Supplemental Material

Supplemental methods

Patient selection and data collection (continued)

Collected patient information comprised demographics, past medical history, information on native biopsy, transplantation characteristics, immunosuppressive regimen and yearly follow-up visits after transplant including clinical parameters, rejection, IgA recurrence and other complications.

Predictor selection

We selected and collected data on the following potential predictors of recurrent IgA deposits, based on prior literature and clinical practice: age at diagnosis, race, BMI, time on dialysis, age at transplantation, pre-emptive transplant, living donor, age of donor, HLA-mismatch, presence of DSA at time of transplant, induction therapy, IgA associated diseases (e.g., auto-immune and Henoch-Schönlein Purpura), immunosuppressive regimen, time to ESKD and steroid free regimen/early steroid withdrawal. To account for the different geographical regions in which the patients were followed up, continent of residence was added as a predictor.

Definitions

Recurrence of IgA was defined as mesangial IgA deposits in kidney biopsy, with or without mesangial expansion and/or endocapillary hypercellularity. If IgA deposits were present in other parts of the biopsy without mesangial deposition, the patient was considered as non-recurrent. Patients with potential IgA recurrence because of proteinuria, hematuria or a rise in creatinine, but without confirmatory kidney biopsy, were also considered non-recurrent.

eGFR was estimated by the Modification of Diet in Renal Disease (MDRD) study equation. Acute antibody- or T cell mediated rejection was recorded if confirmed on renal biopsy by the pathologist of the corresponding center. Borderline rejection was not considered acute rejection. New onset diabetes was defined as a new and persistent elevation of blood glucose levels post-transplantation requiring glucose lowering medication. Early steroid withdrawal was defined as the withdrawal of steroids within 3 months after kidney transplantation. Non-

compliance was recorded if this was highly suspected or confirmed by the patient's physician, noted in the charts. De novo DSA was recorded if MFI (mean fluorescent intensity) of anti-HLA antibodies exceeded the center's threshold for positivity. Proteinuria was checked by spot urine, protein to creatinine ratio, or 24-hour urine collection, depending on transplant center's clinical practice.

Biopsy assessment of IgA nephropathy and scoring of mesangial proliferation and/or intensity of IgA staining was performed in each center by the local pathologist. Biopsy reports were thoroughly reviewed.

Statistical analysis (continued)

Little's missing completely at random (MCAR) test was performed on all predictors and outcome to investigate randomness of missing data and resulted in a significant outcome ($p<0.001$), which implies that the pattern of missing data was not completely at random. However, detailed analysis of missing data showed a low frequency of missing data (overall 4%) and Fisher's exact test showed no difference per predictor between recurrence groups. We therefore proceeded with imputation for missing data.

STATA's multiple imputation by chained equations (MICE) procedure was used to impute missing categorical, ordinal, normal continuous and non-normal continuous variables by logistic regression, ordinal regression, linear regression and predictive mean matching, respectively. For each missing value, 100 values were imputed, using all predefined predictors, including recurrence and graft failure. In case of perfect prediction, augmentation was performed to avoid bias in imputations. Imputations were graphically assessed on outliers and variances and coefficients of the imputed cox-models were checked on agreement with complete case analysis.

Schoenfeld residuals were evaluated to assess the proportional-hazard assumption. In our predictor analysis (Table 2), the proportional-hazard assumption was violated in analyses with the variables "pre-emptive transplant" and "recurrence", tested by Schoenfeld residuals. We therefore proceeded with adding a time-interaction (time after

transplant) to the model and performing stratified analysis to perform a better interpretation of the data. Indeed, for the variables “pre-emptive transplant” and “recurrence”, an interaction with time was significant ($p<0.001$), after which we concluded that proportional hazards for these variables changed over time. Deviance residuals were used to examine model accuracy and outliers, after which time on dialysis and time to kidney failure were log-transformed to improve random scatter of residuals.

Sensitivity analyses

We performed a sensitivity analysis to determine the impact of the chosen method for imputation of missing data. Complete case analysis on the final multivariable model (DSA at time of transplant and pre-emptive kidney transplantation) resulted in an analysis on 461 patients with 73 IgA recurrences. Similar to the imputed model, significant p-values for all variables were observed. Furthermore, univariable complete case analysis for each variable showed similar significance and hazard ratios compared to univariable analysis with imputed values.

We furthermore performed sensitivity analyses limited to patients who were biopsied or who were tested for DSA. These analyses were performed in 455 patients, since in one center, post-transplant information regarding complications, de novo DSA and biopsies were not complete. We therefore decided to remove all data from this center for post-transplant analysis.

Lastly, we performed an analysis to patients who were excluded from the cohort because they died or had follow-up less than one year. In the group of patients lost to follow-up, 19 out of 32 patients did not have any follow-up information entered to the online database, only baseline data, and were therefore excluded. The other 13 patients were lost to follow-up with a median time of 1.6 months (range 2 weeks - 5.8 months) after transplant. Seven patients died within 8 months of transplant. To investigate whether excluding these 7 patients who died and 13 who were lost to follow-up would change our primary outcome, we calculated cumulative incidence of the total cohort with these 20 patients included. Ten-year graft survival was 19% (95%CI 12-27), and increased to 23% (95%CI 14-34) at 15 years, which is in accordance with the numbers of the final cohort.

Data storage

All data was stored in an ad hoc designed database using REDCapTM (Research Electronic Data Capture); a secure, HIPAA-compliant web-based application hosted by the Partners HealthCare Research Computing, Enterprise Research Infrastructure and Services (ERIS) group. (S1,S2) Investigators received access to the secured website to enter and access patient data online, but were only able to access their individual centers' data, not from other centers. Upon downloading of the dataset, specific dates were date-shifted to complete de-identification of the dataset to ensure confidentiality of participants.

Ethical considerations

The overall protocol of TANGO-study was submitted and approved by the ethical committee of the Partners Human Research Committee (PHRC) at the Brigham and Women's hospital in Boston (protocol number: 2015P000993), and at each participating center. In one participating center, the University Medical Center Groningen, ethical approval was waived by the Medical Ethics review Board (METc UMCG). All protocols are in accordance with International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism'.(S3)

Potential sources of bias

We implemented the following strategies to avoid potential sources of bias: Centers were instructed to chronologically add patients according to their date of transplant, to avoid selection bias towards patients who had a recurrence. We recorded detailed medical histories and review of histories and biopsies of patients included in our database was done in a blinded fashion for the primary outcome of post-transplant IgA recurrence. Each case of post-transplant recurrence or graft loss was reviewed and when questions were raised (e.g., important missing information, inconsistencies in data), clarification was asked from the specific center to verify the data. Analyses to graft failure and complications post-transplant were corrected for the most important confounders known from literature. The multi-center setup of this study over multiple continents was done to make sure many ethnical

groups were present to avoid population bias. Unfortunately, some ethnical groups (especially patients with an African-American background) were still underrepresented. An analysis plan with clearly defined outcome and predictors (selected from literature) was made before the start of data-analysis and was followed throughout the analysis of data.

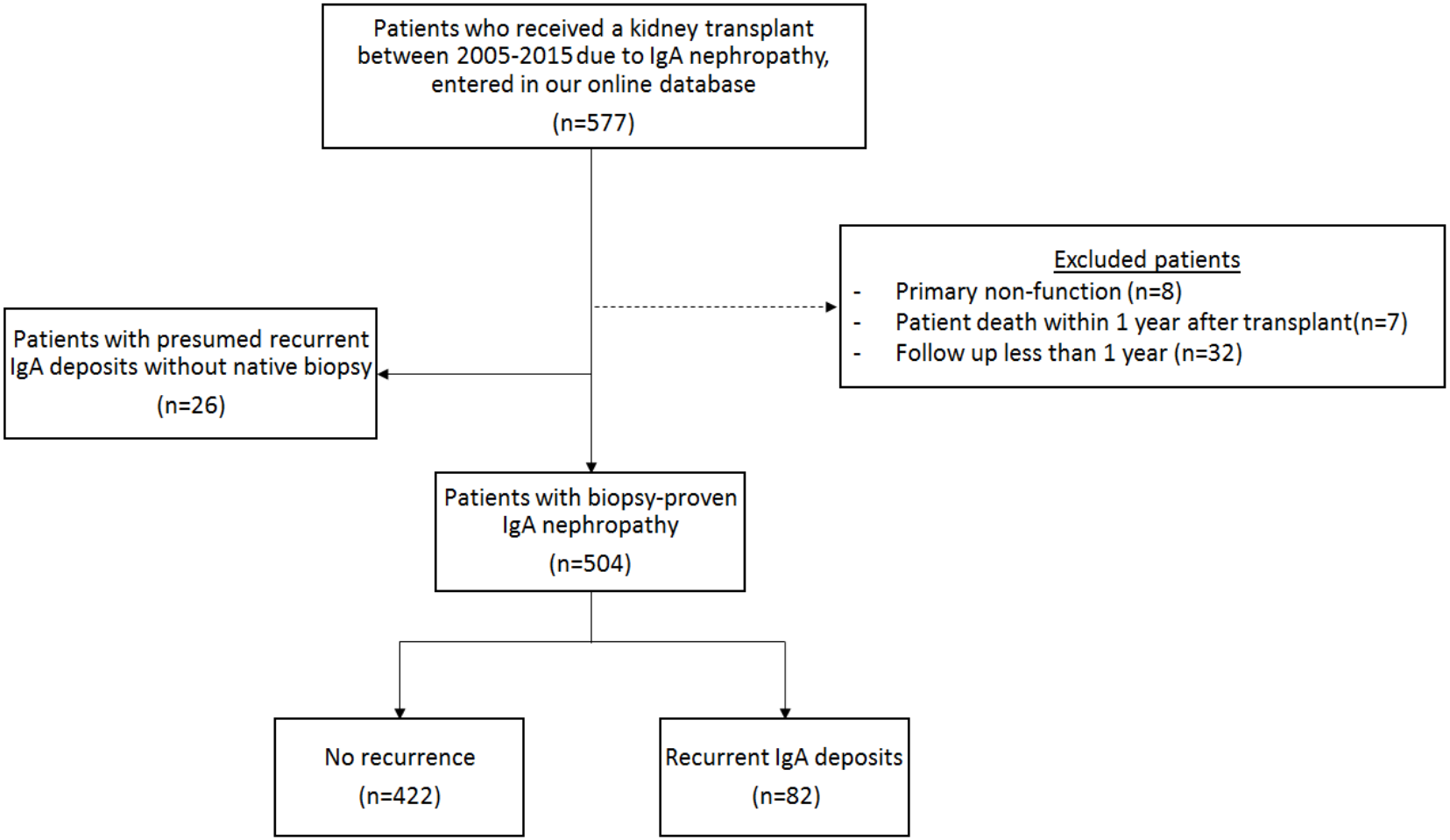
Supplemental Table 1. Published non-registry studies on incidence of recurrence of IgA nephropathy since 2000 including >50 subjects

Year	Population	Total n	Incidence	95% CI	Analysis	Clinical or protocol biopsy	Ethnicity	Risk factors
2001(S4)	Adults	106	35%	26-44	Multivariable	Mixed	Mainly white	Younger age at transplant
2001(S5)	Adults	79	22%	12-31	Univariable	Mixed	Mainly white	Living related donor
2001(S6)	Adults	90	21%	13-30	Univariable	Clinical	Asian	None
2003(S7)	Adults	75	19%	10-27	Univariable	Clinical	Asian	None
2005(S8)	Adults	152	13%	8-19	Univariable	Clinical	Mainly white	None
2006(S9)	Adults	75	17%	9-26	Univariable	Clinical	Mainly white	None
2008(S10)	Adults	116	28%	20-37	Multivariable	Clinical	Mainly white	No induction compared to ATG
2009(S11)	Adults	221	20%	15-25	Multivariable	Clinical	Mainly Asian	Younger age at transplant, living related donor
2012(S12)	Adults	65	32%	21-44	Univariable	Mixed	Mainly white	Younger donor age, use cyclosporine protective
2012(S13)	Adults	142	18%	11-24	Univariable	Clinical	Mainly white	None
2013(S14)	Adults	190	22%	16-28	Multivariable	Clinical	Mainly white	Younger age at transplant, triple immunosuppressive therapy
2014(S15)	Adults	78	15%	7-23	Multivariable	Mixed	Mainly Asian	Unclear (data conflicting)
2014(S16)	Adults	124	22%	15-29	Multivariable	Clinical	Mixed	Steroid free regimen, no induction compared to ATG, sirolimus based regimen, use of MMF protective
2015(S17)	Children and Adults	56	30%	18-42	Univariable	Clinical	Asian	Younger age at transplantation, shorter time on dialysis
2016(S18)	Adults	104	19%	12-27	Univariable	Clinical	Mixed races	Younger age at transplantation
2017(S19)	Adults	96	35%	26-45	NA	Clinical	Unknown	NA
2017(S20)	Adults	62	23%	12-33	Multivariable	Clinical	Mixed races	Younger age at diagnosis, crescents on native biopsy, acute rejection
2018(S21)	Adults	123	23%	15-30	Univariable	Clinical	Mainly white	Early steroid withdrawal
2018(S22)	Adults	67	21%	11-31	Univariable	Clinical	Unknown	Serum IgA level

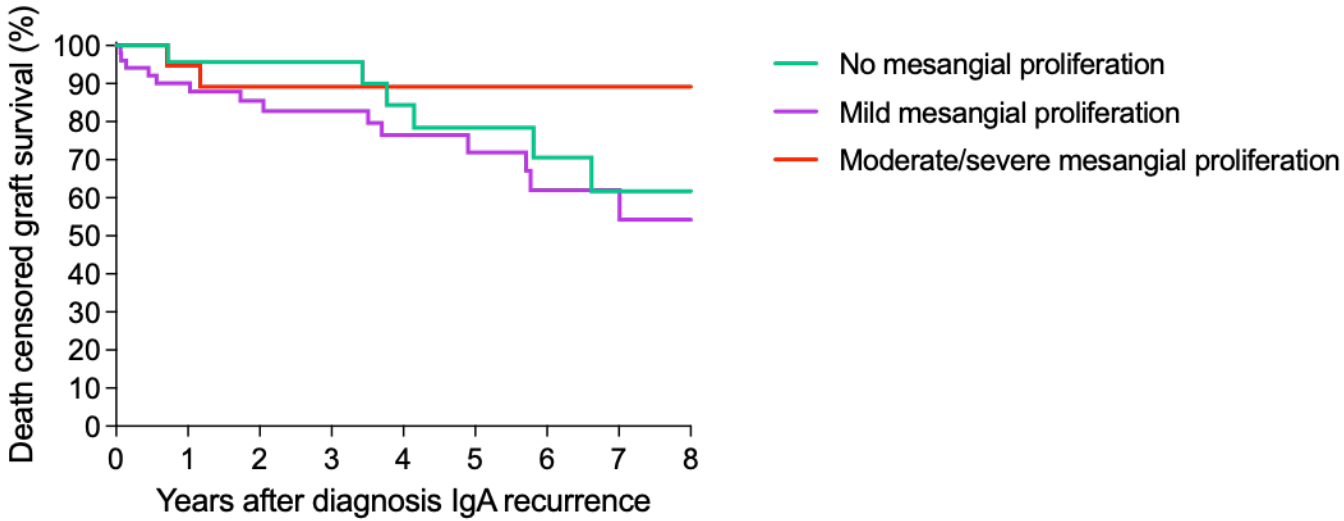
Supplemental Table 2. Missing data in variables comparing patients without and with recurrent IgA

Variable	No recurrence (n=422)	Recurrence (n=82)	P-value
Age at diagnosis	32 (6)	5 (6)	0.81
White race	65 (15)	14 (17)	0.74
BMI	0 (0)	0 (0)	NA
Time on dialysis	10 (2)	0 (0)	0.38
Age at kidney transplantation	0 (0)	1 (1)	0.16
Age donor	45 (11)	10 (12)	0.70
Steroid withdrawal/ steroid free regimen	3(1)	0 (0)	1.00
Induction	7 (2)	1 (1)	0.64
Immunosuppression with Tac +MMF + st	0 (0)	1 (1)	0.16
Geographic location of center	0 (0)	0 (0)	NA
Living transplant	2 (0)	1 (1)	0.41
Pre-emptive transplant	0 (0)	0 (0)	NA
Time to kidney failure	30 (7)	2 (2)	0.14
DSA at time of transplant	34 (8)	9 (11)	0.39
HLA-mismatch	57 (14)	11 (13)	1.00
IgA associated diseases	0 (0)	0 (0)	NA
Total missing values (% of all data)	285 (4)	55 (4)	

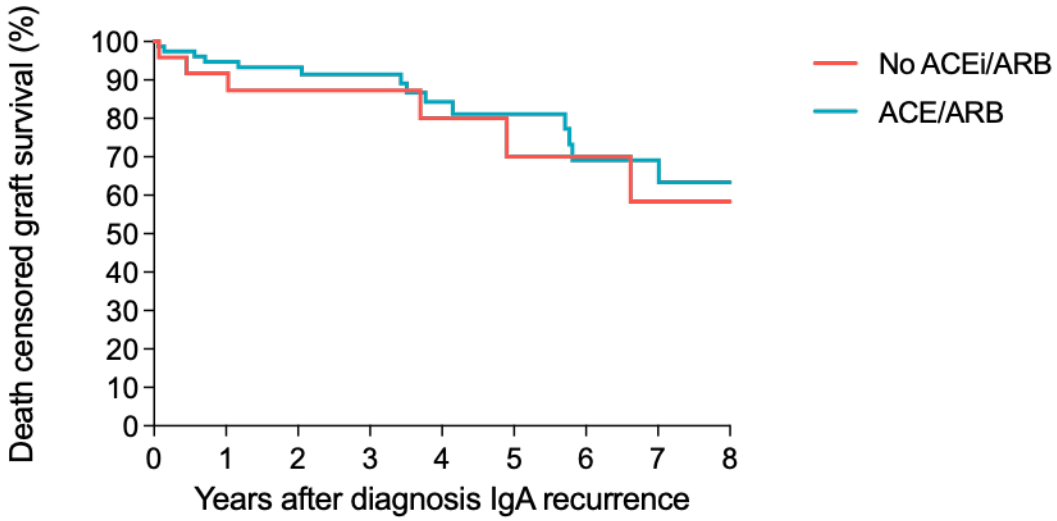
Supplemental Figure 1. Flow chart of the study population



Supplemental Figure 2. Kaplan-Meier analysis to death-censored graft survival in patients with IgA recurrence after diagnosis, stratified by degree of mesangial expansion on kidney biopsy



Supplemental Figure 3. Kaplan Meier analysis to graft survival in patients with recurrent IgA treated with or without ACEi/ARB. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.



Supplemental References

S1. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG: Research Electronic Data Capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 42: 377–381, 2009

S2. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J, Duda SN, REDCap Consortium: The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 95: 103208, 2019

S3. The Declaration of Istanbul on Organ Trafficking and Transplant Tourism (2018 Edition). *Transplantation* 103: 218–219, 2019

S4. Ponticelli C, Traversi L, Feliciani A, Cesana BM, Banfi G, Tarantino A: Kidney transplantation in patients with IgA mesangial glomerulonephritis. *Kidney Int* 60: 1948–1954, 2001

S5. Andresdottir MB, Hoitsma AJ, Assmann KJ, Wetzels JF: Favorable outcome of renal transplantation in patients with IgA nephropathy. *Clin Nephrol* 56: 279–288, 2001

S6. Kim YS, Moon JI, Jeong HJ, Kim MS, Kim SI, Choi KH, Lee HY, Han DS, Park K: Live donor renal allograft in end-stage renal failure patients from immunoglobulin A nephropathy. *Transplantation* 71: 233–238, 2001

S7. Choy BY, Chan TM, Lo SK, Lo WK, Lai KN: Renal transplantation in patients with primary immunoglobulin A nephropathy. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc* 18: 2399–2404, 2003

S8. Chandrakantan A, Ratanapanichkich P, Said M, Barker CV, Julian BA: Recurrent IgA nephropathy after renal transplantation despite immunosuppressive regimens with mycophenolate mofetil. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc* 20: 1214–1221, 2005

S9. Courtney AE, McNamee PT, Nelson WE, Maxwell AP: Does angiotensin blockade influence graft outcome in renal transplant recipients with IgA nephropathy? *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc* 21: 3550–3554, 2006

S10. Berthoux F, El Deeb S, Mariat C, Diconne E, Laurent B, Thibaudin L: Antithymocyte globulin (ATG) induction therapy and disease recurrence in renal transplant recipients with primary IgA nephropathy. *Transplantation* 85: 1505–1507, 2008

S11. Han SS, Huh W, Park SK, Ahn C, Han JS, Kim S, Kim YS: Impact of recurrent disease and chronic allograft nephropathy on the long-term allograft outcome in patients with IgA nephropathy. *Transpl Int Off J Eur Soc Organ Transplant* 23: 169–175, 2010

S12. Ortiz F, Gelpi R, Koskinen P, Manonelles A, Räisänen-Sokolowski A, Carrera M, Honkanen E, Grinyó JM, Cruzado JM: IgA nephropathy recurs early in the graft when assessed by protocol biopsy. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc* 27: 2553–2558, 2012

S13. Kamal Aziz A, Mousson C, Berthoux F, Ducloux D, Chalopin J-M: Renal transplantation outcome in selected recipients with IgA nephropathy as native disease: a bicentric study. *Ann Transplant* 17: 45–51, 2012

S14. Moroni G, Longhi S, Quaglini S, Gallelli B, Banfi G, Montagnino G, Messa P: The long-term outcome of renal transplantation of IgA nephropathy and the impact of recurrence on graft survival. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc* 28: 1305–1314, 2013

S15. Sato Y, Ishida H, Shimizu T, Tanabe K: Evaluation of tonsillectomy before kidney transplantation in patients with IgA nephropathy. *Transpl Immunol* 30: 12–17, 2014

S16. Von Visger JR, Gunay Y, Andreoni KA, Bhatt UY, Nori US, Pesavento TE, Elkhammas EA, Winters HA, Nadasdy T, Singh N: The risk of recurrent IgA nephropathy in a steroid-free protocol and other modifying immunosuppression. *Clin Transplant* 28: 845–854, 2014

S17. Ahn S, Min S-I, Min S-K, Ha IS, Kang HG, Kim YS, Kim SJ, Hao J: Different Recurrence Rates Between Pediatric and Adult Renal Transplant for Immunoglobulin A Nephropathy: Predictors of Posttransplant Recurrence. *Exp Clin Transplant Off J Middle East Soc Organ Transplant* 13: 227–232, 2015

S18. Nijim S, Vujjini V, Alasfar S, Luo X, Orandi B, Delp C, Desai NM, Montgomery RA, Lonze BE, Alachkar N: Recurrent IgA Nephropathy After Kidney Transplantation. *Transplant Proc* 48: 2689–2694, 2016

S19. Berthoux F, Suzuki H, Mohey H, Maillard N, Mariat C, Novak J, Julian BA: Prognostic Value of Serum Biomarkers of Autoimmunity for Recurrence of IgA Nephropathy after Kidney Transplantation. *J Am Soc Nephrol JASN* 28: 1943–1950, 2017

S20. Avasare RS, Rosenstiel PE, Zaky ZS, Tsapepas DS, Appel GB, Markowitz GS, Bomback AS, Canetta PA: Predicting Post-Transplant Recurrence of IgA Nephropathy: The Importance of Crescents. *Am J Nephrol* 45: 99–106, 2017

S21. Di Vico MC, Messina M, Fop F, Barreca A, Segoloni GP, Biancone L: Recurrent IgA nephropathy after renal transplantation and steroid withdrawal. *Clin Transplant* 32: e13207, 2018

S22. Garnier A-S, Duveau A, Demiselle J, Croué A, Subra J-F, Sayegh J, Augusto J-F: Early post-transplant serum IgA level is associated with IgA nephropathy recurrence after kidney transplantation. *PloS One* 13: e0196101, 2018