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Factors associated with antibody mediated rejection in pediatric kidney transplantation

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Introduction

- End-stage chronic kidney disease (ESKD): A source of significant morbidity and mortality in children.
- Kidney transplantation (KT): The treatment of choice for ESKD ➔ Improvement in survival and quality of life.
- Antibody mediated rejection (ABMR): A significant contributor to renal allograft failure and one of the leading causes of graft loss in KT .

Study objectives

- Identify factors associated with ABMR in pediatric kidney transplantion patients.
- Study the impact of ABMR on graft and patient survival.

Patient selection

Inclusion criteria

- All patients who had a KT at an age < 20 years-old.

Exclusion criteria

Patients with :

- Hyper-acute rejection.
- Post-operative vascular thrombosis with immediate graft loss.
- A follow-up of less than 3 months. .
- Biopsy proven cellular rejection with no signs of ABMR.
- Non-biopsy-proven rejection
- Incomplete medical records

Study recordings

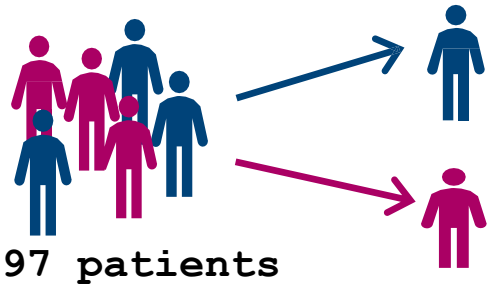
- Donors' / Recipients' and transplant's characteristics
- Immunosuppressive regimen and post transplant complications
- Biopsy proven Antibody mediated rejection ABMR : clinical presentation and histological Subtype (BANFF 2017)

Statistical analysis

- Statistical analysis : IBM SPSS Statistics 26.0 software.
- Univariate analysis :T Student Test / U Mann whitney Test [Continuous variables] - Chi-square test/ Fisher's exact test [Categorical variables].
- Multivariate analysis : Logistic binary regression.
- Survival analysis : Kaplan Meier and log-Rank test ± Cox Regression (if statistical significance in log-Rank test)

A single-center retrospective study (34 years : January 1989 - December 2022))

Recipients' baseline characteristics



97 patients

M= 56 (57.7%)

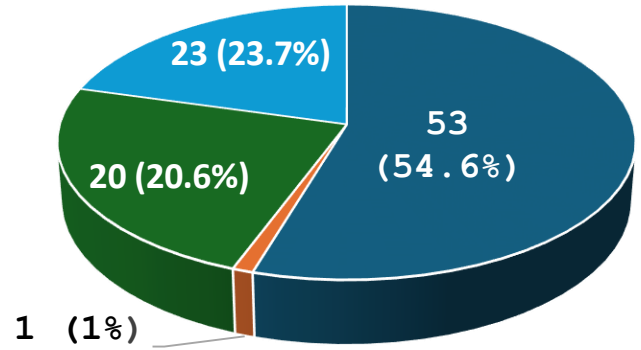
M/F= 1.4 Mean age :15.4 ± 3.2 yo

F= 41 (42.3%)

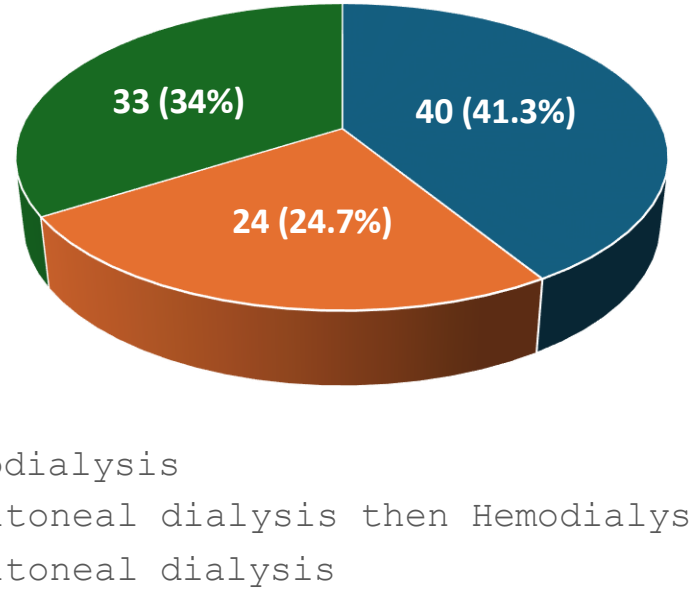
Medical history

- **Renal replacement therapy duration** : 23 months [15 – 44].
- **History of hypertension :** 63.9% (n=62).
- **History of a prior KT :** 3.1% (n=3).
- **Preformed cytotoxic antibodies** : 7.2% (n=7)

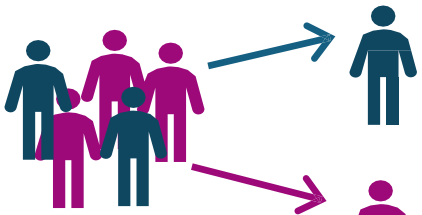
Primary kidney disease



Renal replacement therapy modality



Donors' characteristics



Deceased donors

39 (40.2%)

Live donors

58 (59.8%)

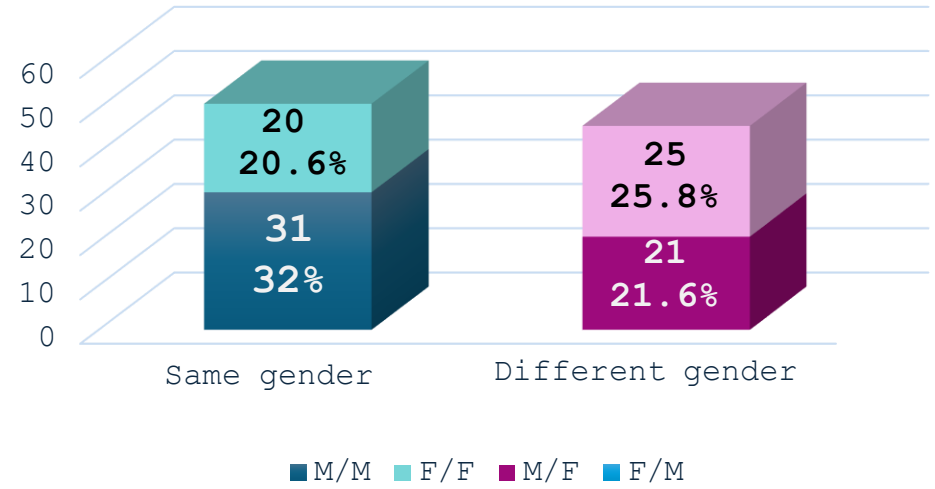
- Mean age : 38.3 ± 10.3 yo
- Sex-ratio : 1.02

Peritransplant characteristics

- **Transplanted kidney :** Left kidney : 71.1% (n=69).
- **Mean cold ischemia time :** 21.1 ± 6.6 hours.
- **Delayed graft function:** 13.4% (n=13).

Donor/Recipient mismatch

Gender mismatch

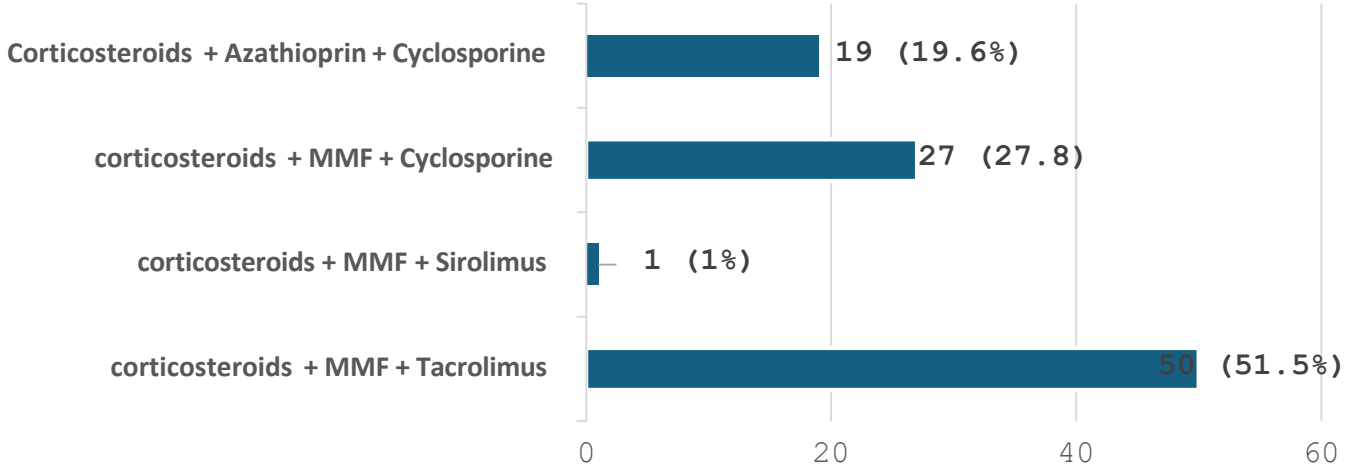


HLA mismatch

Number of HLA mismatch	Total N (%)
0	7 (7.2)
1-2	20 (20.6)
3-5	70 (72.2)

Immunosuppressive regimen

Maintenance therapy



Intraindividual variability

Tacrolimus
20,4% [17,5 – 29,2]

Cyclosporine
52% [25 – 63,5]

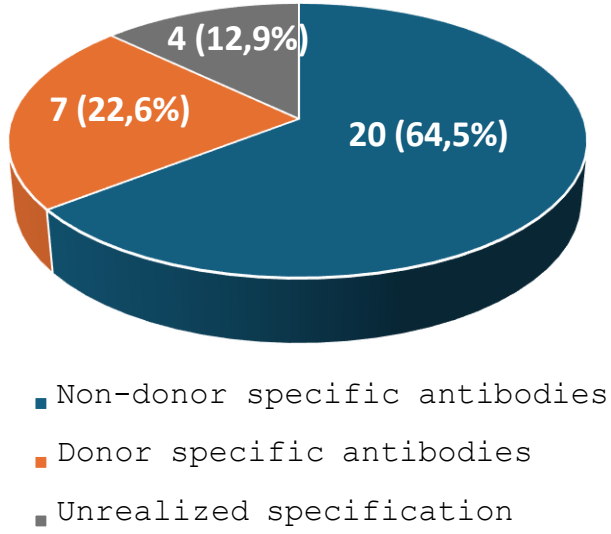
Immunological followup

Cytotoxic antibodies

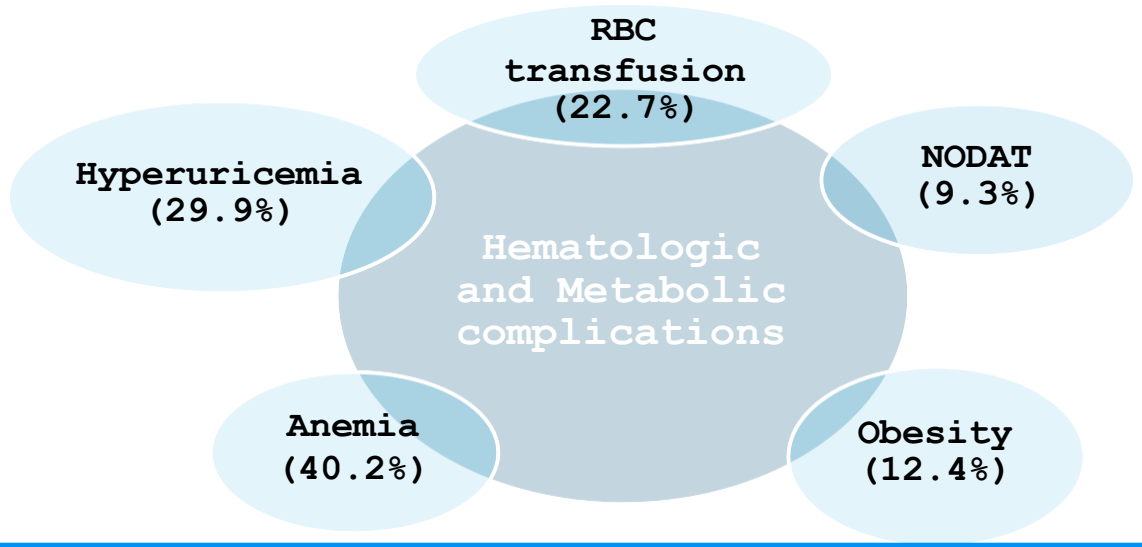
	N (%)
Anti HLA class I Antibodies	20 (64,5)
Anti HLA class II Antibodies	17 (54,8)
Anti-MICA Antibodies	9 (29)

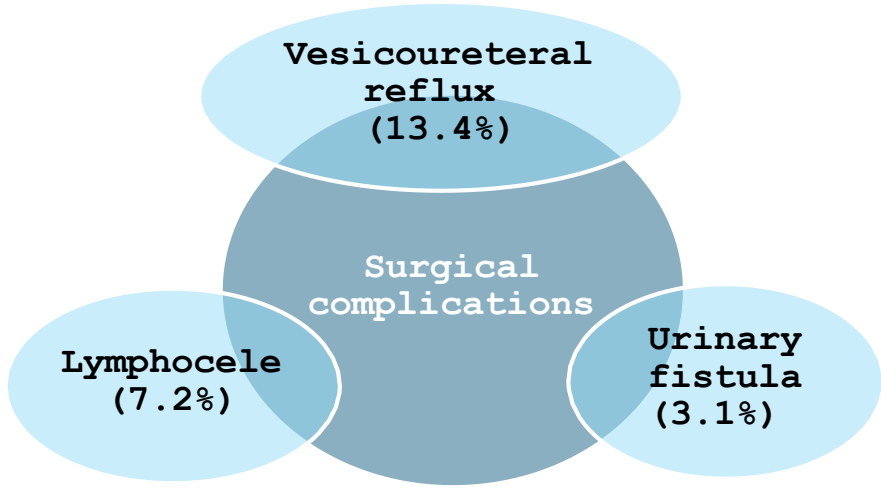
Anti-HLA DQ : 7 (7.2%)

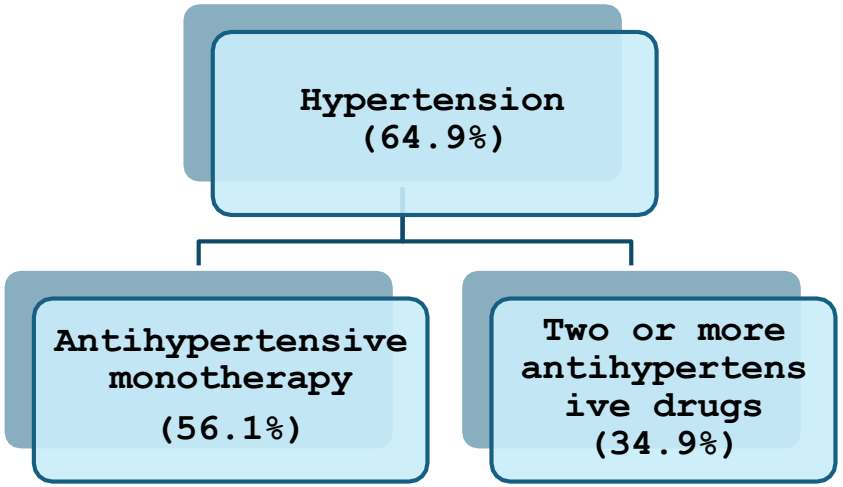
Antibodies' specifity

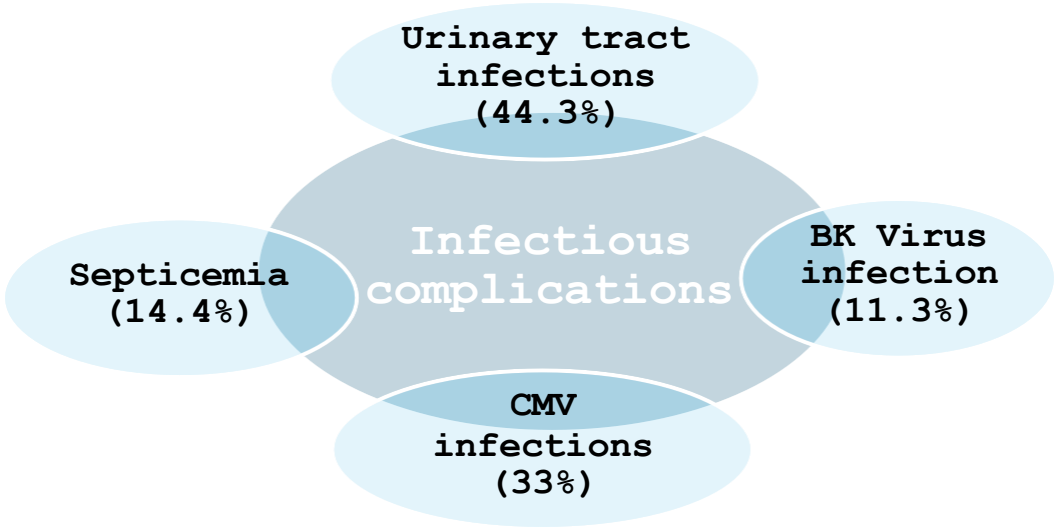


Main Complications following transplantation









Antibody mediated rejection

- **Biopsy proven antibody mediated rejection :** 22.7% (n=22).
- **Diagnostic time to kidney transplantation :** 62 months [23 – 102]
- **Early acute ABMR** : n=4.

Main Clinical findings

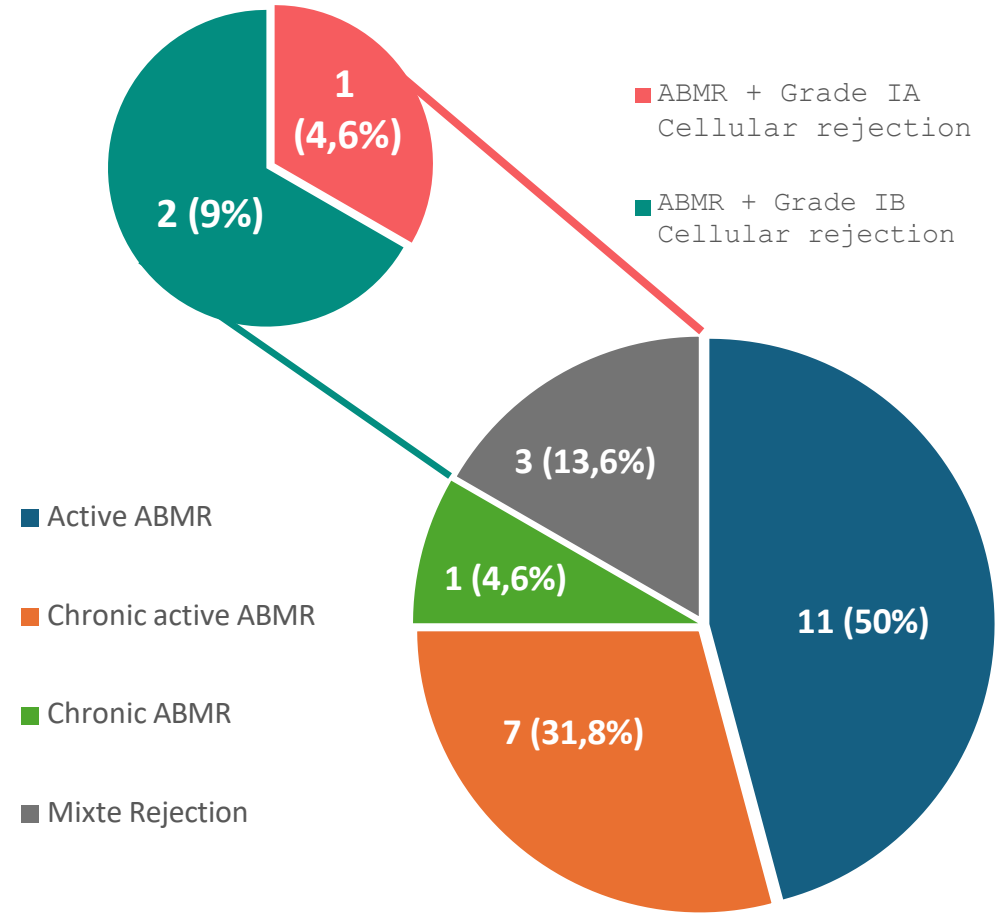
- **Graft dysfunction** : 100 %
- **Proteinuria :** 45.5%
- **Hypertension :** 18.2%
- **Gastro-intestinal disorders :** 36.3%

Main ultrasound findings

- **Normal graft's ultrasound :** n= 9
- **Increase in graft's arterial resistive index** : n=7
- **Increased graft's size** : n = 5

Hisological findings

C4d negative ABMR : 9% (n=2)



Univariate analysis

		ABMR ; N(%)	P
Intraindividual variabiliry [Tacrolimus] N (%)	**<27%**	1 (2.6)	
	≥ 27%	10 (52.6)	**0.001**
Post KT cytotoxic antibodies N (%)	**Absent**	10 (15.2)	
	Present	12 (38.7)	**0.01**
Post KT anti-HLA DQ antibodies, N (%)	**Absent**	16 (17.8)	
	Present	6 (85.7)	**<0.001**
Post KT Anemia N (%)	**Yes**	16 (41)	
	No	6 (10.3)	**<0.001**
Post KT RBC transfusion, N (%)	**No**	10 (13.3)	
	Yes	12 (54.5)	**<0.001**
Post KT obesity, N (%)	**No**	16 (20)	
	Yes	6 (50)	**0.023**
Post KT Hyperuricemia N (%)	**No**	9 (13.2)	
	Yes	13 (44.8)	**0.001**
Number of antihypertensive drugs in post KT N (%)	**< 2**	9 (12)	
	≥2	13 (59.1)	**<0.001**

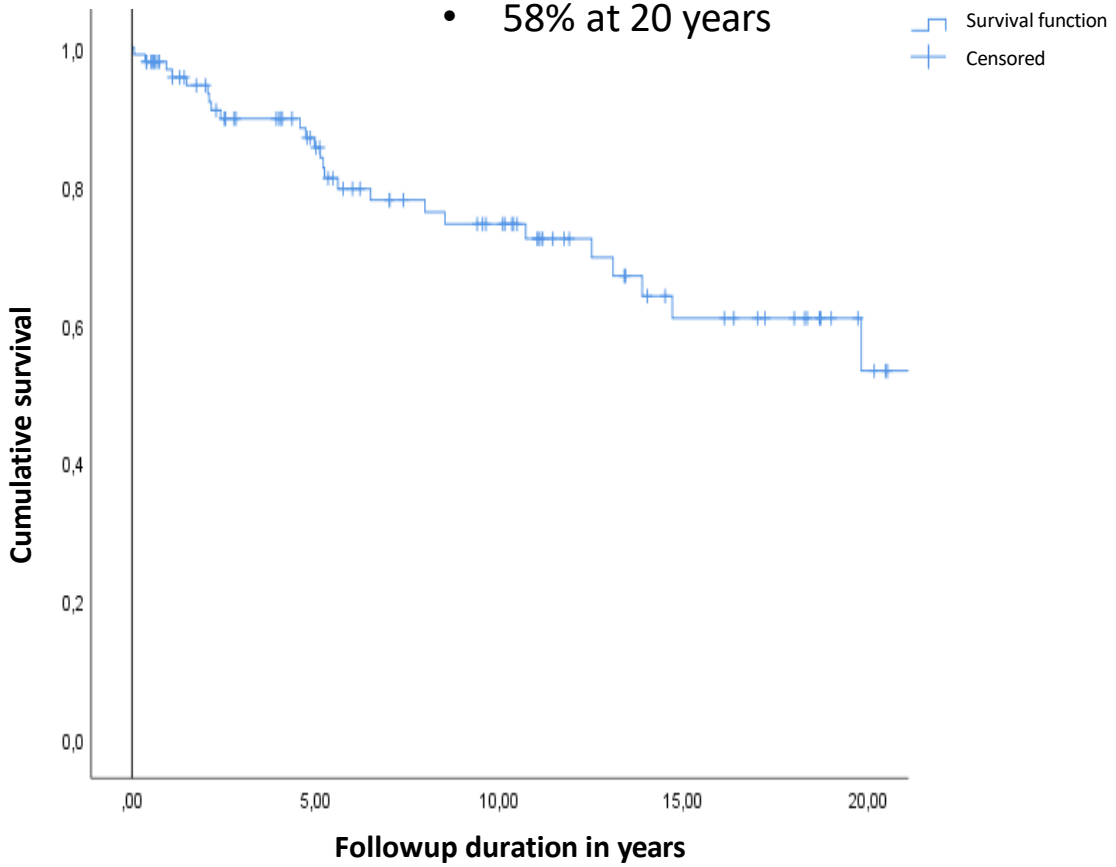
Multivariate analysis

ABMR associated factors	Adjusted OR	95% IC	p
Post transplant hyperuricemia	4	1.2 – 17	0.027
The use of Cyclosporine as a first line calcineurin inhibitor	4	1.1 – 15	0.048
Post transplant anti-HLA DQ antibodies	**44**	**3 – 61**	**0.005**
Post transplant hypertension requiring the use of two or more antihypertensive drugs	10.2	2 - 42	0.007

Graft's survival

Overall graft's survival

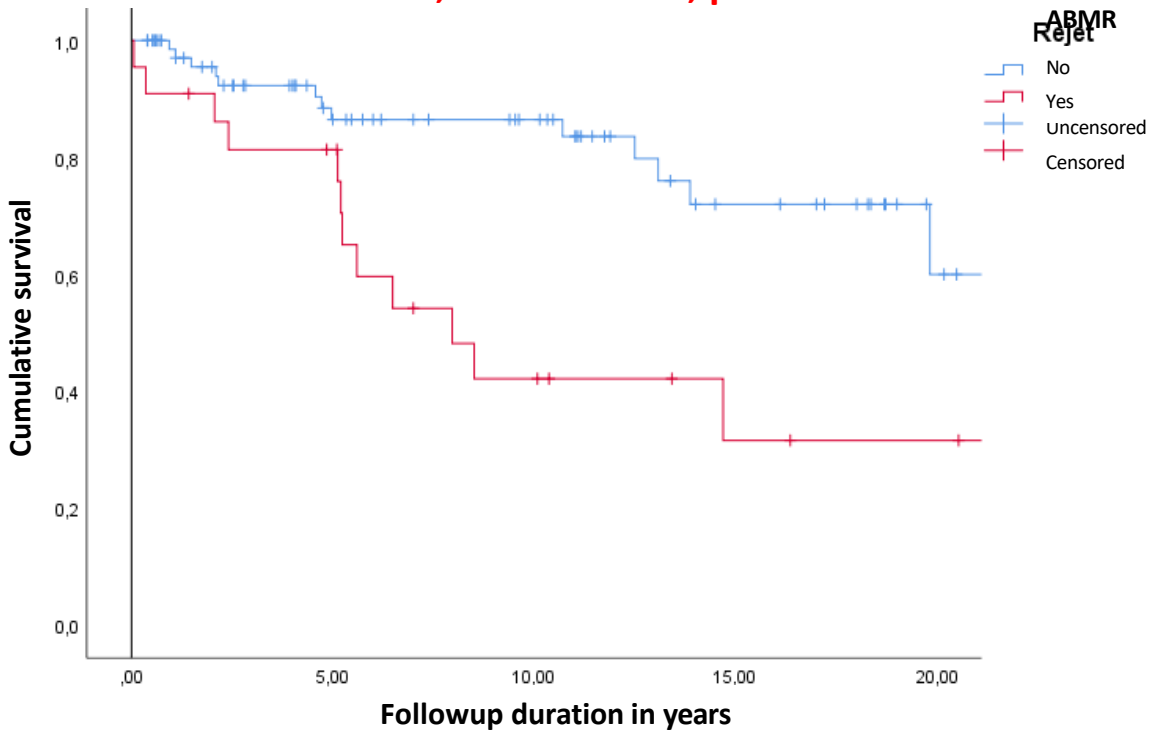
- 86% at 5 years
- 75% at 10 years
- 58% at 20 years



graft's survival and ABMR

- 81% at 5 years
- 43% at 10 years
- 35% at 20 years

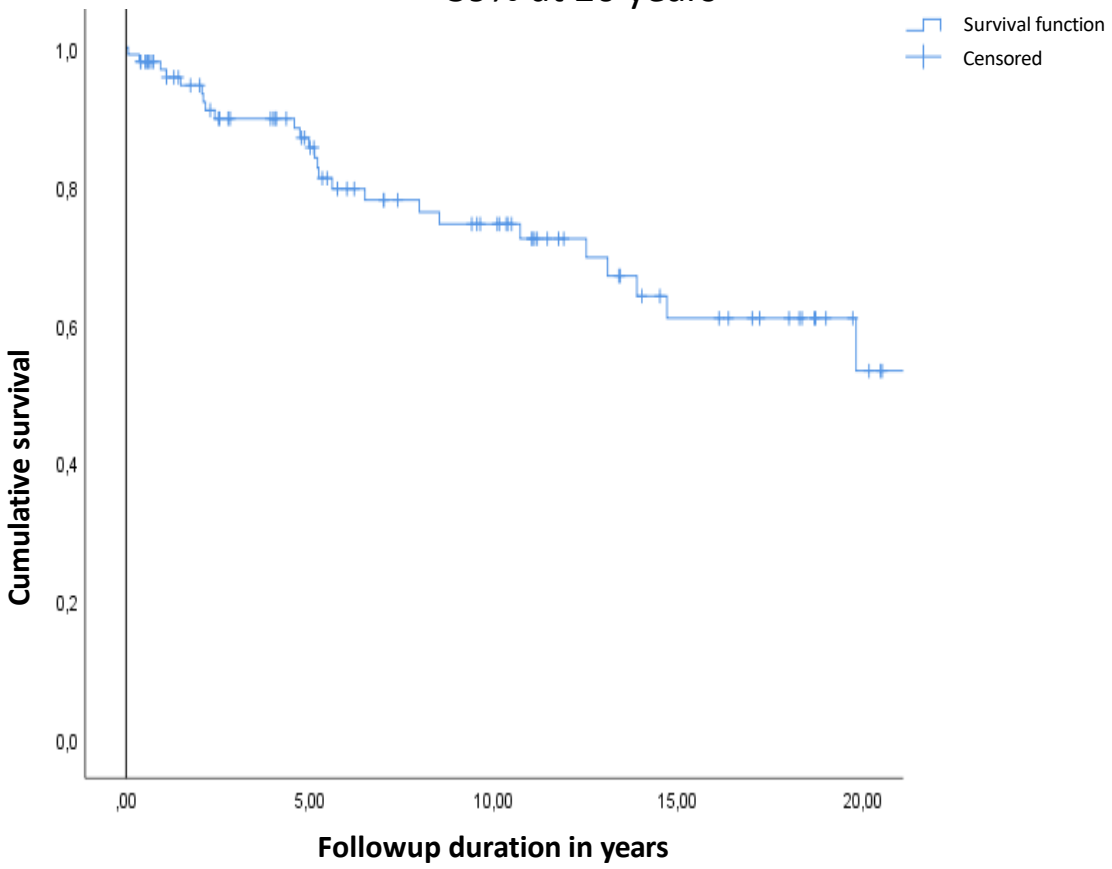
HR= 5.5 ; 95% IC : 2 – 9; p = 0.005



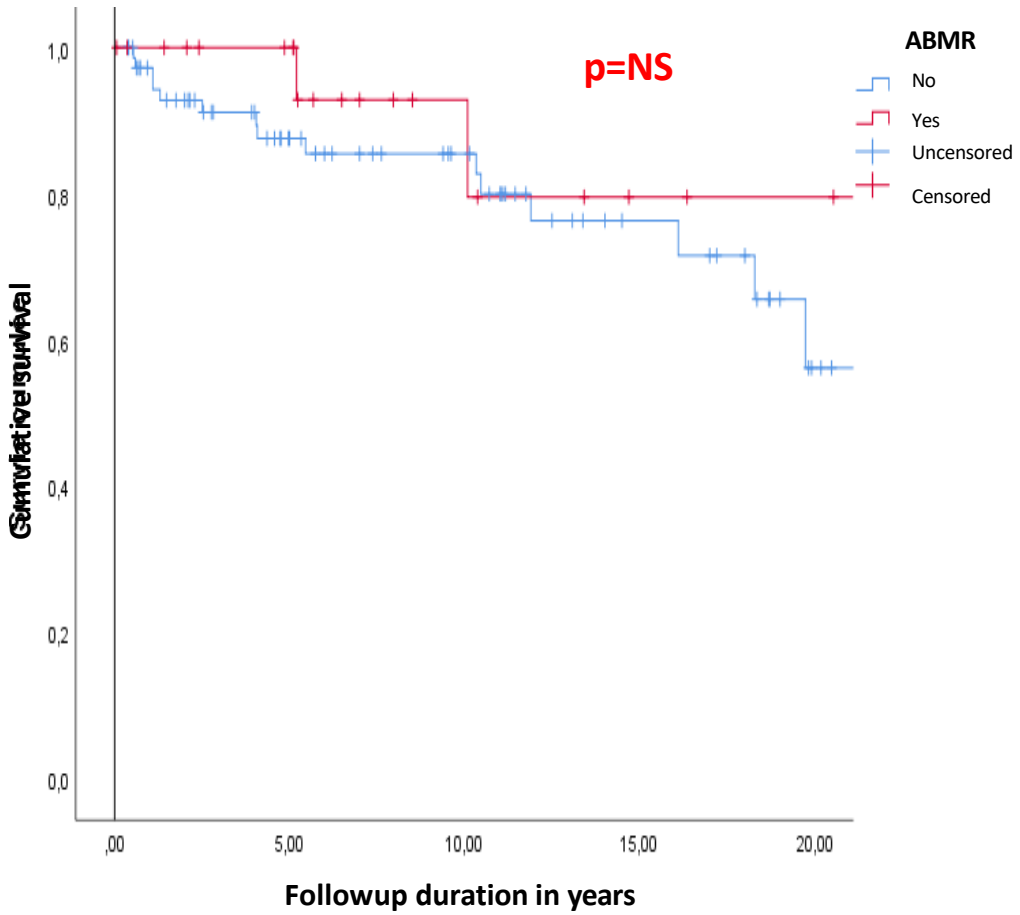
Patient's survival

Overall patient's survival

- 90 % at 5 years
- 87% at 10 years
- 59% at 20 years



Patient's survival and ABMR



The pros and cons of our study

- **A thorough patient selection**
- **Long follow-up duration** : Studying the possible accountability for both early and late complications in pediatric KT.

- **The study period of 34 years** → heterogeneity of the studied population
- **Retrospective nature**

Highlighting points

- ABMR : Independent factor compromising graft survival.
- Impact of HLA-DQ incompatibility on the outcome of pediatric kidney transplants → closer clinical and immunological monitoring in at-risk recipients.
- Potential accountability for biological and metabolic disruptions induced by immunosuppressive therapy such as hyperuricemia and hypertension in the pathogenesis of ABMR.
- We emphasize on the need of ensuring an adequate immunosuppression that should be both effective and steady in order to limit its intra-individual variability and simultaneously minimize the infectious risks as well as the metabolic and hematological disturbances caused by these treatments.
- We also emphasize on the need for larger population-based studies to further confirm our findings.

- ABMR has progressively emerged to become one of the leading causes of graft loss in pediatric KT.
- Although its pathogenesis is based on immunological mechanisms, recent data as well as the results of our study highlight the accountability of metabolic, hematological, and cardiovascular complications in its occurrence.
- Prevention and early management of modifiable associated factors along with the establishment of a more personalized monitoring protocol for high-risk patients will improve outcomes in pediatric KT.