Biomarcadores en el Lupus Eritematoso Sistémico

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Hospital de la Santa Creu i Sant Pau
Hospital Dos de Maig
5 Abril 2019

Conflictos de interés:

- Financiación de actividades formativas:

  Abbie, Asacfarma, Amgen, Gebro, Lilly, Novartis, Pfizer.

- Ponencias

  Amgen, Lilly

- Ensayos Clínicos

  Centrexion, Novartis

Biomarcador:

What is a Biomarker?

The term "biomarker", a portmanteau of "biological marker", refers to a broad subcategory of medical signs – that is, objective indications of medical state observed from outside the patient – which can be measured accurately and reproducibly. Medical signs stand in contrast to medical symptoms, which are limited to those indications of health or illness perceived by patients themselves. There are several more precise definitions of biomarkers in the literature, and they fortunately overlap considerably. In 1998, the National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as "a characteristic

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"A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"

Tipos de Biomarcadores en el LES:

Diagnósticos

- Diagnóstico precoz/preclínico
- Diferenciadores de otras EAS
- Tratamiento precoz

Pronósticos

- Mal pronóstico/ Curso agresivo de la enfermedad
- Predictores de complicaciones
- Riesgo cardio-vascular

Monitorización de actividad inflamatoria

- Evaluación de actividad enfermedad
- Predictores de brotes

Respuesta a tratamiento

- Predictores de respuesta a tratamientos
- Perfiles de pacientes -> perfiles fármacos

Biomarcadores Diagnósticos

Criterios clasificatorios:

	ACR 1997	SLICC 2012	EULAR/ACR
Cohorte derivación	a) Anti-DNA or	1. ANA	
S (IC95%)	b) Anti-Sm or	2. Anti-DNA	98,00 (96.7-99.2)
E (IC95%)	c) Positive finding of antiphospholipid antibodies based on:	3. Anti-Sm	96,40 (94.6-97.9)
Cohorte validación	1. Abnormal IgG/IgM anticardiolipin antibodies	4. Antiphospholipid antibodies	
S (IC95%)	2. Positive Lupus anticoagulant	5. Low complement (C3, C4, CH50)	96,12 (94.7-97.5)
E (IC95%)	3. False positive serologic test for syphilis for 6 months	6. Direct Coombs' test	93,38 (91.2-95.3)
	ANA		

Aringer M et al , ACR 2018 abst 2928
Aringer et al, datos no publicados

*Imagen tomada de la exposición del Dr Rúa-Figueroa en el VI Simposio de EAS de la SER de 2019.

Criterios clasificatorios ACR/EULAR 2018

Clinical domains	Points
Constitutional domain	
Fever	2
Cutaneous domain	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis domain	
Synovitis or tenderness in at least 2 joints	6
Neurologic domain	
Delirium	2
Psychosis	3
Seizure	5
Serositis domain	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic domain	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal domain	
Proteinuria > 0.5 g/24 hr	4
Class II or V lupus nephritis	8
Class III or IV lupus nephritis	10

Immunologic domains	Points
Antiphospholipid antibody domain	
Anticardiolipin IgG > 40 GPL *or* anti-β2GP1 IgG > 40 units *or* lupus anticoagulant	2
Complement proteins domain	
Low C3 *or* low C4	3
Low C3 *and* low C4	4
Highly specific antibodies domain	
Anti-dsDNA antibody	6
Anti-Sm antibody	6

REFERENCE: Aringer et al. Abstract #2928. 2018 ACR/ARHP Annual Meeting

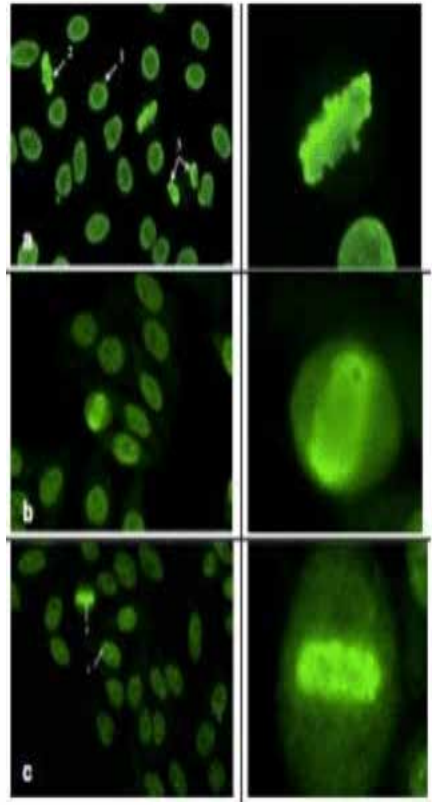
- ✓ **Classification criteria are not diagnosis criteria**
- ✓ All patients classified as having SLE must have ANA ≥ 1:80 (entry criterion)
- ✓ Patients must have ≥ 10 points to be classified as SLE
- ✓ Items can only be counted for classification if there is no more likely cause
- ✓ Only the highest criterion in a given domain counts
- ✓ SLE classification requires points from at least one clinical domain

@Lupusreference

*Imagen tomada de https://t.co/h49IMElo9B (https://twitter.com/Lupusreference/status/1108052022060830720?s=03)

Biomarcadores “Anti-Diagnósticos”

Anticuerpos anti-DFS:



- The Journal of Rheumatology Volume 39, no. 11

Anti-DFS70/LEDGF Antibodies Are More Prevalent in Healthy Individuals Compared to Patients with Systemic Autoimmune Rheumatic Diseases

MICHAEL MAHLER, TODD PARKER, CAROL L. PEEBLES, LUIS E. ANDRADE, ANDREAS SWART, YVETTE CARBONE, DAVID J. FERGUSON, DANILO VILLALTA, NICOLA BIZZARO, JOHN G. HANLY and MARVIN J. FRITZLER

J Rheumatol 2012;39;2104-2110
http://www.jrheum.org/content/39/11/2104

Hindawi Publishing Corporation
Clinical and Developmental Immunology
Volume 2013, Article ID 703759, 8 pages
http://dx.doi.org/10.1155/2013/703759

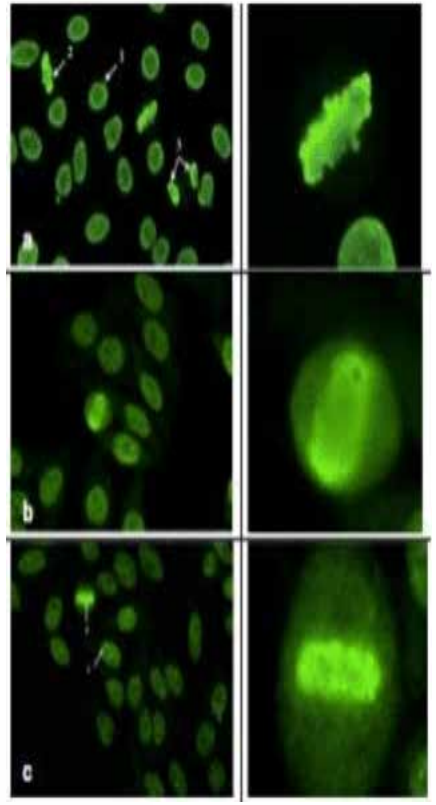
- *Research Article*

Clinical Phenotypes of Patients with Anti-DFS70/LEDGF Antibodies in a Routine ANA Referral Cohort

Makoto Miyara,[1] Roger Albesa,[2] Jean-Luc Charuel,[1] Mohamed El Amri,[1] Marvin J. Fritzler,[3] Pascale Ghillani-Dalbin,[1] Zahir Amoura,[4] Lucile Musset,[1] and Michael Mahler[2]

Biomarcadores “Anti-Diagnósticos”

Anticuerpos anti-DFS:



- ANAS patrón fino denso
- Es más frecuente en población sana: 24-54% frente a LES: 2,7%
- Su prevalencia disminuye a 0,7% en LES y a 11% en sanos si es monoespecífico
- Podría utilizarse como criterio de EXCLUSIÓN si
  - ANA+ sin otras especificidades
  - Cuadro no compatible/ síntomas inespecíficos

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- Respuesta fisiopatológica a fármacos

Respuesta a tratamiento

- Predictores de respuesta a tratamientos
- Perfiles de pacientes -> perfiles fármacos

Biomarcadores de monitorización/Px

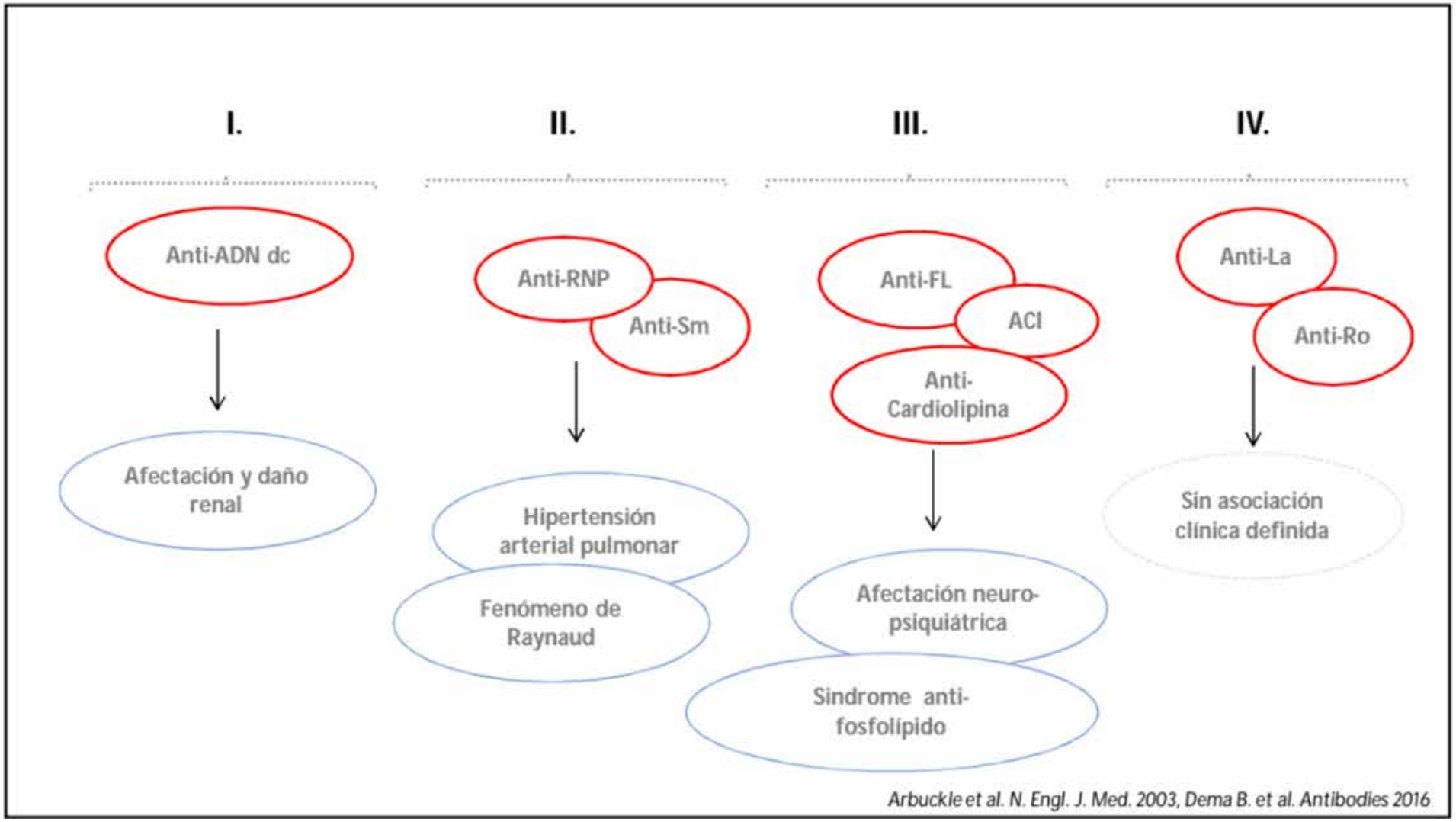


*Imagen tomada de la exposición de la Dra Valor en X Curso de LES y SAF 2018 de la SER

Biomarcadores de monitorización/Px

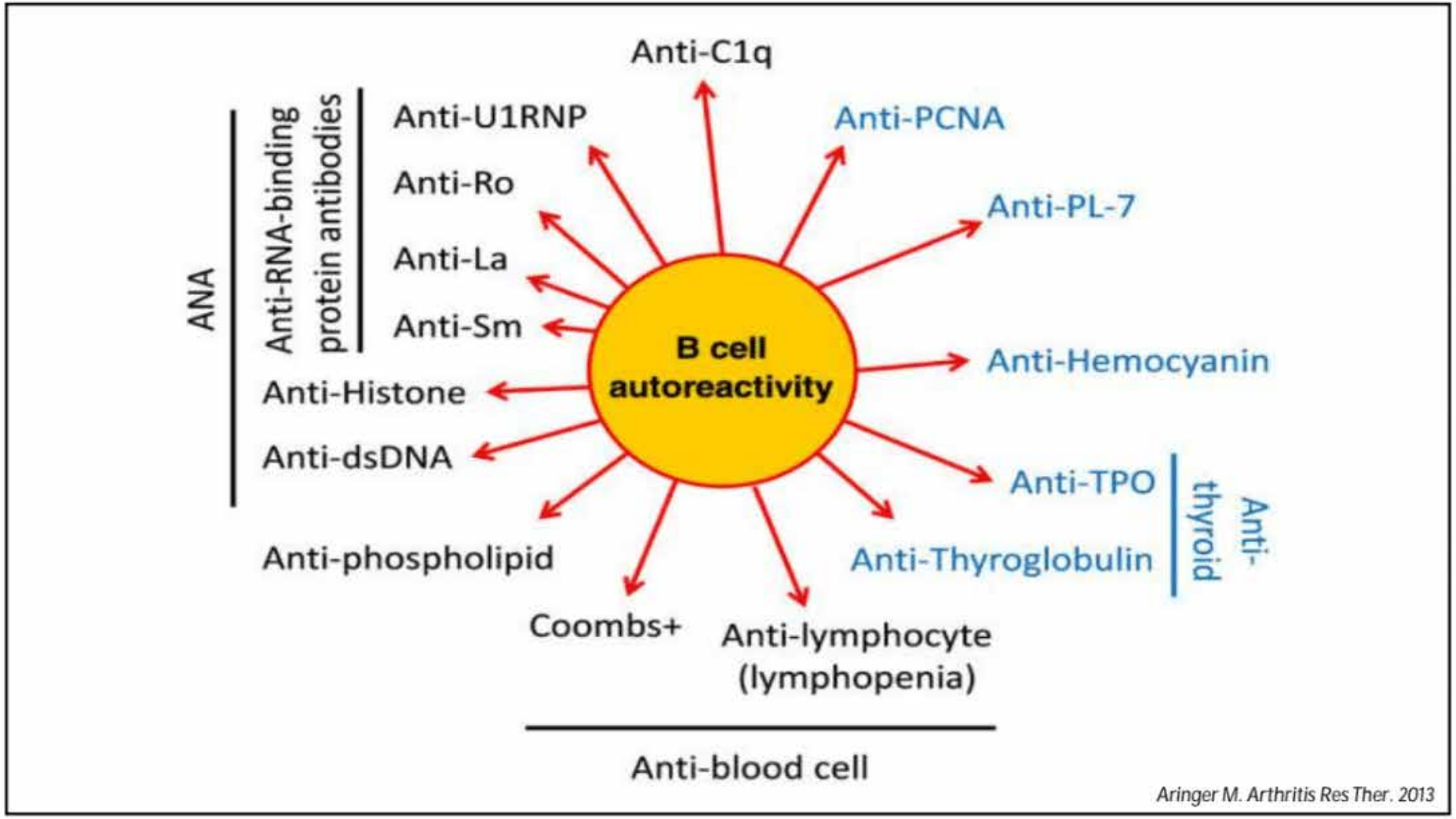


*Imagen tomada de la exposición de la Dra Valor en X Curso de LES y SAF 2018 de la SER

Table 2 Investigated potential biomarkers and their correlations to disease activity

	Concentration*		P value†	Spearman's correlation‡		
	Controls (n=322)	SLE (n=437)	Control vs SLE	SLAM[4] (n=437)	SLEDAI-2K[2] (n=437)	PtGDA§ (n=132)
Cytokines¶						
INF-γ	6.1 (4.6–9.9)	11.7 (7.0–20.2)	<0.001	0.08 (p=0.08)	0.14 (p=0.005)	0.07 (p=0.4)
IL-8	3.0 (2.2–4.0)	4.9 (3.1–8.7)	<0.001	0.16 (p<0.01)	0.16 (p<0.01)	0.23 (p<0.01)
IL-15	2.1 (1.8–2.4)	2.9 (2.3–4.1)	<0.001	**0.28** (p<0.01)	**0.28** (p<0.01)	0.19 (p=0.03)
Eotaxin	88.4 (70.1–113.8)	133.5 (97.6–186.0)	<0.001	0.07 (p=0.14)	0.04 (p=0.4)	0.14 (p=0.1)
MCP-1	69.0 (55.0–85.0)	109.5 (83.0–152.5)	<0.001	0.23 (p<0.01)	0.23 (p<0.01)	**0.28** (p<0.01)
MDC	939.0 (764.3–1109)	844.0 (640.3–1120)	0.002	–0.10 (p=0.04)	–0.17 (p<0.01)	–0.16 (p=0.06)
MIP-1β	43.8 (33.4–56.4)	72.7 (50.8–108.1)	<0.001	0.18 (p<0.01)	0.20 (p<0.01)	0.20 (p=0.02)
IL-10	0.3 (0.2–0.4)	0.8 (0.5–1.5)	<0.001	0.20 (p<0.01)	**0.27** (p<0.01)	0.18 (p=0.04)
IL-6	0.6 (0.5–0.9)	1.2 (0.7–2.2)	<0.001	0.23 (p<0.01)	0.24 (p<0.01)	**0.30** (p<0.01))
TNF-α	2.3 (2.0–2.8)	4.5 (3.1–6.2)	<0.001	**0.34** (p<0.01)	**0.32** (p<0.01)	**0.29** (p<0.01)
IL-12/IL-23p40	131.0 (99.5–179.0)	181.0 (123.0–286.0)	<0.001	0.07 (p=0.12)	0.08 (p=0.11)	–0.05 (p=0.6)
IL-16	182.0 (147.0–225.0)	214.0 (152.0–287.0)	<0.001	0.14 (p<0.01)	0.19 (p<0.01)	0.13 (p=0.2)
IL-1α	6.4 (3.4–11.7)	6.3 (3.2–12.8)	0.6	0.05 (p=0.4)	0.19 (p<0.01)	–0.06 (p=0.5)

Table 2 Investigated potential biomarkers and their correlations to disease activity

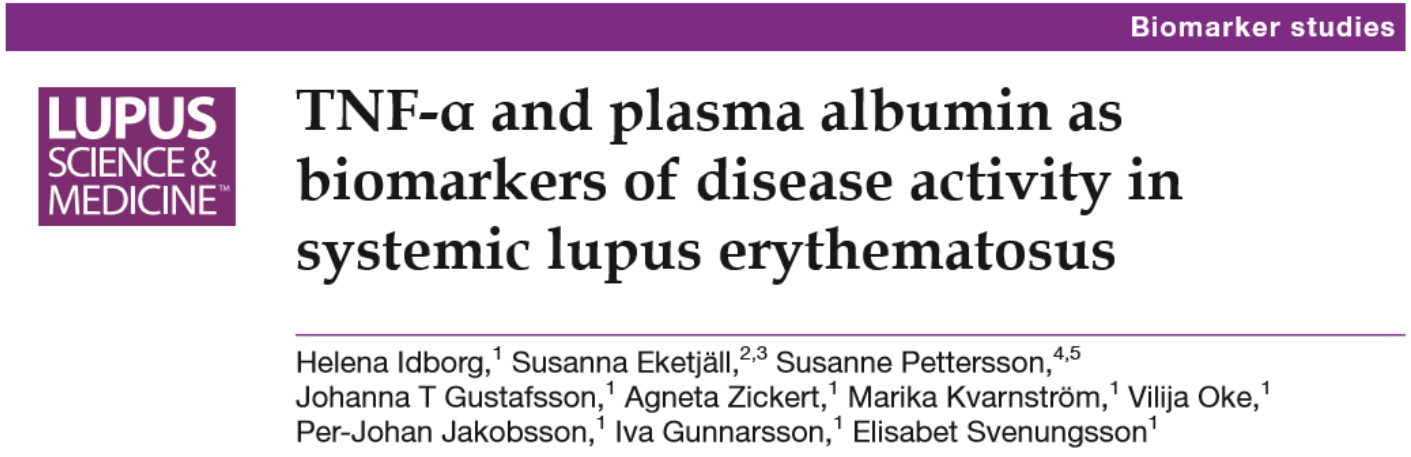
	Concentration*		P value†	Spearman's correlation‡		
	Controls (n=322)	SLE (n=437)	Control vs SLE	SLAM[4] (n=437)	SLEDAI-2K[2] (n=437)	PtGDA§ (n=132)
IL-7	3.7 (2.5–5.5)	5.0 (3.2–8.7)	<0.001	0.11 (p=0.03)	0.16 (p<0.01)	0.10 (p=0.2)
VEGF	56.7 (40.9–81.6)	77.1 (47.7–123.5)	<0.001	0.11 (p=0.03)	0.23 (p<0.01)	0.16 (p=0.07
Eotaxin-3	20.8 (14.9–25.7)	24.4 (19.3–35.1)	0.0008	0.02 (p=0.8)	0.08 (p=0.3)	–0.01 (p=0.9)
IP-10	352.0 (258.8–479.0)	725.0 (446.0–1309)	<0.001	0.19 (p<0.01)	0.23 (p<0.01)	**0.27** (p=0.002)
MCP-4	56.0 (41.0–80.8)	78.0 (53.8–124.0)	<0.001	–0.01 (p=0.8)	–0.03 (p=0.6)	0.04 (p=0.6)
MIP-1α	12.0 (8.8–17.6)	21.5 (17.3–28.6)	<0.0001	**0.27** (p<0.01)	**0.26** (p<0.01)	0.10 (p=0.3)
TARC	54.4 (37.4–84.8)	85.3 (51.9–150.3)	<0.001	0.03 (p=0.5)	0.04 (p=0.4)	0.04 (p=0.6)
Standard clinical laboratory measurements						
ESR	8.5 (5-13)	19 (11-34)	<0.0001	**0.48** *(p<0.01)*	**0.28** (p<0.01)	0.18 (p=0.04)
C4	0.21 (0.17–0.25)	0.15 (0.1–0.2)	<0.0001	–0.12 (p=0.01)	**–0.36** *(p<0.01)*	–0.10 (p=0.3)
C3	1.04 (0.9–1.2)	0.88 (0.7–1.0)	<0.0001	–0.10 (p<0.05)	**–0.31** *(p<0.01)*	–0.02 (p=0.8)
P-albumin	42 (41-44)	39 (36-41)	<0.0001	**–0.31** (p<0.01)	**–0.33** (p<0.01)	**–0.42** (p<0.01)
hsCRP	0.93 (0.4–2.1)	1.7 (0.7–5.3)	<0.0001	0.21 (p<0.01)	0.16 (p<0.01)	**0.25** (p<0.01)
anti-dsDNA	4 (4.0–4.0)	5 (4.0–19.5)	<0.0001	0.21 (p<0.01)	**0.47** *(p<0.01)*	0.19 (P=0.03)
U-albumin/ creatinine	0.45 (0.32–0.76)	1.11 (0.52–5.48)	<0.0001	0.22 (p<0.001)	**0.30** (p<0.001)	0.12 (p=0.2)

Biomarcadores de monitorización/Px

Albúmina:

- Sencillo, barato, disponible
- La albuminemia >3,7 g/dl al año del diagnóstico predice una mejor evolución en nefritis lúpica

- Discrimina entre LES y controles sanos
- Marcador de actividad lúpica



Biomarcadores: DNA, C3/C4 y C1q

Research Article

Anti-Double-Stranded DNA Isotypes and Anti-C1q Antibody Improve the Diagnostic Specificity of Systemic Lupus Erythematosus

Table 6: Diagnostic value of anti-dsDNA isotypes, anti-C1q antibody, and low C3 and/or C4 for disease activity of SLE.

	Sensitivity	Specificity	PPV	NPV	OR (95% CI)
Anti-dsDNA IgG	83%	46%	69%	64%	4.029 (1.592–10.196)
Anti-dsDNA IgA	42%	80%	75%	48%	2.818 (1.103–7.203)
Anti-C1q	63%	74%	78%	58%	4.971 (2.025–12.202)
Anti-dsDNA IgG and IgA	42%	82%	77%	49%	3.325 (1.257–8.790)
Anti-dsDNA IgG and anti-C1q	54%	79%	79%	54%	8.495 (3.436–21.002)
Anti-dsDNA IgA and anti-C1q	32%	87%	78%	47%	3.138 (1.053–9.356)
Anti-dsDNA IgG, IgA, and anti-C1q	32%	90%	82%	47%	4.038 (1.246–13.085)
Low C3 and/or C4	80%	71%	81%	69%	9.6 (3.566–25.844)

Biomarcadores: DNA, C3/C4 y C1q

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TABLE 3: Associations of the presence of anti-dsDNA isotypes and anti-C1q antibody with active/inactive SLE patients, LN/non-LN groups, and active/inactive LN cases.

	Activity of SLE ($N = 96$)			SLE with renal involvement ($N = 96$)			Activity of LN ($N = 50$)		
	Active SLE	Inactive SLE	p value	LN	Non-LN	p value	Active LN	Inactive LN	p value
Anti-dsDNA IgG	82.5% (47/57)	53.8% (21/39)	0.002	76% (38/50)	71.7% (33/46)	NS	78.8% (26/33)	58.8% (10/17)	NS
Anti-dsDNA IgM	49.1% (28/57)	38.5% (15/39)	NS	32% (16/50)	58.7% (27/46)	0.005	33.3% (11/33)	29.4% (5/17)	NS
Anti-dsDNA IgA	42.1% (24/57)	20.5% (8/39)	0.028	28% (14/50)	37.0% (17/46)	NS	30.3% (10/33)	29.4% (5/17)	NS
Anti-C1q	63.2% (36/57)	25.6% (10/39)	0.000	56% (28/50)	39.1% (18/46)	0.032	33.3% (11/33)	23.5% (4/17)	NS

SLE: systemic lupus erythematosus; LN: lupus nephritis; NS: no significance; $p < 0.05$, chi-squared test.

Biomarcadores: C3 vs C3dg

frontiers in Immunology

ORIGINAL RESEARCH
published: 26 March 2018
doi: 10.3389/fimmu.2018.00581

The C3dg Fragment of Complement Is Superior to Conventional C3 as a Diagnostic Biomarker in Systemic Lupus Erythematosus

Anne Troldborg[1,2], Lisbeth Jensen[3], Bent Deleuran[1,3], Kristian Stengaard-Pedersen[1,2], Steffen Thiel[3] and Jens Christian Jensenius[3]*

- Fragmento soluble del complemento
- Indica consumo
- 4 horas de vida media

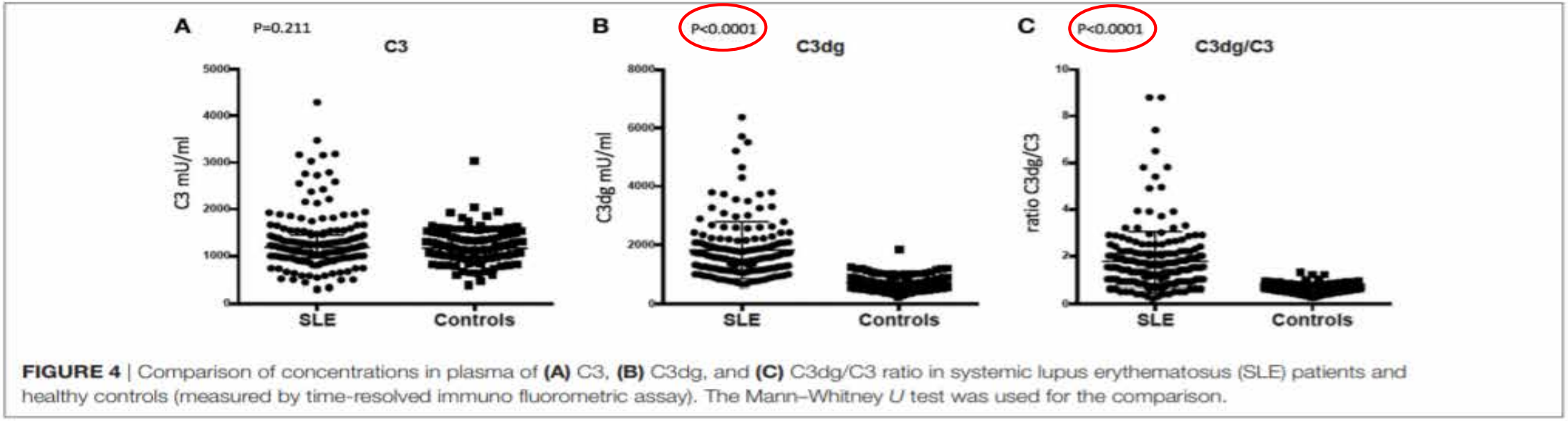
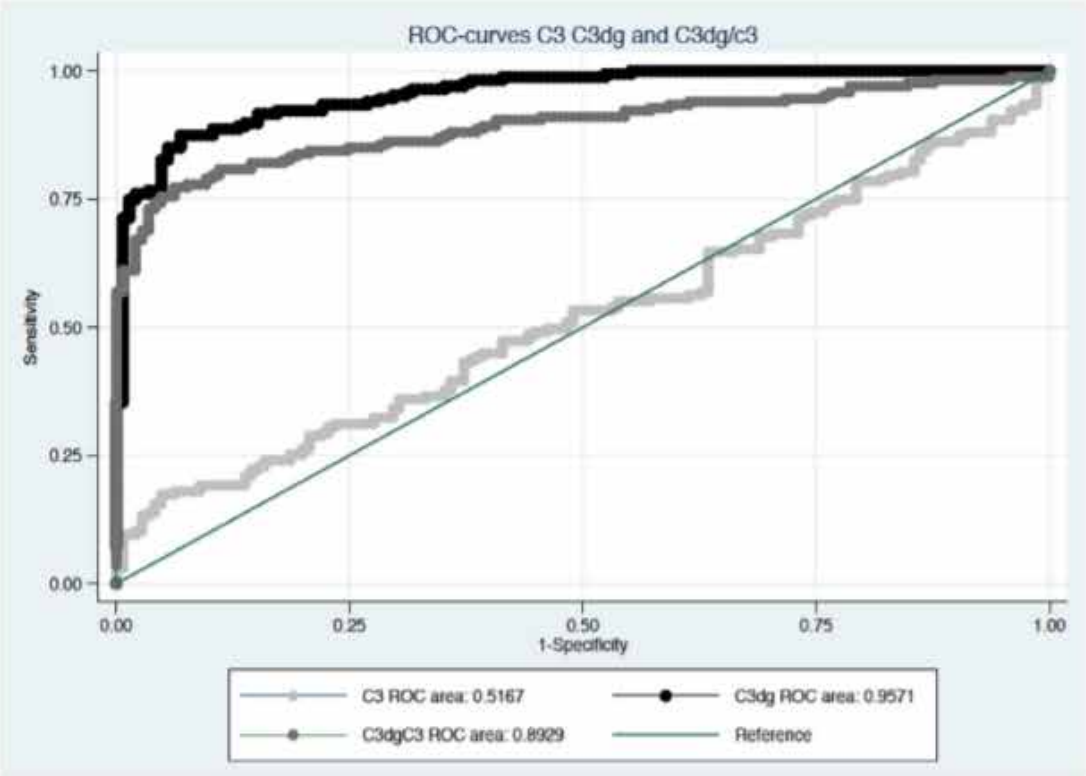


FIGURE 4 | Comparison of concentrations in plasma of **(A)** C3, **(B)** C3dg, and **(C)** C3dg/C3 ratio in systemic lupus erythematosus (SLE) patients and healthy controls (measured by time-resolved immuno fluorometric assay). The Mann–Whitney *U* test was used for the comparison.

Biomarcadores: C3 vs C3dg

A



B

	Obs	ROC Area	Std. Err.	-Asymptotic Normal- [95% Conf.	Interval]
C3	312	0.5167	0.0327	0.45250	0.58083
C3dg	312	0.9571	0.0100	0.93748	0.97671
C3dg/C3	312	0.8929	0.0190	0.85561	0.93022

Ho: area(C3) = area(C3dg) = area (C3dg/C3)
Chi2(2) = 3.75.08 prop>chi2 = 0.0000

C

	Cut-off	Sensitivity (%)	Specificity (%)	LR+	LR-
C3	900 (mU/ml)	80	14	0.98	1.04
	1400 (mU/ml)	28	79	1.47	0.88
C3dg	1000 (mU/ml)	87	90	8.45	0.14
	1100 (mU/ml)	84	94	15.2	0.17
C3dg/C3	0.85 (ratio)	80	89	5.38	0.26
	1.00 (ratio)	67	97	16.1	0.35

FIGURE 5 | Separation of systemic lupus erythematosus patients from controls using C3, C3dg, and C3dg/C3. **(A)** demonstrates ROC-curves for C3 (light gray), C3dg (black), and C3dg/C3 (dark gray). **(B)** represents calculations of area under the curve with 95% confidence intervals for each of the curves in **Figure 1B**. **(C)** shows calculations of sensitivity, specificity, and likelihood ratios for C3, C3dg, and C3dg/C3 using two different cutoffs for each measurement.

Biomarcadores: Futuro (cercano)

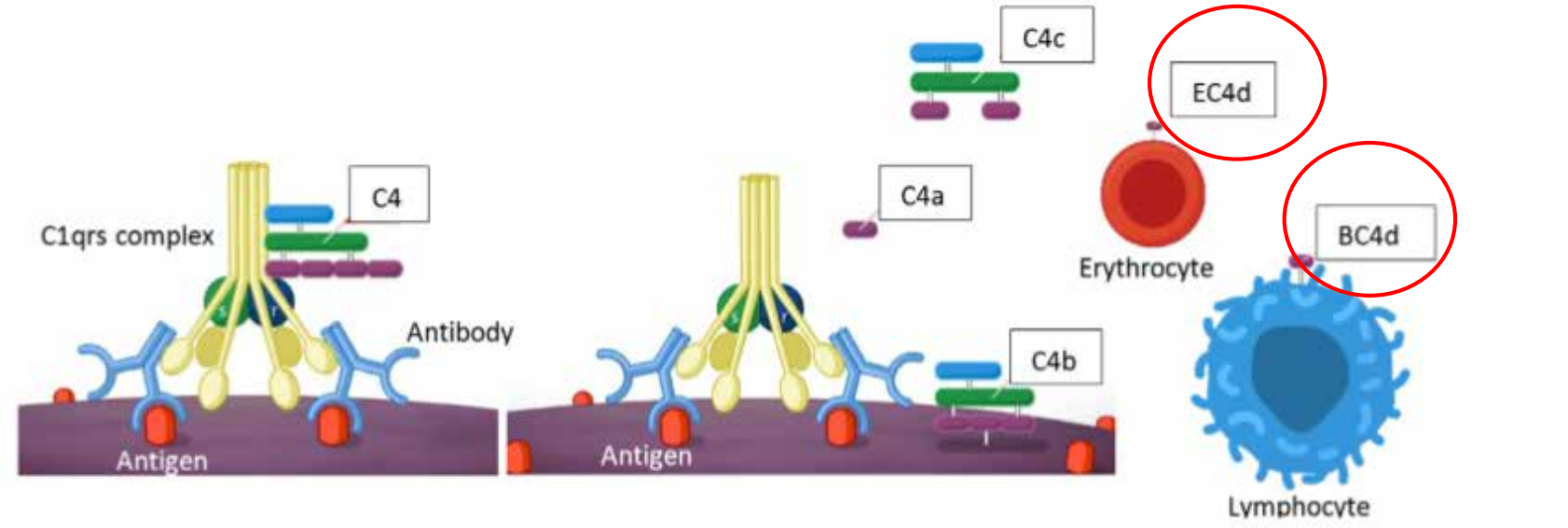
- CB-CAPs: Productos de activación del complemento unido a la célula

Review

LUPUS SCIENCE & MEDICINE™

Cell-bound complement activation products in SLE

Rosalind Ramsey-Goldman,[1] Jian Li,[1] Thierry Dervieux,[2] Roberta Vezza Alexander[2]



Biomarcadores: CB-CAPs

Eritrocitos

Linfos B

Linfos T

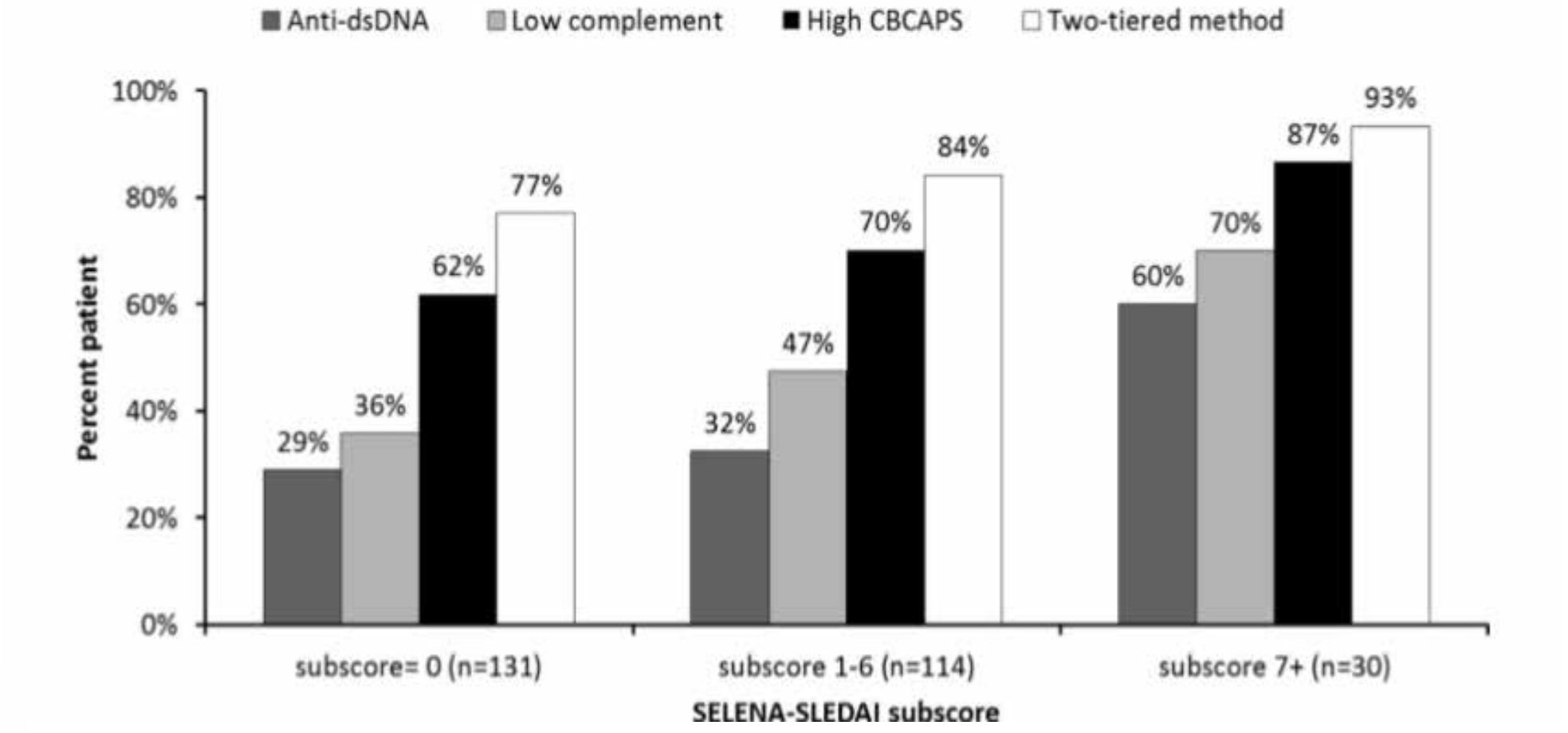
Plaquetas

Table 1 Sensitivity and specificity of EC4d, BC4d, TC4 and PC4d

CB-CAPs	Sensitivity (%)	Specificity	Reference
EC4d	70	83.1% versus other rheumatic diseases 92.7% versus NHV	Kalunian *et al*, 2012[48]
	24	96% versus primary fibromyalgia	Wallace *et al*, 2016[18]
	46	88%–95% versus other rheumatic diseases 99% versus NHV	Putterman *et al*, 2014[14]
BC4d	60	82% versus other autoimmune or inflammatory diseases	Liu *et al*, 2009[49]
	33	100% versus primary fibromyalgia	Wallace *et al*, 2016[18]
	65.7	86.5% versus other rheumatic diseases 95.6% versus NHV	Kalunian *et al*, 2012[48]
	53	90%–96% versus other rheumatic diseases 99% versus NHV	Putterman *et al*, 2014[14]
TC4d	56	80% versus other autoimmune or inflammatory diseases	Liu *et al*, 2009[49]
PC4d	46.2	92.7% versus other rheumatic diseases 99.5% versus NHV	Kalunian *et al*, 2012[48]
	18	98% versus other rheumatic diseases 100% versus NHV	Navratil *et al*, 2006[33]
	48	96% versus NHV	Lood *et al*, 2012[35]

CB-CAP, cell-bound complement activation product; NHV, normal healthy volunteers.

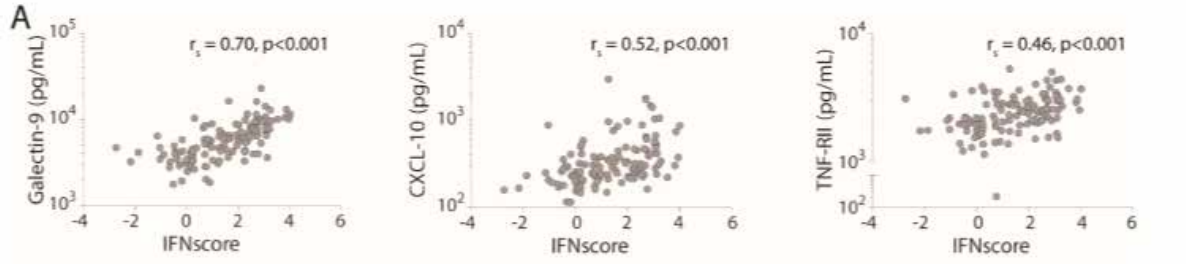
Biomarcadores: CB-CAPs



Biomarcadores: Futuro (cercano)

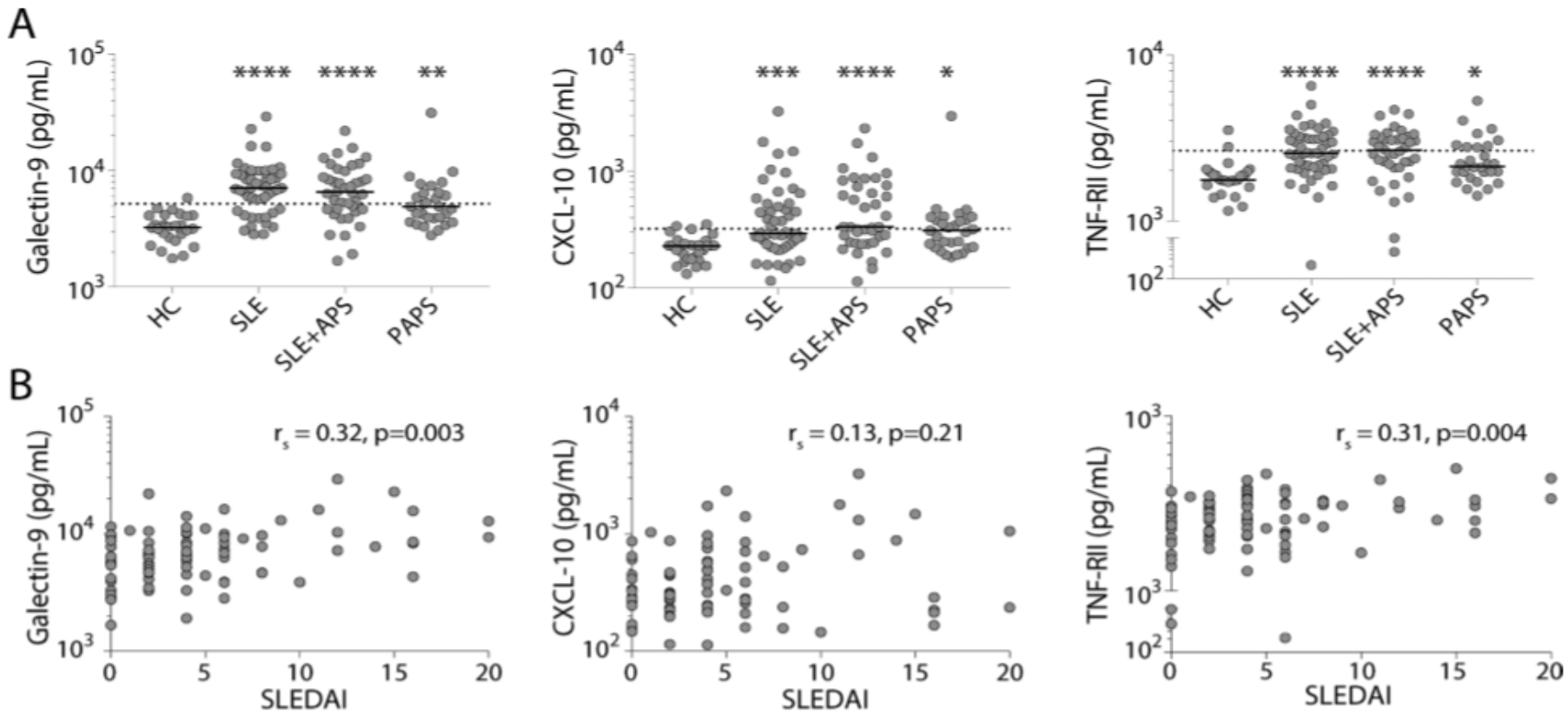
- **Firma del interferón**: expresión aumentada de los genes de interferón inducibles
  - Transcriptómica: análisis de expresión de genes
  - Presente en el 75% de pacientes con LES
  - Relacionado con: niveles altos de Acs, Actividad de la enfermedad, predictor de brotes y bloqueo cardiaco congénito
  - Anifrolumab

- Interferón α en sangre vs marcadores subrogados:
  - Galectina 9 (r=0.70, p<0.001)
  - CXCL-10 (IP-10) (r=0.52, p<0.001)
  - TNF-RII (r=0.46, p<0.001)



Biomarcadores: Firma del Interferón

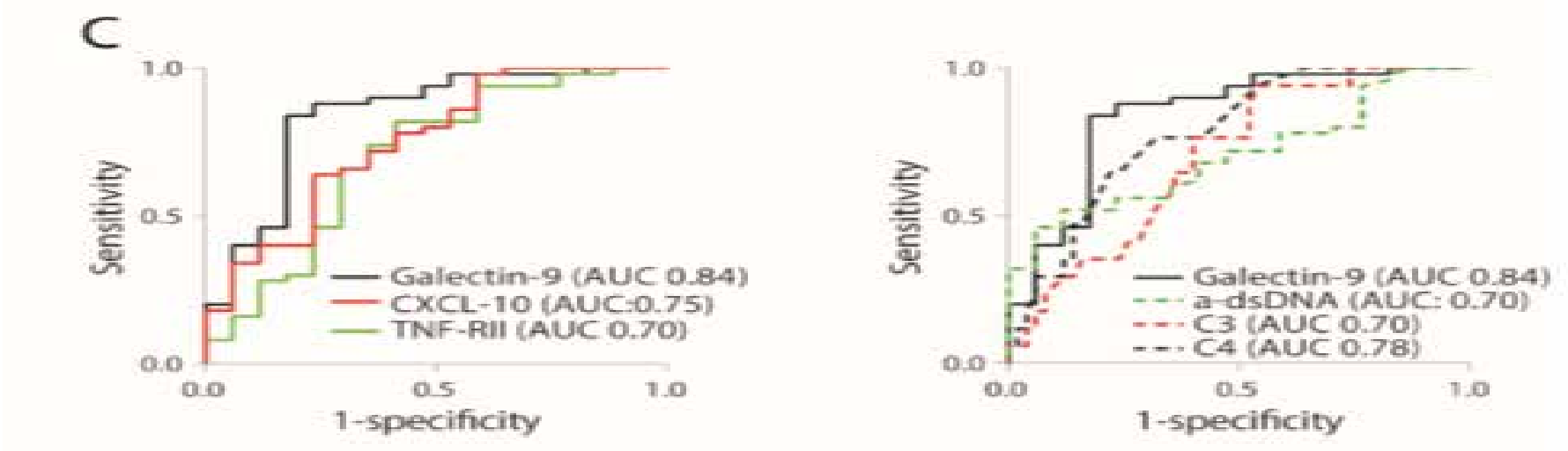
- Galectina 9
- CXCL-10(IP-10)
- TNF-RII



Van den Hoogen LL. Galectin-9 is an easy to measure biomarker for the interferon signature in systemic lupus erythematosus and antiphospholipid syndrome.Ann Rheum Dis. 2018 Dec;77(12):1810-1814.

Biomarcadores: Firma del Interferón

	Galectin-9	CXCL-10	TNF-RII	a-dsDNA	Complement
Sensitivity	84%	57%	48%	55%	62%
Specificity	72%	78%	67%	70%	60%
PPV	91%	89%	82%	85%	83%
NPV	59%	36%	29%	34%	34%

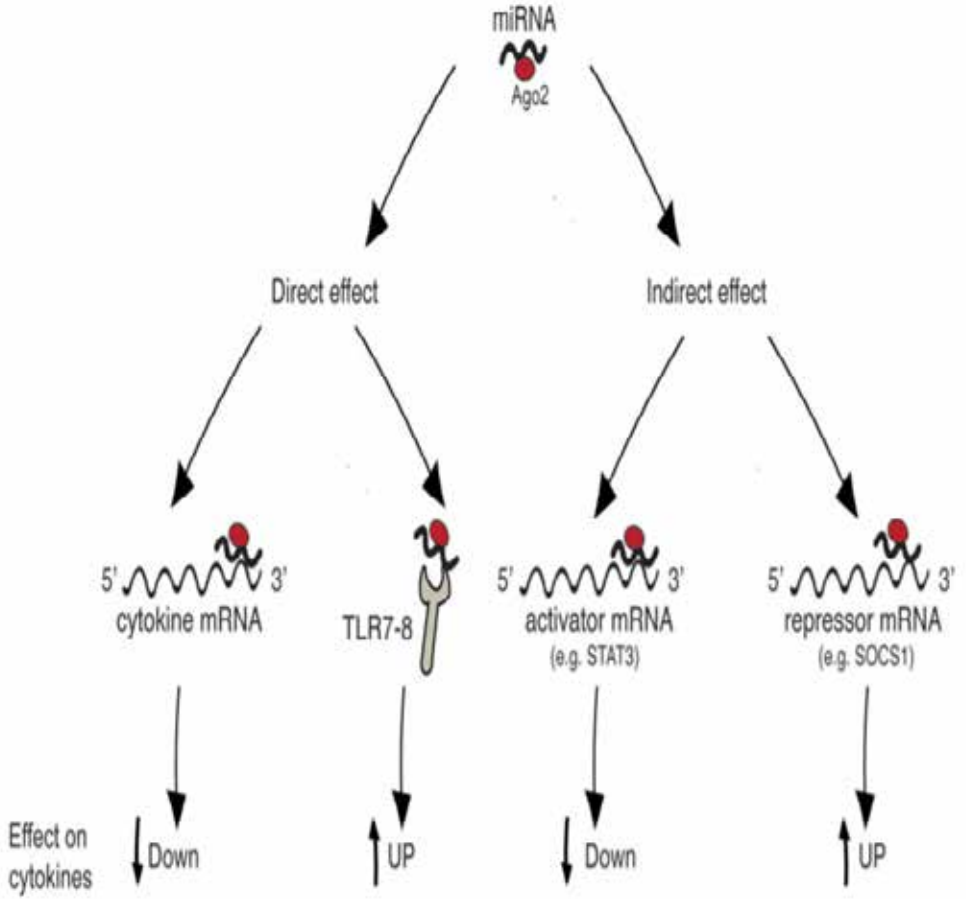


Van den Hoogen LL. Galectin-9 is an easy to measure biomarker for the interferon signature in systemic lupus erythematosus and antiphospholipid syndrome.Ann Rheum Dis. 2018 Dec;77(12):1810-1814.

Biomarcadores en LES: Tratamiento

- Ensayos clínicos
  - Scores de actividad: SLEDAI, BILAG, SRI4

- Biomarcadores como dianas terapéuticas
  - Anifrolumab (ac monoclonal-> R del IF I)
  - Micro-RNA



Gracias

1a Diada Reumatològica

SANT PAU