CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

Milano, UNAHOTELS Galles

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Associazione Linfomi e Malattie Immunologiche/Terapia Immunosoppressiva

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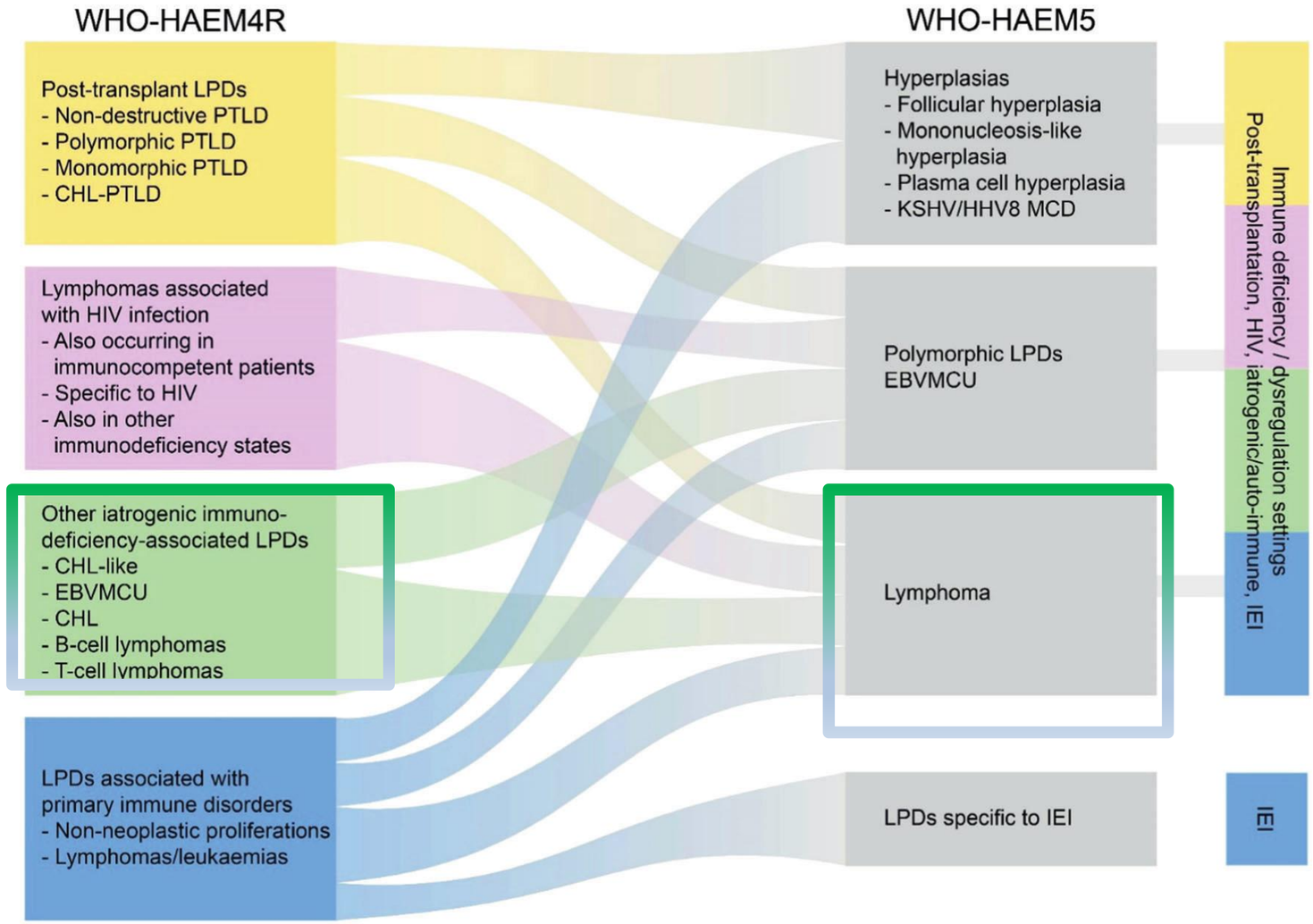
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
SERB						X	
BMS						x	
Gentili						x	

Immune Deficiency / Disregulation settings (IDD-LPDs)

Classificazione



Classificazione IDD-LPDs

WHO HAEM5

- Morfologia (hyperplasia, polymorphic, LPD, Lympoma)
- Virus (EBV and HSV/HHV8, etc..)
- Clinica: Quadro immunologico [trapianto, HIV, CART, malattie autoimmune], immunosenescenza

Note: in questa categoria la classificazione non considera le associazioni noti tra patologie autoimmuni e Linfomi (AHIA e indolenti, Sjogren e MZL)

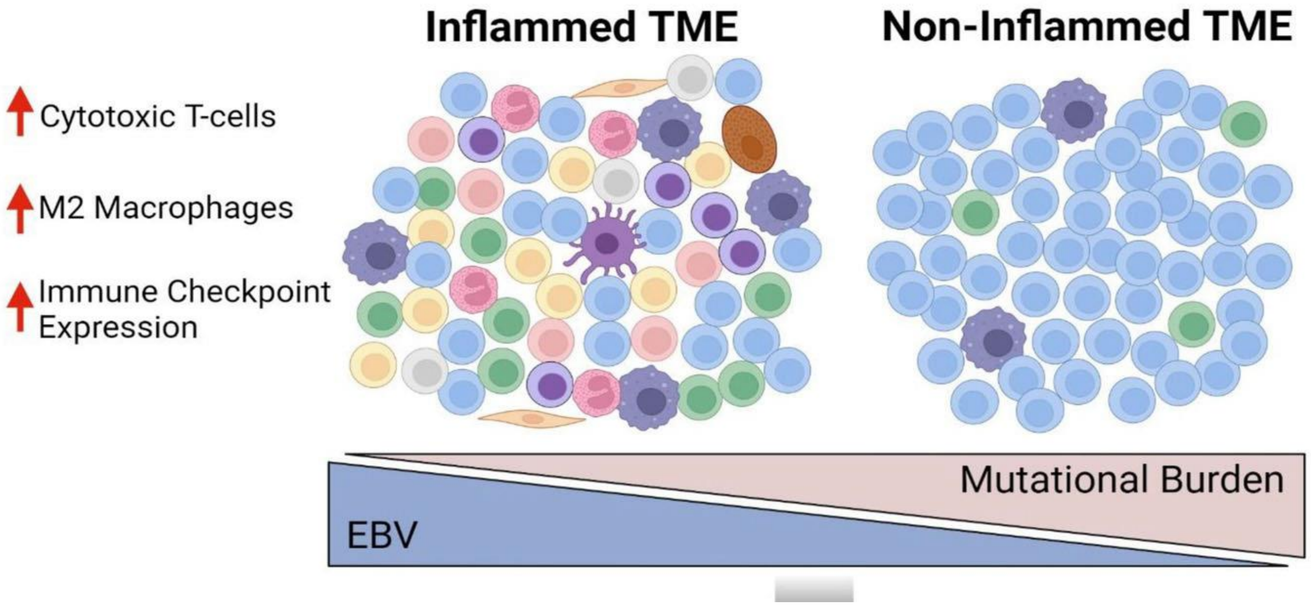
WHO classification, 5th edition	WHO classification, revised 4th edition
Hyperplasia arising in immune deficiency/ dysregulation distincted in - Follicular proliferation - interfollicular and paracortical proliferations Plasma-cell hyperplasia Mononucleosis-like hyperplasia - T-cell and histiocytic proliferations	Non-destructive forms distincted in: - Florid follicular hyperplasia - Plasmacytic hyperplasia - Infectious mononucleosis
KSHV/HHV8 Multicentric Castleman disease (also included in tumor-like lesion with B-cell predominance)	Multicentric Castleman disease
Polymorphic LPD arising in immune deficiency/ dysregulation	Polymorphic
Epstein-Barr virus-positive mucocutaneous ulcer	Epstein-Barr virus-positive mucocutaneous ulcer
Lymphomas arising in immune deficiency/ dysregulation	Monomorphic B and T cell neoplasms, cHL
	Lymphomas associated with HIV infection
	Other iatrogenic immunodeficiency-associated LPDs
In born error of immunity-associated lymphoid proliferations and lymphomas	Lymphoproliferative disease associated with primary immune disorders

Carbone A. Blood Reviews 64 (2024) 101167

Eziopatogenesi IDD LPDs

Microambiente

- Studio con pannello genomico di 770 geni su Linfomi aggressivi post-trapianto
- Microambiente a due modalità: infiammato e non infiammato
- 1) Infiammato: elevata espressione EBV e migliore sopravvivenza e migliore risposta a R o RIS
- 2) non infiammato: peggiore sopravvivenza, elevato burden mutazioni

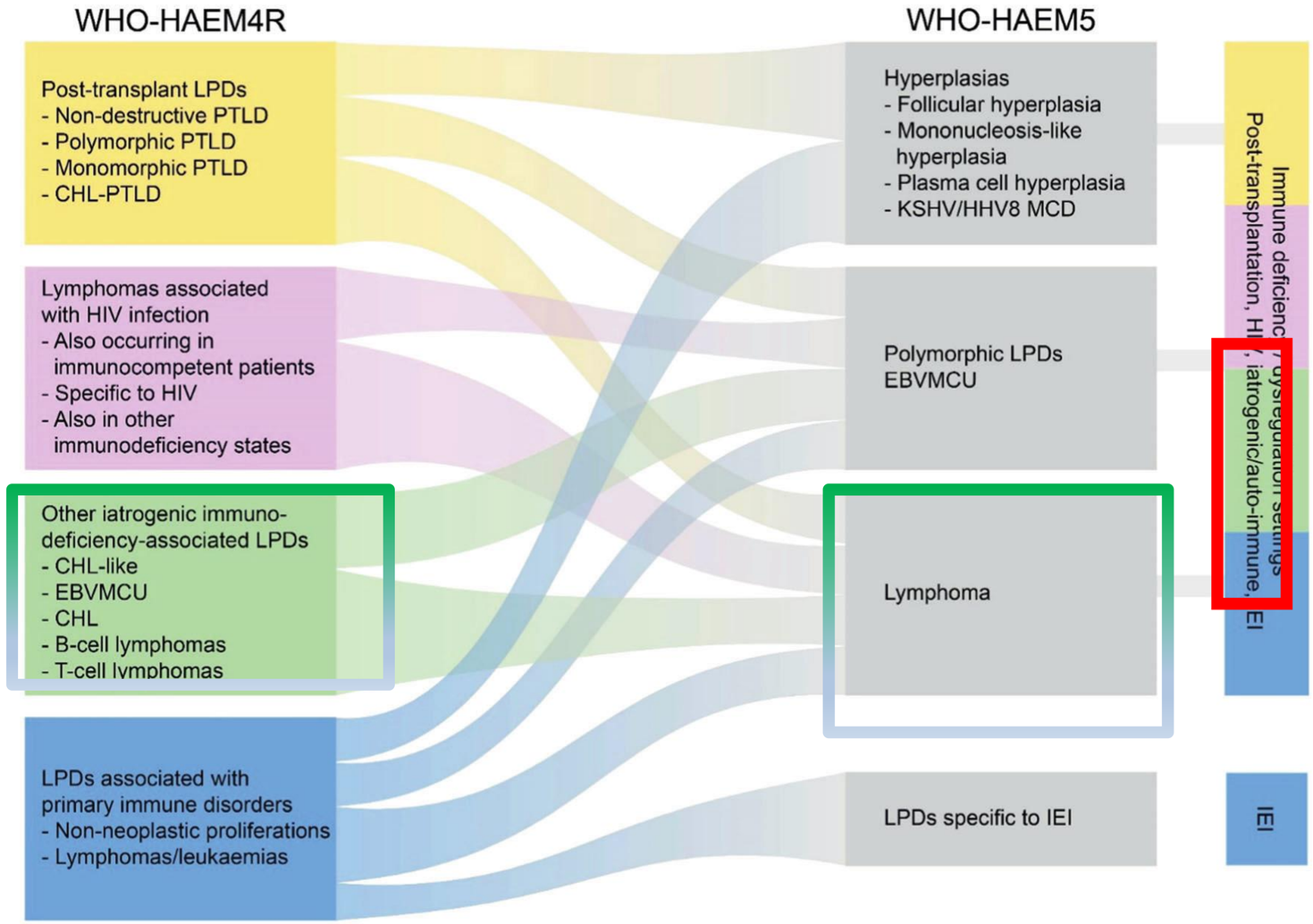


Dierickx et al. Histopathology 2025, 86, 106–118.

Leivonen SK, Friman T, Autio M et al. Haematologica 2023; 108; 3044–3057.

Immune Deficiency / Disregulation settings (IDD-LPDs)
Iatrogenic - immune

OIIA LPD



Classificazione Malattia Autoimmuni (AID)

Immune response		Organ involvement	
B-cell responses	Autoimmune hemolytic anemia	Involvement of multiple organs	Rheumatoid arthritis
	Hashimoto's thyroiditis/hypothyroidism		Sjögren's syndrome
	Myasthenia gravis		Systemic lupus erythematosus
	Pernicious anemia		Dermatomyositis/polymyositis
	Rheumatoid arthritis		Sarcoidosis
	Sjögren's syndrome		Systemic sclerosis/scleroderma
	Systemic lupus erythematosus	Targeted toward a single organ or system	
T-cell responses	Celiac disease	Pancreas	Type 1 diabetes
	Dermatomyositis/polymyositis	Gastrointestinal/hepatobiliary	Pernicious anemia
	Immune thrombocytopenic purpura		Celiac disease
	Inflammatory bowel disease (ulcerative colitis, Crohn's disease)		Inflammatory bowel disease (Crohn's disease, ulcerative colitis)
	Multiple sclerosis	Dermatological	Psoriasis
	Psoriasis	Hematological	Autoimmune hemolytic anemia
	Sarcoidosis		Immune thrombocytopenic purpura
	Systemic sclerosis/scleroderma	Neurological	Myasthenia gravis
	Type 1 diabetes		Multiple sclerosis
		Endocrine	Hashimoto's thyroiditis/hypothyroidism

Wang S. et al. AmJEpidemiol. 2015;181(6):406–421

Epidemiologia: associazione AID e LNH

Disorder*	No. of studies	All NHL: ever/never (%)	Controls: ever/never (%)	OR (95% CI)‡	Study heterogeneity *P*§
Rheumatoid arthritis	12	504/11735 (4.3)	556/15222 (3.7)	1.06 (0.87-1.29)‖	.01
Psoriasis	7	278/7460 (3.7)	279/10122 (2.8)	1.16 (0.98-1.38)	.82
Ulcerative colitis	9	125/9775 (1.3)	138/12148 (1.1)	1.02 (0.79-1.31)	.84
Type 1 diabetes	9	32/10289 (0.3)	58/13613 (0.4)	0.76 (0.49-1.19)	.79
Sarcoidosis	6	19/7607 (0.2)	27/8856 (0.3)	0.73 (0.40-1.32)	.70
Pernicious anemia	5	13/3410 (0.4)	16/5865 (0.3)	1.08 (0.51-2.30)	.25
Crohn disease	7	23/9230 (0.2)	27/10614 (0.3)	0.89 (0.50-1.56)	.74
Celiac disease	7	33/9343 (0.4)	25/10424 (0.2)	1.50 (0.89-2.54)	.72
Hemolytic anemia	5	21/3242 (0.6)	13/5585 (0.2)	2.57 (1.27-5.21)	.7
Systemic lupus erythematosus	11	57/12034 (0.5)	26/15	2.69 (1.68-4.30)	.39
Multiple sclerosis	10	15/9666 (0.2)	18/12341 (0.1)	0.96 (0.48-1.92)	.89
Sjögren syndrome	8	52/8178 (0.6)	8/10543 (0.1)	6.56 (3.10-13.9)	.72
Primary Sjögren syndrome	8	23/8176 (0.3)	5/10543 (0.0)	4.75 (1.79-12.6)	.93
Secondary Sjögren syndrome	8	29/8178 (0.4)	3/10542 (0.0)	9.57 (2.90-31.6)	ND
Scleroderma	7	4/7616 (0.1)	7/10093 (0.1)	0.69 (0.20-2.40)	.81
Immune thrombocytopenia	5	4/4095 (0.1)	3/6529 (0.0)	2.13 (0.47-9.73)	.54
Myasthenia gravis	6	4/6385 (0.1)	3/7413 (0.0)	1.45 (0.31-6.82)	.53
Polymyositis/dermatomyositis	5	6/6662 (0.1)	0/7947 (0.0)	ND	ND

Subtypes of subtype groups

	Diffuse large B-cell lymphoma (n = 3709)		Follicular lymphoma (n = 2712)		CLL/SLL/PLL/MCL‡ (n = 2096)		Marginal-zone lymphoma group§ (n = 744)	
Disorder†	**Ever/ never**	**OR (95% CI)‖**	**Ever/never**	**OR (95% CI)‖**	**Ever/never**	**OR (95% CI)‖**	**Ever/never**	**OR (95% CI)‖**
Psoriasis	70/1974	1.11 (0.85-1.46)	43/1381	0.95 (0.68-1.32)	69/1260	1.18 (0.89-1.57)	10/200	1.08 (0.56-2.08)
Ulcerative colitis	38/2664	1.23 (0.85-1.78)	20/2040	0.89 (0.55-1.45)	16/1579	1.02 (0.59-1.79)	6/417	1.28 (0.54-3.04)
Type 1 diabetes	7/2875	0.59 (0.27-1.31)	4/1963	0.53 (0.19-1.49)	13/1800	1.97 (1.00-3.88)	2/506	1.17 (0.27-5.00)
Sarcoidosis	5/2217	0.69 (0.26-1.80)	4/1810	0.63 (0.22-1.82)	2/1363	0.39 (0.09-1.66)	1/410	0.64 (0.08-4.80)
Pernicious anemia	8/1138	2.12 (0.87-5.16)	0/917	ND	0/110	ND	3/204	2.29 (0.58-8.94)
Crohn disease	10/2523	1.49 (0.71-3.13)	1/1970	0.16 (0.02-1.23)	2/1574	0.49 (0.11-2.16)	3/406	2.41 (0.69-8.46)
Celiac disease	11/2574	1.83 (0.89-3.74)	6/1795	1.13 (0.45-2.85)	3/1937	0.73 (0.21-2.52)	0/518	ND
Hemolytic anemia	8/951	3.22 (1.31-7.89)	3/756	1.46 (0.40-5.37)	1/245	2.90 (0.31-27.2)	1/143	2.23 (0.24-21.0)
Systemic lupus erythematosus	17/3347	2.74 (1.47-5.11)	9/2455	1.70 (0.77-3.74)	6/2045	2.10 (0.825-.42)	10/583	7.52 (3.39-16.7)
Multiple sclerosis	5/2897	1.03 (0.38-2.80)	5/2267	1.08 (0.39-2.98)	2/1483	1.07 (0.23-4.96)	2/603	1.37 (0.30-6.20)
Sjögren syndrome	18/2350	8.92 (3.83-20.7)	7/1794	3.91 (1.39-11.0)	1/1397	0.62 (0.07-5.07)	15/396	30.6 (12.3-76.1)
Primary Sjögren syndrome	8/2348	6.57 (2.12-20.3)	2/1794	1.78 (0.34-9.37)	1/1397	1.01 (0.11-9.15)	8/396	23.1 (7.16-74.6)
Secondary Sjögren syndrome	10/2350	12.8 (3.49-47.3)	5/1794	7.55 (1.75-32.7)	0/1397	ND	7/396	44.6 (10.6-187)

- Studio americano prospettico, che raccoglie gli studi condotti dal Lymphoma Epidemiology (InterLymph) Consortium (1983–2004)
- Associazione con Sjogren e LES
- Dubbia associazione con AR per grande eterogeneità
- Confermata associazione AR e LNH se usi steroidi e IS → gravità malattia

Karin Ekstrom Smedby et al. BLOOD, 15 APRIL 2008, 111, 8

Epidemiologia: associazione AID e LNH

Autoimmune condition, by system	Controls (n=122,531)	Non-Hodgkin lymphoma† (n=33,721)		Diffuse large B-cell lymphoma (n=10,144)	T-cell non-Hodgkin lymphoma (n=1,870)	Marginal zone lymphoma (n=1,908)	Follicular lymphoma (n=4,491)	Chronic lymphocytic lymphoma (n=9,171)
	No.	No.	OR (95% CI) ‡	OR (95% CI) ‡	OR (95% CI) ‡	OR (95% CI) ‡	OR (95% CI) ‡	OR (95% CI) ‡
Systemic/Connective Tissue								
Rheumatoid arthritis	3,289	1,157	1.2 (1.1-1.3)*	1.4 (1.2-1.5)*	1.5 (1.1-1.8)	1.2 (1.0-1.6)	1.3 (1.1-1.5)	1.1 (1.0-1.2)
Sjögren syndrome	255	142	1.9 (1.5-2.3)*	2.0 (1.5-2.8)*	0.8 (0.2-2.4)	6.6 (4.6-9.53)*	1.3 (0.7-2.2)	1.1 (0.7-1.7)
Systemic lupus erythematosus	285	129	1.5 (1.2-1.9)*	1.4 (1.0-2.0)	2.4 (1.3-4.4)	2.8 (1.7-4.7)*	1.0 (0.6-1.8)	1.4 (0.9-2.0)
Sarcoidosis	96	42	1.5 (1.0-2.2)	2.0 (1.2-3.3)	0.6 (0.1-4.6)	1.6 (0.5-5.0)	1.3 (0.5-3.1)	0.7 (0.3-1.8)
Systemic sclerosis	79	33	1.4 (0.9-2.2)	2.0 (1.1-3.6)	0.8 (0.1-5.8)	1.8 (0.5-5.8)	0.8 (0.3-2.7)	0.7 (0.3-1.9)
Polymyalgia rheumatica	1,244	344	0.9 (0.8-1.0)	0.9 (0.8-1.1)	1.2 (0.8-1.8)	0.7 (0.4-1.1)	0.8 (0.6-1.1)	0.8 (0.7-1.0)
Ankylosing spondylitis	128	40	1.1 (0.7-1.5)	0.9 (0.5-1.7)	0.9 (0.2-3.4)	2.2 (0.9-5.4)	0.8 (0.3-2.3)	1.1 (0.6-2.0)
Dermatomyositis/polymyositis	128	38	1.0 (0.7-1.4)	0.8 (0.4-1.5)	1.0 (0.2-3.9)	0.4 (0.1-2.7)	1.1 (0.5-2.5)	1.2 (0.7-2.2)
Blood								
Autoimmune hemolytic anemia	44	87	6.5 (4.4-9.4)*	3.3 (1.7-6.3)*	9.7 (4.3-22)*	7.4 (3.1-18)*	3.4 (1.4-8.2)	8.7 (5.5-14)*
Aplastic anemia	84	45	1.8 (1.3-2.7)	1.9 (1.1-3.3)	2.8 (1.0-7.8)	1.3 (0.3-5.4)	2.4 (1.1-5.2)	1.2 (0.6-2.5)
Cardiovascular								
Systemic vasculitis	25	9	1.1 (0.5-2.7)	1.3 (0.4-4.4)	4.2 (0.9-18)	-	0.9 (0.1-6.6)	1.4 (0.4-4.8)
Chronic rheumatic heart disease	3,948	1,221	1.1 (1.0-1.1)	1.1 (1.0-1.2)	1.0 (0.8-1.3)	1.1 (0.9-1.4)	1.1 (0.9-1.3)	1.0 (0.9-1.1)
Giant cell arteritis	397	91	0.8 (0.6-1.0)	0.7 (0.5-1.0)	1.0 (0.4-2.2)	0.3 (0.1-1.0)	0.8 (0.4-1.3)	0.9 (0.6-1.3)
Polyarteritis nodosa	34	11	1.1 (0.5-2.2)	2.3 (1.0-5.2)	1.8 (0.2-13)	-	1.5 (0.3-6.5)	0.4 (0.1-2.7)
Endocrine								
Addison disease	185	54	1.0 (0.7-1.3)	1.3 (0.8-2.0)	0.6 (0.2-2.6)	0.5 (0.1-2.2)	0.8 (0.4-1.8)	0.7 (0.4-1.4)
Graves disease	354	91	0.9 (0.7-1.1)	1.1 (0.7-1.5)	0.5 (0.2-1.6)	1.0 (0.5-2.2)	0.6 (0.3-1.1)	0.7 (0.4-1.1)
Hashimoto thyroiditis	286	94	1.1 (0.8-1.4)	1.2 (0.8-1.7)	0.7 (0.2-2.1)	1.0 (0.4-2.2)	1.0 (0.6-1.8)	0.9 (0.6-1.4)
Skin								
Psoriasis	1,513	520	1.2 (1.0-1.3)	1.2 (1.0-1.4)	3.1 (2.5-4.0)*	1.3 (1.0-1.9)	1.0 (0.8-1.3)	0.8 (0.7-1.0)
Alopecia areata	97	19	0.7 (0.4-1.1)	0.7 (0.3-1.6)	1.3 (0.3-5.2)	-	0.5 (0.1-2.1)	0.6 (0.2-1.7)
Pemphigus	22	12	1.8 (0.9-3.8)	2.5 (0.9-6.6)	5.9 (1.4-25)	2.3 (0.3-17)	1.3 (0.2-10)	1.1 (0.3-5.0)

Studio SMAHRT da registro: casi controlli Linfomi – AID

SEER Medicare data dal 86 al 02

confermata associazione tra alcune AID e alcuni LNH

Lesley A Anderson et al. *nt J Cancer*. 2009 July 15; 125(2): 398–405.

Epidemiologia: associazione AID e LNH

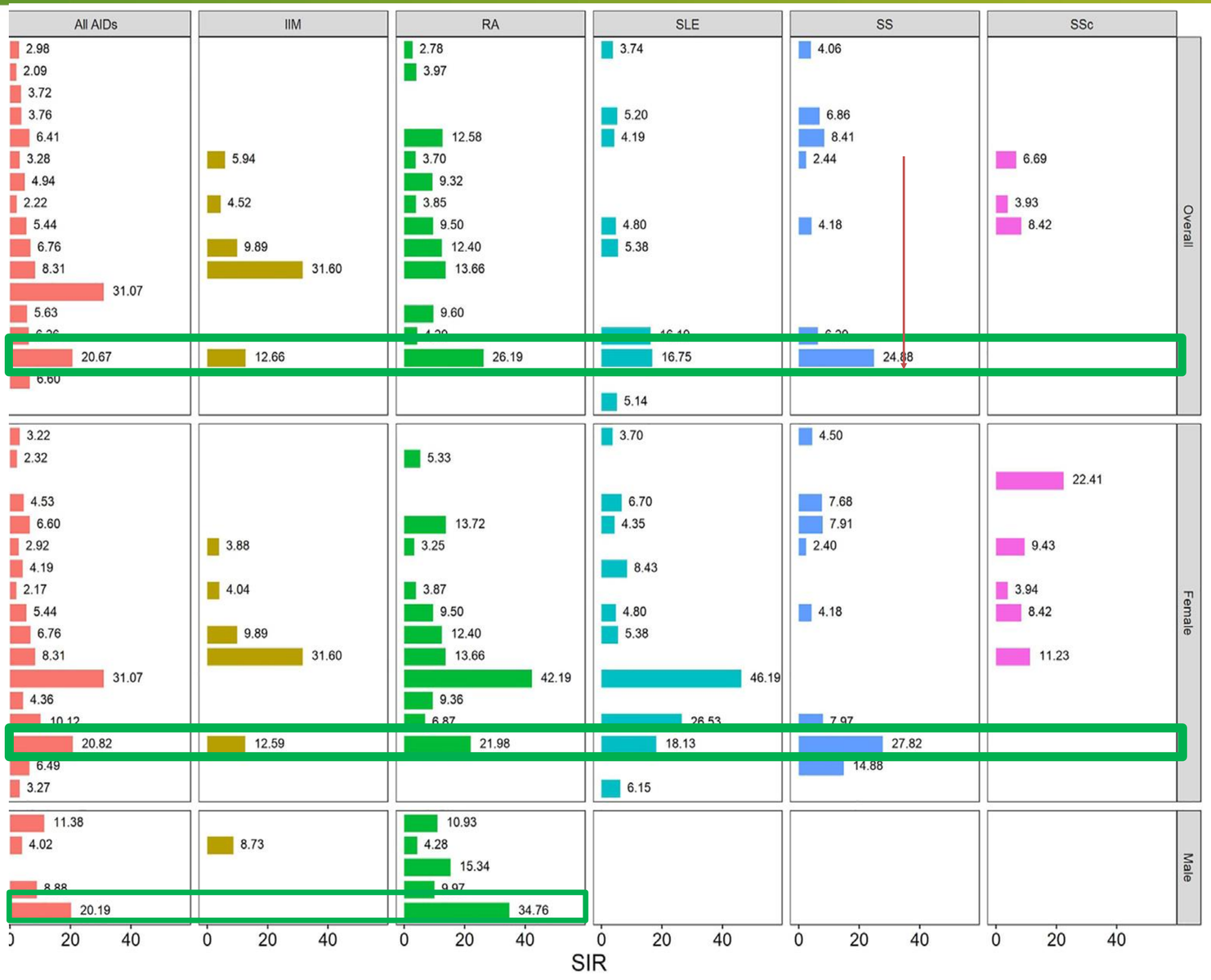
Autoimmune disease	All lymphoma	All NHL[b]	B-cell origin[b]	T/NK-cell origin[b]	HL	Others
All autoimmune disease	**1.45 (1.26–1.67)**	**1.32 (1.10–1.58)**	1.21 (0.995–1.47)	**2.02 (1.33–3.08)**	**2.55 (1.58–4.04)**	**1.50 (1.16–1.93)**
B-cell response	**1.42 (1.15–1.75)**	1.25 (0.95–1.65)	1.24 (0.92–1.68)	1.30 (0.65–2.61)	2.16 (0.99–4.16)	**1.61 (1.12–2.31)**
Hashimoto's thyroiditis	1.09 (0.71–1.68)	1.00 (0.58–1.75)	1.17 (0.67–2.04)	-[c]	1.72 (0.28–5.58)	1.15 (0.54–2.45)
Rheumatoid arthritis	1.34 (0.99–1.81)	1.16 (0.78–1.73)	1.11 (0.72–1.73)	1.44 (0.58–3.56)	1.45 (0.35–3.94)	**1.69 (1.03–2.78)**
Sjogren syndrome	1.38 (0.75–2.51)	0.78 (0.29–2.08)	0.92 (0.34–2.48)	–	3.97 (0.65–12.74)	2.10 (0.86–5.11)
Systemic lupus erythematosus	**3.99 (2.50–6.37)**	**4.17 (2.38–7.31)**	**3.36 (1.72–6.57)**	**8.48 (3.09–23.29)**	**6.64 (1.08–21.40)**	**2.72 (1.002–7.36)**
T-cell response	**1.42 (1.19–1.69)**	**1.32 (1.06–1.65)**	1.16 (0.90–1.49)	**2.30 (1.43–3.72)**	**2.23 (1.23–3.81)**	**1.44 (1.05–1.96)**
Ulcerative colitis	0.89 (0.49–1.63)	0.91 (0.43–1.92)	0.76 (0.31–1.83)	1.78 (0.44–7.23)	–	1.07 (0.40–2.89)
Crohn's disease	1.53 (0.79–2.97)	1.34 (0.55–3.25)	0.94 (0.30–2.95)	3.56 (0.87–14.49)	2.35 (0.13–10.64)	1.70 (0.54–5.35)
Multiple sclerosis	**4.52 (1.82–11.24)**	2.75 (0.67–11.24)	3.23 (0.79–13.24)	–	–	**9.02 (2.80–29.05)**
Psoriasis	**1.61 (1.27–2.05)**	**1.51 (1.11–2.05)**	1.24 (0.86–1.78)	**3.06 (1.70–5.50)**	**2.87 (1.33–5.46)**	1.51 (0.97–2.37)
Sarcoidosis	**26.37 (11.45–55.12)**	**14.82 (5.15–42.62)**	3.77 (0.51–27.86)	**84.59 (20.07–240.47)**	**33.17 (1.83–162.96)**	**32.13 (10.95–94.31)**
Type I diabetes	0.98 (0.74–1.30)	0.94 (0.65–1.36)	1.01 (0.69–1.49)	0.58 (0.18–1.84)	1.53 (0.53–3.52)	0.95 (0.57–1.58)
Others	1.03 (0.74–1.43)	1.07 (0.71–1.60)	1.06 (0.68–1.64)	1.14 (0.42–3.11)	1.73 (0.53–4.21)	0.81 (0.41–1.57)
Ankylosing spondylitis	1.13 (0.70–1.81)	1.10 (0.60–2.00)	0.94 (0.47–1.91)	1.93 (0.61–6.16)	1.96 (0.32–6.35)	1.02 (0.42–2.49)
Behcet's disease	2.30 (0.94–5.61)	1.39 (0.34–5.60)	1.64 (0.41–6.65)	–	7.04 (0.40–32.32)	3.20 (0.79–13.03)
Graves' disease	0.80 (0.48–1.33)	1.00 (0.56–1.78)	1.08 (0.59–1.96)	0.58 (0.08–4.14)	0.84 (0.05–3.82)	0.35 (0.09–1.43)

- Studio **coreano da registro** nazionale fino al 2015
- 13% pazienti con malattie autoimmuni, di queste 322 (0.2%) aveva anche il linfoma.
- Di quelli con il linfoma 155 avevano avuto il linfoma dopo la diagnosi di malattie autoimmuni.
- Le malattie autoimmuni più associate al linfoma sono sarcoidosi, sclerosi multipla e psoriasi tra le autoimmuni t-mediate, LES tra quelle b-mediate.
- Nessuna differenza di OS in chi ha il linfoma con o senza malattie autoimmuni

Kim et al. Autoimmune Journal 2021

Epidemiologia: Associazione AID e LNH

- Studio Cinese su 10,317 pz
- Database retrospettivo, dal ‘06 al 15
- 5 Malattie Autoimmuni in un singolo centro di riferimento
- Incidenza LNH al secondo posto assoluto, confermata associazione con AR, LES e SS
- Primo studio a segnalare associazione con miopatia infiammatoria idiopatica



Zhou et al Cancer Communications. 2022;42:435–446.

Genetica

Associazione SNPs AID e LNH

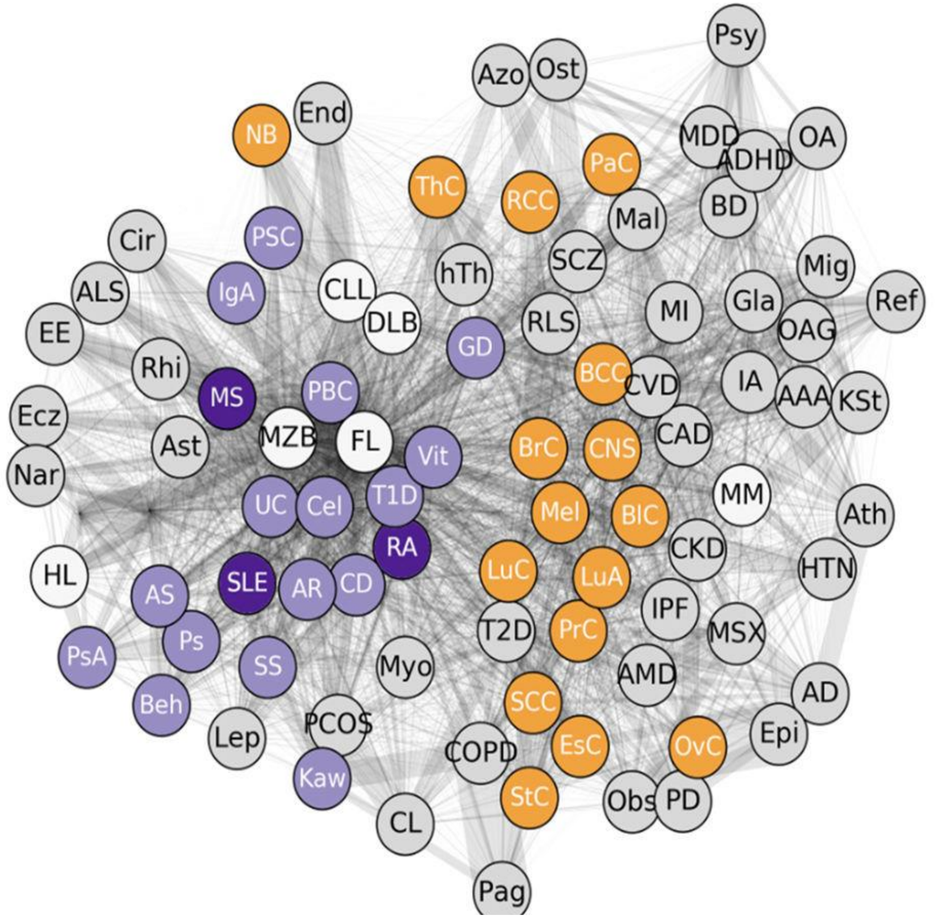
- Largo studio epidemiologico sulla popolazione dell'Interlymph Consortium - 12,982 NHL casi e 16,441 controlli
- Tesi: impatto di SNPs e citochine B sullo sviluppo di linfomi
- Sviluppo: Studiano polimorfismi SNPs su 3 geni principali TNF, IL10 e HLA
- Conclusione: Possibile interazione tra SNPs rs1800629 (TNF G308A – gene coinvolto nelle risposte immunitarie B) in DLBCL e MZL e patologie autoimmuni.
- Ipotesi: sinergia genetica e stato infiammatorio cronico in chi porta il TNF G308A con iperespressione TNF alfa

Wang S. et al. AmJEpidemiol. 2015;181(6):406–421

Genetica

Associazione SNPs AID e LNH

The collective findings further suggest that monitoring and managing inflammation or other factors associated with the disease course as the way to reducing the risk of malignant B-cell lymphoma in patients with AD.



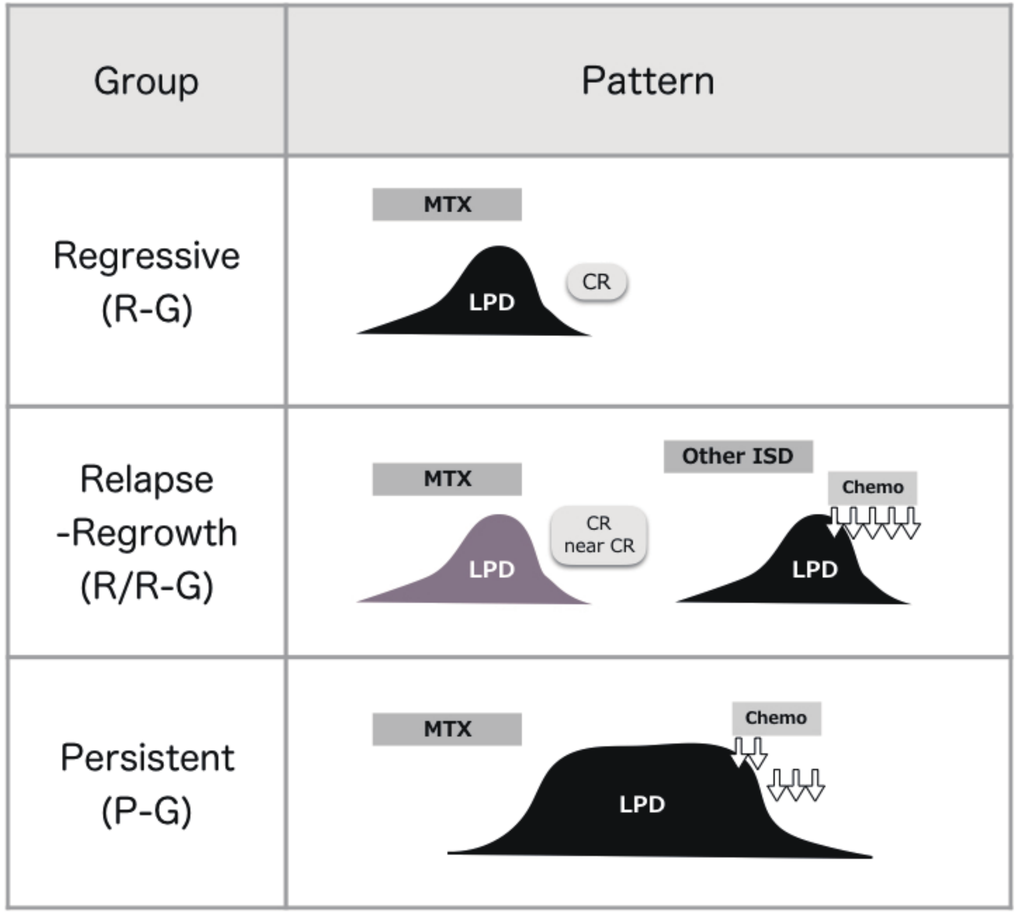
Din et al. Genet Epidemiol . 2019 October

Clinica OIIA - LPDs (MTX-LPDs in Artrite Reumatoide)

Other iatrogenic immunodeficiency-associated lymphoproliferative disorders

MTX-LPD	N	Female (%)	Age* (y)	Basal disease* (y)	MTX dura-tion* (y)	CS 3 or 4	EBV+ (%)	Clinical course (%)				Survival rate (%)				
								R-G	R/R-G	P-G	Ch-G	All	R-G	R/R-G	P-G	Ch-G
EBV+DLBCL	66	71	68	13.5	6.1	62	100	62	3	17	17	91	95	100	72	90
DLBCL-NOS	50	59	66	11.1	5.4	60	0	26	6	36	26	60	100	67	72	53
CHL	51	74	62	13	5.6	75	76	14	40	24	21	78	100	65	67	100
P-LPD	17	64	65	11	7.2	64	100	76	18	0	6	82	92	33	-	0
EBVMUCU	32	84	70	9.4	6.3	-**	100	81	3	13	3	97	100	100	75	100
NS-LPD	9	56	65	16	8.9	33	57	89	11	0	0	89	100	0	-	-
Total	225	70	66	12.5	6.1	54.7	70.6	48	13.5	20.3	16.4	81.3	97.2	67.7	67.2	81

- Review su 274 casi di Linfomi in pazienti trattati con MTX (pubblicati e confermati dalla 4° edizione della WHO)
- Rischio di linfoma in Artrite Reumatoide è tra 3 e 5 di OR
- Controversie sulla definizione di farmaci che causano il linfoma.
- **Genetic and phenotipic differences MTX-DLBCL and DLBCL De novo**



Tokuhira et al. Journal of clinical and experimental hematopathology Vol. 59 No.2, 72-92, 2019
Mamose, 2019. Carreras et al 2018

Clinica: la prospettiva ematologica

- Retrospettivo su 81 OIIA-LPDs in diverse AID (AR 72 su 81, poi artrite psoriasica, dermatomiosite, rettocolite ulcerosa)
- MTX, poi steroidi, biologici, tacrolimus.
- Quasi tutti revisione centralizzata (76 su 81) ed eseguite analisi ulteriori con EBER e COO.
- Lo scopo: fattori prognostici per la risposta alla sola IS e un confronto interno con chi fa la chemioterapia subito insieme alla IS

LPD type	Case (*n*)	EBER positive—*n* (%)
All	67	29 (43)
DLBCL	45	17 (38)
GCB type	12	1 (8)
Non-GCB type	25	12 (48)
Unknown	8	4 (50)
CHL	6	5 (83)
MC	4	4 (100)
LR	1	0
LD	1	1 (100)
Polymorphic LPD	10	6 (60)
Others	6	1 (17)

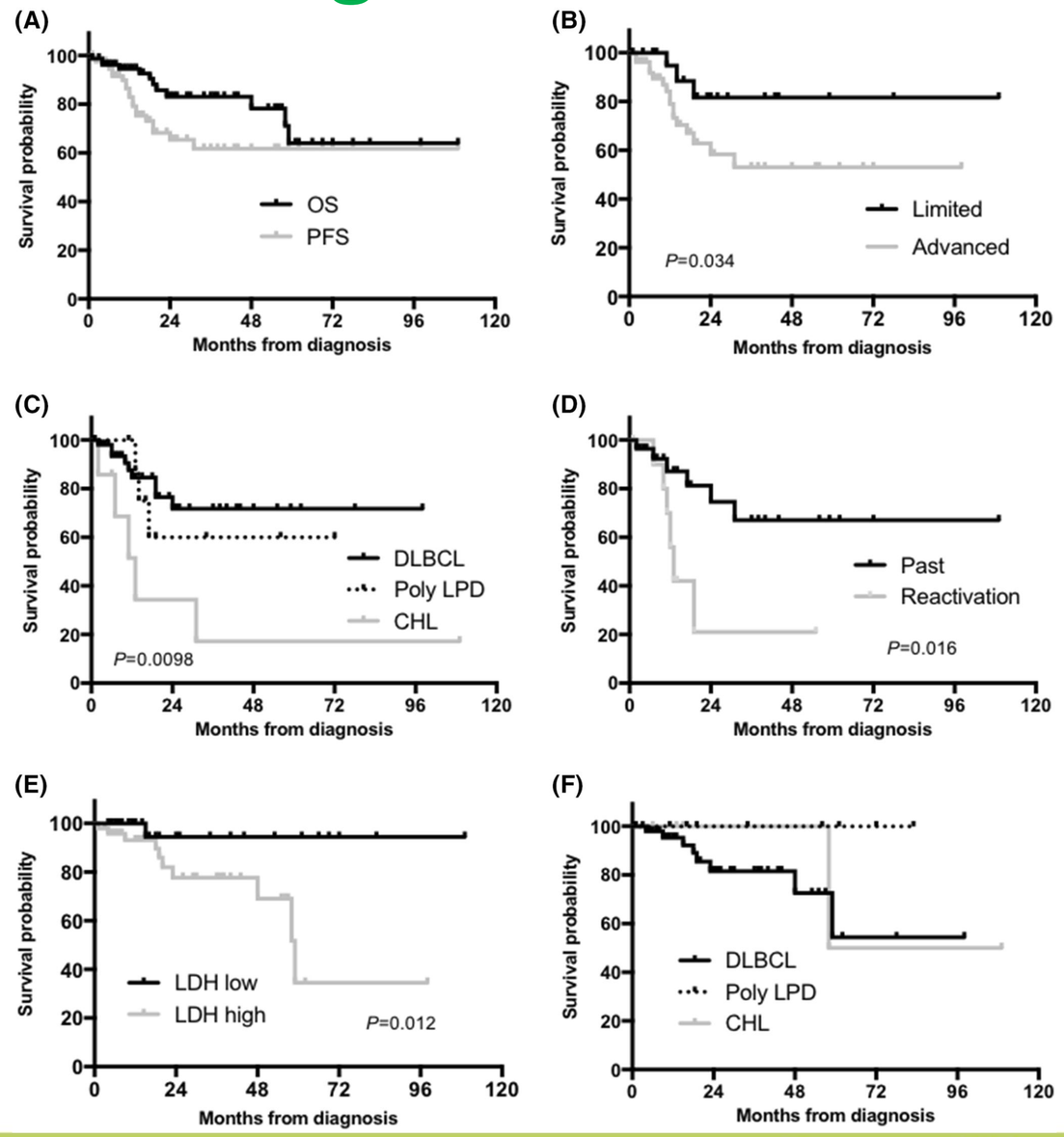
	n (%)				
		IS withdrawal ($n = 59$)			
Finding	All ($n = 81$)	RD ($n = 41$)	PD ($n = 18$)	CRT ($n = 22$)	*p* value
Median age—years (range)	69 (35–87)	67 (41–67)	65 (35–84)	67 (53–80)	NS
Female	55 (68)	32 (78)	8 (44)	15 (68)	0.011
Median AID duration—years (range)	13 (0–42)	15 (0–40)	11 (1–32)	17 (6–42)	NS
AID treatment					
MTX	78 (96)	40 (98)	18 (100)	22 (100)	NS
Median MTX duration—months (range)	60 (11–336)	85 (11–255)	56 (12–168)	88 (11–336)	NS
Steroids	35 (43)	17 (41)	9 (50)	9 (41)	NS
Biologics	21 (26)	11 (27)	4 (22)	6 (27)	NS
Tacrolimus	7 (9)	3 (7)	3 (17)	1 (5)	NS
DMARDs	15 (19)	7 (17)	3 (17)	5 (23)	NS
LPD histology ($n = 76$)	76	37	18	21	-
DLBCL	50 (66)	25 (68)	12 (67)	13 (62)	NS
Polymorphic LPD	10 (13)	8 (22)	1 (6)	1 (5)	NS
CHL	7 (9)	2 (5)	2 (11)	3 (14)	NS
MCL	2 (3)	-	1 (6)	1 (5)	-
LPL	2 (3)	1 (3)	1 (6)	-	-
FL	1 (1)	-	1 (6)	-	-
PTCL	2 (3)	1 (3)	-	1 (5)	-
EATL	1 (1)	-	-	1 (5)	-
ALCL	1 (1)	-	-	1 (5)	-
EBER positive ($n = 67$)	29 (43)	19 (58)	4 (22)	6 (46)	0.0153
Clinical stage					
I	16 (20)	9	3	4	-
II	10 (13)	3	3	4	-
III	18 (23)	11	4	3	-
IV	36 (45)	17	8	11	-
Unknown	1 (1)	1	-	-	
Extranodal disease	53 (66)	24	12	17	NS
Only extranodal disease	27 (34)	12	5	10	NS
Elevated LDH	49 (61)	24	12	13	NS
Performance status > 1	24 (30)	8	6	10	NS
Median lymphocyte count/mm^3 (range)	1058 (107–12,261)	1008 (107–12,261)	1146 (140–5300)	1005 (123–11,245)	NS
Median sIL-2R—U/ml (range)	1087 (247–14,300)	884 (247–9180)	2257 (264–14,300)	1154 (350–14,300)	NS
Reactivation of EBV Ab ($n = 39$)	11 (28)	7 (32)	2 (20)	2 (29)	NS
Detectable EBV-DNA ($n = 24$)	18 (75)	11 (65)	5 (100)	2 (100)	NS

Fujimoto et al. Hematological Oncology. 2020

Clinica: la prospettiva ematologica

Outcome

- Pazienti EBER pos rispondono meglio alla riduzione IS (confermato alla multivariata). Ipotesi: AR la risposta t all'infezione EBV è ridotta, la riduzione della IS ristabilisce la risposta immunologica
- I pazienti con concomitante riattivazione vanno peggio: probabilmente perché avendo un livello più alto non riesce la sola riduzione di IS a vincere la spinta proliferativa dell'EBV
- CHL OIIA outcome sfavorevole. Hodgkin e Reed-Sternberg cells esprimono latent membrane protein (LMP-1 – latenza tipo II) senza EBNA-2 (latenza tipo III – più frequente in HIV e PTLD)



Fujimoto et al. Hematological Oncology. 2020

Clinica: la prospettiva ematologica

- Retrospettivo
- Istologie molto diverse, 55 DLBCL o HD, 12 di istologie restanti
- 67 casi su 3 ospedali in 9 anni.
- 20 con tessuto disponibile → analisi molecolare
- Revisionati

Table II. Clinical features of other iatrogenic immunodeficiency-associated lymphoproliferative disorders (OIIA-LPDs).

Clinical characteristics	All patients (n = 67)	DLBCL-type (n = 36)	HL-type (n = 19)
Age, years, median (range)	69 (30–85)	71 (30–85)	67 (52–79)
Sex (male/female), n	16/51	5/31	6/13
ECOG PS score 0–1/2–4, n	50/15	24/12	16/2
Stage I/II/III/IV, n	15/15/11/26	11/9/3/13	3/2/6/8
Underlying disease, n/N (%)			
Rheumatoid arthritis	62/67 (93)	33/36 (92)	18/19 (95)
SLE	3/67 (4)	1/36 (3)	2/19 (11)
Myasthenia gravis	1/67 (1)	0/36 (0)	0/19 (0)
Polymyalgia rheumatica	1/67 (1)	0/36 (0)	1/19 (5)
Polymyositis	1/67 (1)	1/36 (3)	0/19 (0)
Ulcerative colitis	1/67 (1)	1/36 (3)	0/19 (0)
Immunosuppressant, n/N (%)			
MTX	60/67 (90)	32/36 (89)	17/19 (89)
MTX and biological agents	19/67 (28)	10/36 (28)	6/19 (32)
Biological agents without MTX	2/67 (3)	1/36 (3)	1/19 (5)
B symptoms, n/N (%)	19/65 (29)	6/36 (17)	9/18 (50)
IPI score 3–5, n/N (%)	29/63 (46)	17/36 (47)	9/18 (50)
Hb level ≤100 g/l, n/N (%)	12/65 (18)	5/36 (14)	5/19 (26)
Elevated serum LDH level, n/N (%)	37/65 (57)	21/36 (58)	13/19 (68)
Serum CRP level >5·0 mg/dl, n/N (%)	15/65 (23)	8/36 (22)	6/19 (32)
Serum albumin level ≤3 g/dl, n/N (%)	14/65 (22)	8/36 (22)	4/19 (21)
Lymphocyte count ≤800/μl, n/N (%)	19/64 (30)	10/35 (29)	5/18 (28)
Duration of MTX administration, years, median (range)	7·4 (0·2–24·0) (n = 45)	8·4 (0·5–22·3) (n = 21)	8·2 (0·2–24·0) (n = 14)
Extranodal disease, n/N (%)	32/63 (51)	20/36 (56)	6/18 (33)
EBER positive, n/N (%)	39/65 (60)	15/36 (42)	15/18 (83)
Died, n/N (%)	8/67 (12)	4/36 (11)	4/19 (21)

Kaji et al. British Journal of Haematology, 2021, 195, 585–594

Clinica: la prospettiva ematologica

Outcome

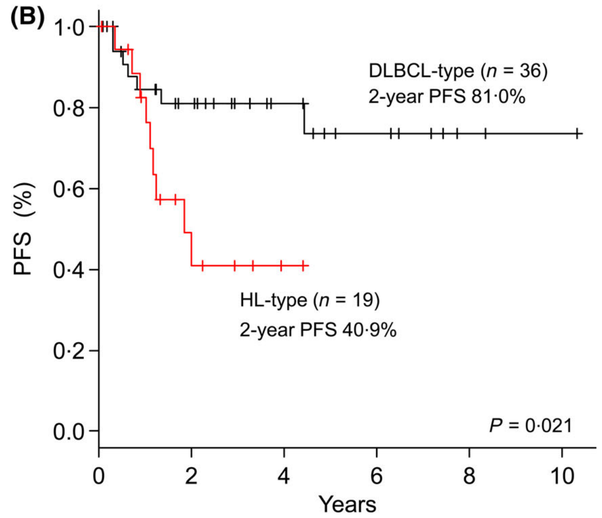
- Regressione più frequente nei DLBCL EBV pos rispetto agli EBV neg (67 Vs 33%).
- FFT dei DLBCL EBV pos migliore di quella dei DLBCL EBV neg
- PFS migliore dei DLBCL rispetto HL

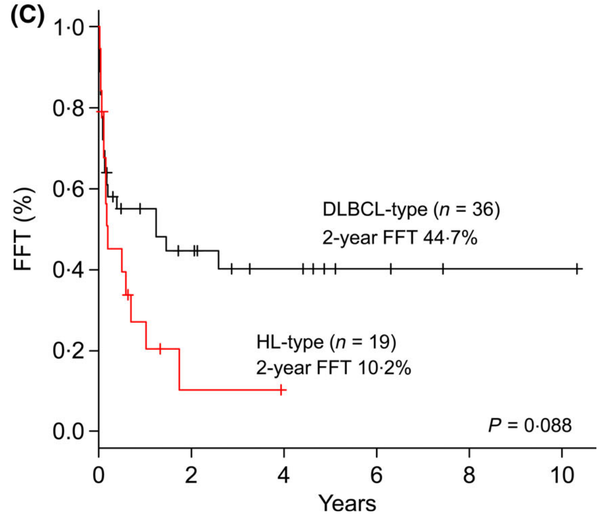
Table IV. Initial chemotherapy for other iatrogenic immunodeficiency-associated lymphoproliferative disorders (OIIA-LPDs).

	DLBCL-type	HL-type	*P*
Patients receiving initial chemotherapy, % (*n*/*N*)	58 (21/36)	75 (15/19)	0·149
ORR, % (*n*/*N*)	90 (18/20)	63 (9/15)	0·052
CR, % (*n*/*N*)	65 (13/20)	53 (8/15)	0·511
The content of initial chemotherapy	RCHOP (*n* = 17) Rituximab (*n* = 3) RTHPCOP (*n* = 1)	RCHOP (*n* = 2) CHOP (*n* = 3) CVP (*n* = 2) ABVD (*n* = 5) Rituximab (*n* = 3)	

Table III. Clinical outcome following withdrawal of MTX or tacrolimus in the onset of other iatrogenic immunodeficiency-associated lymphoproliferative disorders (OIIA-LPDs).

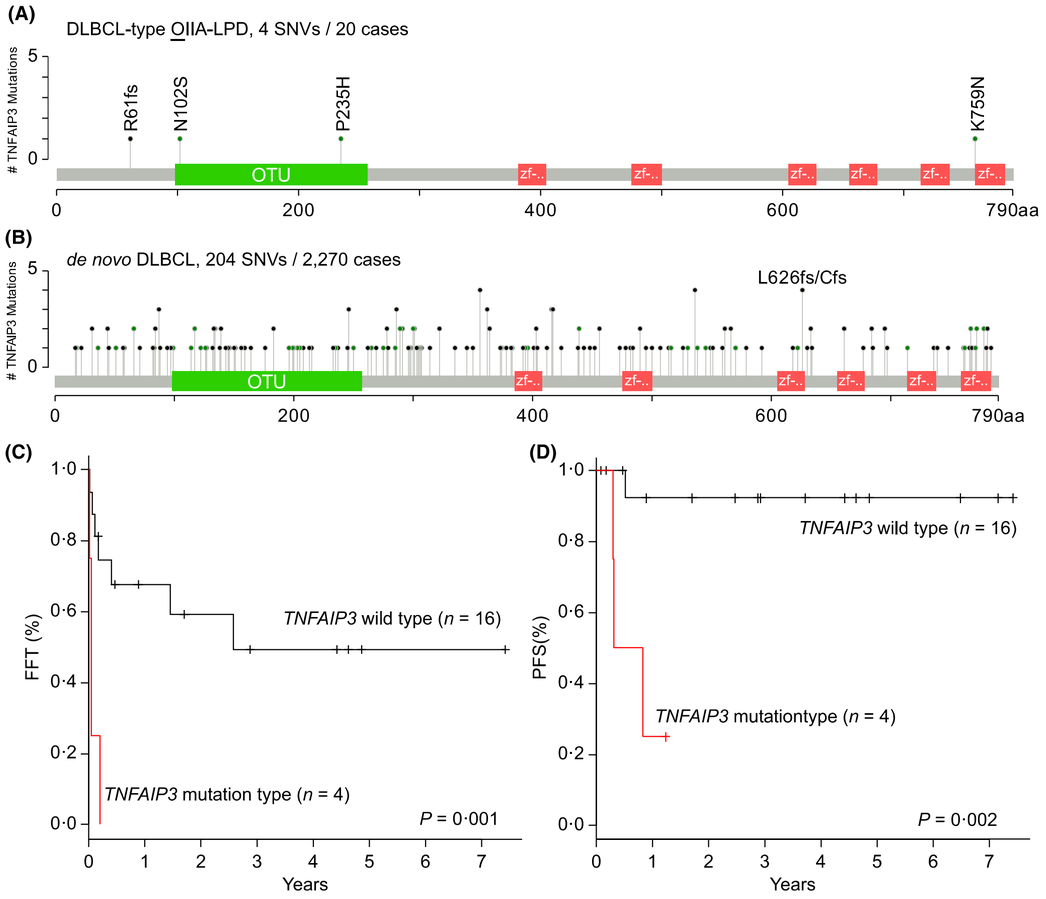
MTX or tacrolimus use in the onset	All patients (*n* = 59)	DLBCL-type (*n* = 32)	HL-type (*n* = 15)
Only MTX use in the onset, *n* (%)	50 (85)	27 (84)	13 (87)
Only tacrolimus use in the onset, *n* (%)	4 (7)	2 (6)	1 (7)
MTX and tacrolimus use in the onset, *n* (%)	5 (8)	3 (9)	1 (7)
MTX or tacrolimus cessation, *n*	58	32	15
Regression and no relapse, *n* (%)	22 (38)	15 (47)	3 (20)
Relapse after regression, *n* (%)	12 (21)	4 (13)	5 (33)
Persistent, *n* (%)	12 (21)	5 (16)	4 (27)
Initiation of immediate chemotherapy, *n* (%)	11 (19)	8 (25)	2 (13)
Lost follow-up, *n* (%)	1 (1)	0	1 (7)
MTX continuation, *n*	1	0	0

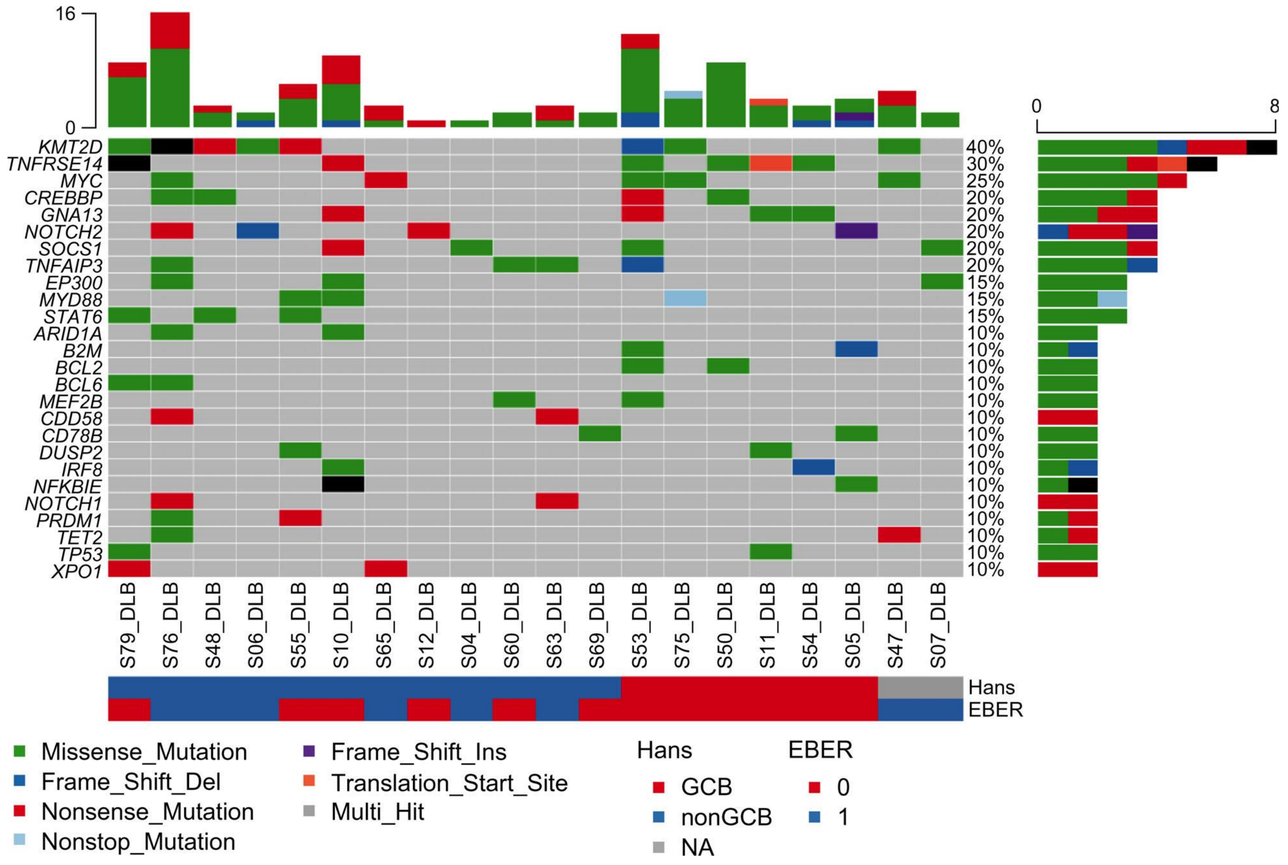




Kaji et al. British Journal of Haematology, 2021, 195, 585–594

Mutazione TNFAIP3





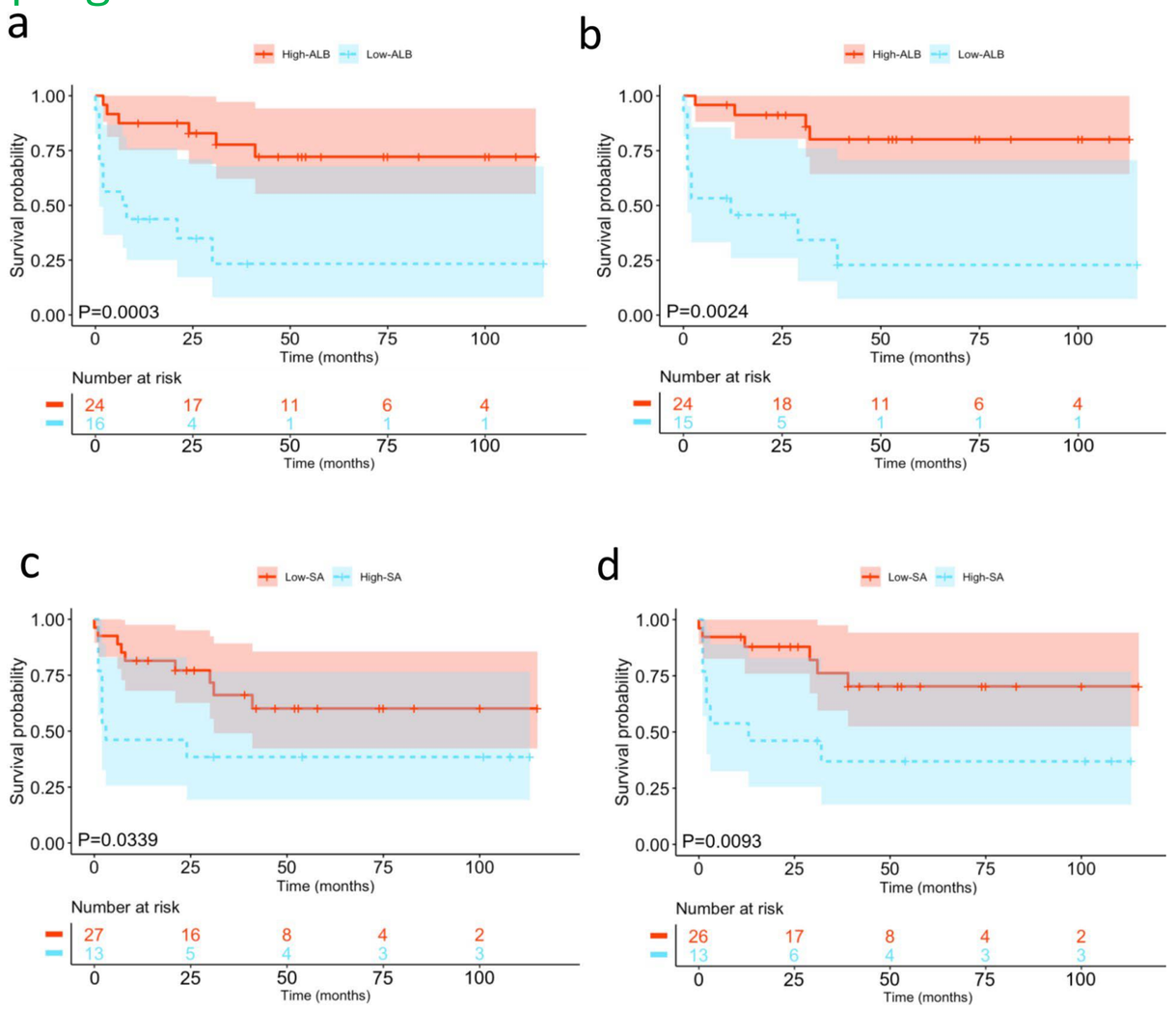
Mutazione TNFAIP3 associata a prognosi sfavorevole
Divisi per classificazione molecolare (MCD, BN2, N1 e EZB)

Kaji et al. British Journal of Haematology, 2021, 195, 585–594

Clinica: la prospettiva ematologica

Fattori prognostici

- Retrospettivo, su 12 aa in una provincia cinese: 55 pts con linfoma e AID
- Linfoma con revisione istologica e storia di malattia autoimmune
- Esclusi disturbi autoimmuni associati a linfoma e malattie autoimmuni da meno di 1 aa.
- Studio di associazione AID – Linfoma
- Associazione tra livelli di albumina e acido sialico e outcome LNH



Zhan et al. BMC Cancer (2025) 25:351

Farmaci

IDD LPDs secondari a diversi farmaci in AR

Table 1 Baseline characteristics and crude incidence rate of lymphomas among biologic-naïve, TNFi, rituximab, tocilizumab or abatacept-treated patients with RA

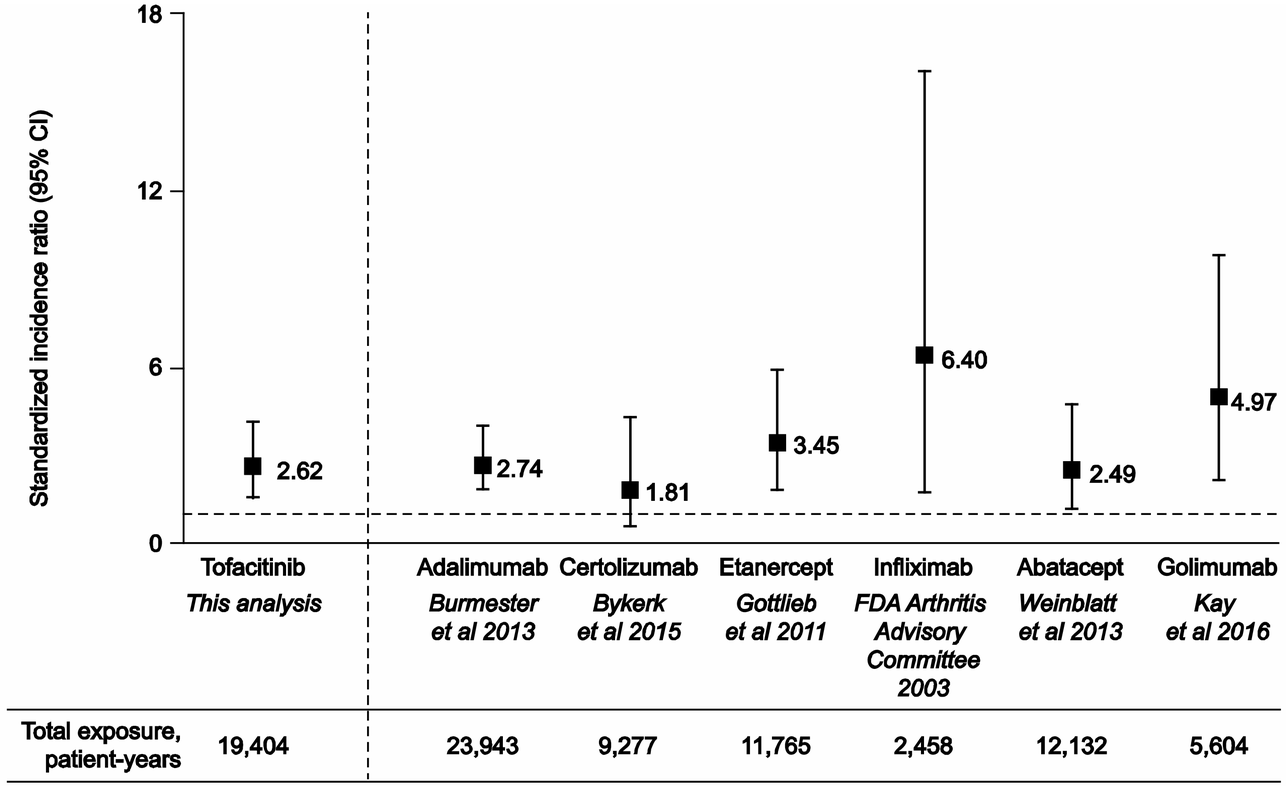
	Bionaïve	TNFi	Rituximab	Tocilizumab	Abatacept	Total
No. of patients	71 088	47 864*	9094	2029	1708*	124 997*
Follow-up time (pyrs)	322 167	242 260*	29 810	2827	3352*	584 236*
Female (%)	72.1	74.8	79.0	80.1	78.0	73.7
Age mean (mean range)	61.1 (57–62)	55.0 (50–57)	57.9 (58–58)	55.9 (55–57)	57.5 (56–58)	58.5 (50–62)
No. of lymphomas	288	230	6	6	3	533
Incidence per 100 000 pyrs (95% CI)	89 (79–100)	81 (70–94)	20 (7–44)	177 (57–413)	60 (7–216)	85 (77–92)

- Studio su 12 registri europei, 12.000 pazienti con Artrite Reumatoide, 533 pazienti con Linfoma.
- Valutano l'incidenza di linfomi nei pazienti con artrite reumatoide esposti a vari farmaci biologici
- Non ci sono differenza statisticamente rilevanti
- Non c'è stata alcuna revisione centralizzata.
- AR > farmaci anti-TNF?

Mercer et al. Ann Reum 2017

Farmaci

- Tofacitinib: Inibitore di JAK 2 utilizzato per AR
- Rischio aumentato di 2.62 volte di linfoma
- 19 linfomi insorti, diversa istologia (MZL, HD, DLBCL, T)
- Caso-controllo: maggiore frequenza di anti-CCP; positivita FR, DASS28, SS



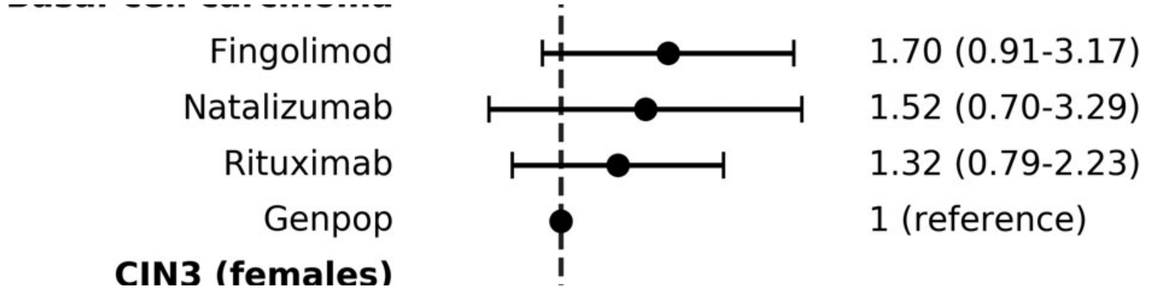
Mariette et al Arthritis Care & Research Vol. 70, No. 5, May 2018, pp 685–694

Farmaci

Sclerosi Multipla: Fungolimod

- Sclerosi Multipla è una malattia infiammatoria demielinizzante del sistema nervoso centrale causata da immunizzazione della proteina mielinica o oligodendrociti
- Terapia: base steroidea iniziale, poi shift a terapia di mantenimento.
- Fungolimod è un antagonista del recettore type 1 sphingosine-1- phosphate. Effetto: riduce la sensibilità di linfociti autoaggressivi alle citochine circolanti, riducendo l'uscita dagli organi linfoidi delle cellule t. Molecola lipofilica.
- Effetti collaterali confermati: PML
- Alcuni casi riportati di Linfomi Primitivi Cerebrali in corso di Fungolimod. Pazienti giovani, con Primitivi Cerebrali Diffusi a Grandi Cellule B. Particolare aspetto istopatologico (CD20 pos, EBV neg, CD3 su diffusi piccoli linfociti T policlonali) su 3 pazienti.

Studio Svedese su 1700 pazienti che hanno ricevuto il farmaco:
Confermato da incremento di dose: più alta la dose maggiore la probabilità di linfoma



Peter Alping. Ann Neurol. 2020 May;87(5):688-699.
Saeed Vaheb Clin Case Rep. 2023;11, Takanashi K. Cureus 15(12)

Primary Sjogren Syndrome (SS)

Studio italiano

- Sindrome di Sjogren è una malattia cronica autoimmune infiammatoria, caratterizzata da ridotta secrezione lacrimale e salivare. Primaria se è solo ghiandolare secondaria se è associata con altri disturbi autoimmuni (overlap).
- Retrospettivo, caso controllo
- 144 pazienti, 27% diagnosi concomitante pSS e LNH
- Nota associazione con Malattie Linfoproliferative indolenti.
- Parotide spesso coinvolta come primo organo dal Linfoma: focus su tumefazione parotidea in pSS
- Fattori di rischio per sviluppare Linfomi da pSS: positività fattore reumatoide, crioglobulinemia, C4 consumato e leucopenia
- Sviluppo di tumefazione parotide è un fattore associato allo sviluppo di Linfoma, sia esordio pSS sia esordio LNH.

Sex F, *n*/*N* (%)	129/144 (89.58)
Age at NHL diagnosis, mean (S.D.), years	55.9 (12.5)
Follow-up from pSS diagnosis to NHL diagnosis, median (range), years	4 (0–30)
NHL histotype, *n*/*N* (%)	
MZL	120/144 (83.33)
MZL MALT	108/144 (75.00)
MZL primary splenic	3/144 (2.08)
MZL primary nodal	9/144 (6.25)
DLBCL	17/144 (11.81)
Follicular	4/144 (2.78)
Lymphoplasmacytic	2/144 (1.39)
Mantle cell	1/144 (0.69)
NHL clinical localization, *n*/*N* (%)	
Isolated nodal NHL	17/144 (11.81)
Isolated extranodal NHL	94/144 (65.27)
Extranodal + nodal NHL	127/144 (88.19)
Parotid glands	83/144 (57.64)
Submandibular glands	5/144 (3.47)
Minor salivary glands	3/144 (2.08)
Salivary glands (whole)	90/144 (62.5)
Lachrymal glands	6/144 (4.17)
Salivary or lachrymal glands	95/144 (65.97)
Stomach	12/144 (8.33)
Lung	10/144 (6.94)
Spleen	5/144 (3.47)
Skin	2/144 (1.39)
Breast	2/144 (1.39)
Ocular adnexa	2/144 (1.39)
Thymus	2/144 (1.39)
Ovary	1/144 (0.69)
Large intestine	1/144 (0.69)
Liver	1/144 (0.69)
Larynx	1/144 (0.69)
Bone marrow NHL positivity	30/144 (20.83)
NHL stage, *n*/*N* (%)	
I	67/142 (47.18)
II	22/142 (15.49)
III	9/142 (6.34)
IV	44/142 (30.99)

Salvatore De Vita et al. Rheumatology, 2023, 62, 1586–1593

Sclerosi Sistemica (SSc)

Studio italiano

- Su 454 SS afferenti alla Reumatologia di Modena, 2 linfomi (DLBCL morto di sepsi e BALT guarito con ch)
- Review: 130 pazienti con SSc che hanno sviluppato patologie ematologiche, Linfomi erano il 66, 55 LNH B (soprattutto DLBCL).
- Spesso le due malattie vicine (di queste il 30% sospetto paraneo?), un 30% però entro 5 aa dalla diagnosi.
- Interessante: spesso overlap, con Sjogren e Artrite Reumatoide
- Suggestione: SSc di breve durata, relative elevata frequenza dei maschi, ANA pos (MCL e FL in letteratura), sesta decade.

Colaci et al. Case Reports in Rheumatology Volume 2017, Article ID 6230138

Sclerosi Sistemica (SSc)

Diagnosi differenziale

POEMS Syndrome

Table II. Symptoms suggestive of lymphoproliferation in systemic sclerosis

Haematological abnormalities		Characteristic features and clinical symptoms
Hypergammaglobulinaemia		Overlapping of systemic sclerosis with another autoimmune disease, particularly Sjögren's syndrome
Presence of monoclonal protein		Older age, short duration of the disease, diffuse cutaneous systemic sclerosis, worse lung function parameters, pulmonary arterial hypertension
Presence of cryoglobulins	Type I	An extremely high risk of lymphoma, severe course of systemic sclerosis, worse prognosis, lower-limb ulcerations, kidney failure, vasculitis
	Type II	Ulcerations, symptoms of vasculitis, severe course of systemic sclerosis, worse prognosis
	Type III	

Table 2: Consensus Diagnostic Criteria for iMCD

Type of Criteria	Description
Major criteria (need both)	Histopathologic lymph node features consistent with iMCD spectrum
	Enlarged lymph nodes (≥1 cm in short-axis diameter) at two or more lymph node stations
Minor criteria (need at least two of 11)	Laboratory criteria
	Elevated CRP level or ESR
	Anemia
	Thrombocytopenia
	Hypoalbuminemia
	Renal dysfunction
	Polyclonal hypergammaglobulinemia
	Clinical criteria
	Constitutional symptoms: night sweats, fever, weight loss, or fatigue
	Large spleen or liver
	Fluid accumulation: edema, anasarca, ascites, or pleural effusion
	Eruptive cherry hemangiomatosis or violaceous papules
	Lymphocytic interstitial pneumonitis
Exclusion criteria (must rule out diseases that can mimic iMCD)	Infection-related disorders (HHV8, clinical EBV-lymphoproliferative disorders such as infectious mononucleosis or chronic active EBV, other uncontrolled infections causing widespread inflammation and adenopathy such as CMV, toxoplasmosis, HIV, active tuberculosis)
	Autoimmune or autoinflammatory diseases (SLE, RA, adult-onset Still disease, JIA, autoimmune lymphoproliferative syndrome)
	Malignant or lymphoproliferative disorders (lymphoma, multiple myeloma, primary lymph node plasmacytoma, FDC sarcoma, POEMS syndrome)

Note.—Adapted and reprinted, with permission, from reference 23. CMV = cytomegalovirus, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, JIA = juvenile idiopathic arthritis, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus.

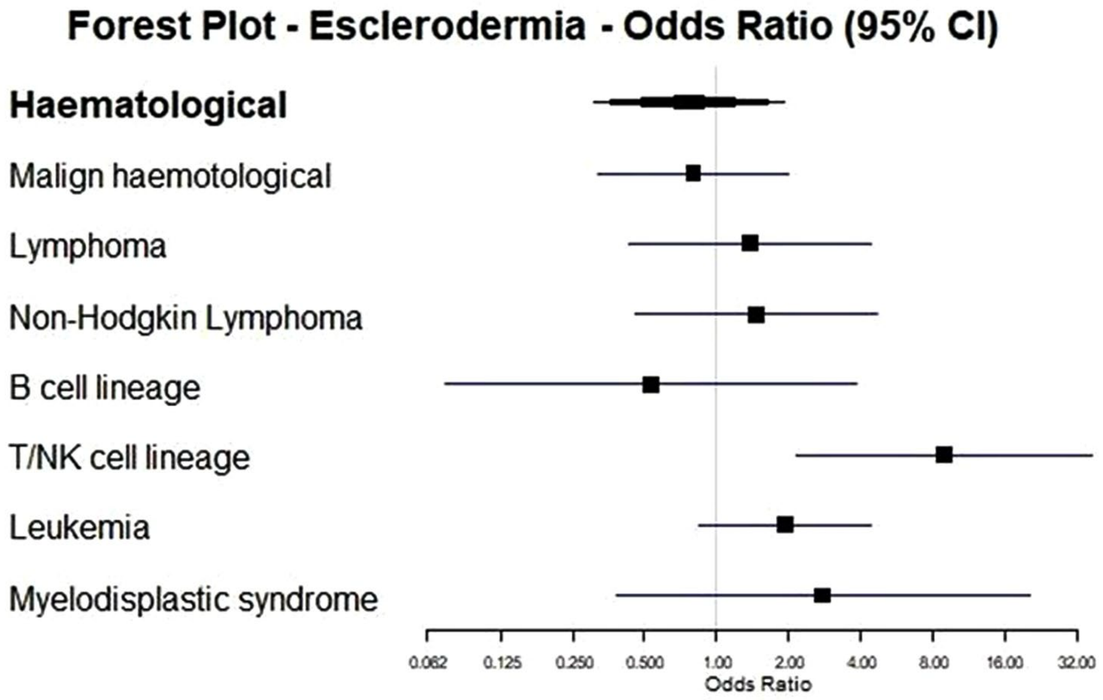
Ewa Wielosz, Maria Majdan Reumatologia 2020; 58, 3: 162–166

Sclerosi Sistemica e Linfomi

Mortalità

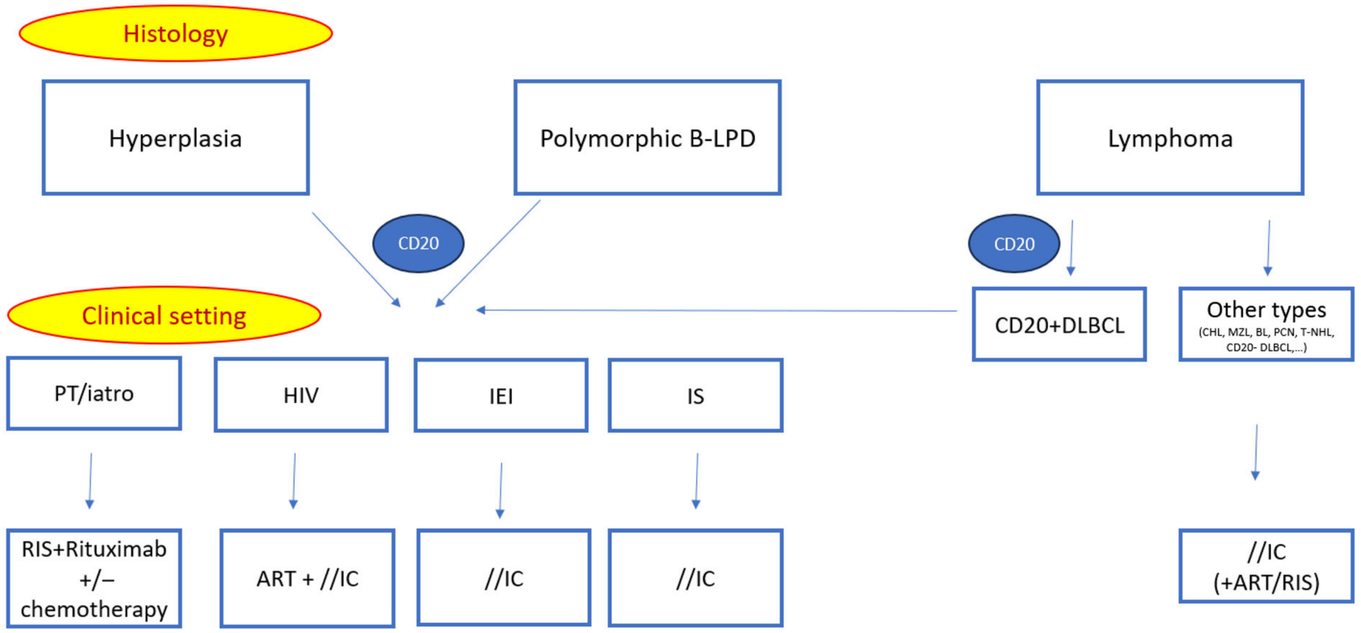
- Studio su mortalità da neoplasia in pazienti con SSc su database spagnolo nazionale (10.000 pazienti) Spagna

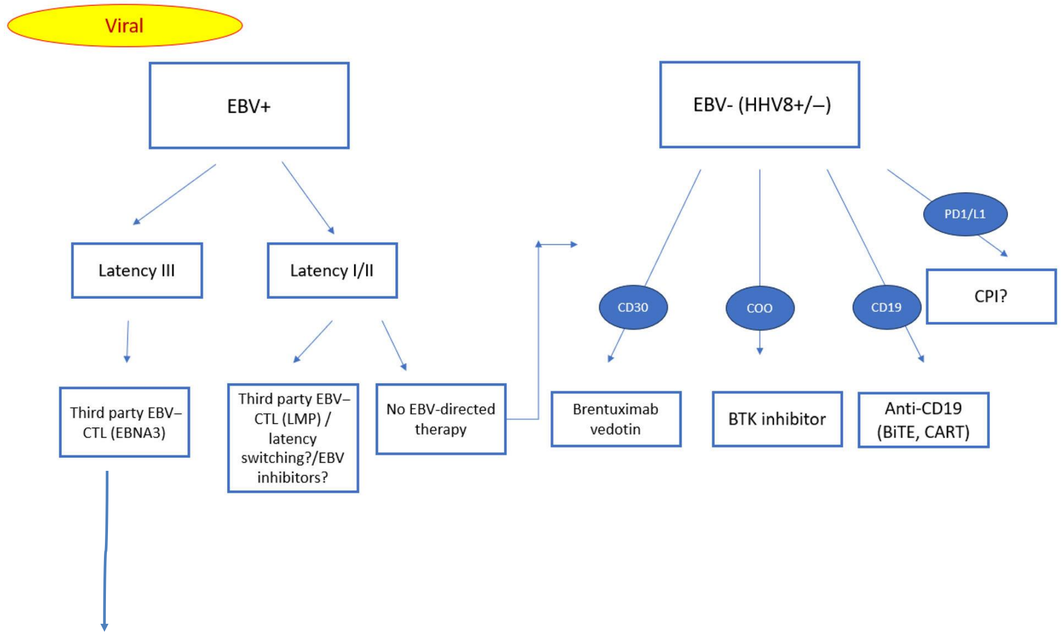
- Incremento mortalità in Linfomi T associati a SSc



Martínez-Urbistondo et al. BMC Rheumatology (2025) 9:27

Terapia





Da donatori ‘’terzi’’ con HLA parzialmente compatibile

Conclusioni

1) Incidenza bassa delle patologie linfoproliferative in AID
2) Difficile discriminazione tra LPD iatrogenici e autoimmuni
3) Studi da registro e metanalisi, assenza di studi prospettici, solo retrospettivi
4) Base patologica affascinante: importanza comune di TNF e del ruolo dell'infiammazione
5) Linfomi EBER pos in AID hanno caratteristiche particolari: ruolo della riduzione IS
6) Pochi studi dalla prospettiva ematologica in Italia, pochi dati su come influenza la terapia la malattia autoimmune o su outcome dei pazienti affetti da IDD LPD


thank you
danke
merci
gracias
obrigado
dziękuję
bedankt
go raibh maith agat
teşekkür ederim
ngiyabonga
謝謝
спасибо
рахмат
Баярлалаа
dank je
tapadh leat
mochchakkeram
sukriya
kop khun krap
terima kasih
arigatô
dakujem
grazie
takk
taiku
sagolun
mauruuru
hvala
dankie
kiitos
faafetai lava
vinaka
blagodaram
misaotra
matondo
paldies
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