

17º CONGRESO BARCELONA



22-24  
marzo  
2023



SOCIETAT  
CATALANA DE  
TRASPLANTAMENT

# Biomarcadores de disfunción del injerto en el trasplante pulmonar

**M<sup>a</sup> Piedad Ussetti GIL**

**H. U. Puerta de Hierro Majadahonda**

# Biomarcadores de disfunción del injerto en el trasplante pulmonar



Citoquinas  
DSA  
Poblaciones celulares

miRNA  
ddcfDNA  
KL6

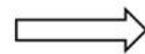
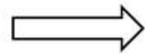
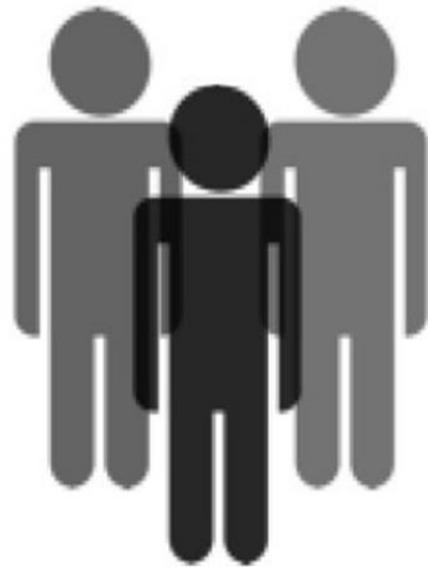
Espiromería  
Biospia

TC  
torácico

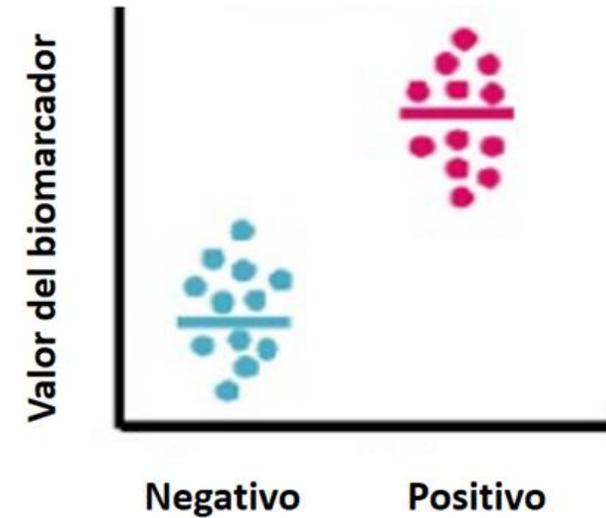
FUTURO

# BIOMARCADOR: Introducción

---



Pronóstico Diagnóstico Respuesta



# BIOMARCADOR: Introducción

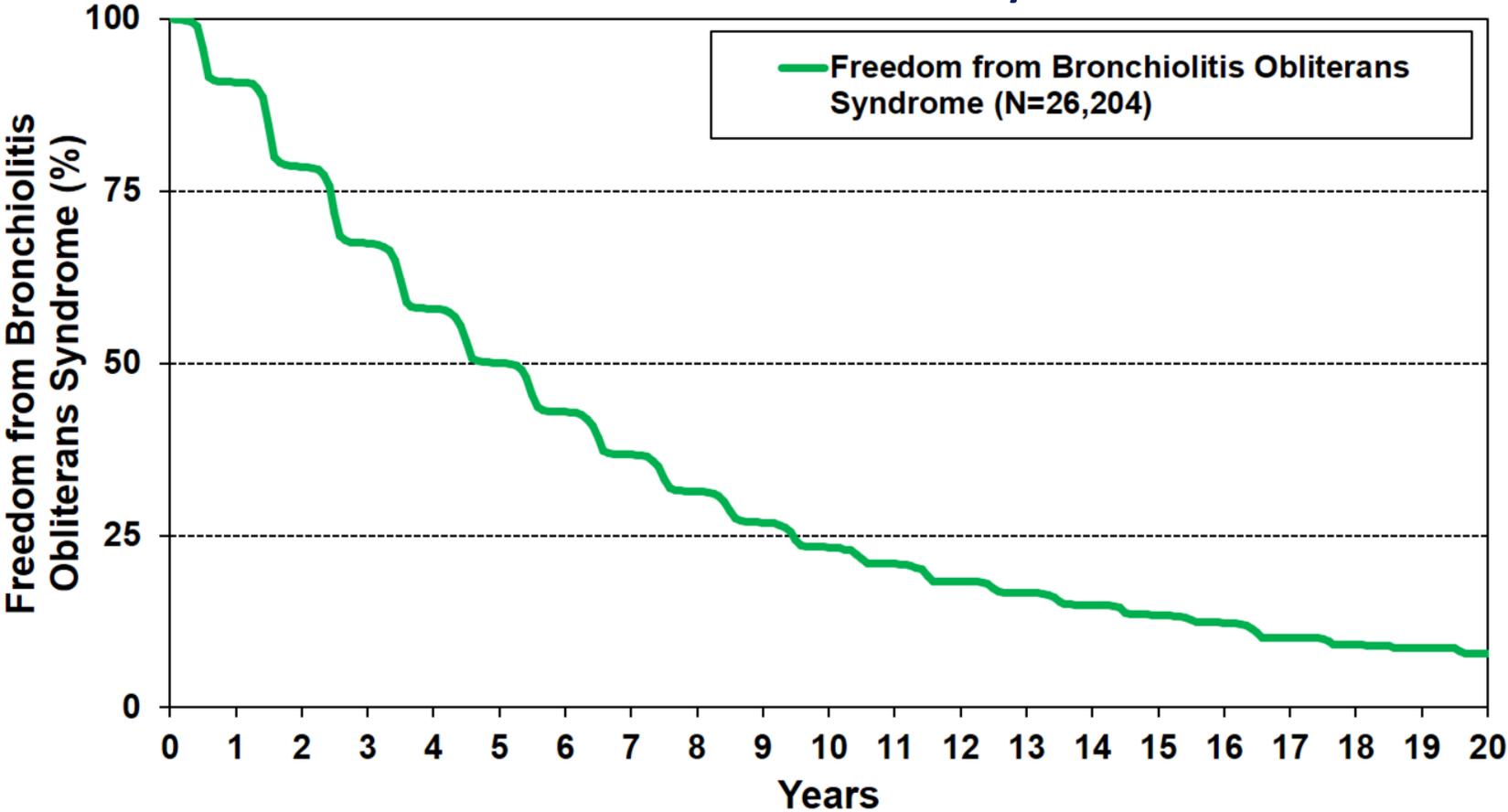
---

- Debe estar presente en el tejido o en sangre periférica
- Su detección debe ser fácil y asequible
- Debe ser posible su cuantificación y asociarse de la forma más específica posible a la patología.

# Adult Lung Transplants

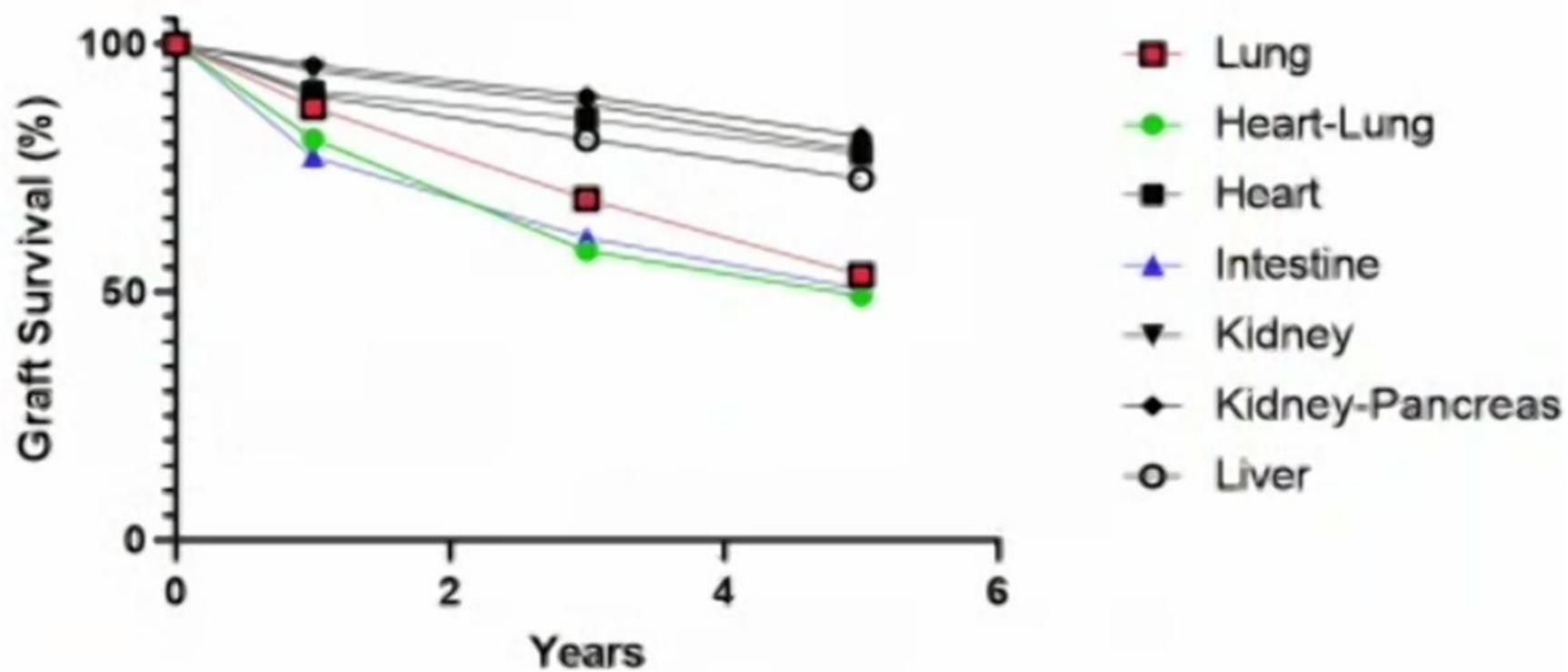
## Freedom from Bronchiolitis Obliterans Syndrome

Conditional on Survival to 14 days



# Lung Allograft Survival worse than Kidney, Heart & Liver

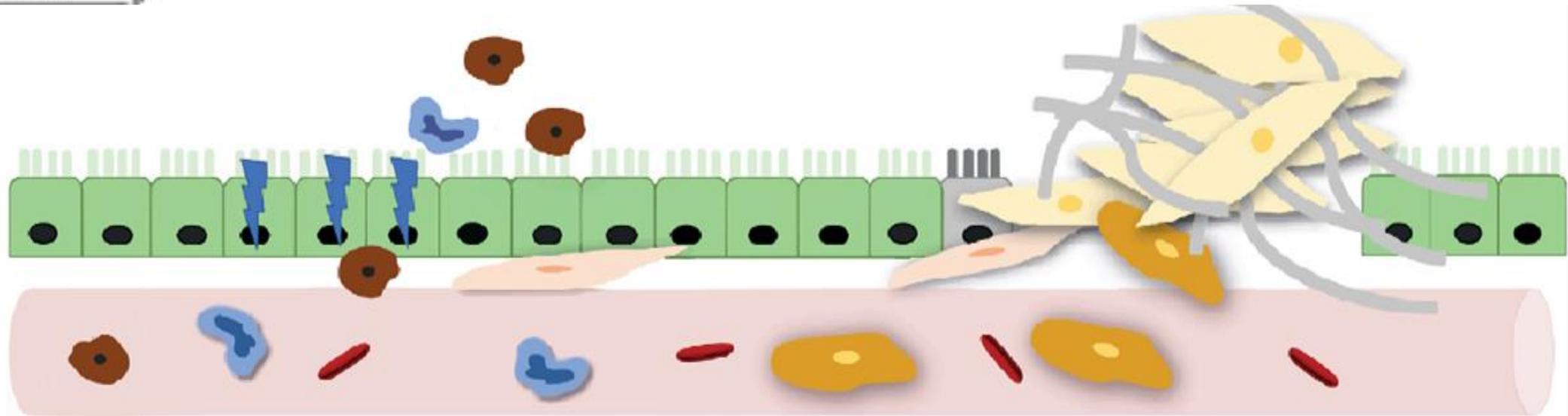
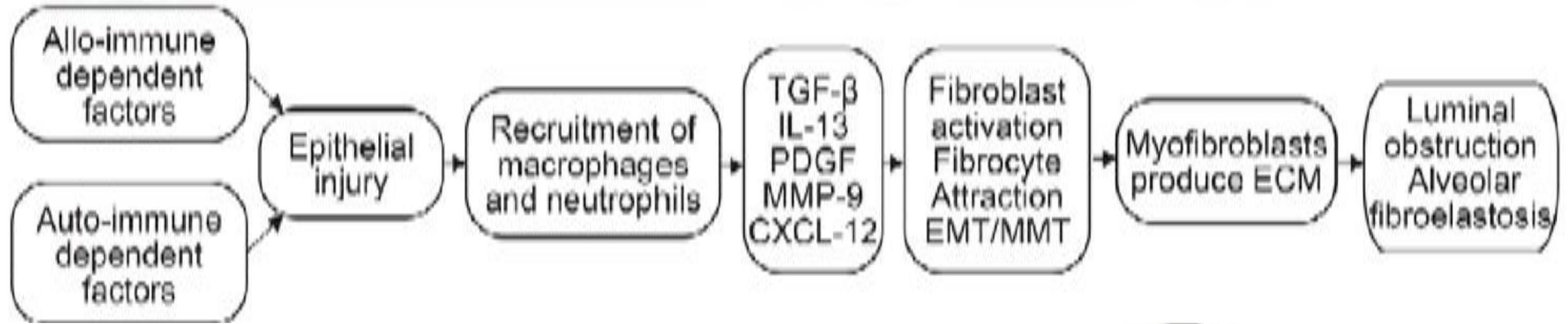
CLAD the predominant cause...



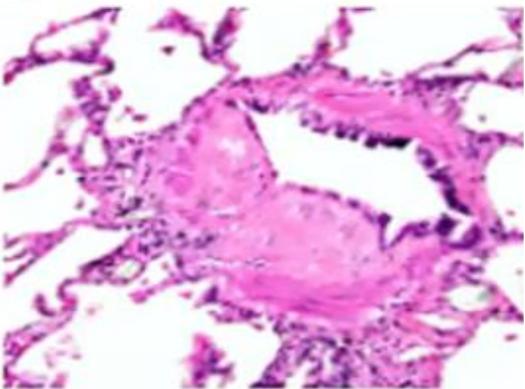
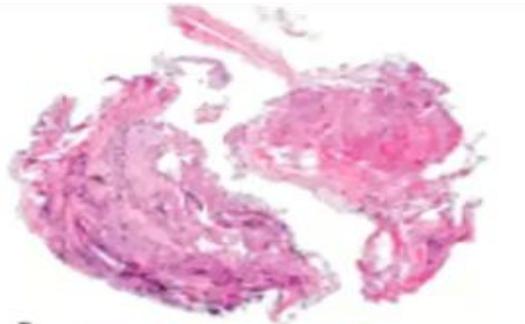
OPTN Data (1/29/2021) <https://optn.transplant.hrsa.gov/data>

# The potential of biomarkers of fibrosis in chronic lung allograft dysfunction

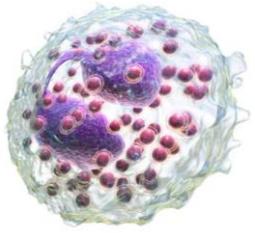
Eline A. van der Ploeg<sup>a,\*</sup>, Barbro N. Melgert<sup>b,c</sup>, Janette K. Burgess<sup>c,d</sup>, C. Tji Gan<sup>a</sup>



# BIOMARCADORES: Rechazo agudo y cónico



- Debe estar presente en el tejido o en sangre periférica
- Su detección debe ser fácil y asequible
- Debe ser posible su cuantificación y asociarse de la forma más específica posible a la patología.



# BIOMARCADORES EN SANGRE: Rechazo agudo y trasplante renal

0041-1337/85/3910-0354\$02.00/0  
TRANSPLANTATION  
Copyright © 1985 by The Williams & Wilkins Co.

Vol. 40, No. 4  
Printed in U.S.A.

## BLOOD EOSINOPHILIA, STEROIDS, AND REJECTION<sup>1</sup>

IRMELI LAUTENSCHLAGER, EEVA VON WILLEBRAND, AND PEKKA HÄYRY<sup>2</sup>

*Transplantation Laboratory and Fourth Department of Surgery, University of Helsinki, Helsinki Finland*

Un aumento de EOS > 400/mm<sup>3</sup> en sangre periférica era un marcador precoz de rechazo del injerto en trasplante renal.

### Original Paper

---

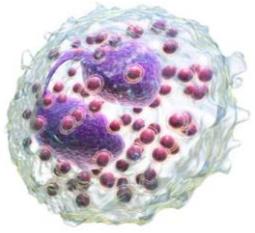
Nephron 1993;65:304-309

*Jaume Almirall<sup>a</sup>  
Josep M. Campistol<sup>b</sup>  
Manel Solé<sup>c</sup>  
Jordi Andreu<sup>b</sup>  
Lluís Revert<sup>a</sup>*

## Blood and Graft Eosinophilia as a Rejection Index in Kidney Transplant

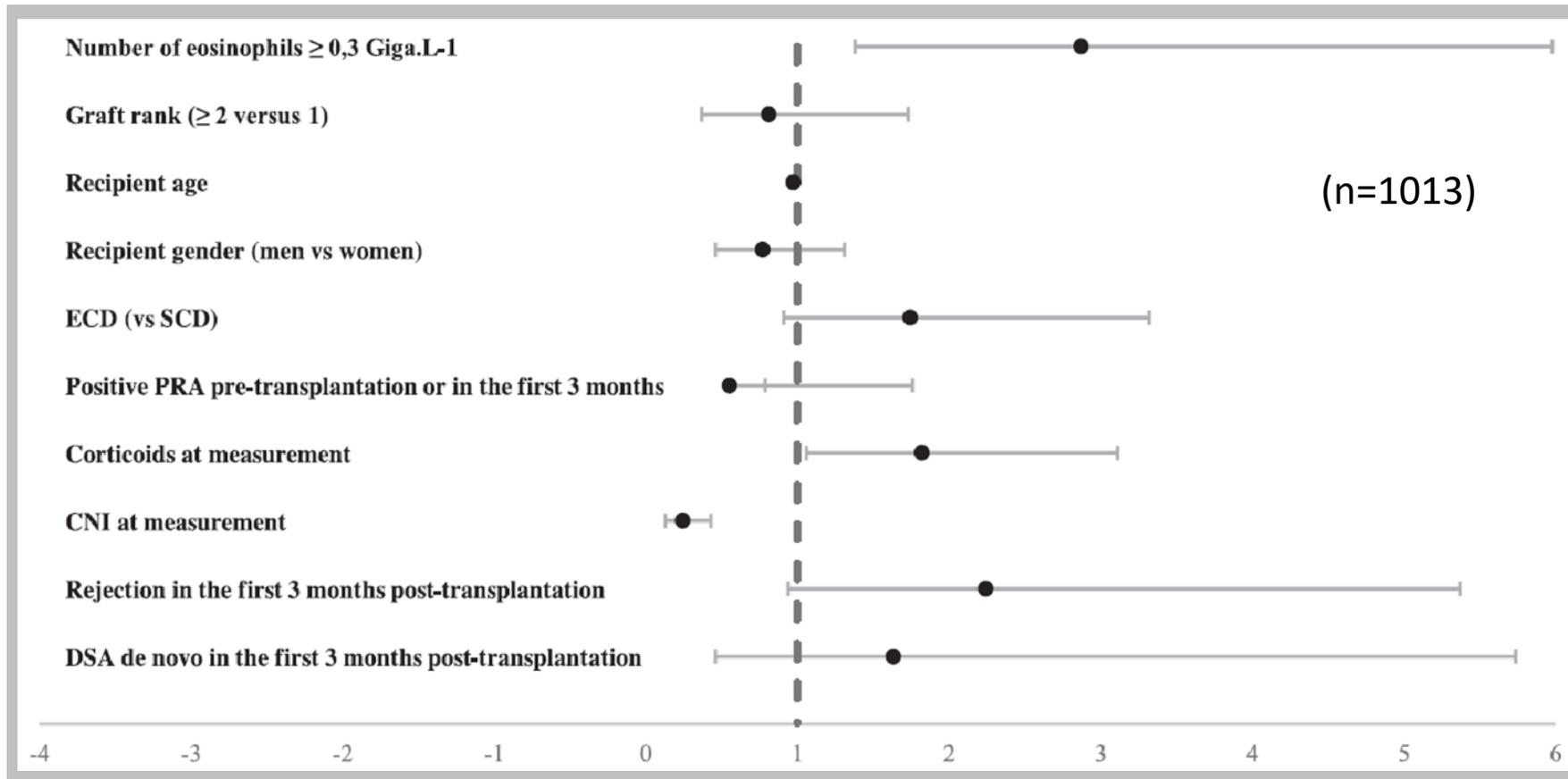
<sup>a</sup> Nephrology Department,  
<sup>b</sup> Renal Transplant Unit and  
<sup>c</sup> Pathology Department,  
Hospital Clinic i Provincial,  
University of Barcelona, Spain

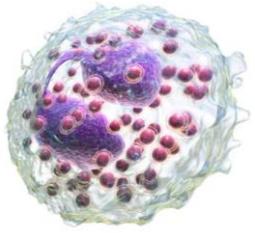
El aumento de EOS y la infiltración eosinofílica del injerto renal se considera criterios de gravedad del rechazo.



# Time-dependent blood eosinophilia count increases the risk of kidney allograft rejection

Luc Colas, MD, PhD<sup>a,1</sup>, Linh Bui, MD<sup>b,1</sup>, Clarisse Kerleau<sup>c</sup>, Mohamed Lemdani, PhD<sup>d</sup>,  
Karine Autain-Renaudin, MD, PhD<sup>a,e</sup>, Antoine Magnan, MD<sup>f</sup>, Magali Giral, MD, PhD<sup>a,c,g,h,1,\*</sup>,  
Sophie Brouard, VMD, PhD<sup>a,g,h,1,\*\*</sup>, for the DIVAT Consortium<sup>2</sup>





# BIOMARCADORES EN SANGRE: Rechazo agudo y trasplante hepático

ORIGINAL ARTICLE

## Predicting severity and clinical course of acute rejection after liver transplantation using blood eosinophil count

Manuel Rodríguez-Perálvarez,<sup>1</sup> Giacomo Germani,<sup>1</sup> Emmanuel Tsochatzis,<sup>1</sup> Nancy Rolando,<sup>1</sup> Tu Vinh Luong,<sup>2</sup> Amar Paul Dhillon,<sup>2</sup> Douglas Thorburn,<sup>1</sup> James O'Beirne,<sup>1</sup> David Patch<sup>1</sup> and Andrew Kenneth Burroughs<sup>1</sup>

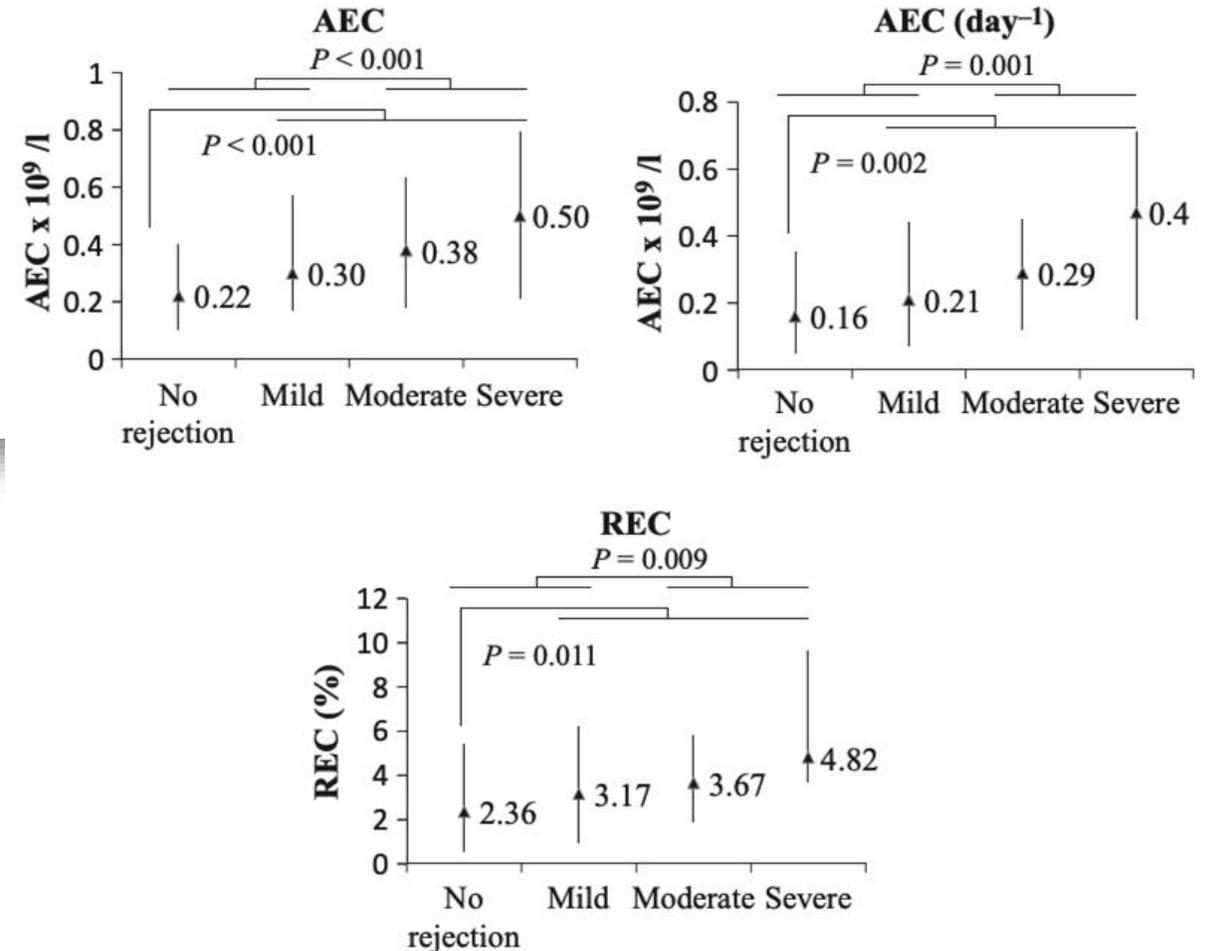
<sup>1</sup> The Royal Free Sheila Sherlock Liver Centre and University Department of Surgery, Royal Free Hospital London, UK

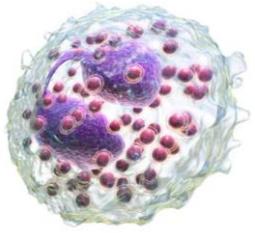
<sup>2</sup> Department of Histopathology, Royal Free Hospital, London, UK

Correlación entre la severidad del rechazo y EOS.

Aumento de EOS es el signo mas específico y confiable de la presencia de rechazo en pacientes Tx hepático

Transpl Int. 2012 May;25(5):555-63





# BIOMARCADORES EN SANGRE: Rechazo agudo y trasplante hepático

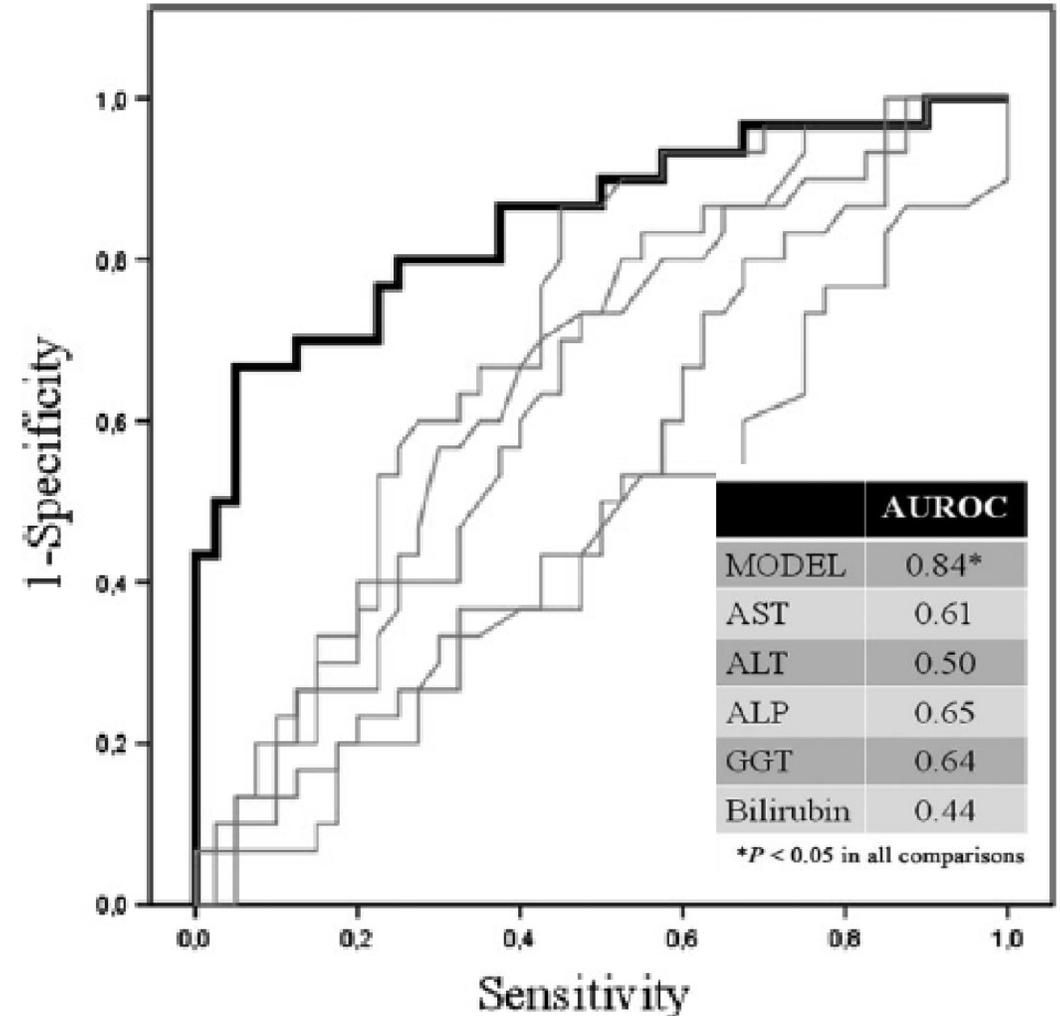
ORIGINAL ARTICLE

## Lack of agreement for defining 'clinical suspicion of rejection' in liver transplantation: a model to select candidates for liver biopsy

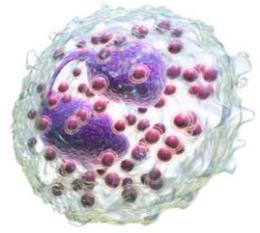
Manuel Rodríguez-Perálvarez,<sup>1</sup> Carmen García-Caparrós,<sup>1</sup> Emmanuel Tsochatzis,<sup>2</sup> Giacomo Germani,<sup>2,3</sup> Brian Hogan,<sup>2</sup> Antonio Poyato-González,<sup>1</sup> James O'Beirne,<sup>2</sup> Marco Senzolo,<sup>3</sup> Marta Guerrero-Misas,<sup>1</sup> Jose L. Montero-Álvarez,<sup>1</sup> David Patch,<sup>2</sup> Pilar Barrera,<sup>1</sup> Javier Briceño,<sup>1</sup> Amar P. Dhillon,<sup>2</sup> Patrizia Burra,<sup>3</sup> Andrew K. Burroughs<sup>2</sup> and Manuel De la Mata<sup>1</sup>

<sup>1</sup> Department of Hepatology and Liver Transplantation, Reina Sofía University Hospital, IMBIC, CIBERehd, Córdoba, Spain

$$\text{Score} = \frac{e^{(-0.07093)+0.00206 \times (\text{Age} \times \text{MELD}) - 2.43720 \times (\text{Red\_Immunos}) - 0.00407 \times (\Delta \text{EOS})}}{1 + e^{(-0.07093)+0.00206 \times (\text{Age} \times \text{MELD}) - 2.43720 \times (\text{Red\_Immunos}) - 0.00407 \times (\Delta \text{EOS})}}$$





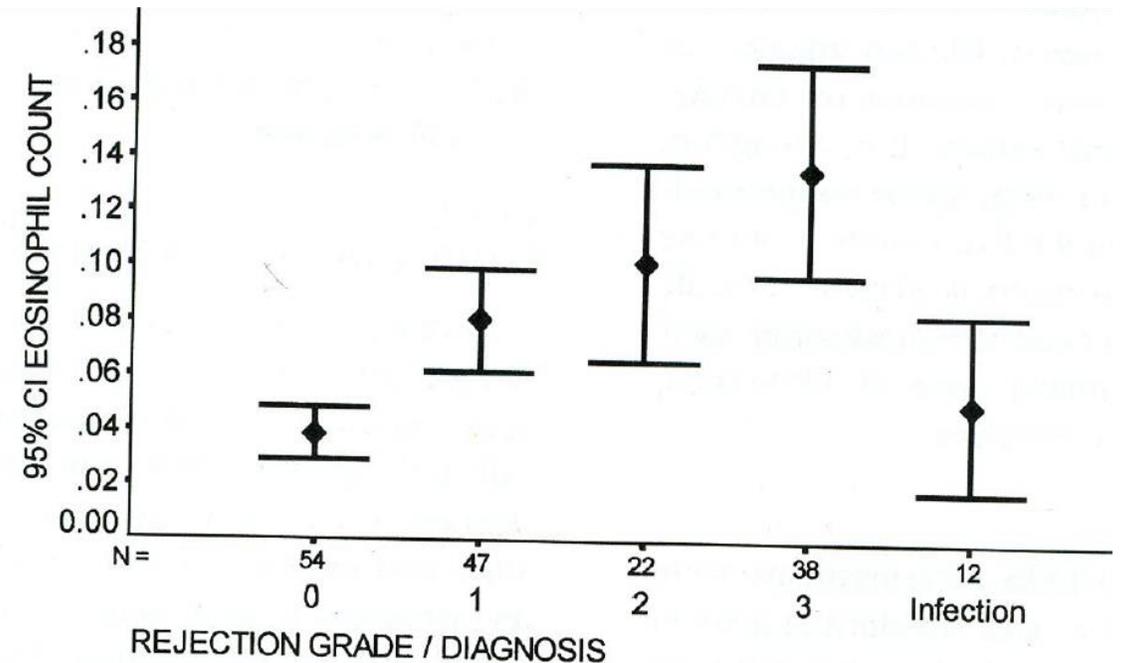


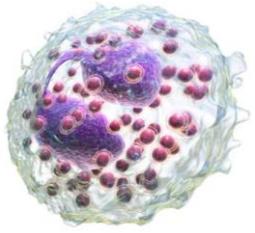
# BIOMARCADORES EN SANGRE: Rechazo agudo y trasplante pulmonar

## Association Between Blood Eosinophil Counts and Acute Cardiac and Pulmonary Allograft Rejection

Andrew Trull, PhD,<sup>a</sup> Louise Steel,<sup>a</sup> Jacqueline Cornelissen,<sup>a</sup> Teresa Smith, PhD,<sup>b</sup> Linda Sharples, PhD,<sup>b,c</sup> Nathaniel Cary, FRCPath,<sup>d</sup> Susan Stewart, FRCPath,<sup>d</sup> Stephen Large, FRCS,<sup>e</sup> John Wallwork, FRCS<sup>e</sup>

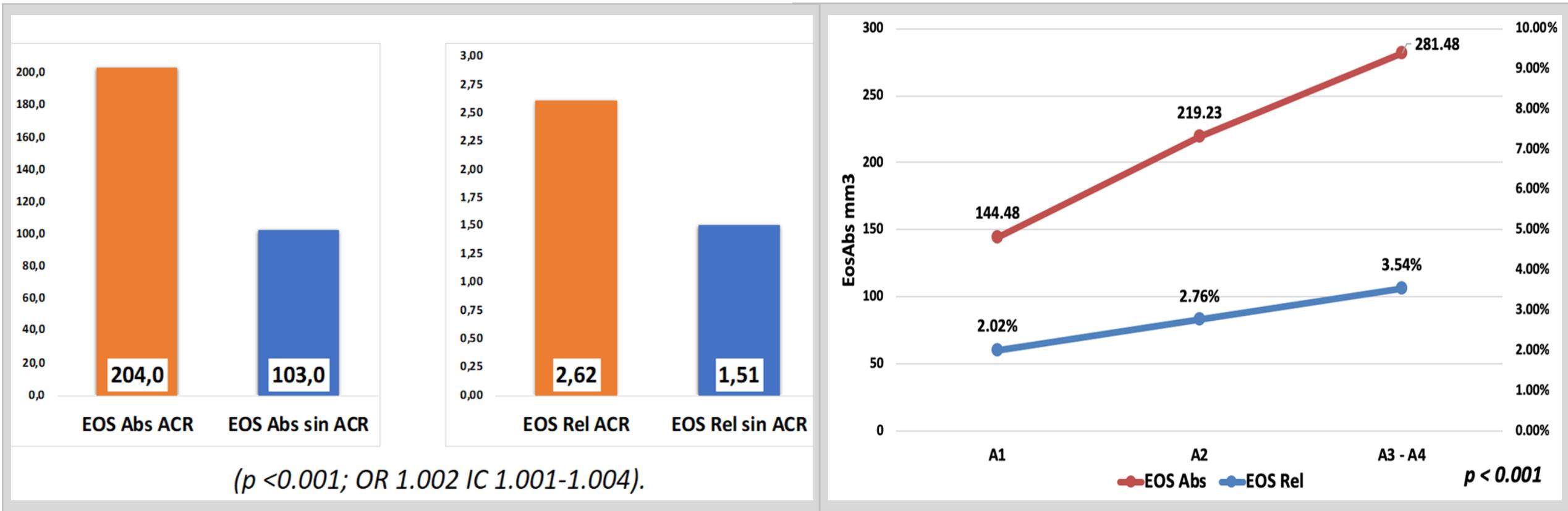
**Asociación entre EOS > 140/mm<sup>3</sup> y ACR en BTB en pacientes trasplantados pulmonares**

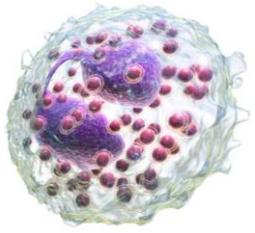




# BIOMARCADORES EN SANGRE : Rechazo agudo

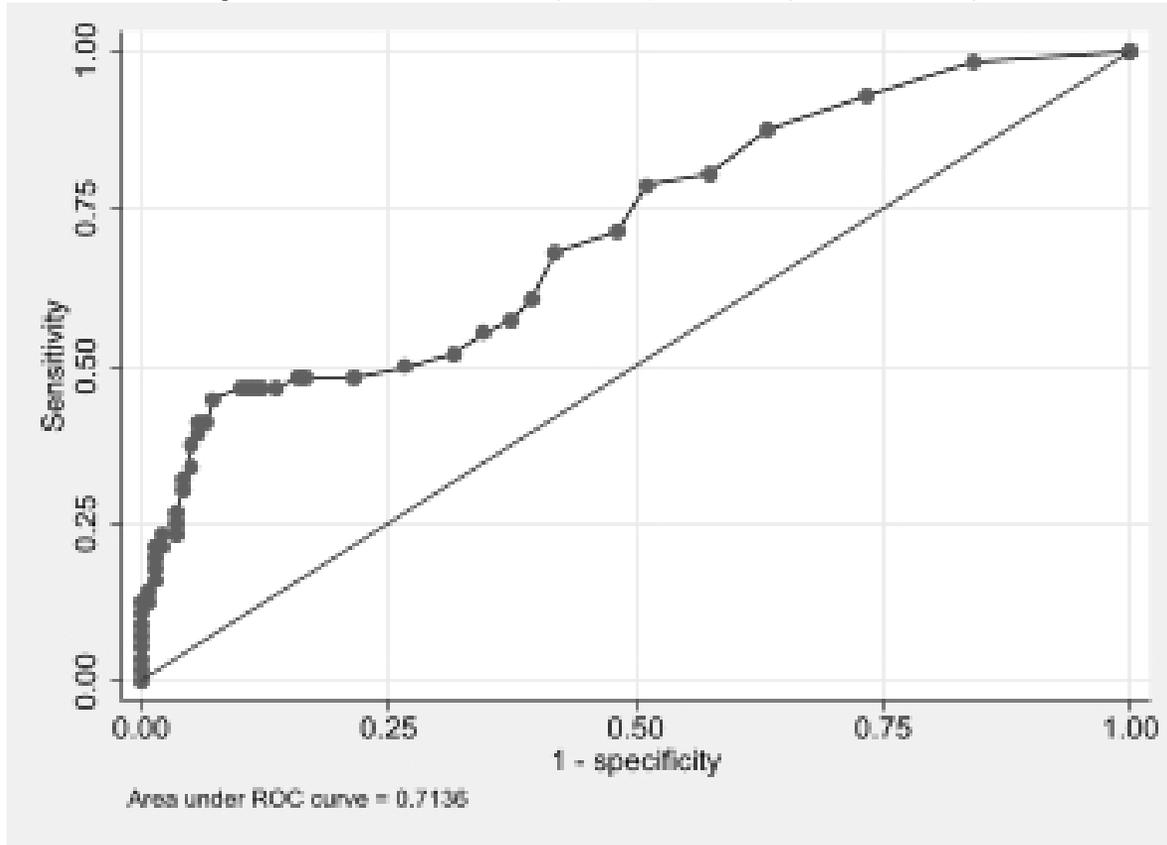
- 583 biopsias transbronquiales (29% con rechazo agudo)
- 256 pacientes Tx pulmonares



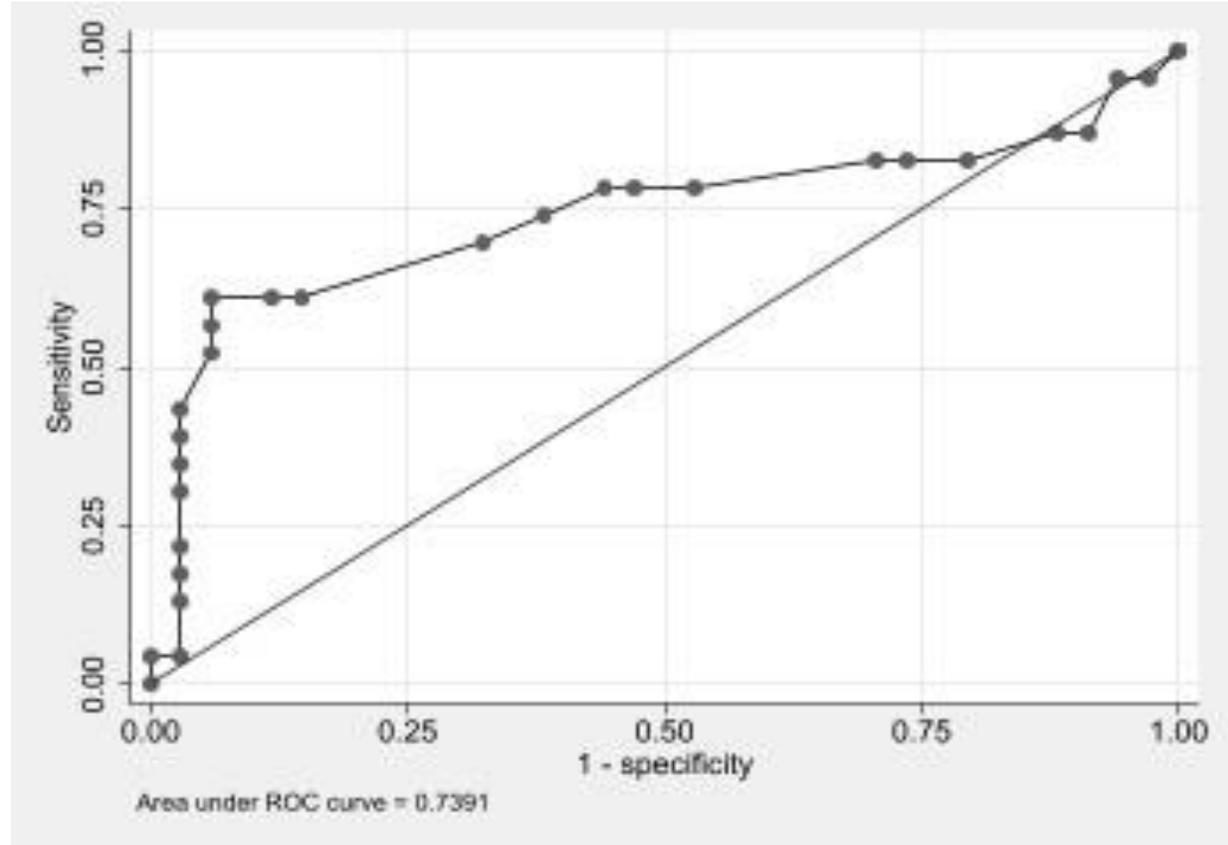


# BIOMARCADORES EN SANGRE : Rechazo agudo

Especificidad 90% ( 195/mm<sup>3</sup> (12meses)



Especificidad 94% (180/mm<sup>3</sup>) (>12meses)



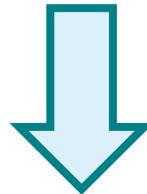


# BIOMARCADORES EN LAVADO BRONCOALVEOLAR (BAL)

**CELULARIDAD**



Ventana al microambiente del injerto pulmonar  
Mecanismos fisiopatológicos que contribuyen a la presencia de rechazo



Método para el diagnóstico y detección precoz

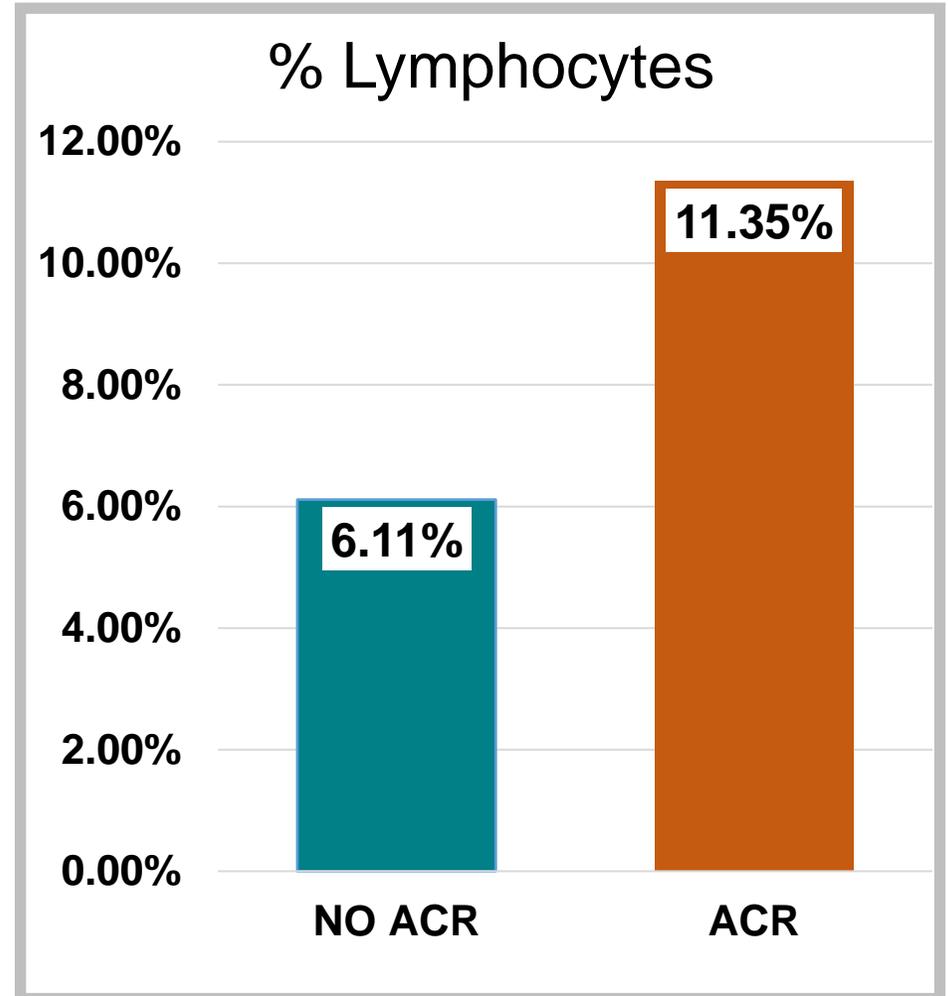


# BIOMARCADORES EN LAVADO BRONCOALVEOLAR (BAL): Rechazo agudo

- 887 biopsias transbronquiales (29% rechazo agudo)
- 362 pacientes con Tx Pulmonar

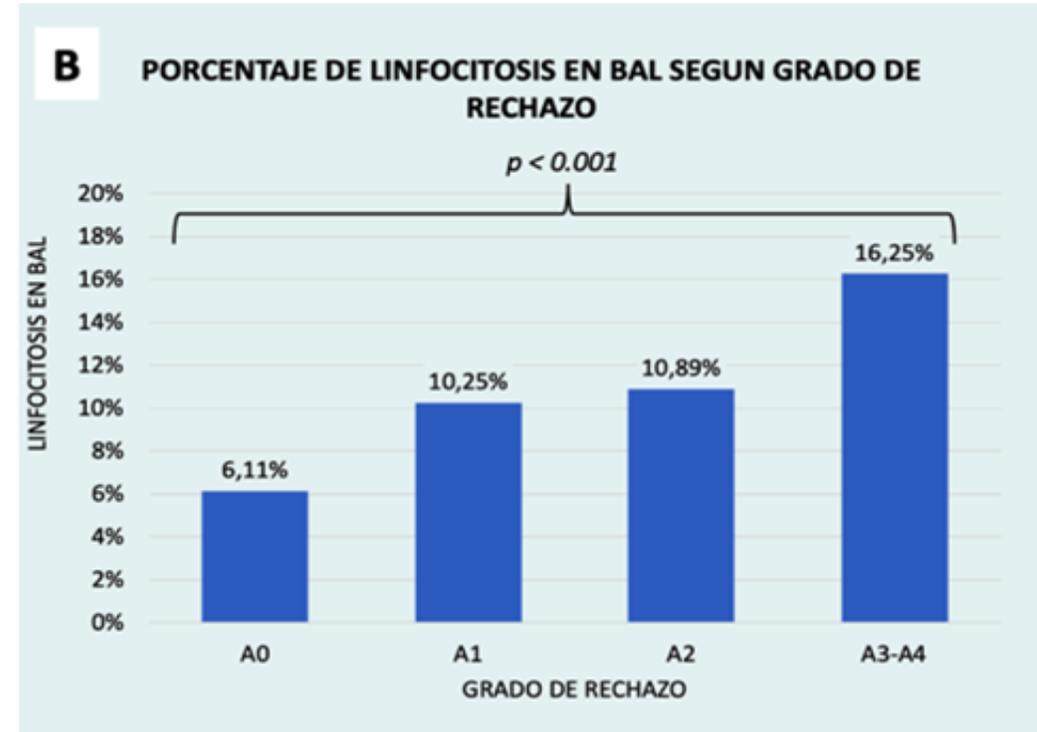
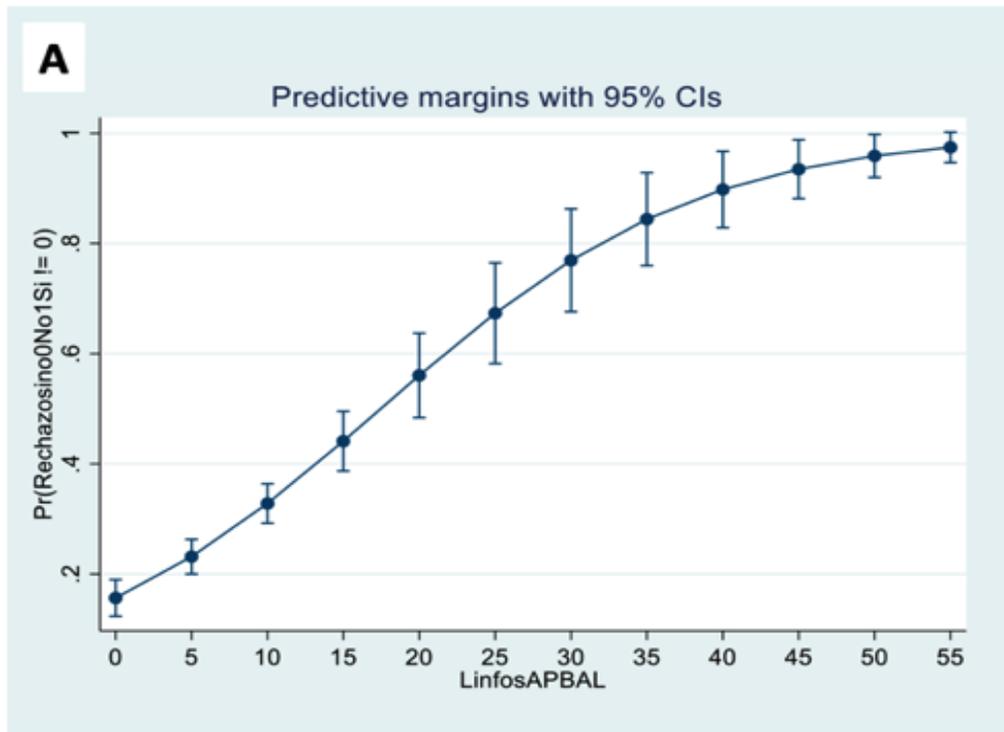
TBB	Total (N = 887)	No ACR (n = 628; 70.8%)	ACR (n = 259; 29.2%)	<i>p</i>
<b>Differential cell count in BALF</b>				
% Neutrophils	9.04 ± 13.08	7.48 ± 11.04	12.90 ± 16.49	<i>p</i> =.106
% Lymphocytes	7.64 ± 7.38	6.11 ± 5.83	11.35 ± 9.25	<i>p</i> <.001
% Macrophages	82.92 ± 16.71	85.94 ± 14.26	75.49 ± 19.73	<i>p</i> =.107
% Eosinophils	0.36 ± 2.12	0.31 ± 1.97	0.48 ± 2.44	<i>p</i> =.311

ACR: acute cellular rejection; CF: cystic fibrosis; COPD: chronic obstructive pulmonary disease; DILD: diffuse interstitial lung disease; IPF: idiopathic pulmonary fibrosis; TBB: transbronchial biopsy; BE: bronchiectasis; BALF: bronchoalveolar lavage fluid.





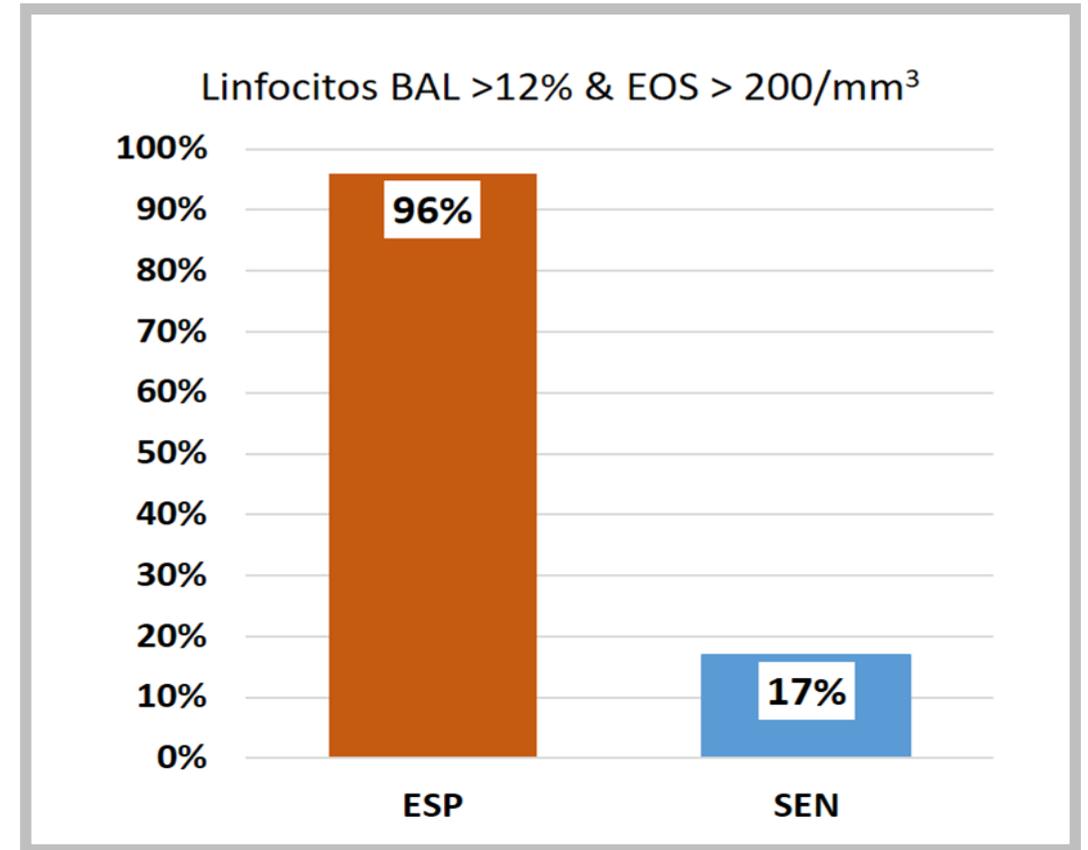
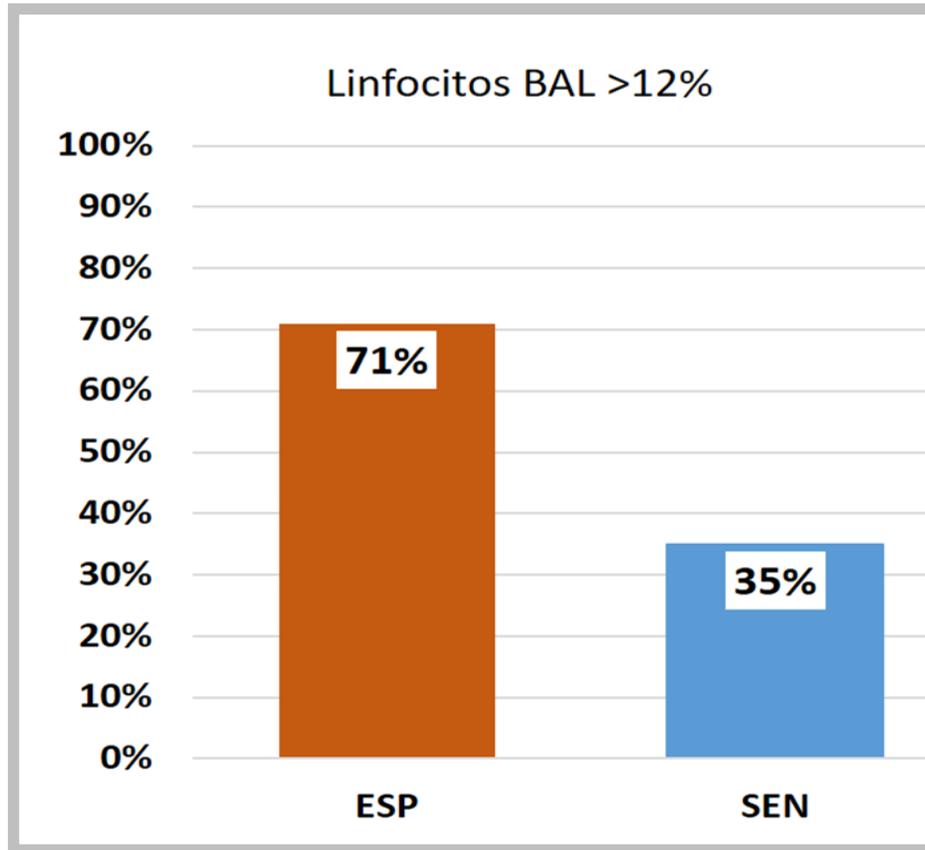
# BIOMARCADORES EN LAVADO BRONCOALVEOLAR (BAL): Rechazo agudo

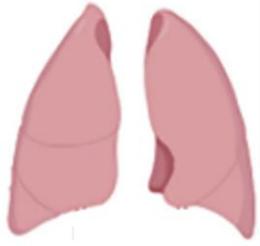


A mayor porcentaje de linfocitos, mayor riesgo de presentar ACR ((OR 1.10 IC 95% 1.080-1.131)



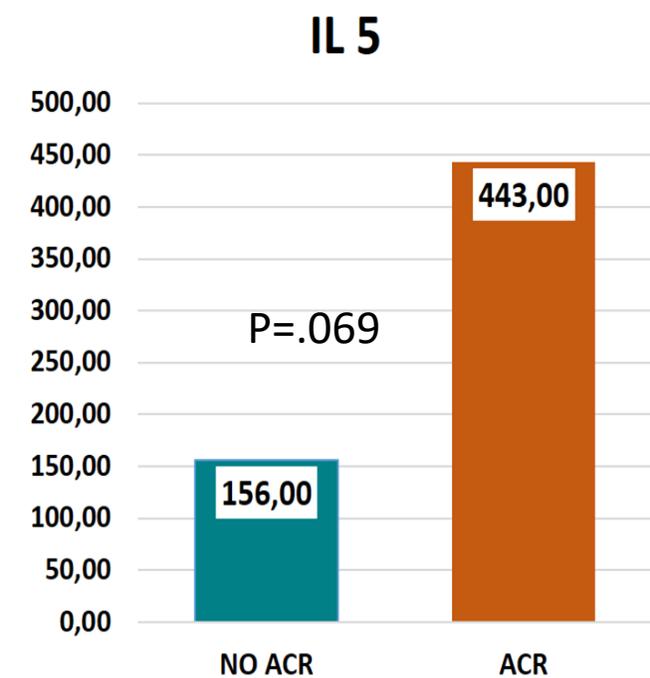
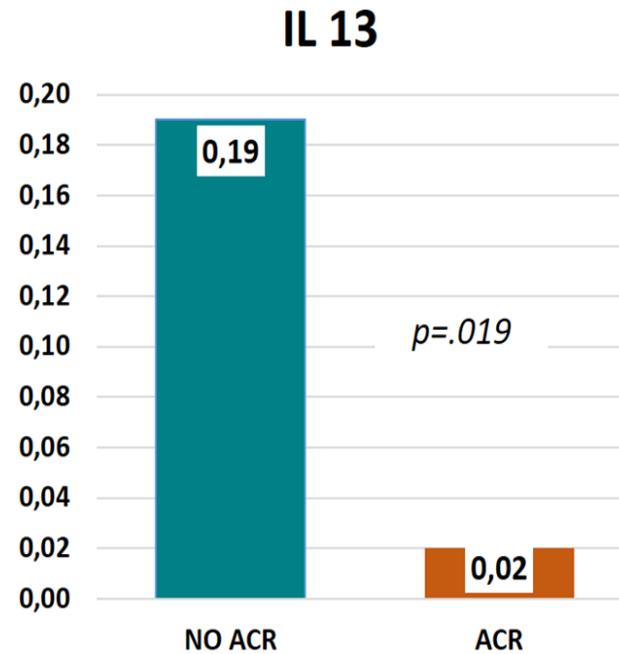
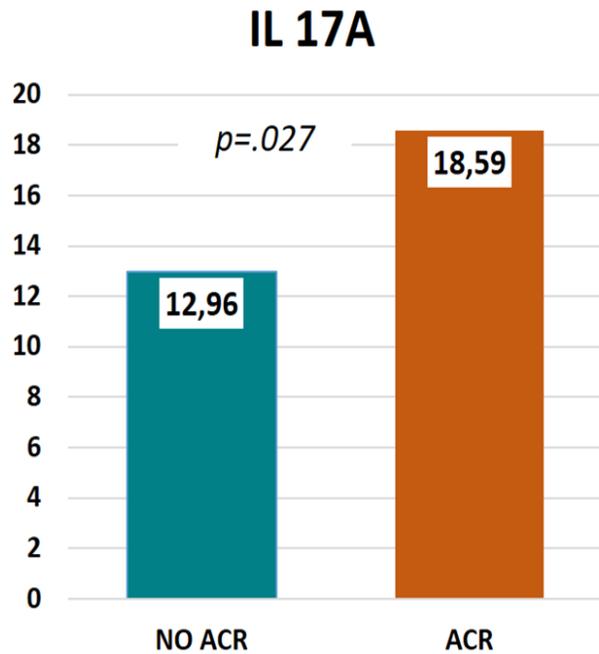
# BIOMARCADORES EN LAVADO BRONCOALVEOLAR (BAL): Rechazo agudo





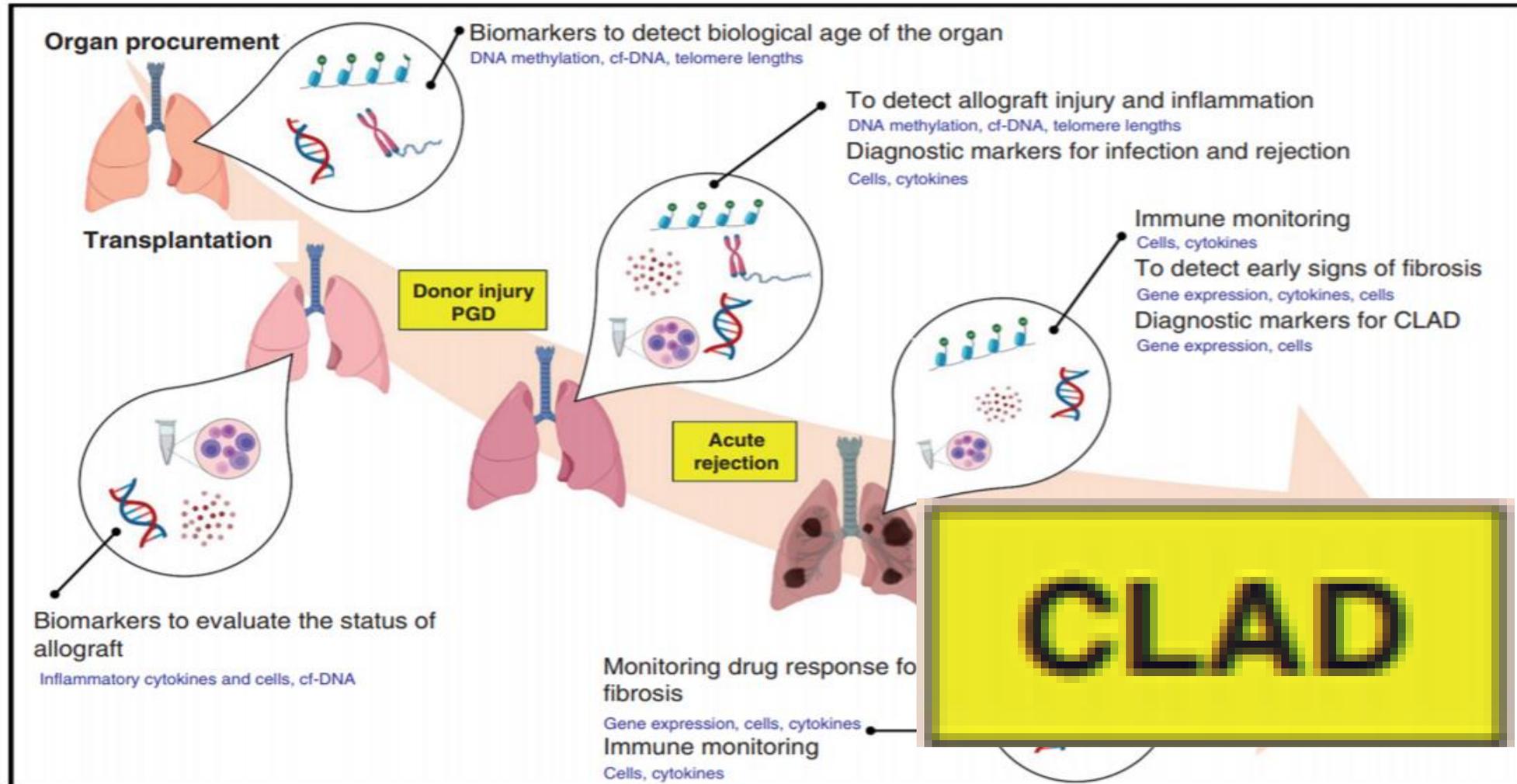
# BIOMARCADORES EN LAVADO BRONCOALVEOLAR (BAL): Rechazo agudo

	Total (N = 108)	No ACR (n = 628; 70.8%)	ACR (n = 259; 29.2%)	<i>p</i>
IL 17A (pg/ml)	15.92 ± 12.55	12.96 ± 7.96	18.59 ± 15.17	<i>p</i> = .027
IL-13 (pg/ml)	0.10 ± 0.37	0.19 ± 0.51	0.02 ± 0.11	<i>p</i> = .019
IL-5 (fentogr/ml)	306.98 ± 775.04	156.18 ± 205.83	443.00 ± 1037.02	<i>p</i> = .069



# Markers of rejection of a lung allograft: state of the art

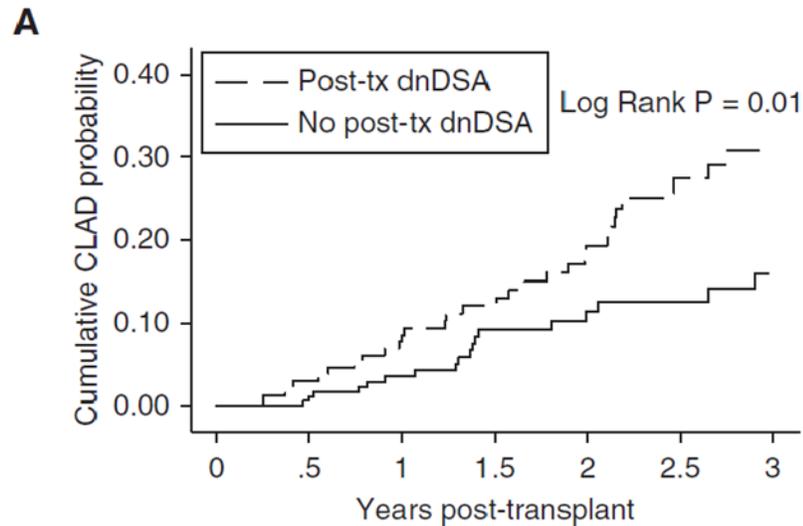
Tharushi de Silva<sup>1,2</sup>  Joanne Voisev<sup>1</sup>  Peter Hopkins<sup>2,3</sup> Simon Ante<sup>2,3</sup>  Daniel



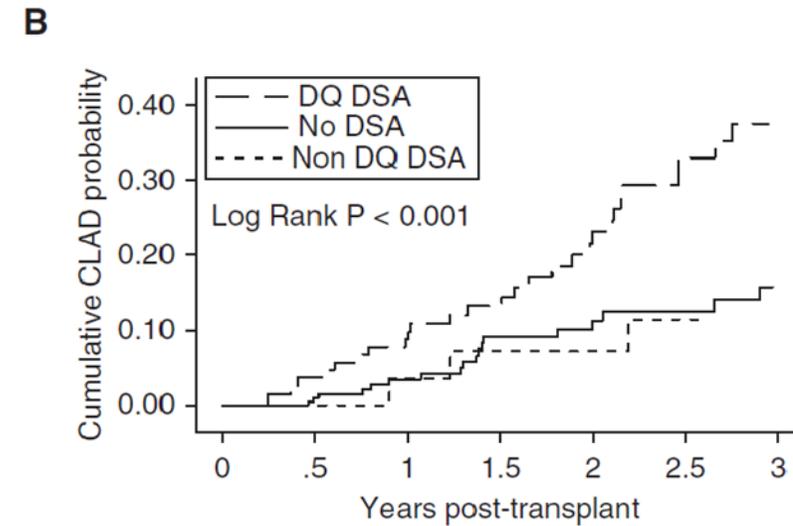
# De Novo DQ Donor-Specific Antibodies Are Associated with Chronic Lung Allograft Dysfunction after Lung Transplantation

Jussi M. Tikkanen<sup>1</sup>, Lianne G. Singer<sup>1</sup>, S. Joseph Kim<sup>2</sup>, Yanhong Li<sup>2</sup>, Matthew Binnie<sup>1</sup>, Cecilia Chaparro<sup>1</sup>, Chung-Wai Chow<sup>1</sup>, Tereza Martinu<sup>1</sup>, Sassan Azad<sup>1</sup>, Shaf Keshavjee<sup>1</sup>, and Kathryn Tinckam<sup>2,3</sup>

<sup>1</sup>Toronto Lung Transplant Program, <sup>2</sup>Division of Nephrology, Department of Medicine, and <sup>3</sup>HLA Laboratory, Laboratory Medicine



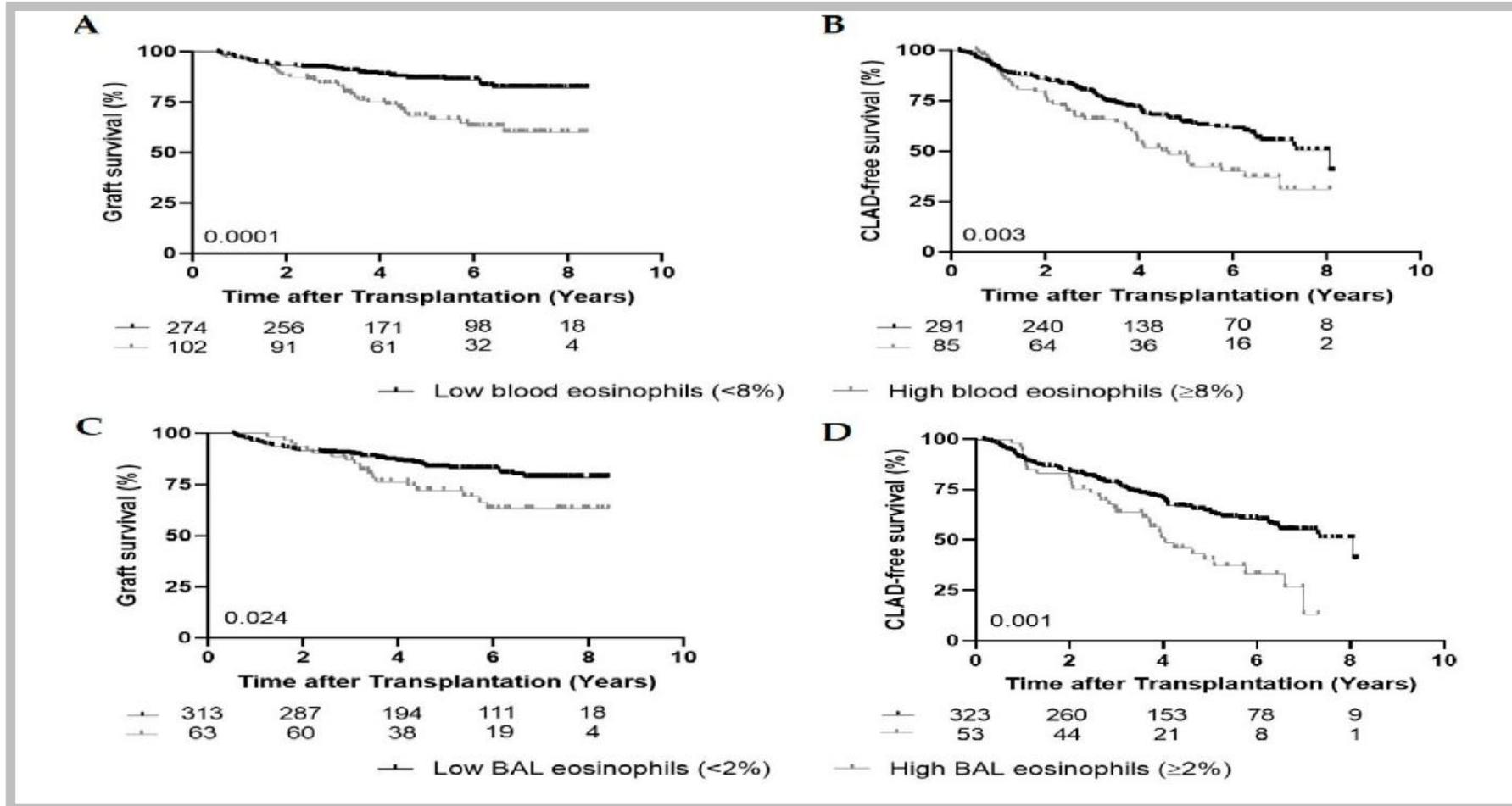
Number at risk		0	.5	1	1.5	2	2.5	3
Post-tx dnDSA		0	114	112	95	73	57	36
No post-tx dnDSA		340	196	134	97	75	57	45



Number at risk		0	.5	1	1.5	2	2.5	3
DQ DSA		0	89	86	72	50	37	22
No DSA		340	196	134	97	75	57	45
Non DQ DSA		0	25	26	23	23	20	14

# Peripheral Blood Eosinophilia Is Associated with Poor Outcome Post-Lung Transplantation

Janne Kaes <sup>1</sup> , Elise Van der Borgh <sup>1</sup>, Arno Vanstapel <sup>1,2</sup>, Anke Van Herck <sup>1,3</sup>,

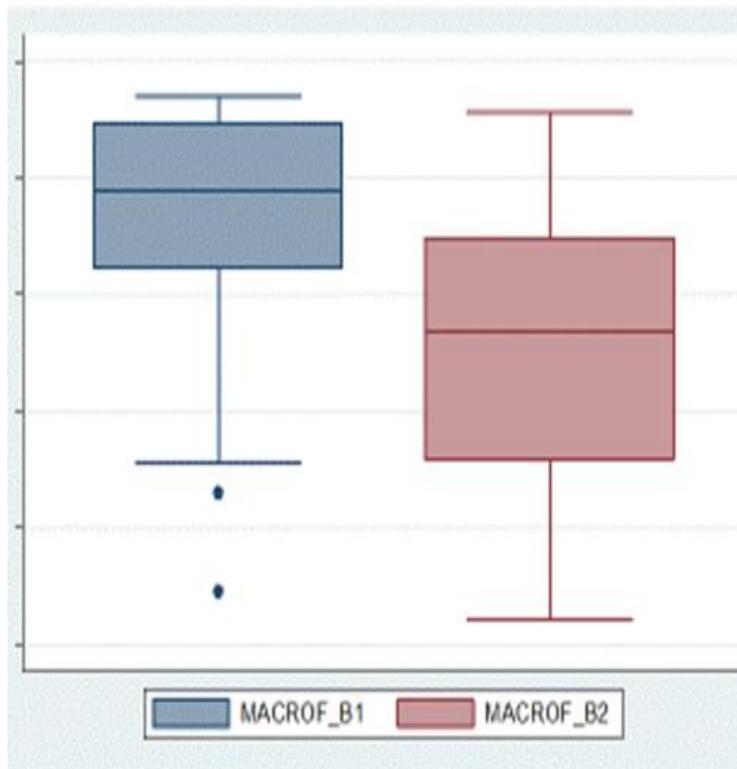




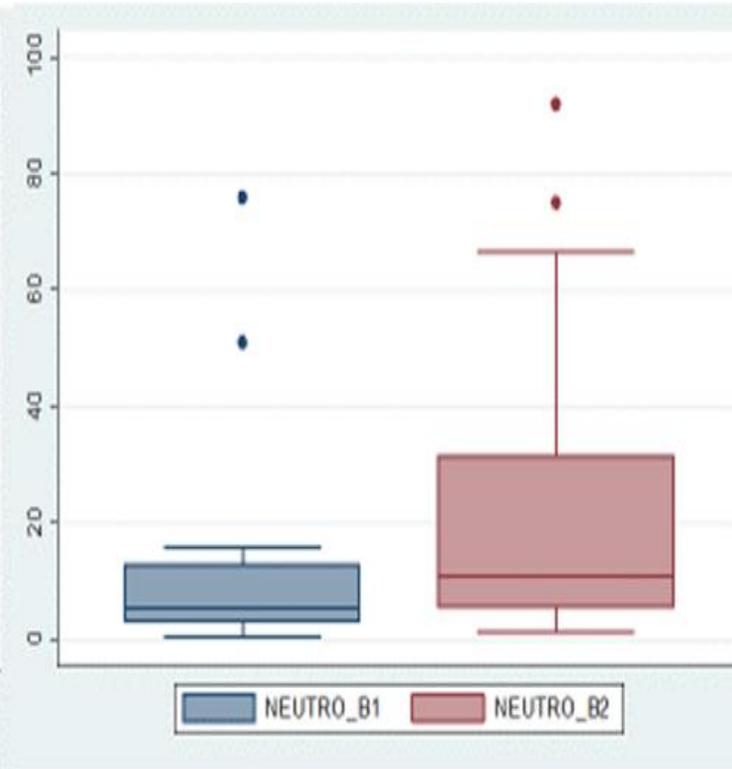
# BIOMARCADORES EN LAVADO BRONCOALVEOLAR (BAL): Rechazo crónico

(n= 27 pacientes con BOS)

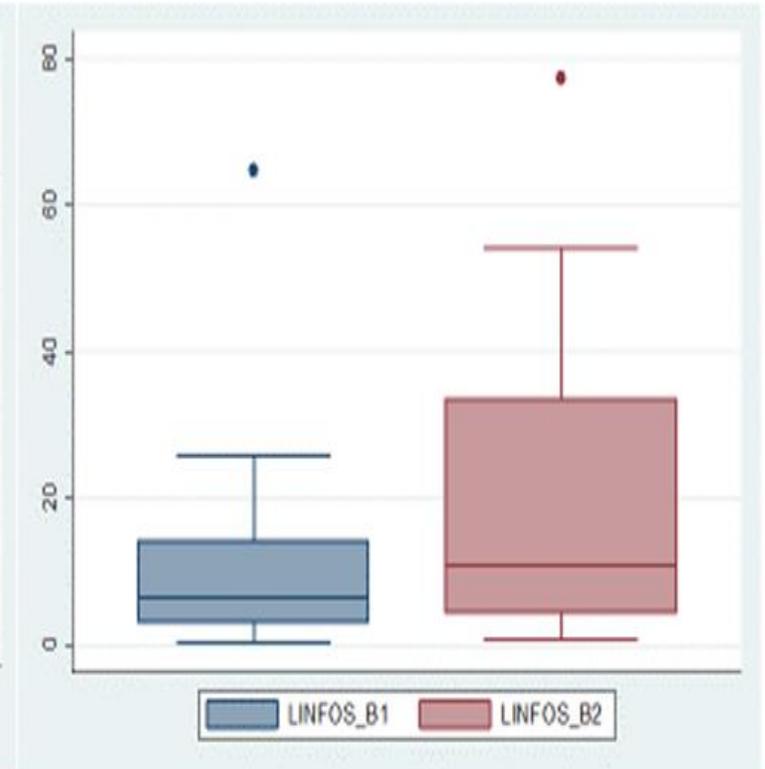
## MACROFAGOS

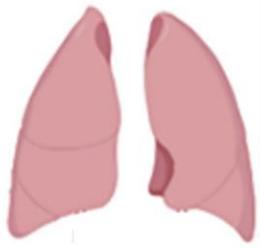


## NEUTROFILOS



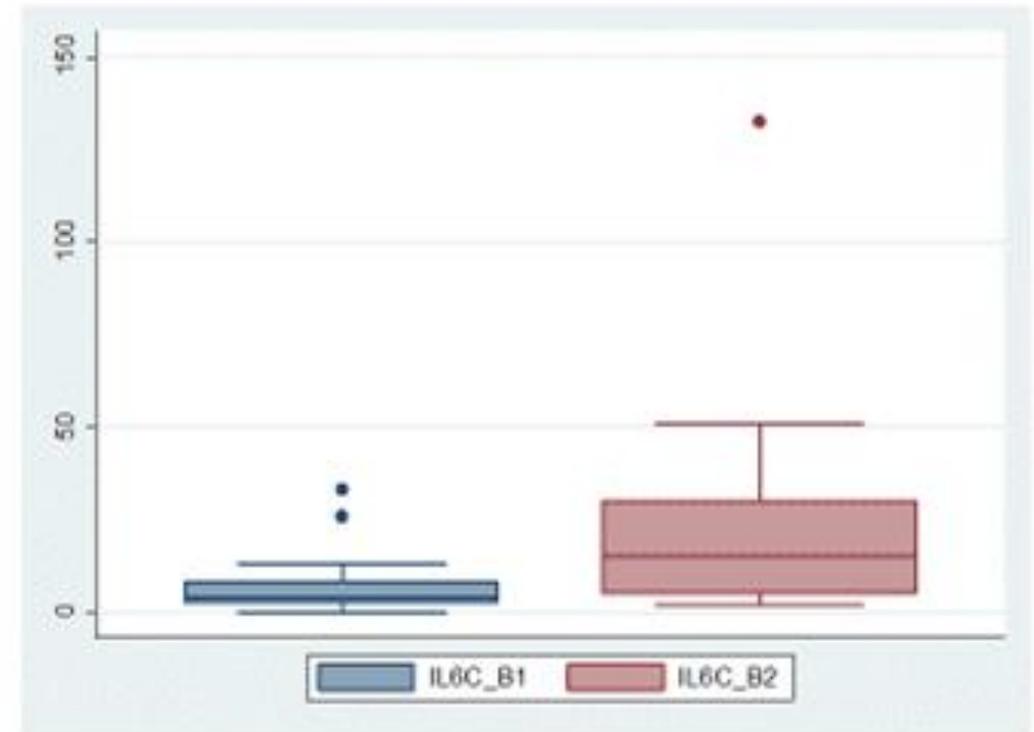
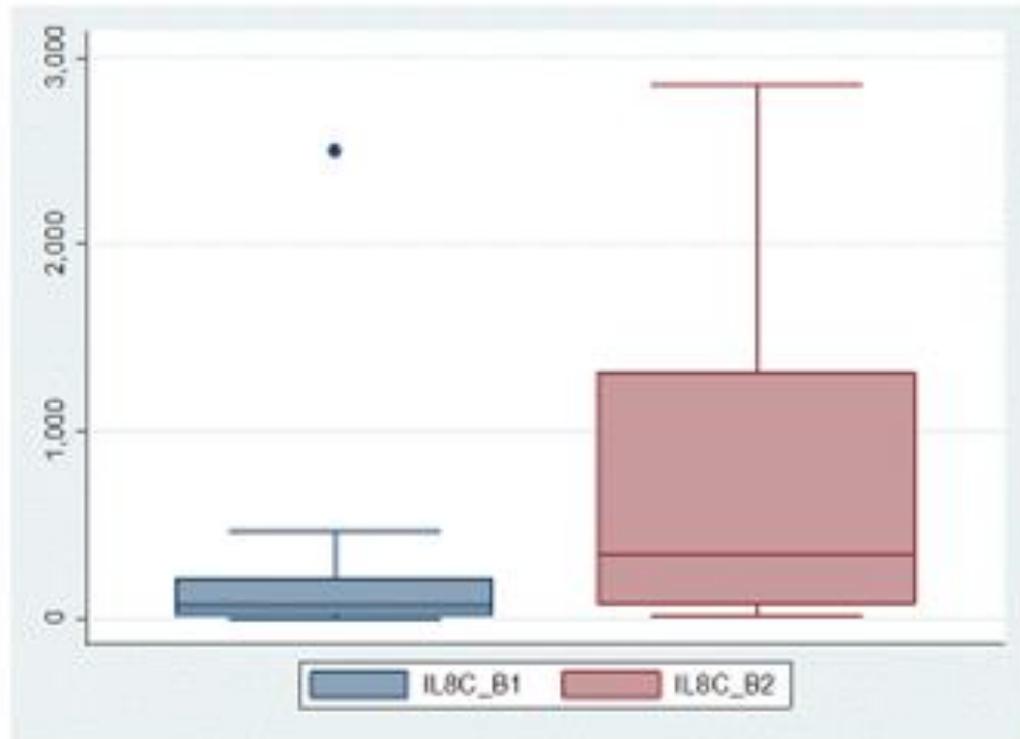
## LINFOCITOS

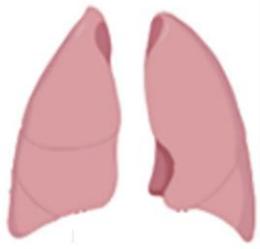




# BIOMARCADORES EN LAVADO BRONCOALVEOLAR (BAL): Rechazo crónico

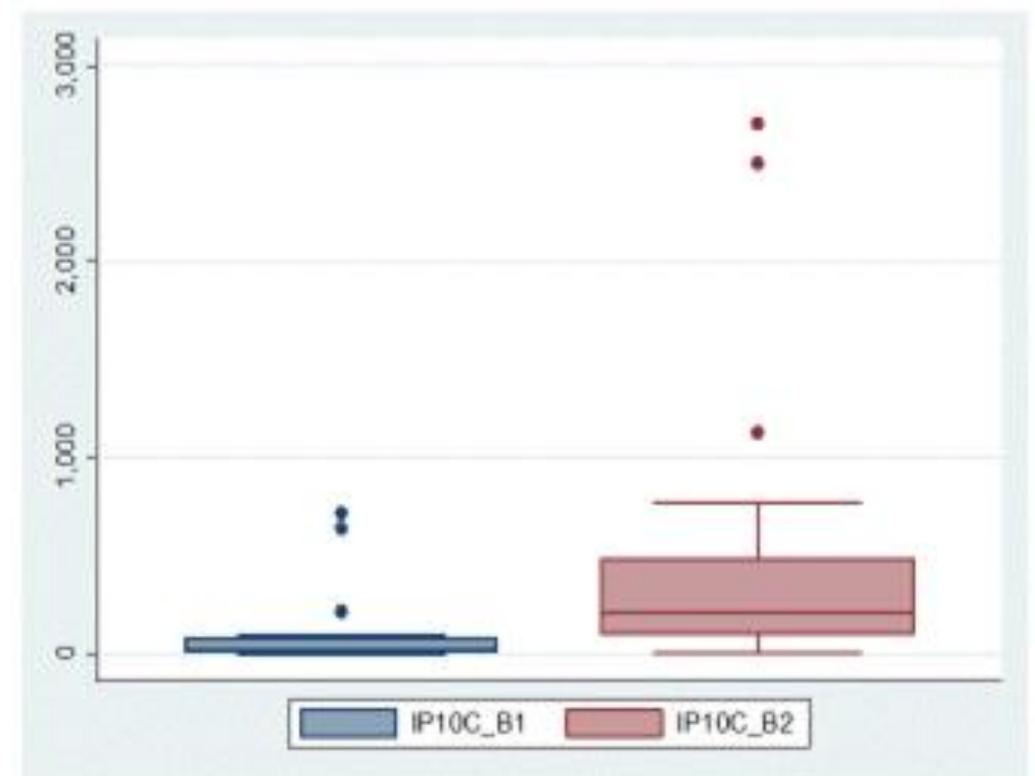
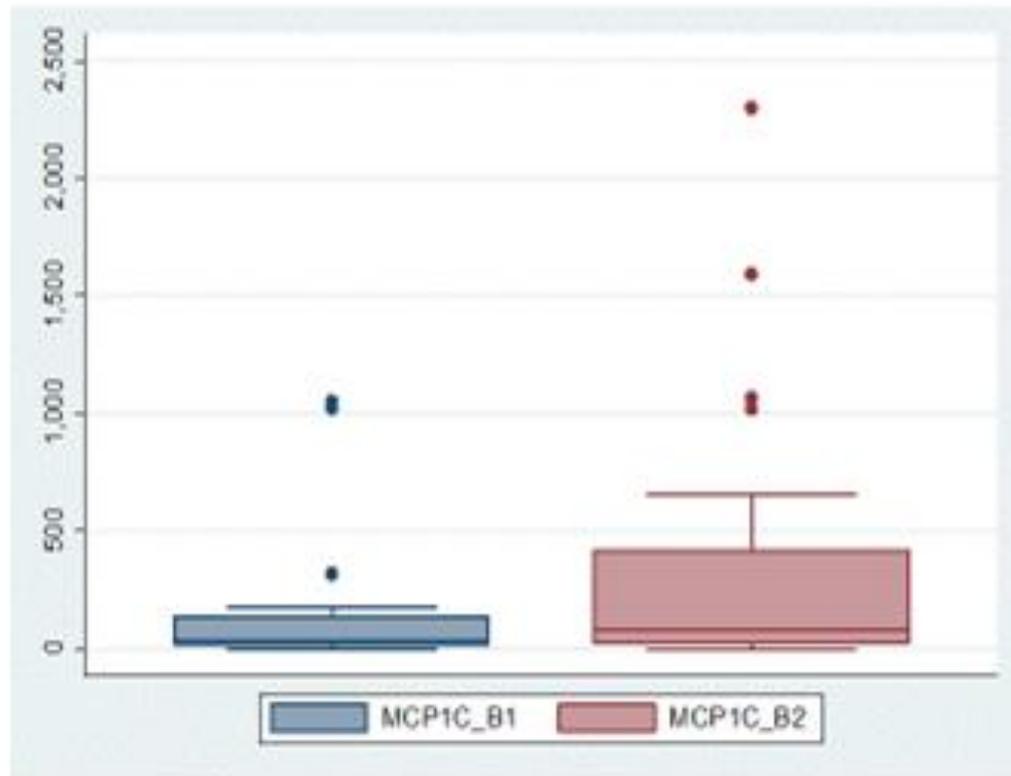
(n= 27 pacientes con BOS)





# BIOMARCADORES EN LAVADO BRONCOALVEOLAR (BAL): Rechazo crónico

(n= 27 pacientes con BOS)



# Biomarcadores de disfunción del injerto en el trasplante pulmonar

