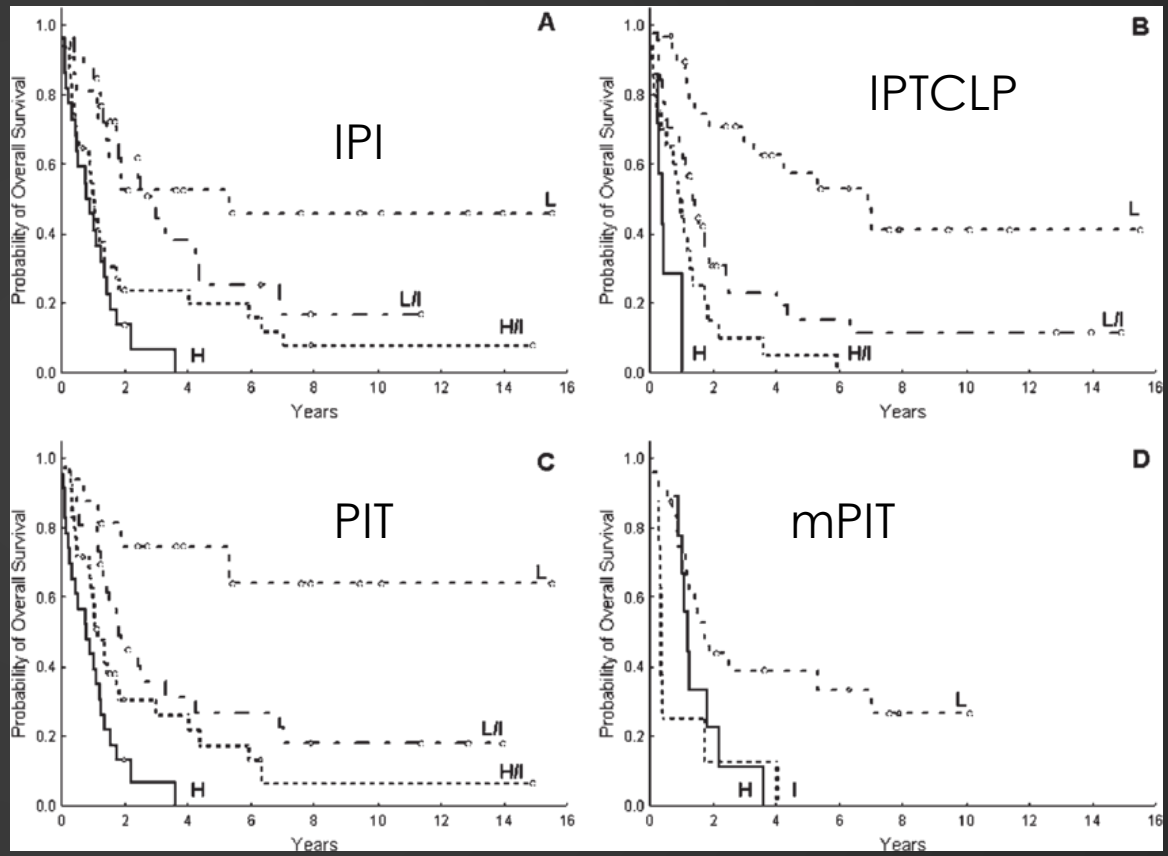
- 121 patients, only 100 were analyzed (excluded ALK+)
- All from Spain, not as ethnically diverse as other studies
- Included NK (12%), HSTCL 7%
- Most received CHOP, 56% ORR
- 21% had autoBMT

Comparing prognostic indices

Prognostic scores	*N* (%)	CR rate (%)	5-year PFS (%)	5-year OS (%)
Whole group	100 (100)	36	10	25
IPI				
Low risk	21 (21)	36	24	52
Low-intermediate risk	27 (27)	33	15	25
High-intermediate risk	30 (30)	17	0	20
High risk	22 (22)	14	0	0
PIT				
Low risk	16 (16)	25	29	75
Low-intermediate risk	27 (27)	31	13	30
High-intermediate risk	36 (36)	33	4	19
High risk	22 (22)	11	0	0
IPTCLP				
Low risk	29 (29)	31	23	58
Low-intermediate risk	44 (44)	52	6	15
High-intermediate risk	20 (20)	14	0	5
High risk	7 (7)	3	0	0
mPIT[a]				
Low risk	24 (58)	57	10	39
Intermediate risk	8 (20)	7	0	0
High risk	9 (22)	36	0	0

[a]mPIT was available in 41 cases.

ALCL, anaplastic large-cell lymphoma; CR, complete response; IPI, International Prognostic Index; IPTCLP, International peripheral T-cell lymphoma Project; mPIT, modified Prognostic Index for T-cell lymphoma; OS, overall survival; PFS, progression-free survival.



(A) International Prognostic Index (IPI), P < 0.0001; (B) International peripheral T-cell lymphoma Project score (IPTCLP), P < 0.0001; (C) PIT, P < 0.0001 and (D) modified Prognostic Index for T-cell lymphoma (mPIT), P = 0.005.

Prognostic scores	*N* (%)	CR rate (%)	5-year PFS (%)	5-year OS (%)
Whole group	100 (100)	36	10	25
IPI				
Low risk	21 (21)	36	24	52
Low-intermediate risk	27 (27)	33	15	25
High-intermediate risk	30 (30)	17	0	20
High risk	22 (22)	14	0	0
PIT				
Low risk	16 (16)	25	29	75
Low-intermediate risk	27 (27)	31	13	30
High-intermediate risk	36 (36)	33	4	19
High risk	22 (22)	11	0	0
IPTCLP				
Low risk	29 (29)	31	23	58
Low-intermediate risk	44 (44)	52	6	15
High-intermediate risk	20 (20)	14	0	5
High risk	7 (7)	3	0	0
mPIT[a]				
Low risk	24 (58)	57	10	39
Intermediate risk	8 (20)	7	0	0
High risk	9 (22)	36	0	0

[a]mPIT was available in 41 cases.

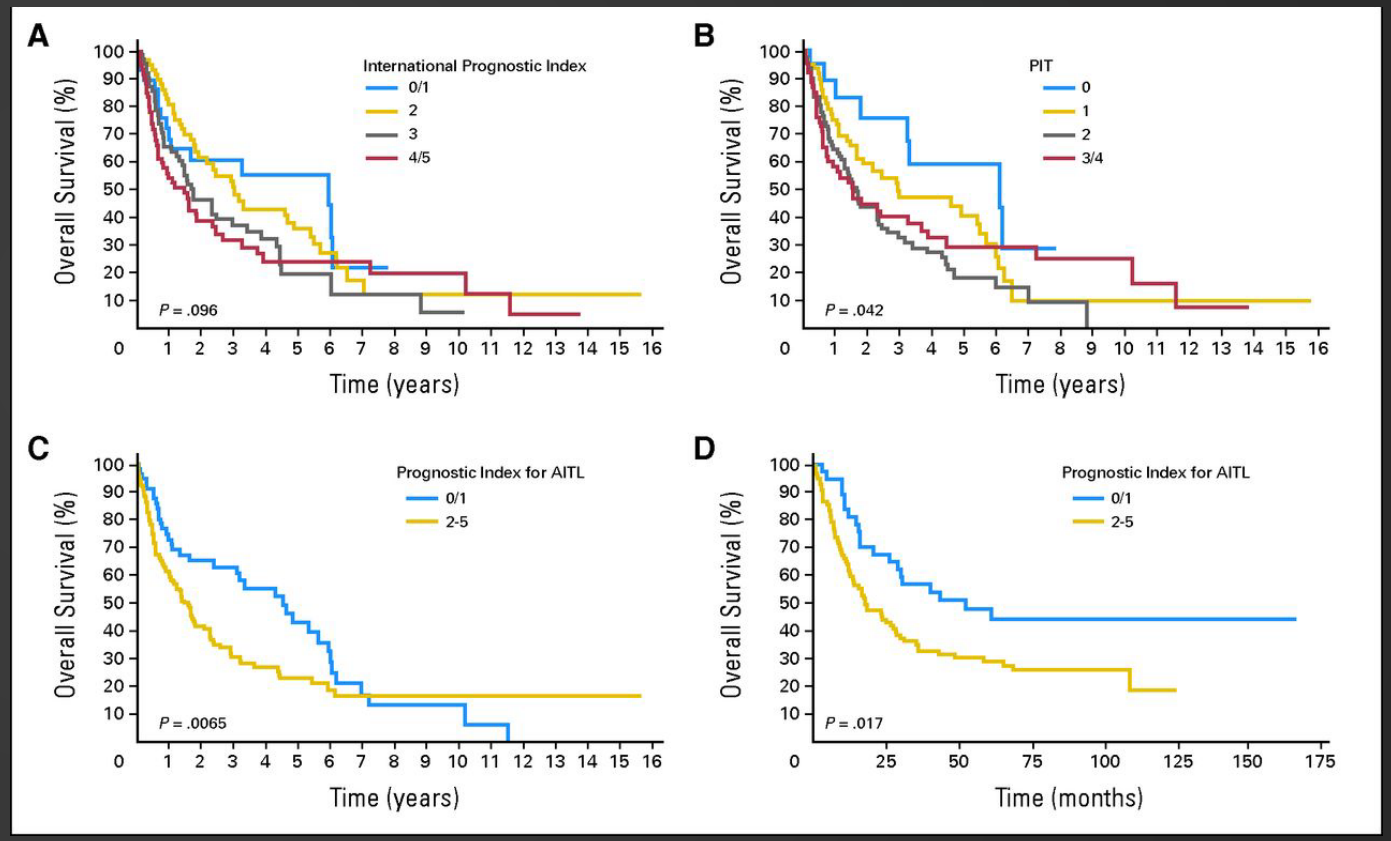
ALCL, anaplastic large-cell lymphoma; CR, complete response; IPI, International Prognostic Index; IPTCLP, International peripheral T-cell lymphoma Project; mPIT, modified Prognostic Index for T-cell lymphoma; OS, overall survival; PFS, progression-free survival.

Comparing prognostic indices

- All prognostic indices identified a patient group with low risk who had a better outcome
- IPTCLP was most important to predict OS
- IPTCLP remained the most important when only PTCLnos was analyzed
- mPIT could not be assessed in all patients due to lack of Ki-67 data in 50% of cases

Analysis of Angioimmunoblastic T-cell lymphoma of the IPTCLP

- 243 AITL patients, Validation GELA cohort
- Standard IPI evaluated
- Alternative Prognostic Index for AITL (PIAI)
  - Age > 60
  - PS > 2
  - ENS > 1
  - B-symptoms present
  - Platelet count < 150K



Federico, et al: JCO 31: 240-246, 2013

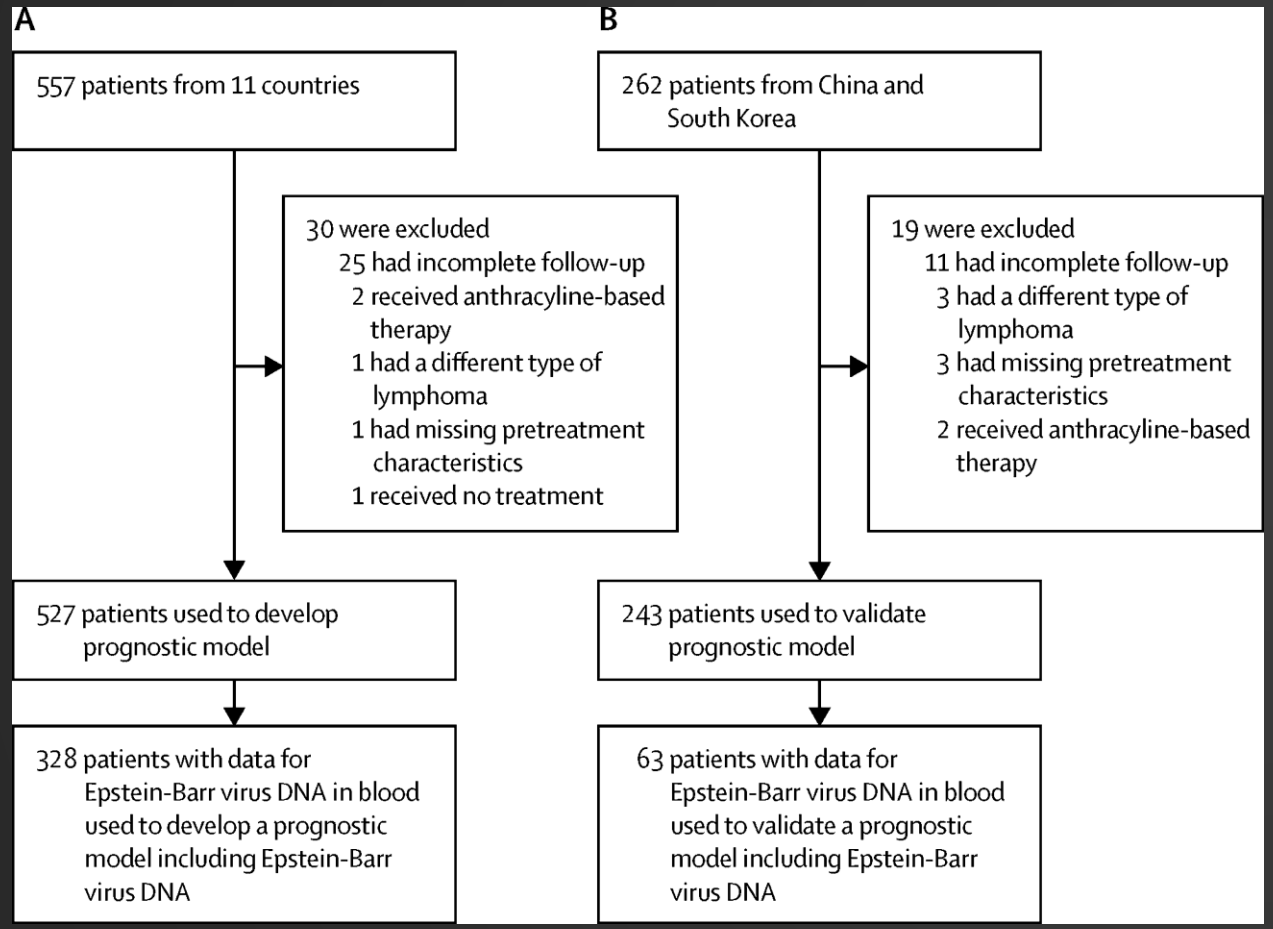
A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis (PINK)

Prof Seok Jin Kim, MD, Dok Hyun Yoon, MD, Arnaud Jaccard, MD, Wee Joo Chng, MD, Soon Thye Lim, MD, Huangming Hong, MD, Yong Park, MD, Kian Meng Chang, MD, Yoshinobu Maeda, MD, Prof Fumihiro Ishida, MD, Dong-Yeop Shin, MD, Jin Seok Kim, MD, Seong Hyun Jeong, MD, Deok-Hwan Yang, MD, Jae-Cheol Jo, MD, Gyeong-Won Lee, MD, Prof Chul Won Choi, MD, Won-Sik Lee, MD, Tsai-Yun Chen, MD, Kiyeun Kim, Sin-Ho Jung, PhD, Tohru Murayama, MD, Yasuhiro Oki, MD, Ranjana Advani, MD, Prof Francesco d'Amore, MD, Prof Norbert Schmitz, MD, Prof Cheolwon Suh, MD, Ritsuro Suzuki, MD, Prof Yok Lam Kwong, MD, Tong-Yu Lin, MD, Prof Won Seog Kim, MD

The Lancet Oncology , 2016

- 527 patients with untreated NK-T cell lymphoma from 1997-2013
- Patients were treated with non-anthracycline chemotherapy
- Nasal and non-nasal types included
- Results from training cohort were validated in independent cohort
- EBV titers were measures as was extranodal sites of involvement

PINK study design



- 69% of patients < age 60
- 65% were male
- 87% had ECOG 0-1
- 35% were stage III/IV
- 20% were non-nasal type
- EBV testing available for 62% of cohort A and only 24% of cohort B
- 36% had detectable EBV in blood
- 25% received SMILE
- 38% got chemotherapy alone and 4% got only radiotherapy

The Lancet Oncology 2016 17, 389-400DOI: (10.1016/S1470-2045(15)00533-1)

PINK independent prognostic factors

	All patients (n=527)						Patients with data for Epstein-Barr virus in DNA (n=328)					
	Overall survival			Progression-free survival			Overall survival			Progression-free survival		
	Parameter estimate	p	Hazard ratio	Parameter estimate	p	Hazard ratio	Parameter estimate	p	Hazard ratio	Parameter estimate	p	Hazard ratio
Age >60 years	0·774	<0·0001	2·168	0·760	<0·0001	2·138	0·820	<0·0001	2·271	0·762	<0·0001	2·142
ECOG performance status ≥2	0·527	0·003	1·694	--	--	--				0·583	0·004	1·792
Stage III-IV	0·942	<0·0001	2·565	0·722	<0·0001	2·058	0·906	<0·0001	2·475	0·839	<0·0001	2·315
Non-nasal type	0·662	<0·0001	1·939	0·692	<0·0001	1·998	0·495	0·018	1·640	0·536	0·005	1·709
Distant lymph-node involvement	0·547	0·002	1·727	0·527	0·002	1·693	0·845	<0·0001	2·329	0·507	0·024	1·660
Serum albumin ≤35 g/L	0·530	0·001	1·699	0·400	0·006	1·492	--	--	--	--	--	--
Platelet ≤75 000 mm³	0·562	0·006	1·754	0·490	0·016	1·632	--	--	--	--	--	--
Lymphocyte ≤3·5 g/dL	--	--	--	0·312	0·032	1·366	--	--	--	--	--	--
Haemoglobin ≤100 g/L	--	--	--	--	--	--	0·672	0·004	1·958	--	--	--
Detectable Epstein-Barr virus DNA	--	--	--	--	--	--	0·516	0·011	1·675	0·538	0·002	1·712

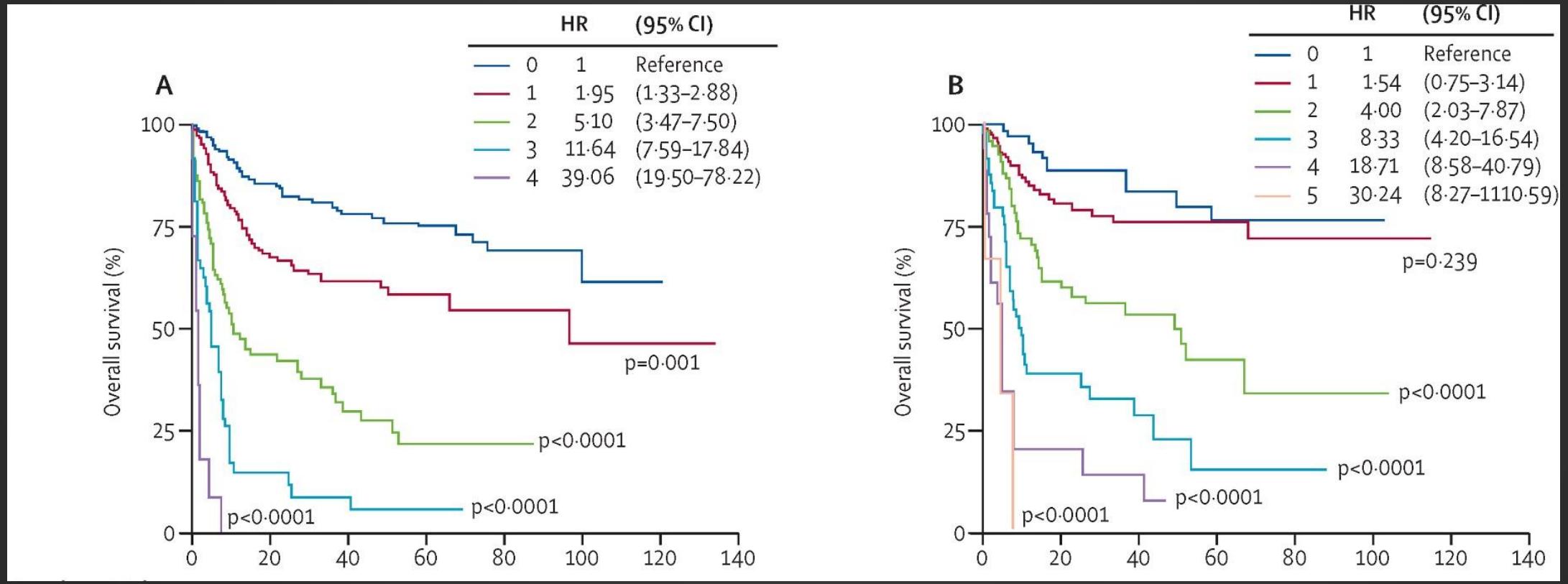
Parameter estimates are regression estimates that are used to calculate a risk score for patients. ECOG=Eastern Cooperative Oncology Group.

Table 2: **Factors independently prognostic of overall and progression-free survival in the training cohort**

Multivariate analysis overall
Age >60
Stage III/IV
Non-Nasal Type
Distant LN

PINK by number of prognostic factors

When EBV was available
Age >60
Stage III/IV
Non-Nasal Type
Distant LN
Detectable EBV

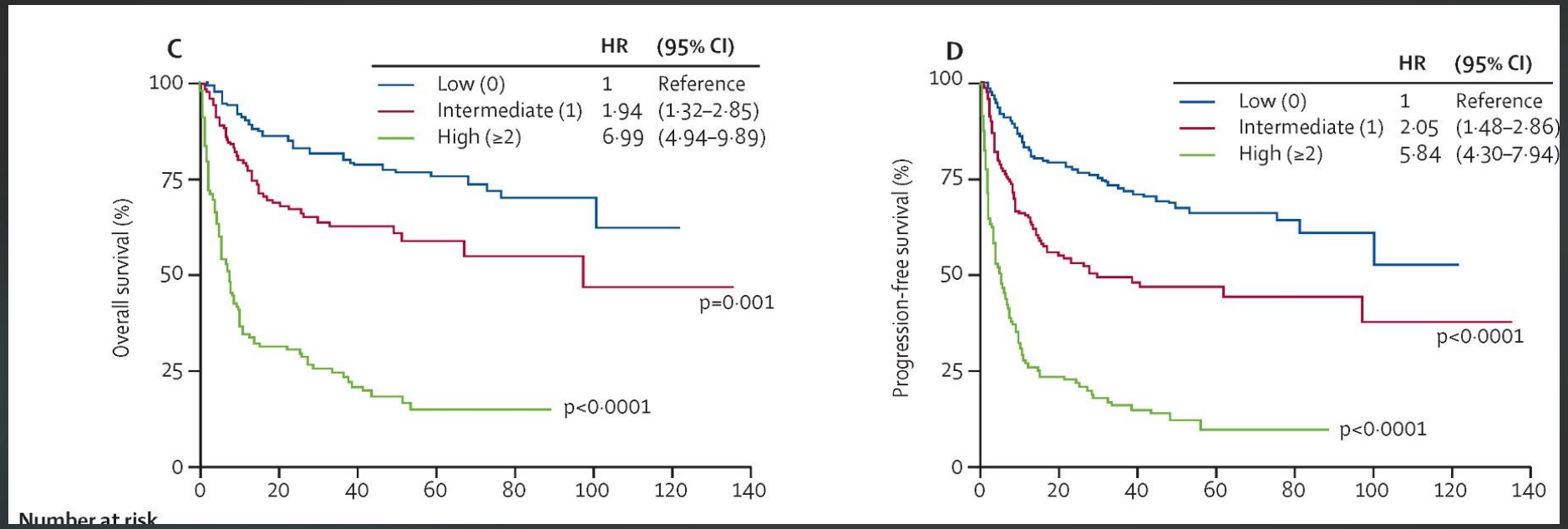


The Lancet Oncology 2016 17, 389-400DOI: (10.1016/S1470-2045(15)00533-1)

Multivariate analysis overall
Age >60
Stage III/IV
Non-Nasal Type
Distant LN

PINK by prognostic group

When EBV was available
Age >60
Stage III/IV
Non-Nasal Type
Distant LN
Detectable EBV



Low Risk – no factors
Intermediate risk- 1
High risk- 2 or more

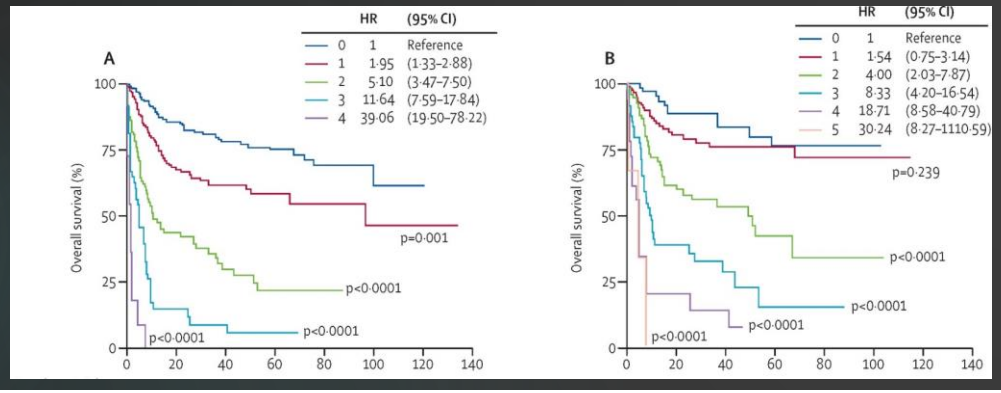
Low Risk – no factors
Intermediate risk- 1
High risk- 2 or more

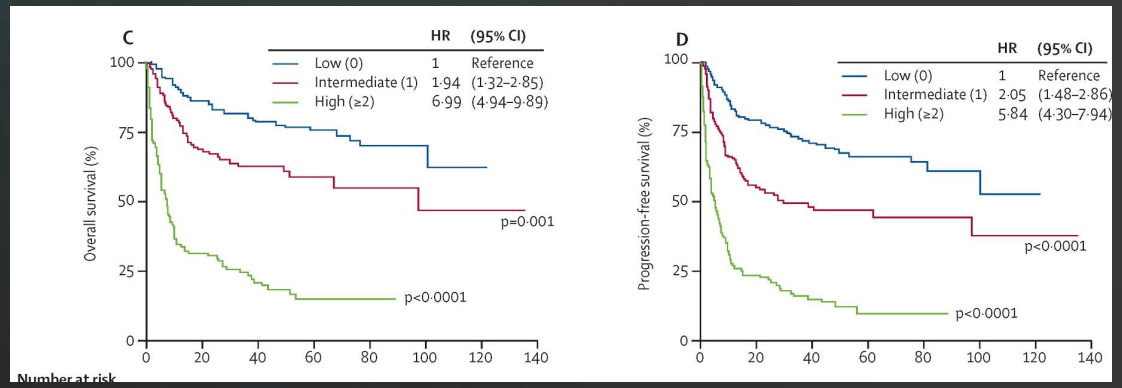
The Lancet Oncology 2016 17, 389-400DOI: (10.1016/S1470-2045(15)00533-1)

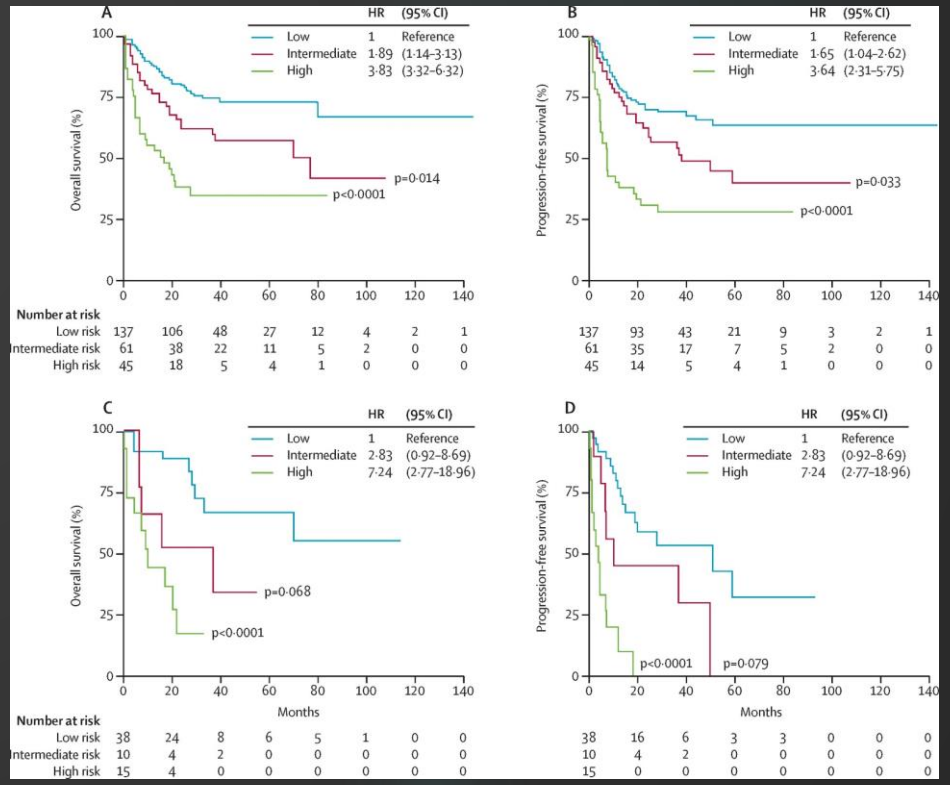
Training Cohort

Factor	Training cohort (%) N=527	Validation cohort (%) N=243
Age>60	31	19
Nasal type	80	86
Distant nodes	16	10
EBV detectable	36	12
SMILE chemotherapy	25	12 (GemOx 38%)

Validation Cohort



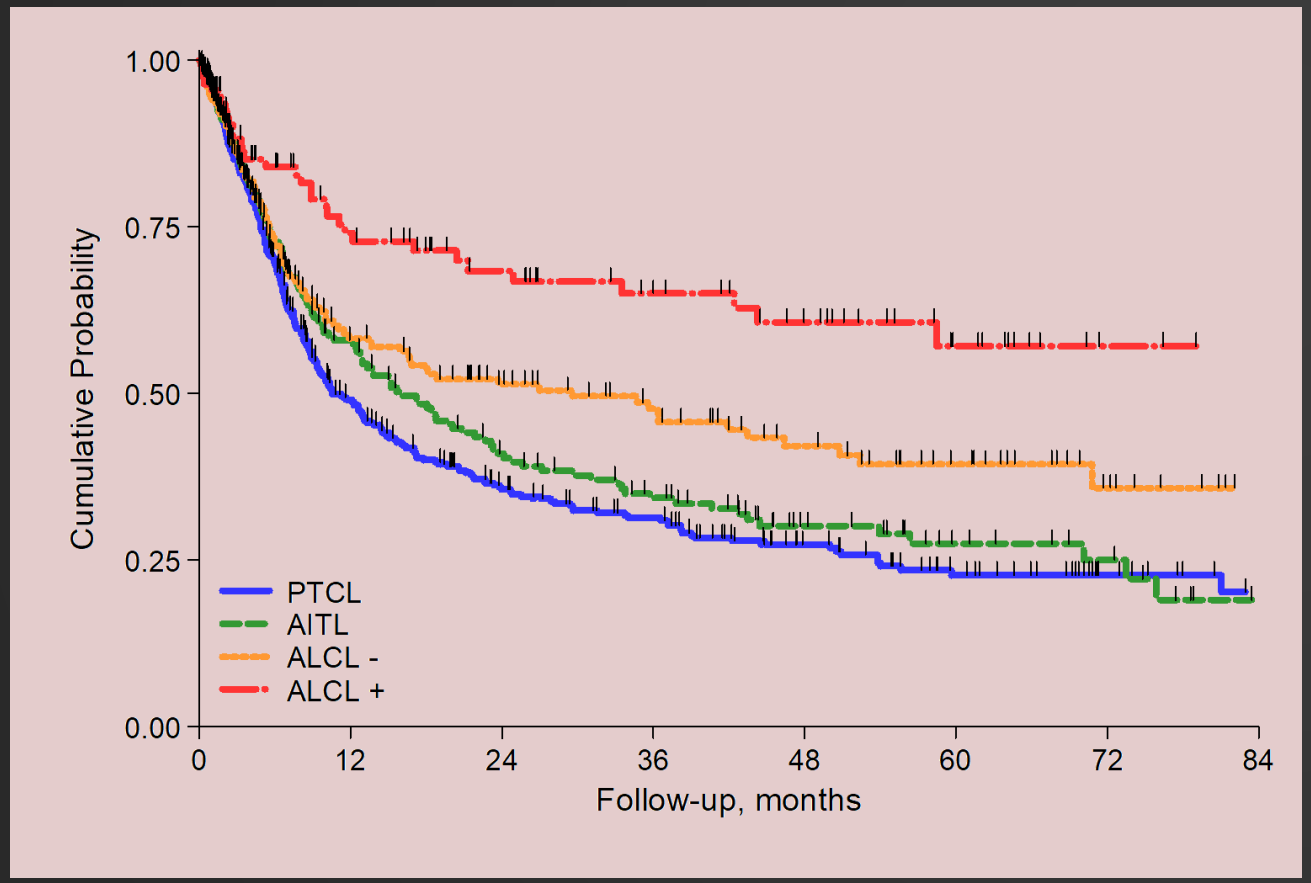


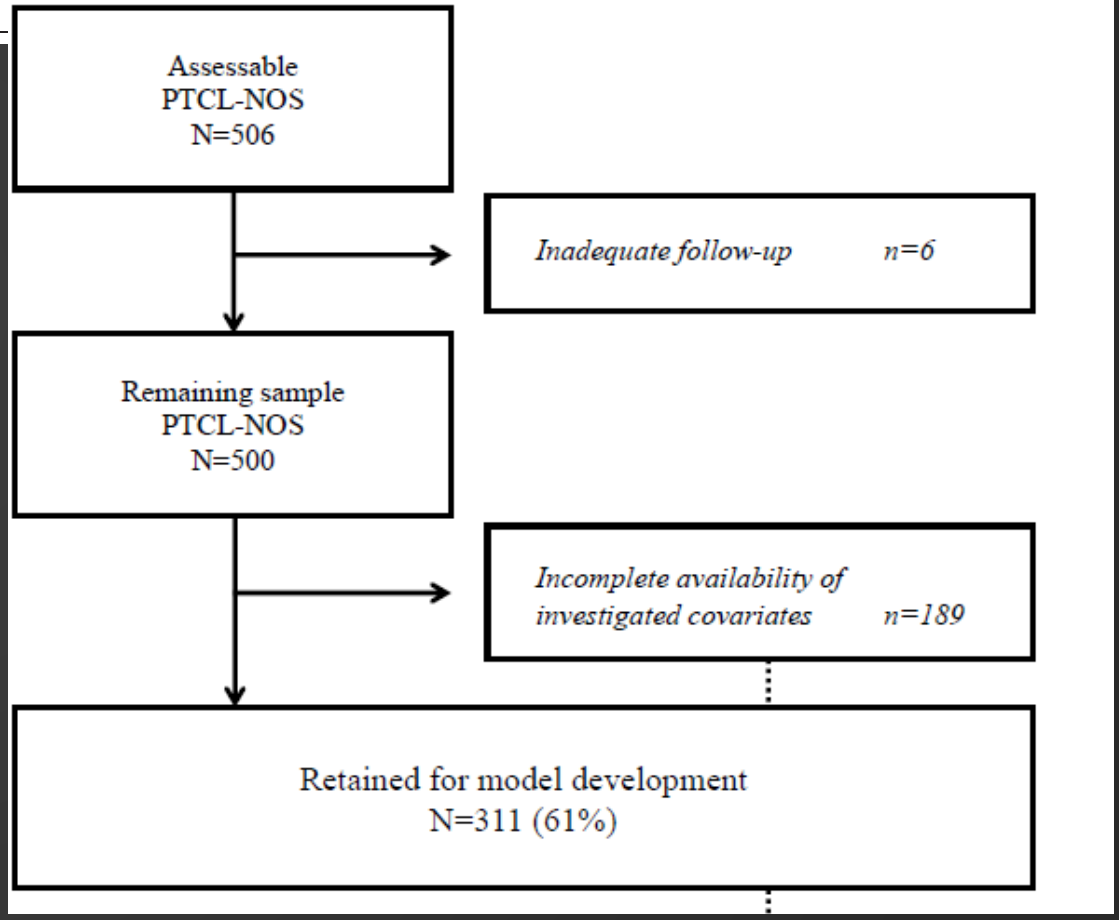


bjh research paper

Peripheral T cell lymphoma, not otherwise specified (PTCL-NOS). A new prognostic model developed by the International T cell Project Network

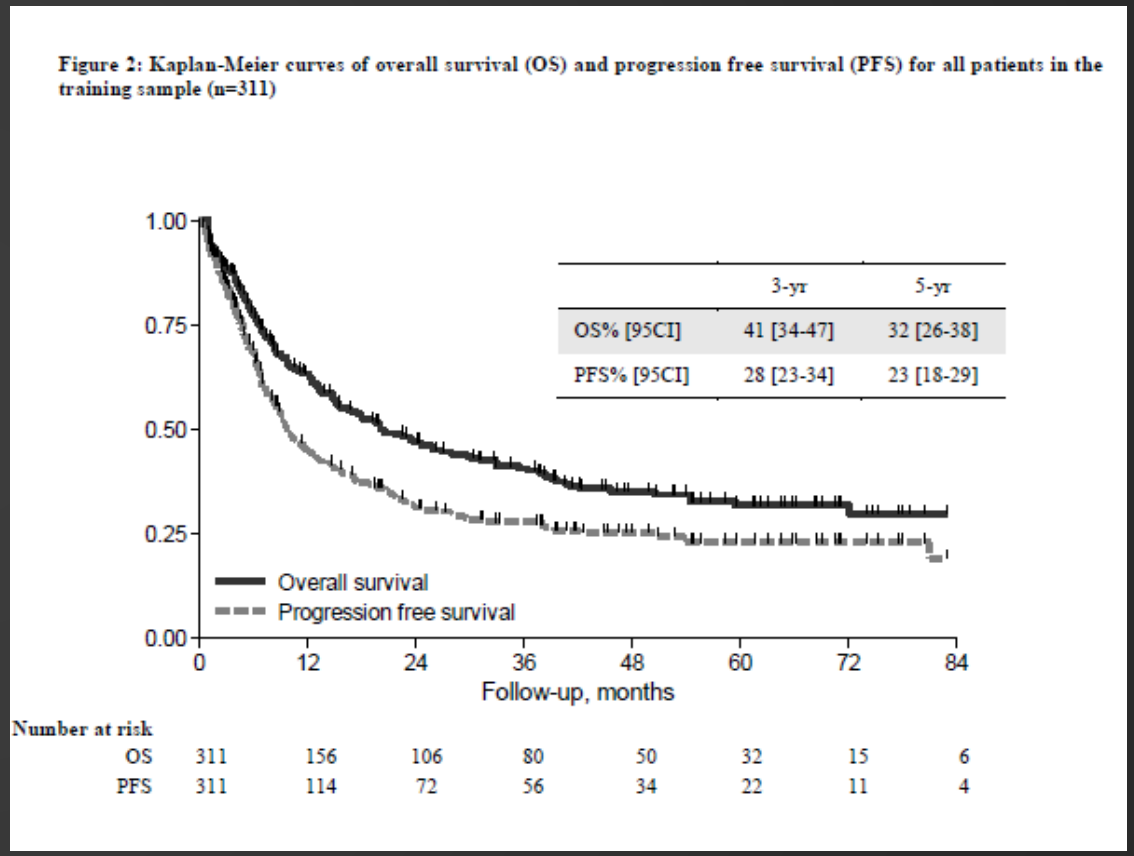
Federico et al, for T Cell Project, 2018





Patient Demographics and outcomes

- 311 patients in training sample with PTCLnos
- Median age 63
- 79% received chemo with curative intent
- 74% received CHOP, 18% had etoposide regimens
- 4% had autoBMT
- 3 yr PFS was 28%



Variables with potential prognostic impact that were examined

- chosen from literature among those reported with a prognostic impact on survival in this subset

	Variable
1.	Age>60 yrs
2.	LDH >ULN
3.	Albumin, <3.5 g/dL
4.	Hemoglobin <12, g/dL
5.	Platelets <150/mm^3
6.	Lymphocyte to Monocyte Ratio (LMR) ≤2.1
7.	Neutrophil to Lymphocyte Ratio (NLR) >6.5
8.	ECOG Performance Status >1
9.	Stage III-IV
10.	B-symptoms
11.	Extra nodal sites>1
12.	Male Gender

Factor	%
Age > 60	55
Stage III/IV	76
ECOG>1	26
LDH	53
Albumin<35	38
Plts <150	21
ANC>6.5	23
LMR≤2.1	41

TCP Model: The Winners are…

Albumin

Performance status

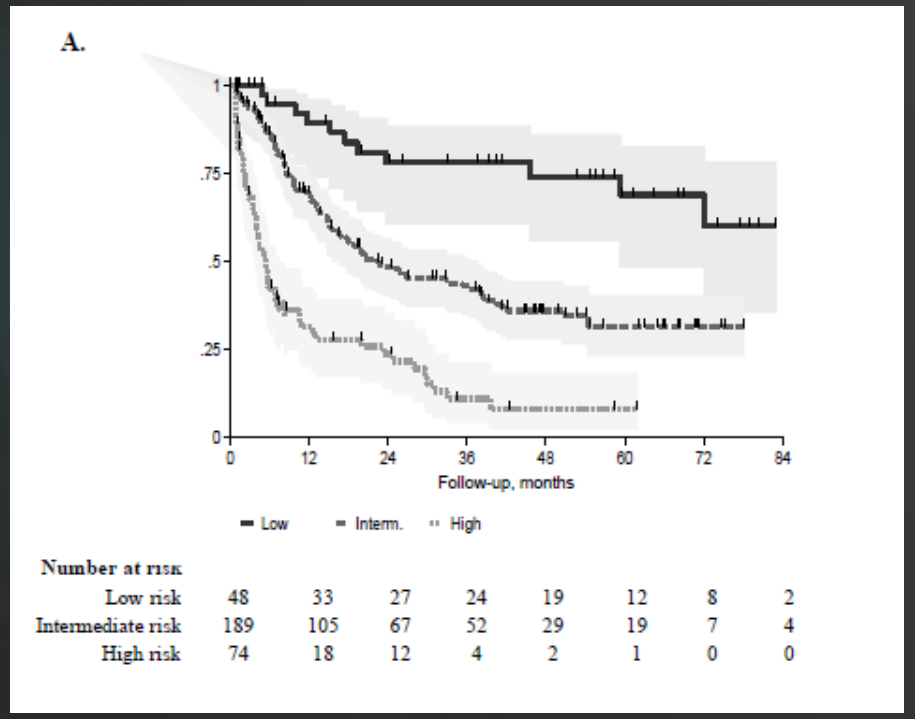
Stage

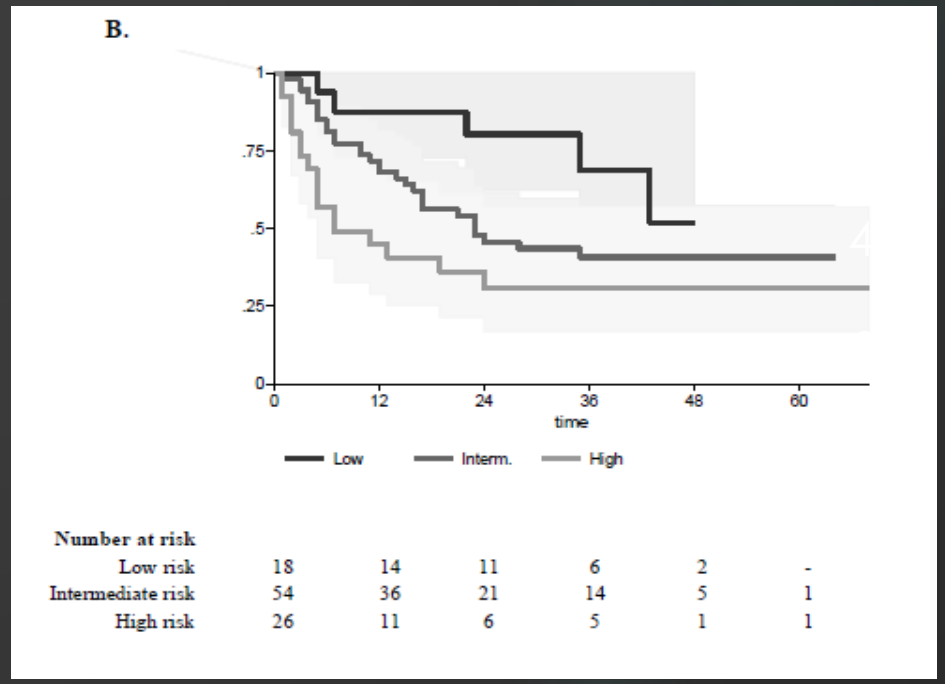
Absolute neutrophil count

Univariate and Multivariate Analysis for OS- training sample

		Univariate			Multivariate		
Factor	**%**	**HR**	**CI95**	**P**	**HR**	**CI95**	**P**
Age >60	55	**1.25**	**0.92-1.70**	0.151			
Male gender	62	**1.52**	**1.09-2.12**	0.013			
PS > 1	26	**2.60**	**1.89-3.57**	<0.001	2.12	1.5-2.94	<0.001
Stage III-IV	76	**2.18**	**1.44-3.29**	<0.001	1.74	1.14-2.65	0.010
ENS >1	28	**1.17**	**0.84-1.62**	0.354			
B symptoms	44	**1.79**	**1.32-2.42**	<0.001			
LDH > ULN	53	**1.98**	**1.45-2.72**	<0.001			
Hb < 12 g/dL	39	**1.43**	**1.05-1.94**	0.022			
Albumin <3.5 g/dL	38	**2.63**	**1.94-3.58**	<0.001	2.03	1.47-2.81	<0.001
LMR <2.1	41	**1.55**	**1.15-2.10**	0.005			
ANC >6.5	21	**2.05**	**1.48-2.85**	<0.001	1.85	1.33-2.58	<0.001
Plt <150/mm^3	21	**1.52**	**1.07-2.18**	0.020			

	Training (N=311)	Validation (N=98)
Median follow up (mo)	46	18
Median survival (mo)	20	23
Risk Group (%)		
Low	15	18
Intermediate	61	55
High	24	27





Conclusions from the T cell Project Prognostic study

- This is a prospective study with relatively uniformly treated patients (most got CHOP like regimens)
- This prognostic score applies to PTCLnos, ?if it will apply to other subtypes
- Albumin has previously been reported as adverse prognostic factor (Watanabe,Chihara, Raina,)
- In CHOP treated DLBCL, elevated ANC and low albumin were important in multi-variate analysis (Spassov et al.), elevated ANC is marker of inflammation and adverse prognostic factor in a number of solid tumors
- CD30 was not studied as it was only available on 43% of cases
- No molecular or genotypic findings were included in this analysis

New Prognostic Models- where we have been

- Earlier indices incorporated mostly easily obtainable clinical features
- Biological features reflecting tumor kinetics (Ki-67) added
- Other investigators have identified prognostic impact of other feature such as albumin, ANC, neutrophil/lymphocyte ratio, etc reflecting tumor and microenvironment effects
- T cell Score builds on clinical and biological variables and is a prospective database of relatively uniformly treated patients
- All models identify a favorable group of patients with a plateau on survival curve
- All models identify patients who have very poor outcome with existing treatment strategies

The Next Frontier for Prognostic Modeling

- Molecular determinants
  - ALCL- DUSP22, TP63 identify very good and poor outcome patients
  - PTCLnos- GATA-3 and TBX21 identify distinct subgroups
  - AITL- microenvironment signatures (B-cell, cytotoxic, monocytoid/dendritic cell, etc)
- Creating the matrix to better understand and predict outcomes
  - Tumor characteristics
  - Microenvironment and immune milieu
  - Patient factors
  - Treatment modalities

The Next Frontier for Prognostic Modeling

Are we ready yet to change treatment algorithm for any group of patients? What about those that fall into the low risk groups?

Can we use these prognostic models to invoke changes in treatment strategies in the very high risk patients?