

Post-transplant rejection diagnostics: a Bermuda triangle between HLA specialists, nephrologists and pathologists

Maarten Naesens, MD PhD
KU Leuven, Belgium

Mechelen, 10 March 2023



NEPHROLOGY
LEUVEN



BERMUDA

BERMUDA TRIANGLE

FLORIDA

CUBA

PUERTO RICO

PATHOLOGY

Precision
medicine

HISTOCOMPAT.
LABORATORY

Precision
medicine

NEPHROLOGY

HISTOCOMPAT.
LABORATORY

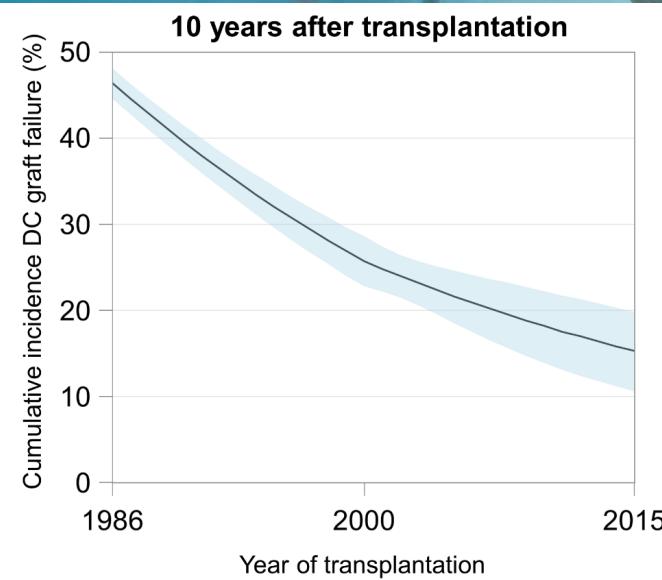
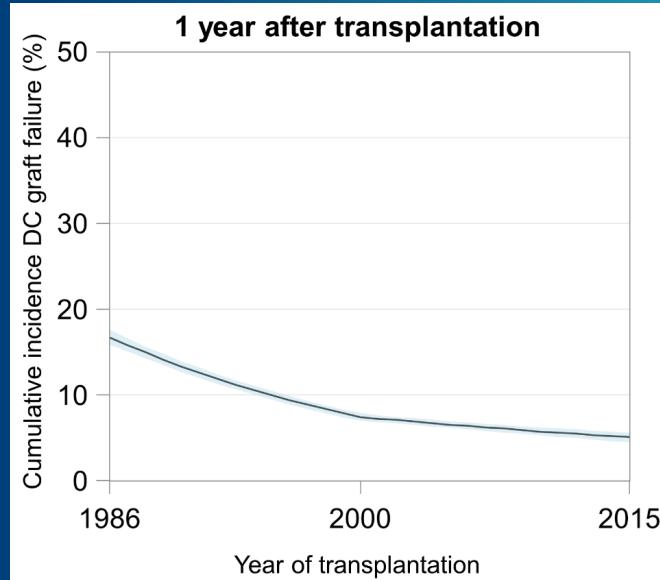
PATHOLOGY

Allograft
rejection

NEPHROLOGY

Kidney transplantation - a quiet revolution

Graft failure

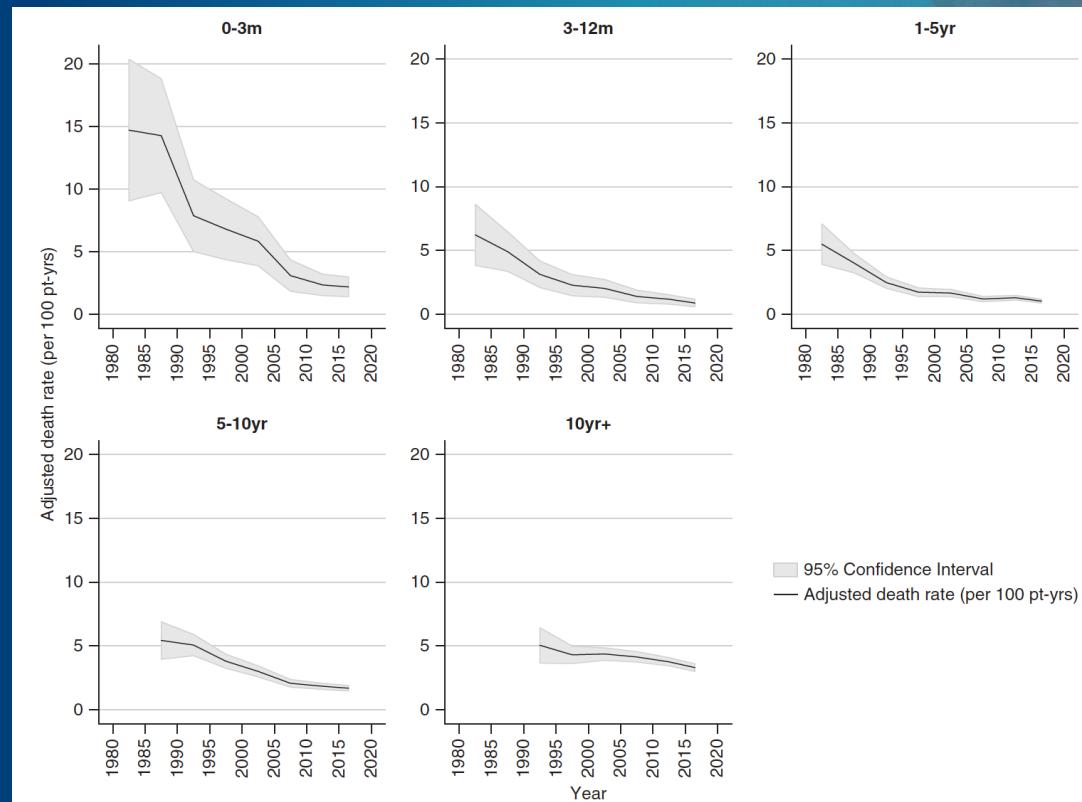


Coemans, Callemeyn, Naesens. N Engl J Med, 2022
Coemans et al Kidney Int 2018

E .Delacroix, 1830

Kidney transplantation - a quiet revolution

Patient death

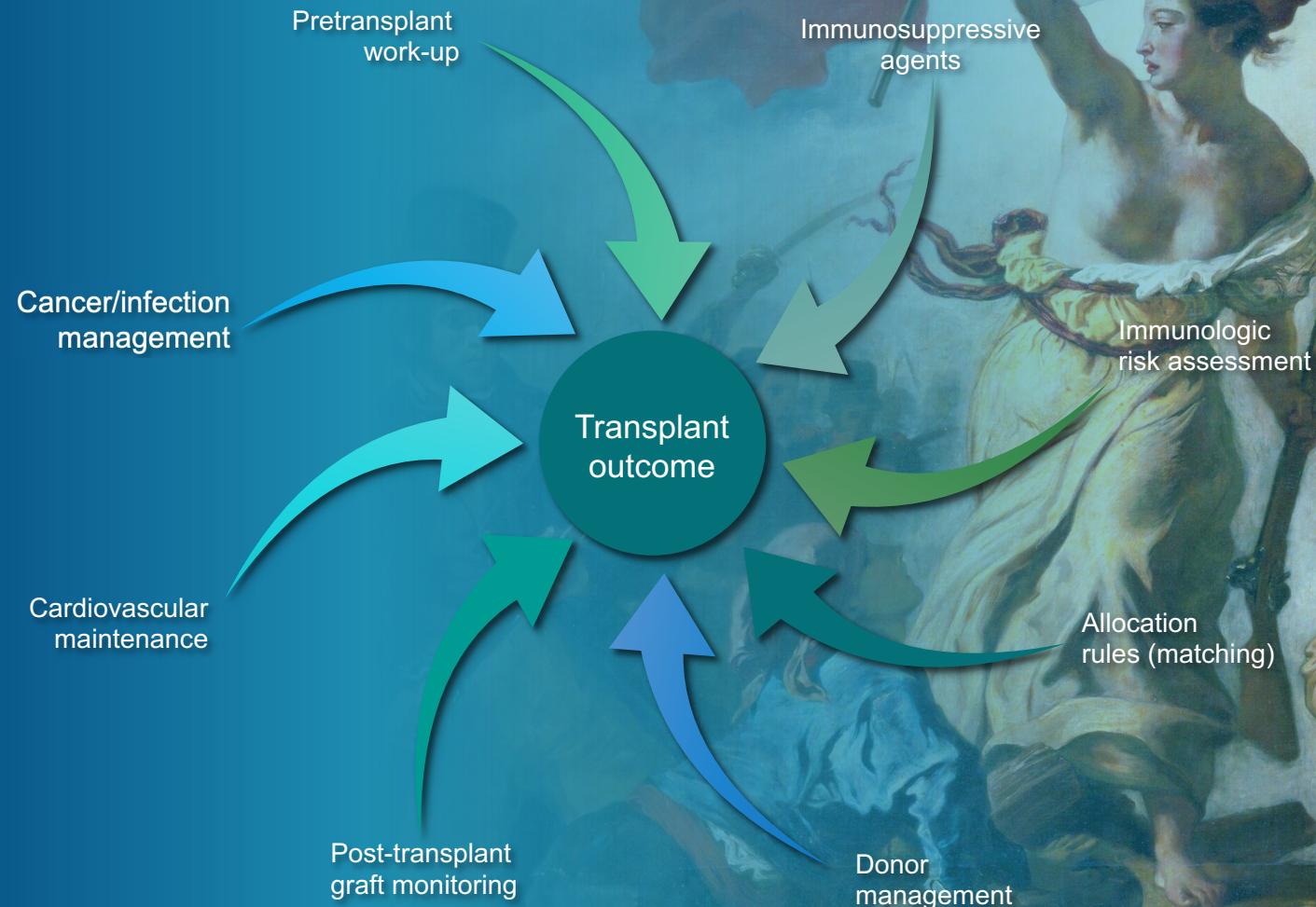


Ying et al J Am Soc Nephrol 2020



E. Delacroix, 1830

The quiet revolution



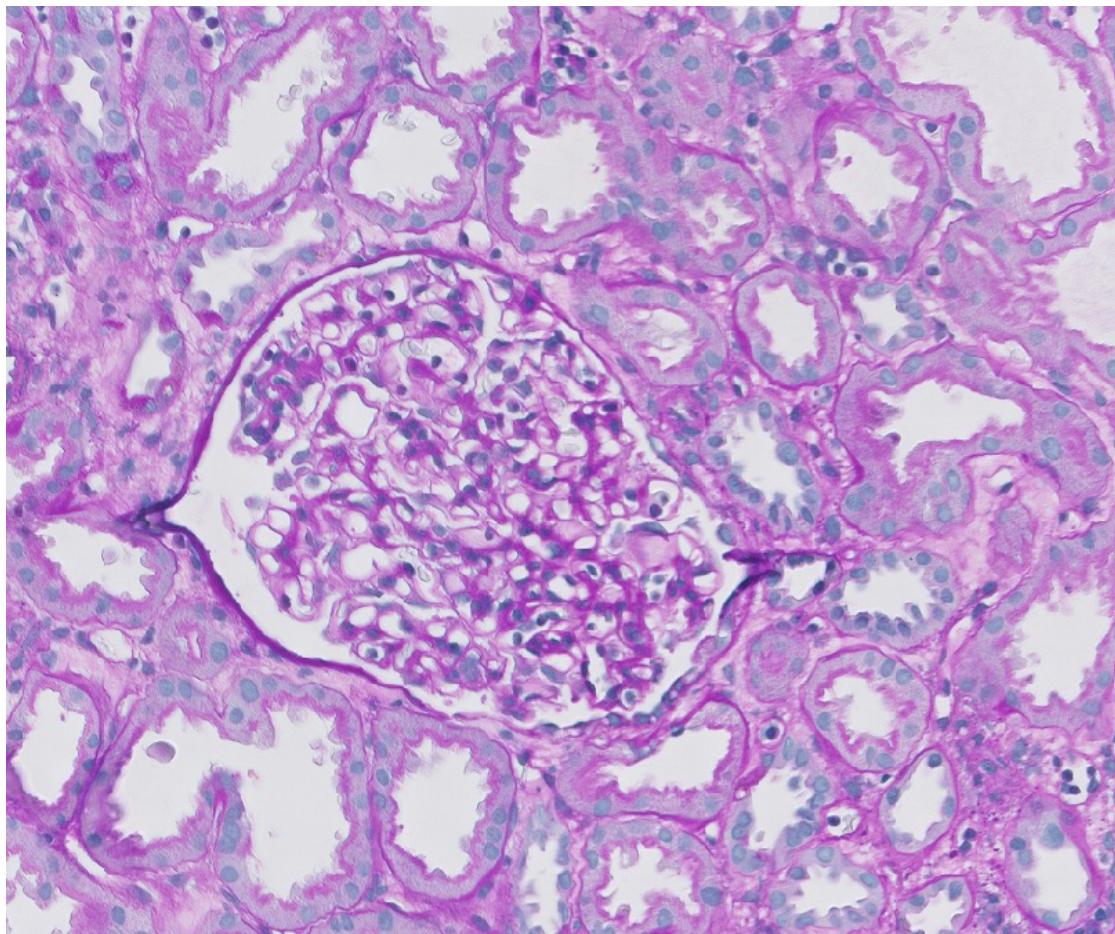
E. Delacroix, 1830



Today, rejection is diagnosed
in biopsies

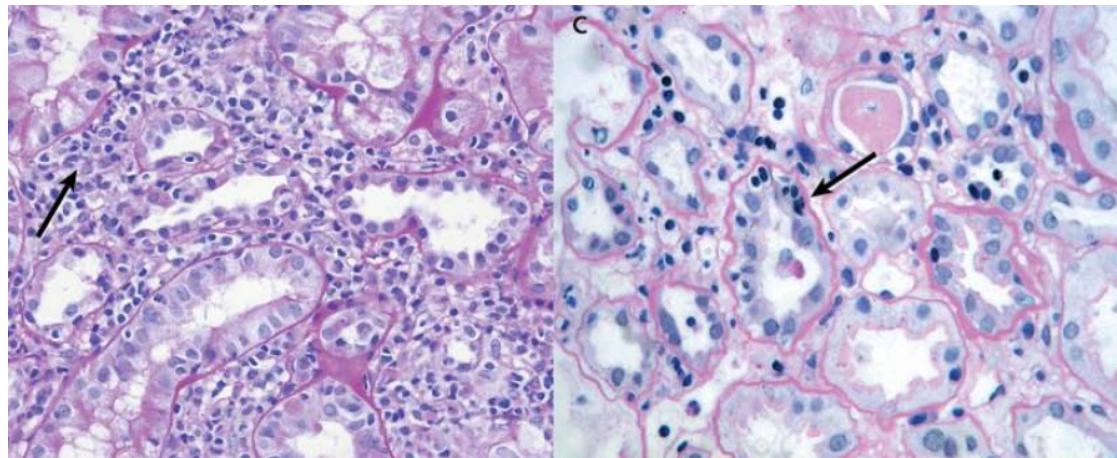
(Banff classification as *current* ground truth)

The histology of a transplant kidney

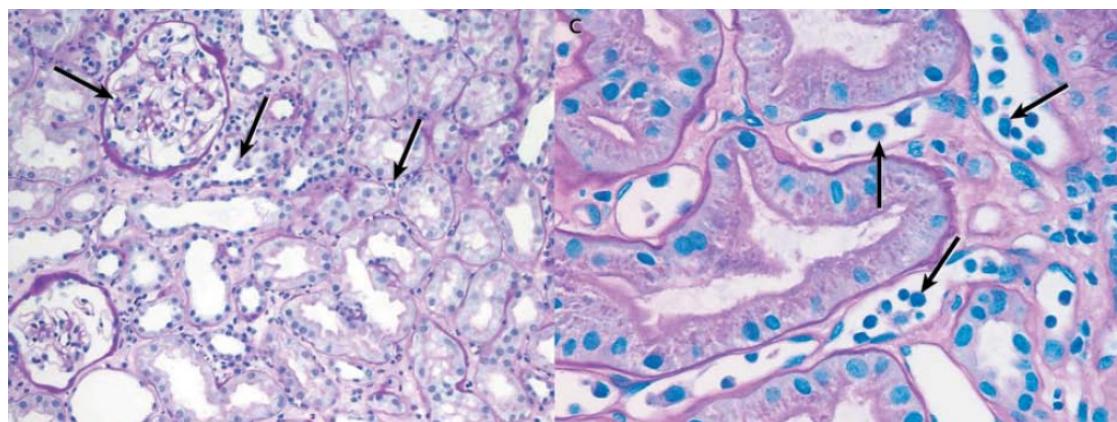


Nankivell New Engl J Med 2010

Two different entities: “TCMR” and “AMR”

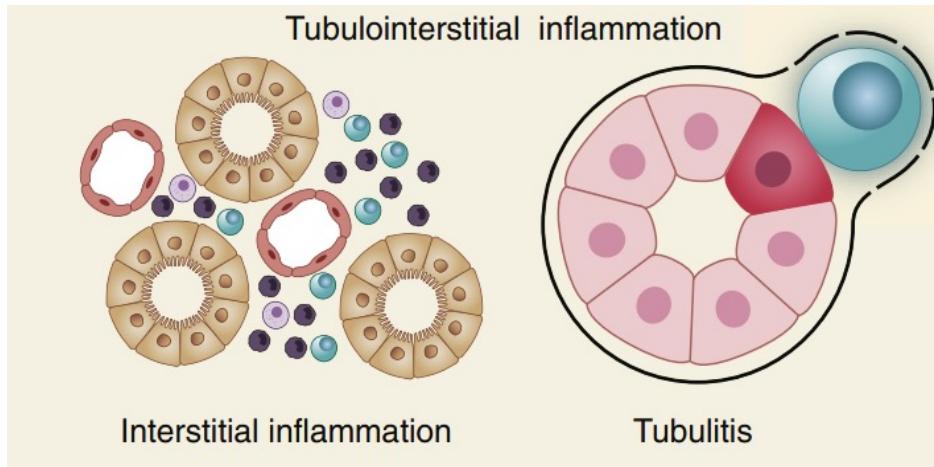


Tubulo-interstitial inflammation
“T-cell *mediated* rejection”

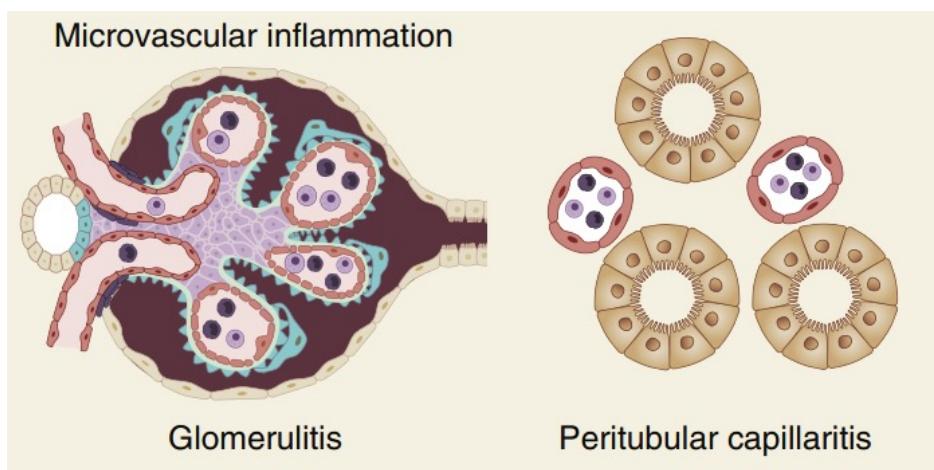


Microvascular inflammation
“Antibody-*mediated* rejection”

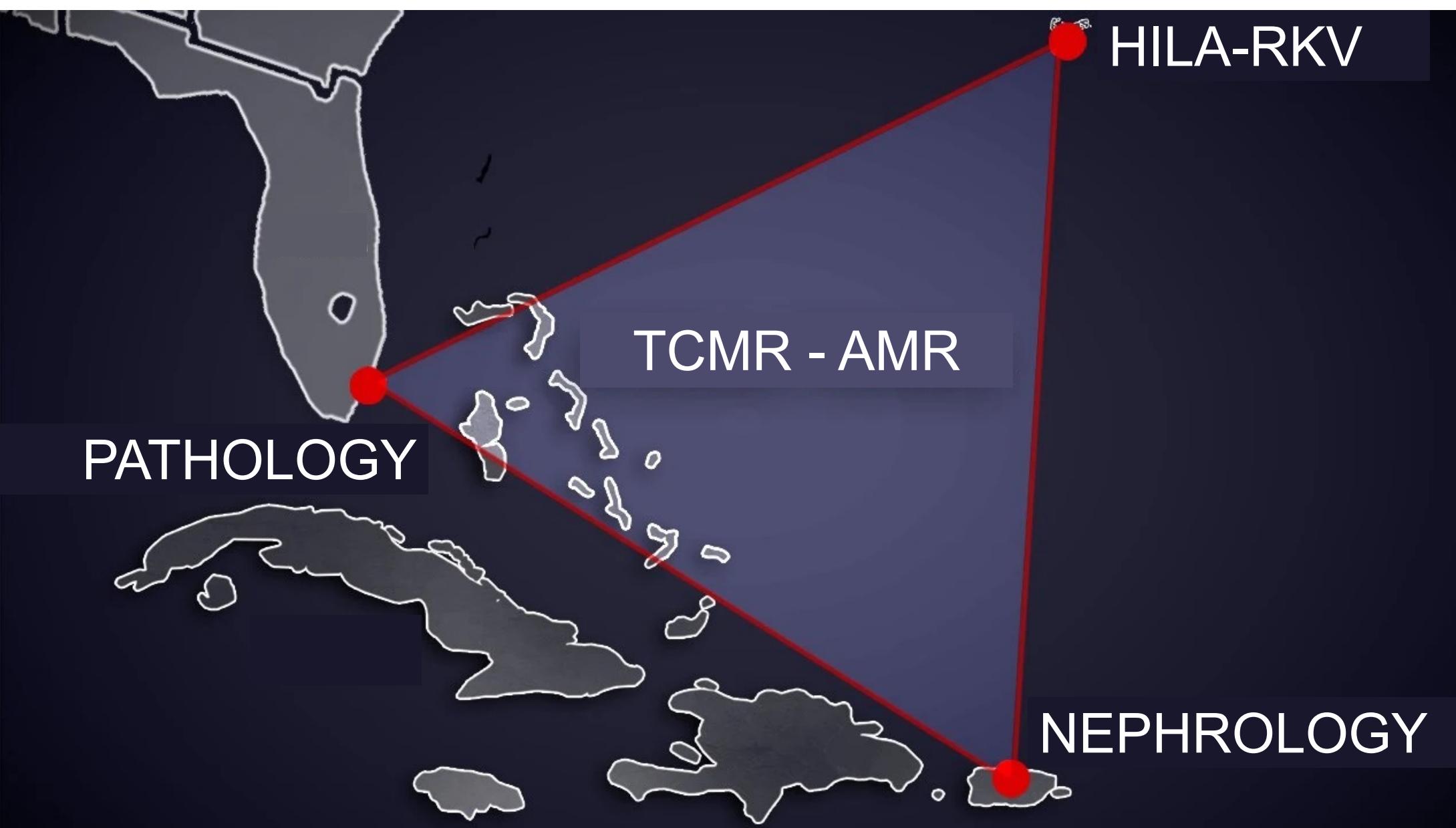
Two different entities: “TCMR” and “AMR”



Tubulo-interstitial inflammation
“T-cell *mediated* rejection”



Microvascular inflammation
“Antibody-*mediated* rejection”



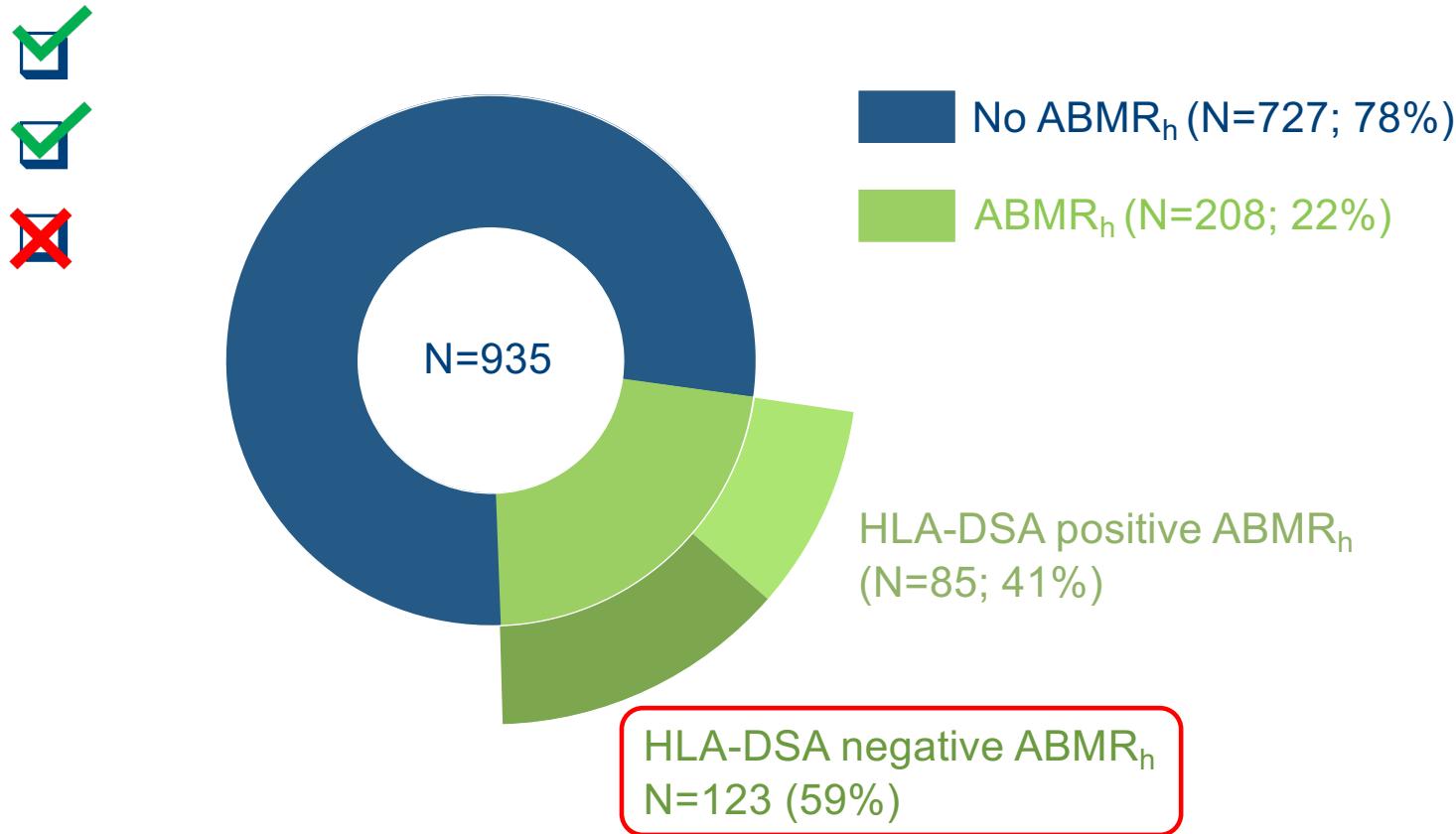
PATHOLOGY

TCMR - AMR

NEPHROLOGY

HILA-RKV

We observed a very high percentage
of patients with ABMR_h without HLA-DSA



Senev et al. Am J Transplant 2019

Clinical presentation



Impact



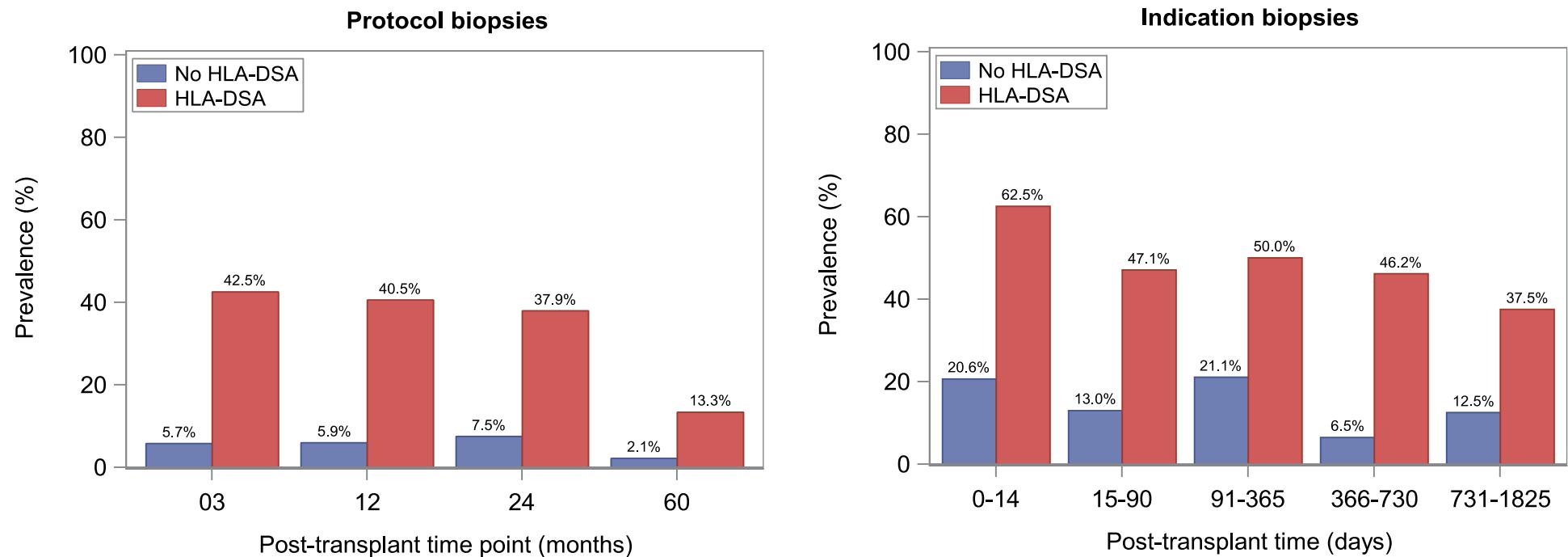
Causes

M_{icro}V_{ascular} I_{nflammation}

Diagnosis

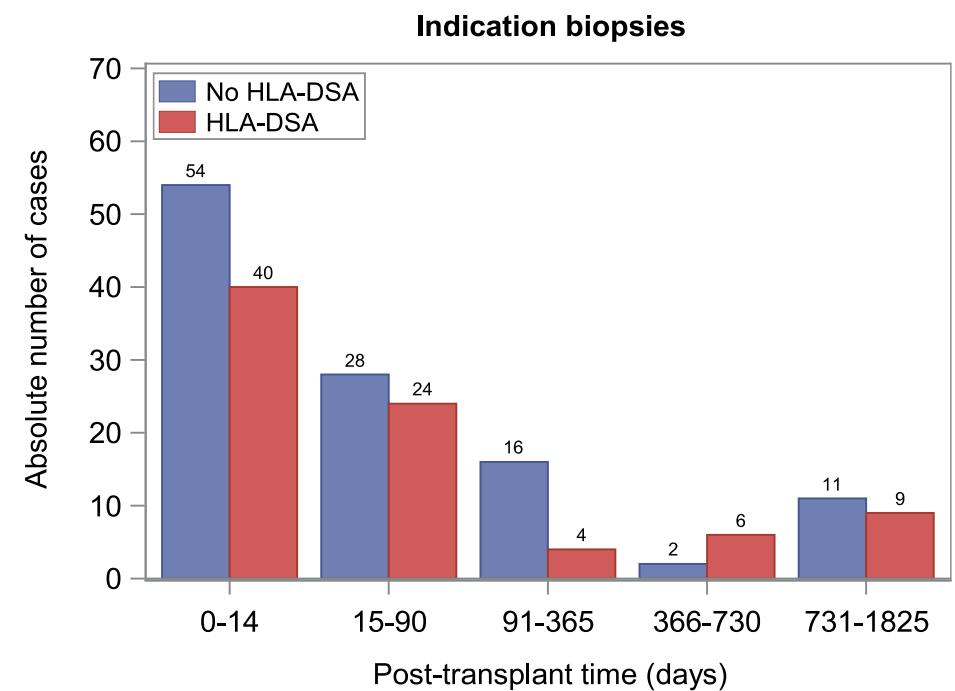
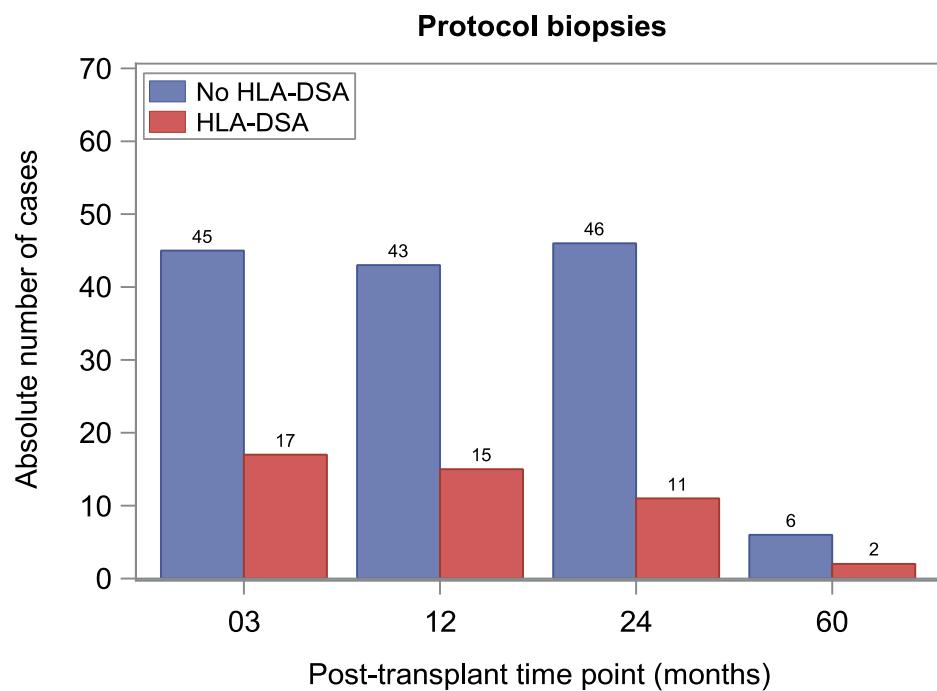


MVI is more prevalent in HLA-DSA positive patients



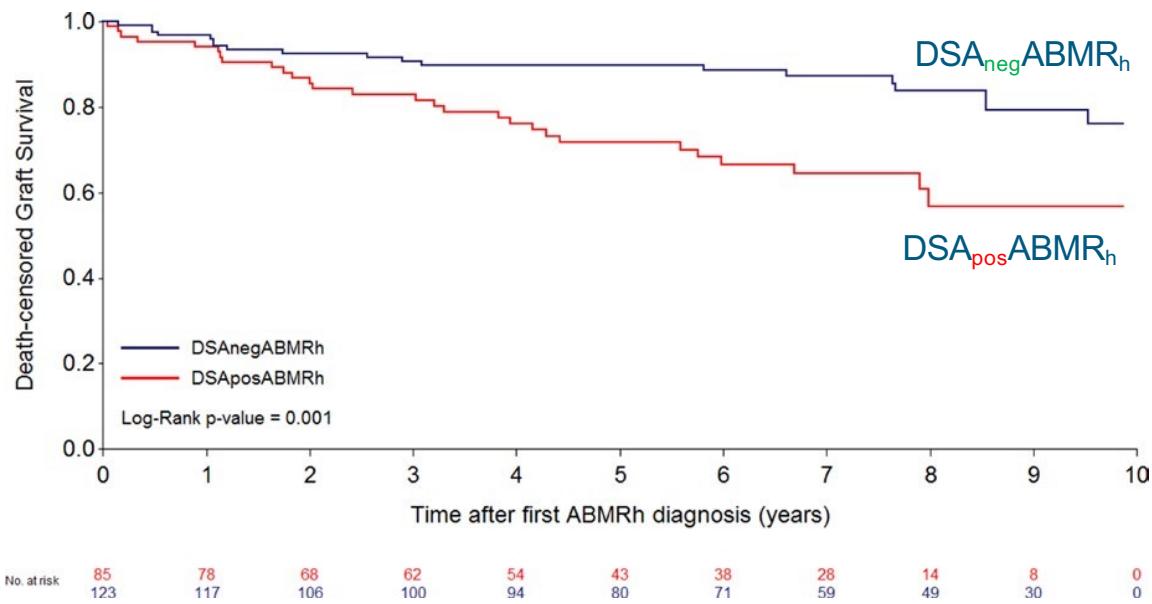
N = 1000 transplants; 3594 posttransplant biopsies

There is a high number of cases with MVI without HLA-DSA



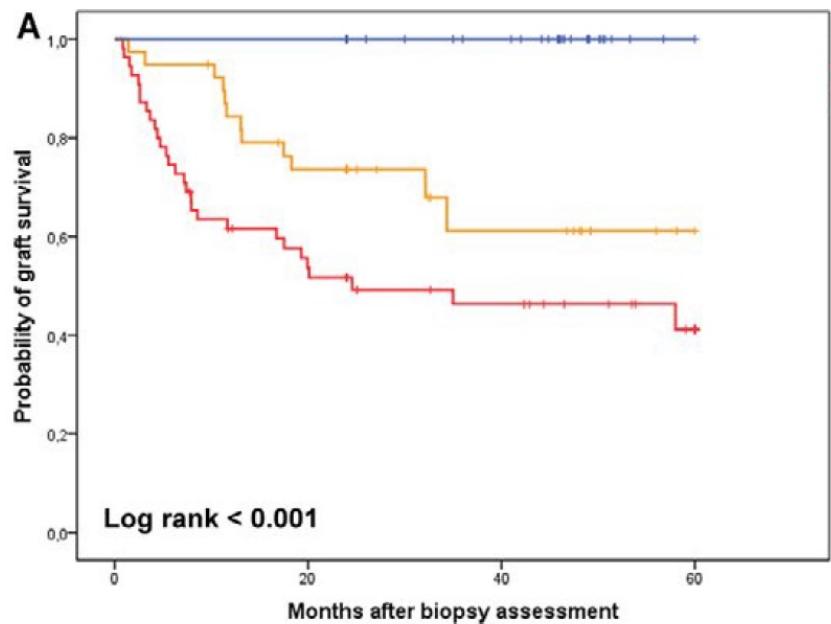
N = 1000 transplants; 3594 posttransplant biopsies

Outcome of HLA-DSA negative MVI is better than in HLA-DSA positive ABMR_h

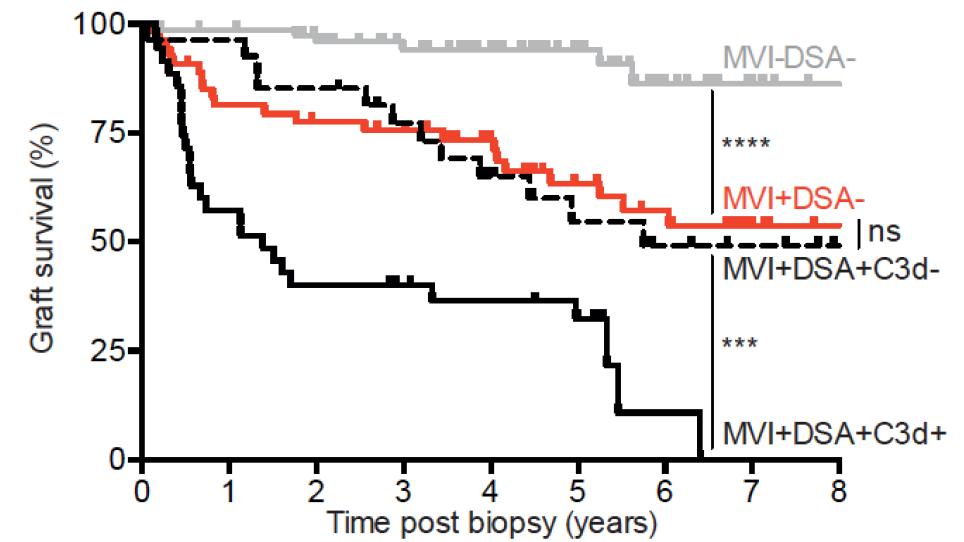


Senev et al. Am J Transplant 2018

Outcome of HLA-DSA negative ABMRh is better than in HLA-DSA positive ABMR_h

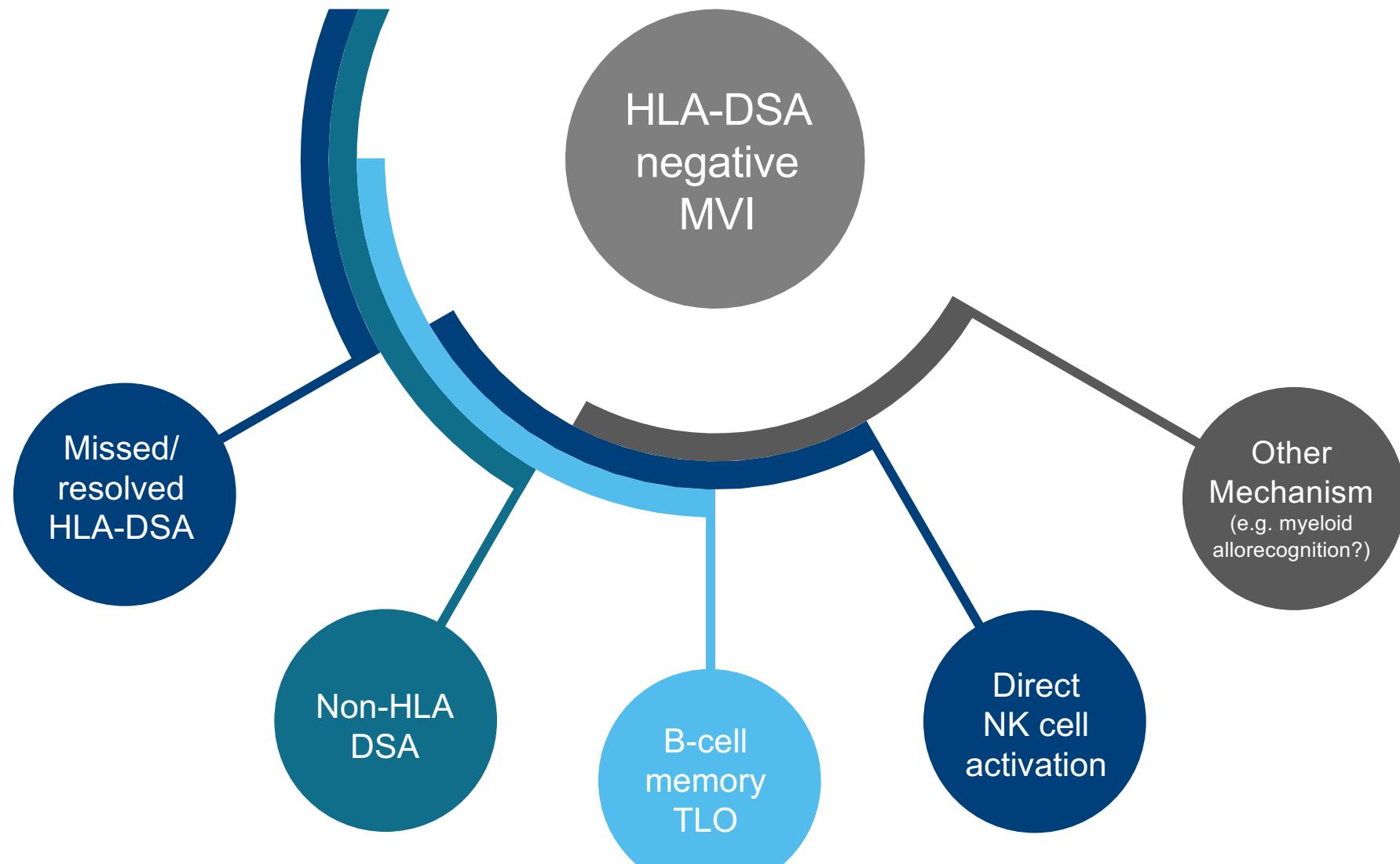


Bestard & Grinyo, Am J Transplant 2018

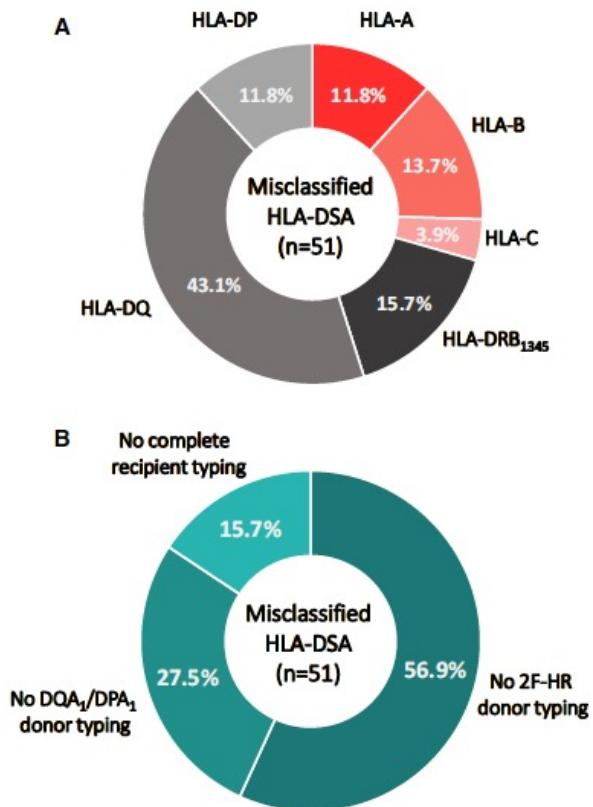


Koenig et al Nat Comm 2019

How can we explain DSA-negative MVI?

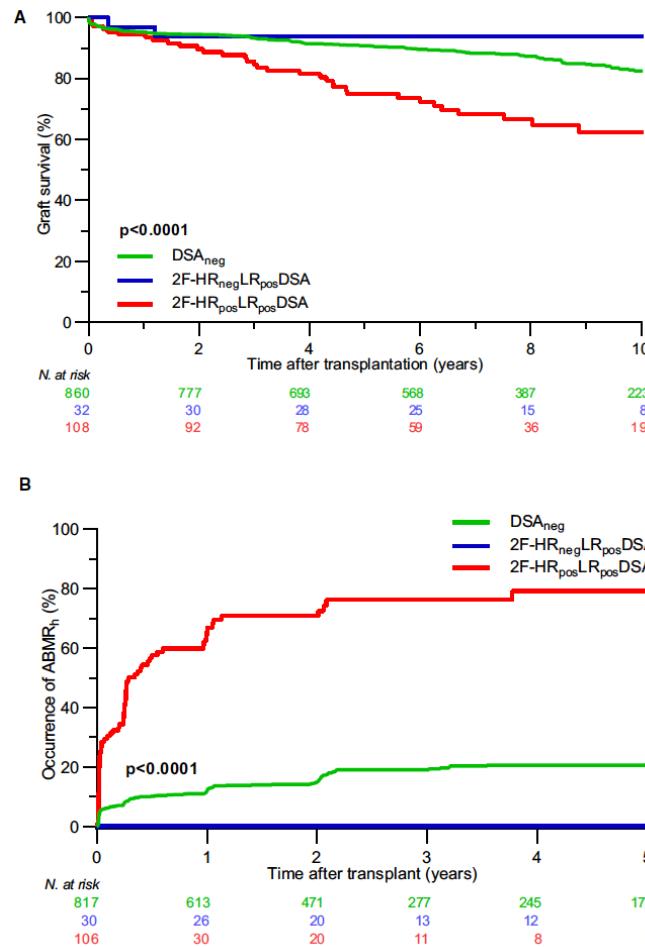
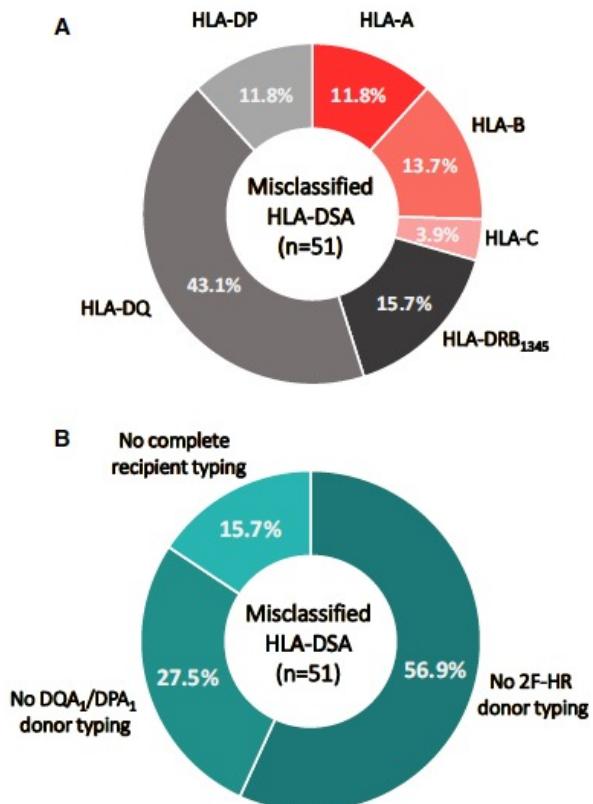


DSA negative MVI can be explained by missed HLA-DSA Talk to the HLA lab!



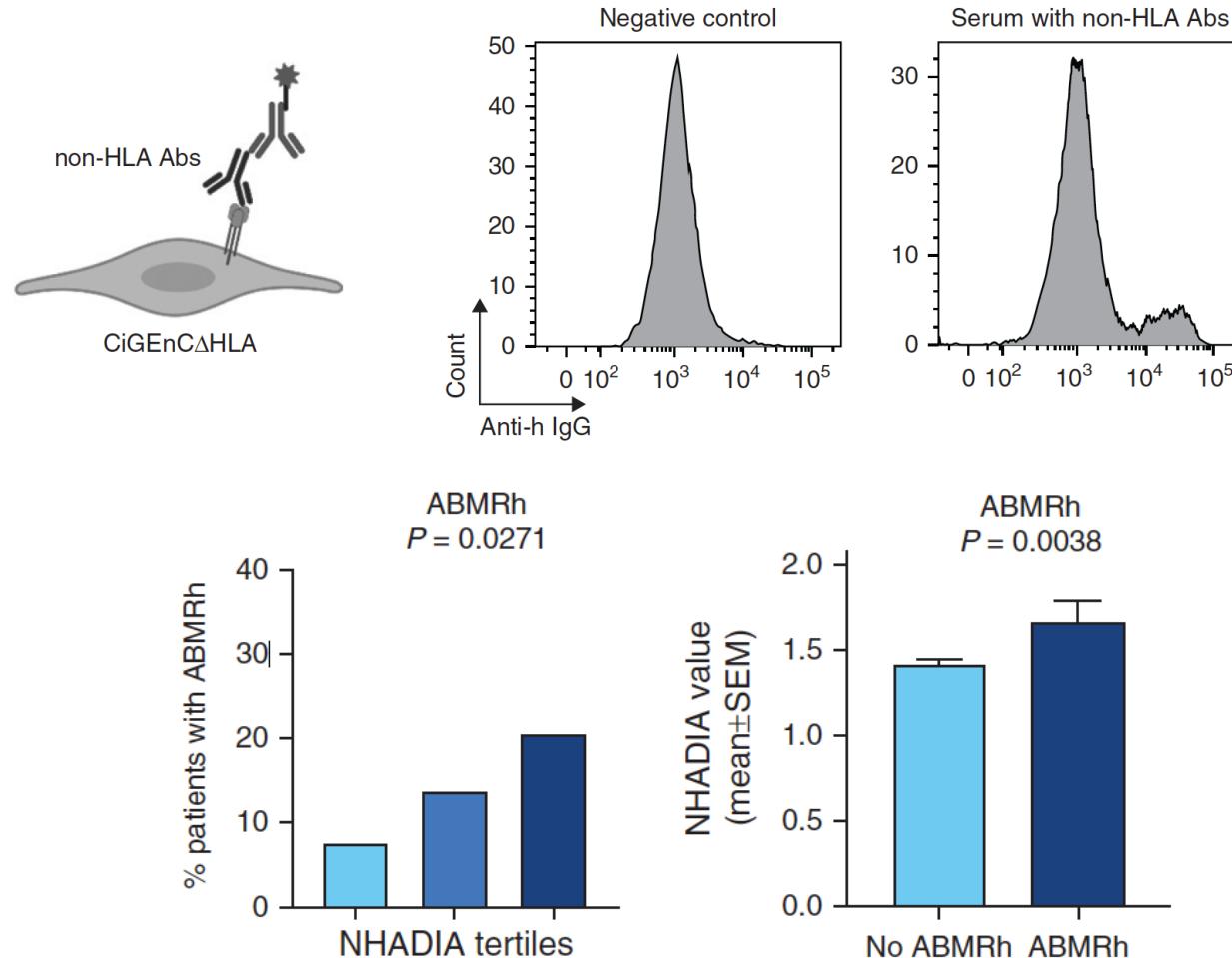
	Donor genotyping HLA level			
	LR split antigen level		Inferred 2F-HR level	
DSA ≥ 500	pos	neg	pos	neg
Final DSA positive	83	25	63	45
Final DSA negative	28	126	16	138
Accuracy (%)	79.8		76.7	
Sensitivity (%)	76.9		58.3	
Specificity (%)	81.8		89.6	
PPV (%)	74.8		79.8	
NPV (%)	83.4		75.4	

DSA negative MVI can be explained by missed HLA-DSA Talk to the HLA lab!



Senev et al AJT 2020

Non-HLA Ab detection immunoassay (NHADIA) to detect non-HLA DSA



Lamarthée et al JASN 2021

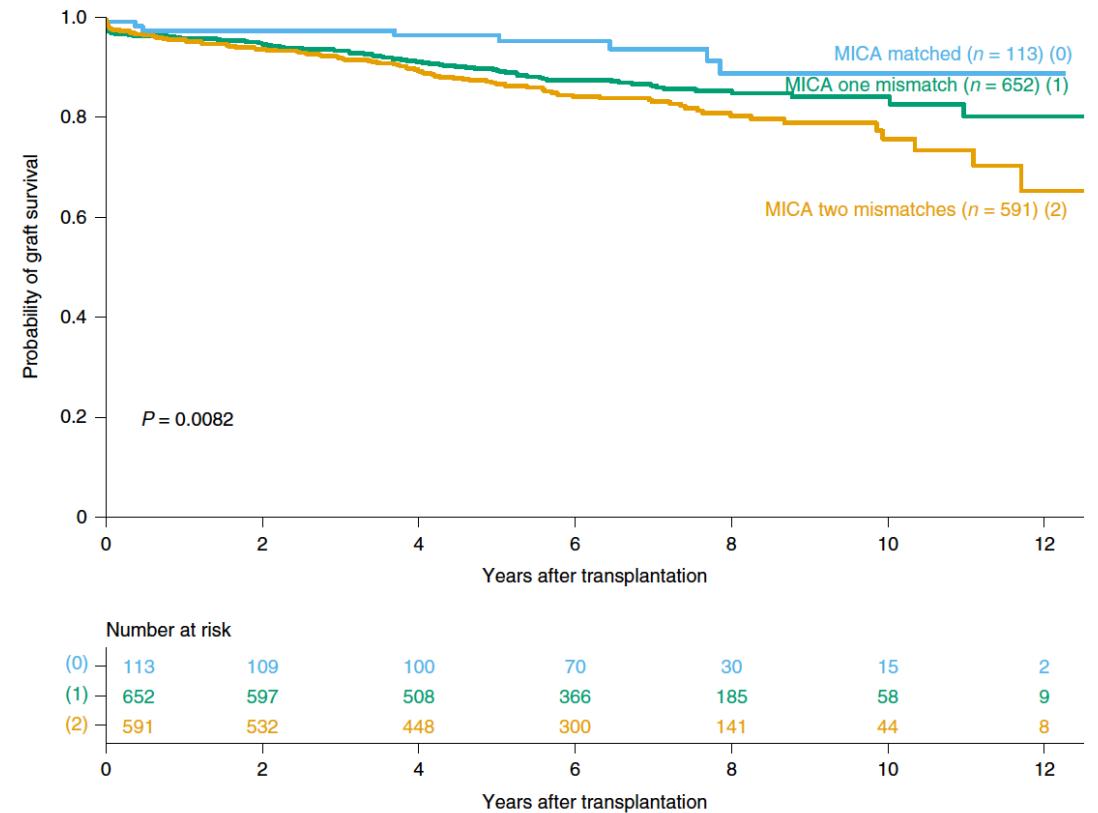
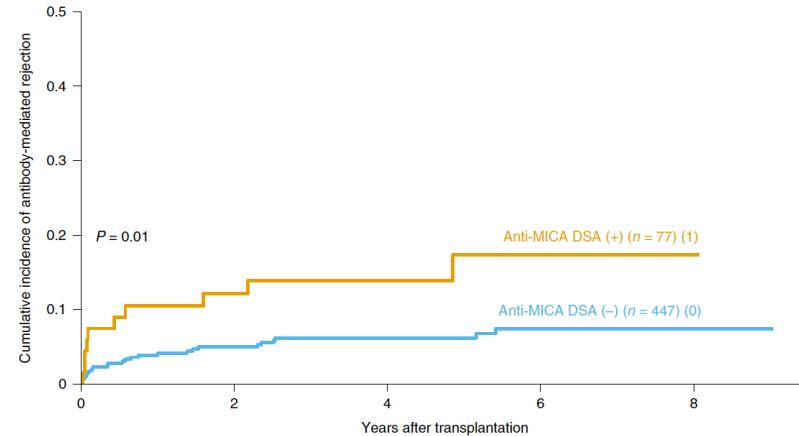
MICA is confirmed as minor histocompatibility antigen in kidney transplantation leading to anti-MICA DSA and MVI



OPEN

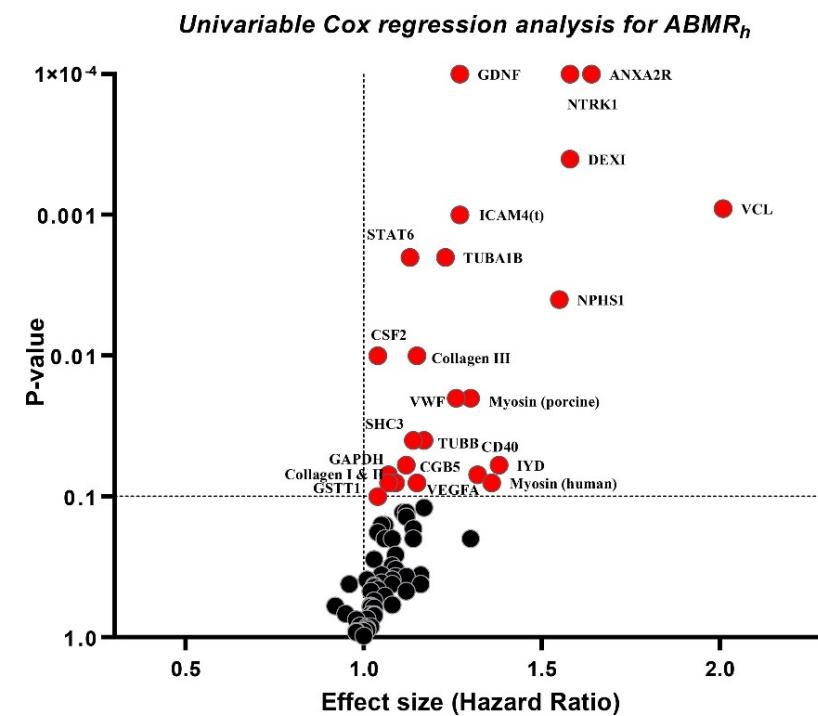
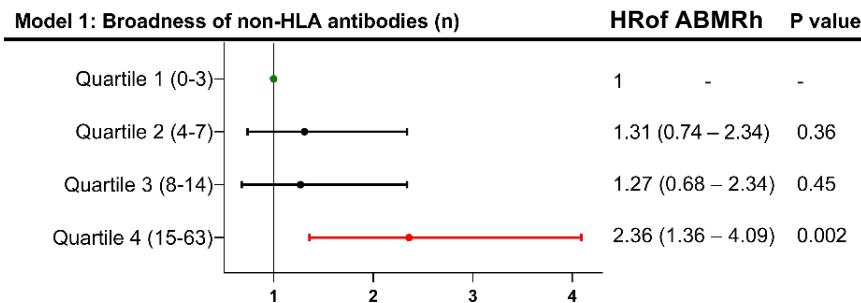
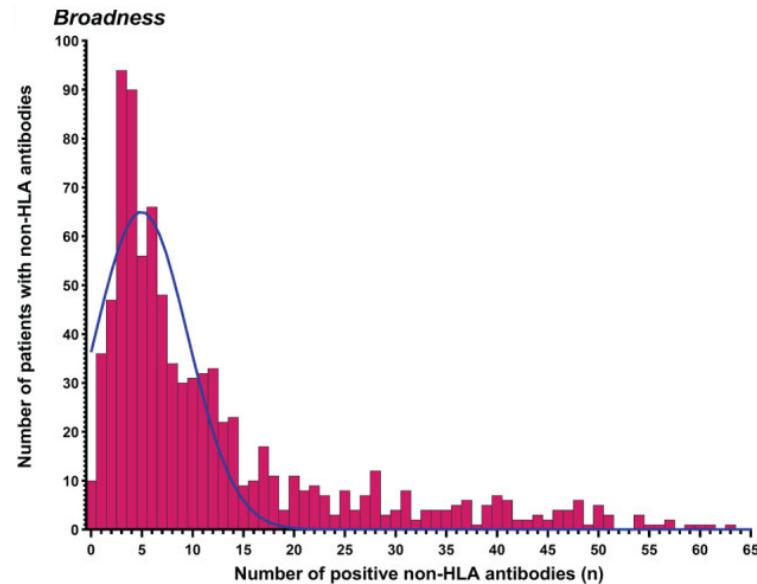
The MHC class I MICA gene is a histocompatibility antigen in kidney transplantation

Raphael Carapito^{1,2,3,4,5}, Ismail Aouadi^{1,2,3,5}, Martin Verniquet^{1,2,3,5}, Meiggie Untrau^{1,2,3,5}, Angélique Pichot^{1,2,3,5}, Thomas Beaudrey^{1,2,5,6}, Xavier Bassand^{1,2,5,6}, Sébastien Meyer^{1,2,3,5}, Loïc Faucher^{2,7}, Juliane Posson^{8,9}, Aurore Morlon^{2,10}, Irina Kotova^{2,10}, Florent Delbos^{2,11}, Alexandre Walencik^{2,11}, Alice Aarnink¹², Anne Kennel¹², Caroline Suberbielle^{2,13}, Jean-Luc Taupin^{2,13}, Benedict M. Matern^{10,14}, Eric Spierings^{10,14}, Nicolas Congy-Jolivet^{2,15,16}, Arnaud Essaydi¹⁷, Peggy Perrin^{12,5,6}, Antoine Blancher^{2,15,18}, Dominique Charron^{2,5,13}, Nezih Cereb¹⁸, Myriam Maumy-Bertrand^{2,5,19}, Frédéric Bertrand^{2,5,19}, Valérie Garrigue^{2,20}, Vincent Pernin^{2,20}, Laurent Weekers^{2,21}, Maarten Naesens^{10,22}, Nassim Kamar^{2,23}, Christophe Legendre^{2,24}, Denis Glotz^{2,8,9}, Sophie Caillard^{1,2,5,6}, Marc Ladrière²⁵, Magali Giral^{2,7}, Dany Anglicheau^{2,24,26}, Caner Süsan^{27,28} and Seiamak Bahram^{1,2,3,4,5}



Carapito et al Nat Med 2022

Broad sensitization against non-HLA targets associates with an increased risk of ABMR histology



The STAR guideline on non-HLA antibody testing

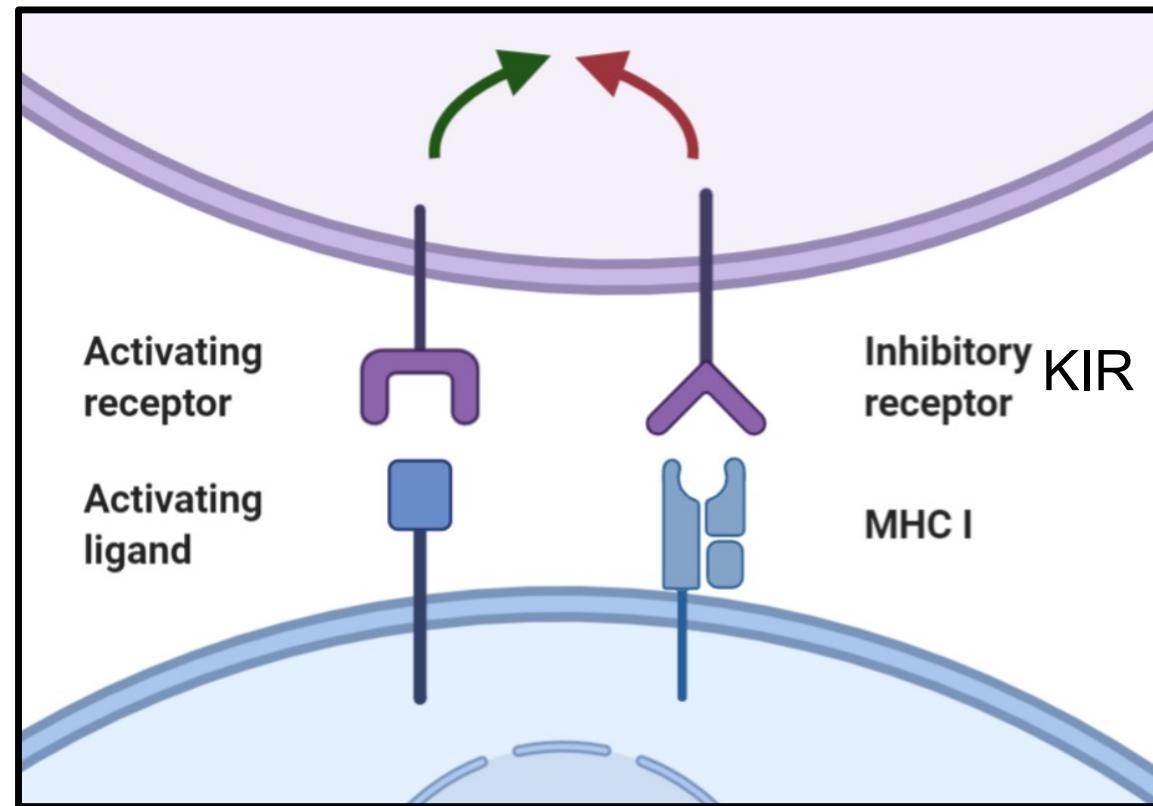
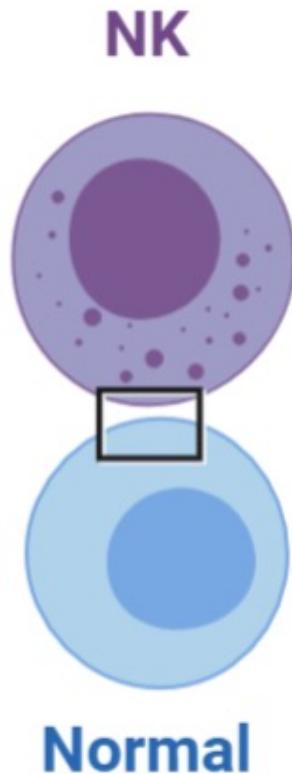
Organ-Specific Recommendations for Non-HLA antibody Testing

Indication	Heart/Lung		kidney		liver	
	AT1R/ETAR	MICA	AT1R/ETAR	MICA	XM one	AT1R/ETAR
Pre transplant						
First transplant	3C**	3D	3C	3D	3C	3D
Special circumstances or at-risk categories*	EO	IE	EO	3D	2D	EO/2D
Post transplant						
Stable graft	3C	3D	3C	3D	IE	3D
Immediate/early graft dysfunction no HLA DSA	2C	IE	EO	EO	IE	IE
Rejection TCMR on biopsy HLA DSA negative	3C	IE	3C	3D	IE	IE
Rejection TCMR on biopsy HLA DSA positive	3D	IE	3D	3D	IE	IE
Rejection ABMR on biopsy HLA DSA negative	EO	EO	2B/C	2D	IE	EO
Rejection ABMR on biopsy HLA DSA positive	EO	IE	EO	3D	IE	3D
follow up pre transplant non-HLA testing positive	EO***		EO***		EO***	

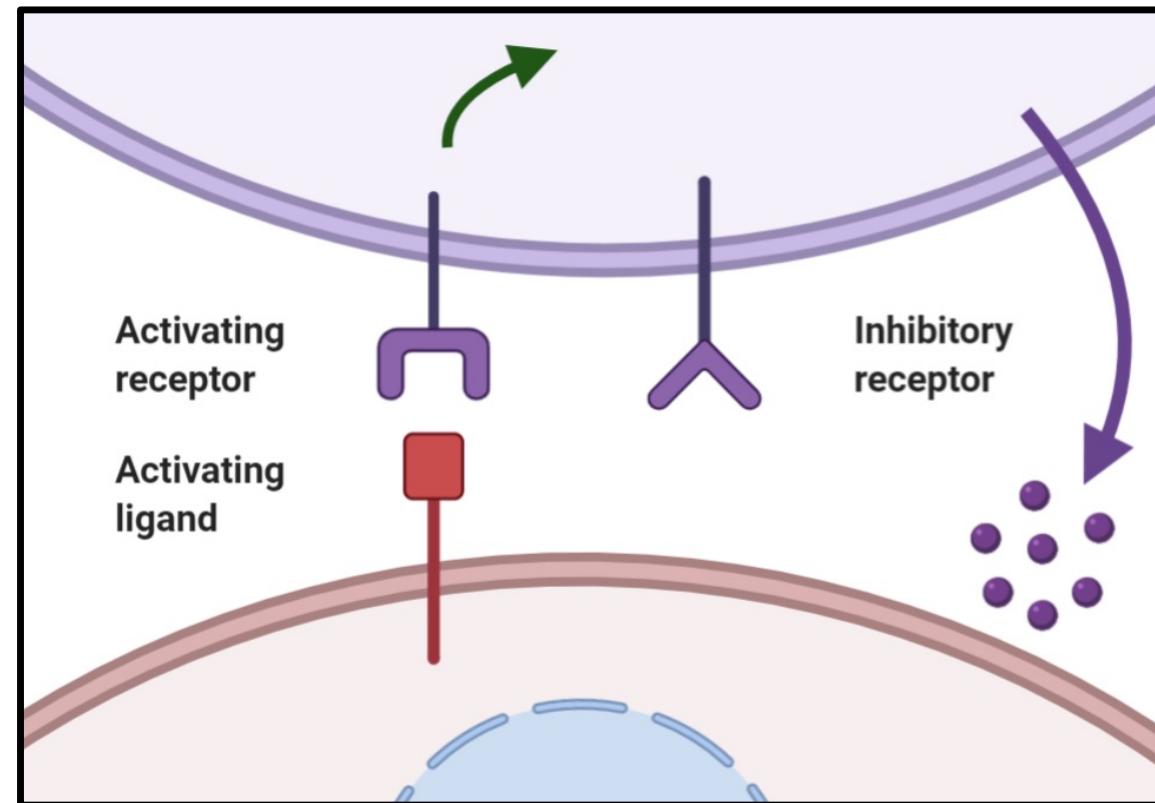
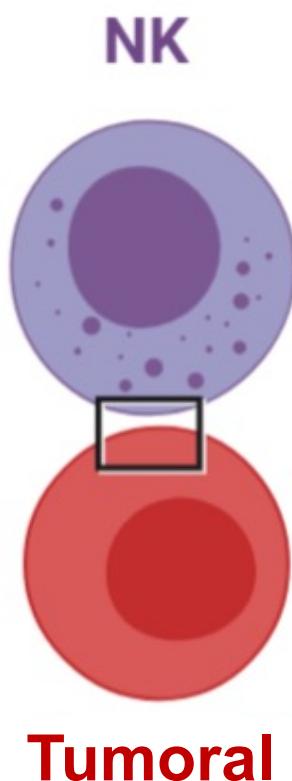
Non-HLA DSA testing not recommended (Score 3)
with low to very low (C-D) quality of evidence

Tambur et al In Press

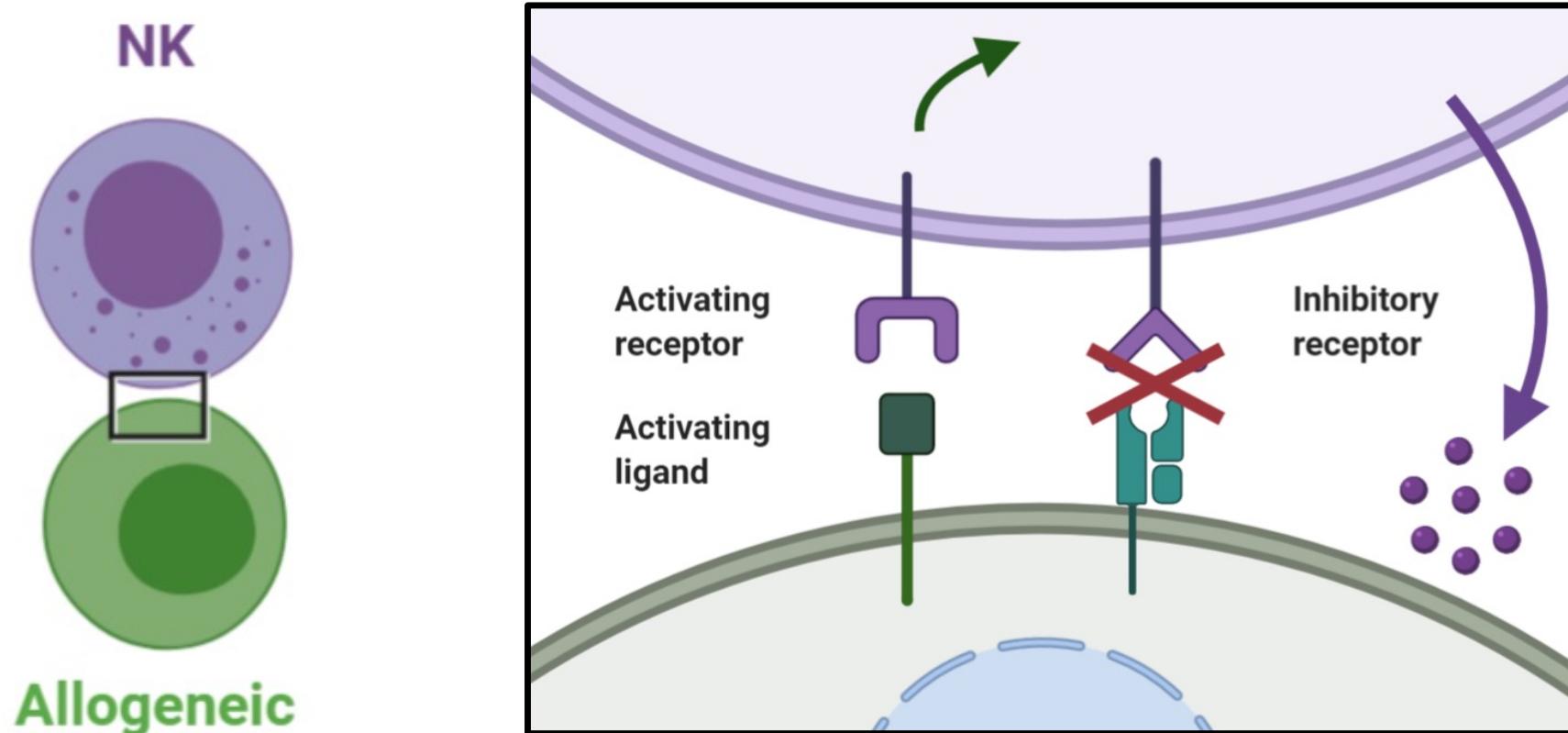
NK cells are kept in balance by inhibitory and activating receptors



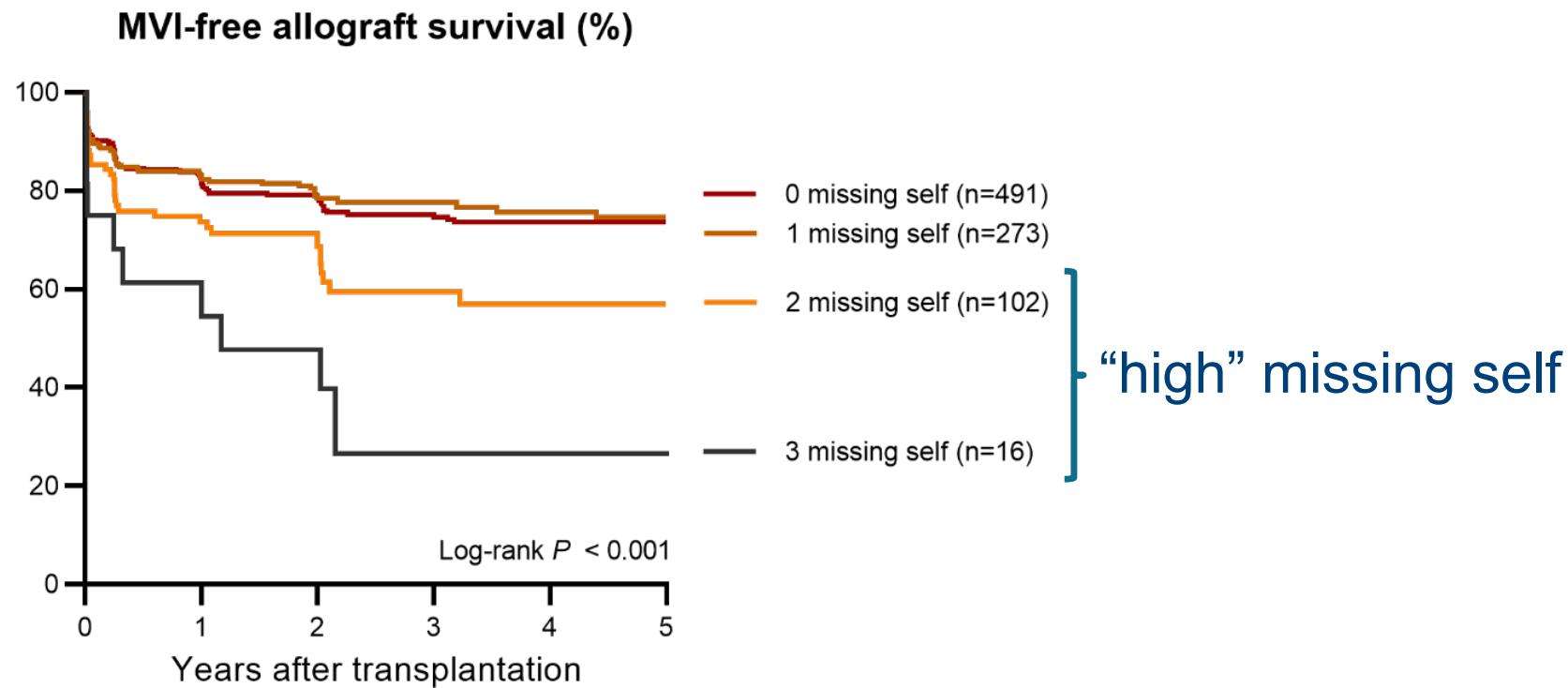
NK cells activate by “absence of self” (missing self)



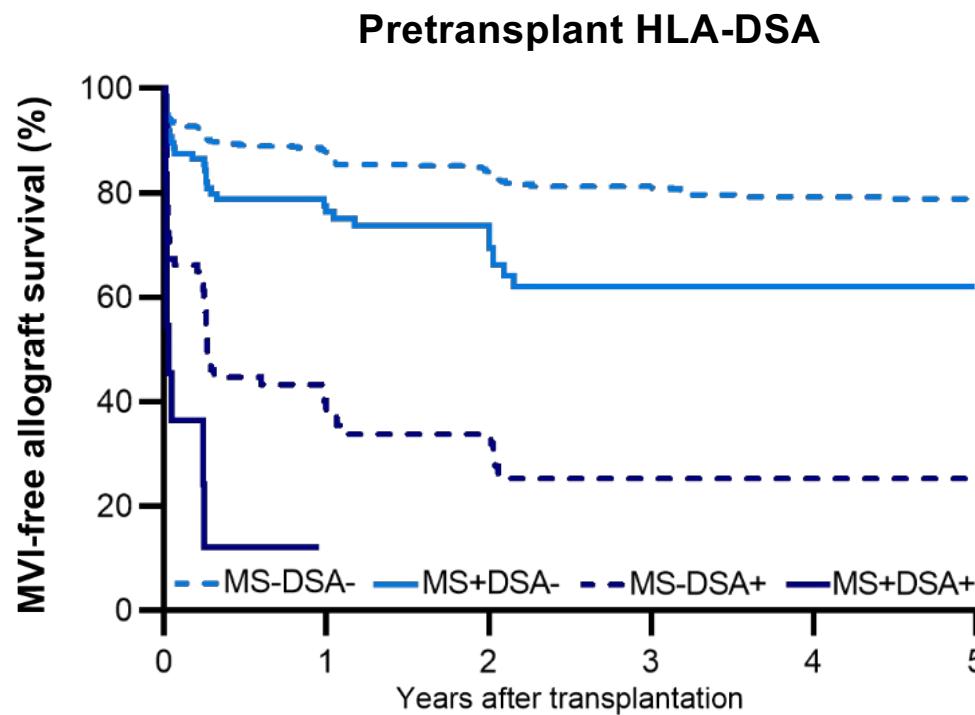
NK cells activate by “absence of self” (missing self)



Missing self associates with MVI

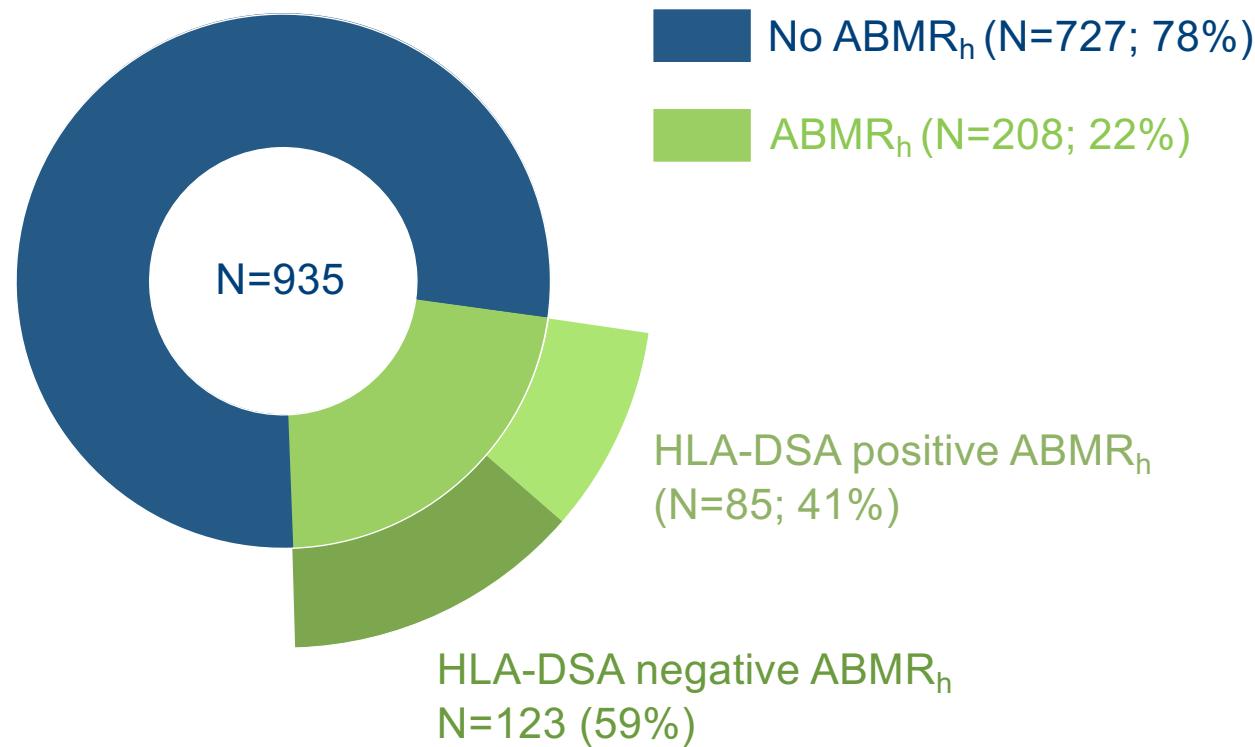


Missing self independently increases the risk of MVI



CONCLUSION:

DSA-negative MVI is very common
and further research is needed



Senev et al. Am J Transplant 2019

Recent research on DSA-negative MVI

Phenotype, prevalence and outcome

- Sablik Transplant Int 2018
- Senev et al. Am J Transplant 2019
- Bestard et al. Am J Transplant 2019
- Koenig et al Nat Commun 2019
- Lubetzky et al Clin Transplant 2019
- Parajuli et al Transplantation 2019
- Coemans et al Transplant Int 2021
- Vaulet et al JASN 2021
- Crespo et al Front Immunol 2021
- Halloran et al Am J Transplant 2022
- Saba et al ATC 2022 meeting abstract #209

Association with NK missing self

- Koenig et al Nat Commun 2019
- Callemyen et al JASN 2021
- Koenig et al JASN 2021

Relation to HLA mismatches and TCMR

- Senev et al cJASN 2022

Phenotype in the molecular microscope

- Lubetzky et al Clin Transplant 2019
- Callemyen et al JASN 2021
- Halloran et al JASN 2022
- Rosales et al JASN in press
- Callemyen et al under review (sparse models)



Relation with non-HLA antibodies

- Reindl-Schwaighofer et al Lancet 2019
- Lefaucheur et al Kidney Int 2019
- Delville et al JASN 2019
- Lamartheé et al JASN 2021
- Crespo et al Front Immunol 2021
- Senev et al Front Immunol 2022
- Carapito et al Nat Med 2022
- Asano et al Nat Comm 2021; Chong present.

Non-invasive biomarkers

- Van Loon et al Nephrol Dial Transplant 2020 - mRNA
- Halloran et al JASN 2022 TRIFECTA study - ddcfDNA
- Van Loon et al under review - urinary CXCL9/10

Recent research on DSA-negative MVI, indicating a need for definition

Phenotype, prevalence and outcome

- Sablik Transplant Int 2018
- Senev et al. Am J Transplant 2019
- Bestard et al. Am J Transplant 2019
- Koenig et al Nat Commun 2019
- Lubetzky et al Clin Transplant 2019
- Parajuli et al Transplantation 2019
- Coemans et al Transplant Int 2021
- Vaulet et al JASN 2021
- Crespo et al Front Immunol 2021
- Halloran et al Am J Tr
- Saba et al ATC 2022

Association with NK missing self

- Koenig et al Nat Commun 2019
- Callemeyn et al JASN 2021
- Koenig et al JASN 2021

Relation to HLA mismatches and TCMR

- Senev et al cJASN 2022

Phenotype in the molecular microscope

- Lubetzky et al Clin Transplant 2019
- Callemeyn et al JASN 2021
- Halloran et al JASN 2022
- Rosales et al JASN in press
- Callemeyn et al under review (sparse models)

Relation with non-HLA antibodies

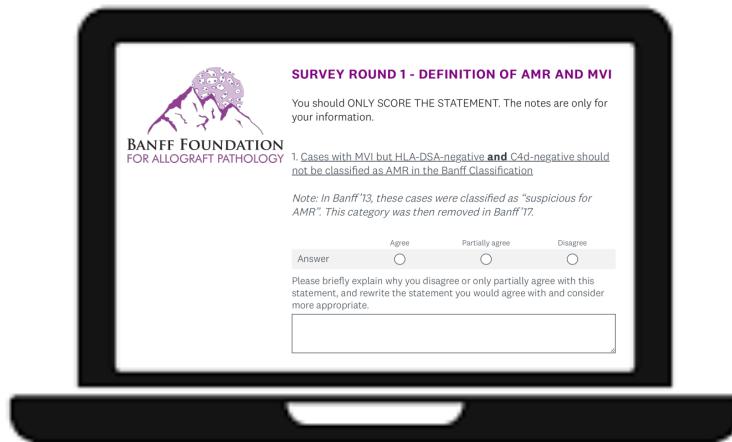
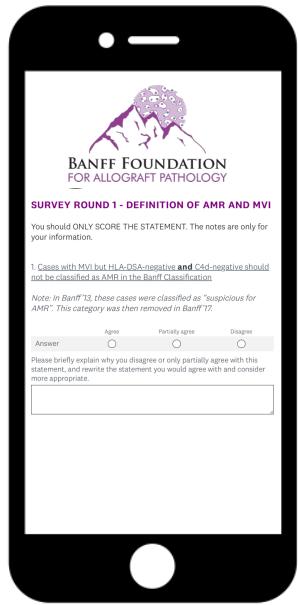
- Endl-Schwaighofer et al Lancet 2019
- Laucheur et al Kidney Int 2019
- Ville et al JASN 2019
- Marthée et al JASN 2021
- Crespo et al Front Immunol 2021
- Dev et al Front Immunol 2022
- Carapito et al Nat Med 2022
- Asano et al Nat Comm 2021

All these studies use DIFFERENT DEFINITIONS of the phenotype of DSA negative MVI, complicating interpretation

Non-invasive biomarkers

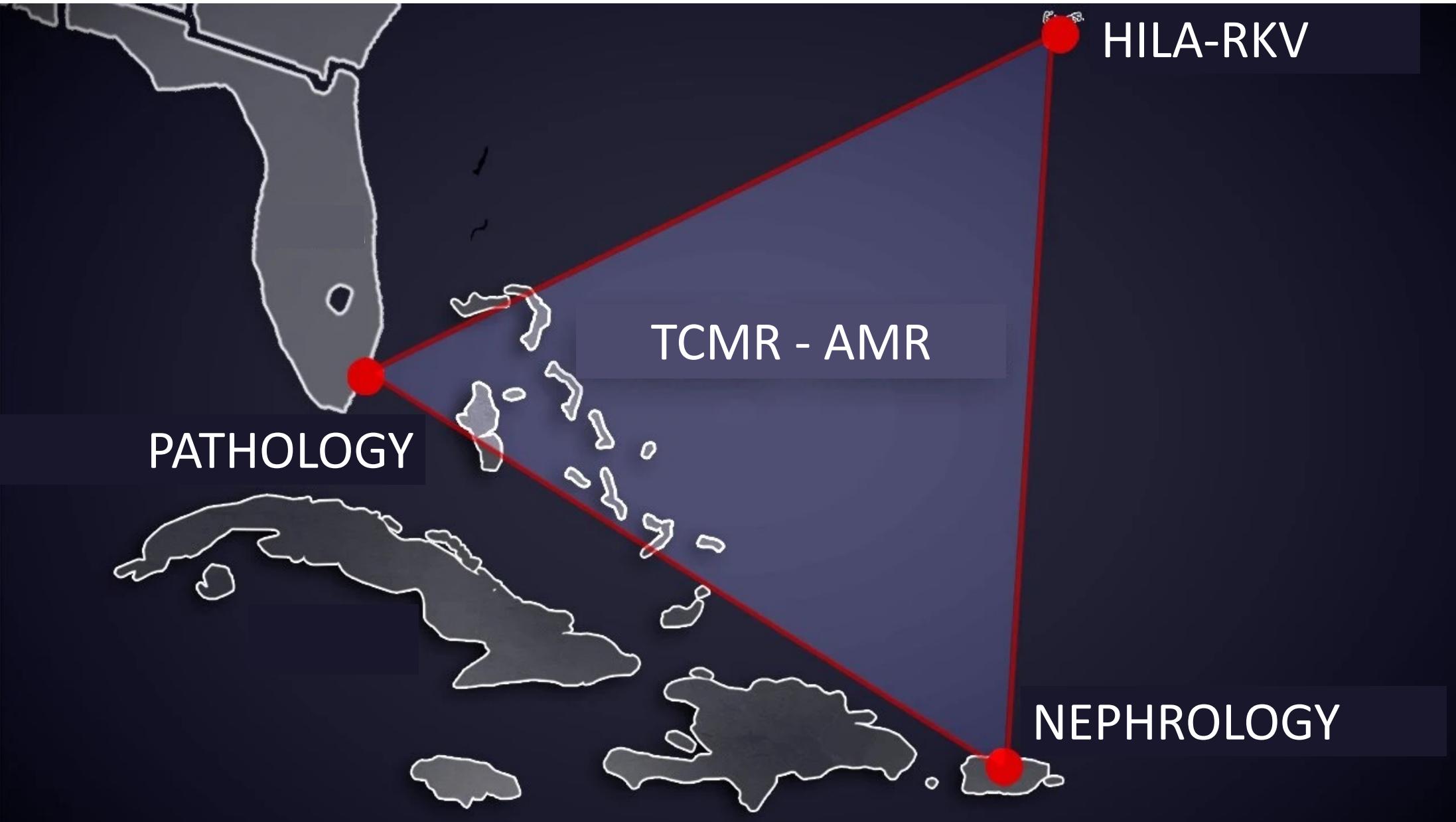
- Van Loon et al Nephrol Dial Transplant 2020 - mRNA
- Halloran et al JASN 2022 TRIFECTA study - ddcfDNA
- Van Loon et al under review - urinary CXCL9/10

Banff Survey!



Unanswered questions

- The role of historic DSA
- The role and clinical testing of non-HLA *mismatch*
- The role and clinical testing of non-HLA *antibodies*
 - Autoreactive?
 - Alloreactive?
- The role of other pathways of allorecognition
 - Missing self
 - CD7-SIRPA
-



Thank you!



NEPHROLOGY
LEUVEN



Rode Kruis
Vlaanderen

