17º CONGRESO BARCELONA
SCT BCN
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SOCIETAT CATALANA DE TRASPLANTAMENT

# *Clinical and molecular spectrum of v-lesion*

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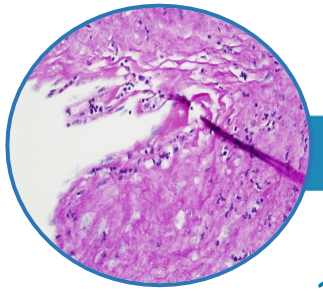
# ¿Cómo se clasifica la endarteritis según los criterios de Banff?



1991 1993 1995 **1997** 1999 2001 2003 2005 2007 2009 2011 2013 2015 2017 2019 2022

## 1. TCMR

*Category 4: TCMR*

| | |
|---|---|
| Acute TCMR | |
| Grade IA | Interstitial inflammation involving >25% of nonsclerotic cortical parenchyma (i2 or i3) with moderate tubulitis (t2) involving 1 or more tubules, not including tubules that are severely atrophic[5] |
| Grade IB | Interstitial inflammation involving >25% of nonsclerotic cortical parenchyma (i2 or i3) with severe tubulitis (t3) involving 1 or more tubules, not including tubules that are severely atrophic[5] |
| Grade IIA[1] | Mild to moderate intimal arteritis (v1), with or without interstitial inflammation and/or tubulitis |
| Grade IIB[1] | Severe intimal arteritis (v2), with or without interstitial inflammation and/or tubulitis |
| Grade III[1] | Transmural arteritis and/or arterial fibrinoid necrosis of medial smooth muscle with accompanying mononuclear cell intimal arteritis (v3), with or without interstitial inflammation and/or tubulitis |

*Racusen LC, et al. Kidney Int 1999*

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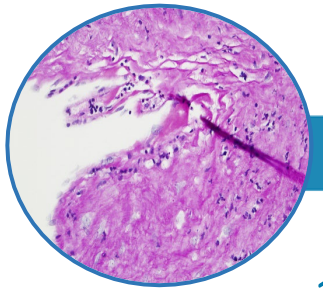

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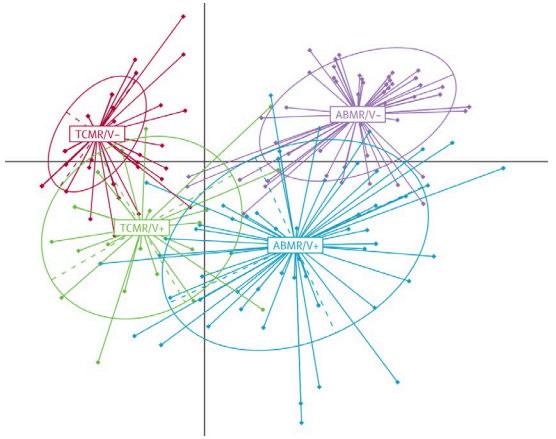
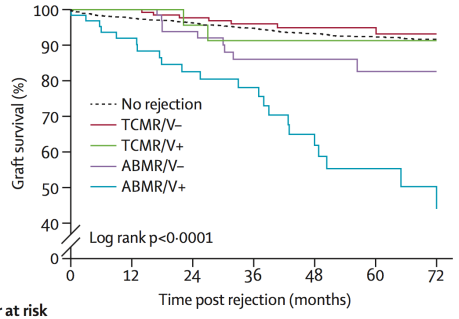
## 2. ABMR

**Table 2:** Revised (Banff 2013) classification of antibody-mediated rejection (ABMR) in renal allografts

**Acute/active ABMR; all three features must be present for diagnosis**[1,2]

1. Histologic evidence of acute tissue injury, including one or more of the following:
   Microvascular inflammation ($g > 0$[3] and/or $ptc > 0$)
   Intimal or transmural arteritis ($v > 0$)[4]
   Acute thrombotic microangiopathy, in the absence of any other cause
   Acute tubular injury, in the absence of any other apparent cause
2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
   Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or $C4d > 0$ by IHC on paraffin sections)
   At least moderate microvascular inflammation ($[g + ptc] \geq 2$)[5]
   Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated[6]
3. Serologic evidence of donor-specific antibodies (DSAs) (HLA or other antigens)



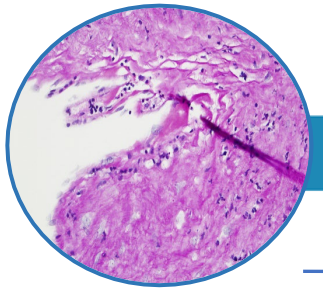




**Number at risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| No rejection | 1777 | 1600 | 1408 | 1152 | 933 | 673 | 473 |
| TCMR/V– | 139 | 136 | 121 | 101 | 77 | 54 | 29 |
| TCMR/V+ | 26 | 26 | 23 | 20 | 15 | 12 | 4 |
| ABMR/V– | 73 | 68 | 56 | 42 | 28 | 19 | 7 |
| ABMR/V+ | 64 | 52 | 41 | 32 | 21 | 12 | 9 |

*Racusen LC, et al. Kidney Int 1999; Lefaucheur C, et al. Lancet 2013; Haas M, et al. AJT 2014*

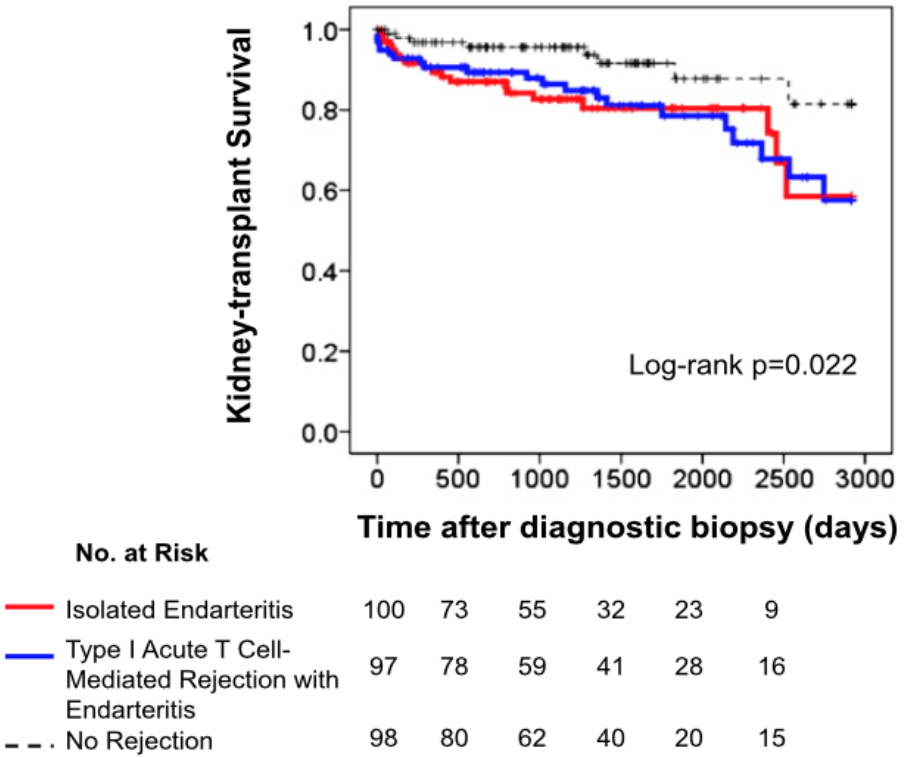
# ¿Qué sabemos de la endarteritis aislada?



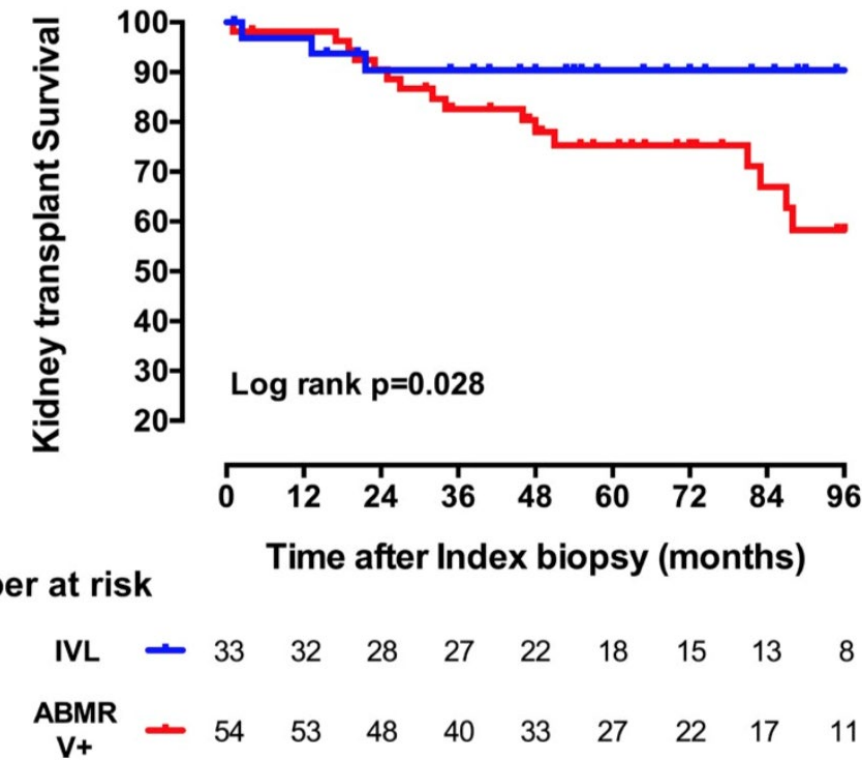
1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011 2013 2015 2017 2019 2022

## SUPERVIVENCIA DEL INJERTO

### v-aislada vs TCMR+v

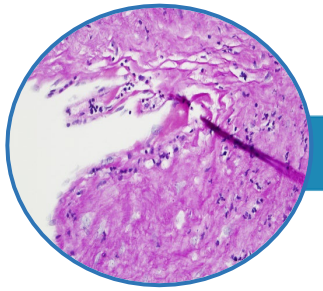



### v-aislada vs ABMR+v




*Sis B, et al. JASN 2015; Rabant M, et al AJT 2018*

# La endarteritis aislada temprana puede no representar rechazo

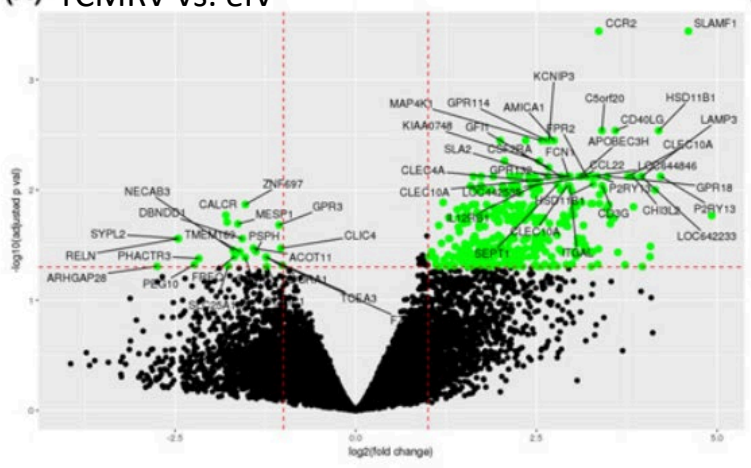


1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011 2013 2015 2017 2019 2022

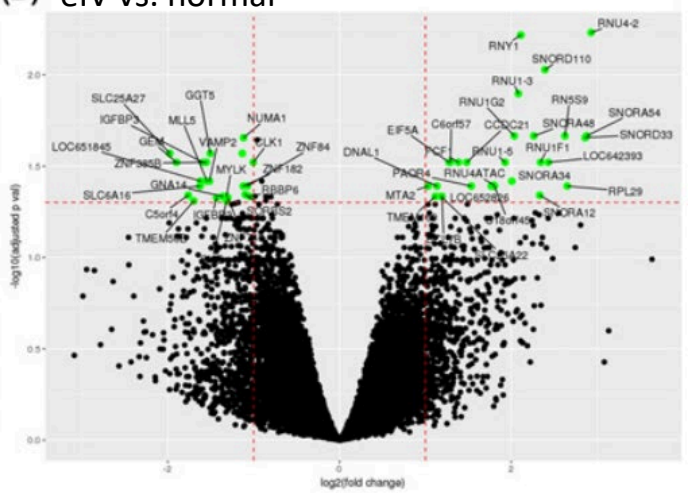
Kidney transplant recipients at Dept. of Nephrology IKEM (years 2009-2014) n=1211

- no acute vascular rejection
- Acute vascular rejection (AVR) n=136
  - AVR > 1 month after Tx
  - early AVR (< 1 month after Tx) n= 84
    - Antibody- mediated phenotype of AVR (histology and/or DSA positivity)
    - early T cell- mediated phenotype of AVR n= 35
      - biopsy sample unavailable or insufficient for microarray evaluation
      - biopsy sample eligible for microarray evaluation n= 10
        - TCMRV n= 4
        - eIV n= 6

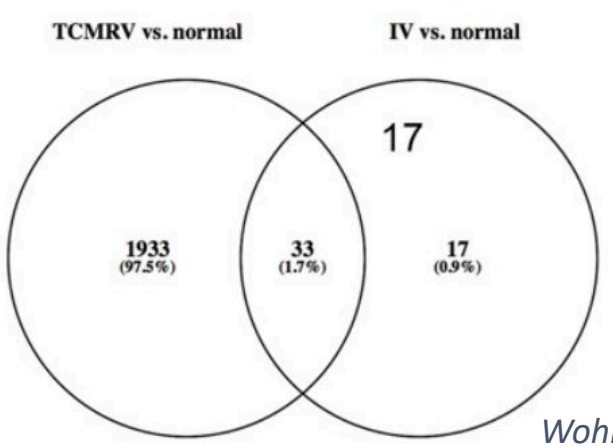
(A) TCMRV vs. eIV




(B) eIV vs. normal

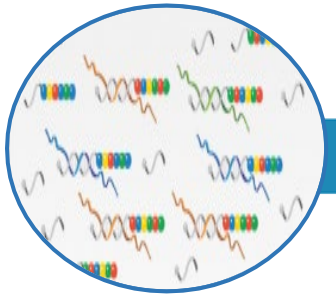



(C)



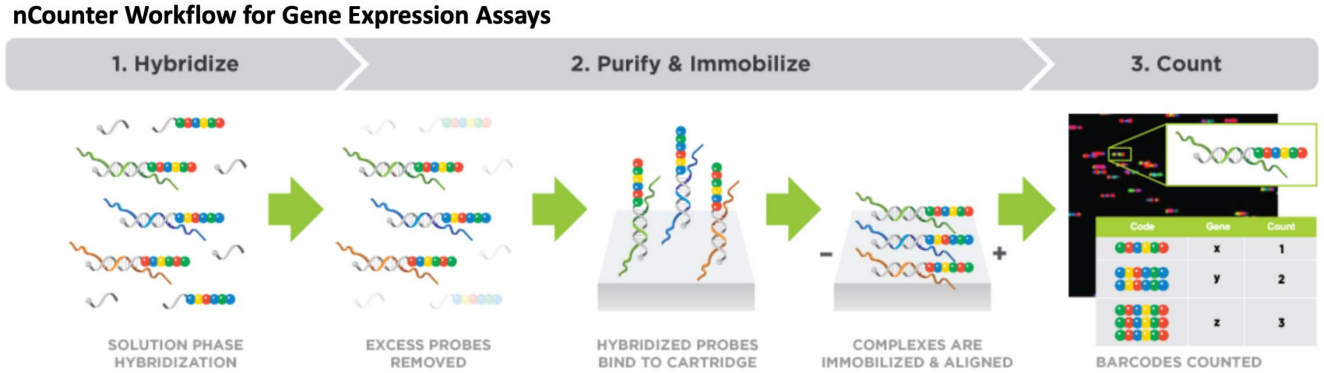

*Wohlfahrtova M, et al. Clin Science 2018*

# ¿Qué sabemos de la Tecnología nCounter® Nanostring?



1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011 2013 2015 2017 2019 2022

- Permite cuantificar digitalmente moléculas de RNA, DNA y proteínas mediante detección molecular directa.
- Sistema de identificación mediante un “código de barras” molecular: combinación secuencial de 6 unidades de fluorocromos de 4 colores diferentes asociados a cada molécula.
- Los “códigos de barras” (*reporter probes*) hibridan directamente con las moléculas de interés → cuantificados individualmente sin necesidad de amplificación de las muestras.



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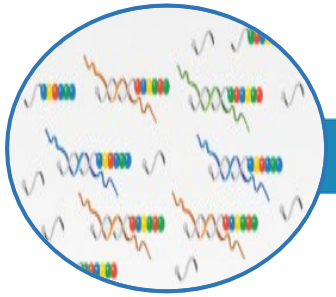

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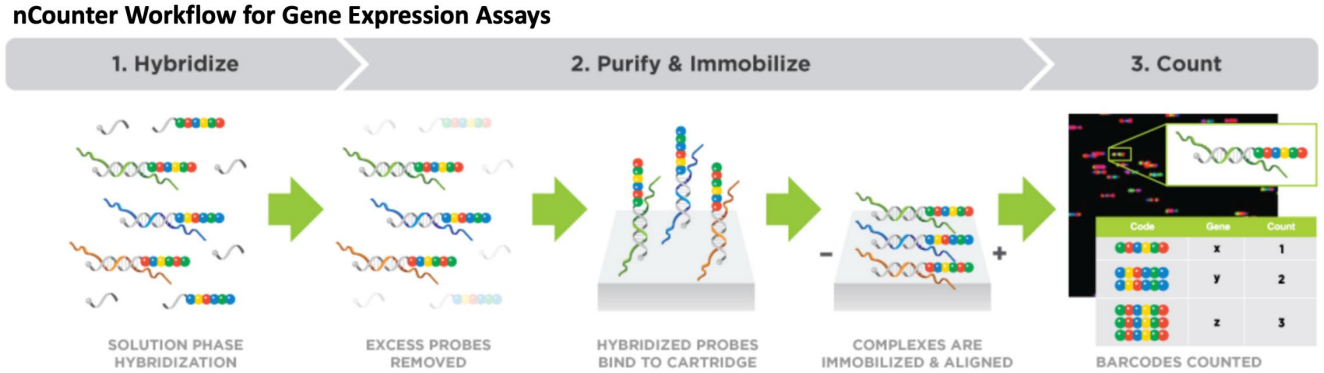
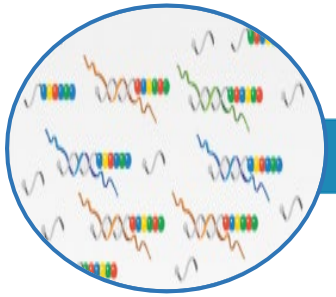
- Los "códigos de barras" (*reporter probes*) hibridan directamente con las moléculas de interés → cuantificados individualmente sin necesidad de amplificación de las muestras.
- Poca cantidad de muestra (100 nucleótidos continuos).
- Capacidad de multiplexar 800 genes en una sola reacción.
- Gran sensibilidad y reproducibilidad.



# B-HOT gene panel



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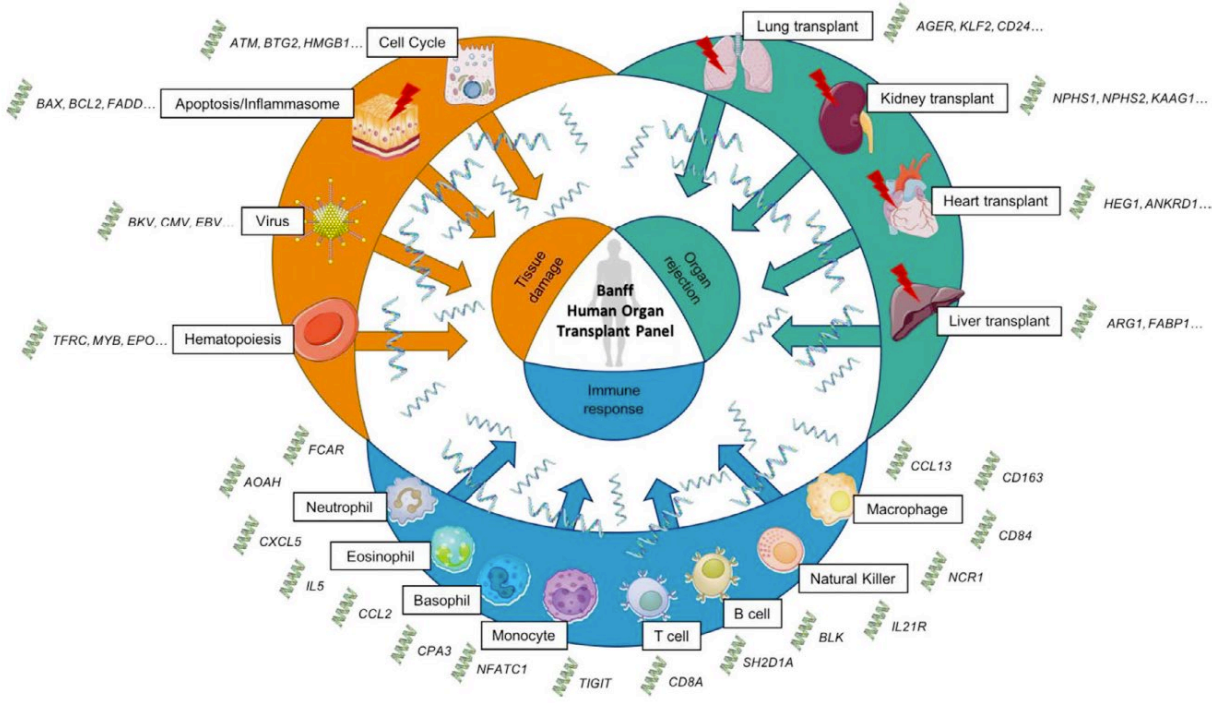
AJT

MEETING REPORT

## Banff 2019 Meeting Report: Molecular diagnostics in solid organ transplantation–Consensus for the Banff Human Organ Transplant (B-HOT) gene panel and open source multicenter validation

Michael Mengel[1] | Alexandre Loupy[2] | Mark Haas[3] | Candice Roufosse[4] | Maarten Naesens[5,6] | Enver Akalin[7] | Marian C. Clahsen-van Groningen[8] | Jessy Dagobert[2] | Anthony J. Demetris[9] | Jean-Paul Duong van Huyen[2] | Juliette Gueguen[2] | Fadi Issa[10] | Blaise Robin[2] | Ivy Rosales[11] | Jan H. Von der Thüsen[8] | Alberto Sanchez-Fueyo[12] | Rex N. Smith[11] | Kathryn Wood[10] | Benjamin Adam[1] | Robert B. Colvin[11]




770 genes

# Objetivos

El **objetivo** de este trabajo fue:

1) Caracterizar los resultados del injerto renal en pacientes con lesiones de v-aislada según el tiempo de aparición pos-TR (**precoz**: ≤1 mes posTR *vs*. **tardía**: >1 mes posTR ).
2) Utilizar la tecnología **NanoString®** para comparar el **fenotipo molecular** de las lesiones de v-aislada con el de otras formas de rechazo v+.

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2) Utilizar la tecnología **NanoString®** para comparar el **fenotipo molecular** de las lesiones de v-aislada con el de otras formas de rechazo v+.

Para este propósito, comparamos los resultados clínicos y el fenotipo molecular (transcritos de ARN en tejido renal) en receptores de trasplante renal (TR) con biopsias de injerto que incluían:

a) Isolated v+
b) ABMR v+
c) TCMR v+
d) Mixed rejection v+
e) Controls (biopsias pre-implante)

# Métodos

**92 biopsias TR**

(tejido parafinado)

- **Isolated v+** (n=23)
  - **Early** (n=10)
  - **Late** (n=13)
- **ABMR v+** (n=26)
- **TCMR v+** (n=10)
- **Mixed rejection v+** (n=23)
- **Controls** (n=10)

Evaluamos conjuntos de genes que incluyen transcritos previamente asociados a:

**ABMR**, DSA (**DSAST**), daño endotelial (**ENDAT**), **TCMR**, **lesión aguda/precoz**, **lesión tardía**

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- **Controls** (n=10)

- Comparamos la **expresión génica** entre grupos mediante **PCA** y la **media geométrica** de los recuentos normalizados.
- Analizamos la **SPV del injerto** censurada por muerte según el diagnóstico y tiempo posTR

# Resultados

# Características clínicas y demográficas de la población de estudio

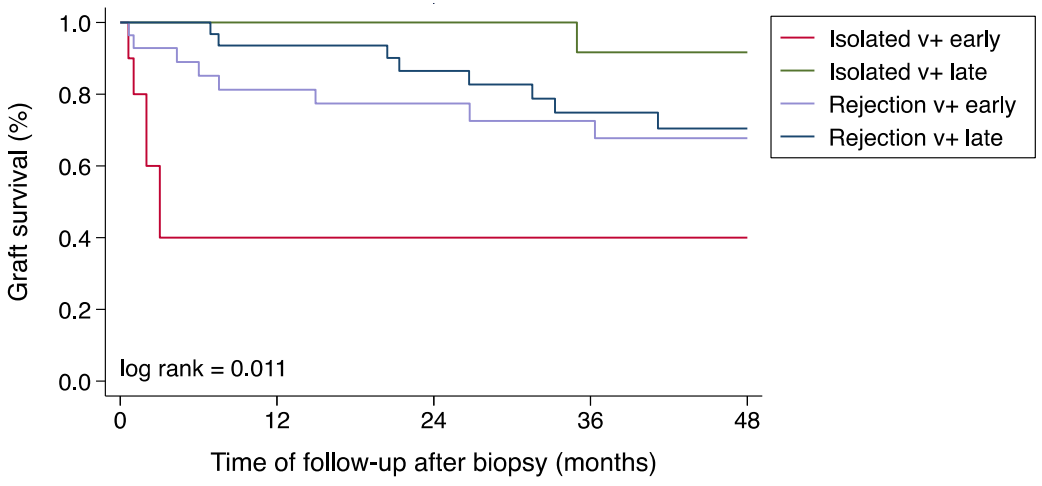
| | Isolated v+ early (n=10) | Isolated v+ late (n=13) | ABMR v+ (n=26) | TCMR v+ (n=10) | Mixed Rejection v+ (n=23) | p-value |
|---|---|---|---|---|---|---|
| **Immunologic profile** | | | | | | |
| HLA-A/B/DR mismatch, mean ± SD | 4.5 ± 1.2 | 4.1 ± 1.0 | 4.4 ± 0.9 | 4.4 ± 1.1 | 4.0 ± 1.5 | 0.799 |
| Pre-transplant HLA-DSA | 0 (0) | 0 (0) | 5 (19.2) | 0 (0) | 3 (13) | 0.247 |
| Post-transplant HLA-DSA (at Bx) | 0 (0) | 0 (0) | **8 (30.8)** | 0 (0) | **8 (34.8)** | **0.007** |
| Post-transplant HLA-DSA (ever after KT) | 0 (0) | 2 (15.4) | **10 (38.5)** | 4 (40) | **12 (52.2)** | **0.019** |
| **Baseline immunosuppression** | | | | | | |
| Induction therapy, N (%) | | | | | | |
| None | 0 (0) | 0 (0) | 0 (0) | 1 (10) | 0 (0) | |
| Antithymocyte globulin | 0 (0) | 1 (7.7) | **9 (34.6)** | 1 (10) | 0 (0) | **0.001** |
| Basiliximab | 8 (80) | 8 (61.5) | 17 (65.4) | 8 (80) | 18 (78.3) | |
| Daclizumab | 2 (20) | 4 (30.8) | 0 (0) | 0 (0) | 5 (21.7) | |
| **Maintenance immunosuppression** | | | | | | |
| Corticosteroids, N (%) | 10 (100) | 13 (100) | 26 (100) | 10 (100) | 22 (95.7) | 0.683 |
| CNI, N (%) | 10 (100) | 13 (100) | 26 (100 | 10 (100) | 23 (100) | n.s. |
| Mycophenolate mofetil, N (%) | **4 (40)** | 13 (100) | 23 (88.5) | 10 (100) | 19 (92.6) | **0.002** |
| De novo mTORi, N (%) | **6 (60)** | 0 (0) | 3 (11.5) | 0 (0) | 4 (17.4) | **0.002** |
| **Follow-up times** | | | | | | |
| Median time from KT to Bx, months, median (IQR) | **0.4 (0.3 – 0.7)** | 4.8 (2.4 – 12.0) | **0.5 (0.4 – 6.4)** | 2.4 (0.9 – 5.8) | 2.3 (0.5- 5.7) | **0.002** |
| Follow-up time after KT, years, median (IQR) | **0.3 (0.2 – 4.7)** | 4.3 (3.2 – 5.8) | 2.6 (1.2 – 4.5) | 6.9 (4.8 – 9.4) | 3.0 (1.7 – 6.2) | **0.001** |
| Follow-up time after Bx, years, median (IQR) | **0.2 (0.1 – 4.7)** | 3.8 (3.1 – 4.7) | 2.0 (1.2 – 3.7) | 5.7 (4.0 – 8.7) | 3.0 (1.2 – 5.5) | **0.002** |

# Resultados del injerto y del paciente

| | Isolated v+ early (n=10) | Isolated v+ late (n=13) | ABMR v+ (n=26) | TCMR v+ (n=10) | Mixed Rejection v+ (n=23) | p-value |
|---|---|---|---|---|---|---|
| Delayed graft function, N (%) | **9 (90)** | 2 (15.4) | 16 (61.5) | 1 (10) | 9 (39.1) | **<0.001** |
| Primary non-function, N (%) | **6 (60)** | 0 (0) | 2 (7.7) | 0 (0) | 0 (0) | **<0.001** |
| Chronic graft dysfunction after the episode, N (%) | 0 (0) | 3 (23.1) | 9 (45) | 0 (0) | 7 (31.8) | 0.066 |
| Graft loss due to the episode, N (%) | **6 (60)** | 0 (0) | 5 (19.2) | 1 (10) | 1 (4.4) | **0.001** |
| Global death-censored graft failure, N (%) | **6 (60)** | 1 (7.7) | 8 (30.8) | 3 (30) | 12 (52.2) | **0.035** |
| Mortality, N (%) | 1 (10) | 3 (23.1) | 6 (23.1) | 3 (30) | 2 (8.7) | 0.505 |

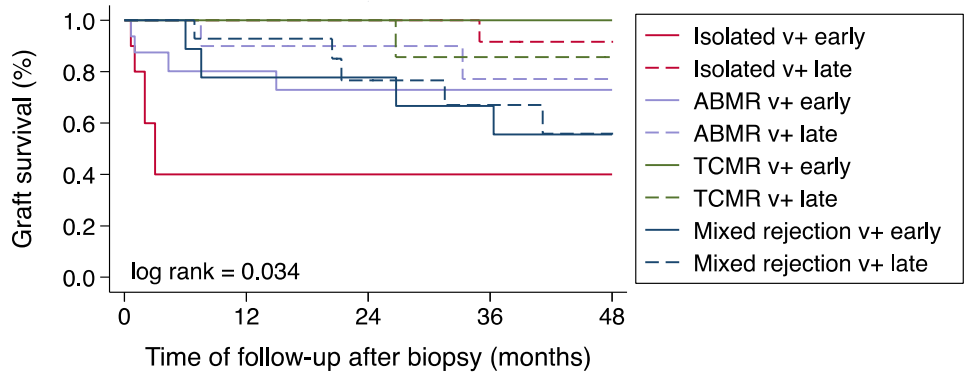
# Supervivencia del injerto censurada por muerte

A



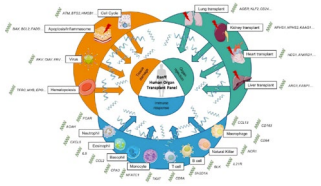

| Number at risk | | | | | |
|---|---|---|---|---|---|
| Early isolated-v | 10 | 3 | 3 | 3 | 3 |
| Late isolated-v | 13 | 13 | 13 | 11 | 8 |
| Early v-rejection | 28 | 21 | 18 | 15 | 12 |
| Late v-rejection | 31 | 29 | 24 | 18 | 15 |

B




| Number at risk | | | | | |
|---|---|---|---|---|---|
| Isolated v+ early | 10 | 3 | 3 | 3 | 3 |
| Isolated v+ late | 13 | 13 | 13 | 11 | 8 |
| ABMR v+ early | 16 | 11 | 8 | 6 | 4 |
| ABMR v+ late | 10 | 9 | 8 | 6 | 5 |
| TCMR v+ early | 3 | 3 | 3 | 3 | 3 |
| TCMR v+ late | 7 | 7 | 7 | 6 | 5 |
| Mixed rejection v+ early | 9 | 7 | 7 | 6 | 5 |
| Mixed rejection v+ late | 14 | 13 | 9 | 6 | 5 |

# Patrones de expresión génica entre los diferentes fenotipos v+

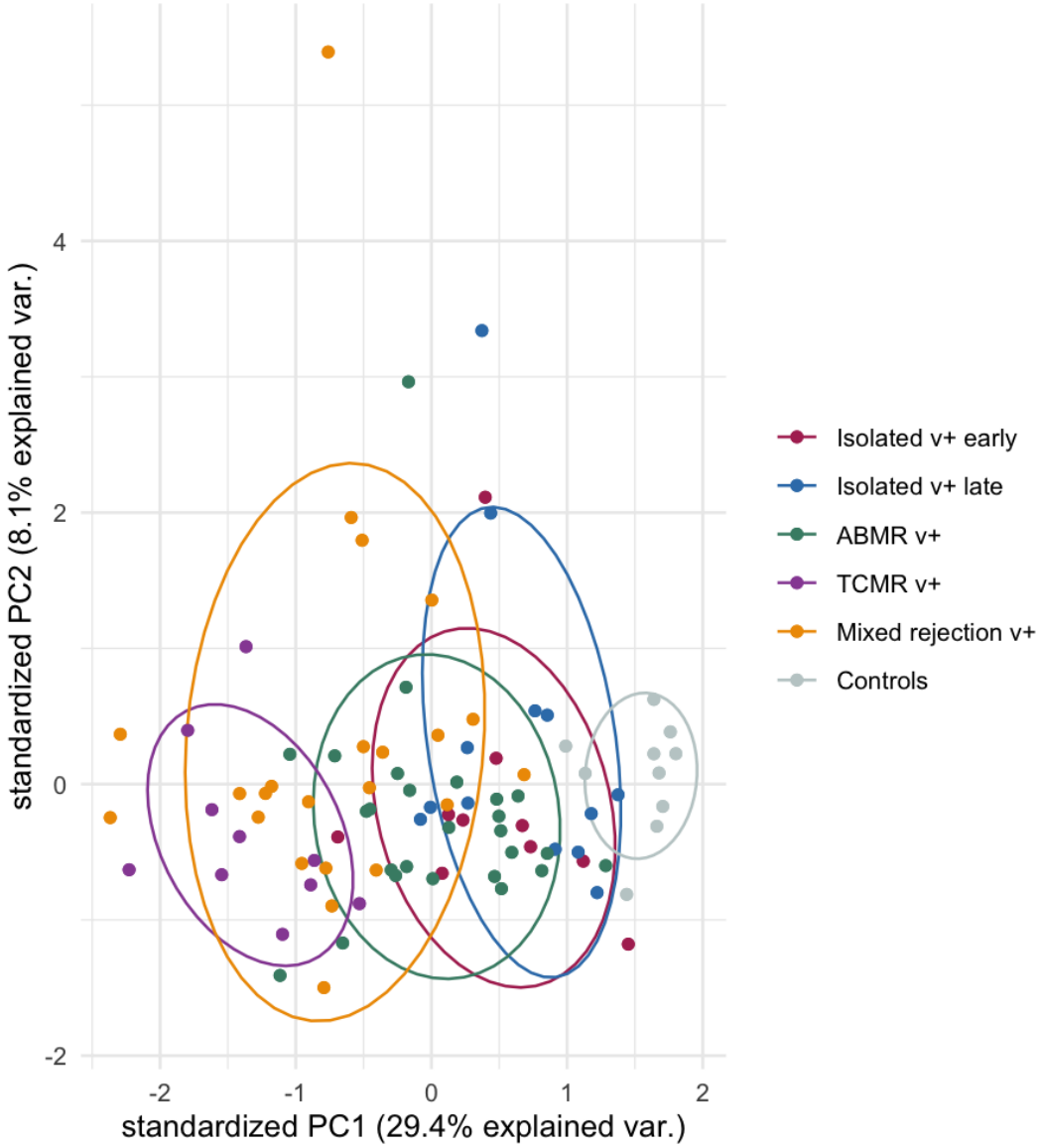


770 genes

268 excluded due to low expression

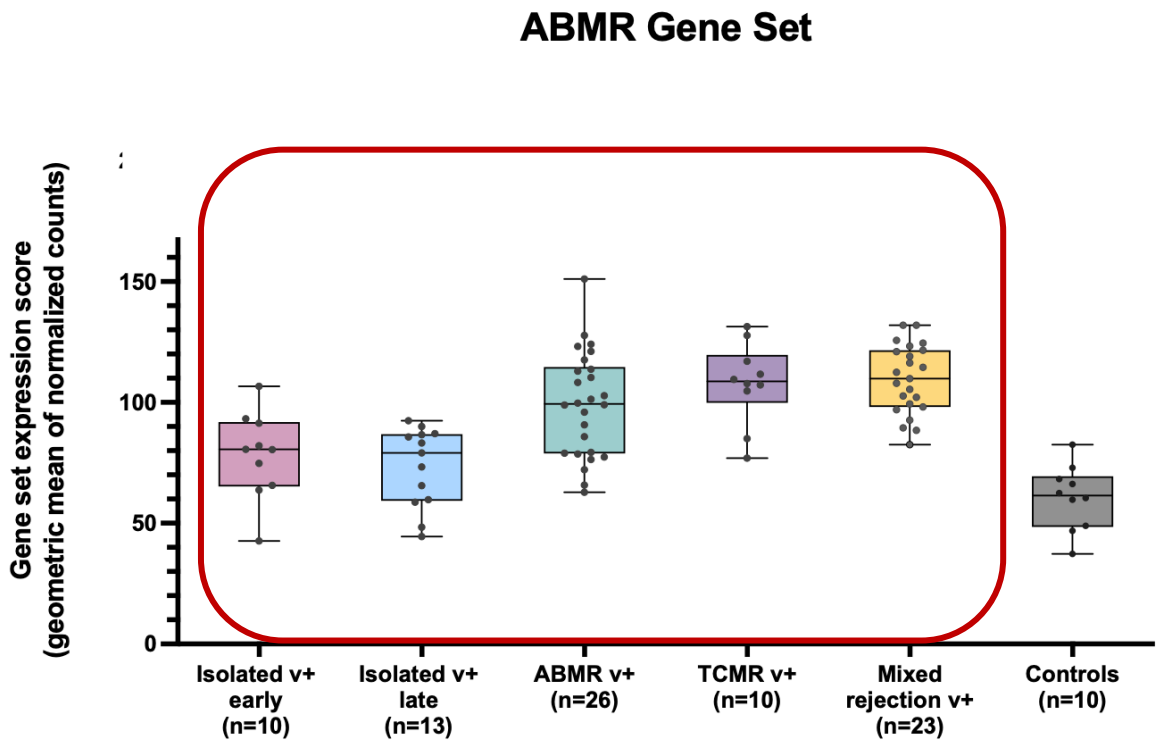
490 experimental genes

12 housekeeping genes



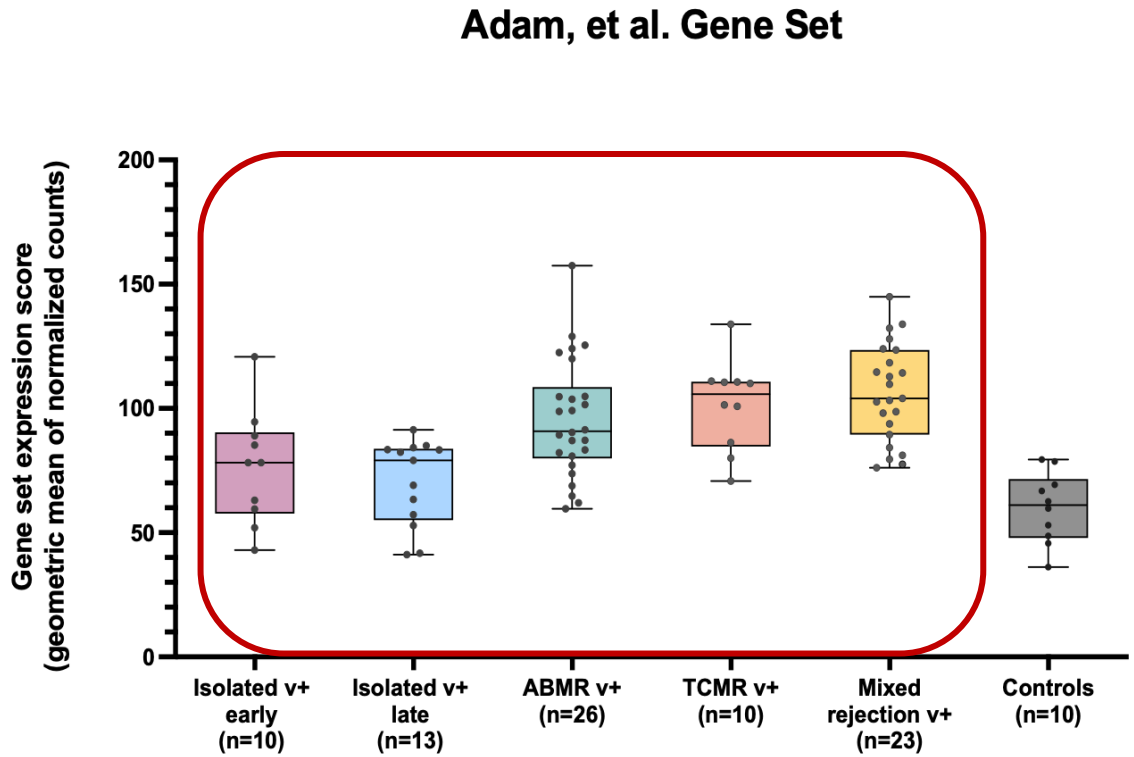
# Análisis de conjuntos de genes entre los diferentes fenotipos v+

A




| | | | | | | |
|---|---|---|---|---|---|---|
| Isolated v+ Early | | 0.577 | **0.022** | **0.003** | **<0.001** | 0.137 |
| Isolated v+ Late | 0.577 | | **0.002** | **0.001** | **<0.001** | 0.072 |
| ABMR v+ | **0.022** | **0.002** | | 0.230 | 0.060 | **<0.001** |
| TCMR v+ | **0.003** | **0.001** | 0.230 | | 0.845 | **0.002** |
| Mixed rejection v+ | **<0.001** | **<0.001** | 0.060 | 0.845 | | **<0.001** |
| Controls | 0.137 | 0.072 | **<0.001** | **0.002** | **<0.001** | |

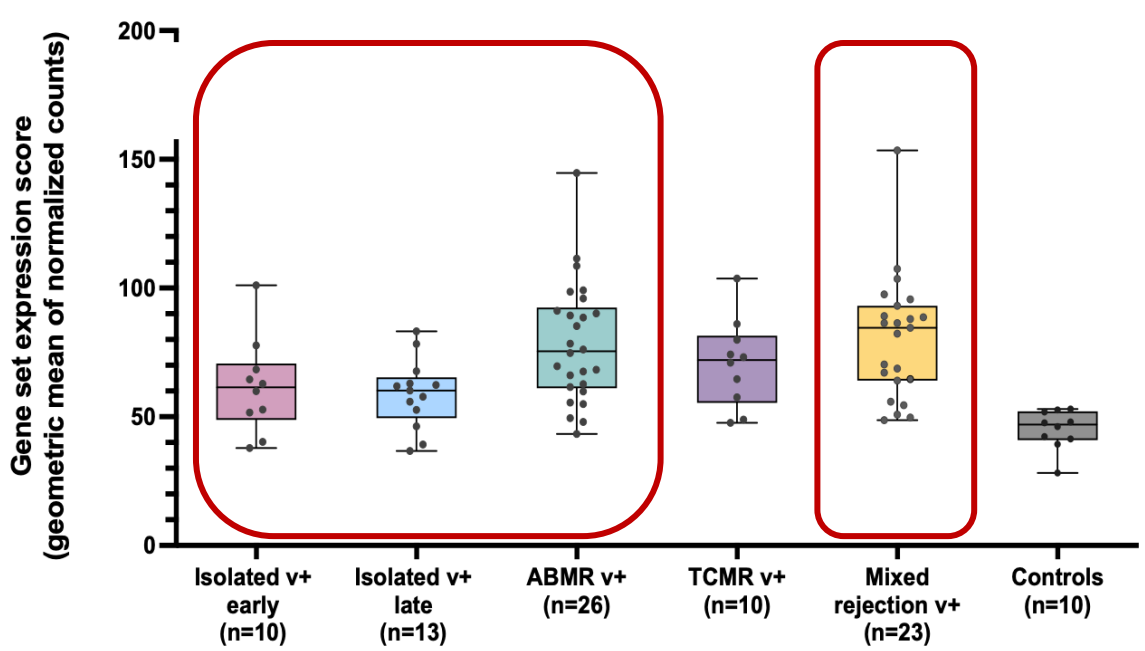
B




| | | | | | | |
|---|---|---|---|---|---|---|
| Isolated v+ Early | | 0.577 | **0.031** | **0.019** | **0.003** | 0.256 |
| Isolated v+ Late | 0.577 | | **0.003** | **0.002** | **<0.001** | 0.107 |
| ABMR v+ | **0.031** | **0.003** | | 0.359 | 0.096 | **<0.001** |
| TCMR v+ | **0.019** | **0.002** | 0.359 | | 0.557 | **<0.001** |
| Mixed rejection v+ | **0.003** | **<0.001** | 0.096 | 0.557 | | **<0.001** |
| Controls | 0.256 | 0.107 | **<0.001** | **<0.001** | **<0.001** | |

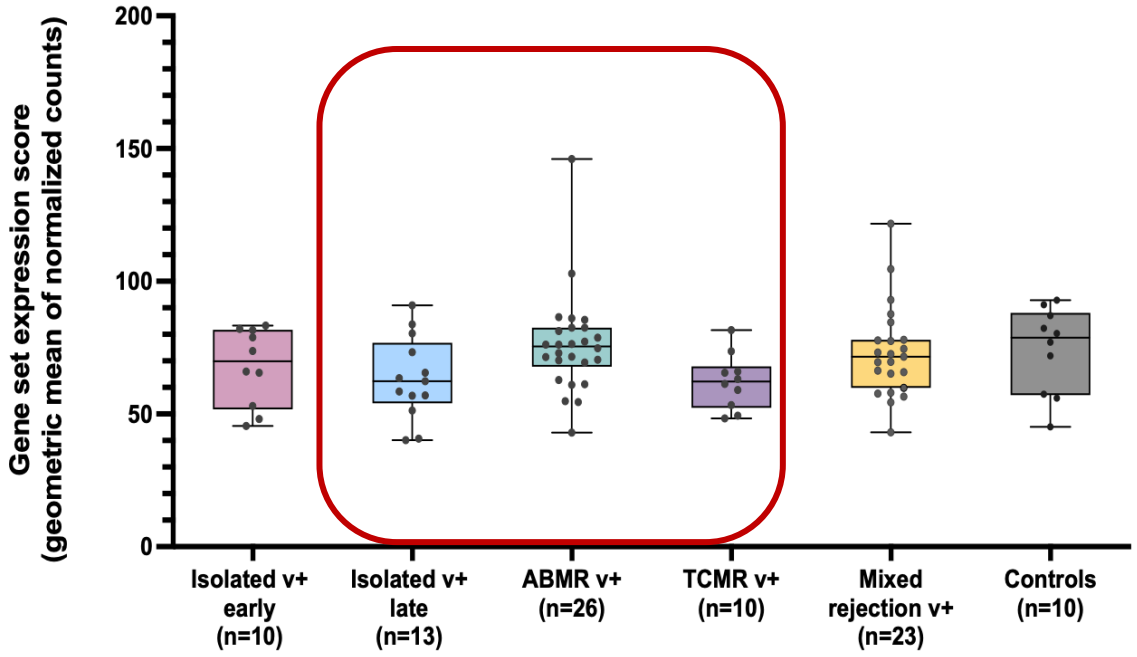
# Análisis de conjuntos de genes entre los diferentes fenotipos v+

C




| | | | | | | |
|---|---|---|---|---|---|---|
| **Isolated v+ Early** | | 0.710 | 0.057 | 0.199 | **0.031** | 0.170 |
| **Isolated v+ Late** | 0.710 | | **0.009** | 0.094 | **0.004** | **0.016** |
| **ABMR v+** | 0.057 | **0.009** | | 0.397 | 0.841 | **<0.001** |
| **TCMR v+** | 0.199 | 0.094 | 0.397 | | 0.240 | **0.001** |
| **Mixed rejection v+** | **0.031** | **0.004** | 0.841 | 0.240 | | **<0.001** |
| **Controls** | 0.170 | **0.016** | **<0.001** | **0.001** | **<0.001** | |

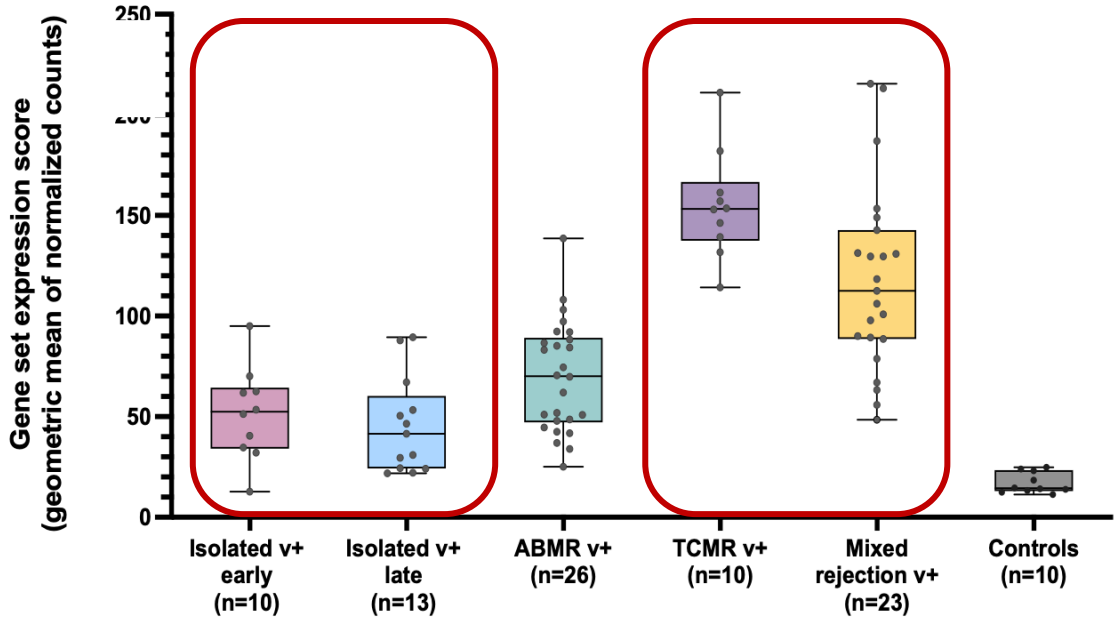
D




| | | | | | | |
|---|---|---|---|---|---|---|
| **Isolated v+ Early** | | 0.420 | 0.359 | 0.364 | 0.667 | 1.000 |
| **Isolated v+ Late** | 0.420 | | **0.046** | 1.000 | 0.110 | 0.137 |
| **ABMR v+** | 0.359 | **0.046** | | **0.013** | 0.447 | 0.646 |
| **TCMR v+** | 0.364 | 1.000 | **0.013** | | 0.060 | 0.096 |
| **Mixed rejection v+** | 0.667 | 0.110 | 0.447 | 0.060 | | 0.611 |
| **Controls** | 1.000 | 0.137 | 0.646 | 0.096 | 0.611 | |

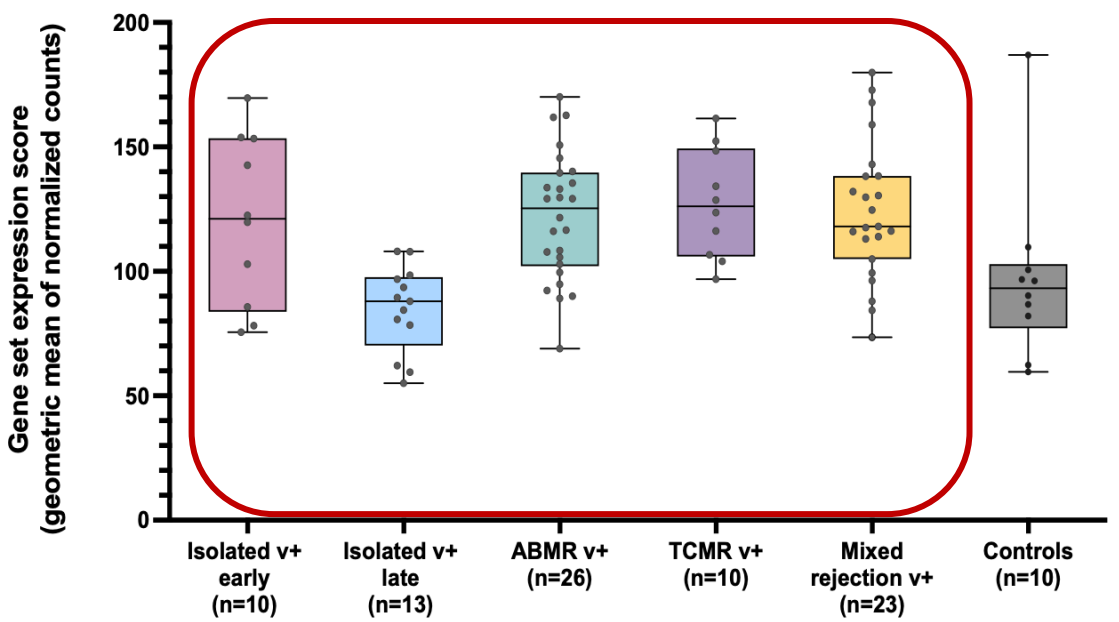
# Análisis de conjuntos de genes entre los diferentes fenotipos v+

E




| | | | | | | |
|---|---|---|---|---|---|---|
| Isolated v+ Early | | 0.321 | 0.112 | <0.001 | <0.001 | 0.023 |
| Isolated v+ Late | 0.321 | | 0.009 | <0.001 | <0.001 | <0.001 |
| ABMR v+ | 0.112 | 0.009 | | <0.001 | <0.001 | <0.001 |
| TCMR v+ | <0.001 | <0.001 | <0.001 | | 0.007 | <0.001 |
| Mixed rejection v+ | <0.001 | <0.001 | <0.001 | 0.007 | | <0.001 |
| Controls | 0.023 | <0.001 | <0.001 | <0.001 | <0.001 | |

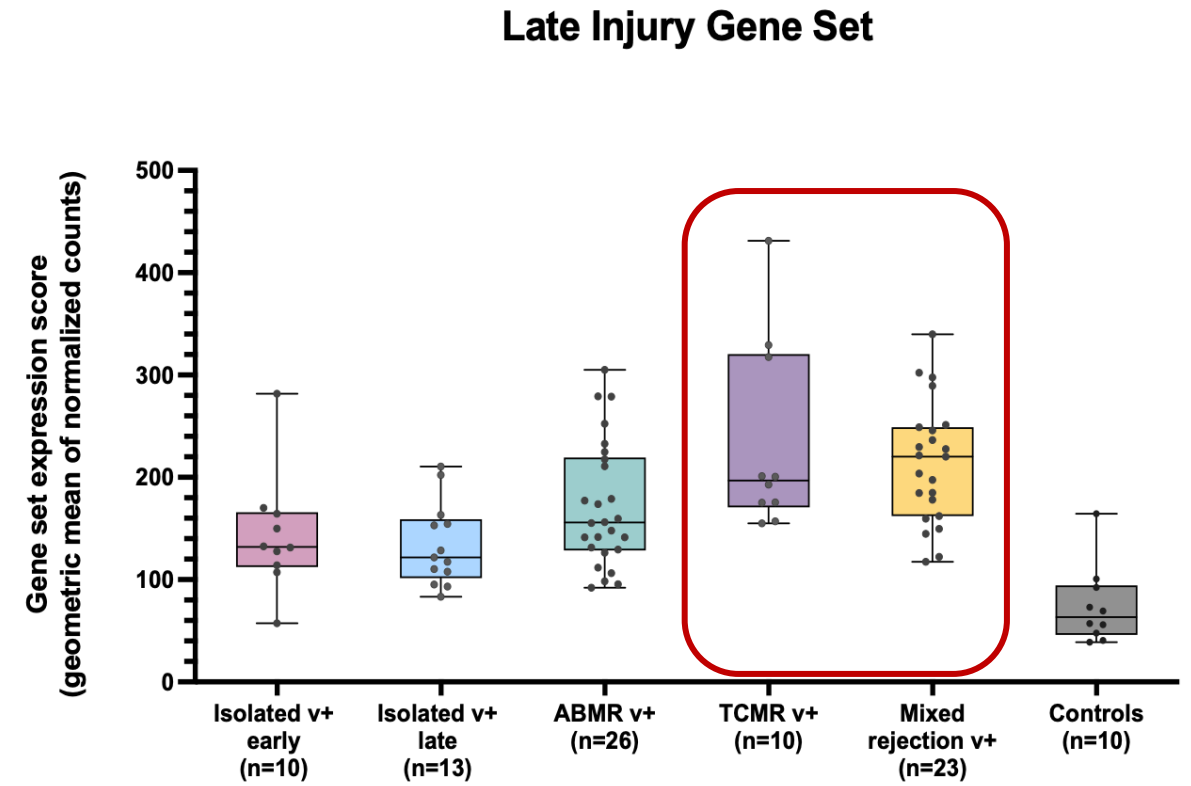
F




| | | | | | | |
|---|---|---|---|---|---|---|
| Isolated v+ Early | | 0.026 | 0.888 | 0.650 | 0.845 | 0.031 |
| Isolated v+ Late | 0.026 | | <0.001 | <0.001 | <0.001 | 0.385 |
| ABMR v+ | 0.888 | <0.001 | | 0.646 | 0.904 | 0.010 |
| TCMR v+ | 0.650 | <0.001 | 0.646 | | 0.754 | 0.007 |
| Mixed rejection v+ | 0.845 | <0.001 | 0.904 | 0.754 | | 0.008 |
| Controls | 0.031 | 0.385 | 0.010 | 0.007 | 0.008 | |

# Análisis de conjuntos de genes entre los diferentes fenotipos v+

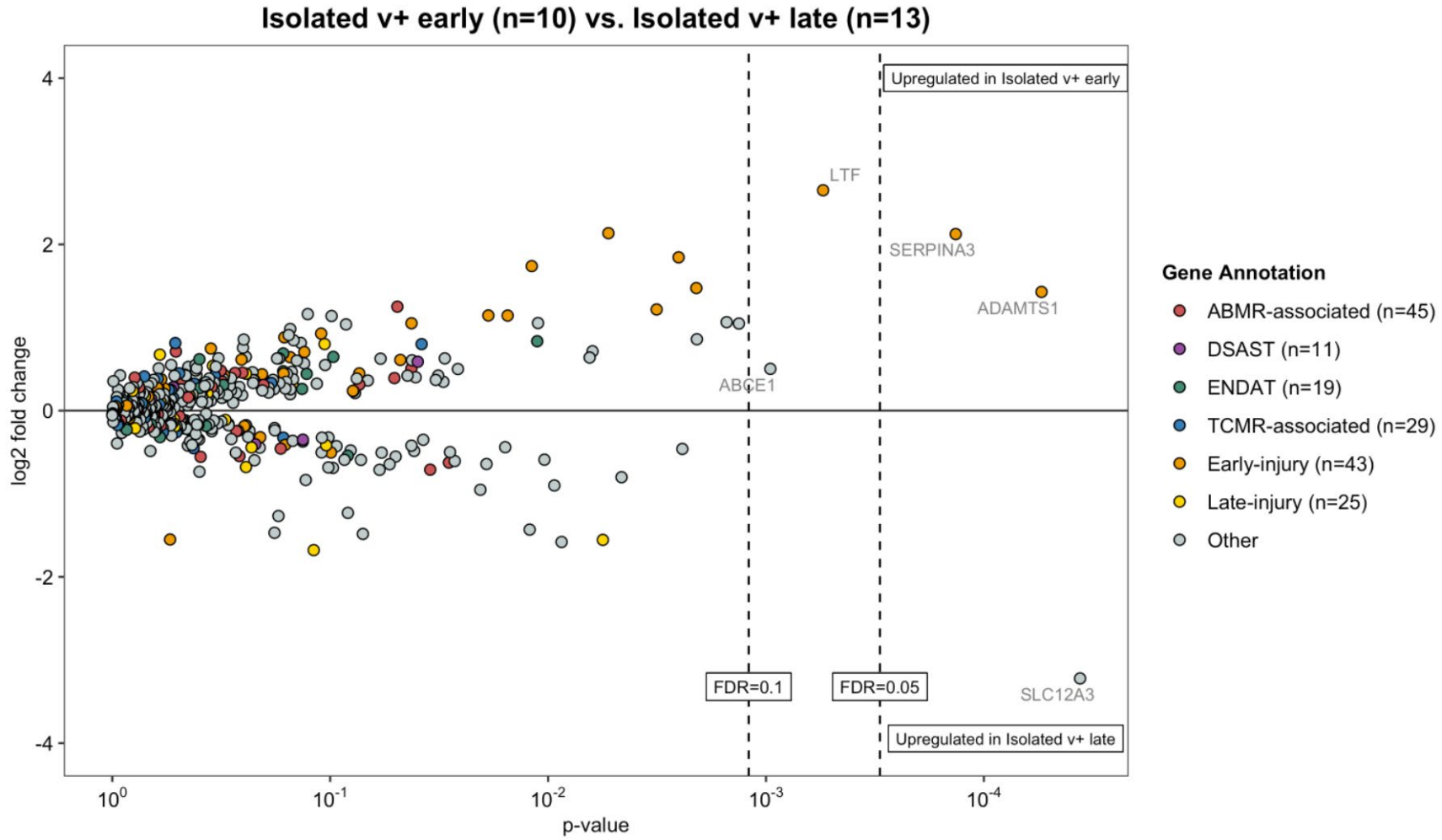
G




| | | | | | | |
|---|---|---|---|---|---|---|
| **Isolated v+ Early** | | 0.577 | 0.258 | **0.003** | **0.004** | 0.066 |
| **Isolated v+ Late** | 0.577 | | **0.043** | **0.002** | **<0.001** | **0.002** |
| **ABMR v+** | 0.258 | **0.043** | | **0.034** | **0.013** | **<0.001** |
| **TCMR v+** | **0.003** | **0.002** | **0.034** | | 0.969 | **<0.001** |
| **Mixed rejection v+** | **0.004** | **<0.001** | **0.013** | 0.969 | | **<0.001** |
| **Controls** | 0.066 | **0.002** | **<0.001** | **<0.001** | **<0.001** | |

# Comparación por pares de expresión génica entre diferentes fenotipos v+

A



# Conclusiones

- Estos resultados sugieren que las lesiones de v-aislada muestran **menor expresión de genes relacionados con TCMR** que el grupo de TCMR v+ y rechazo mixto v+.

- Asimismo, las lesiones de v-aislada muestran una **menor expresión de genes relacionados con ABMR** que el grupo de ABMR.

- La v-aislada temprana confiere un **mal pronóstico** y se asocia a **mayor expresión de genes de lesión precoz/aguda** en comparación con la v-aislada tardía, cosa que sugiere una etiología distinta.

- Estos resultados son de interés de cara a optimizar las estrategias terapéuticas. Sin embargo, son necesarios más trabajos para validar los resultados observados.

# Agradecimientos

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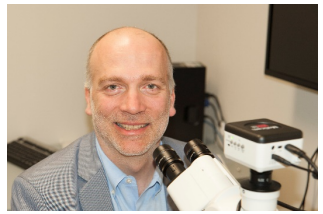
Institut Hospital del Mar d'Investigacions Mèdiques



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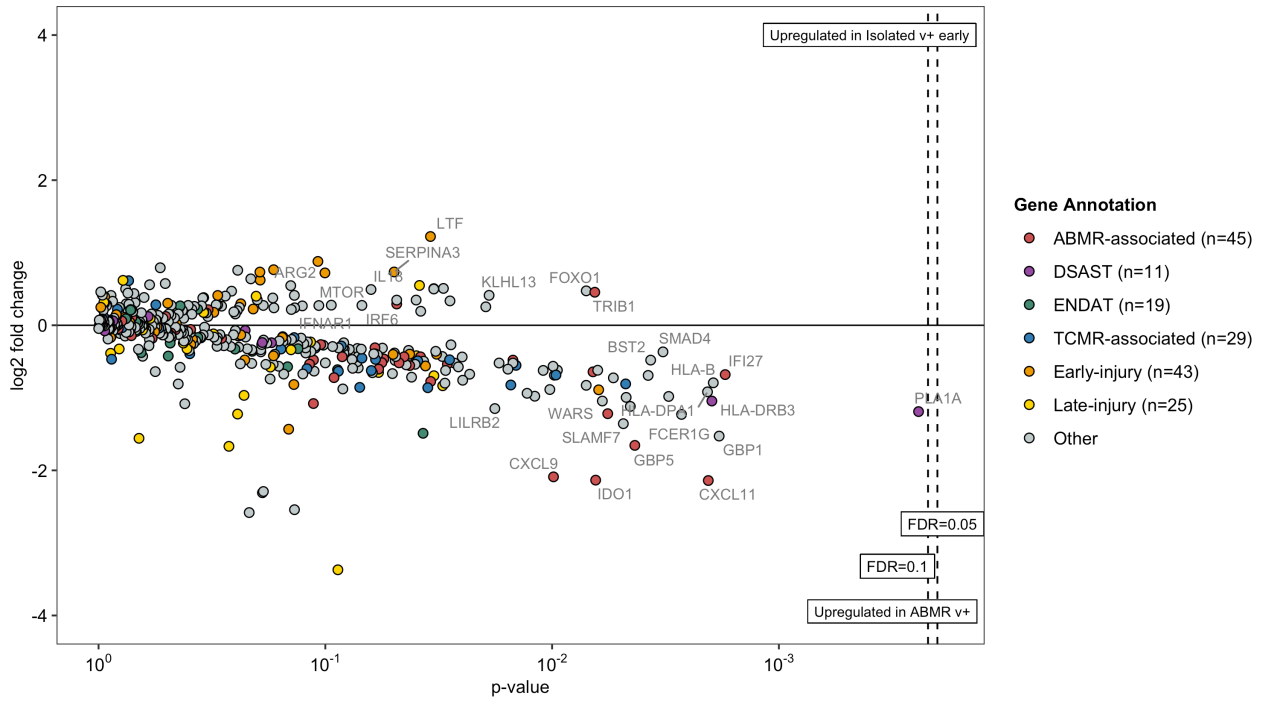
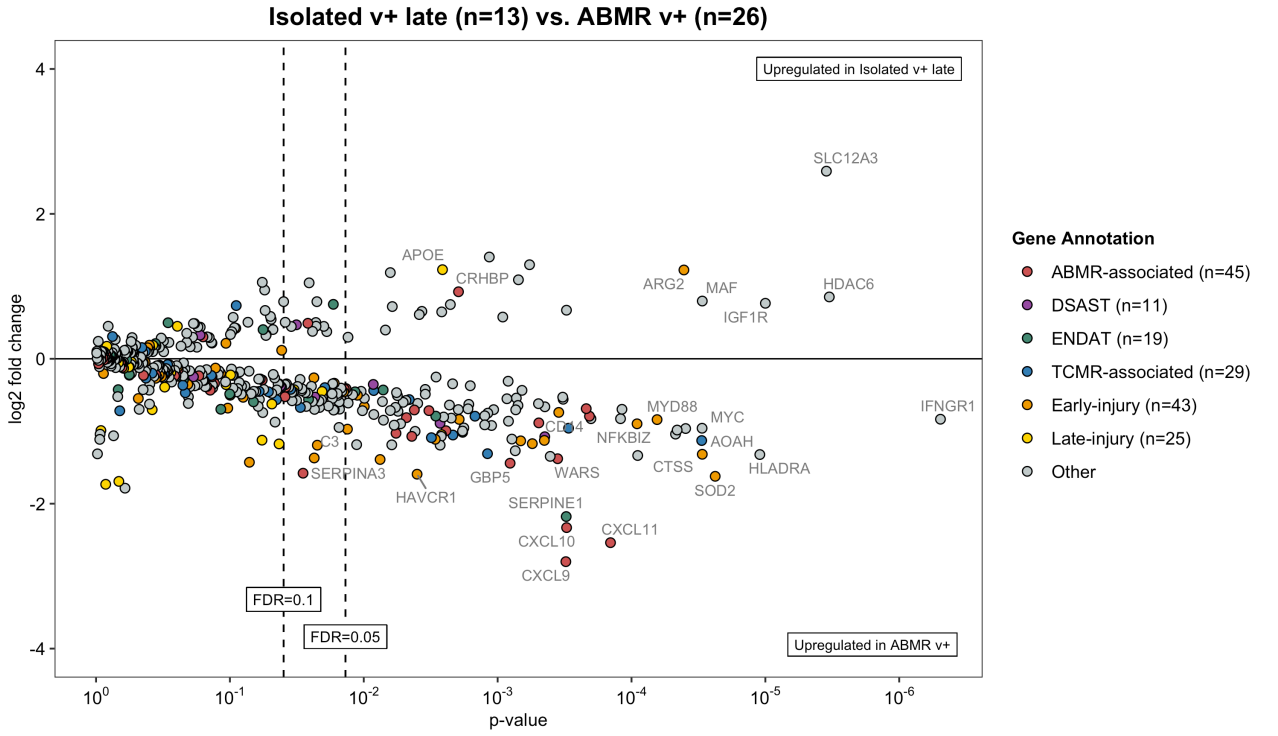
Parc de Salut MAR Barcelona

# Comparación por pares de expresión génica entre diferentes fenotipos v+

B

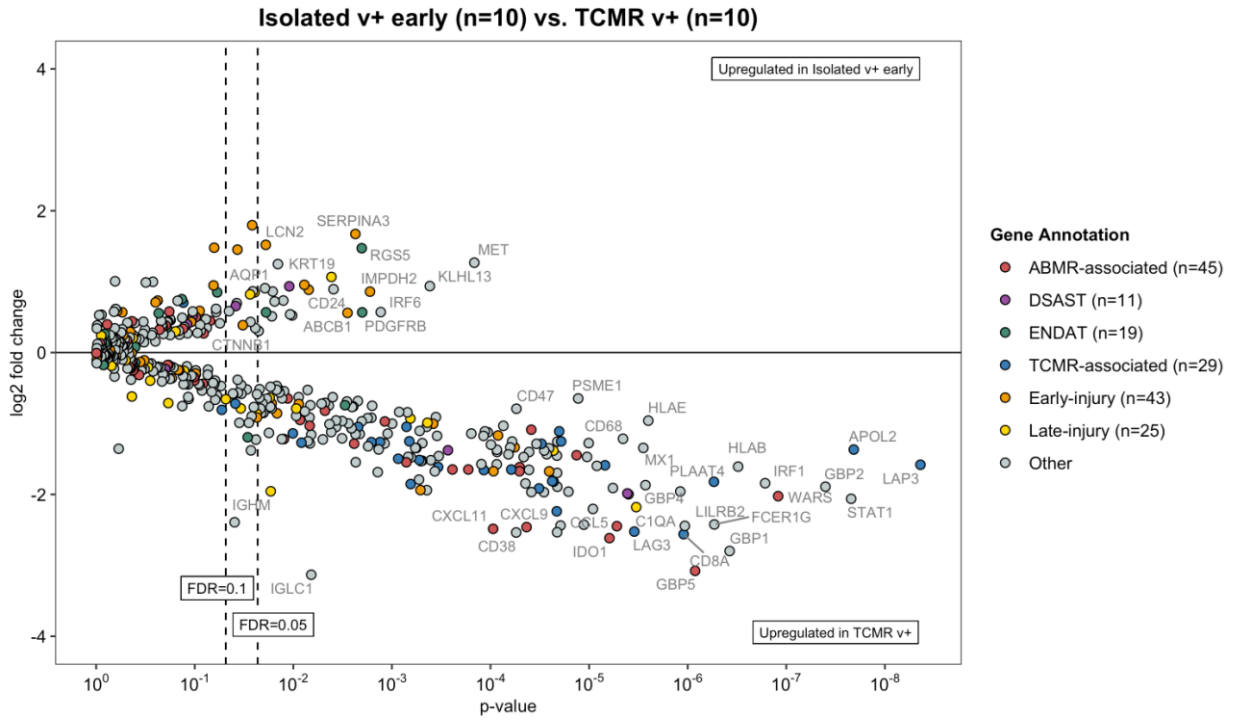



C

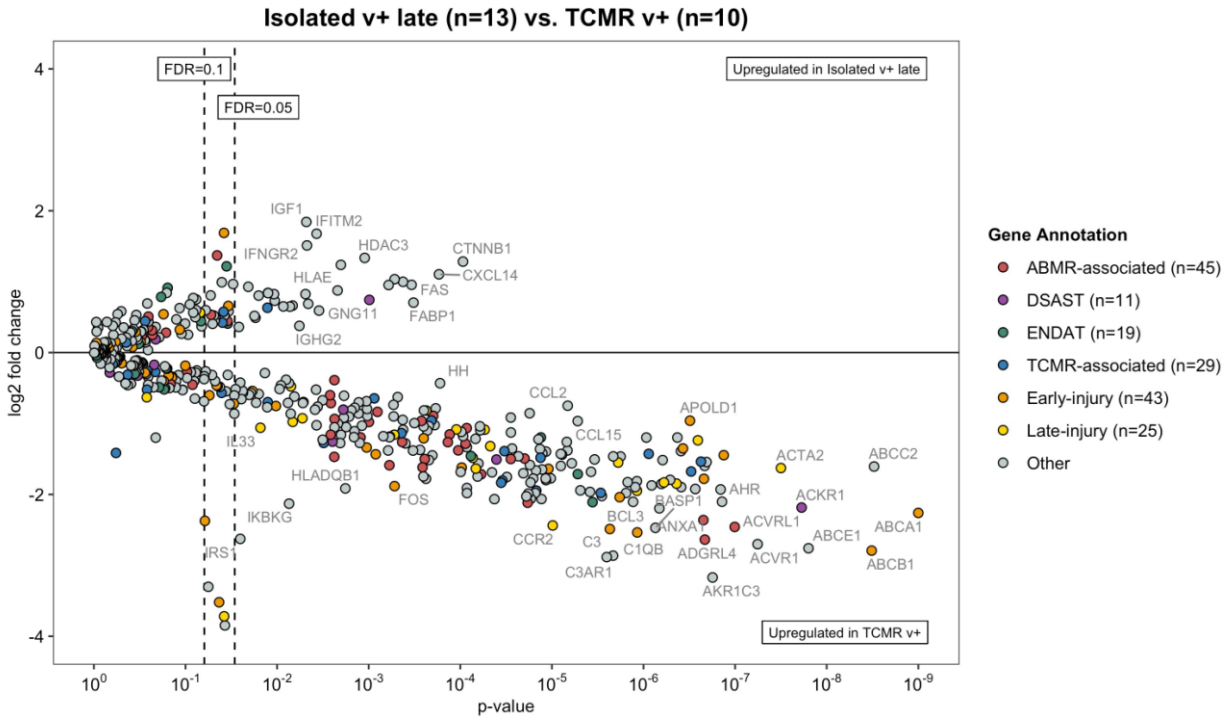


# Comparación por pares de expresión génica entre diferentes fenotipos v+

D

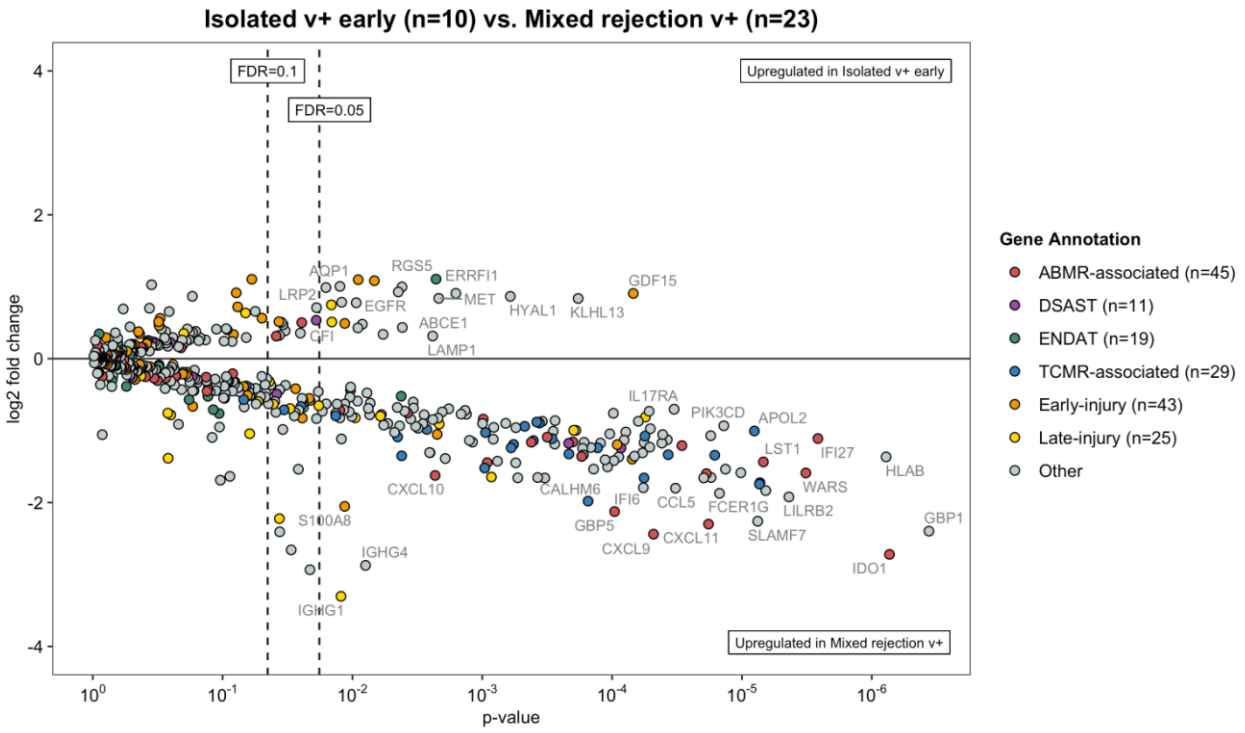



E

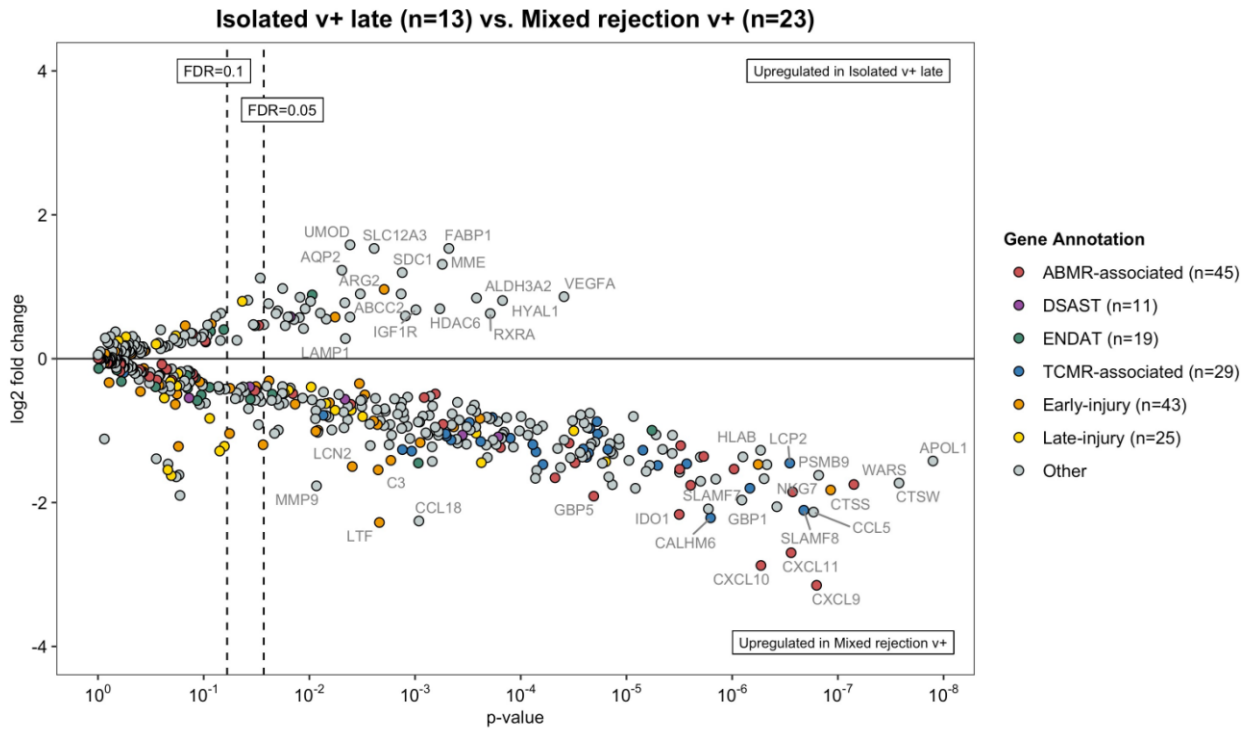


# Comparación por pares de expresión génica entre diferentes fenotipos v+

F




G



# Características clínicas y demográficas de la población de estudio

| | Isolated v+ early (n=10) | Isolated v+ late (n=13) | ABMR v+ (n=26) | TCMR v+ (n=10) | Mixed Rejection v+ (n=23) | Global p-value |
|---|---|---|---|---|---|---|
| Percentage of glomerulosclerosis, mean ± SD | 13.40 ± 11.58 | 7.23 ±7.05 | 10.42 ± 12.16 | 7.30 ± 10.04 | 12.13 ± 10.45 | 0.430 |
| g, mean ± SD | 0 ± 0 | 0 ± 0 | 1.81 ± 1.02 | 0 ± 0 | 1.26 ± 1.25 | **<0.001** |
| g ≥1, n (%) | 0 (0) | 0 (0) | 23 (88.5) | 0 (0) | 14 (60.9) | **<0.001** |
| ptc, mean ± SD | 0.50 ± 0.53 | 0.38 ± 0.51 | 1.46 ± 0.71 | 0.90 ± 0.32 | 1.83 ± 0.49 | **<0.001** |
| ptc ≥1, n (%) | 5 (50) | 5 (38.5) | 23 (88.5) | 9 (90) | 23 (100) | **<0.001** |
| MVI score (g + ptc), mean ± SD | 0.50 ± 0.53 | 0.38 ± 0.51 | 3.27 ± 1.19 | 0.90 ± 0.32 | 3.09 ± 1.47 | **<0.001** |
| MVI (g + ptc ≥2), n (%) | 0 (0) | 0 (0) | 25 (96.2) | 0 (0) | 22 (95.7) | **<0.001** |
| C4d, mean ± SD | 0 ± 0 | 0 ± 0 | 0.85 ± 1.22 | 0 ± 0 | 0.39 ± 0.94 | **0.005** |
| C4d ≥1, n (%) | 0 (0) | 0 (0) | 10 (38.5) | 0 (0) | 4 (17.4) | **0.005** |
| cg, mean ± SD | 0 ± 0 | 0 ± 0 | 0.23 ± 0.65 | 0 ± 0 | 0.09 ± 0.29 | 0.273 |
| cg, n (%) | 0 (0) | 0 (0) | 4 (15.4) | 0 (0) | 2 (8.7) | 0.458 |
| v, mean ± SD | 1.10 ± 0.32 | 1.08 ± 0.28 | 1.15 ± 0.46 | 1.20 ± 0.63 | 1.35 ± 0.71 | 0.699 |
| v ≥1, n (%) | 10 (100) | 13 (100) | 26 (100) | 10 (100) | 23 (100) | n.a. |
| i, mean ± SD | 0.30 ± 0.48 | 0.23 ± 0.44 | 0.15 ± 0.37 | 2.60 ± 0.70 | 1.96 ± 0.88 | **<0.001** |
| i ≥1, n (%) | 3 (30) | 3 (23.1) | 4 (15.4) | 10 (100) | 23 (100) | **<0.001** |
| t, mean ± SD | 0.30 ± 0.48 | 0.31 ± 0.48 | 0.08 ± 0.27 | 2 ± 0.82 | 1.65 ± 0.83 | **<0.001** |
| t ≥1, n (%) | 3 (30) | 4 (30.8) | 2 (7.7) | 10 (100) | 22 (95.7) | **<0.001** |
| Borderline (Banff 2019), n (%) | 2 (20) | 3 (23.1) | 0 (0) | n.a. | 12 (52.2) | **<0.001** |
| ti, mean ± SD | 1.25 ± 0.71 | 0.20 ± 0.42 | 0.64 ± 0.50 | 1 ± 0 | 1.94 ± 0.85 | **<0.001** |
| ti ≥1, n (%) | 8 (100, n=8) | 2 (20, n=10) | 7 (63.6, n=11) | 2 (100, n=2) | 15 (93.8, n=16) | **<0.001** |
| i-IFTA, mean ± SD | 1.25 ± 0.71 | 0.50 ± 0.97 | 0.91 ± 0.94 | 0.50 ± 0.71 | 1.88 ± 1.20 | **0.019** |
| i-IFTA ≥1, n (%) | 8 (100, n= 8) | 3 (30, n=10) | 7 (63.6, n=11) | 1 (50, n= 2) | 13 (81.3, n=16) | **0.010** |
| mm, mean ± SD | 0.20 ± 0.63 | 0.08 ± 0.28 | 0.12 ± 0.33 | 0 ± 0 | 0.09 ± 0.29 | 0.867 |
| mm ≥1, n (%) | 1 (10) | 1 (7.7) | 3 (11.5) | 0 (0) | 2 (8.7) | 0.972 |
| ci, mean ± SD | 1.50 ± 0.85 | 1.00 ± 0.91 | 1.12 ± 0.71 | 0.70 ± 0.67 | 0.91 ± 0.51 | 0.125 |
| ci ≥1, n (%) | 10 (100) | 9 (69.2) | 22 (84.6) | 6 (60) | 19 (82.6) | 0.160 |
| ct, mean ± SD | 1.00 ± 0.94 | 1.31 ± 0.75 | 0.81 ± 0.80 | 0.70 ± 0.67 | 1 ± 0.60 | 0.127 |
| ct ≥1, n (%) | 7 (70) | 12 (92.3) | 16 (61.5) | 6 (60) | 20 (87) | 0.100 |
| cv, mean ± SD | 1.60 ± 0.84 | 1.31 ± 1.11 | 1.35 ± 0.85 | 0.70 ± 1.06 | 1.04 ± 0.71 | 0.131 |
| cv ≥1, n (%) | 9 (90) | 9 (69.2) | 22 (84.6) | 4 (40) | 18 (78.6) | 0.068 |
| ah, mean ± SD | 1.00 ± 1.15 | 0.23 ± 0.60 | 0.65 ± 0.89 | 0.50 ± 0.71 | 0.83 ± 0.89 | 0.567 |
| ah ≥1, n (%) | 5 (50) | 2 (15.4) | 10 (38.5) | 4 (40) | 13 (56.5) | 0.218 |
| TMA, n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | n.a. |
| ATN, n (%) | 9 (90) | 4 (30.8) | 17 (65.4) | 4 (40) | 6 (26.1) | **0.002** |
| Glomerulonephritis, n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | n.a. |

# Características clínicas y demográficas de la población de estudio

| | Isolated v+ early (n=10) | Isolated v+ late (n=13) | ABMR v+ (n=26) | TCMR v+ (n=10) | Mixed Rejection v+ (n=23) | p-value |
|---|---|---|---|---|---|---|
| Recipient characteristics | | | | | | |
| Age at transplantation, years, mean ± SD | 66.4 ± 8.9 | 57.1 ± 16.6 | 61.9 ± 14.7 | 52.7 ± 18.8 | 57.2 ± 14.5 | 0.298 |
| Female sex, N (%) | 2 (20) | 7 (53.9) | 12 (46.2) | 2 (20) | 5 (21.7) | 0.230 |
| Ethnicity, N (%) | | | | | | |
| Caucasian | 8 (80) | 10 (76.9) | 22 (84.6) | 7 (70) | 20 (90.1) | |
| Black | 0 (0) | 0 (0) | 0 (0) | 1 (10) | 0 (0) | |
| Latin American | 1 (10) | 1 (7.7) | 5 (15.4) | 2 (20) | 0 (0) | 0.459 |
| Asian | 0 (0) | 1 (7.7) | 0 (0) | 0 (0) | 2 (9.1) | |
| Other | 1 (10) | 1 (7.7) | 0 (0) | 0 (0) | 0 (0) | |
| Hypertension, N (%) | 10 (100) | 12 (92.3) | 22 (84.6) | 10 (100) | 21 (91.3) | 0.839 |
| Diabetes mellitus, N (%) | 4 (40) | 7 (53.9) | 9 (34.6) | 4 (30) | 8 (34.8) | 0.473 |
| Cardiovascular disease, N (%) | 2 (20) | 3 (23.1) | 6 (23.1) | 2 (20) | 2 (8.7) | 0.115 |
| Cerebrovascular disease, N (%) | 1 (10) | 1 (7.7) | 1 (3.9) | 0 (0) | 4 (17.4) | 0.942 |
| Peripheral vascular disease, N (%) | | | | | | |
| None | 5 (50) | 8 (61.5) | 21 (80.8) | 9 (90) | 17 (78.3) | |
| Mild | 1 (10) | 3 (23.1) | 2 (7.7) | 1 (10) | 2 (8.7) | 0.177 |
| Moderate/severe | 4 (40) | 2 (15.4) | 3 (11.5) | 0 (0) | 3 (13) | |
| BMI, kg/m2, mean ± SD | 28.9 ± 3.9 | 28.5 ± 4.6 | 26.6 ± 5.2 | 28.6 ± 4.9 | 25.5 ± 5.4 | 0.058 |
| HCV, N (%) | 1 (10) | 1 (7.7) | 2 (7.7) | 1 (10) | 1 (4.4) | 0.125 |
| Cause of ESKD, N (%) | | | | | | |
| Glomerulonephritis | 0 (0) | 1 (7.7) | 4 (15.4) | 1 (10) | 3 (13) | |
| PKD | 2 (20) | 2 (15.4) | 2 (7.7) | 1 (10) | 1 (4.4) | |
| Reflux/obstructive nephropathy | 0 (0) | 0 (0) | 2 (7.7) | 0 (0) | 1 (4.4) | |
| Hypertension | 0 (0) | 2 (15.4) | 1 (3.9) | 1 (10) | 0 (0) | 0.433 |
| Diabetes | 3 (30) | 6 (46.2) | 5 (19.2) | 1 (10) | 7 (30.4) | |
| Other | 1 (10) | 1 (7.7) | 2 (7.7) | 0 (0) | 3 (13) | |
| Unknown | 4 (40) | 1 (7.7) | 10 (38.5) | 6 (60) | 8 (34.8) | |
| Type of RRT, N (%) | | | | | | |
| Hemodialysis | 7 (70) | 9 (69.2) | 22 (84.6) | 8 (80) | 16 (69.6) | |
| Peritoneal dialysis | 1 (10) | 2 (15.4) | 1 (3.9) | 2 (20) | 4 (17.4) | 0.957 |
| None (pre-emptive transplant) | 2 (20) | 2 (15.4) | 3 (11.5) | 0 (0) | 3 (13) | |
| Time on RRT, months, median (IQR) | 3.4 (2.1 – 5.4) | 1.4 (1.0 – 2.7) | 3.2 (1.0 – 6.8) | 1.5 (1.0 – 2.0) | 1.6 (1.9 – 3.3) | 0.183 |
| Retransplantation, N (%) | 0 (0) | 1 (7.7) | 6 (23.1) | 1 (10) | 4 (17.4) | 0.269 |

# Características clínicas y demográficas de la población de estudio

| | Isolated v+ early (n=10) | Isolated v+ late (n=13) | ABMR v+ (n=26) | TCMR v+ (n=10) | Mixed Rejection v+ (n=23) | p-value |
|---|---|---|---|---|---|---|
| Immunologic profile | | | | | | |
| HLA-A/B/DR mismatch, mean ± SD | 4.5 ± 1.2 | 4.1 ± 1.0 | 4.4 ± 0.9 | 4.4 ± 1.1 | 4.0 ± 1.5 | 0.799 |
| Pre-transplant HLA-DSA | 0 (0) | 0 (0) | 5 (19.2) | 0 (0) | 3 (13) | 0.247 |
| Post-transplant HLA-DSA (at Bx) | 0 (0) | 0 (0) | 8 (30.8) | 0 (0) | 8 (34.8) | **0.007** |
| Post-transplant HLA-DSA (ever after KT) | 0 (0) | 2 (15.4) | 10 (38.5) | 4 (40) | 12 (52.2) | **0.019** |
| Donor characteristics | | | | | | |
| Donor age, years, mean ± SD | 63.7 ± 5.5 | 63.5 ± 14.0 | 64.7 ± 16.6 | 52 ± 20.2 | 59 ± 14.2 | 0.226 |
| Donor sex female, N (%) | 2 (20) | 7 (53.9) | 14 (53.9) | 6 (60) | 8 (34.8) | 0.240 |
| Type of donor, N (%) | | | | | | |
| Living donor | 2 (20) | 0 (0) | 4 (15.4) | 2 (20) | 5 (21.7) | 0.146 |
| DBD | 6 (60) | 8 (61.5) | 10 (38.5) | 7 (70) | 12 (52.2) | |
| DCD (controlled) | 1 (10) | 5 (38.5) | 12 (46.2) | 1 (10) | 4 (17.4) | |
| DCD (uncontrolled) | 1 (10) | 0 (0) | 0 (0) | 0 (0) | 2 (8.7) | |
| Expanded criteria donor, N (%) | 7 (70) | 9 (69.2) | 20 (76.9) | 5 (50) | 11 (47.8) | 0.237 |
| History of hypertension, N (%) | 5 (50) | 9 (69.2) | 12 (46.2) | 3 (30) | 11 (47.8) | 0.612 |
| History of diabetes mellitus, N (%) | 1 (10) | 4 (30.8) | 4 (15.4) | 2 (20) | 1 (4.4) | 0.244 |
| BMI, kg/m2, mean ± SD | 29.3 ± 2.9 | 26 ± 9.6 | 28 ± 5.3 | 28.3 ± 4.7 | 27.8 ± 5.4 | 0.690 |
| Cerebrovascular disease as death cause, N (%) | 5 (62.5) | 6 (46.2) | 11 (50) | 4 (50) | 9 (47.4) | 0.981 |
| HCV positive, N (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (8.7) | 0.374 |
| ABOi | 0 (0) | 0 (0) | 2 (7.7) | 0 (0) | 1 (4.4) | 0.912 |
| Cold ischemia time, hours, mean ± SD | 14.6 ± 7.1 | 15.7 ± 6.8 | 14.5 ± 7.2 | 13.2 ± 5.1 | 11.5 ± 7.7 | 0.322 |

# Características clínicas y demográficas de la población de estudio

| | Isolated v+ early (n=10) | Isolated v+ late (n=13) | ABMR v+ (n=26) | TCMR v+ (n=10) | Mixed Rejection v+ (n=23) | p-value |
|---|---|---|---|---|---|---|
| **Baseline immunosuppression** | | | | | | |
| Induction therapy, N (%) | | | | | | |
| None | 0 (0) | 0 (0) | 0 (0) | 1 (10) | 0 (0) | |
| Antithymocyte globulin | 0 (0) | 1 (7.7) | 9 (34.6) | 1 (10) | 0 (0) | **0.001** |
| Basiliximab | 8 (80) | 8 (61.5) | 17 (65.4) | 8 (80) | 18 (78.3) | |
| Daclizumab | 2 (20) | 4 (30.8) | 0 (0) | 0 (0) | 5 (21.7) | |
| **Maintenance immunosuppression** | | | | | | |
| Corticosteroids, N (%) | 10 (100) | 13 (100) | 26 (100) | 10 (100) | 22 (95.7) | 0.683 |
| CNI, N (%) | 10 (100) | 13 (100) | 26 (100 | 10 (100) | 23 (100) | n.s. |
| Mycophenolate mofetil, N (%) | 4 (40) | 13 (100) | 23 (88.5) | 10 (100) | 19 (92.6) | **0.002** |
| De novo mTORi, N (%) | 6 (60) | 0 (0) | 3 (11.5) | 0 (0) | 4 (17.4) | **0.002** |
| **Follow-up times** | | | | | | |
| Median time from KT to Bx, months, median (IQR) | 0.4 (0.3 – 0.7) | 4.8 (2.4 – 12.0) | 0.5 (0.4 – 6.4) | 2.4 (0.9 – 5.8) | 2.3 (0.5- 5.7) | 0.002 |
| Follow-up time after KT, years, median (IQR) | 0.3 (0.2 – 4.7) | 4.3 (3.2 – 5.8) | 2.6 (1.2 – 4.5) | 6.9 (4.8 – 9.4) | 3.0 (1.7 – 6.2) | 0.001 |
| Follow-up time after Bx, years, median (IQR) | 0.2 (0.1 – 4.7) | 3.8 (3.1 – 4.7) | 2.0 (1.2 – 3.7) | 5.7 (4.0 – 8.7) | 3.0 (1.2 – 5.5) | 0.002 |