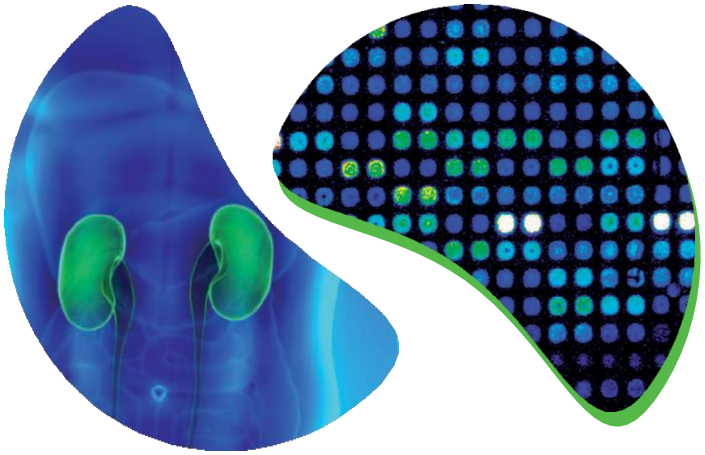


Do we need different scoring rules in early and late allograft biopsies?

Maarten Naesens, MD PhD
University of Leuven, Belgium

Banff meeting, Barcelona 2017

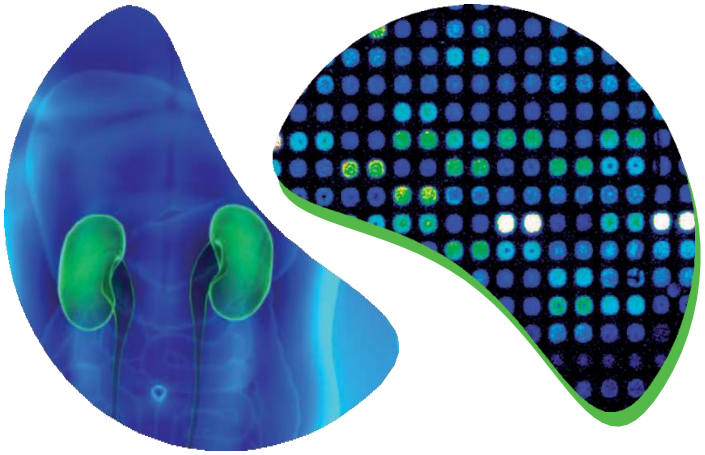
BIOMARGIN KU LEUVEN UZ LEUVEN European Commission COOPERATION fwo

Disclosures

Consultancy:

- Galapagos
- Roche
- Novartis
- Sanofi

I will not discuss off-label use of therapeutics



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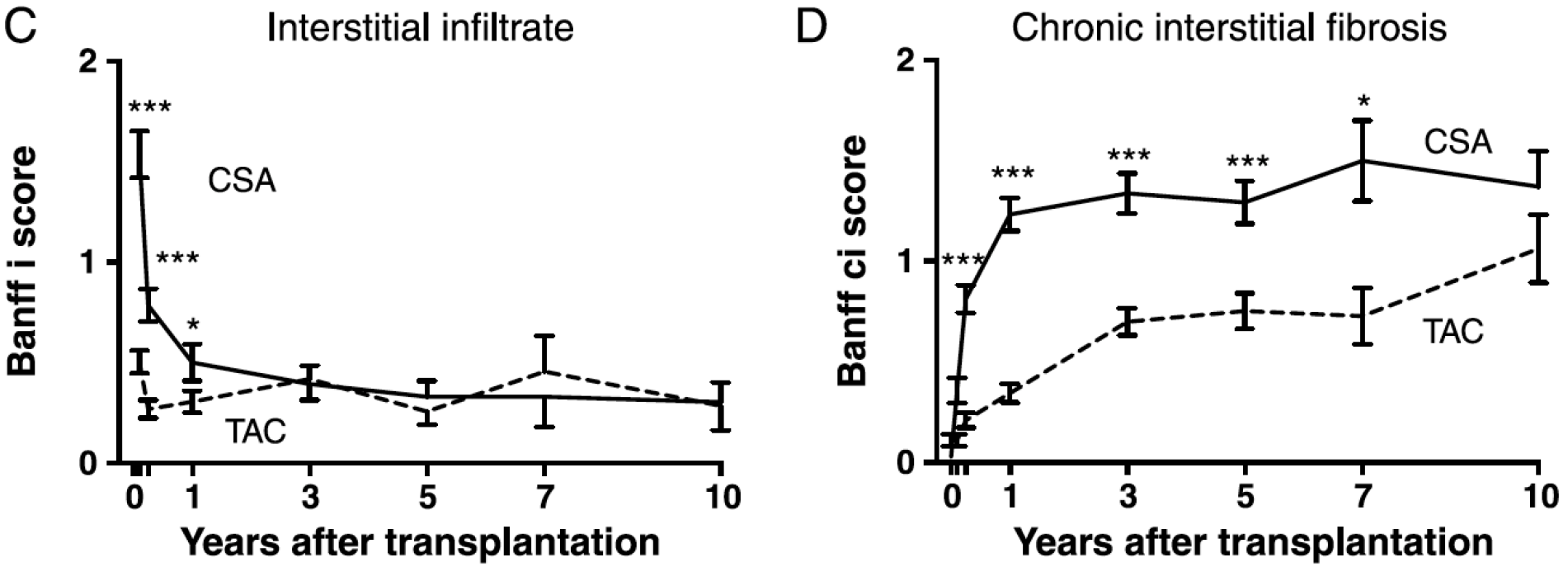
1) Is time post-transplant relevant in kidney transplant histology?

2) Do we need different scoring rules in early vs. late allograft biopsies?

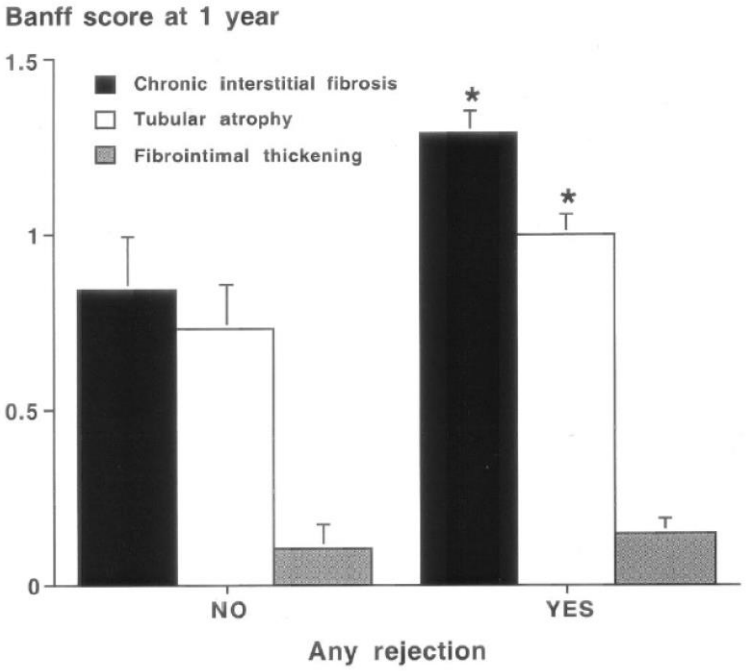
Kidney allograft histology is time-dependent

Acute lesions disappear over time
Chronic lesions accumulate over time

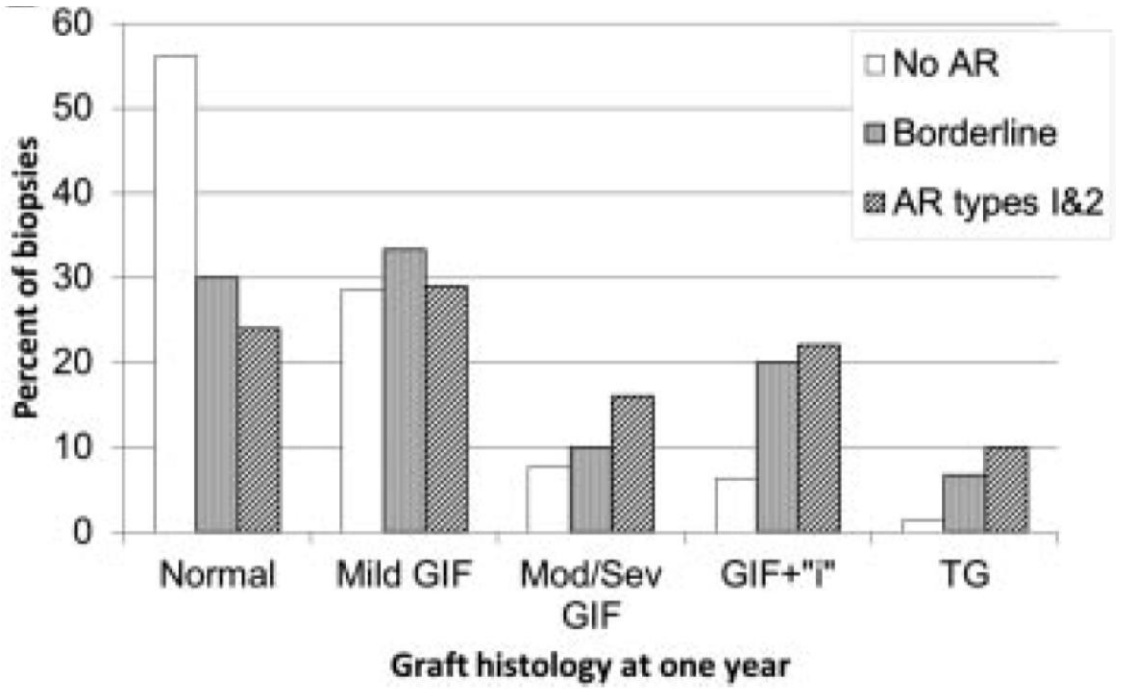


Nankivell et al Transplantation 2016

Later IF/TA associates with prior TCMR, in univariate analyses

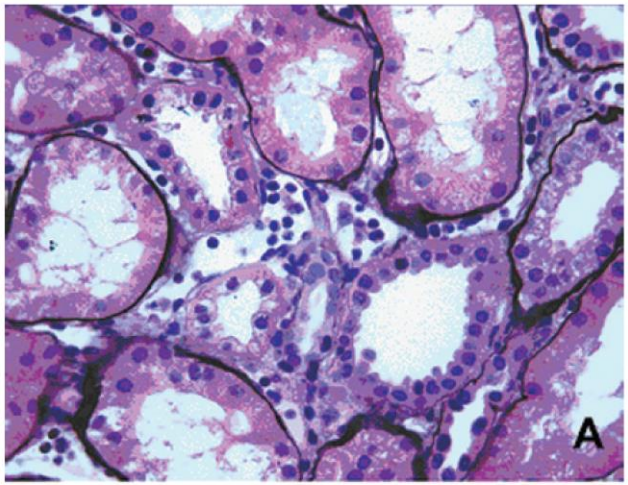


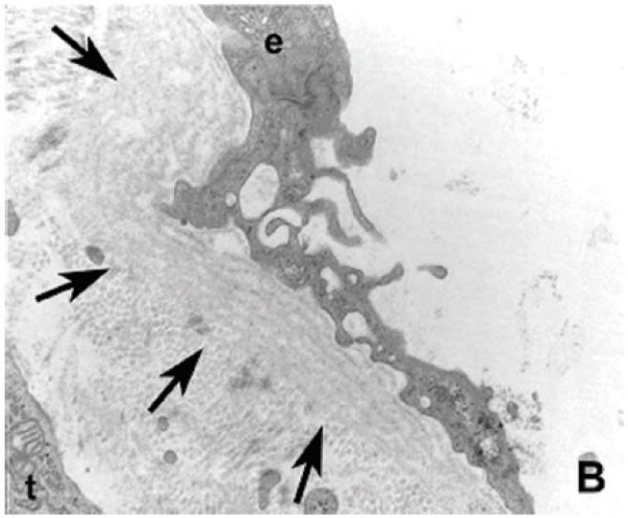
Nankivell et al Transplantation 2004



El Ters et al Am J Transplant 2013

Demonstration that microcirculation inflammation precedes later cg



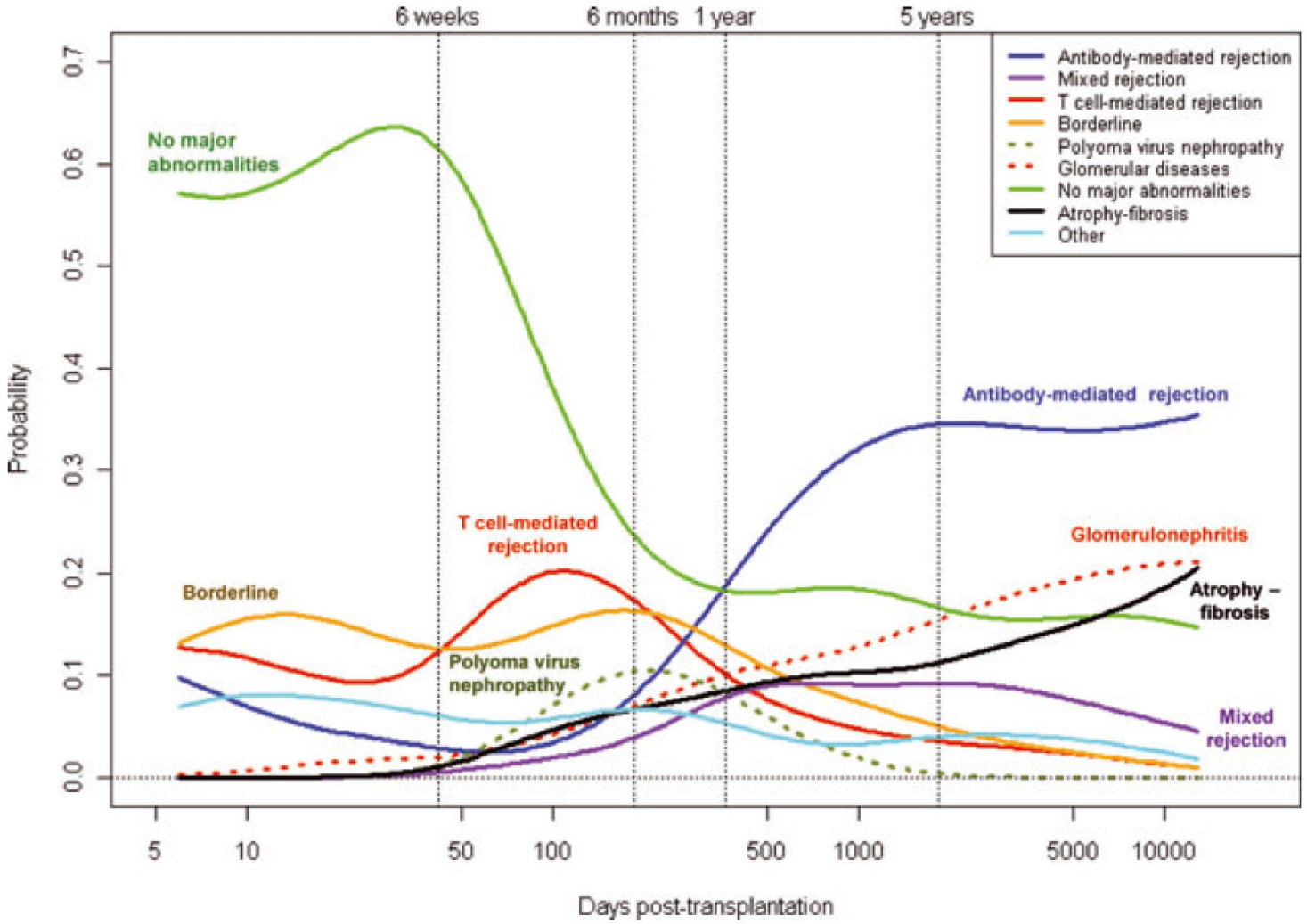


	TG with Ab/C4d	TG with no Ab/C4d
n	33	12
Glomerulitis, mean score[1]	0.7 ± 0.8**	0.2 ± 0.6
Peritubular capillaritis, mean score[1]	1.7 ± 1.0*	1.0 ± 1.1
Peritubular capillaritis, extent[1]		
Absent, n (%)	7 (21)	6 (50)
Present, n (%),	26 (78)*	6 (50)
Diffuse/Focal, n	7/19	4/2
Inflammatory cell type, n		
MN cells only	10 of 26	1 of 6
Neutrophils (<50%) and MN cells	16 of 26	3 of 6
Neutrophils (>50%) and MN cells	0	2 of 6
PTC dilatation, n (%)	15 (45)	5 (42)

Lerut et al Transplantation 2007

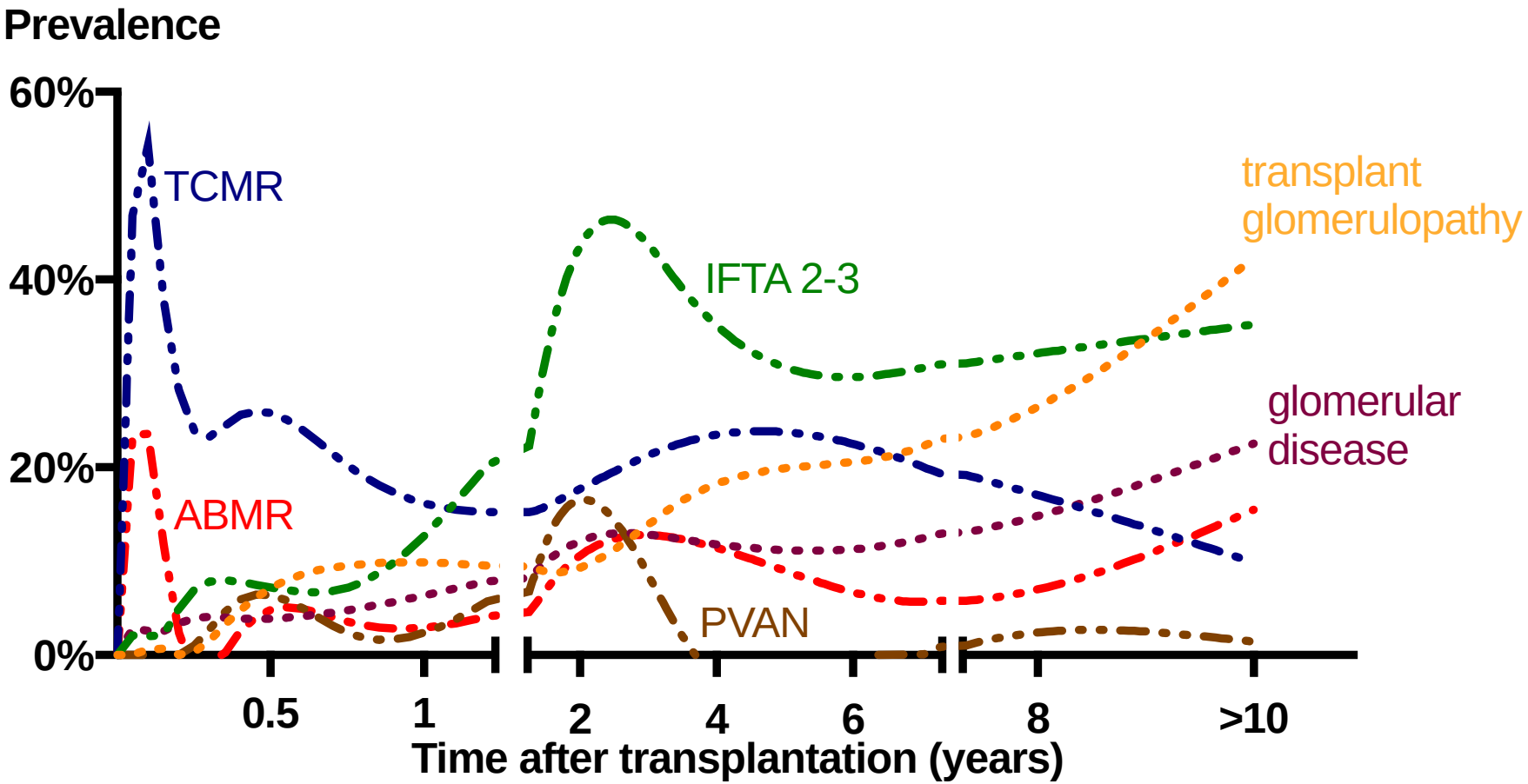
Sis et al Am J Transplant 2007

Low-risk groups have late ABMR while TCMR occurs mostly early post-transplant



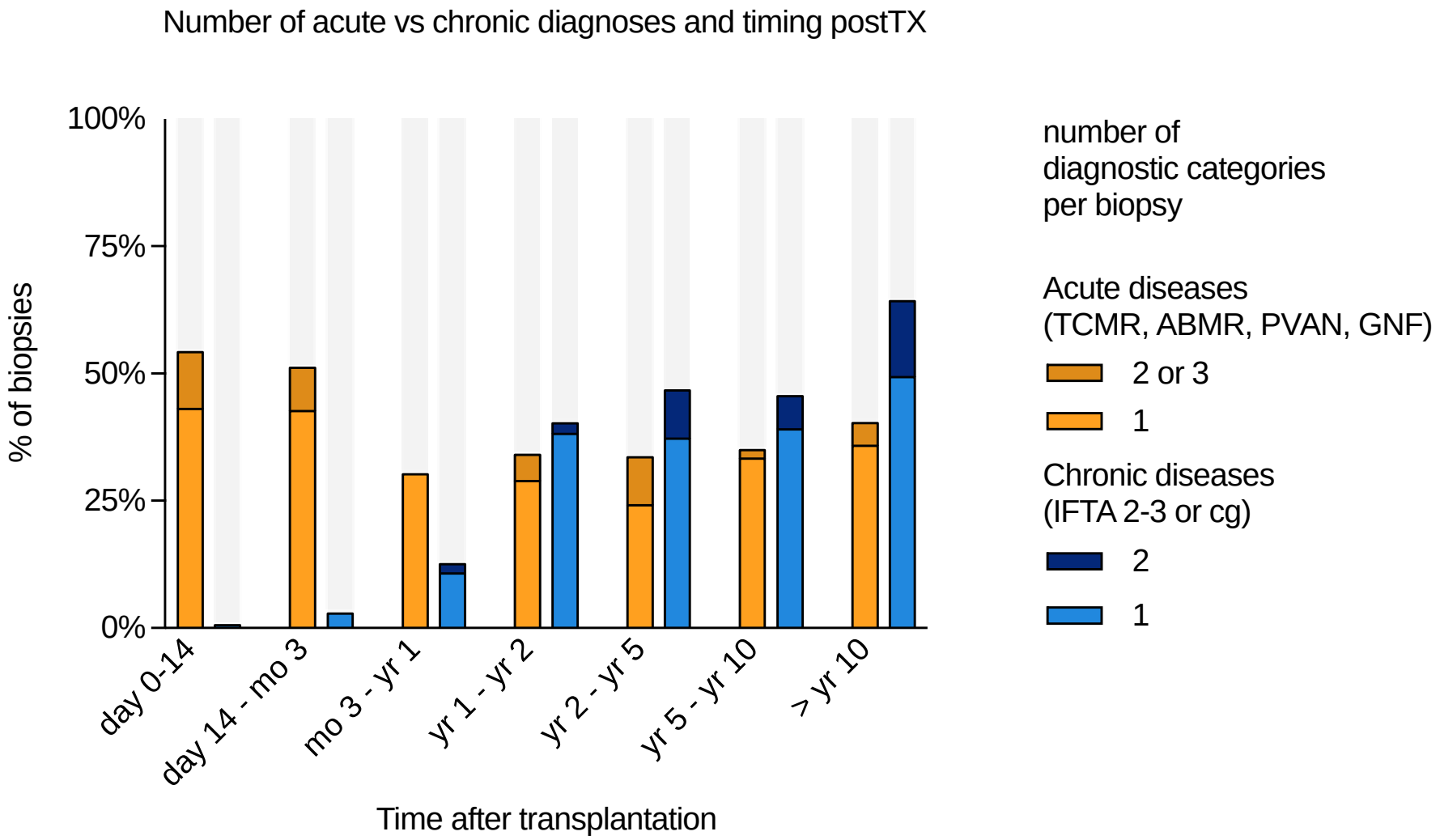
Sellares et al Am J Transplant 2012

Intermediate risk patients have a different prevalence of histologic lesions over time



Naesens et al Transplantation 2014

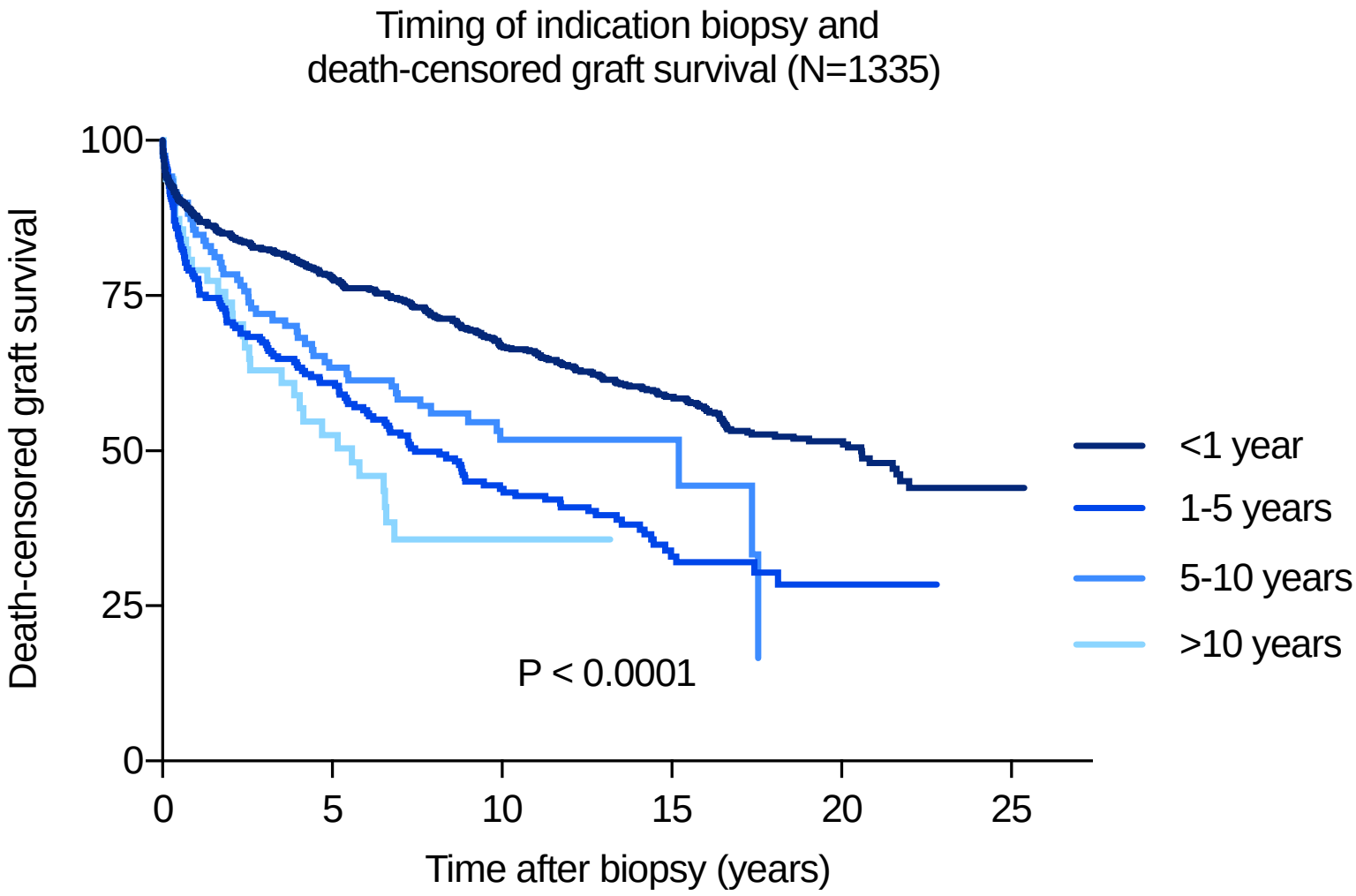
The complexity of a biopsy is time-dependent: early biopsies are less complex, later more



Leuven - Unpublished data

Timing of the biopsy associates with outcome

Time after transplantation associates with post-biopsy survival *in univariate analysis*



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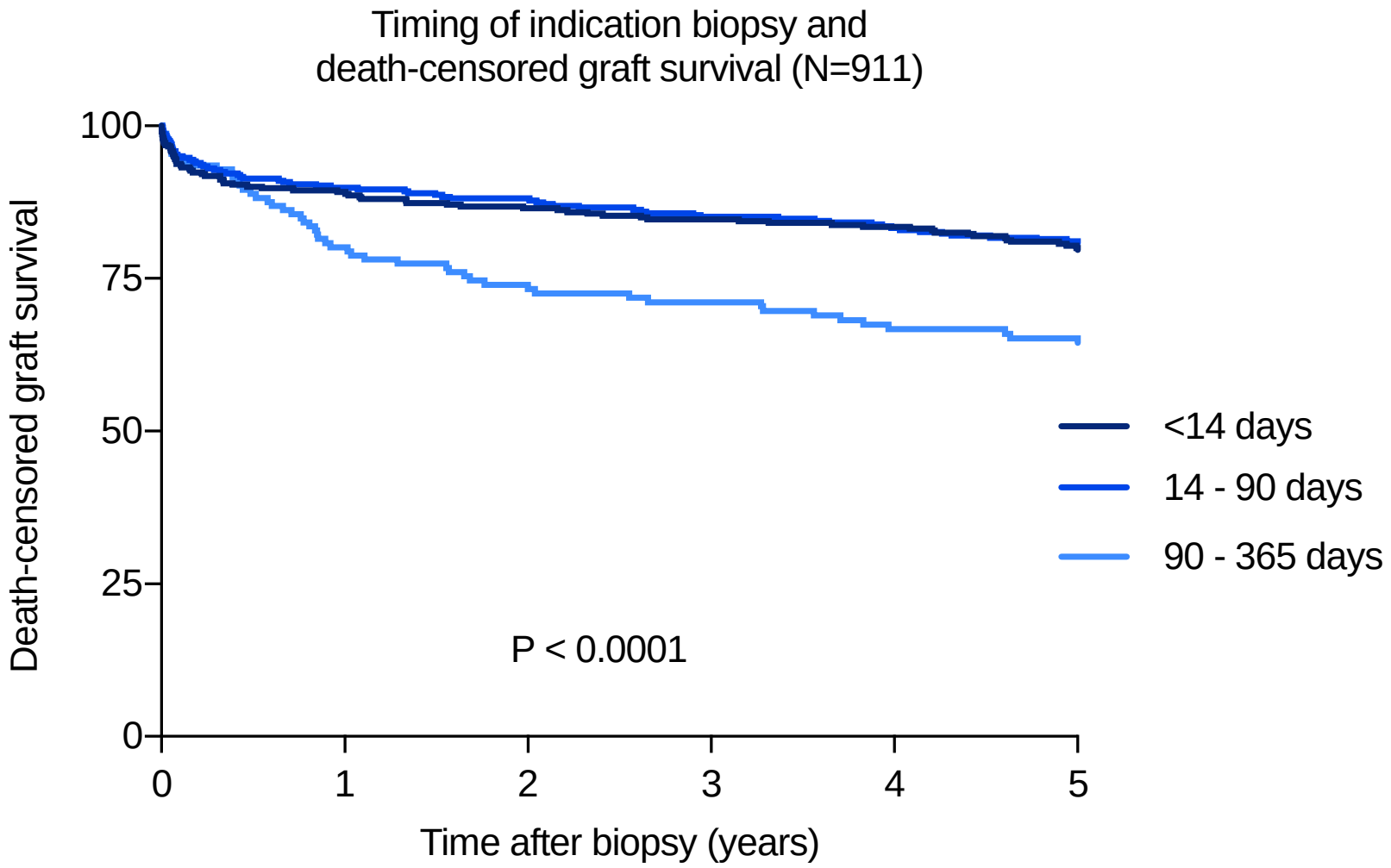
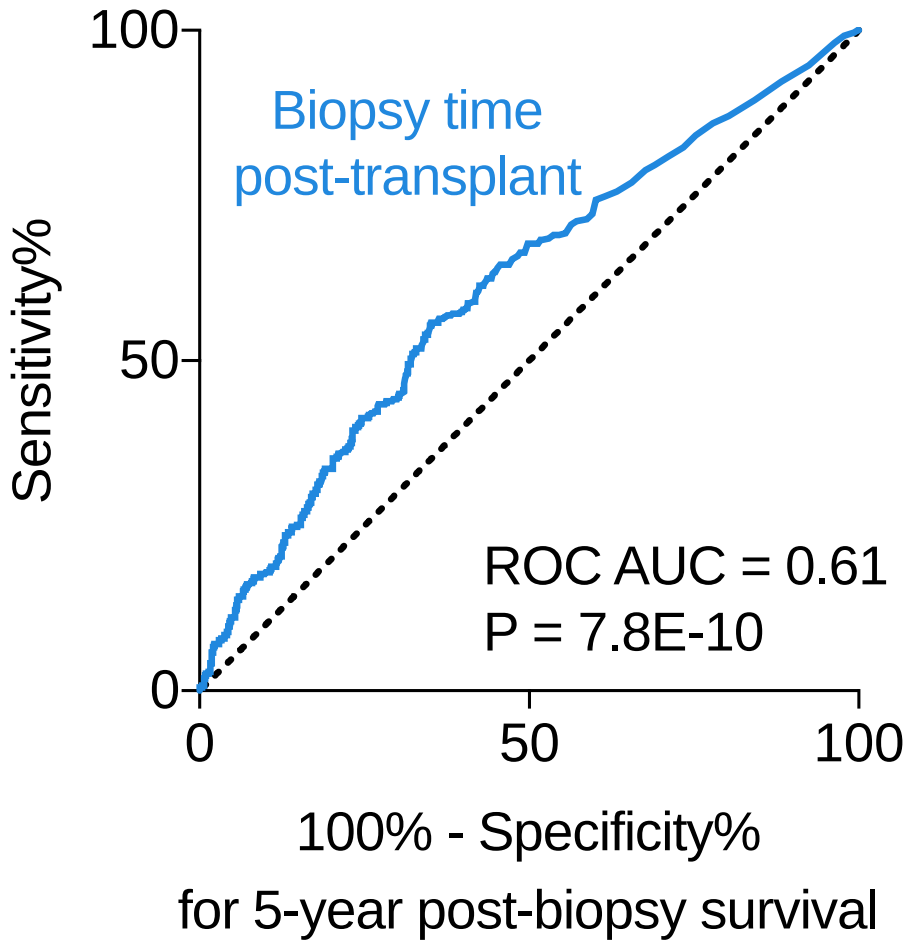
Time after transplantation associates with post-biopsy survival *in univariate analysis*



Leuven - Unpublished data

The predictive accuracy of biopsy time is comparable to that of eGFR or proteinuria



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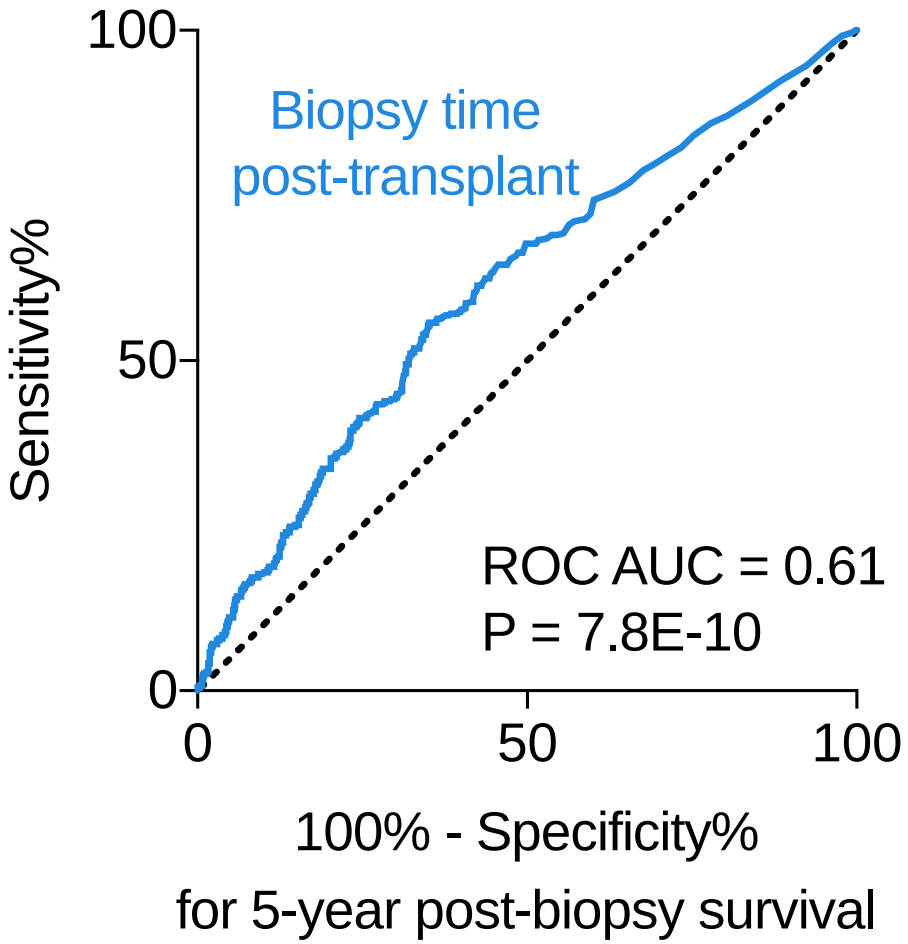
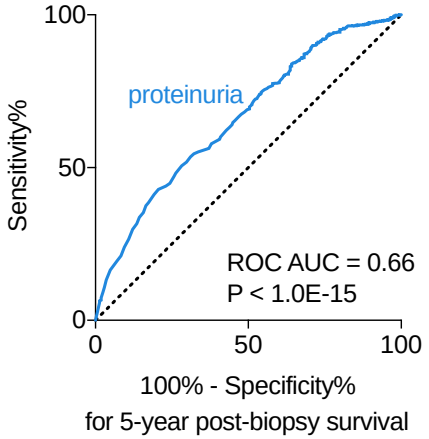
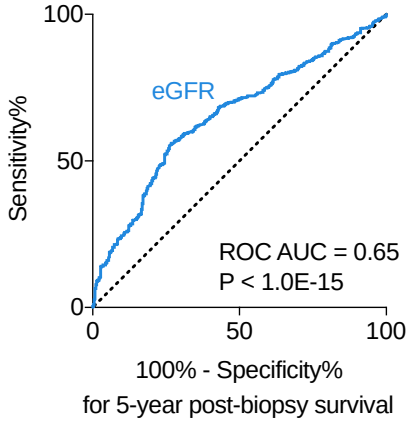






Leuven - Unpublished data

1) Is time post-transplant relevant in kidney transplant histology?

2) Do we need different scoring rules in early vs. late allograft biopsies?

How Dr. Colvin sees the Banff classification moving towards “precision pathology”:

- For mechanistic insight
- For choice of treatment
- Follow-up of treatment effect
- As surrogate endpoint

Adapted from presentation by Dr. Colvin at Banff 2017

How I see the Banff classification moving towards "precision pathology":

- For mechanistic insight
- For diagnosis (ABMR; TCMR; PVAN; IFTA; NL; GNF; etc.)
- To decide which patients with these diagnoses to treat
- For choice of treatment
- Follow-up of treatment effect
- As surrogate endpoint

How a simple clinician like me uses the Banff classification in his routine clinical practice:

- *(For mechanistic insight)*
- For diagnosis (ABMR; TCMR; PVAN; IFTA; NL; GNF; etc.)
- To decide which patients with these diagnoses to treat
- For choice of treatment *(but currently purely based on the diagnosis)*
- *(Follow-up of treatment effect)*
- *(As surrogate endpoint)*

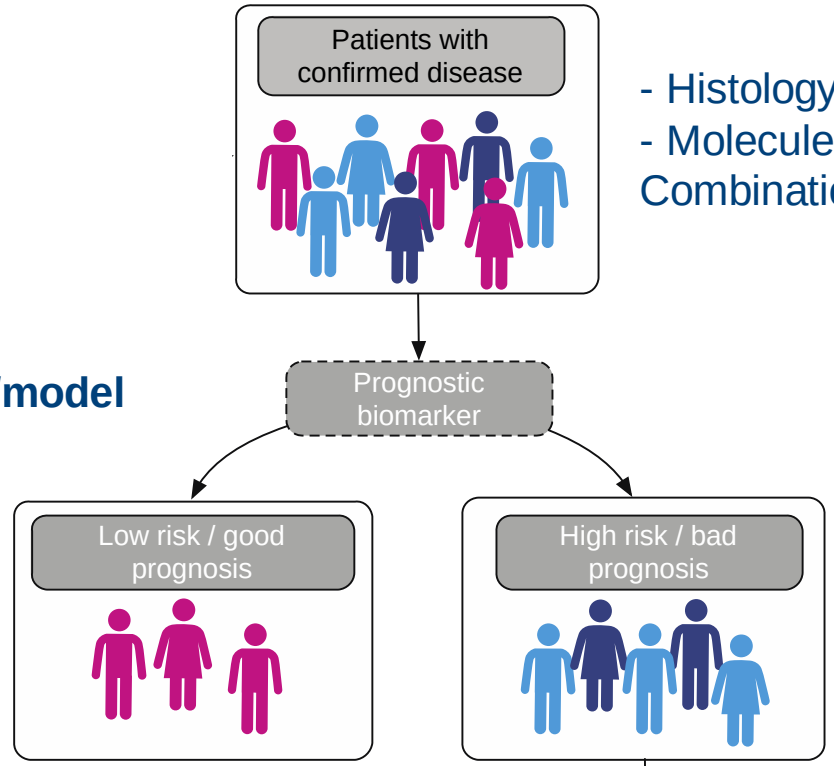
A clinician's view

- Histology
- Molecules?

Combination

A clinician's view

Prognostic markers/model



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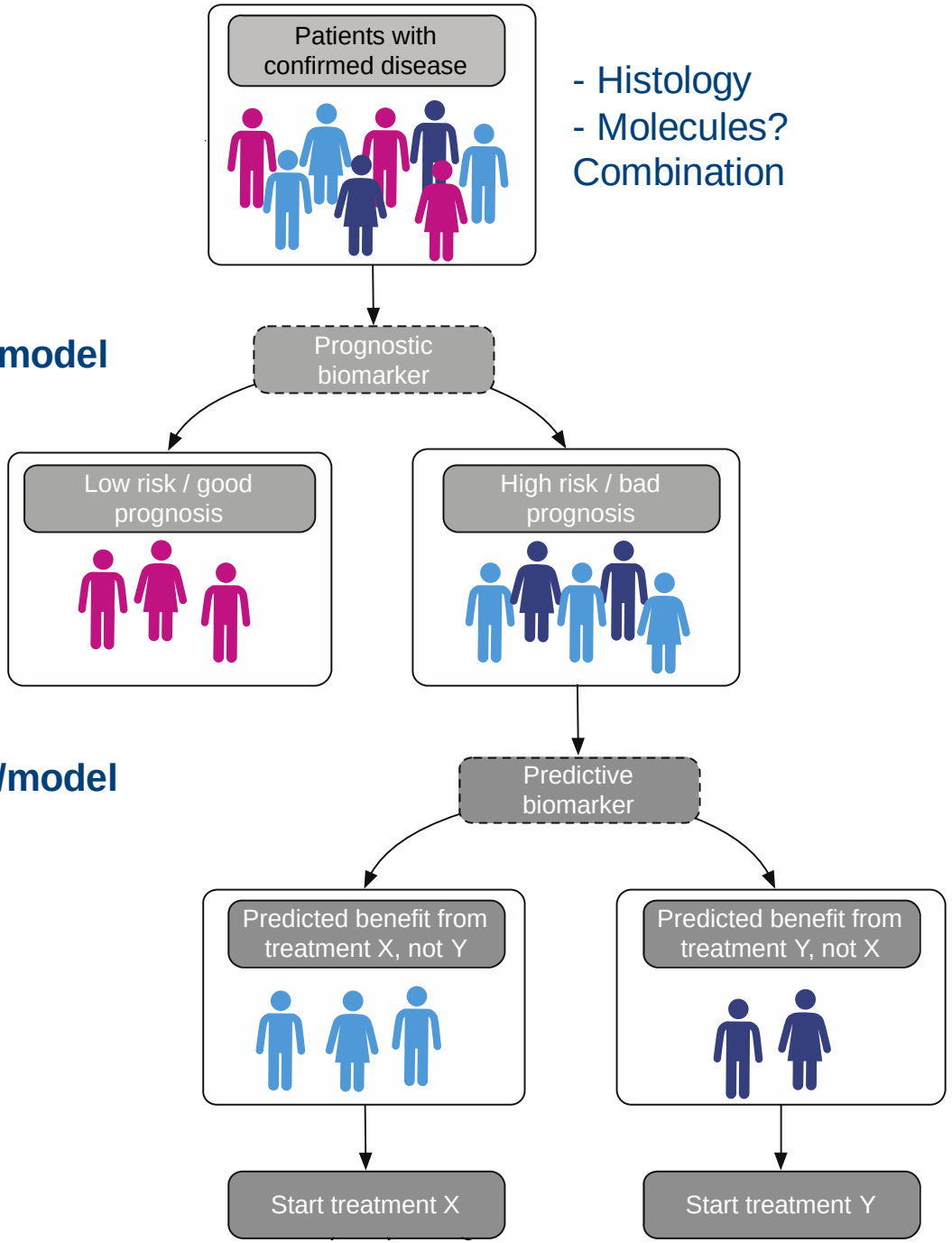
Combination

A clinician's view

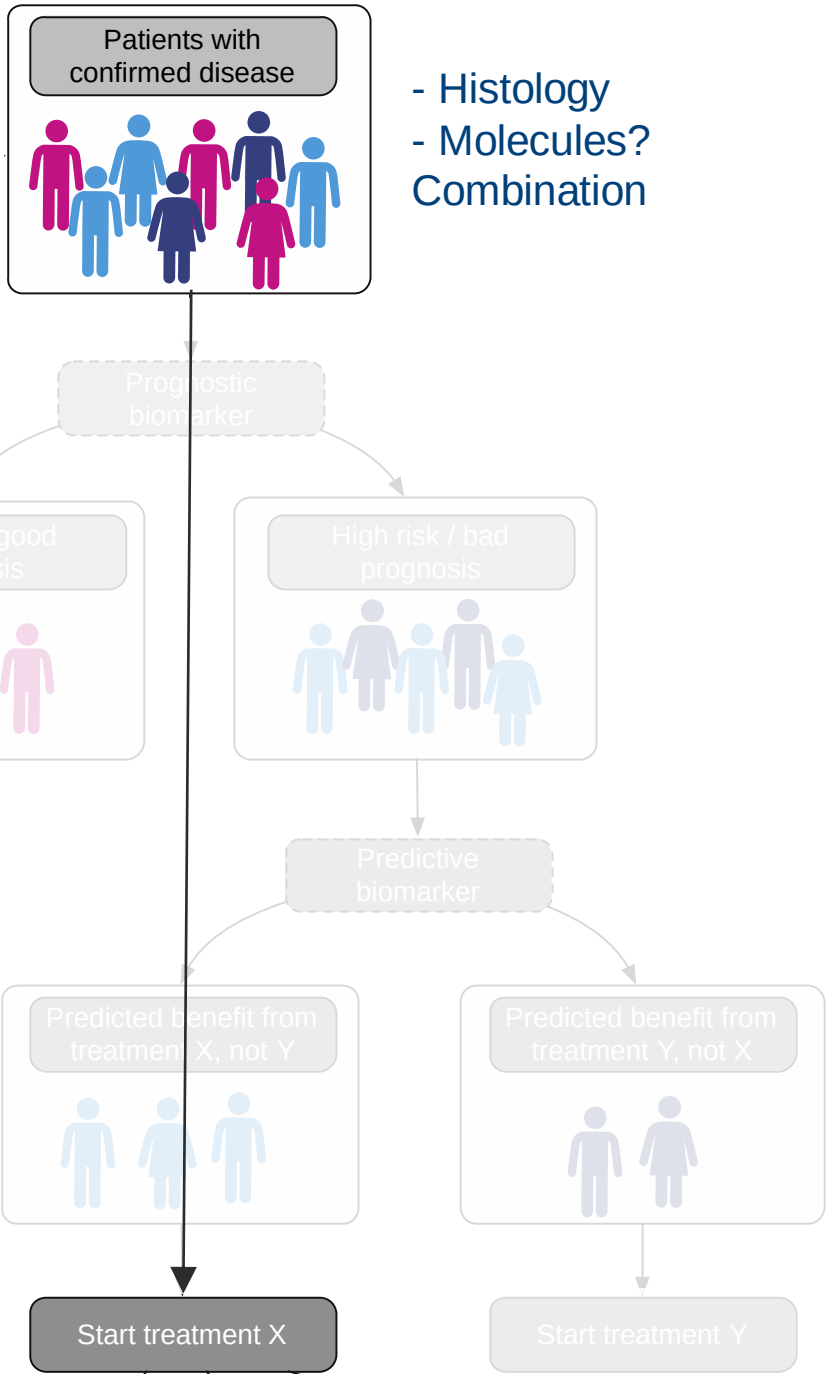
- Histology
- Molecules?
Combination

Prognostic markers/model

Predictive markers/model



A clinician's view



A clinician's view

- Histology
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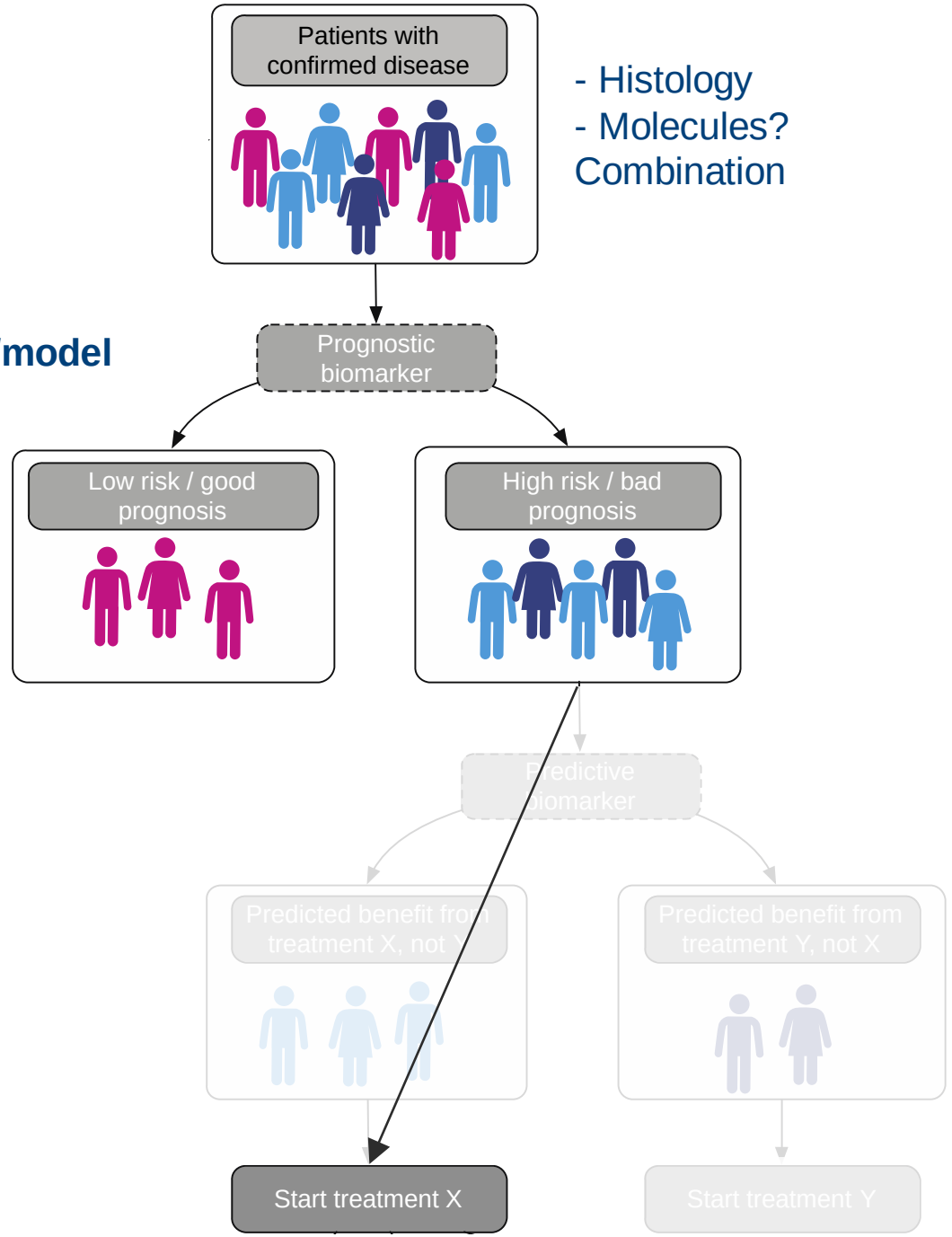
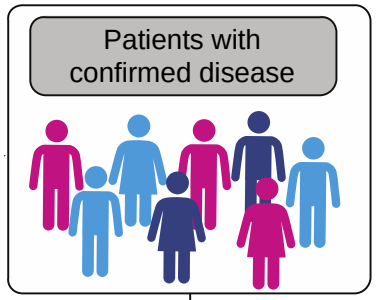


A clinician's view



- Histology
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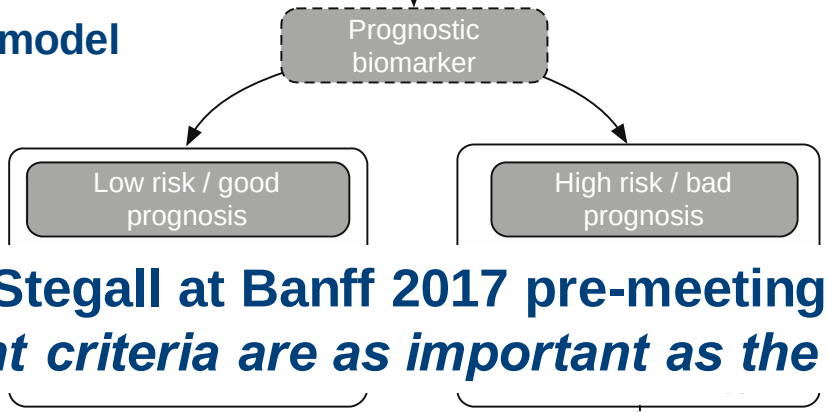
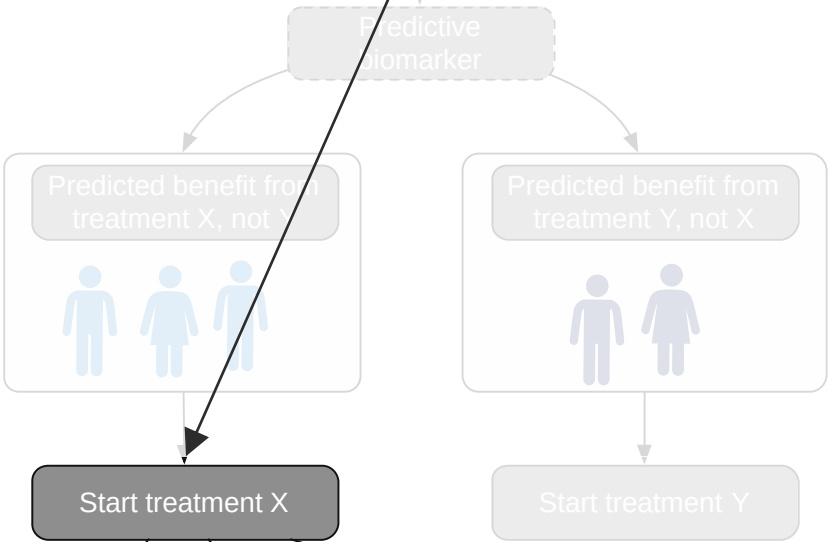


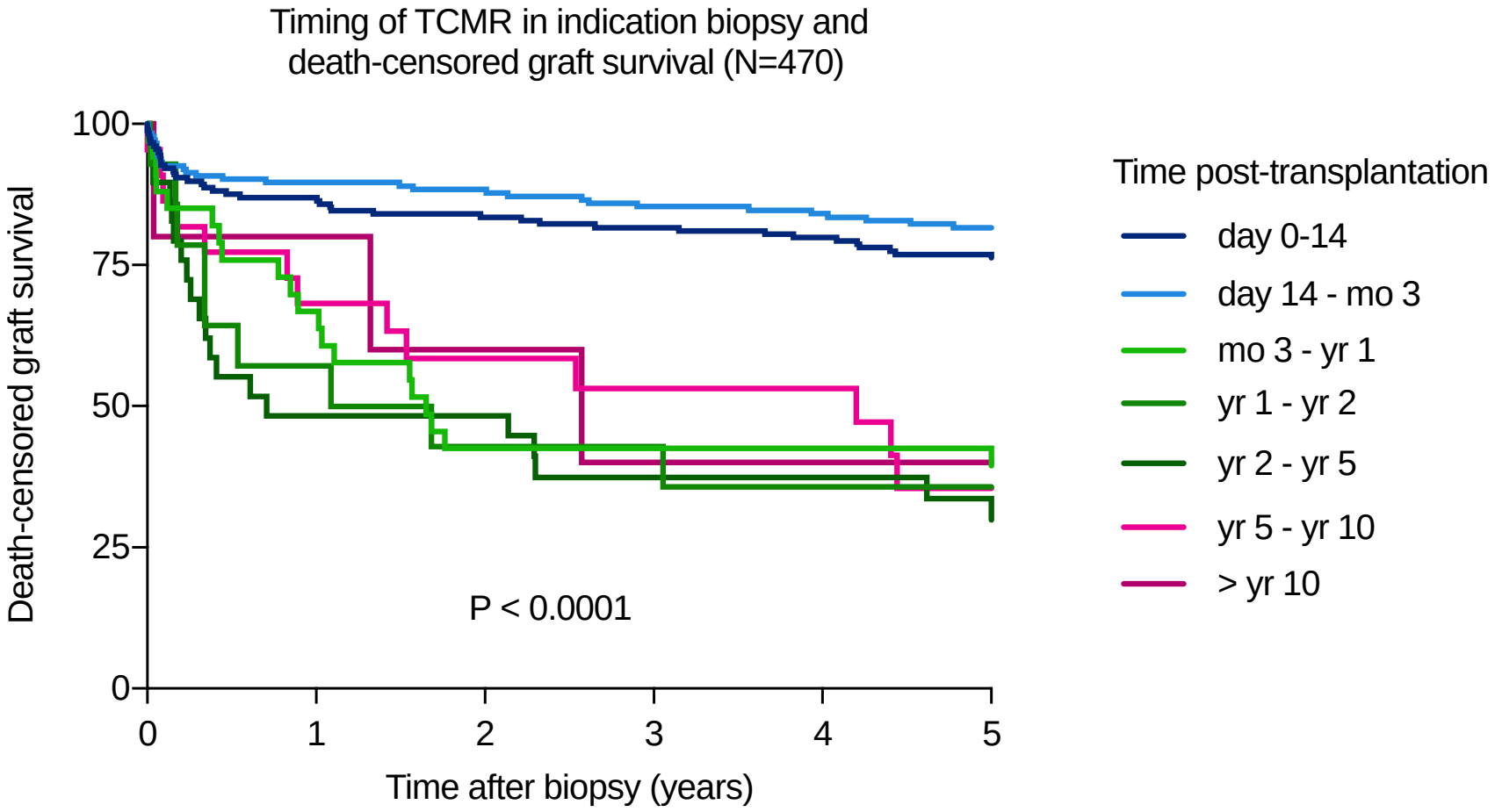
Dr. Stegall at Banff 2017 pre-meeting:

"The enrollment criteria are as important as the endpoints!"



Is time post-TX important for TCMR prognosis?

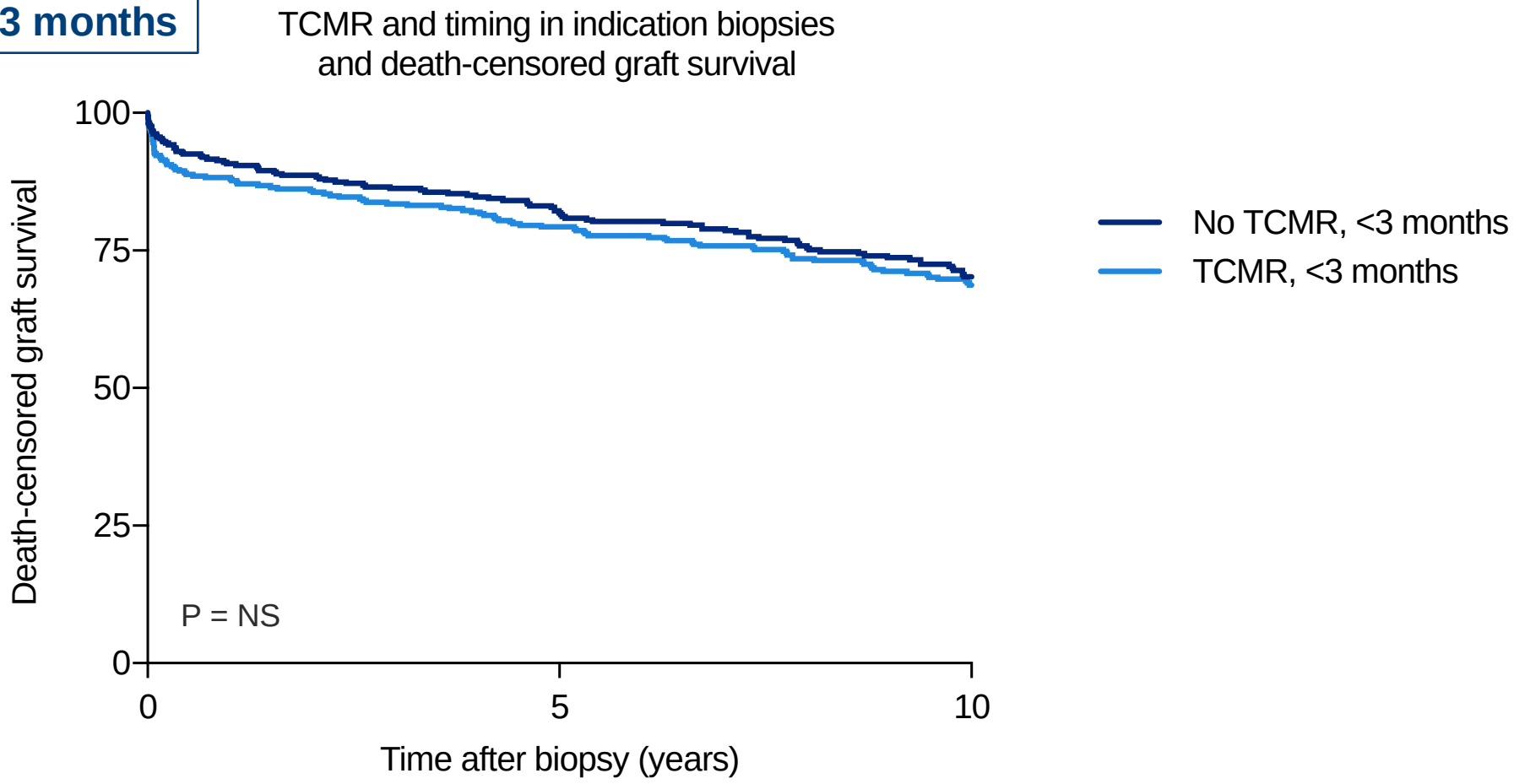
The timing of TCMR (grade 1-2) diagnosis seems important for prognosis



Leuven - Unpublished data

The timing of TCMR (grade 1-2) diagnosis seems important for prognosis

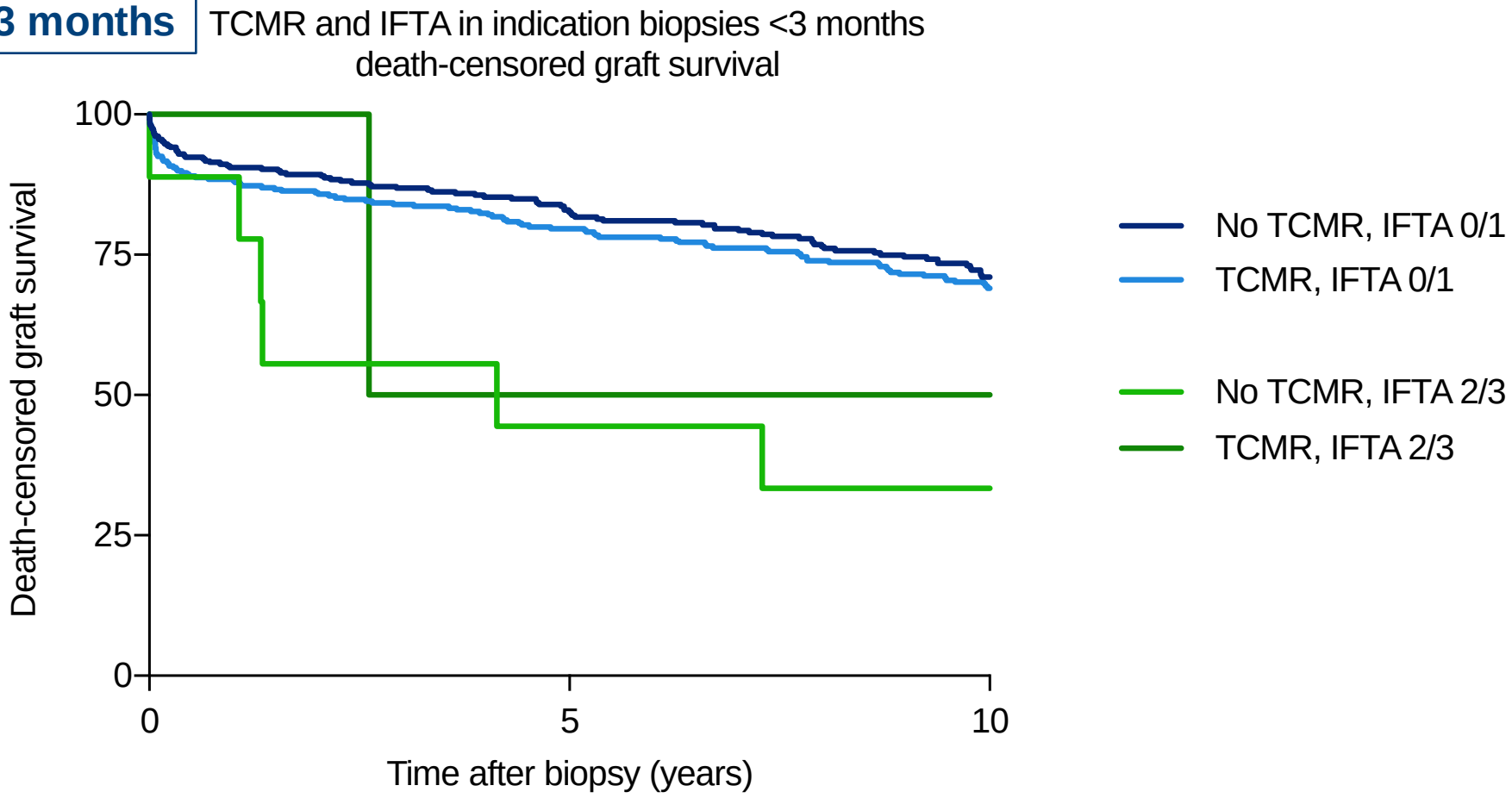
< 3 months



Leuven - Unpublished data

Early TCMR (< 3 months) grade 1-2 has no effect on graft outcome

< 3 months



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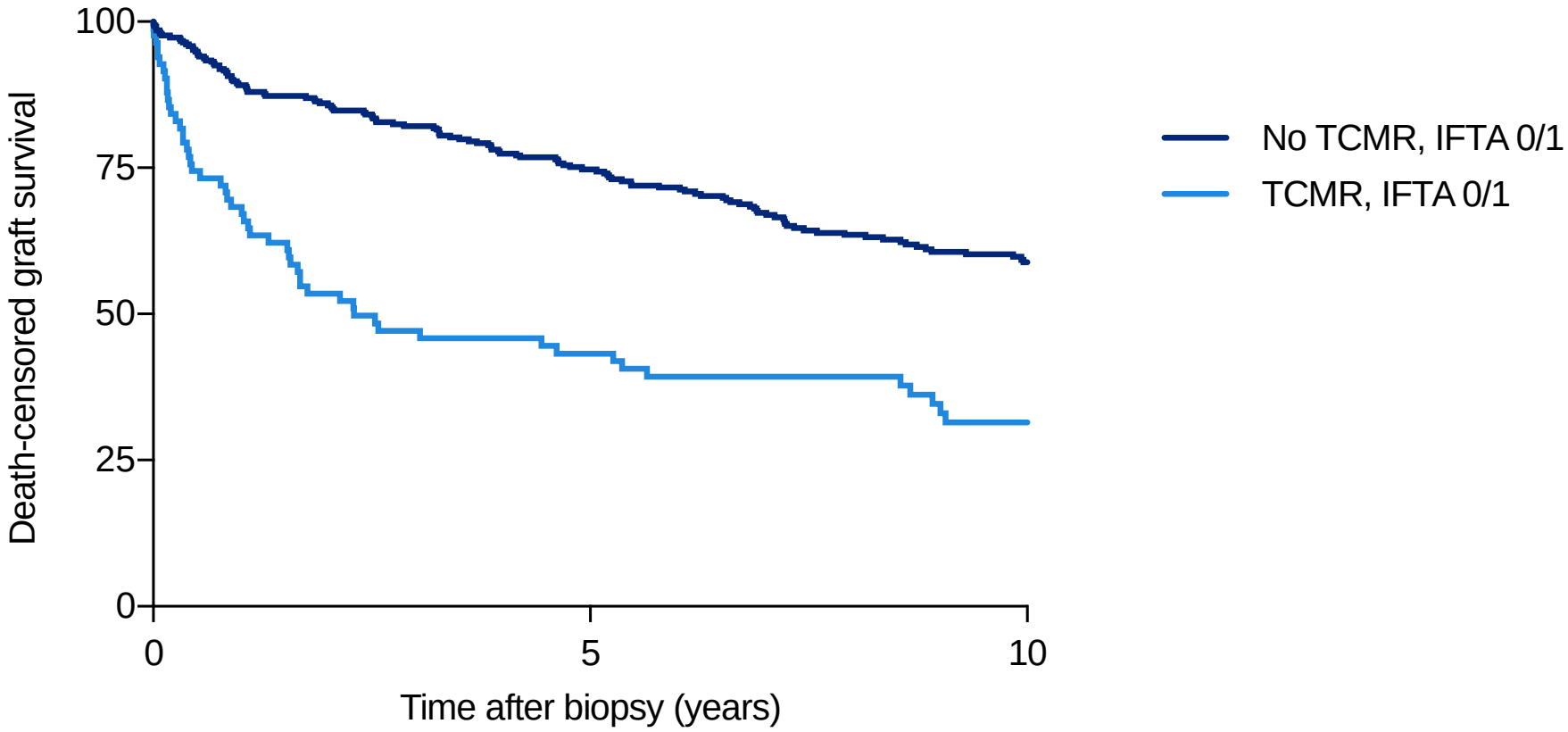
Later TCMR grade 1-2 and IFTA have cumulative effects on outcome

> 3 months

TCMR and IFTA in indication biopsies >3 months
death-censored graft survival (N=583)



Leuven - Unpublished data

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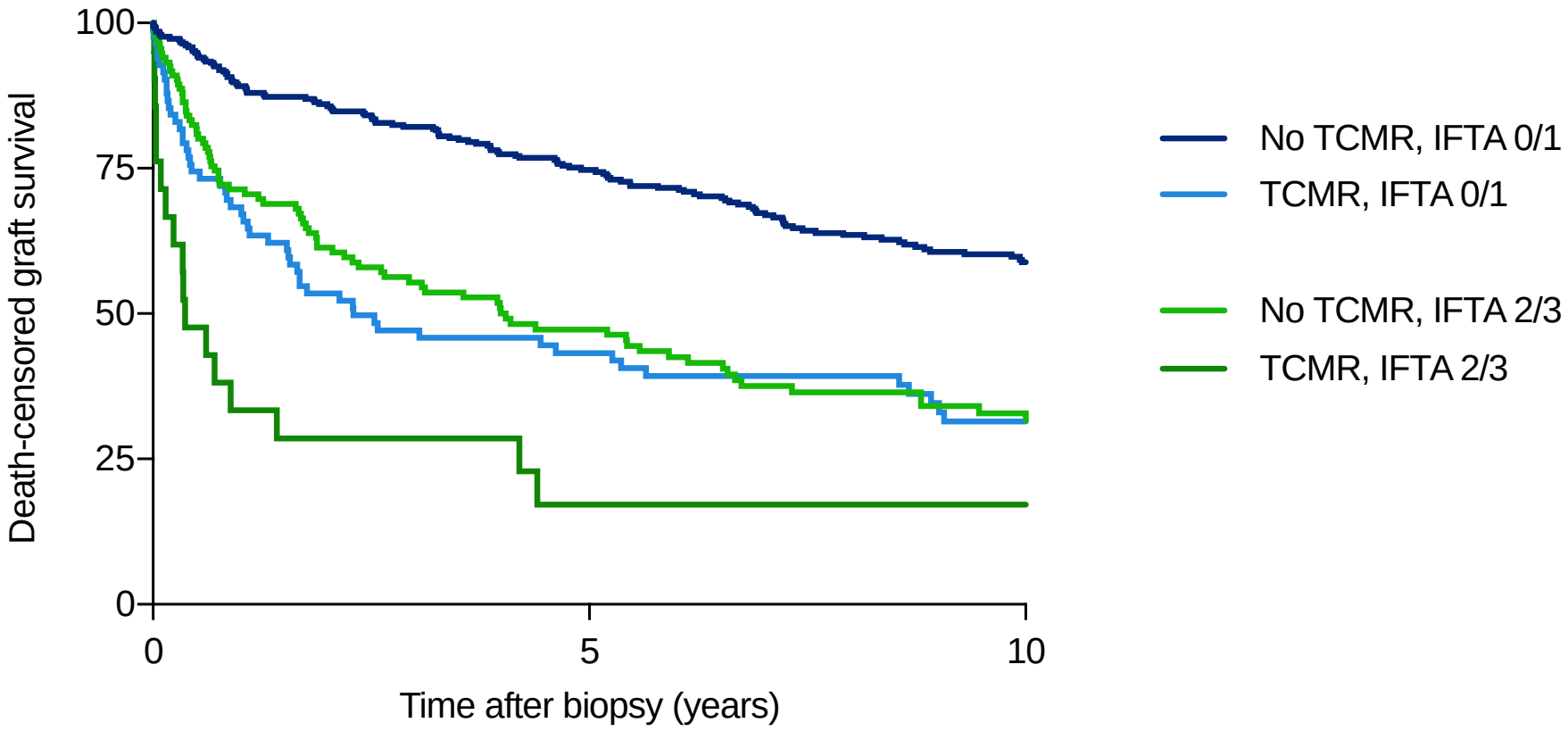
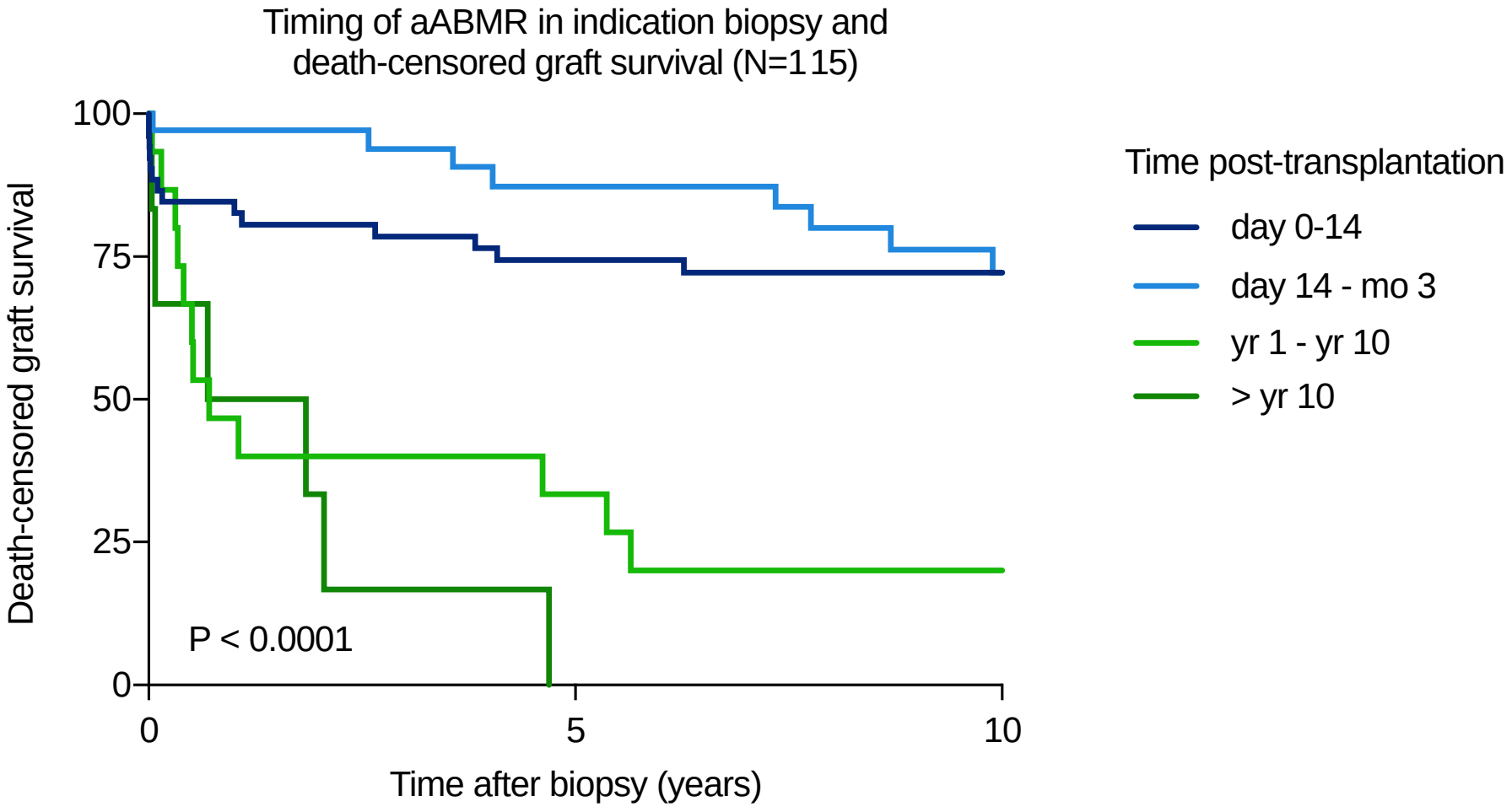


Leuven - Unpublished data

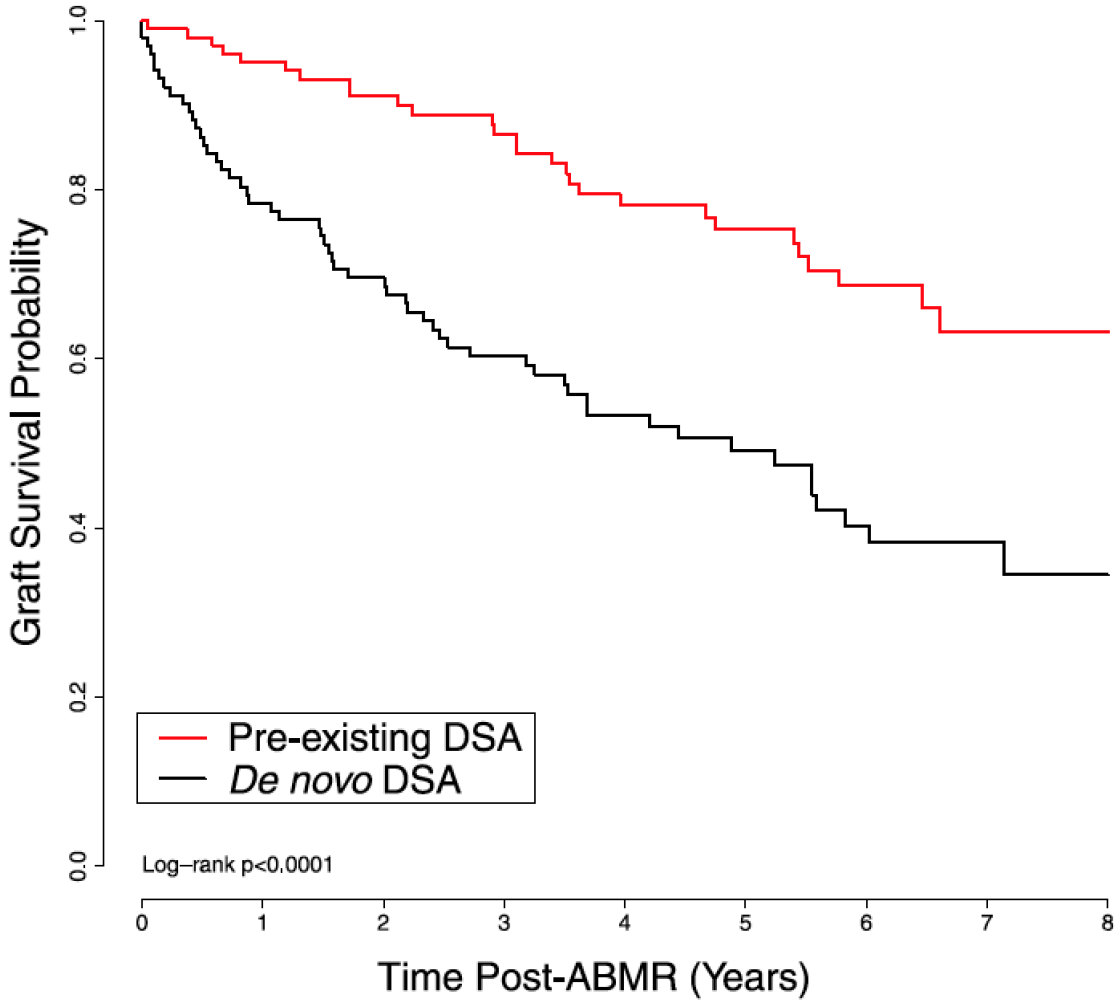
Is time post-TX important for ABMR prognosis?

The timing of ABMR diagnosis seems important for prognosis



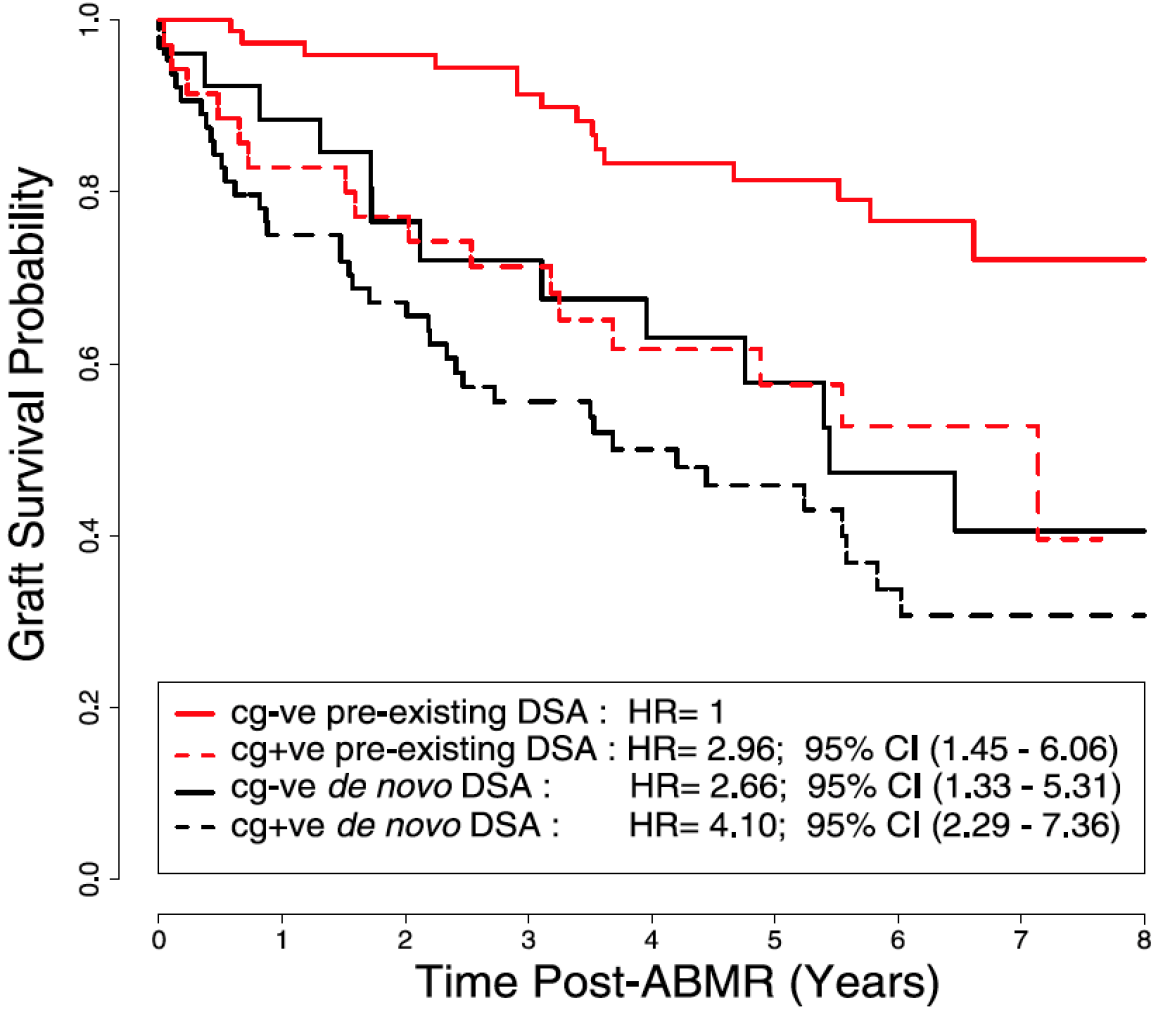
Leuven - Unpublished data

The timing of DSA occurrence seems important for prognosis



Aubert, Loupy et al JASN 2017

Transplant glomerulopathy has an effect on ABMR outcome



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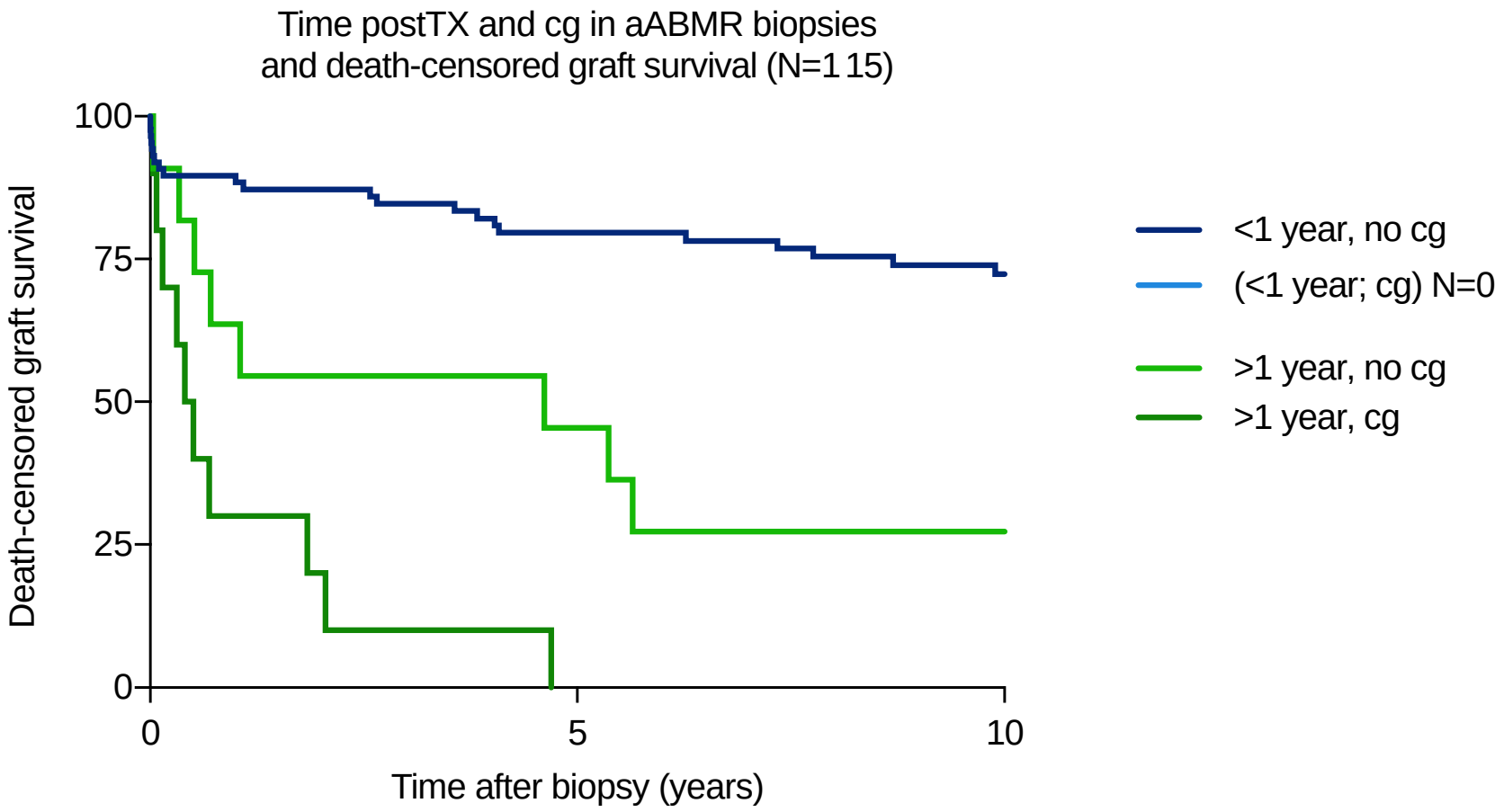
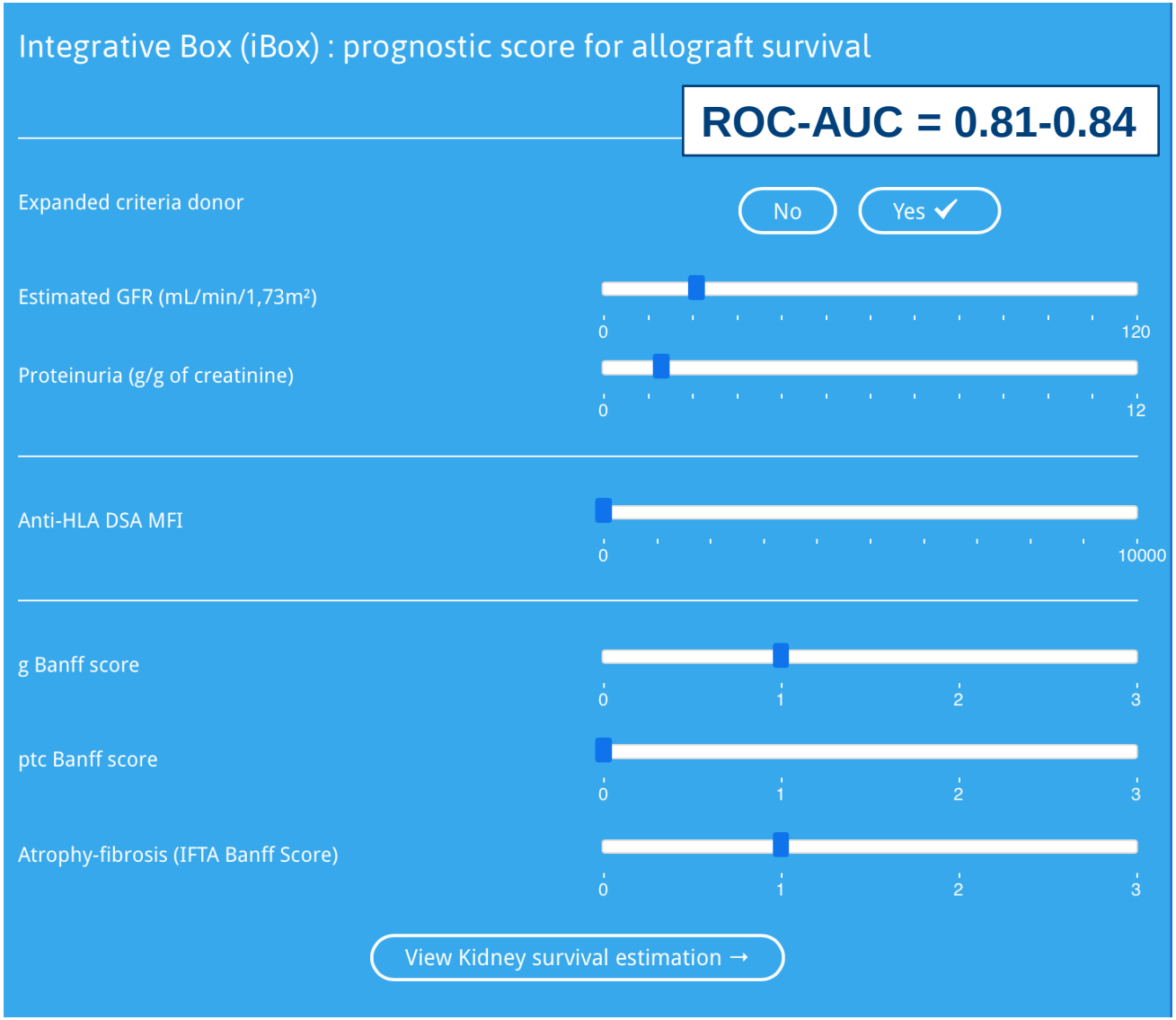


Leuven - Unpublished data

Multivariate models for disease prognosis

iBox provides a prognostic nomogram, but is not (yet) disease-specific

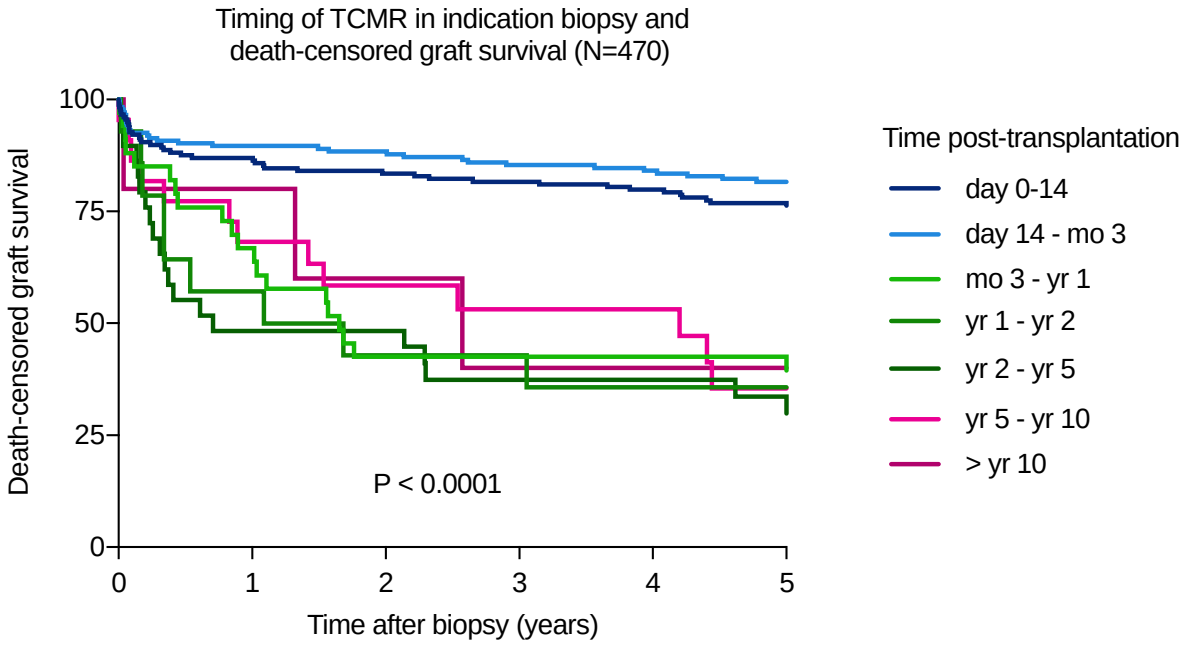


In biopsies with TCMR, concomitant PVAN and IFTA, and timing of the biopsy, drive outcome

In a multivariate Cox model (N=467 TCMR grade 1-2 biopsies)

we retain:

- **Time after transplantation (< vs. > 3 months; HR 3.97, p < 0.001)**
- Concomitant PVAN
- IFTA grade
- eGFR



Leuven - Unpublished data

In biopsies with ABMR, concomitant cg but also timing of DSA, drive the outcome

Table 4. Factors associated with kidney allograft loss in the multivariate analysis

Factors		No. of patients	No. of events	HR	95% CI	*P* Value
GFR, ml/min per 1.73 m^2	≥60	29	8	1	—	
	30–60	105	37	1.30	(0.60 to 2.82)	
	<30	60	32	3.27	(1.48 to 7.23)	<0.001
Proteinuria, g/g creatinine	<0.30	96	22	1	—	
	≥0.30	98	55	2.44	(1.47 to 4.09)	<0.001
DSA characteristic	Preexisting DSA	101	28	1	—	
	De novo DSA	93	49	1.82	(1.07 to 3.08)	0.03
Transplant glomerulopathy (cg) score	Low score: 0	109	29	1	—	
	High score ≥1	85	48	2.25	(1.34 to 3.79)	0.002

Aubert, Loupy et al JASN 2017

Why is time post-transplant so important for prognosis?

- Reflects **pathophysiology** of the disease:
  - Tubulo-interstitial inflammation - “TCMR”:
    - early = non-specific ischemia reperfusion injury, wound healing etc.
    - late = donor-specific allo-immune phenomena; insufficient immunosuppression; non-adherence etc.
  - ABMR: de novo vs. pretransplant DSA different (class; MFI etc.)?

- Time is often a **proxy of chronicity** (and reversibility) of the diseases

  (late = more often ongoing for a long time; chronic injury)

- Organ **functional reserve**/regenerative capacity?

1) Is time post-transplant relevant in kidney transplant histology?

2) Do we need different scoring rules in early vs. late allograft biopsies?

1) Is time post-transplant relevant in kidney transplant histology?

~~2) Do we need different scoring rules in early vs. late allograft biopsies?~~

After a diagnosis, if further validated, time post-transplantation could be used for disease prognosis.

Usefulness of a two-step diagnostic + prognostic Banff classification:

- Streamline ***inclusion/exclusion criteria*** for study entry based on these prognostic categories

  ("enrichment of the patient population", see Dorry Segev)

- Allow **Banff-predefined subgroups for post-hoc analyses** of interventional trials

- Build **routine clinical protocols based on the prognostic categories**, instead of center-specific or even doctor-specific patient stratification for therapy.

Thank you!

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