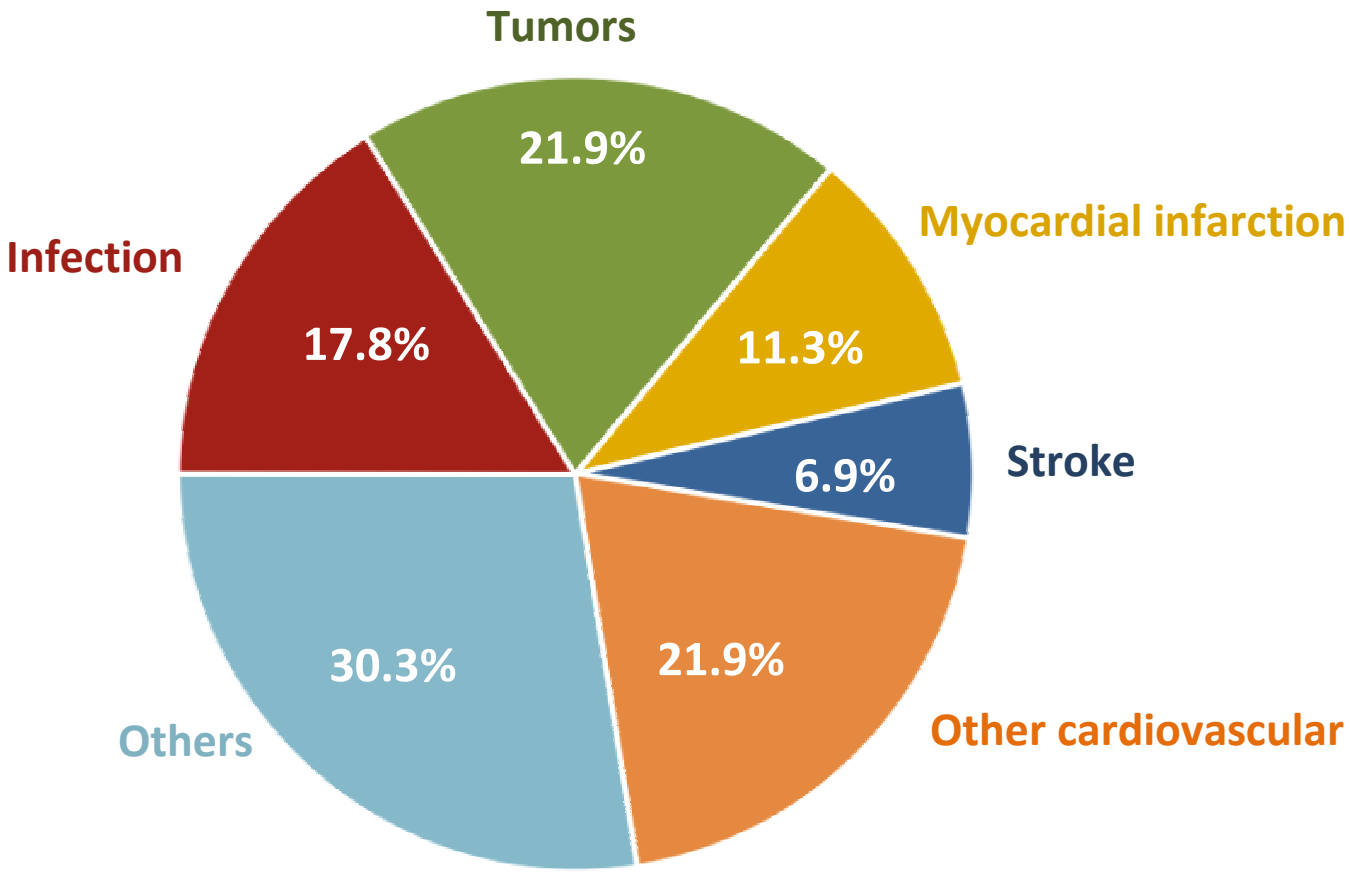
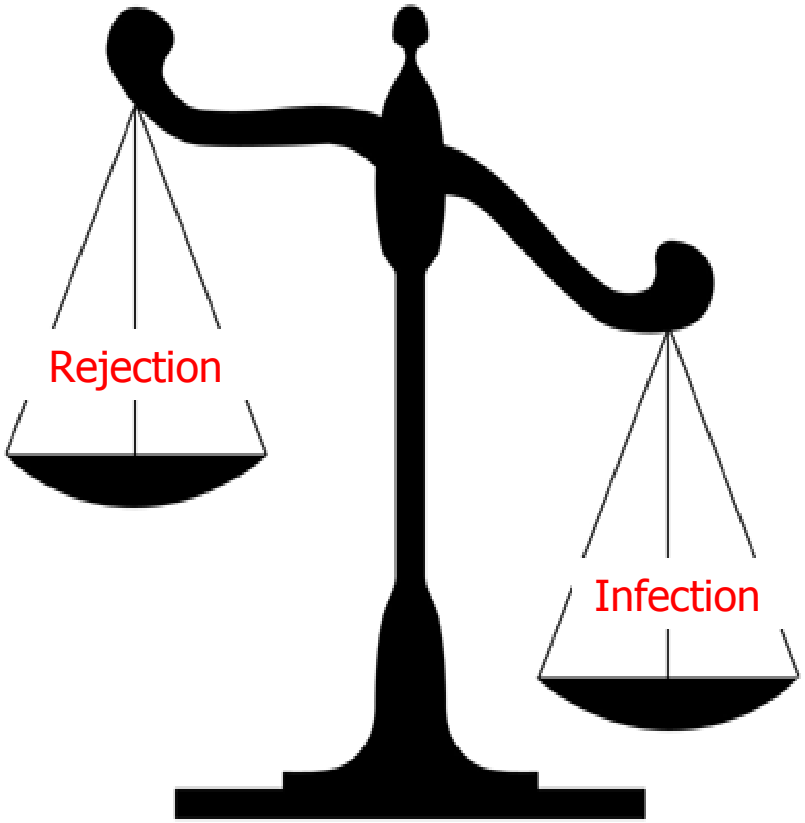
Marcadores Biológicos de Inmunosupresión en Trasplantados de Órgano Sólido

José M. Aguado
Unidad de Enfermedades Infecciosas
Hospital Universitario 12 de Octubre,
Instituto de Investigación I+12
Universidad Complutense de Madrid

Causes of death after kidney transplantation…



United Network for Organ Sharing (UNOS) Annual report 2014


Rejection
Infection

- **Pathogen-specific immune biomarkers**
  - **CMV-specific**
  - **EBV-specific**
  - **BK-specific**

  } **release of Th_1 effector cytokines** (IFN-γ, TNF-α) **upon specific antigen stimulation**

- **Non-pathogen-specific immune biomarkers**
  - **Quantitative**
  - **Functional**

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Non-pathogen-specific immune biomarkers

- **Quantitative**
  - Serum immunoglobulins
  - Serum complement factors
  - Peripheral blood lymphocyte subpopulations
- **Functional**
  - Intracellular ATP in stimulated CD4 T-cells
  - Serum sCD30
  - SNPs in innate immunity genes
  - Viremia as a marker of immunosuppression

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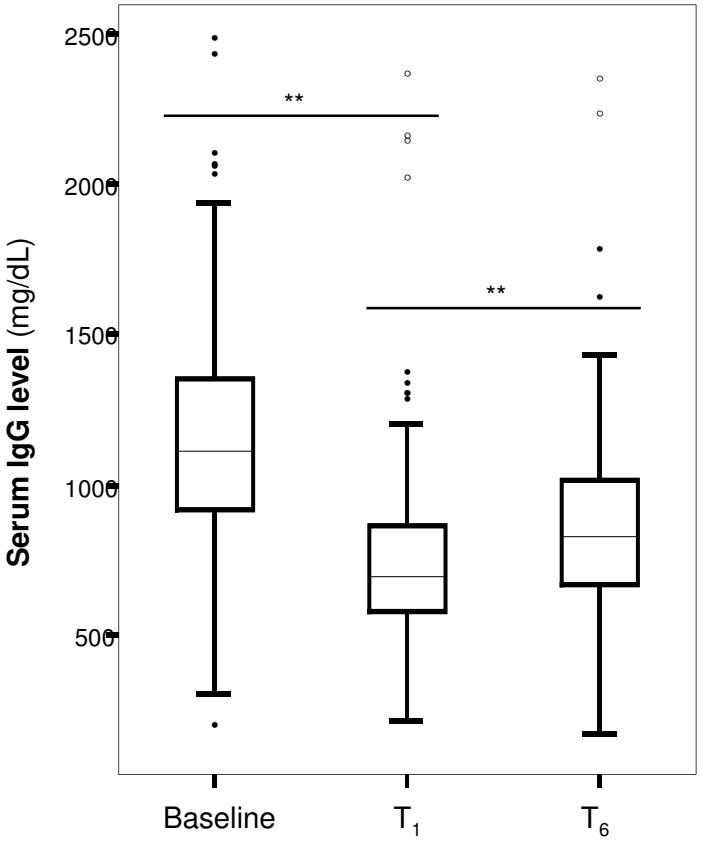
Monitoring of Immunoglobulin Levels Identifies Kidney Transplant Recipients at High Risk of Infection

M. Fernández-Ruiz[a,b,*], F. López-Medrano[a,b], P. Varela-Peña[c], D. Lora-Pablos[d,e], A. García-Reyne[a,b], E. González[f], J. M. Morales[f], R. San Juan[a,b], C. Lumbreras[a,b], E. Paz-Artal[c], A. Andrés[f] and J. M. Aguado[a,b]

Am J Transplant 2012;12:2763-73

226 kidney transplant recipients

- Serum IgG levels at baseline and months 1 and 6
- Assessment of infection at three different periods
  - Early period (first month)
  - Intermediate period (months 1 to 6)
  - Late period (beyond month 6)



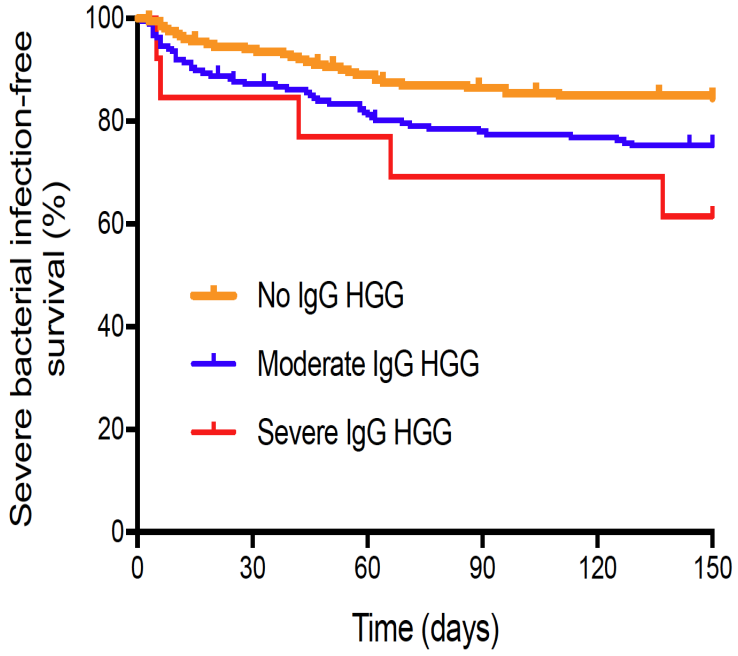
Post-transplant hypogammaglobulinemia and risk of infection after kidney transplantation: Magnitude matters

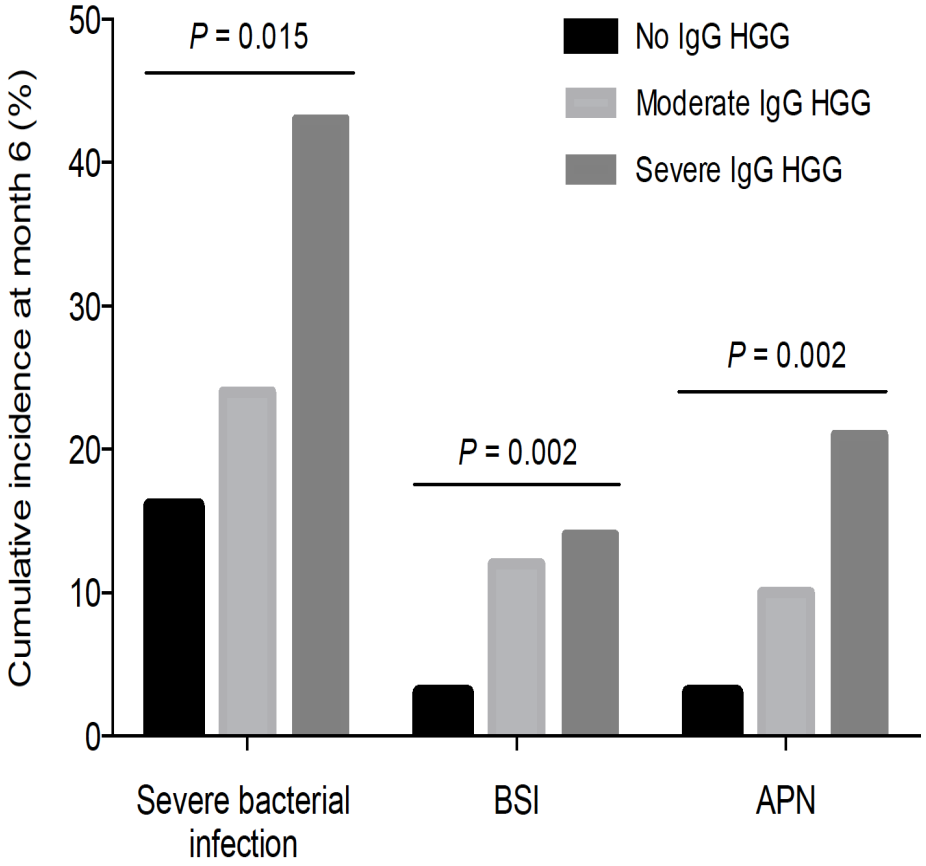
Mario Fernández-Ruiz
Francisco López-Medrano
Rafael San-Juan
José María Aguado
Unit of Infectious Diseases, Hospital Universitario "12 de Octubre", Instituto de Investigación Hospital "12 de Octubre"

Transpl Infect Dis. 2017 Feb;19(1)

407 kidney transplant recipients

- **Serum IgG levels at month 1**





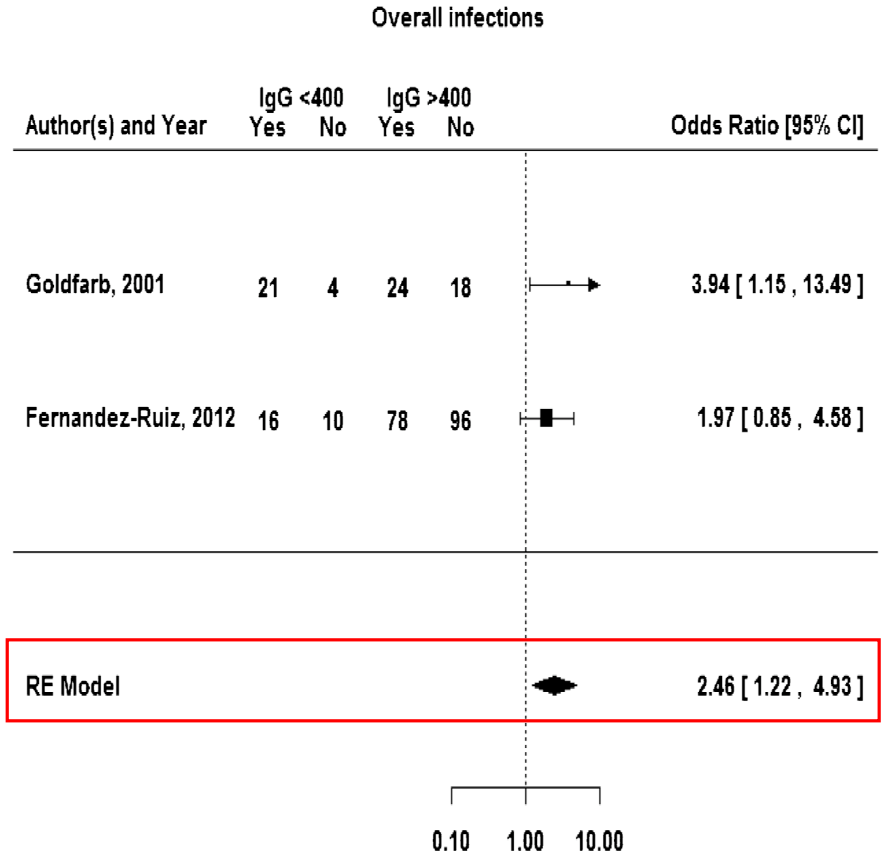
What Is the Impact of Hypogammaglobulinemia on the Rate of Infections and Survival in Solid Organ Transplantation? A Meta-Analysis

Am J Transplant 2013;13:2601-10

D. F. Florescu[1,2,*], A. C. Kalil[1], F. Qiu[3],
C. M. Schmidt[4] and U. Sandkovsky[1]

Severe IgG HGG (<400 mg/dL)

- **OR for respiratory tract infection:** 4.83; *P* = 0.004
- **OR for CMV disease:** 2.40; *P* = 0.002
- **OR for IPA:** 8.19; *P* = 0.0009



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Hypocomplementemia in Kidney Transplant Recipients: Impact on the Risk of Infectious Complications

Am J Transplant 2013;13:685-94

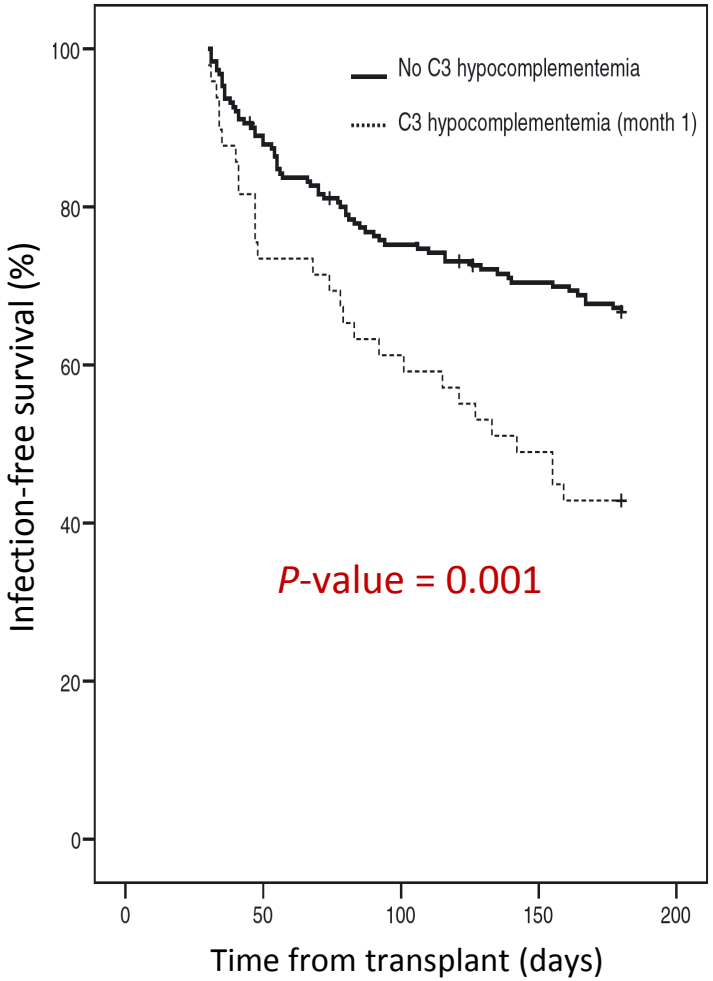
M. Fernández-Ruiz[a,*], F. López-Medrano[a], P. Varela-Peña[b], J. M. Morales[c], A. García-Reyne[a], R. San Juan[a], C. Lumbreras[a], D. Lora-Pablos[d,e], N. Polanco[c], A. Andrés[c], E. Paz-Artal[b] and J. M. Aguado[a]

270 kidney transplant recipients

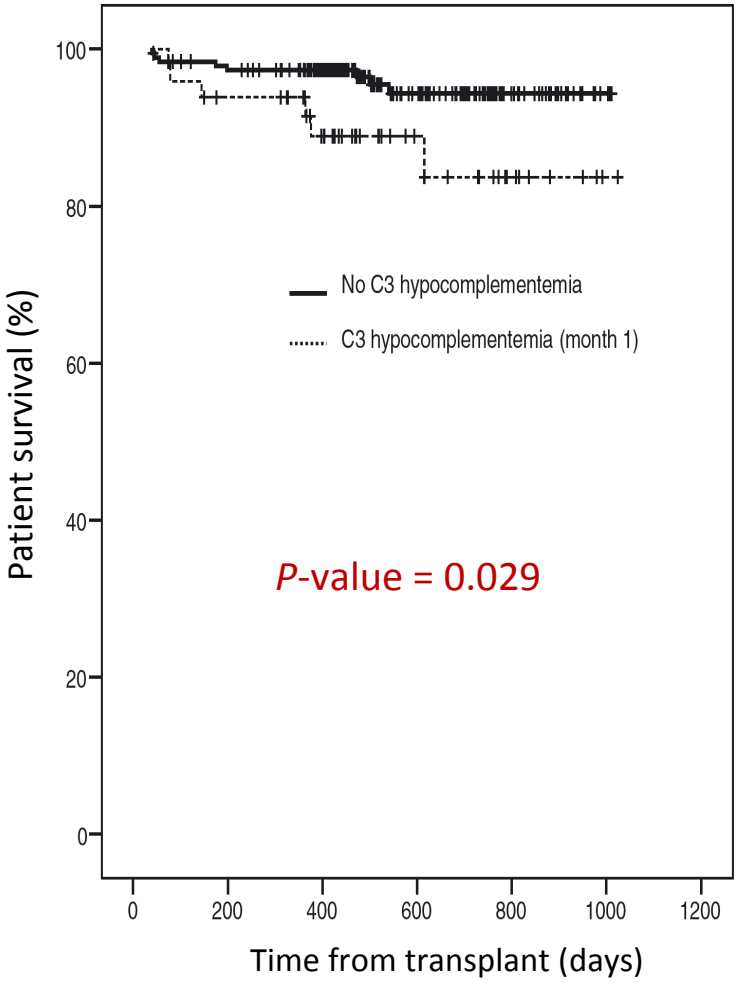
- **Serum C3 and C4 levels at baseline and months 1 and 6**
- **Nephelometry**

Incidence of infection in the intermediate posttransplant period (months 1–6) (%)	C3 hypocomplementemia at month 1		
	Present (n = 49)	Absent (n = 191)	p-Value
Any infection	28 (57.1)	63 (33.0)	0.002
Episodes (mean number ± SD)	1.2 ± 1.3	0.6 ± 0.9	0.000
Incidence rate[1]	8.2	4.0	0.000
Bacterial infection	18 (36.7)	34 (17.8)	0.004
Bloodstream infection	6 (12.2)	13 (6.8)	0.167
Pneumonia	6 (12.2)	8 (4.2)	0.043
APN	6 (12.2)	10 (5.2)	0.082
Intraabdominal infection	3 (6.1)	6 (3.1)	0.271
Fungal infection	6 (12.2)	6 (3.1)	0.019
CMV disease	17 (34.7)	42 (22.0)	0.065
CMV end-organ disease	4 (8.2)	8 (4.2)	0.212
Non-CMV viral infection	7 (14.3)	8 (4.2)	0.017
HSV or VVZ infection	6 (12.2)	3 (1.6)	0.003

Overall infection



Patient survival



Am J Transplant 2013;13:2601-10

Non-pathogen-specific immune biomarkers

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  - SNPs in innate immunity genes
  - Viremia as a marker of immunosuppression

ORIGINAL ARTICLE

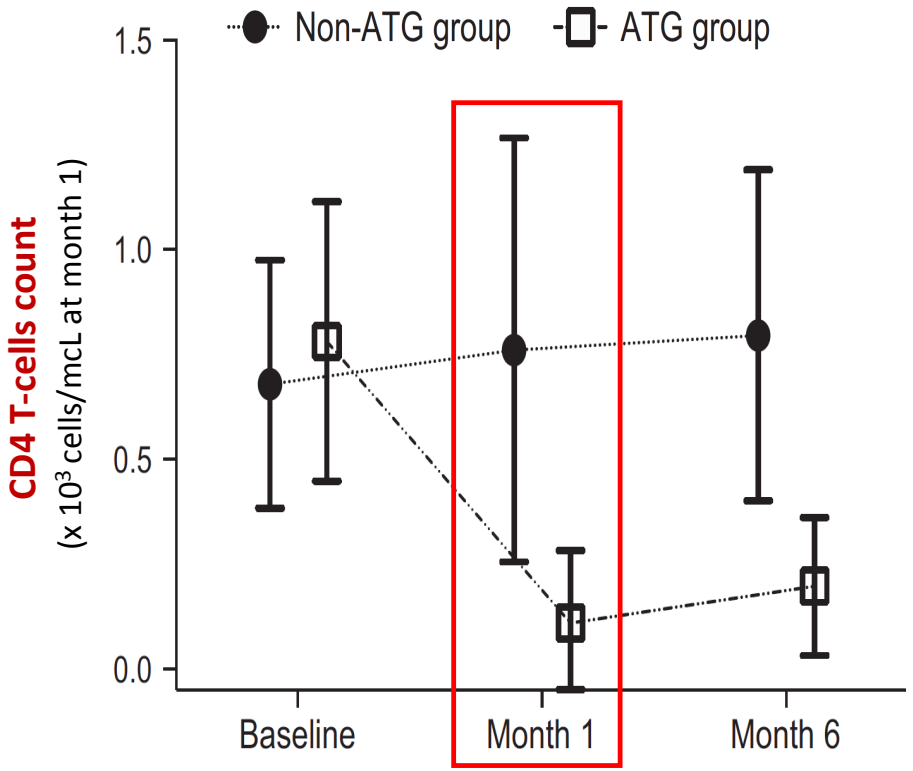
Kinetics of peripheral blood lymphocyte subpopulations predicts the occurrence of opportunistic infection after kidney transplantation

Transpl Int 2014;27:674-85

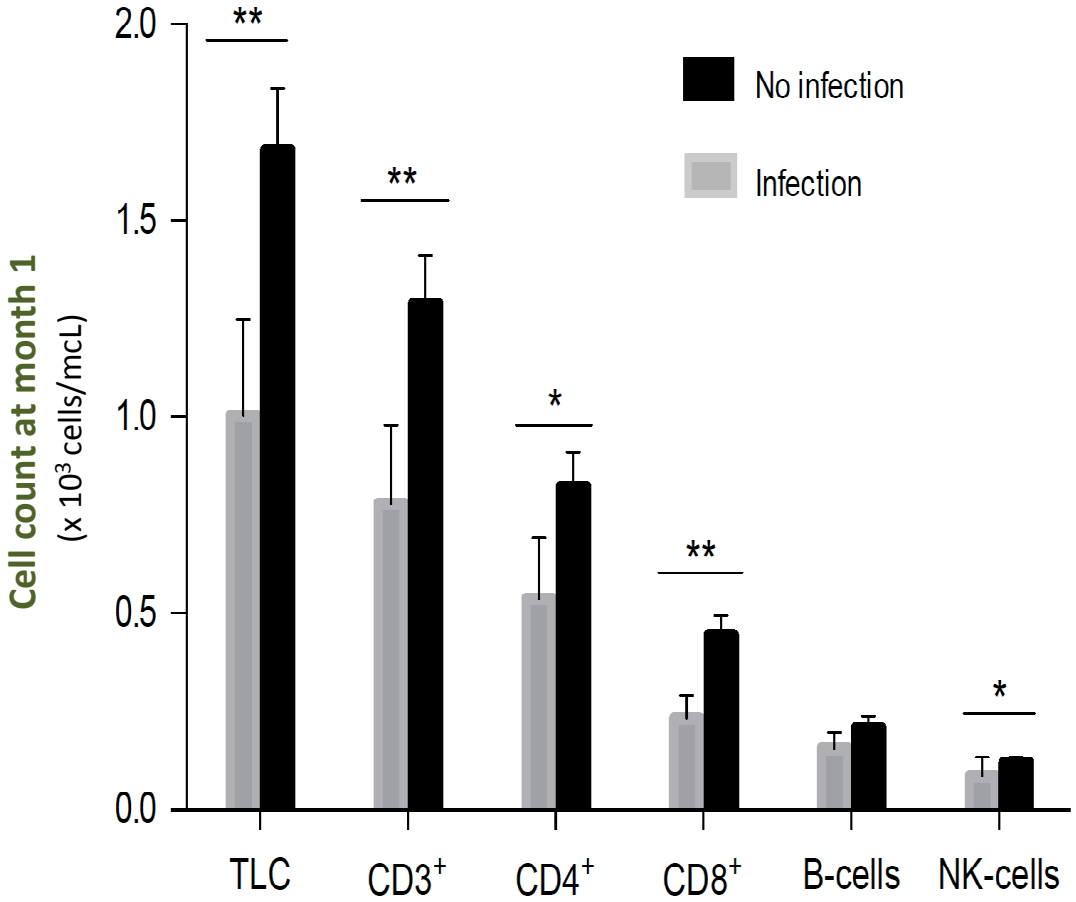
Mario Fernández-Ruiz,[1] Francisco López-Medrano,[1] Luis M. Allende,[2] Amado Andrés,[3] Ana García-Reyne,[1] Carlos Lumbreras,[1] Rafael San-Juan,[1] José M. Morales,[3] Estela Paz-Artal[2] and José M. Aguado[1]

304 kidney transplant recipients

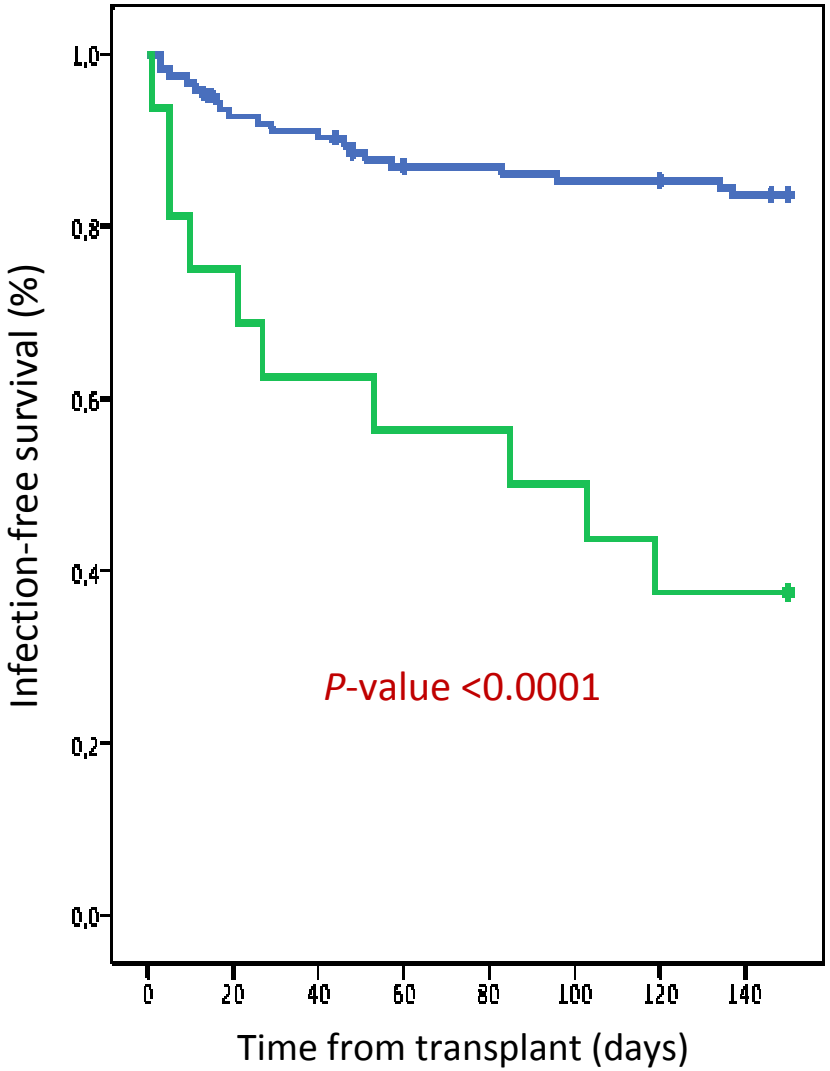
- Peripheral blood lymphocyte populations
- Automated flow cytometry
- Stratified analysis by the use of antithymocyte globulin (ATG) as induction therapy
- auROC analysis to find optimal cut-off values



Patients not receiving ATG as induction therapy



Transpl Int 2014;27:674-85

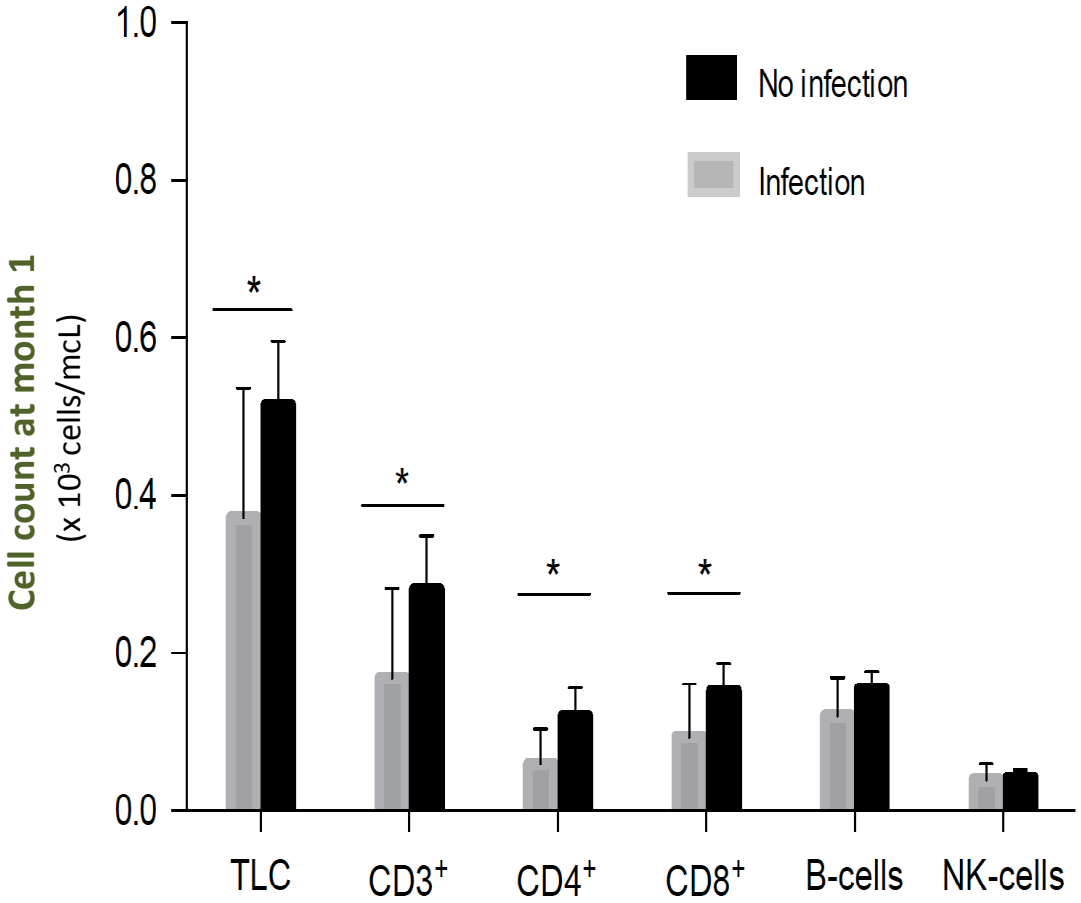


CD8 T-cell count at month 1

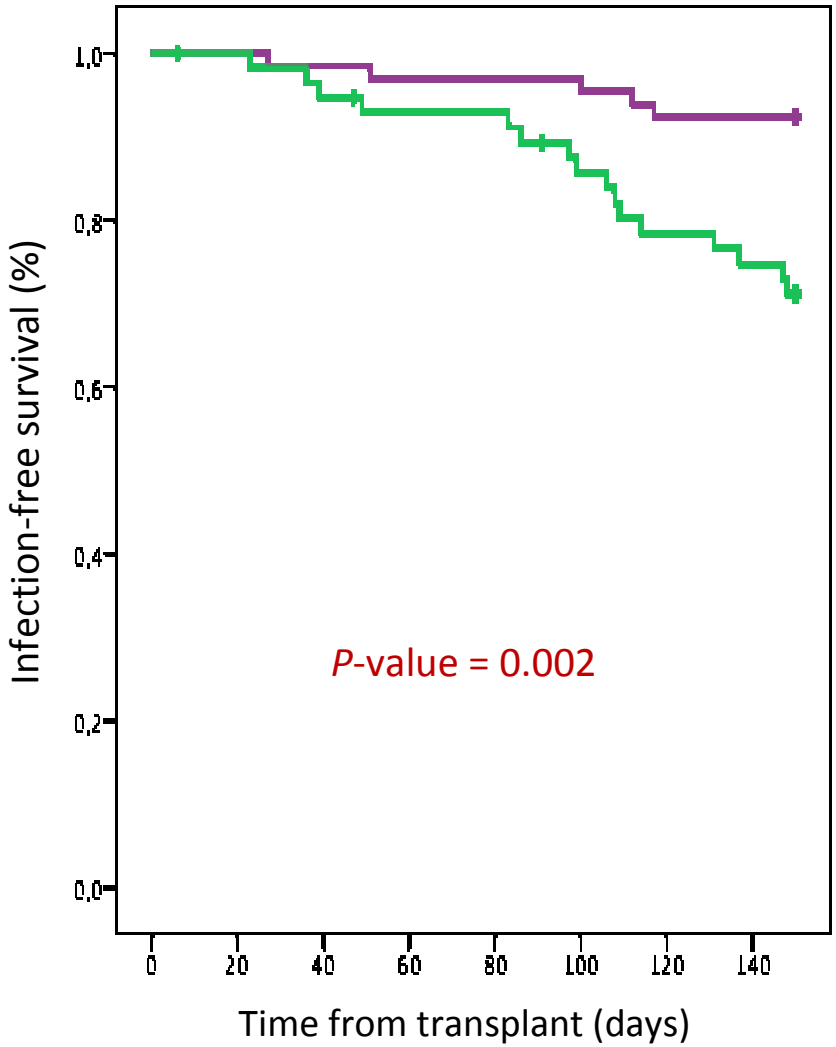
- ≥0.100 x 10^3/µL
- <0.100 x 10^3/µL

Transpl Int 2014;27:674-85

Patients receiving ATG as induction therapy



Transpl Int 2014;27:674-85



Transpl Int 2014;27:674-85

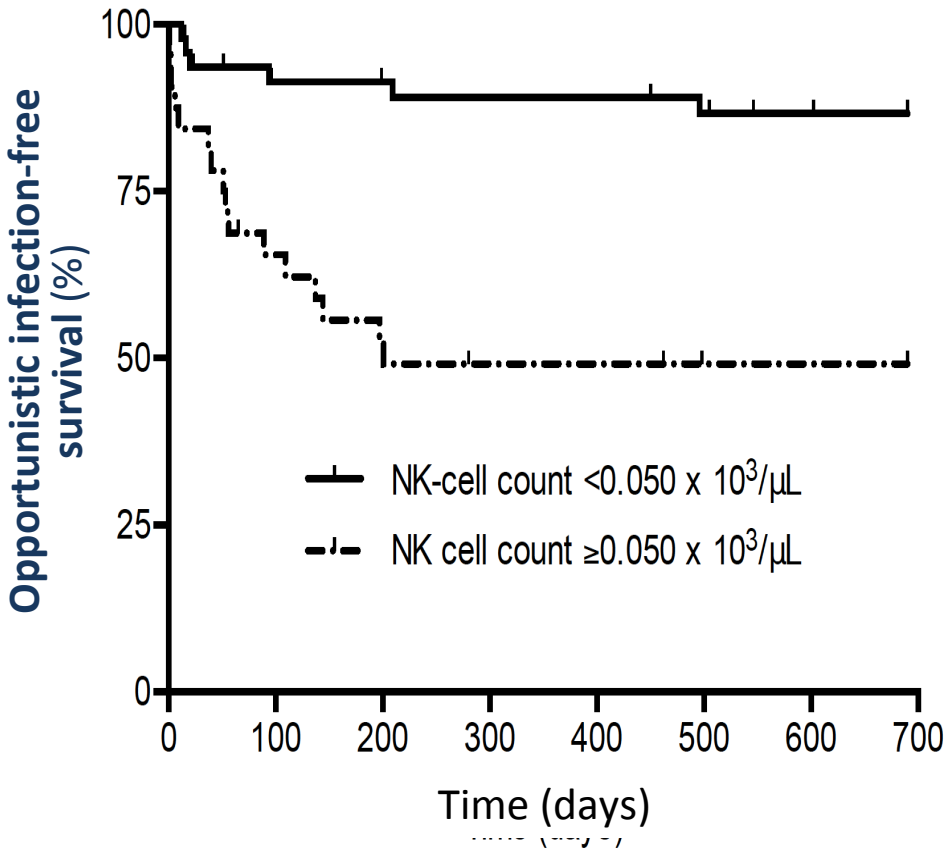
Post-transplant monitoring of NK cell counts as a simple approach to predict the occurrence of opportunistic infection in liver transplant recipients

Transpl Infect Dis 2016:18:552–65

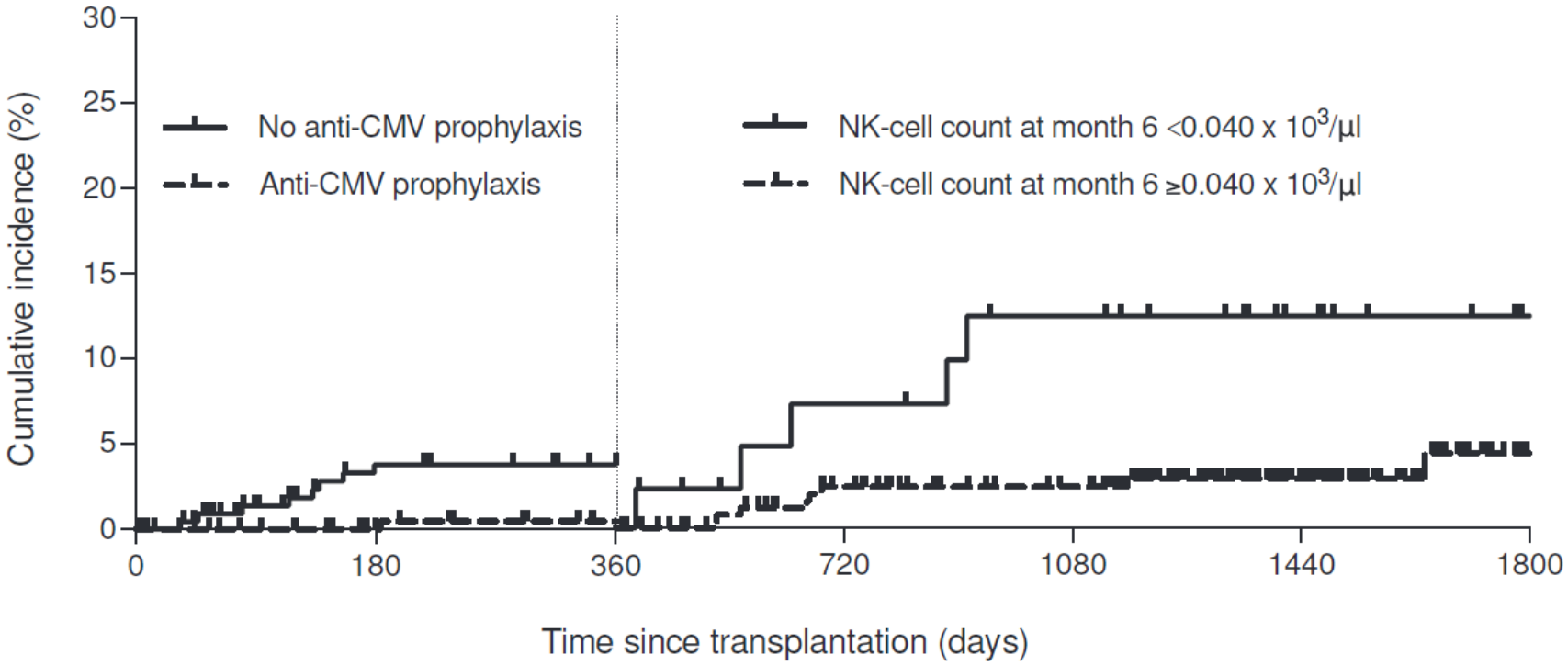
M. Fernández-Ruiz[1], J.T. Silva[1],
F. López-Medrano[1], L.M. Allende[2],
R. San Juan[1], F. Cambra[3], I. Justo[3],
E. Paz-Artal[2], C. Jiménez[3],
J.M. Aguado[1]

92 liver transplant recipients

- Peripheral blood lymphocyte populations at months 1 and 6 by automated flow cytometry
- Opportunistic infection



Herpes zoster in kidney transplant recipients: protective effect of anti-cytomegalovirus prophylaxis and natural killer cell count. A single-center cohort study

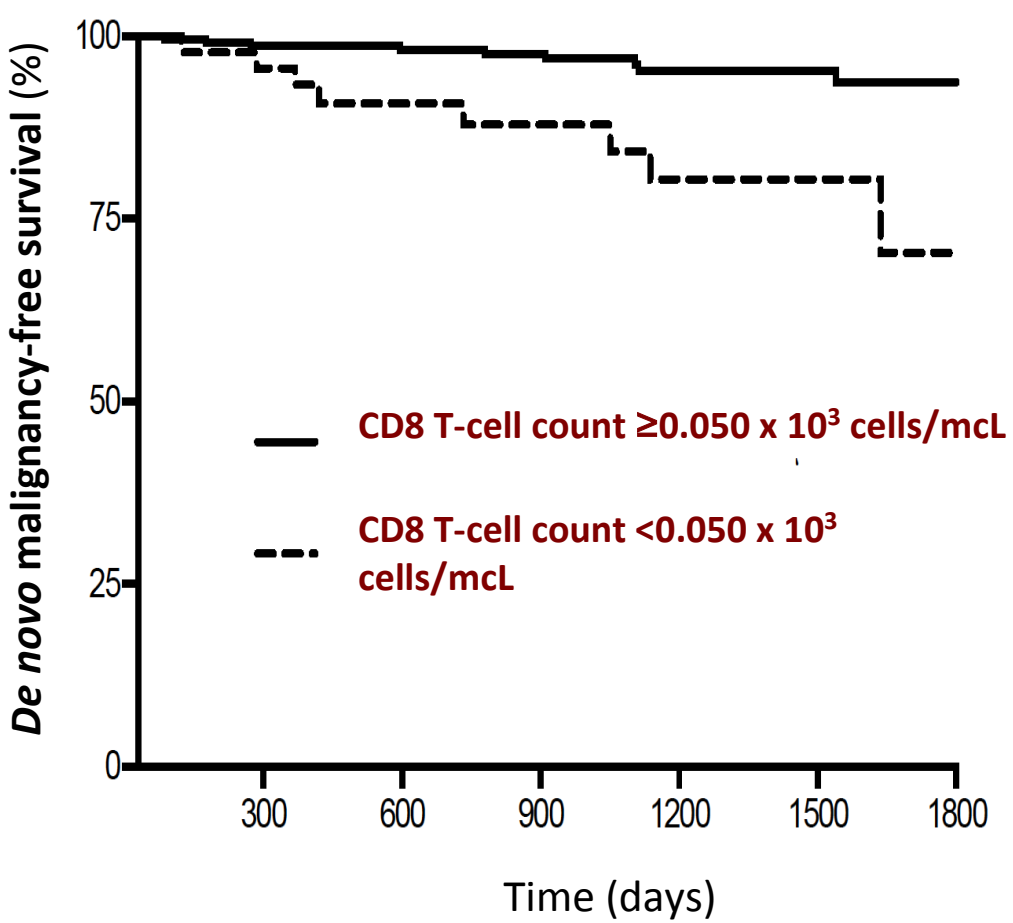


Fernández-Ruiz M, et al. Transpl Int. 2017 Sep 22. doi: 10.1111/tri.13076.

Assessing the Risk of De Novo Malignancy in Kidney Transplant Recipients: Role for Monitoring of Peripheral Blood Lymphocyte Populations

Transplantation 2014; 98: e36-7.

Mario Fernández-Ruiz[1]
Francisco López-Medrano[1]
Luis M. Allende[2]
Amado Andrés[3]
Estela Paz-Artal[2]
José María Aguado[1]



Adjusted HR for post-transplant cancer: 5.03; 95% CI: 1.82-13.91; *P*-value = 0.002

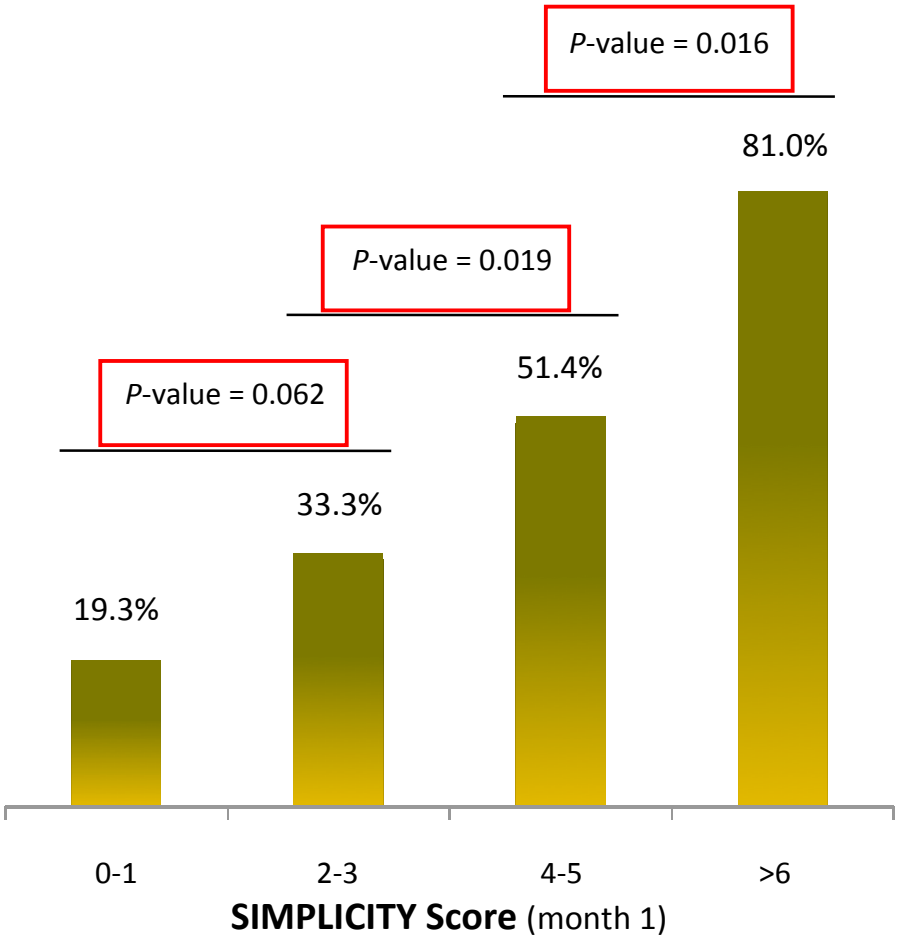
A simple post-transplant immunological score accurately predicts the risk of infection in kidney transplant recipients

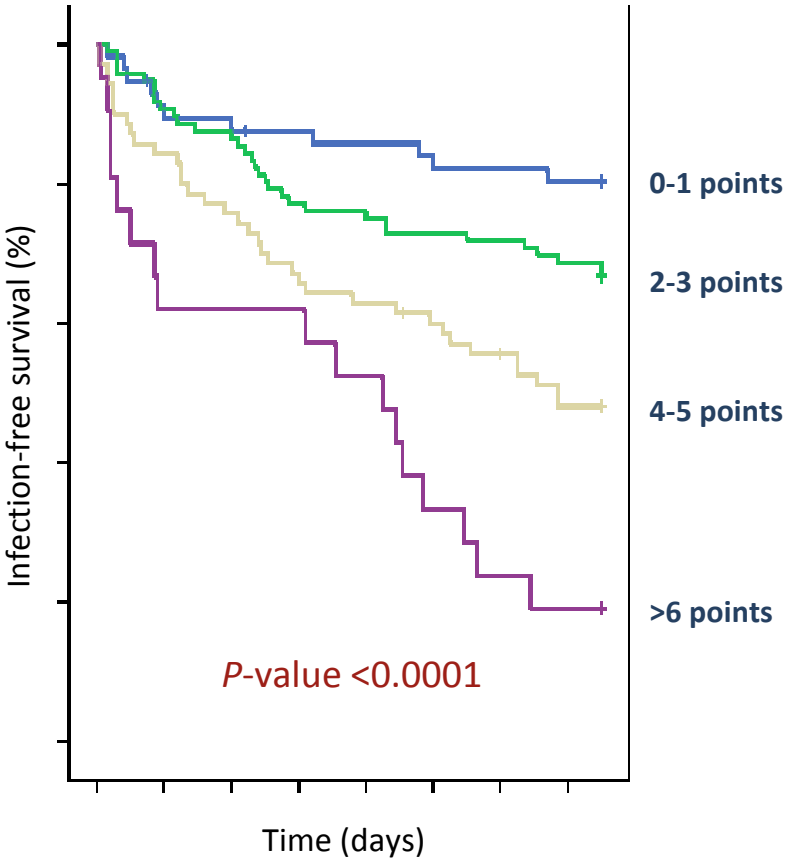
Fernández-Ruiz M *et al.* American Transplant Congress 2013 (oral communication)

SIMPLICITY Score (Seeking for Immune Status based on Peripheral Blood Lymphocytes, Immunoglobulins and Complement Activity)

Parameter (month 1)	Points
Severe IgG hypogammaglobulinemia (<400 mg/dL)	4
$CD8^+$ T-cell lymphocytopenia (<0.150 x 10^3/mcL)	3
B-cell lymphocytopenia (<0.100 x 10^3/mcL)	2
C3 hypocomplementemia (<83 mg/dL)	2

- ***Cumulative incidence of infection at month 6***





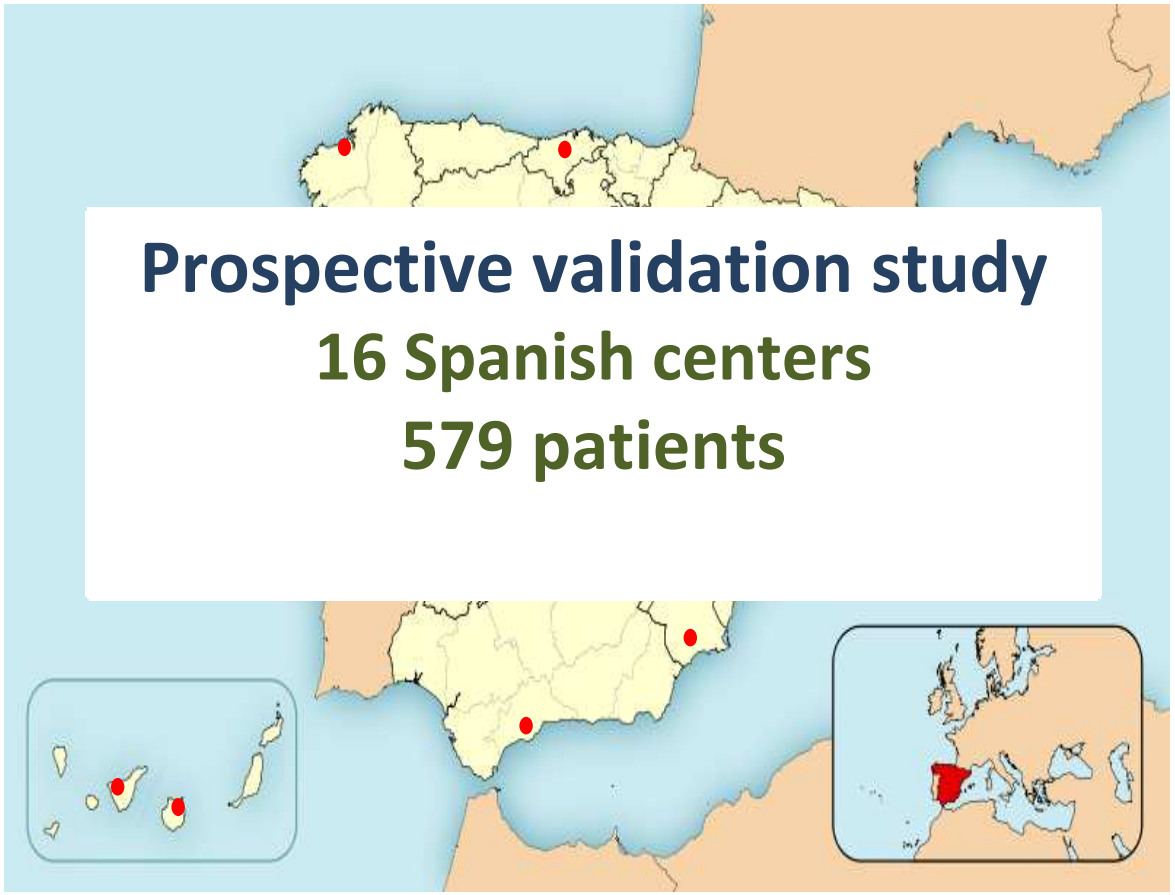
Fernández-Ruiz M *et al.* ATC 2013 (oral communication)

estudio SIMPLICITY

INFECCIONES EN TRASPLANTE RENAL

www.e-clinical.org/simplicity

Estudio observacional prospectivo para la validación de un score de riesgo de desarrollo de infecciones oportunistas en pacientes trasplantados renales



Prospective validation study

16 Spanish centers

579 patients

Non-pathogen-specific immune biomarkers

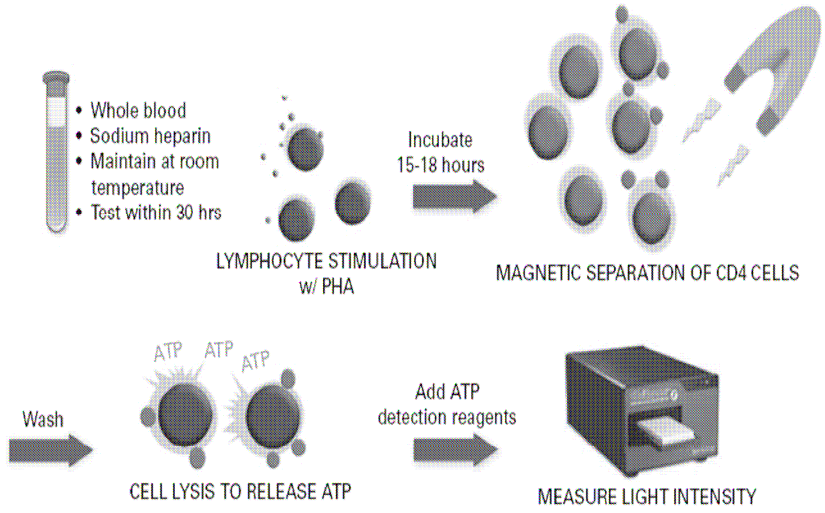
- **Quantitative**
  - Serum immunoglobulins
  - Serum complement factors
  - Peripheral blood lymphocyte subpopulations
- **Functional**
  - **Intracellular ATP in stimulated CD4 T-cells**
  - Serum sCD30
  - SNPs in innate immunity genes
  - Viremia as a marker of immunosuppression

ORIGINAL ARTICLE

Monitoring of intracellular adenosine triphosphate in CD4$^+$ T cells to predict the occurrence of cytomegalovirus disease in kidney transplant recipients

María Asunción Pérez-Jacoiste Asín[1,*], Mario Fernández-Ruiz[1,*], Francisco López-Medrano[1], Carolina Aquilino[2], Esther González[3], Tamara Ruiz-Merlo[1], Eduardo Gutiérrez[3], Rafael San Juan[1], Estela Paz-Artal[2], Amado Andrés[3] & José Maria Aguado[1]

Transpl Int 2016;29:1094-105

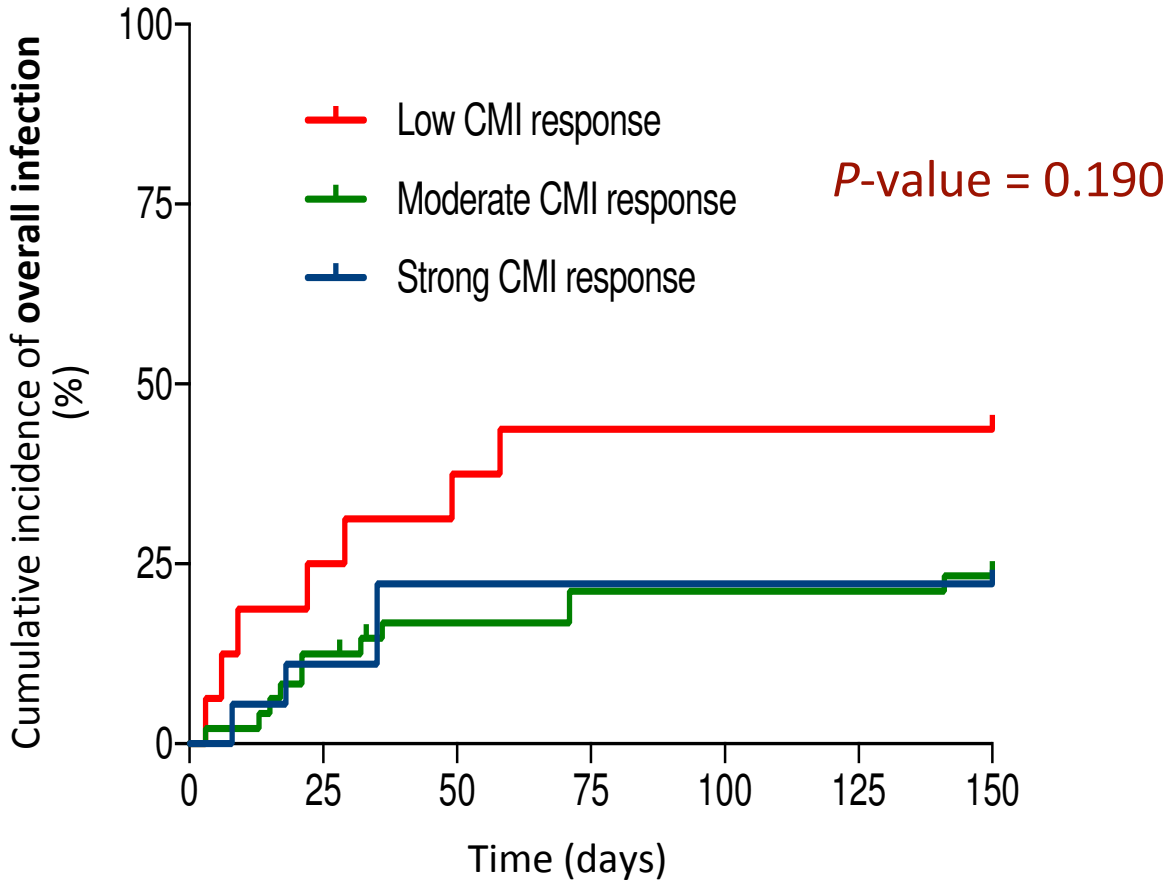


FDA-approved since 2002

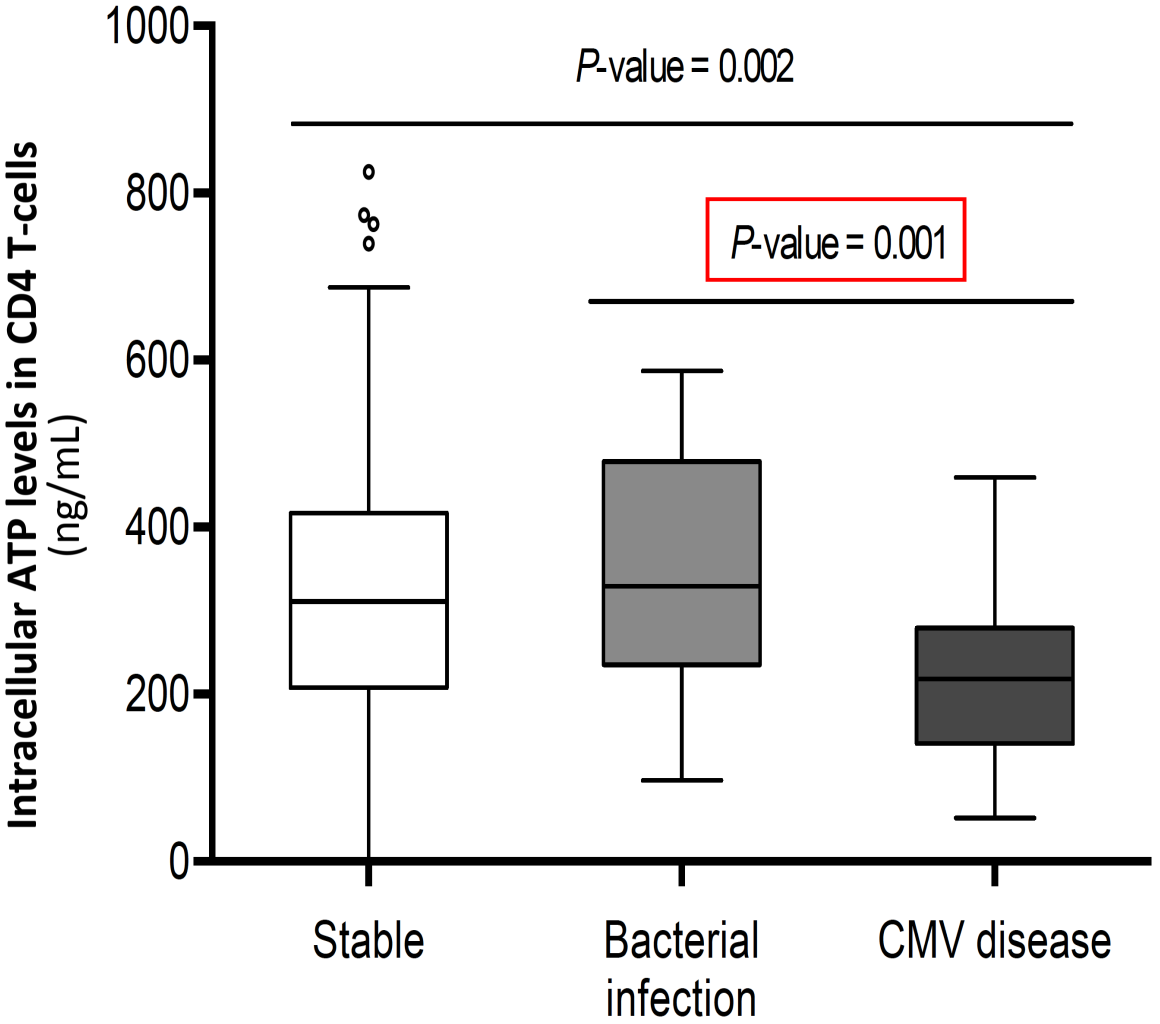
Suboptimal test performance to predict overall infection

Transplantation 2012;93:737-43

- ***Occurrence of overall infection according to iATP levels***

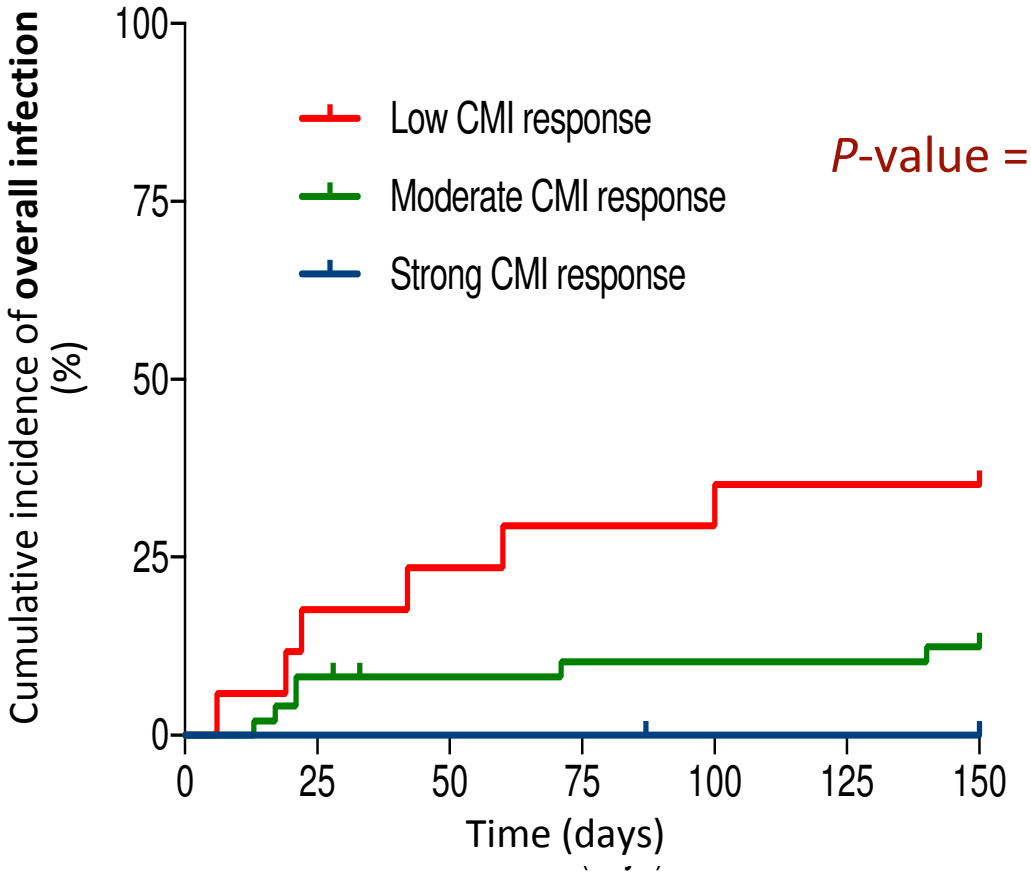


Transpl Int 2016;29:1094-105



Transpl Int 2016;29:1094-105

- ***Occurrence of CMV disease according to iATP levels***



P-value = 0.008

Transpl Int 2016;29:1094-105

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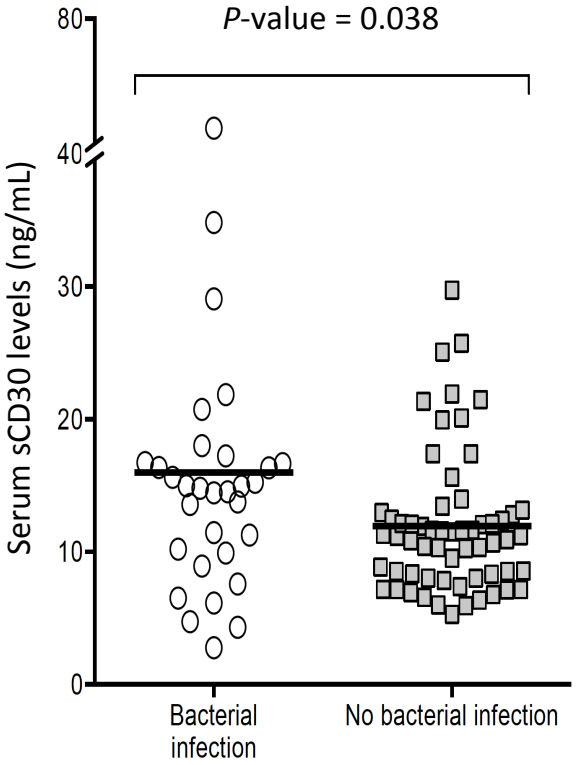
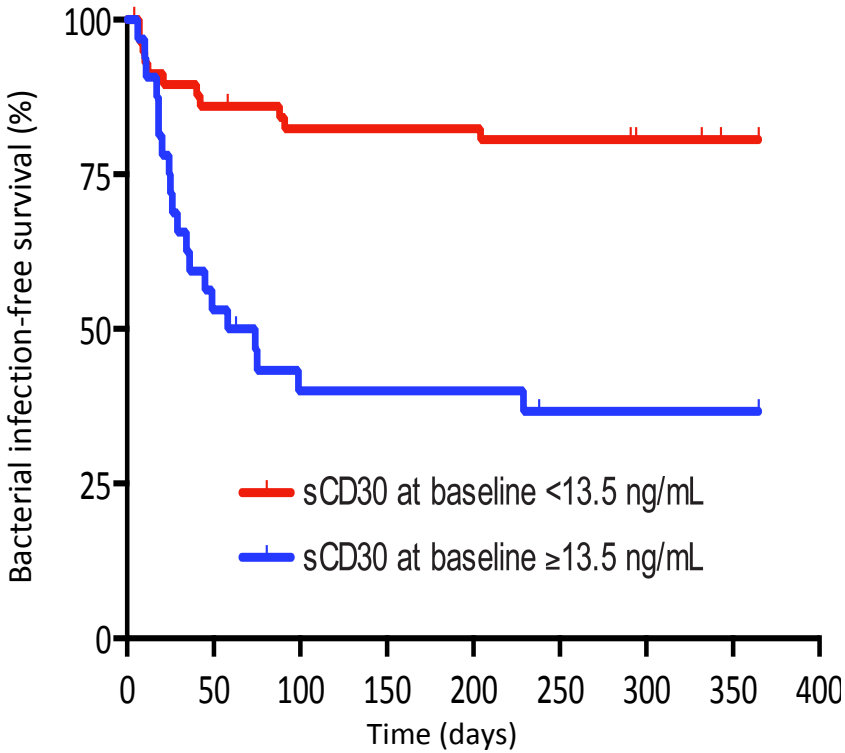
ORIGINAL ARTICLE

Serum sCD30: A promising biomarker for predicting the risk of bacterial infection after kidney transplantation

Transpl Infect Dis 2017 Apr;19(2)

Mario Fernández-Ruiz[1] | Patricia Parra[1] | Francisco López-Medrano[1] | Tamara Ruiz-Merlo[1] | Esther González[1] | Natalia Polanco[2] | Julia Origüen[1] | Rafael San Juan[1] | Amado Andrés[2] | José María Aguado[1]





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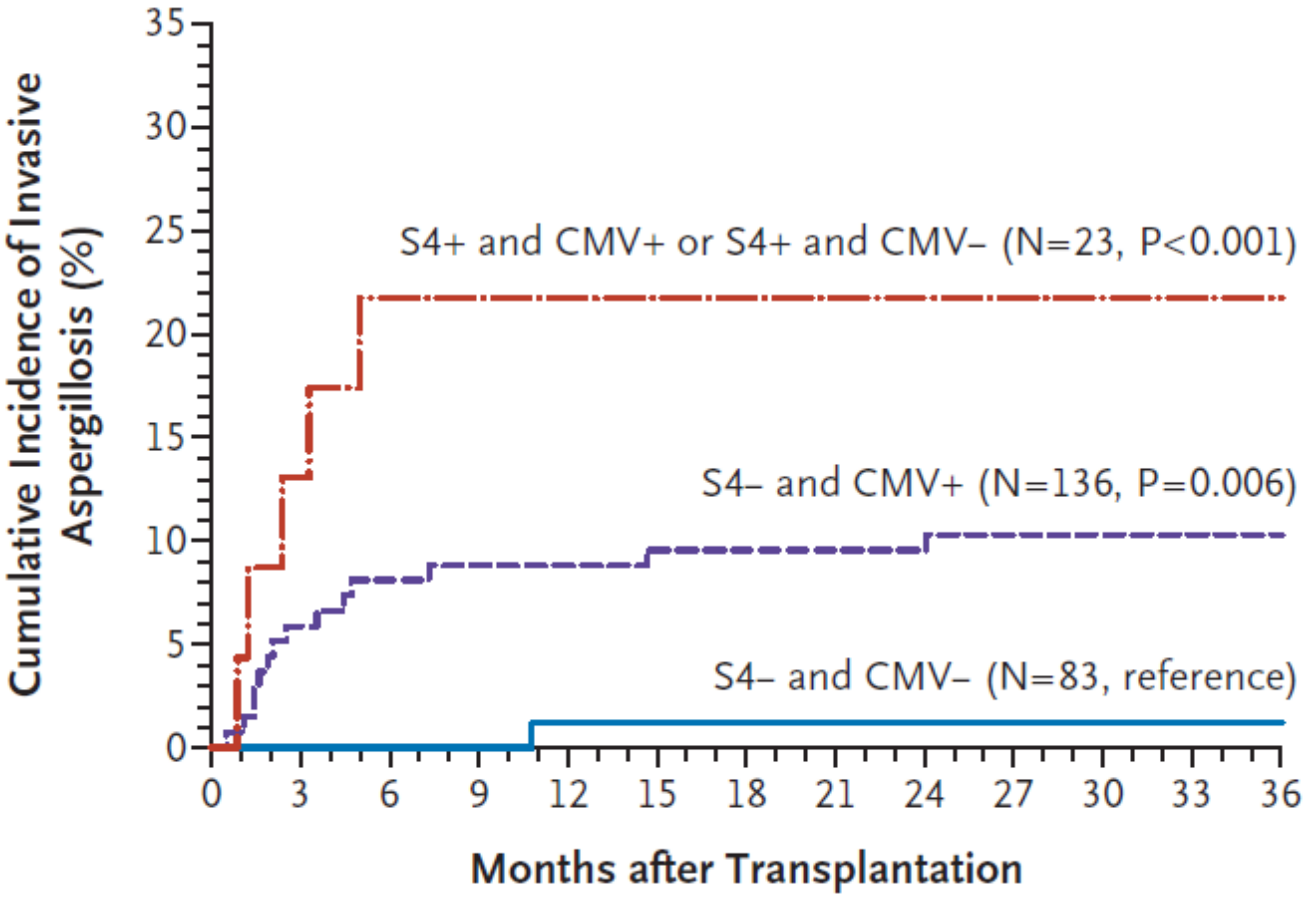
Polimorfirmos de TLR-4 y riesgo de aspergillosis en HSCT

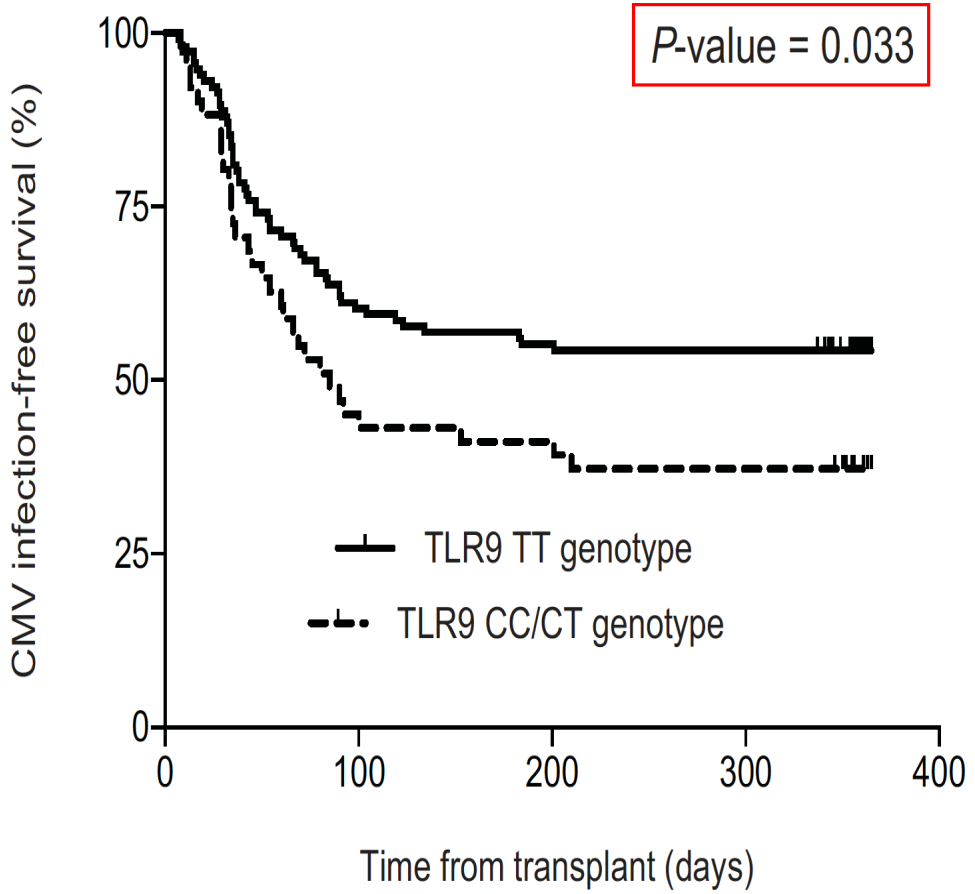


Bochud PY et al. N Engl J Med 2008; 359:1766

Association Between Individual and Combined SNPs in Genes Related to Innate Immunity and Incidence of CMV Infection in Seropositive Kidney Transplant Recipients

Am J Transplant 2015;15:1323-35

M. Fernández-Ruiz[1,†], I. Corrales[2,†], M. Arias[3], J. M. Campistol[4], E. Giménez[2], J. Crespo[5], M. O. López-Oliva[6], I. Beneyto[7], P. L. Martín-Moreno[8], F. Llamas-Fuente[9], A. Gutiérrez[10], T. García-Álvarez[11], R. Guerra-Rodríguez[12], N. Calvo[13], A. Fernández-Rodríguez[14], J. M. Tabernero-Romo[15], M. D. Navarro[16], A. Ramos-Verde[17], J. M. Aguado[1] and D. Navarro[2,*] on behalf of the OPERA Study Group[‡]



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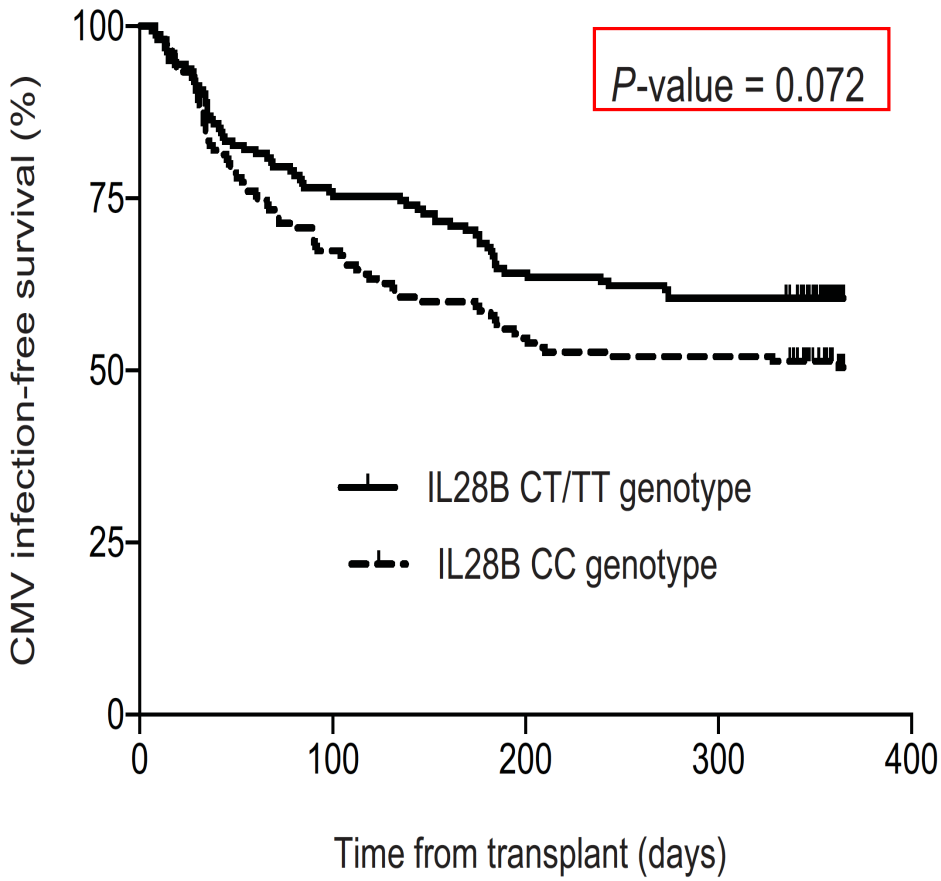
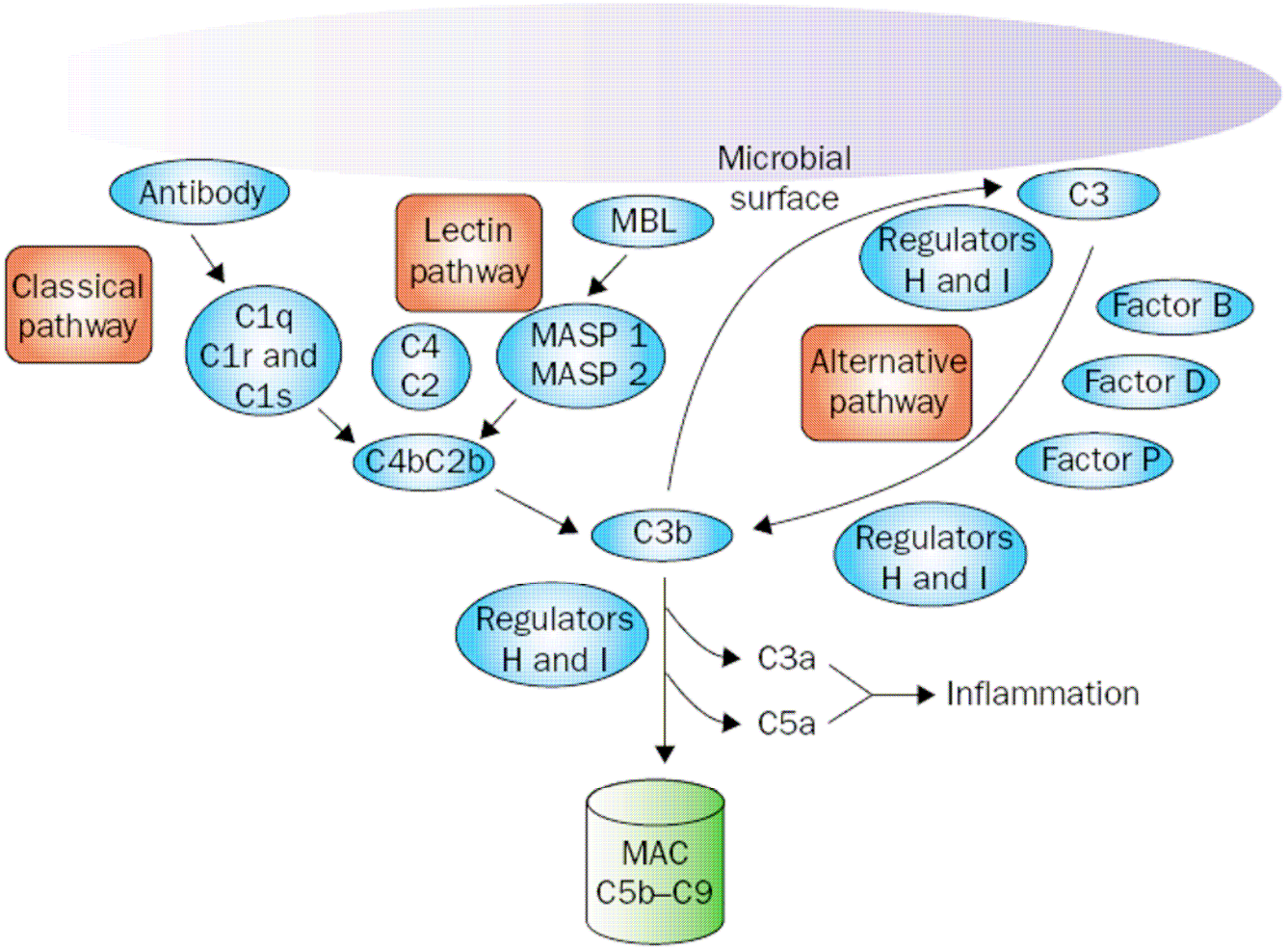


Combined effects of unfavorable genotypes of selected SNPs on CMV-infection free survival

Number of unfavorable genotypes[1]	Overall cohort (n = 315)			
	n	aHR[2]	95% CI	p-Value
0–1	77	1	–	–
2	142	2.29	1.37–3.82	0.002
3–4	96	2.36	1.38–4.03	0.002

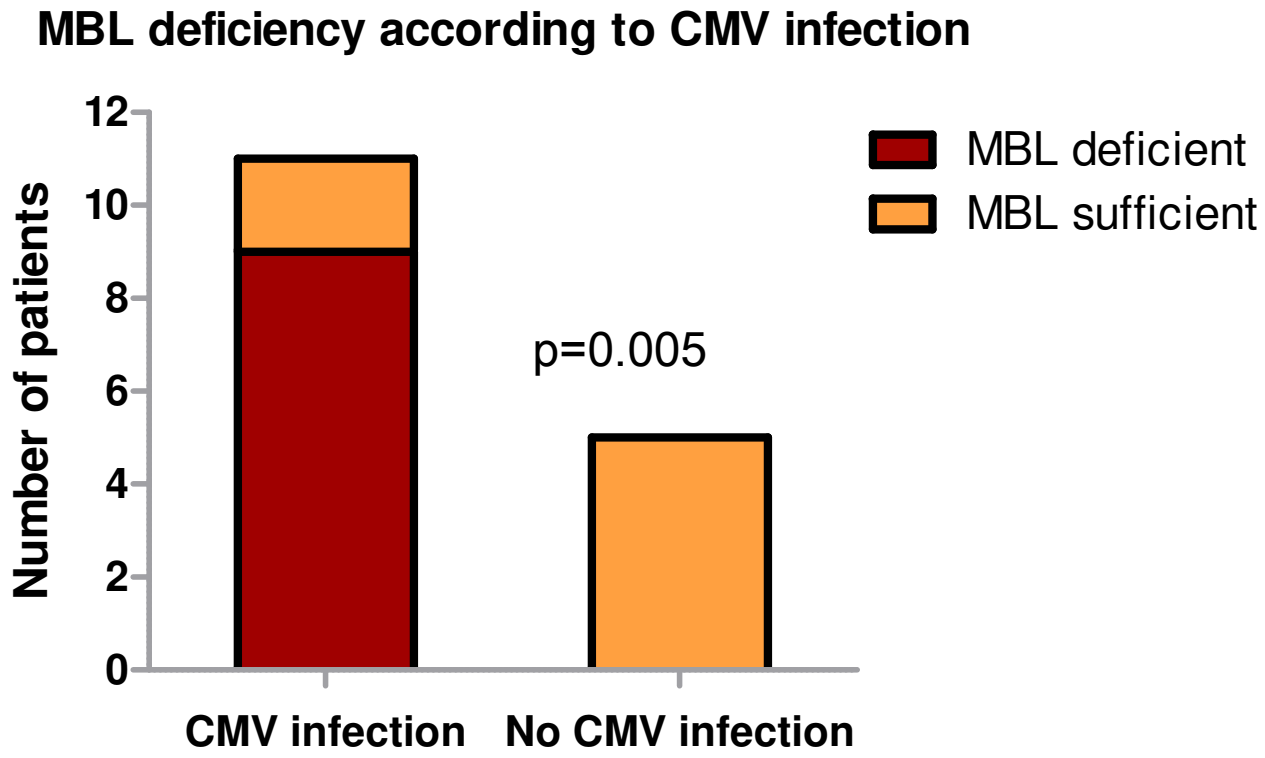
Am J Transplant 2015;15:1323-35

Mannose binding lectin (MBL)



Emonts et al. Lancet ID. 2003; 3: 565

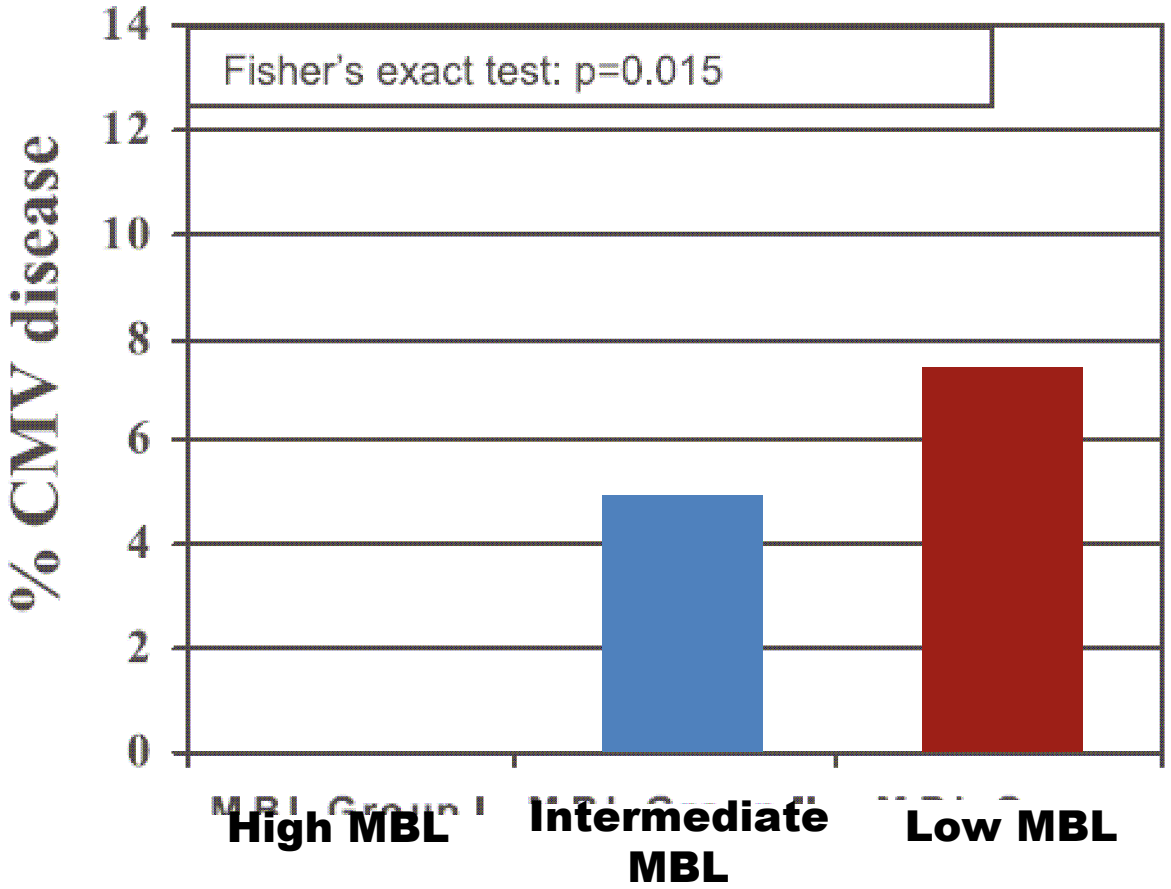
Déficit de MBL y infección por CMV



Manuel et al. Transplantation. 2007; 83: 359

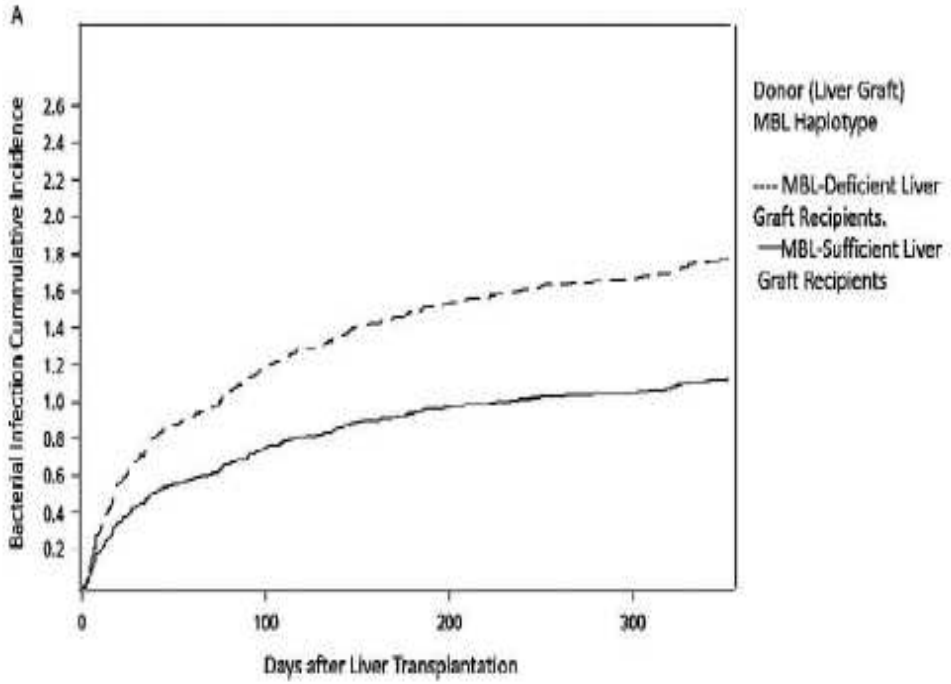
Déficit de MBL y infección por CMV

195 trasplantados renales seropositivos al CMV



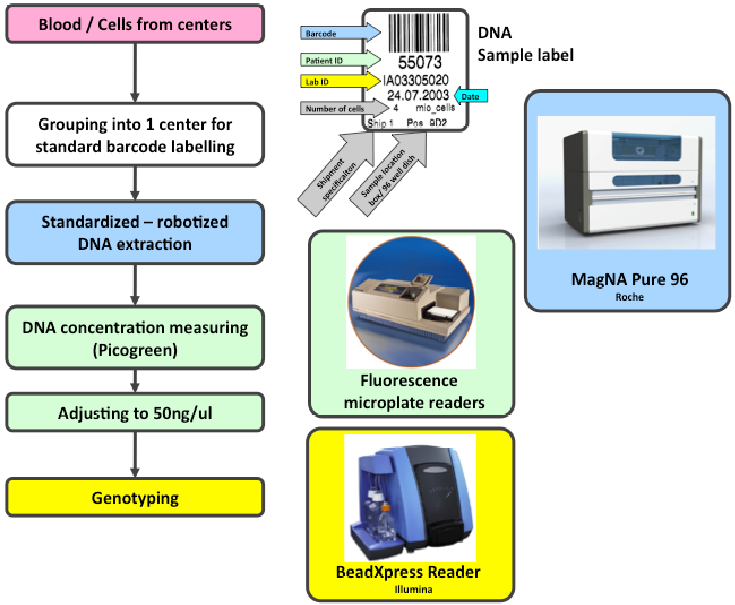
Cervera C. Transplantation 2007; 83: 1493

Mannose-Binding Lectin–Deficient Donors Increase the Risk of Bacterial Infection and Bacterial Infection–Related Mortality After Liver Transplantation

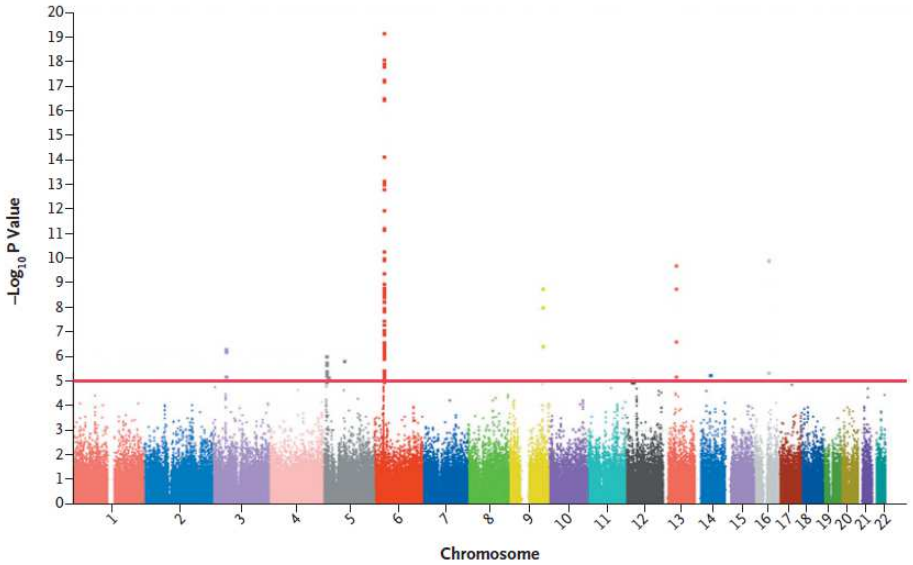


Lombardo-Quezada J et al. Am J **Transplant**. 2017 Jun 26.

Nuevas técnicas de genotipaje



384 simultaneous SNPs analysis

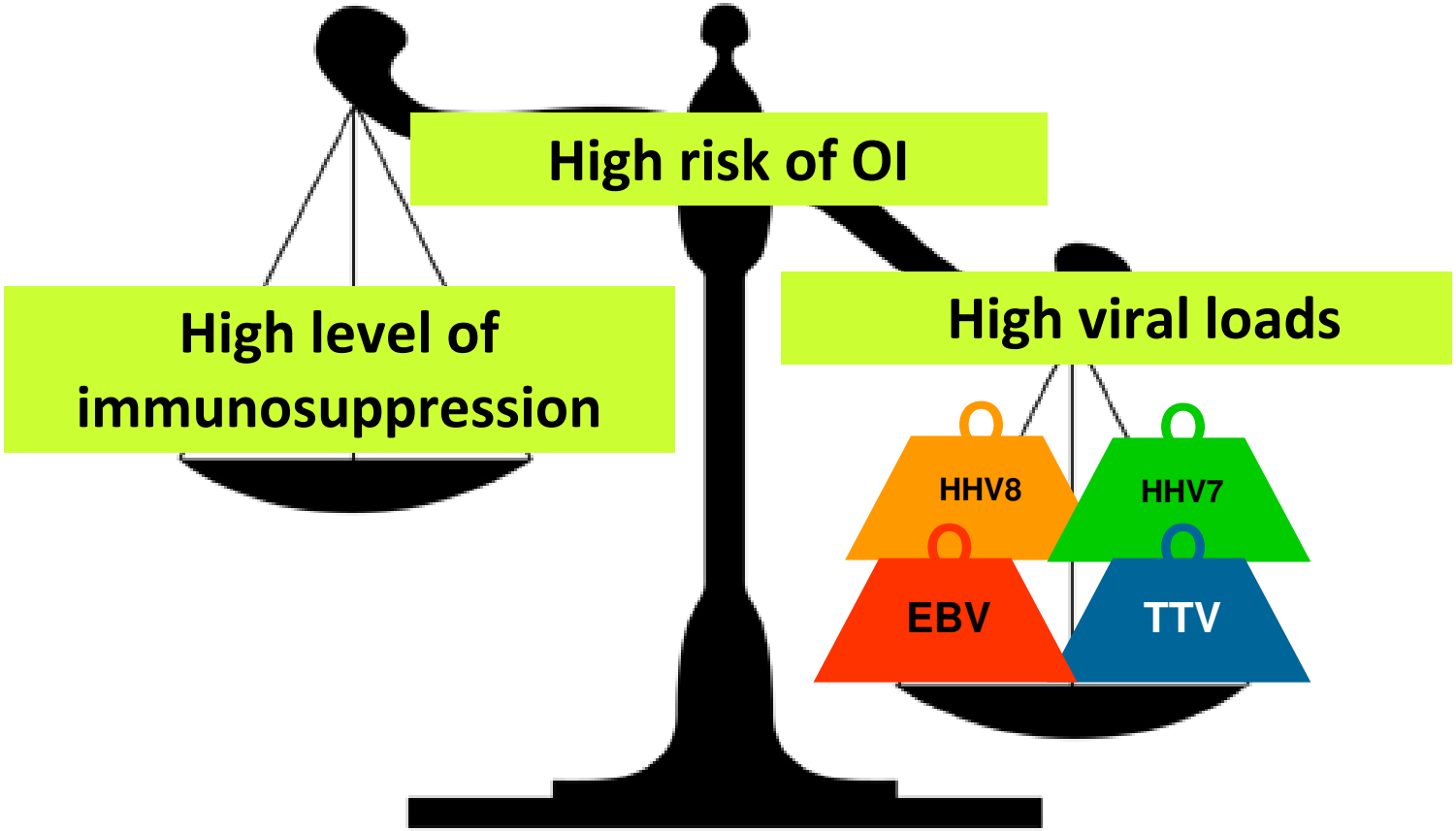


GWA studies: 500’000 SNPs

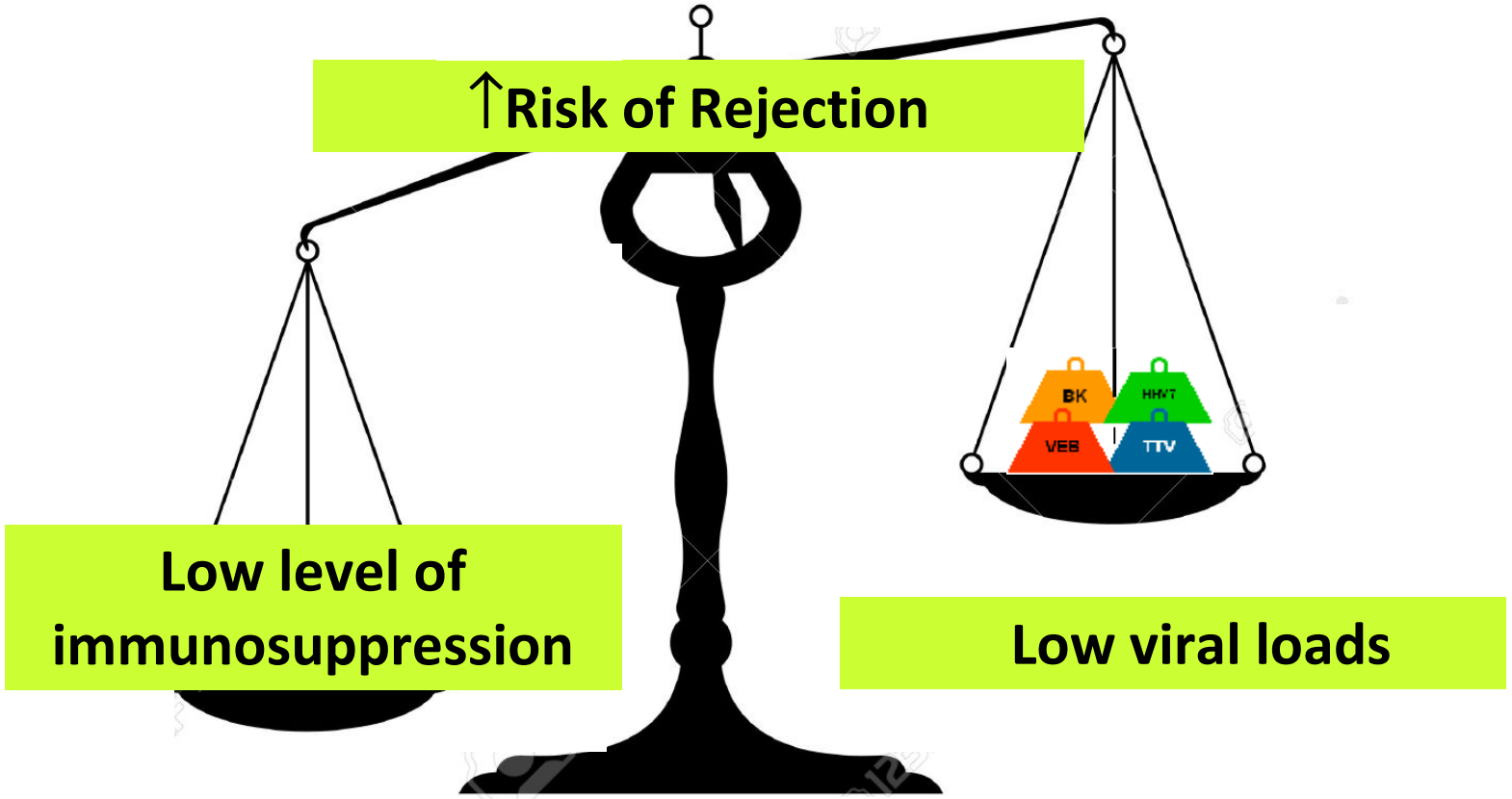
Non-pathogen-specific immune biomarkers

- **Quantitative**
  - Serum immunoglobulins
  - Serum complement factors
  - Peripheral blood lymphocyte subpopulations
- **Functional**
  - Intracellular ATP in stimulated CD4 T-cells
  - Serum sCD30
  - SNPs in innate immunity genes
  - **Viremia as a marker of immunosuppression**

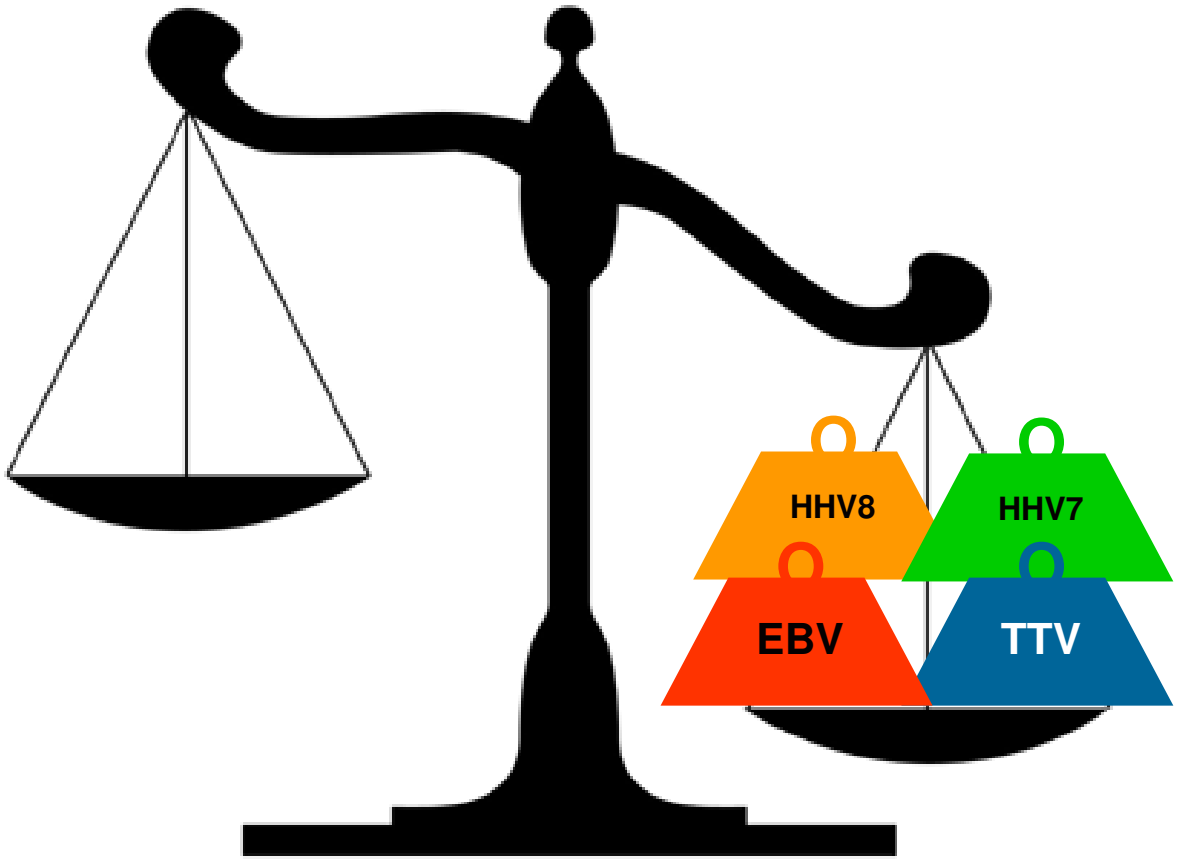
How to know the net state of immunosuppression?



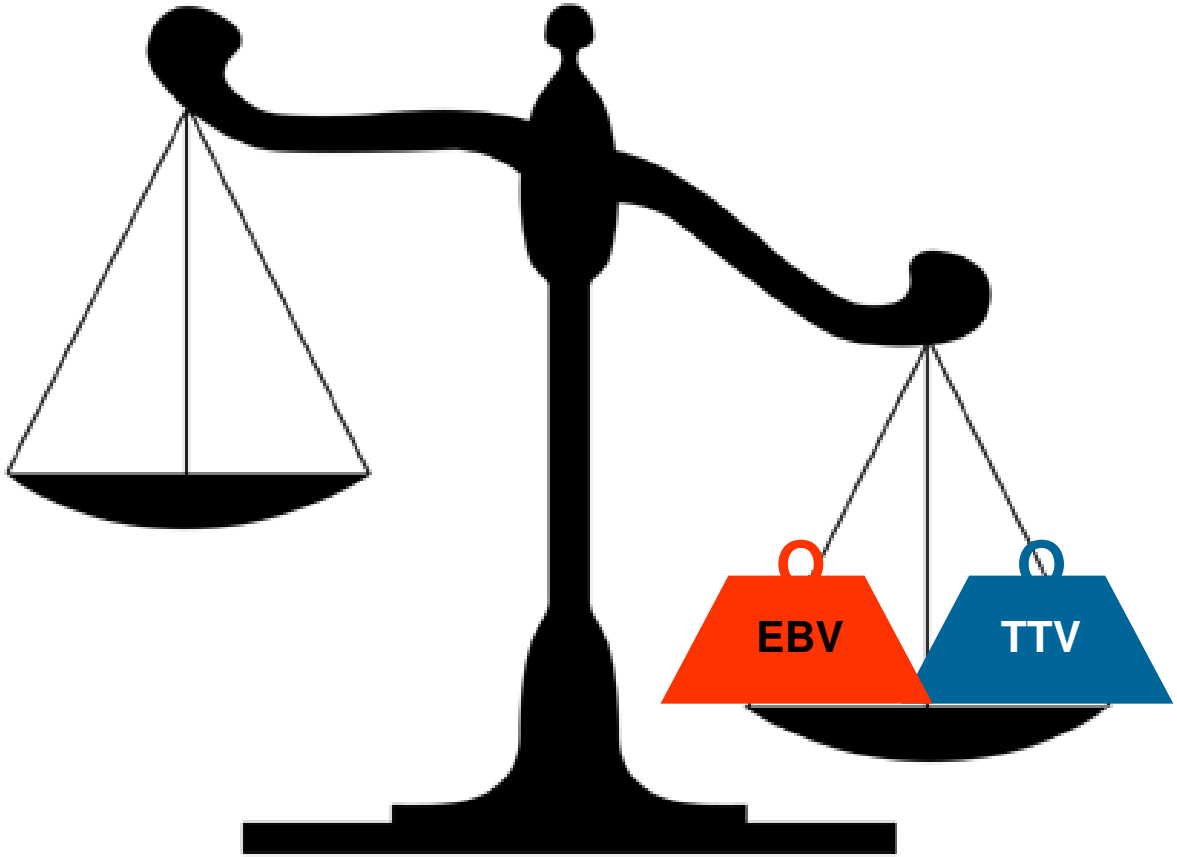
How to know the net state of immunosuppression?



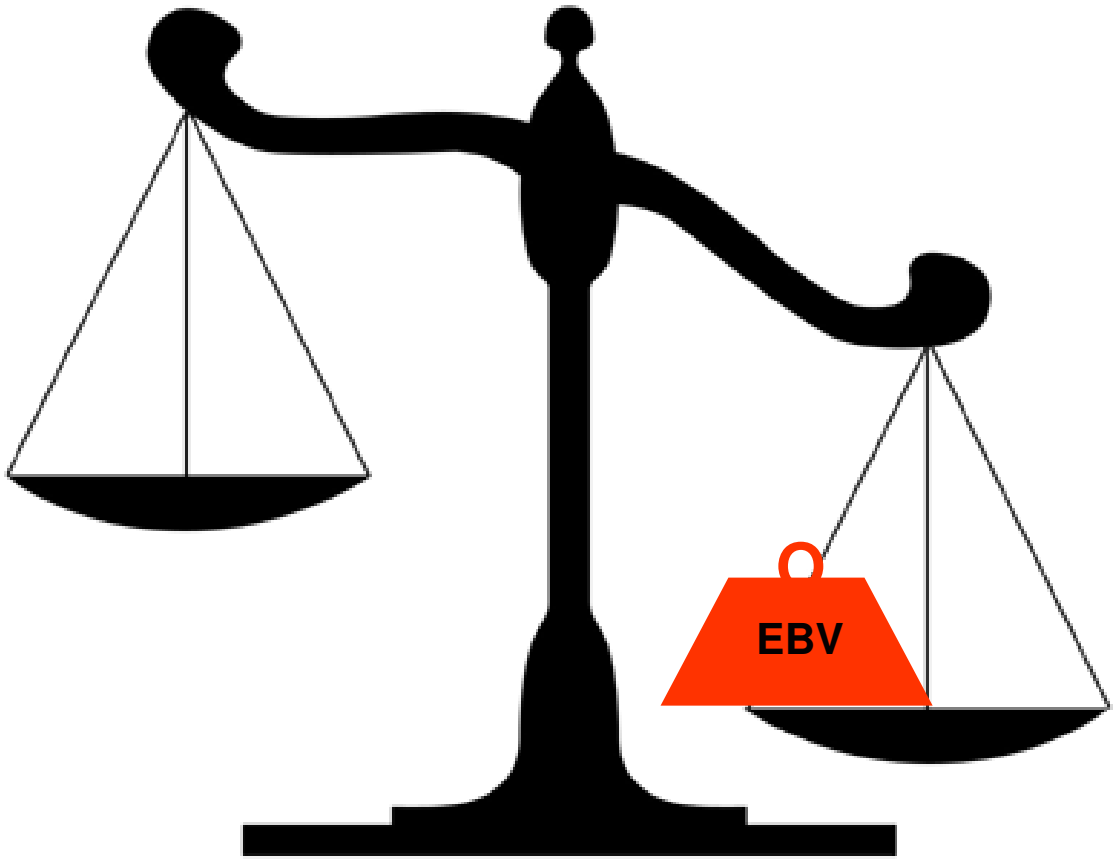
How to know the net state of immunosuppression?



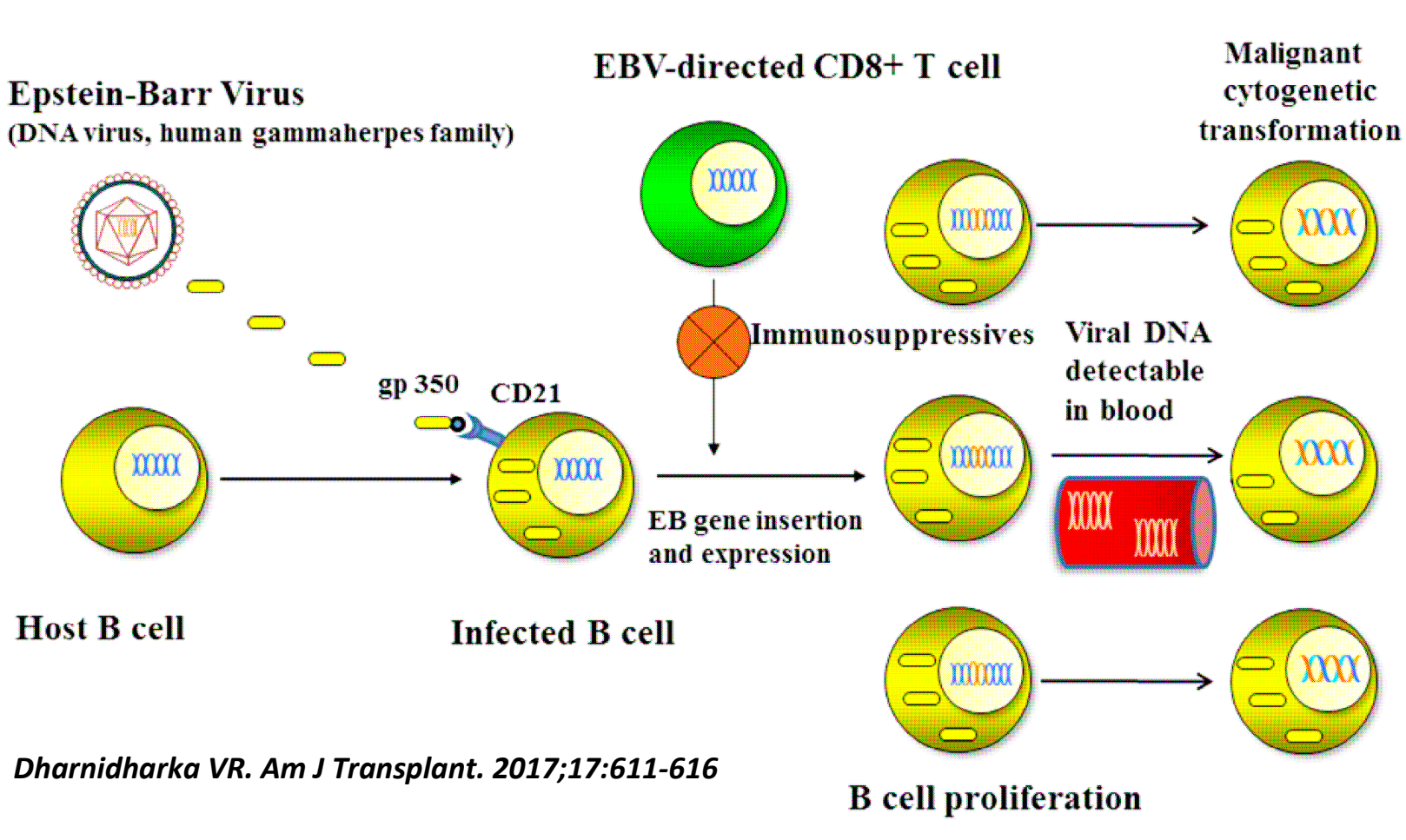
How to know the net state of immunosuppression?



How to know the net state of immunosuppression?



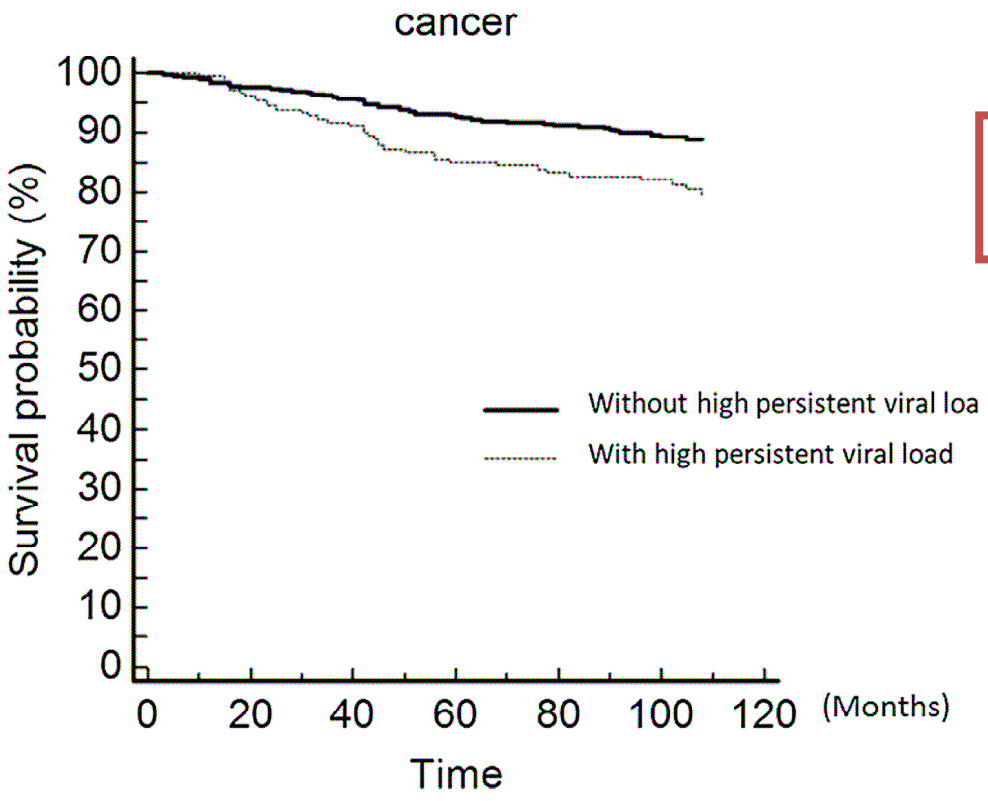
Peripheral Blood Epstein–Barr Viral Nucleic Acid Surveillance as a Marker for Posttransplant Cancer Risk



Dharnidharka VR. Am J Transplant. 2017;17:611-616

Late Persistent Positive EBV Viral Load and Risk of Solid Cancer in Kidney Transplant Patients

Bamoulid J, et al. Transplantation. 2017;101:1473-1478.



Cancer sites according to EBV viral load

	Persistent high EBV viral load (n = 147)	Others (n = 552)	*P*
Nonmelanoma skin	13 (7.4)	20 (3.8)	0.023
Lung	4 (2.6)	3 (0.5)	0.074
Cervix	2 (1.3)	0	0.069
Upper airways	5 (3.4)	1 (0.1)	0.002
Prostate	4 (2)	9 (1.7)	NS
Kidney	1 (0.6)	9 (1.7)	NS
Bladder	1 (0.6)	1 (0.2)	NS
Breast	1 (0.6)	3 (0.6)	NS
Colon	1 (0.6)	2 (0.4)	NS
Stomach	0	1 (0.2)	NS
Glioblastoma	0	1 (0.2)	NS
Thyroid	0	1 (0.2)	NS
Melanoma	1 (0.6)	0	NS
Ovary	0	1 (0.2)	NS
Testis	0	1 (0.2)	NS
	33	53	0.005

Reactivation of EBV as a marker of immunosuppression

Association Between Elevated Whole Blood Epstein–Barr Virus (EBV)-encoded RNA EBV Polymerase Chain Reaction and Reduced Incidence of Acute Lung Allograft Rejection

Vivek N. Ahya, MD,[a] Lisa P. Douglas, BSN, RN,[a] Charalambos Andreadis, MD,[b] Sharon Arnoldi, PhD,[c] Jakub Svoboda, MD,[b] Robert M. Kotloff, MD,[a] Denis Hadjiliadis, MD,[a] Jeffery S. Sager, MD,[a] Y. Joseph Woo, MD,[d] Alberto Pochettino, MD,[d] Stephen J. Schuster, MD,[b] Edward A. Stadtmauer, MD,[b] and Donald E. Tsai, MD, PhD[b]

The Journal of Heart and Lung Transplantation
August 2007

Reactivation of EBV as a marker of immunosuppression

High incidence of PCR negative in patients with acute rejection

Table 2. Correlation Between Intracellular EBER PCR and Grade 2A Allograft Rejection[b]

Ahya et al. JHLT 2007

	Diagnosis of any grade 2A allograft rejection		
	Yes	No	Total
EBER EBV positive	5	6	11
PCR[a] negative	15	3	18
Total	20	9	29

83%

P=0.04

Reactivation of EBV as a marker of immunosuppression

High incidence of PCR positive in patients with infections

Table 3. Correlation Between Intracellular EBER PCR and Infectious Complications[c]

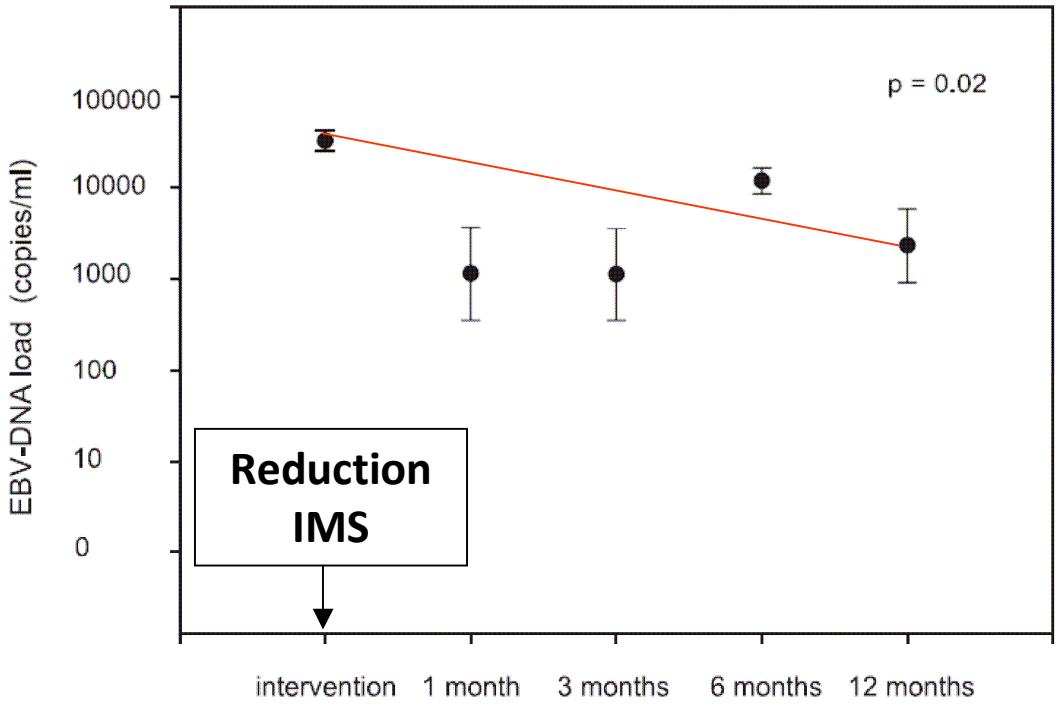
Ahya et al. JHLT 2007

	Infectious complications[a]		
	Yes	No	Total
EBER EBV positive	4	9	13
PCR[b] negative	4	14	18
Total	8	23	31

23%

P=0.04

Epstein-Barr Virus–DNA Load Monitoring Late After Lung Transplantation: A Surrogate Marker of the Degree of Immunosuppression and a Safe Guide to Reduce Immunosuppression



50% reduction of IS:

✓ VL >10.000 cop/ml

✓ +/- valaciclovir

✓PTLD: 1.5%

✓no influence in chronic allograft rejection or survival

Bakker NA. Transplantation 2007; 83:483-88

CLINICAL AND TRANSLATIONAL RESEARCH

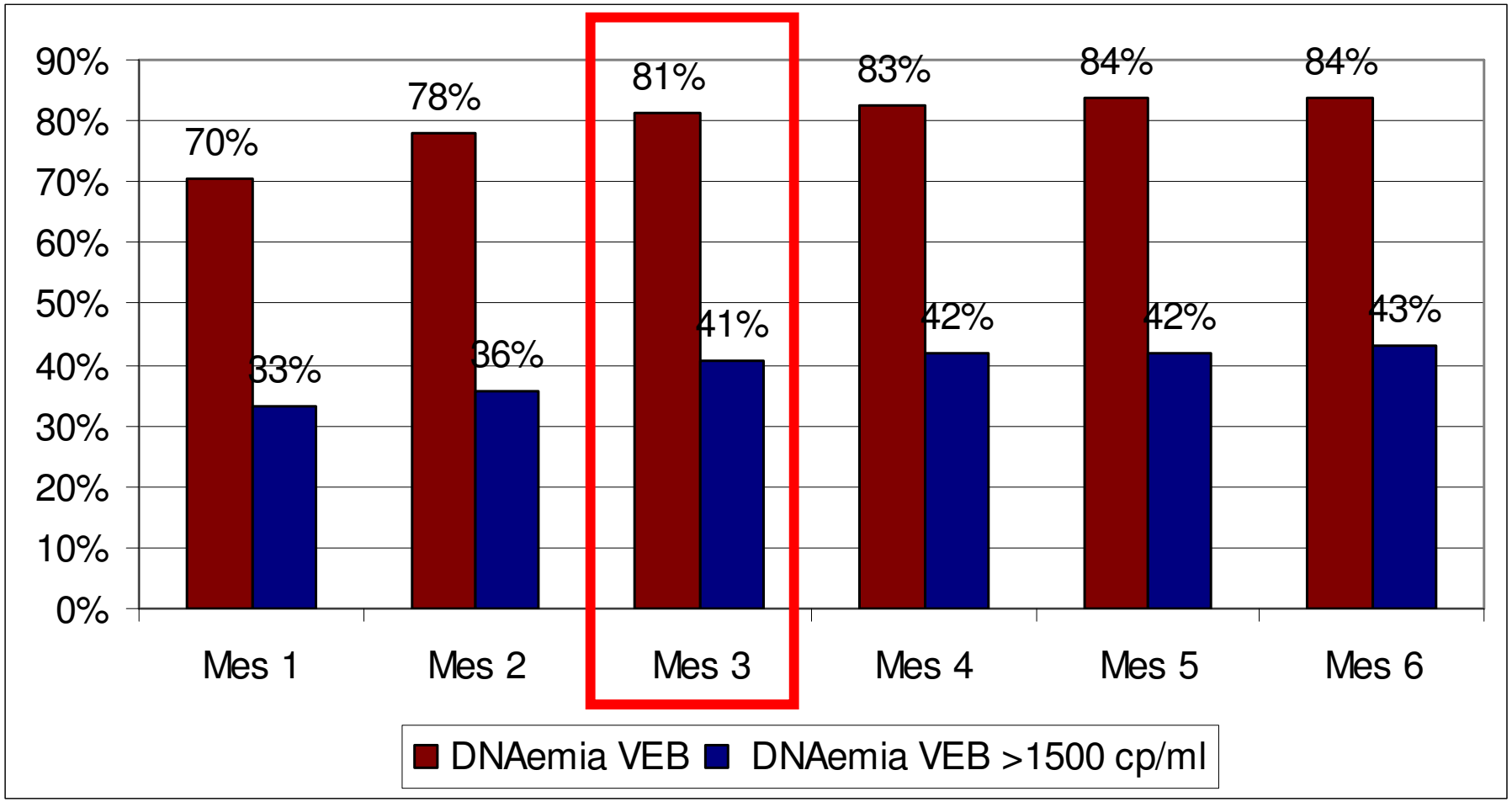
Epstein-Barr Virus DNAemia Is an Early Surrogate Marker of the Net State of Immunosuppresion in Solid Organ Transplant Recipients

Rafael San-Juan,[1,6] Begoña De Dios,[1] David Navarro,[2] Ana García-Reyne,[1] Carlos Lumbreras,[1] Dayana Bravo,[2] Elisa Costa,[2] Jose Maria Morales,[3] Amado Andres,[3] Carlos Jiménez-Romero,[4] Juan Delgado,[5] Mario Fernández-Ruiz,[1] Francisco López-Medrano,[1] and Jose M. Aguado[1]

(*Transplantation* 2013;95: 688–693)

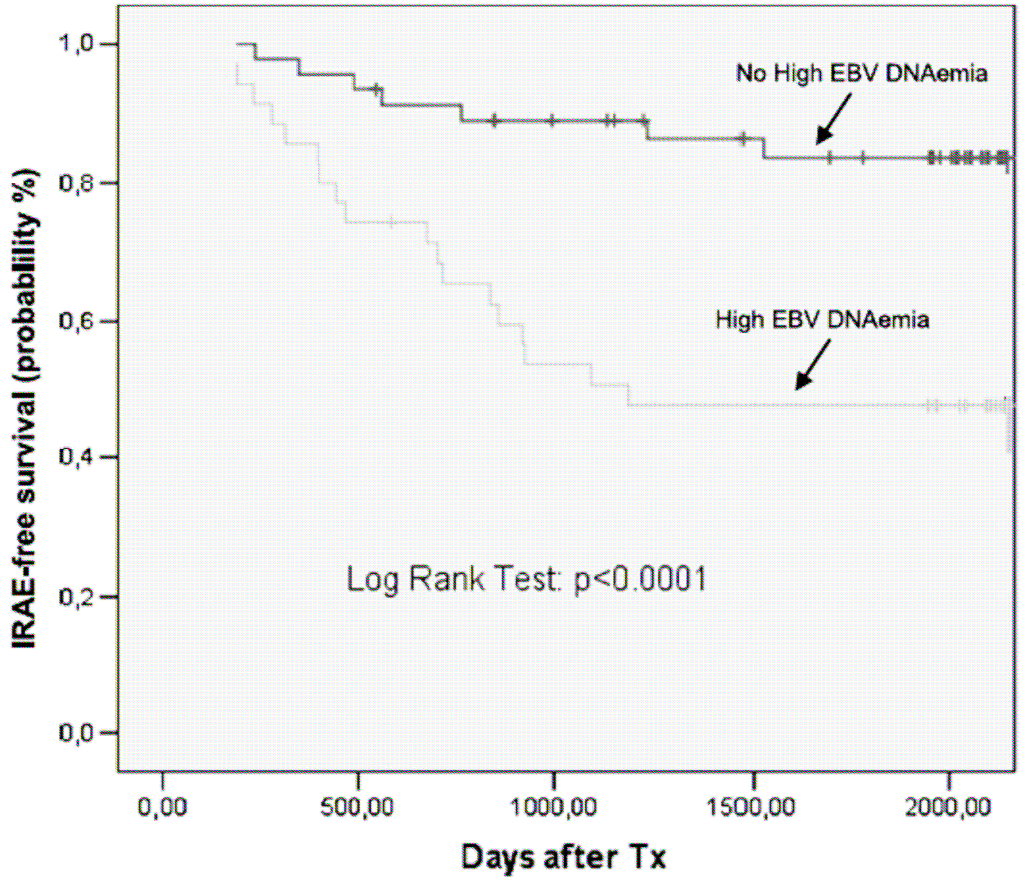
Dynamic of EBV DNAemia 6 months post TX

Persistent EBV DNAemia in 40 patients (49.4%)



San Juan R et al. Transplantation. 2013;95:688-693

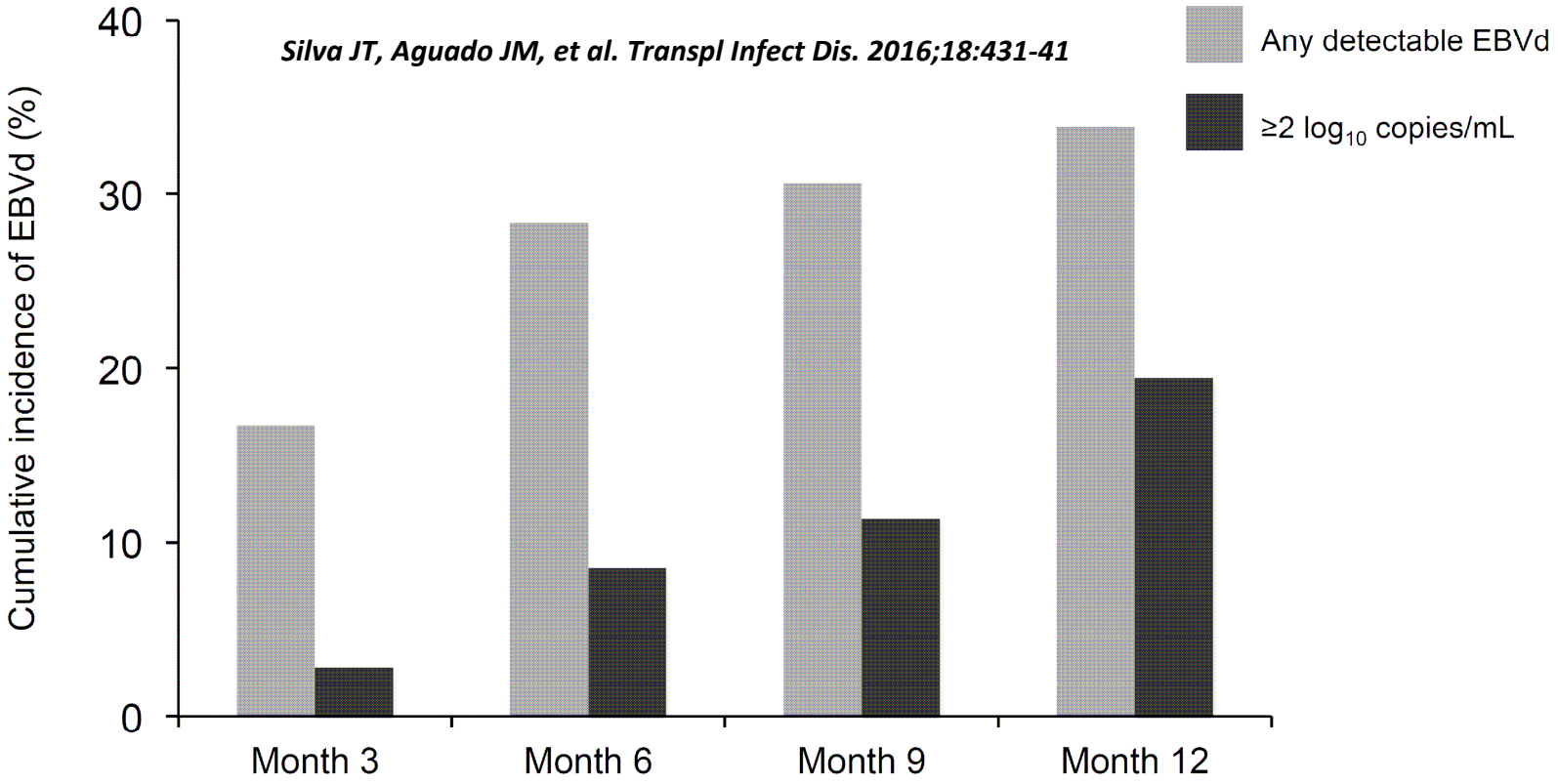
EBV DNAemia and Immunosuppression-related adverse effects



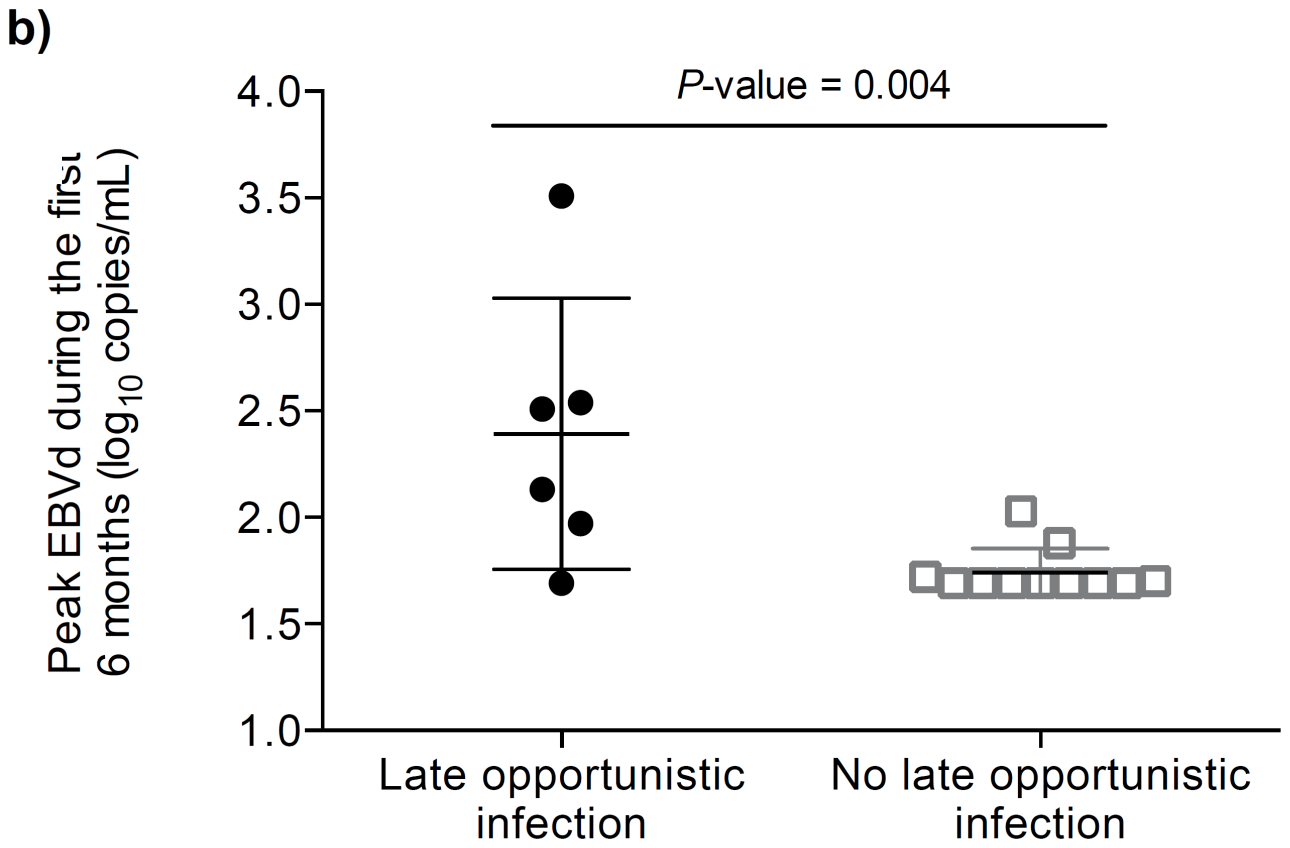
IRAE (immunosuppression-related adverse events): solid organ tumor, OIs, and severe infections.

San Juan R et al. Transplantation. 2013;95:688-693

Detection of Epstein–Barr virus DNAemia after lung transplantation and its potential relationship with the development of post-transplant complications

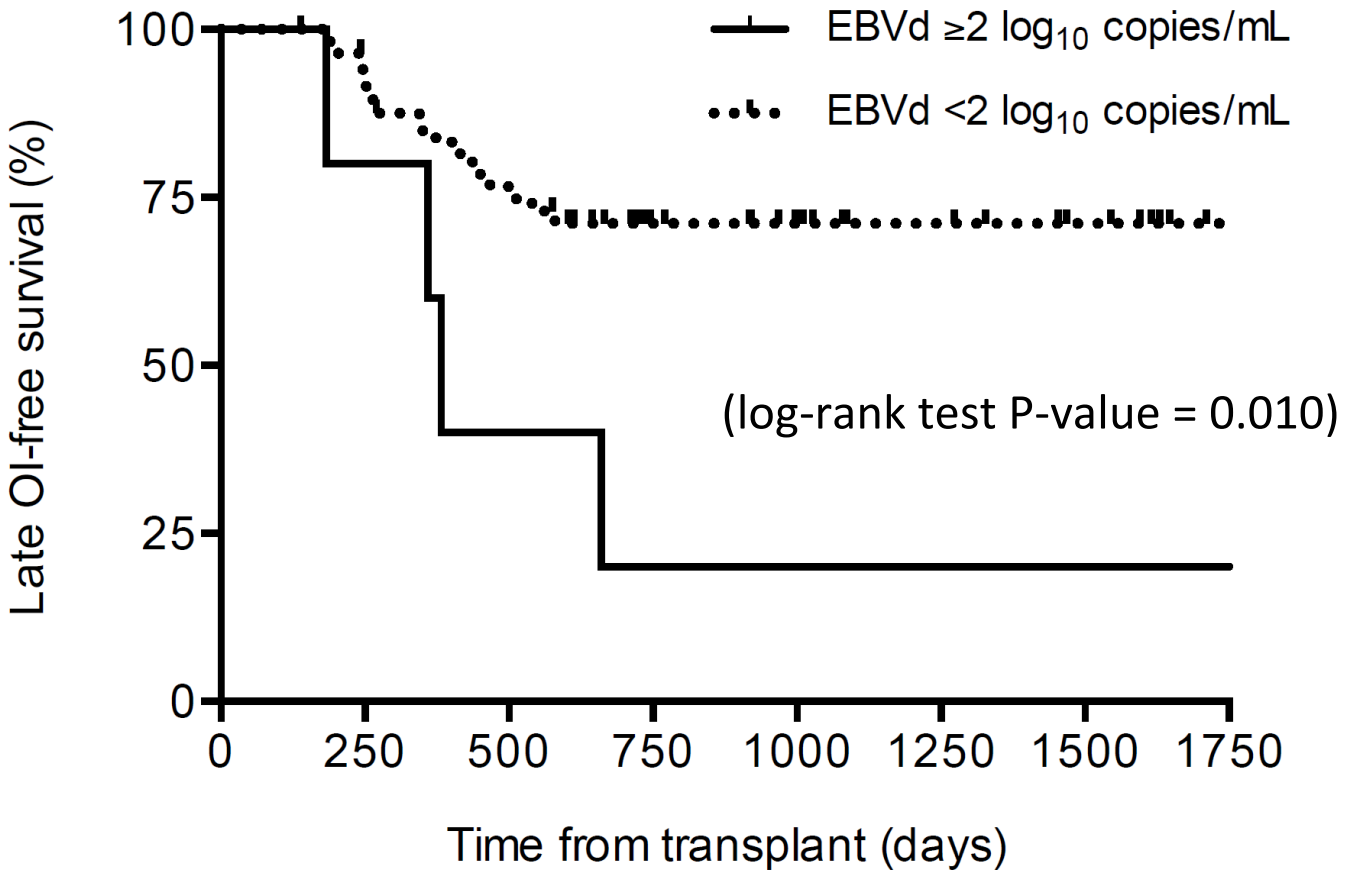


Peak EBV DNAemia (log10 copies/mL) during the first 6 months after LT and late opportunistic infection



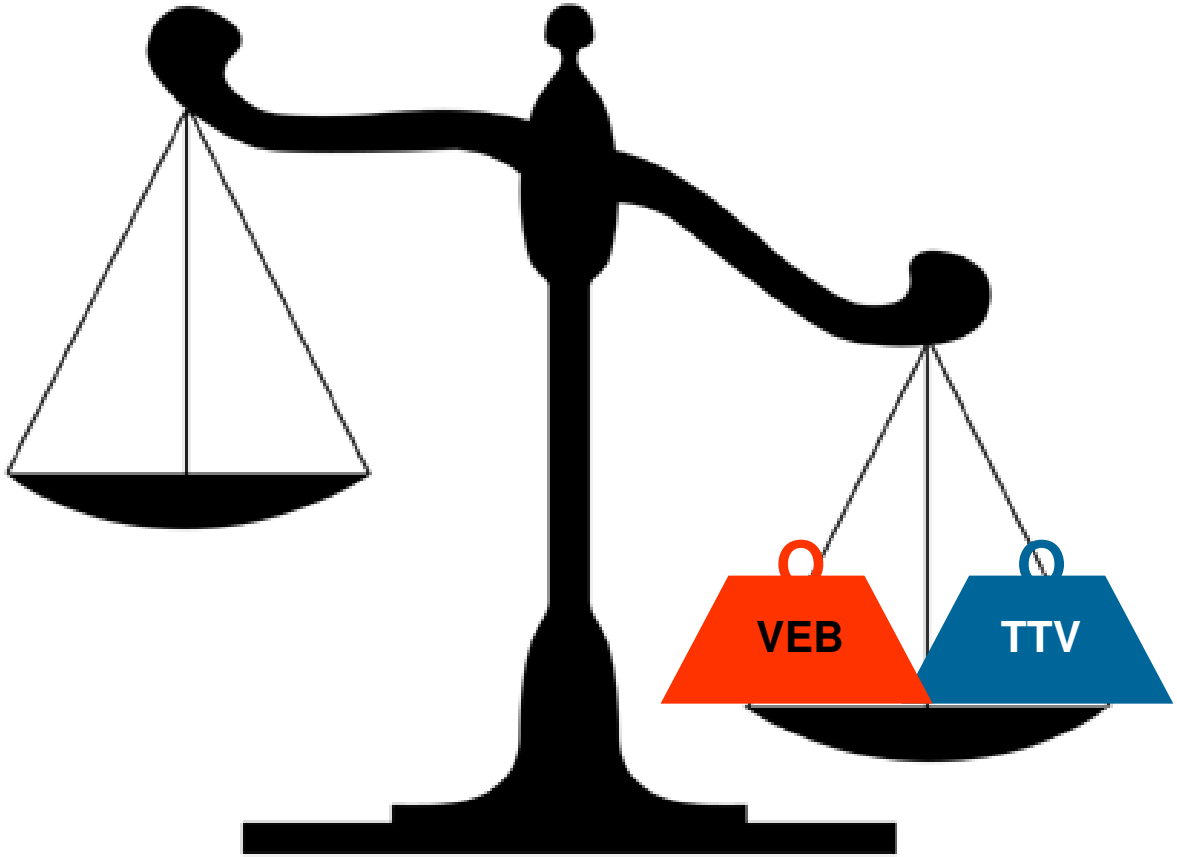
Silva JT, Aguado JM, et al. Transpl Infect Dis. 2016;18:431-41

Late OI-free survival according to the presence of EBV virus DNAemia >2 log10 copies/mL during the first 6 months

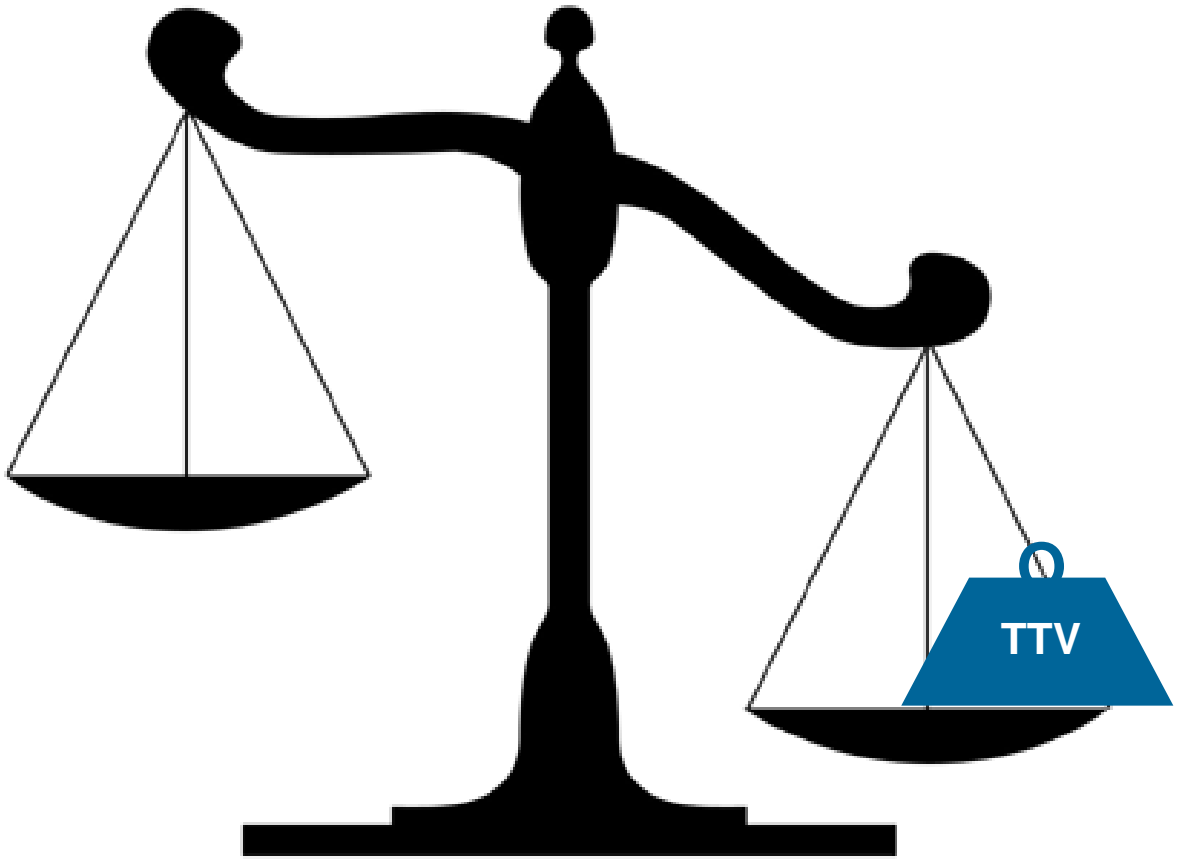


Silva JT, Aguado JM, et al. Transpl Infect Dis. 2016;18:431-41

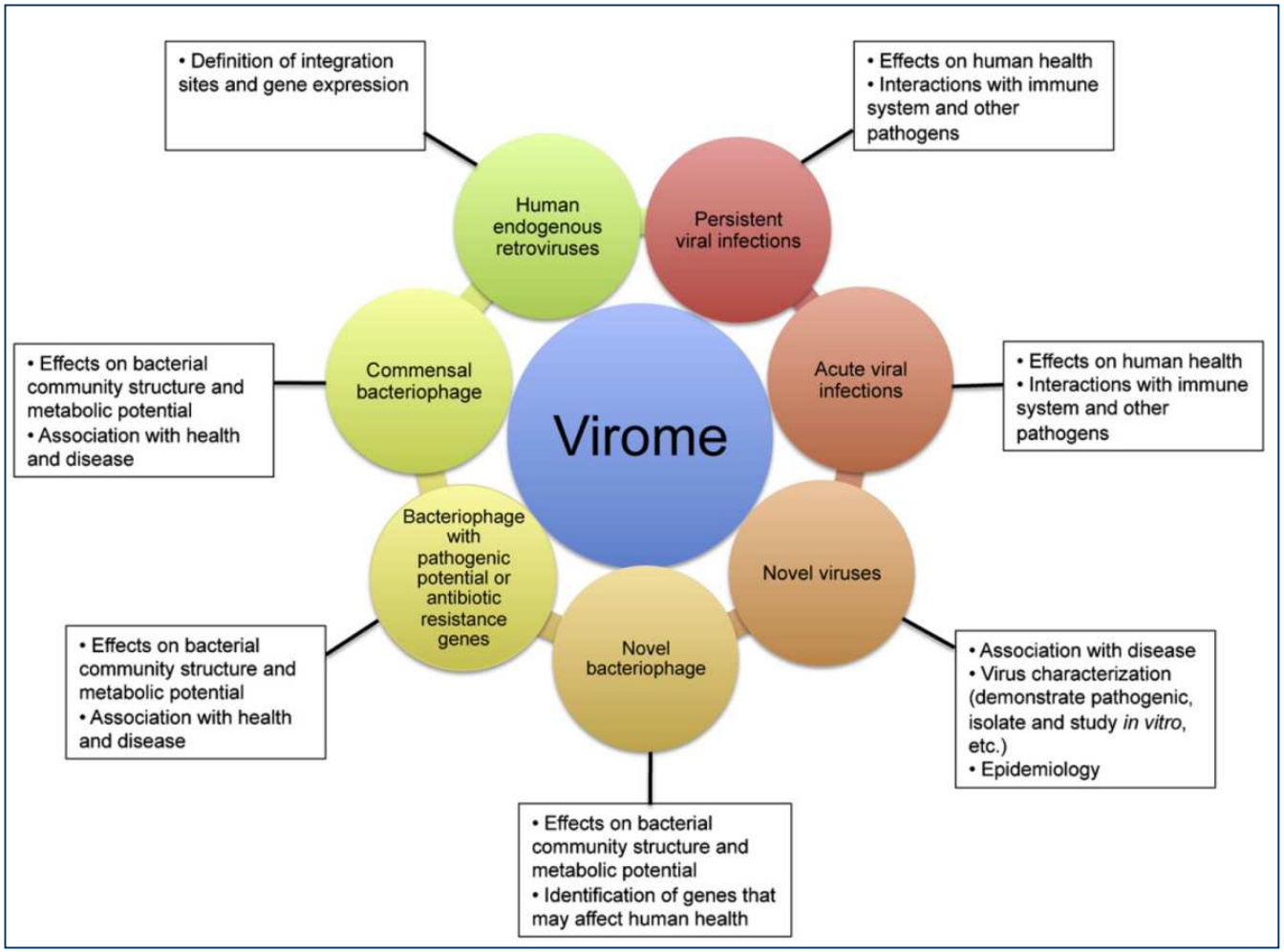
How to know the net state of immunosuppression?



How to know the net state of immunosuppression?

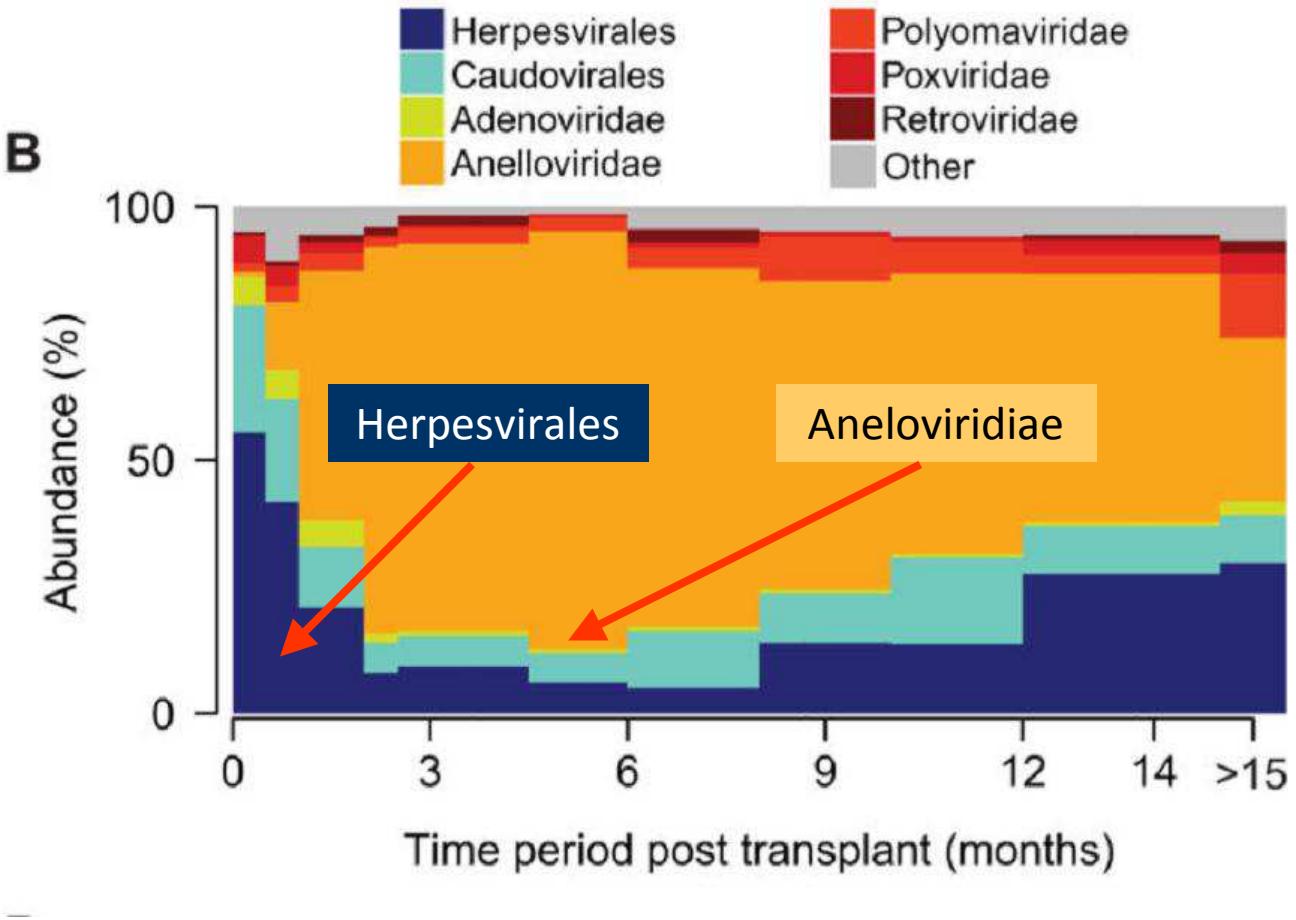


A new concept : «the virome»



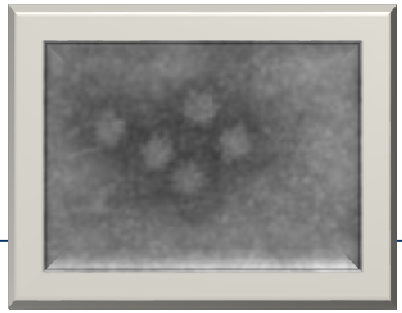
Abeles et al. 2014

Temporal Response of the Human Virome to Immunosuppression and Antiviral Therapy



De Vlaminck I et al. Cell. 2013; 155: 1178–1187

Anelloviridae

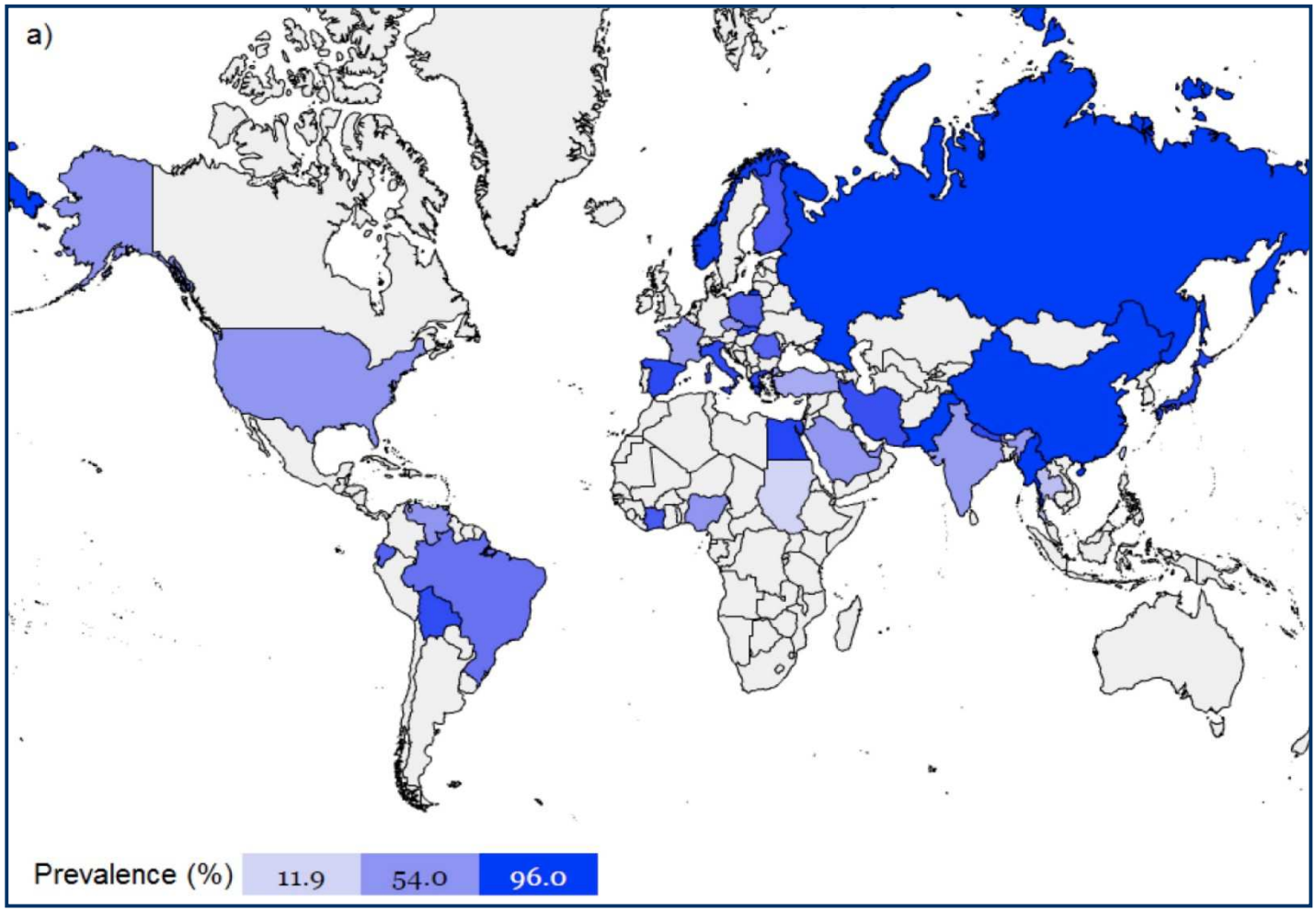


- **Viruses of small size**
- **Lack of envelope**
- **Circular single-stranded DNA genome**
  - 1997: Isolation of **Torque Teno virus (TTV)** in Japan

    Hepatitis? Transfusion-transmitted virus

  - 2000: Isolation of **Torque Teno Mini virus (TTMV)**
- **Great genetic diversity**

World heat map of TTV prevalence in humans detected by UTR-derived primers



What was already known about TTV

- **No attributable pathogenic effect in man**

  "Orphan virus"

- **Frequent reactivation of latent infection in:**
  - *Patients with debilitating chronic diseases*
  - *Patients with cancer*
- **Inverse relationship between TTV viral load and CD4+ cell count in patients infected with HIV**

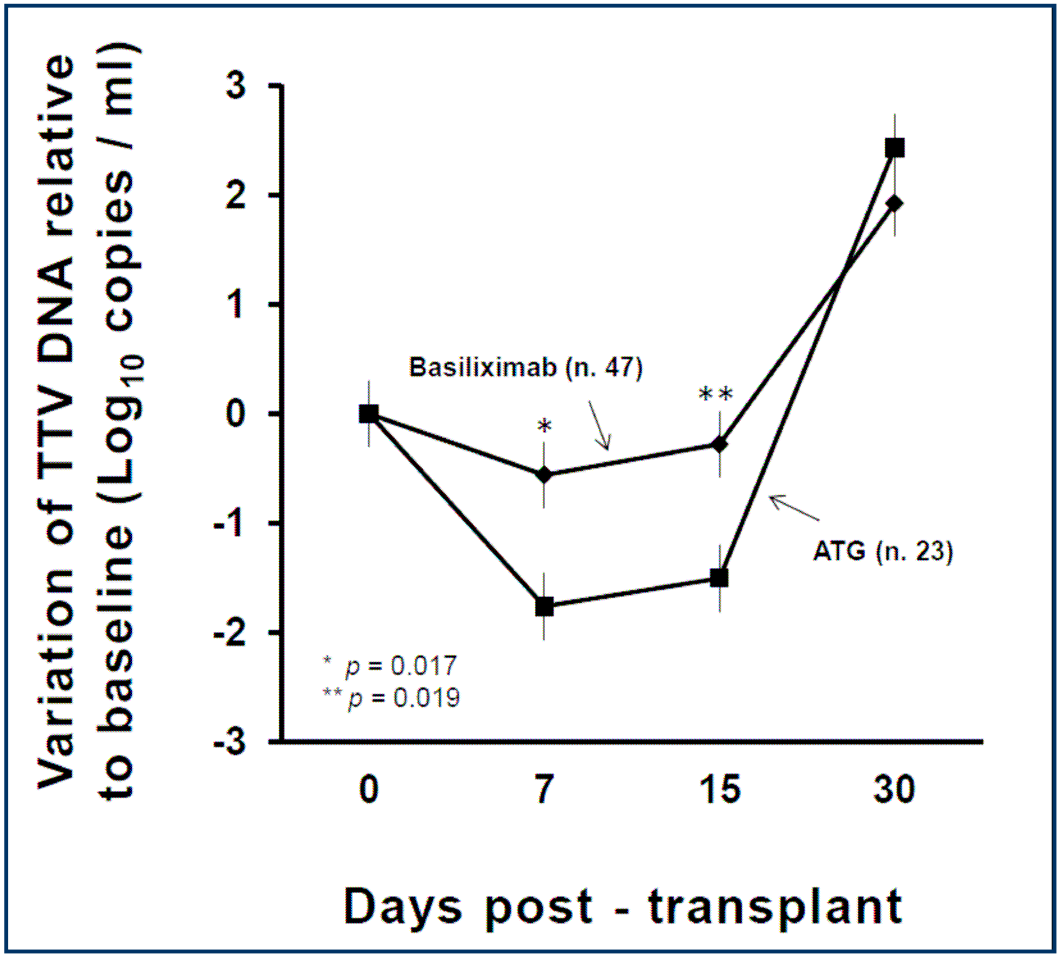
Feyzioglu B, et al Int J Clin Exp Med. 2014;7:3461-6.

Zhong S, et al. Ann N Y Acad Sci. 2001;945:84-92.

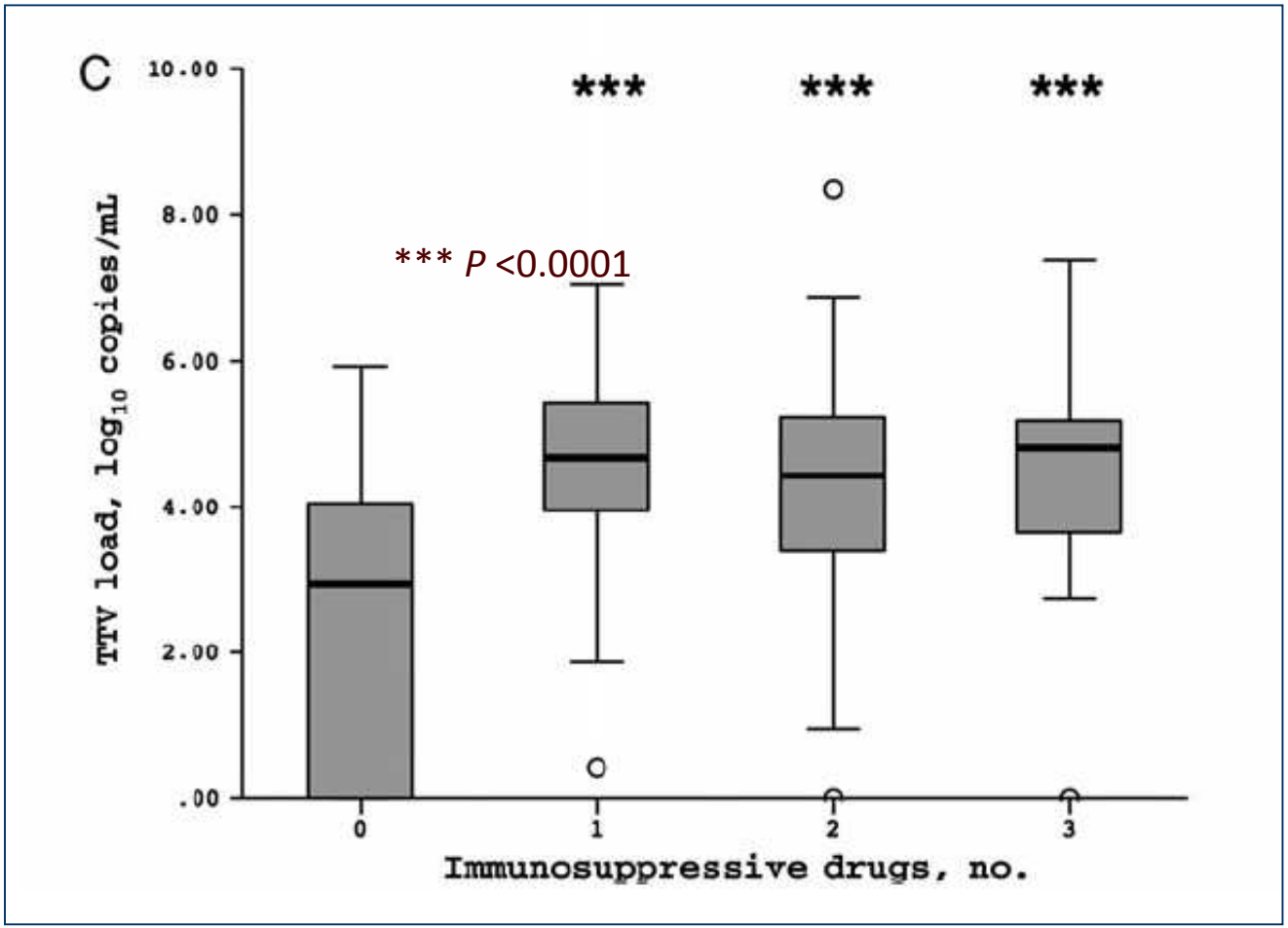
Shibayama T, et al. AIDS. 2001;15:563-70.

Kinetics of variation in TTV viraemia relative to baseline in recipients receiving basiliximab 20 mg on days 0–4 or ATG

Focosi D et al. J Gen Virol 2015;96:115-17



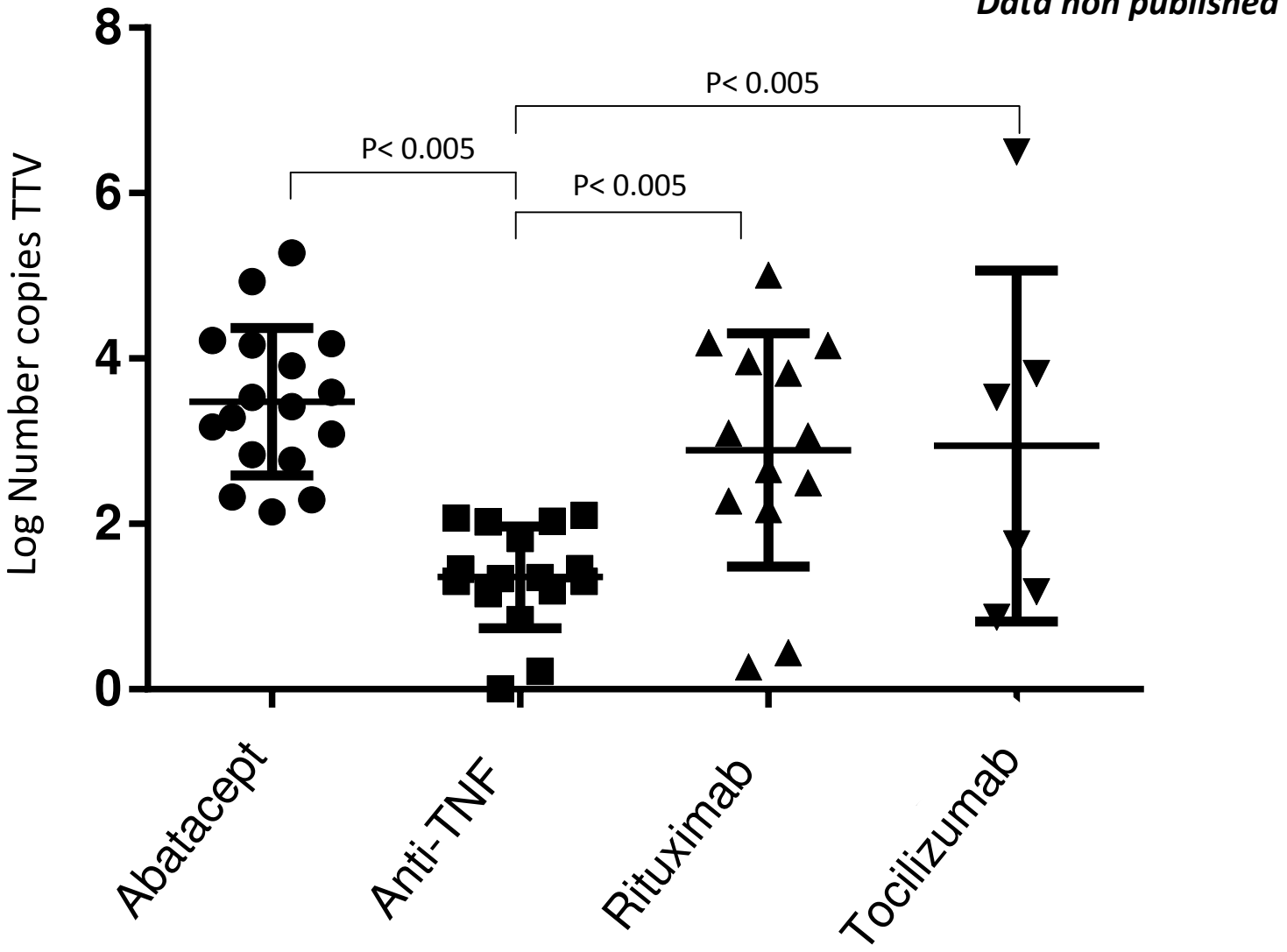
TTV-VL and number of immunosuppressive drugs



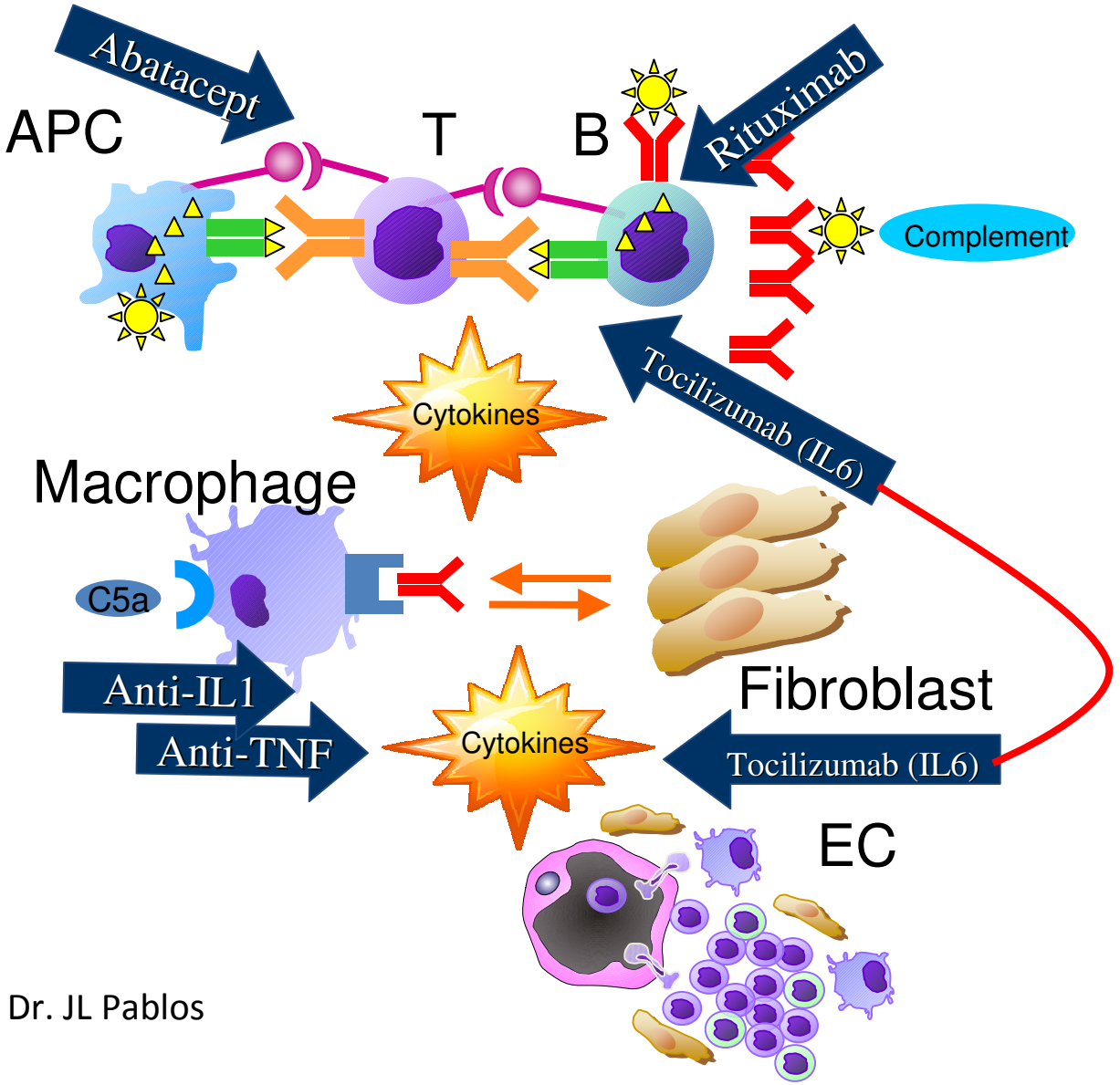
Béland K et al The Journal of Infectious Diseases 2014;209:247–54

TTV-VL and type of immunosuppressive drugs

Data non published

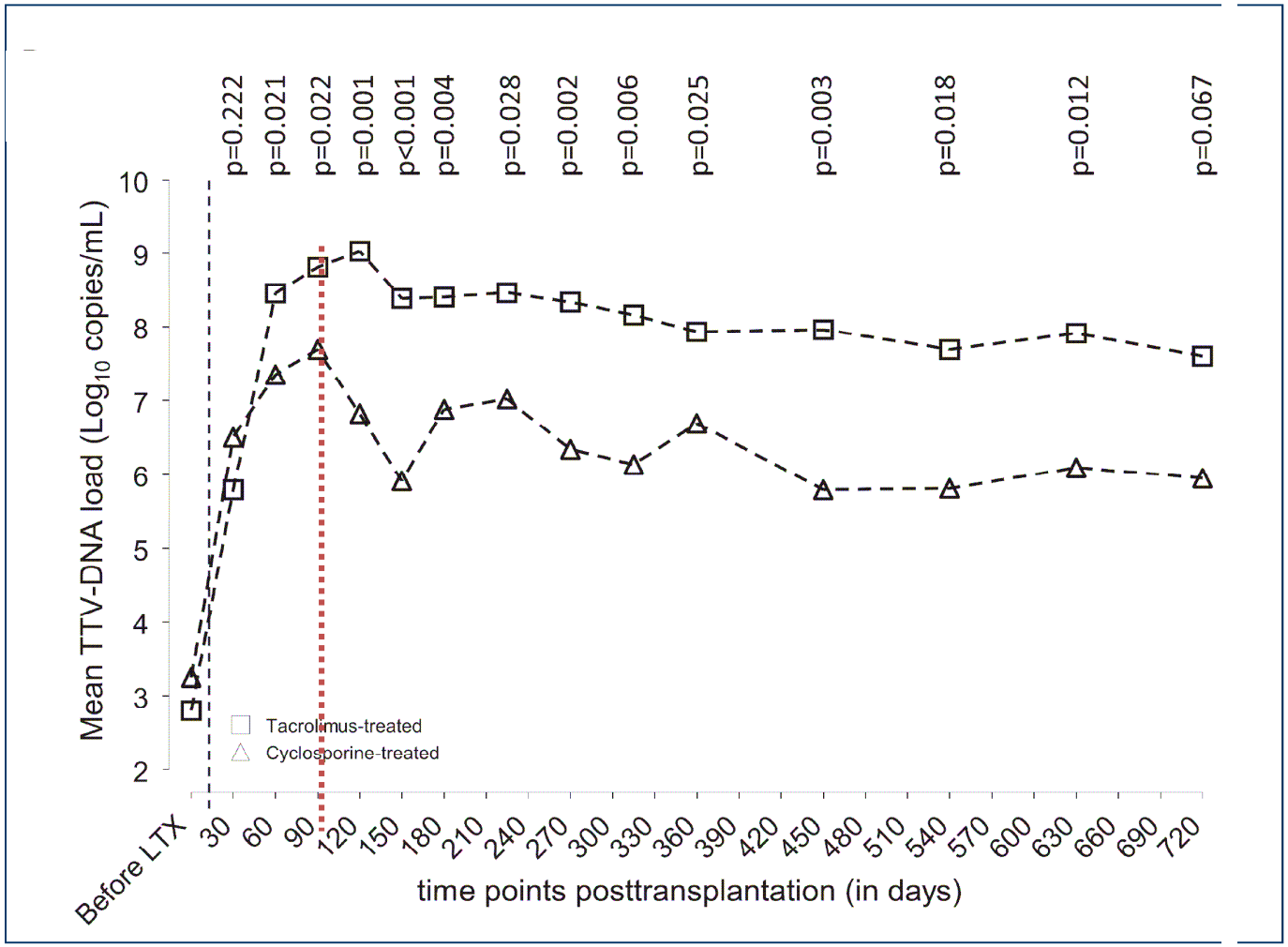


Immune/Inflammatory Targets of Biological Therapies



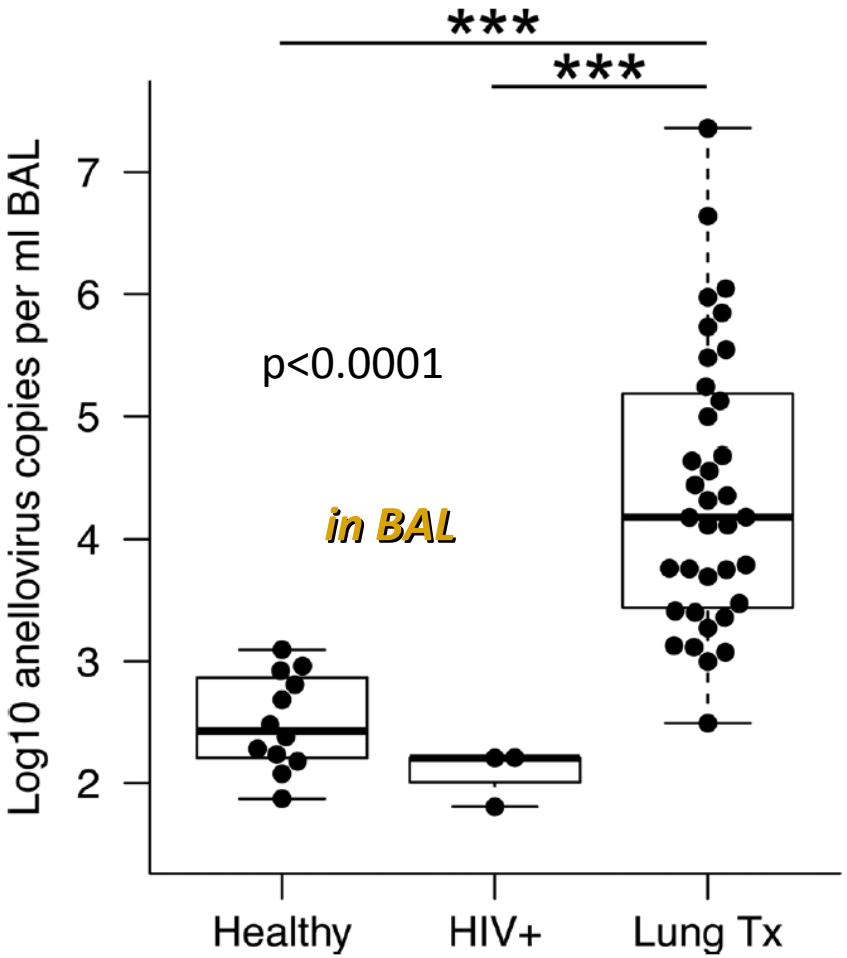
Cortesía del Dr. JL Pablos

Plasma DNA levels of Torque teno virus and immunosuppression after lung transplantation



Görzer I, et al. J Heart Lung Transplant. 2014;33:320-3

Viral Metagenomics Reveal Blooms of Anelloviruses in the Respiratory Tract of Lung Transplant Recipients



Young JC et al.. American Journal of Transplantation 2015; 15: 200-209

Plasma DNA levels of Torque teno virus and immunosuppression after lung transplantation

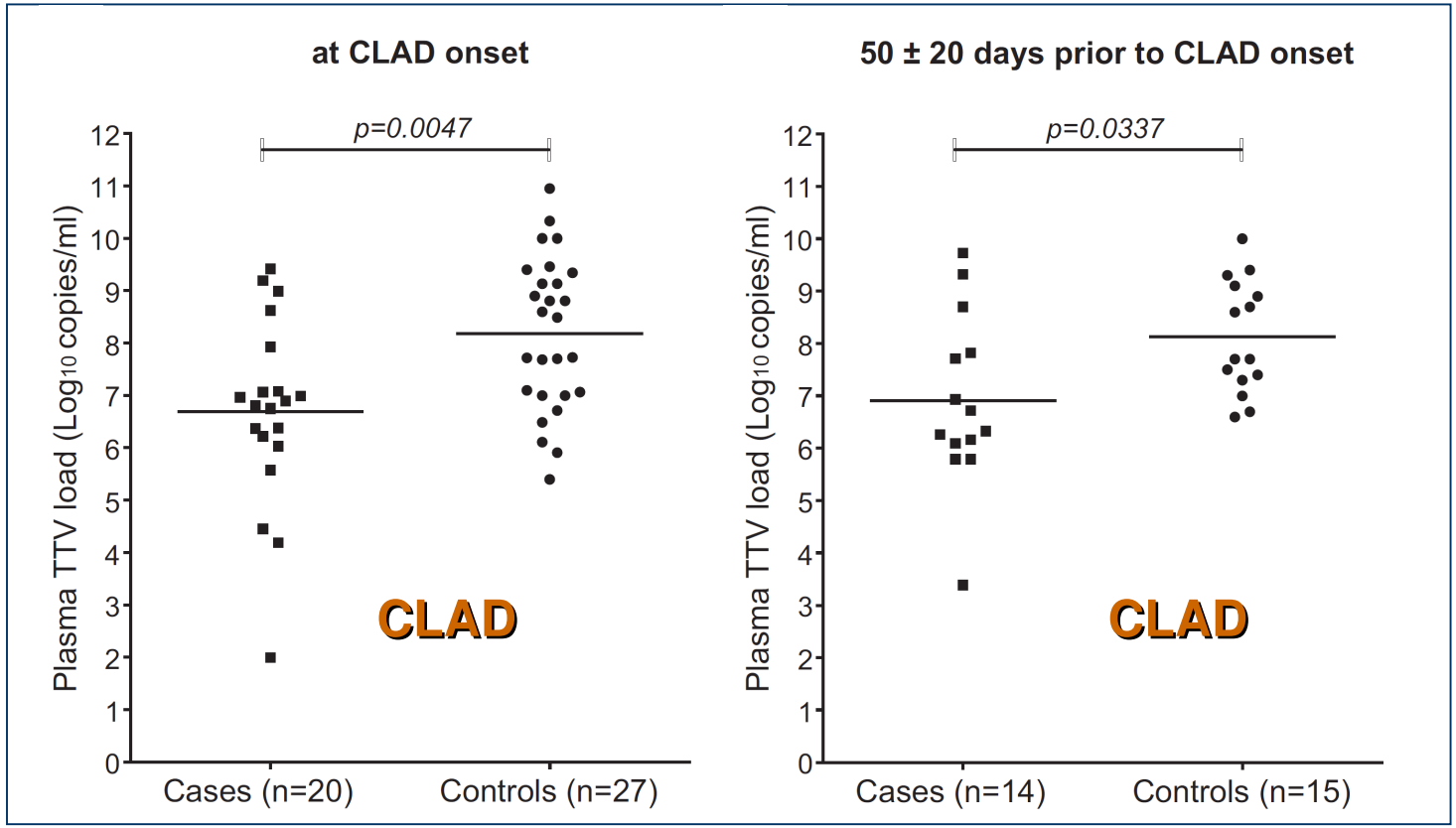
20 patients with post-transplant infection

- **TTV-VL higher in patients with infection (P=0.045)**
- **TTV-VL cut-off point: 9.3 $\log_{10}$/mL**

Sensitivity:	**53.8%**
Specificity:	**91%**
AuROC:	**0.744 (P = 0.043)**

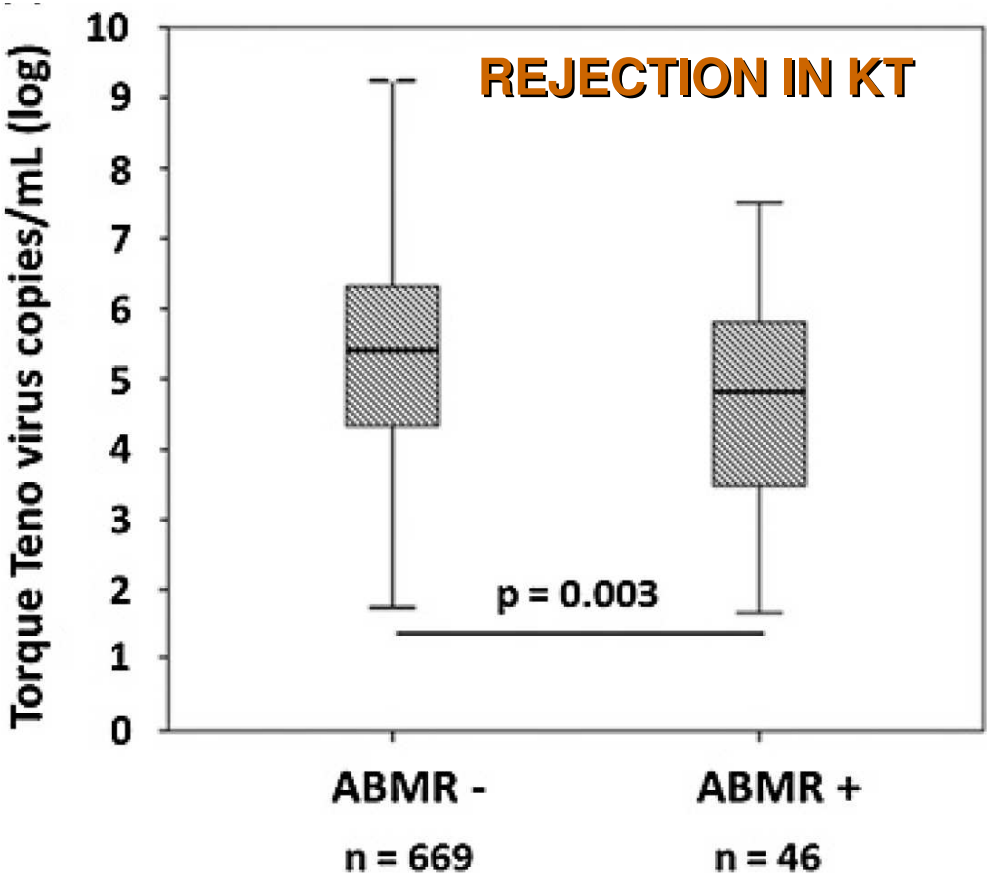
Görzer I, et al. J Heart Lung Transplant. 2014;33:320-3

Association between plasma Torque teno virus level and chronic lung allograft dysfunction after lung transplantation



Görzer I, et al. J Heart Lung Transplant. 2017;36:366-368

Torque Teno Virus Load—Inverse Association With Antibody-Mediated Rejection After Kidney Transplantation



Schiemann M, et al. Transplantation. 2017; 101:360-367.

Conclusiones

- Hay numerosos acercamientos para controlar el estado inmune.
- No existen estudios de intervención basados en estas estrategias.
- Se necesitan biomarcadores fácilmente disponibles en la práctica clínica.
- Propuesta para construir y validar un *score* de riesgo inmune integrado.
- Ciertos polimorfismos genéticos confieren un mayor riesgo de infección.
- La viremia por VEB y TTV parece ser útil para predecir IO y rechazo.
- Objetivo final, mejorar la evolución del trasplante a corto y largo plazo