Award *"Prof. Epsa Urumova"* for the best article published in a medical journal for 2019:

"Specificity, strength and evolution of pretransplant donor-specific HLA antibodies determine outcome after kidney transplantation"

- American Journal of Transplantation -

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ORIGINAL ARTICLE

Specificity, strength, and evolution of pretransplant donor-specific HLA antibodies determine outcome after kidney transplantation

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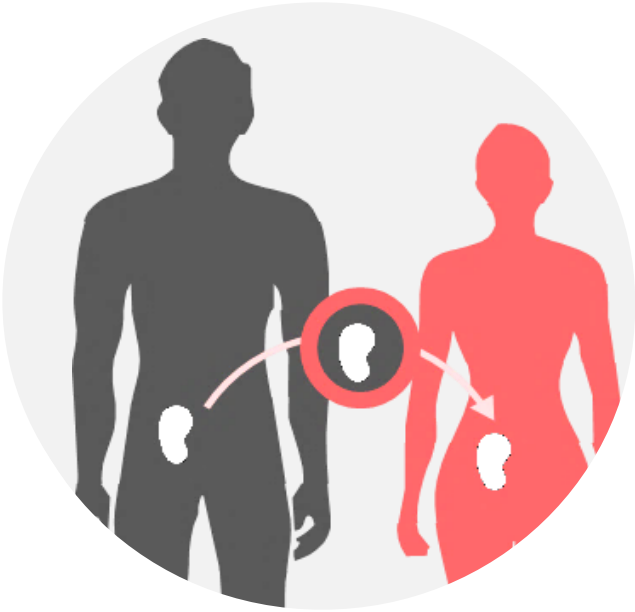
Article selected for *Continuing Medical Education (**CME**) & Maintenance of Certification (**MOC**)* by *American Society of Transplant Surgeons*

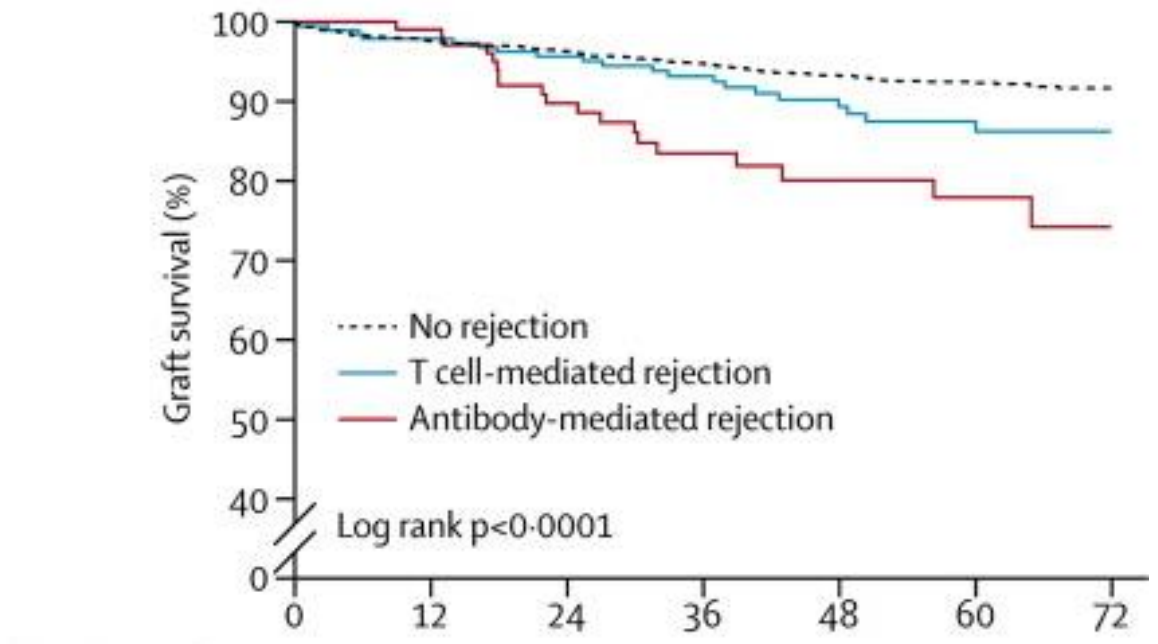
Kidney Transplantation



Kidney transplantation

- Kidney transplant is the best treatment option for people facing kidney failure.

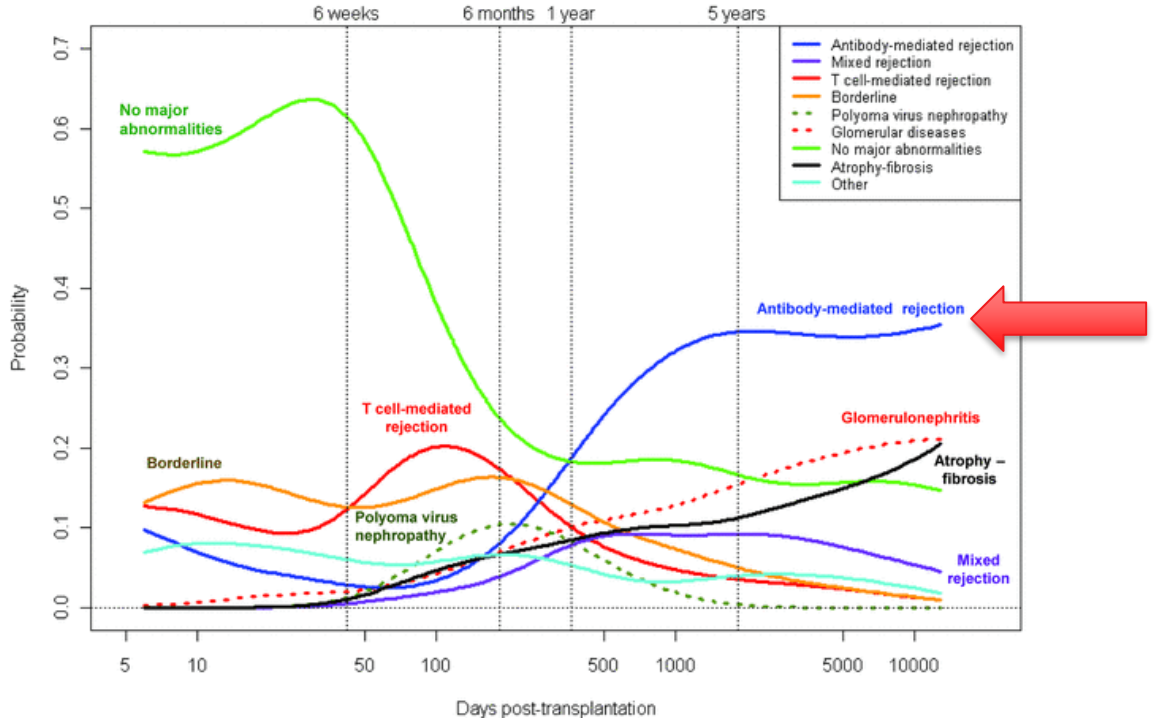
Kidney Transplantation and antibody-mediated rejection



Lefaucheur et al. *The Lancet* 2013;381:313-319

- Antibody-mediated rejection (**ABMR**) was recognized as a distinct diagnostic entity in 2001 and it's associated with worse renal allograft survival.

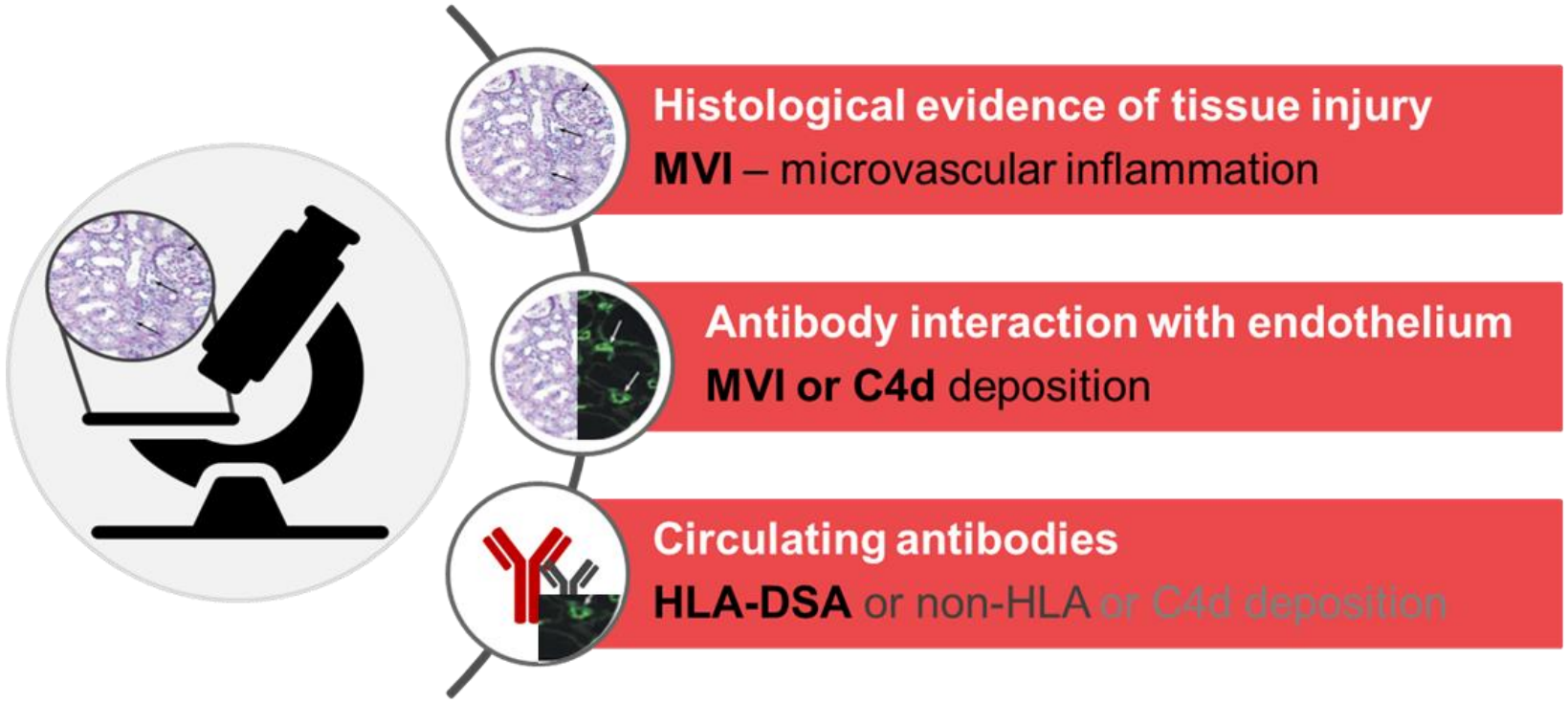
Kidney Transplantation and antibody-mediated rejection



J. Sellarés et al. *Am J Transplant.* 2012; 12: 388-399

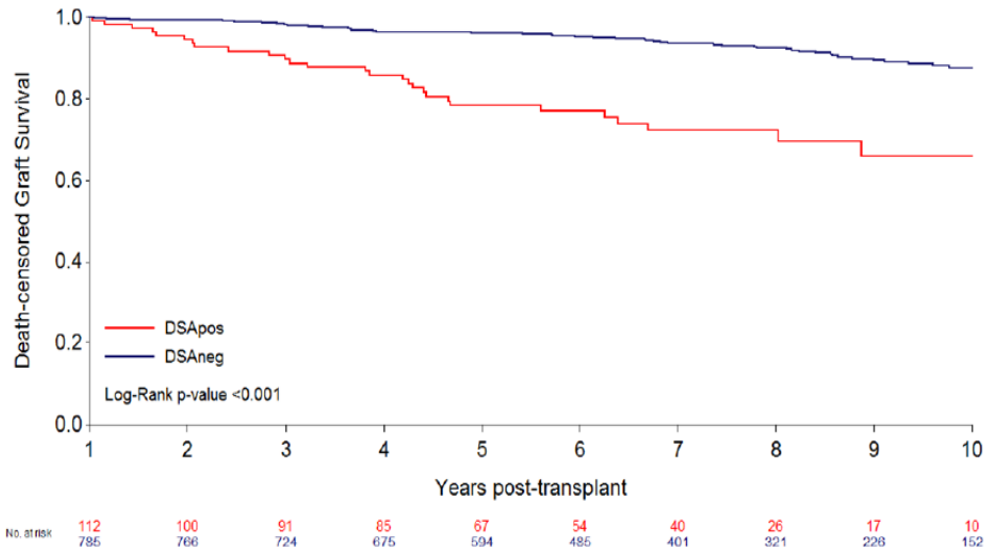
- Antibody-mediated rejection is considered a major cause of late kidney allograft failure.

Banff classification 2019 for diagnosing active ABMR



Loupy et al. *Am J Transplant*. 2020; 20: 2318– 2331.

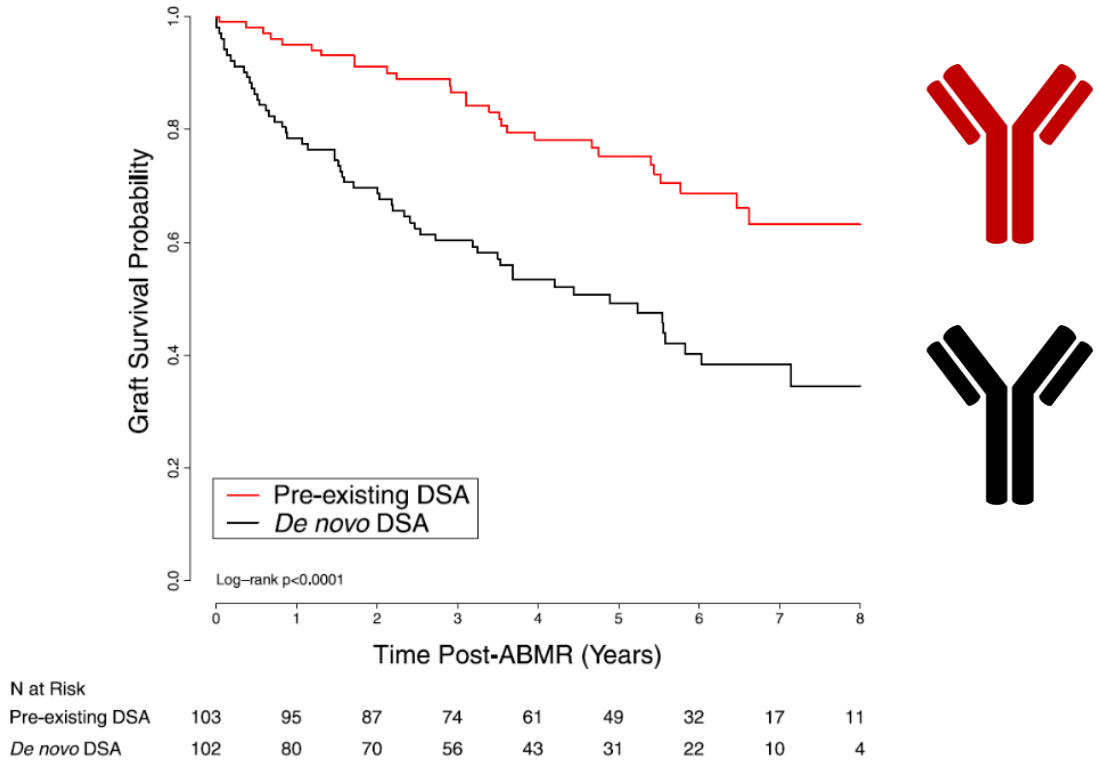
Kidney Transplantation and anti-HLA antibodies



Senev et al. *Am J Transplant*. 2019; 19: 763– 780.

The main predictor of poor kidney graft outcome is the presence of **pretransplant** or/and **de novo** donor-specific HLA antibodies (DSA).

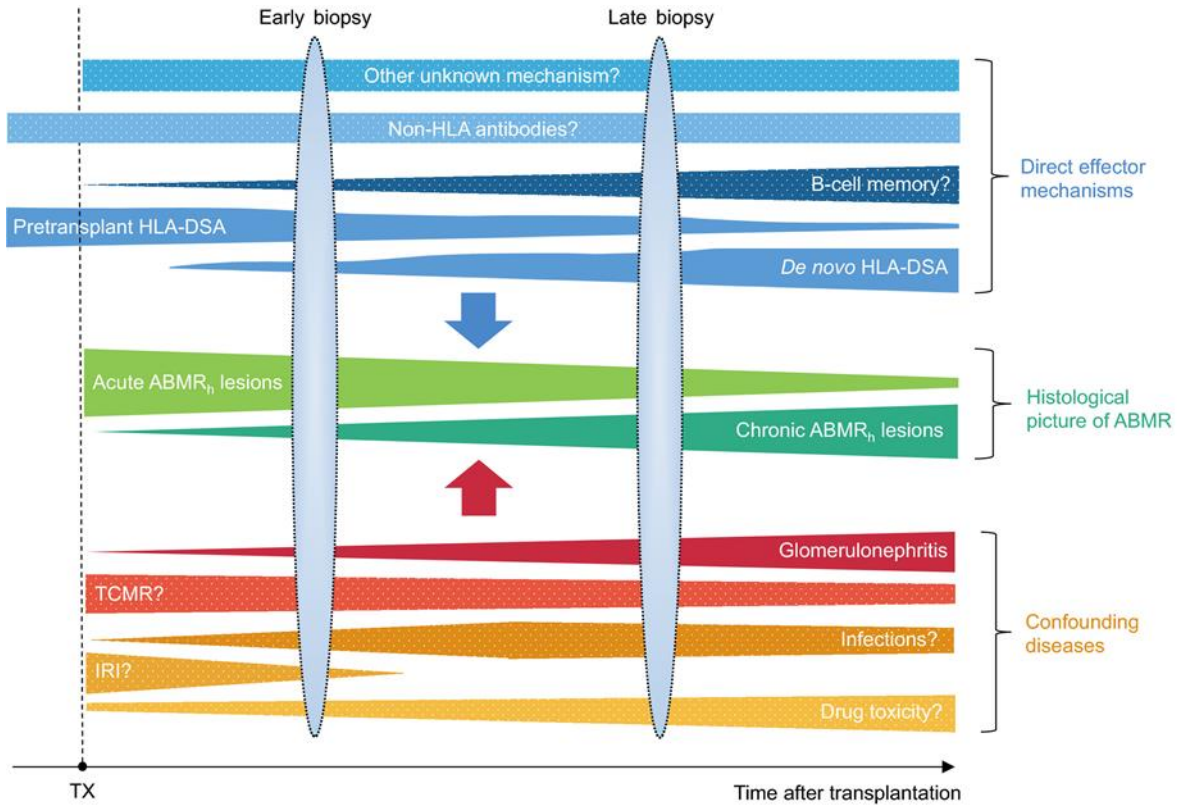
Different effects of HLA-DSA and pretransplant are less harmful



- Pretransplant DSA (unknown):
  - Class I or class II **?** MFI **?**
  - Evolution after transplantation **?**
- De novo DSA (known):
  - Majority against Class II (predominantly DQ)
  - Persistent de novo DSA – bad graft outcome

Aubert et al. *J Am Soc Nephrol.* 2017; 28:1912–1923

Temporal dynamics of pretransplant HLA-DSA and diagnosis of ABMR after transplantation



Senev et al. *Am J Transplant* 2019: 954-955

- It is unclear whether pretransplant **DSA evolution** is to be considered in the diagnostic, treatment decisions and prognostic use of the Banff classification for diagnosing ABMR

Objectives

The aims of this study were:

- To investigate the evolution and clinical significance of pretransplant DSA, positive with the single antigen beads assay but negative in CDC crossmatch;

- To elucidate which pretransplant DSA characteristics have a negative impact on post-transplant graft histology and graft survival.

Patients and allograft histology

- Included **924 single kidney transplantations**:
  - consecutive adult recipients with CDC-XM,

N=924

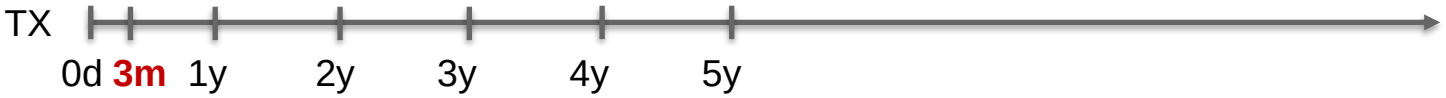
- Transplanted at **University Hospitals Leuven** (Belgium):
  - between March 2004 and February 2013
  - No patient received preconditioning HLA antibody desensitization

UZ Leuven

2004 - 2013

- **Indication and protocol** kidney allograft biopsies:
  - Post-transplant at 3M, 1-, 2-, 3-, 4-, 5-year
  - All rescored to the latest Banff 2015/2017

3611 biopsies



HLA profiling of the cohort

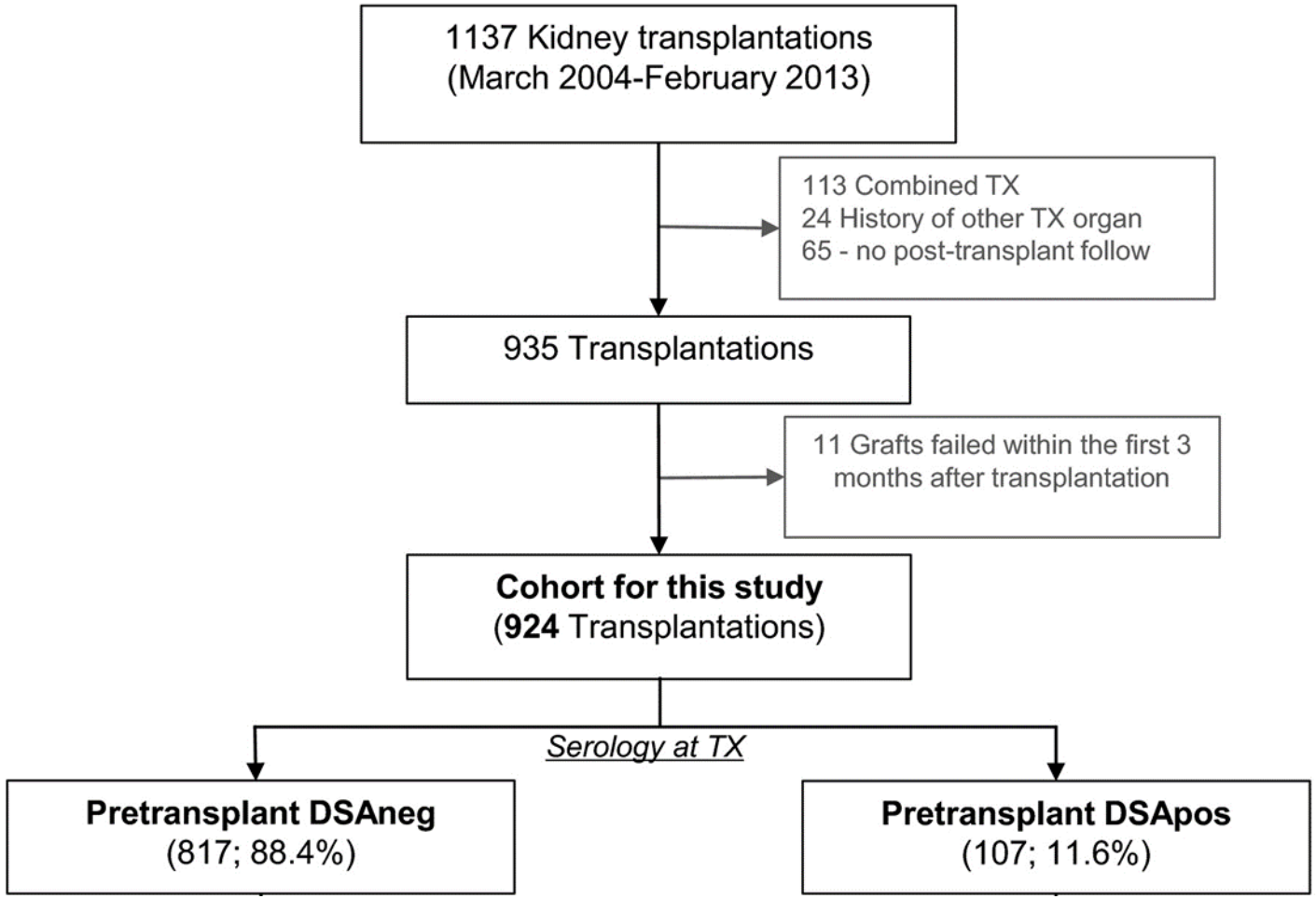
- The pre- and posttransplant follow-up of anti-HLA antibodies by *Luminex*:
  - LIFECODES LifeScreen Deluxe (LMX) kit
  - LIFECODES Single Antigen Bead (LSA) kits

- Second field High-resolution HLA typing of the transplant pairs by *Next-Generation Sequencing* for *HLA-A,-B,-C,-DRB$_{1345}$,-DQA$_1$,-DQB$_1$,-DPA$_1$,-DPB$_1$*:
  - MIA FORA NGS FLEX 11 HLA Typing Kit (Immucor)
  - Extracellular domains of the HLA molecules

    (exon 2, 3 and 4 of HLA class I and exon 2 and 3 of HLA class II molecules)

DSA - Background-corrected median fluorescence intensity (MFI) value equal or above **500.**

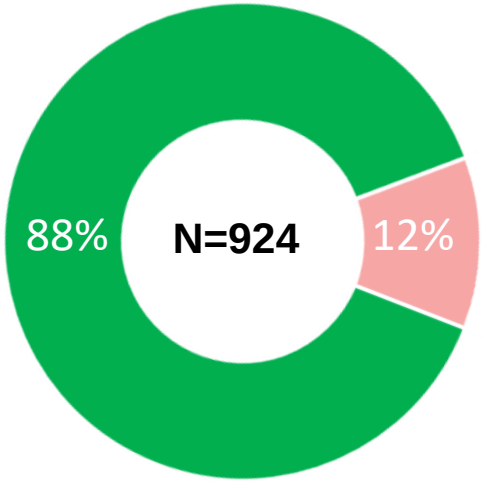
Flow chart of patient enrollment and subgroup definition according to preexistence of HLA-DSA



Senev et al. *Am J Transplant*. 2019; 19: 3100- 3113.

Evolution of pretransplant HLA-DSA early after transplantation

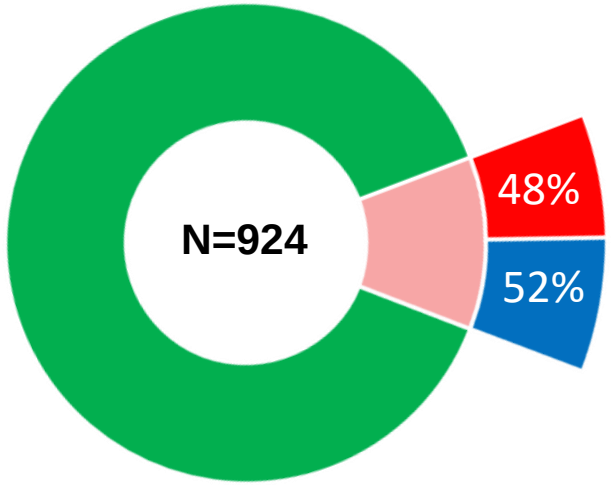
Pretransplant HLA-DSA at day 0



No DSA (N=817; 88%)

preDSA (N=107; 12%)

Posttransplant HLA-DSA at 3 months



Persistent DSA (N=51, 48%)

Resolved DSA (N=56, 52%)

Senev et al. *Am J Transplant*. 2019; 19: 3100- 3113.

Similar demographic and clinical characteristics

Characteristics	Resolved DSA (n=56)	Persistent DSA (n=51)	p-value	test
Recipient characteristics at transplantation				
Age (years), mean ±SD	53.1 ±12.9	53.5 ±15.8	0.89	t-test
Gender (male), n (%)	21 (37.5%)	26 (50.9%)	0.16	x^2-test
Caucasian ethnicity, n (%)	54 (96.4%)	50 (98.0%)	0.61	x^2-test
Repeat transplantation, n (%)	29 (51.8%)	30 (58.8%)	0.46	x^2-test
Diabetes mellitus, n (%)	9 (16.1%)	10 (19.6%)	0.63	x^2-test
Donor characteristics at transplantation				
Age (years), mean ±SD	47.3 ±17.6	47.5 ±16.7	0.73	t-test
Gender (male), n (%)	30 (53.6%)	24 (47.1%)	0.50	x^2-test
Deceased donor, n (%)	51 (91.1%)	48 (94.1%)	0.55	x^2-test
Donation after brain death, n (%)	47 (92.2%)	40 (83.3%)	0.18	x^2-test
Transplant characteristics, treatment at transplantation and follow-up				
Cold ischemia time (hours), mean ±SD	14.3 ±5.7	14.7 ±6.0	0.75	t-test
Delayed graft function, n (%)	14 (25.0%)	20 (39.2%)	0.11	x^2-test
Immunosuppression regimen: TAC-MPA-CS, n (%)	52 (92.9%)	48 (94.1%)	0.79	x^2-test
Induction therapy, n (%)	35 (62.5%)	36 (70.6%)	0.38	x^2-test

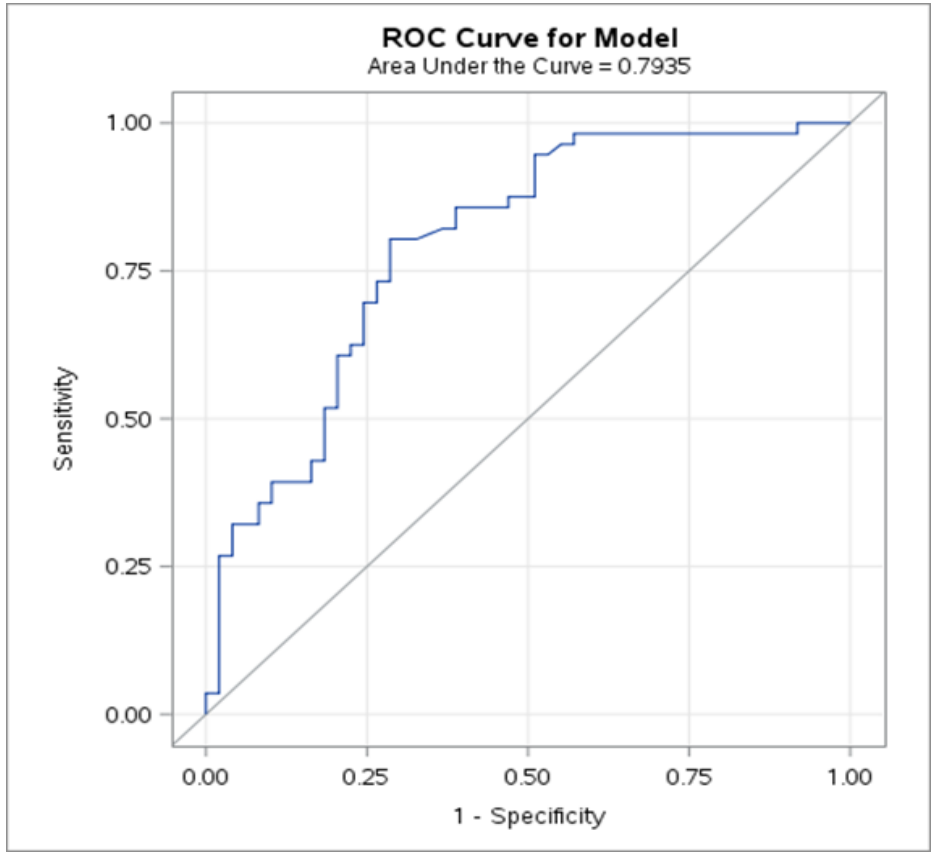
Senev et al. *Am J Transplant*. 2019; 19: 3100- 3113.

Different pretransplant DSA characteristics

Characteristics	Resolved DSA (n= 56)	Persistent DSA (n=51)	p-value	test
HLA allele mismatches				
Total HLA-A/B/C/DRB1/DRB345/DQB1/DQA1/ DPB1/ DPA1 mismatches, mean ±SD	9.06 ±2.5	8.78 ± 2.8	0.62	t-test
Pretransplant HLA DSA				
Total number of DSA, mean ±SD	1.45 ±0.7	1.80 ±0.9	**0.03**	t-test
Locus specificity of anti-HLA-DSA				
DSA against locus A	15 (26.8%)	10 (19.6%)	0.38	x^2-test
DSA against locus B	23 (41.1%)	13 (25.5%)	0.09	x^2-test
DSA against locus C	5 (9.3%)	8 (15.7%)	0.29	x^2-test
DSA against locus DR	14 (25.0%)	14 (27.5%)	0.77	x^2-test
DSA against locus DQ	10 (17.9%)	25 (**49.0%**)	**0.0006**	x^2-test
DSA against locus DP	7 (12.5%)	14 (27.6%)	0.05	x^2-test
Immunodominant HLA-DSA				
Anti-HLA class I	32 (57.1%)	13 (25.5)	**0.0009**	x^2-test
Anti-HLA class II	24 (42.9%)	38 (**74.5%**)	**0.0009**	x^2-test
MFI value of immunodominant preDSA, median (IQR)	2083 (3139)	**5581** (6825)	**<.0001**	Wilcoxon

Senev et al. *Am J Transplant*. 2019; 19: 3100- 3113.

The persistence of pretransplant DSA after transplantation can be predicted



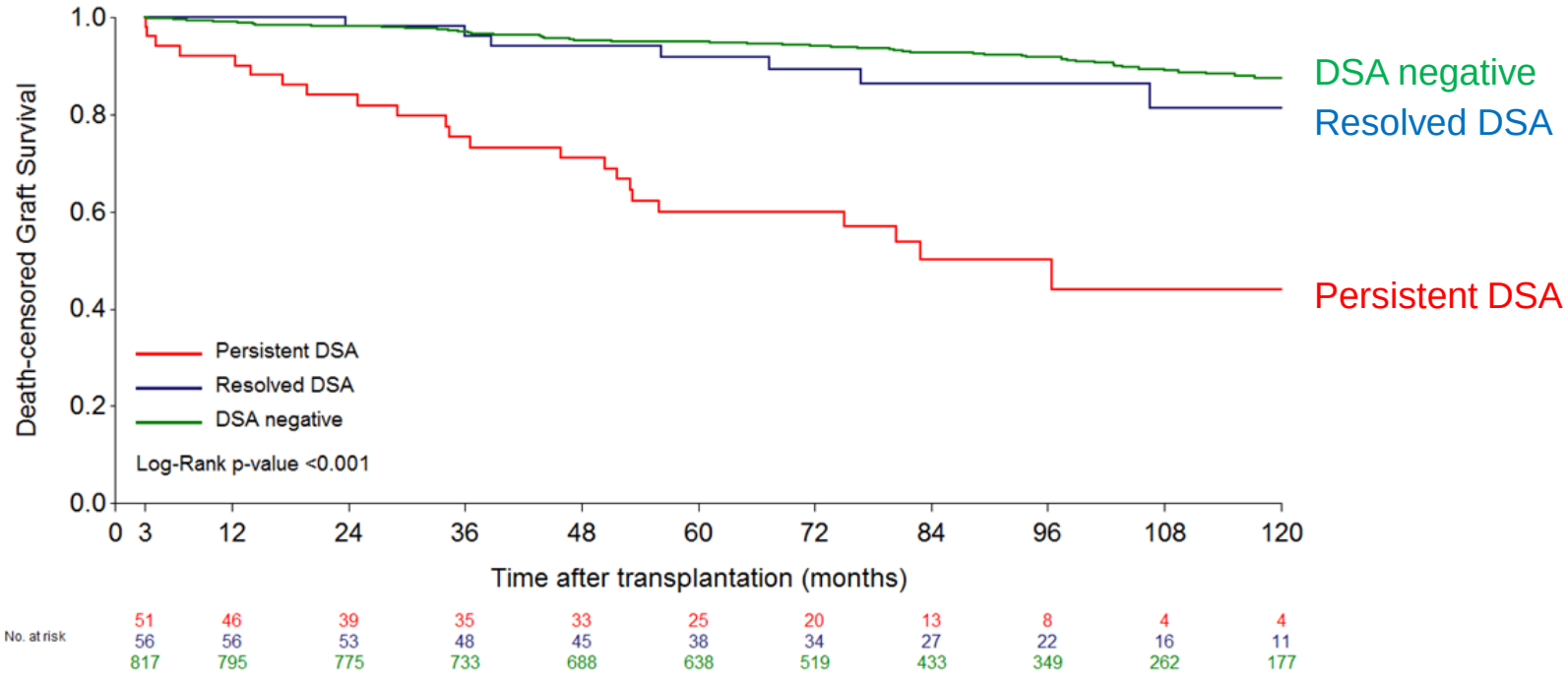
Multivariable logistic regression model

- **MFI** of the immunodominant pretransplant DSA
- Pretransplant DSA with **DQ specificity**

The area under the ROC curve for the model was AUC **= 0.79** (95% CI, 0.71-0.88; p<.0001).

Senev et al. *Am J Transplant*. 2019; 19: 3100- 3113.

Outcome of patients with resolved DSA is better than in patients with persistent DSA



DSA negative

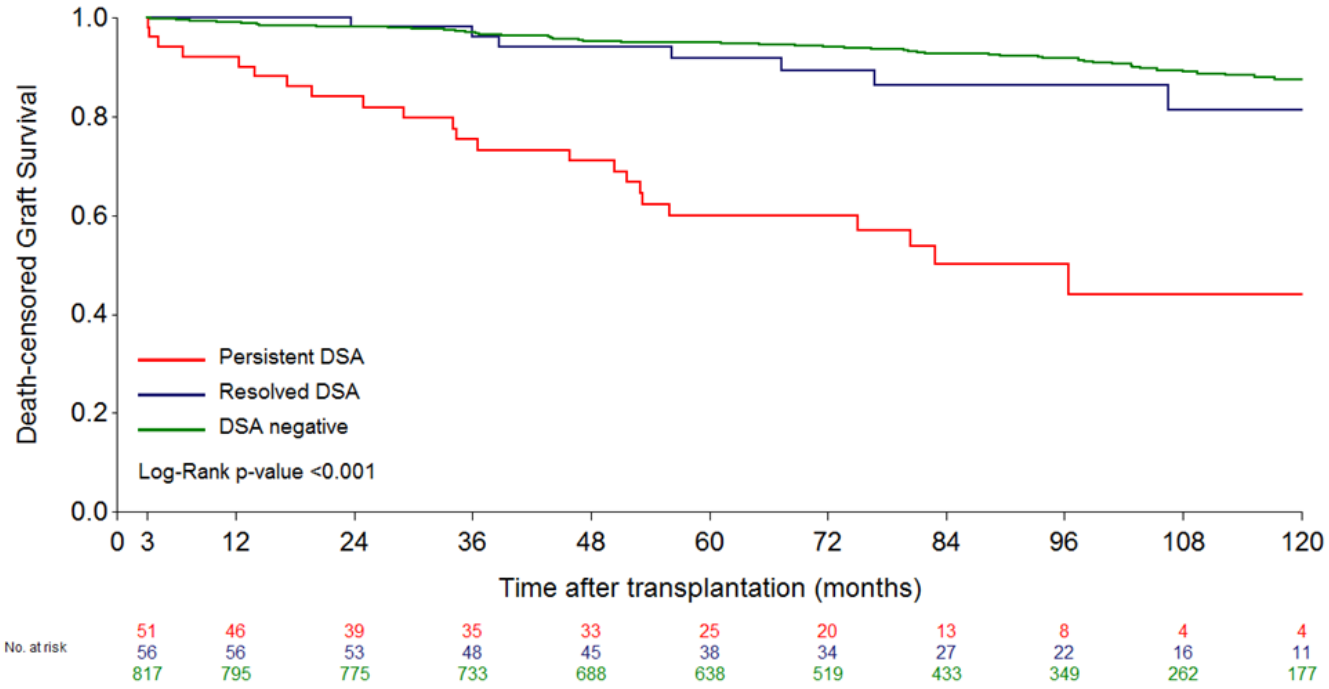
Resolved DSA

Persistent DSA

Landmark survival analysis at 3 months after transplantation

Senev et al. *Am J Transplant*. 2019; 19: 3100- 3113.

But high incidence of histological lesions of ABMR in the resolved DSA group

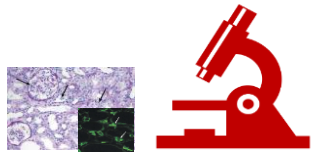


DSA negative
Resolved DSA

Persistent DSA

9.3% $ABMR_h$
53.6% $ABMR_h$

58.8% $ABMR_h$

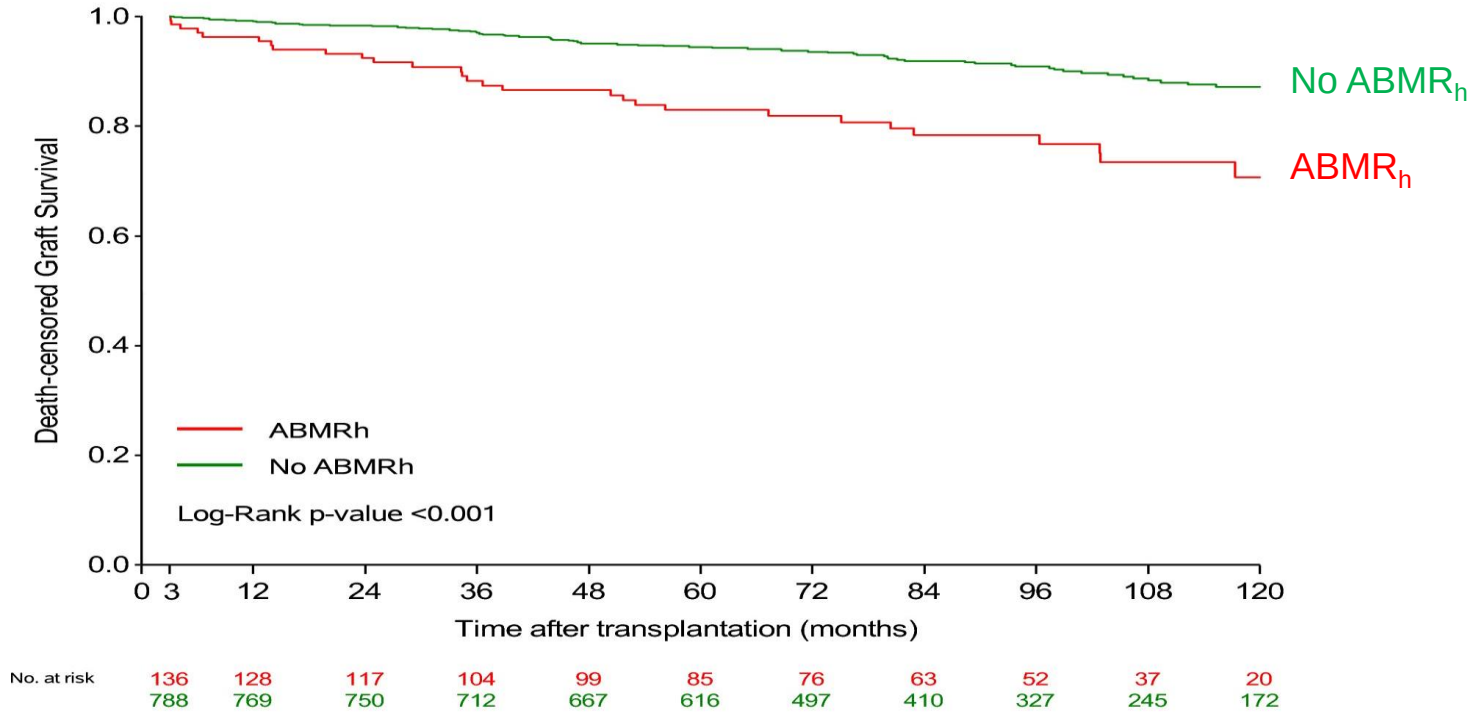


$ABMR_h$

Landmark survival analysis at 3 months after transplantation

Senev et al. *Am J Transplant*. 2019; 19: 3100- 3113.

Patients who developed $ABMR_h$ within the first 3 months are associated with impaired allograft survival



Landmark survival analysis at 3 months after transplantation

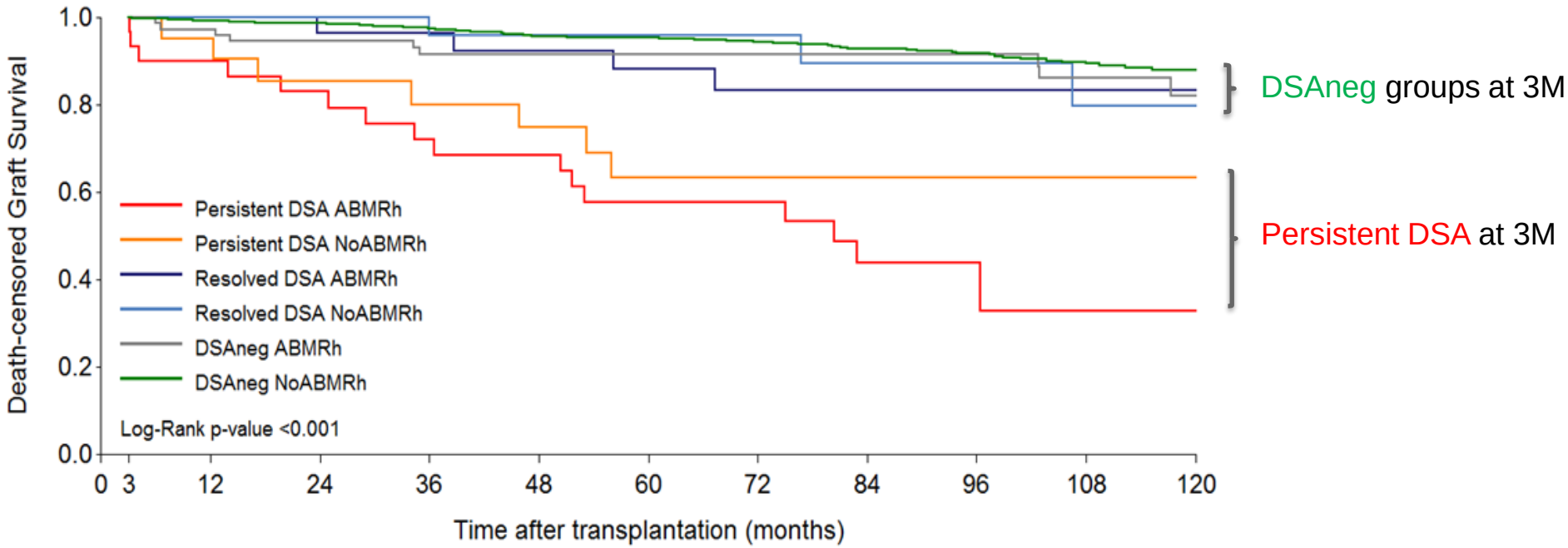
Senev et al. *Am J Transplant*. 2019; 19: 3100- 3113.

Comparison of the histological appearance of the first biopsy with $ABMR_h$ in the patients with pretransplant HLA-DSA

Characteristics	Resolved DSA (N = 56)	Persistent DSA (N = 51)	p-value	Test
Histology				
Patients with $ABMR_h$ within first 3 months after TX, n (%)	30 (53.6%)	30 (58.8%)	0.58	χ^2 test
Time until $ABMR_h$ (days), mean ± SD	36.2 ± 40.8	32.8 ± 38.9	0.74	t test
Histological appearance of $ABMR_h$ cases				
Glomerulitis Banff score ≥ 1, n (%)	23 (76.7%)	21 (70.0%)	0.56	χ^2 test
Peritubular capillaritis Banff score ≥ 1, n (%)	22 (73.3%)	25 (83.3%)	0.35	χ^2 test
C4d depostion Banff score ≥ 1, n (%)	20 (66.7%)	16 (53.3%)	0.29	χ^2 test
C4d depostion Banff score ≥ 2, n (%)	18 (60.0%)	15 (50.0%)	0.44	χ^2 test
Endarteritis Banff score ≥ 1, n (%)	13 (43.3%)	17 (56.7%)	0.30	χ^2 test
Chronic allograft glomerulopathy Banff score≥ 1, n (%)	1 (3.3%)	0 (0.0%)	0.50	χ^2-test
Interstitial inflammation Banff score ≥ 1, n (%)	15 (50.0%)	14 (46.7%)	0.80	χ^2 test
Tubulitis Banff score ≥ 1, n (%)	20 (66.7%)	17 (54.8%)	0.43	χ^2 test
Interstitial fibrosis Banff score ≥ 1, n (%)	4 (13.3%)	3 (10.0%)	0.29	χ^2 test
Tubular atrophy Banff score ≥ 1, n (%)	16 (53.3%)	9 (30.0%)	0.07	χ^2 test
Mesangial matrix expansion score Banff score ≥ 1, n (%)	2 (6.7%)	0 (0.0%)	0.25	χ^2 test
Arteriolar hyalinosis Banff score ≥ 1, n (%)	8 (26.7%)	4 (13.3%)	0.11	χ^2 test
Vascular intimal thickening Banff score ≥ 1, n (%)	17 (56.7%)	15 (50.0%)	0.60	χ^2 test
Microcirculation inflammation Banff score ≥ 2, n (%)	28 (93.3%)	24 (80.0%)	0.13	χ^2 test
Concomitant TCMR, n (%)	15 (50.0%)	13 (43.3%)	0.60	χ^2 test

Senev et al. *Am J Transplant*. 2019; 19: 3100- 3113.

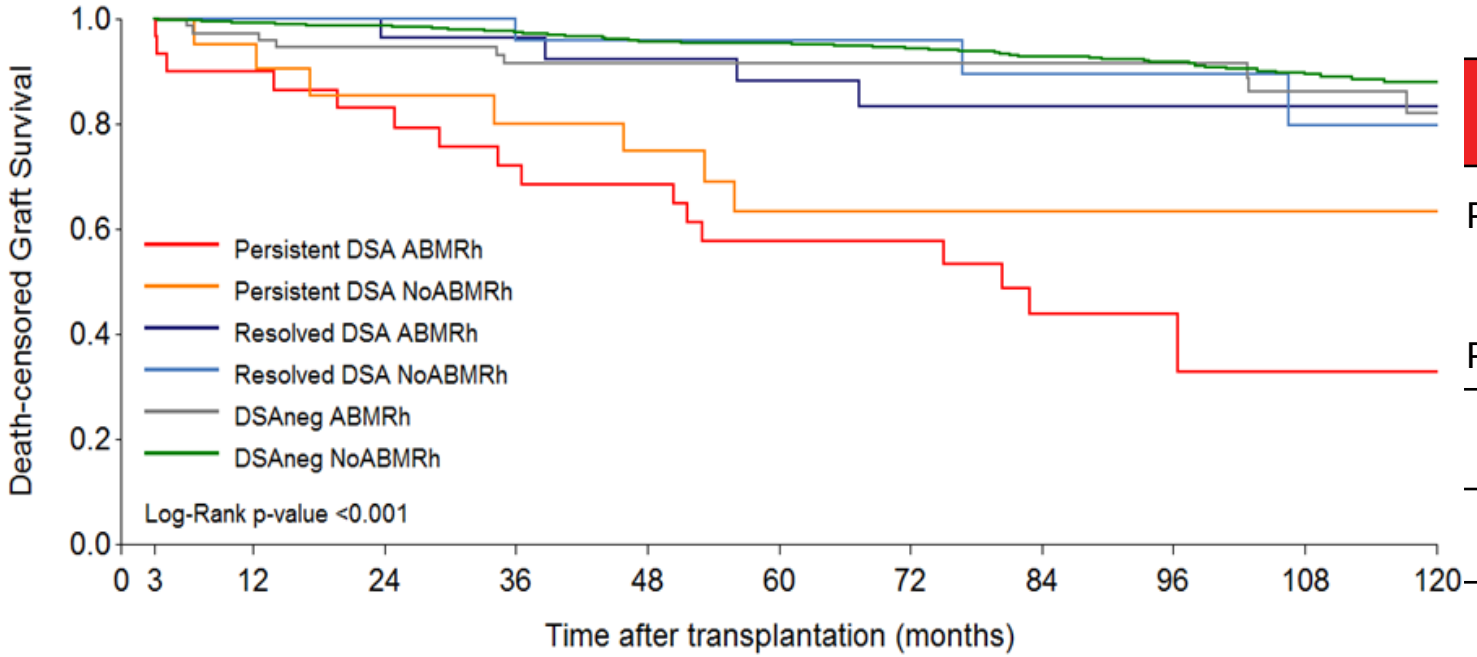
Only patients with persistent pretransplant DSA have impaired allograft survival



Landmark survival analysis at 3 months after transplantation

Senev et al. *Am J Transplant*. 2019; 19: 3100- 3113.

Only patients with persistent pretransplant DSA have impaired allograft survival



Multivariable Cox model (vs. DSA-neg)	HR	*p*-value
Persistent DSA with $NoABMR_h$	4.3	0.001
Persistent DSA with $ABMR_h$	8.3	<.0001
DSA against DQ	**4.6**	<0.0001
MFI ≥ 1400	**3.2**	0.0004

Landmark survival analysis at 3 months after transplantation

Senev et al. *Am J Transplant*. 2019; 19: 3100- 3113.

Multivariable Cox proportional hazards models for graft survival on the biopsies showing $ABMR_h$

Variables	No. of biopsies	No. of events	HR	95% CI	*P* value
Multivariate model-1					
Biopsy with ABMR	370	88			
Absent: MFI < 500	262	51	1	–	–
Present: MFI ≥ 500 < 1400	21	1	0.30	0.0-2.2	.23
Present: MFI ≥ 1400	87	36	2.73	1.7-4.3	**<.0001**
Multivariate model-2					
Biopsy with ABMR (Banff 2015 diagnosis)	370	88			
Absent: HLA-DSA MFI < 1400	283	52	1	–	–
Present: HLA-DSA MFI ≥ 1400	87	36	2.89	1.8-4.5	**<.0001**
Multivariate model-3					
Biopsy with ABMR	389	104			
Absent: preDSA MFI < 1400	211	41	1	–	–
Present: resolved pretransplant HLA-DSA	80	11	0.66	0.3-1.3	.23
Present: persistent pretransplant HLA-DSA	79	36	3.07	1.9-4.9	**<.0001**
Present: de novo HLA-DSA	19	16	7.34	4.0-13.5	**<.0001**

Senev et al. *Am J Transplant*. 2019; 19: 3100- 3113.

Summary

- **Resolved pretransplant DSA**
  - Low-MFI and non-DQ pretransplant DSA, even in the absence of antibody-targeting therapy, often disappear early after transplantation and are not deleterious for graft outcome, despite the association with transient histological abnormalities indicative for ABMR.

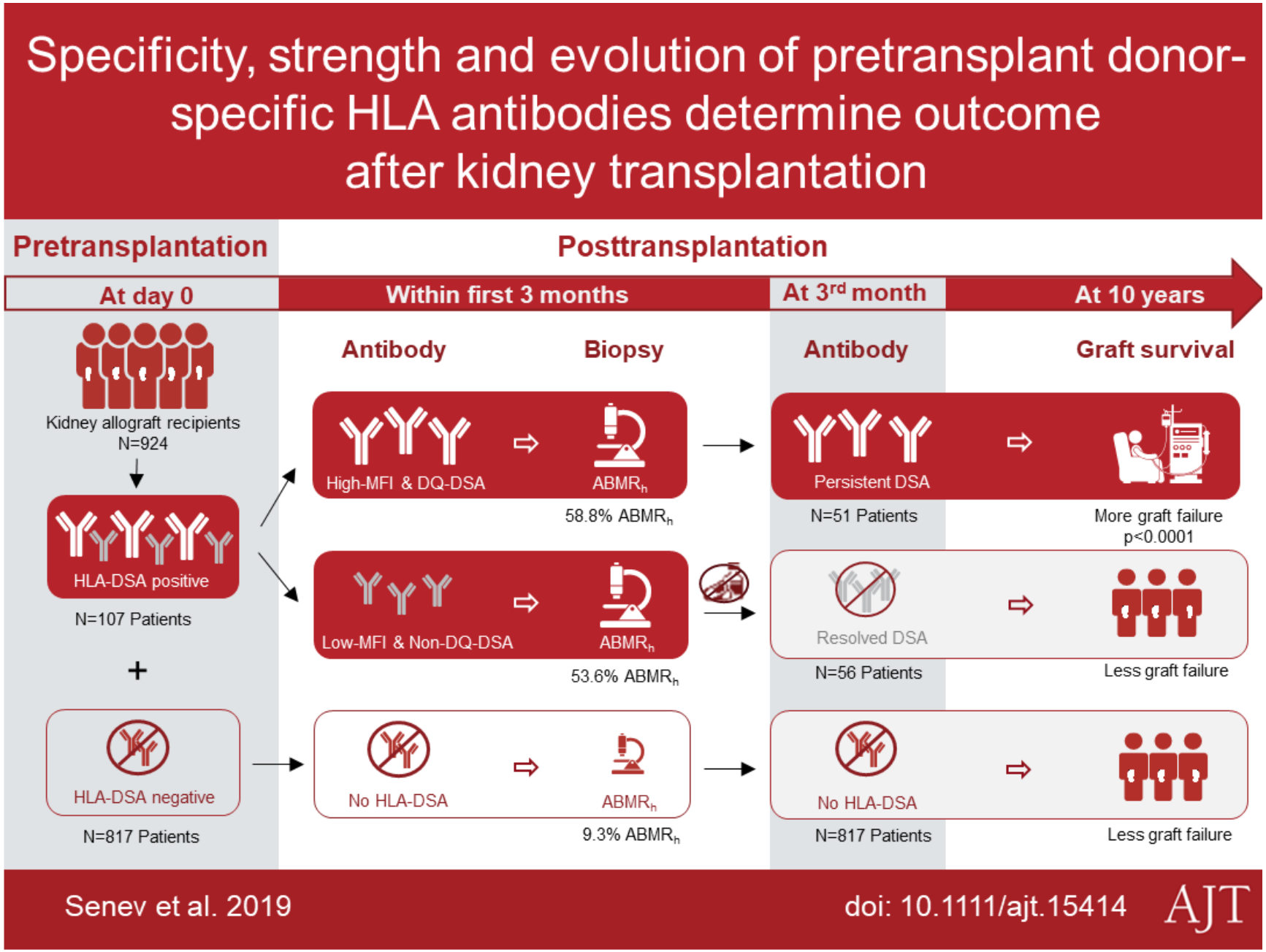
  No need of antibody removal therapy

- **Persistent pretransplant DSA**
  - Persistence of pretransplant DSA after transplantation has a negative impact on graft survival, beyond the diagnosis of $ABMR_h$ according to the current Banff classification.
  - DQ-DSA specificity and DSA with MFI > 1400 persisted after TX and associated with impaired graft outcome.

  Antibody removal therapy

Senev et al. *Am J Transplant*. 2019; 19: 3100- 3113.

Visual abstract



American Journal of Transplantation - Highlights

AJT November 2019 Editors' Picks

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