RECURRENT GN BWG

Chairs

Nada Alachkar, MD

Serena Bagnasco, MD

Johns Hopkins University School of Medicine, Baltimore, MD, USA

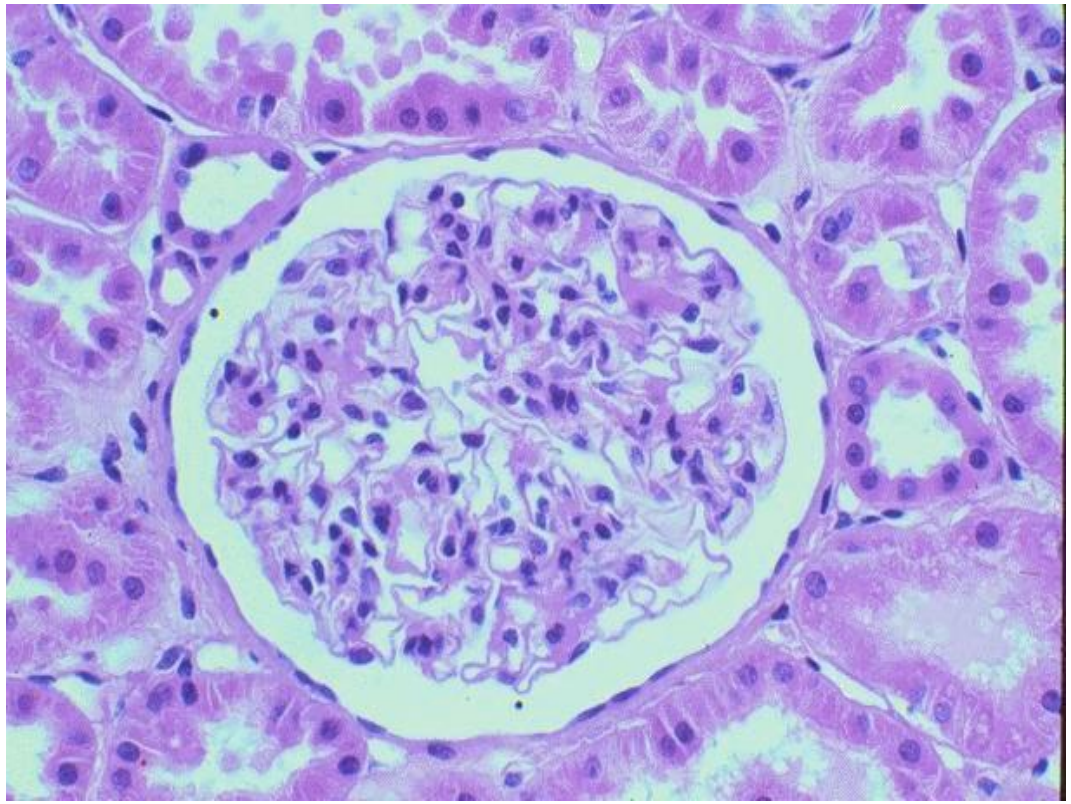
28 March 2017

DISCLOSURE

- Nothing to disclose

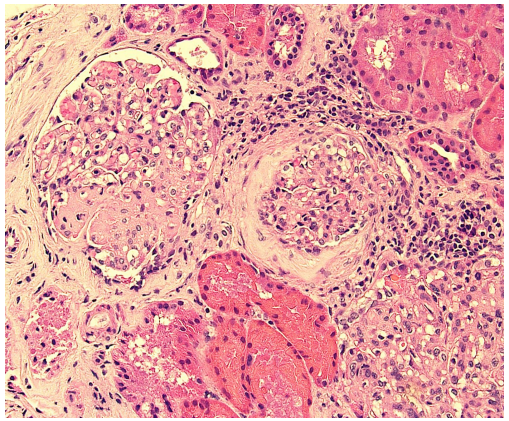
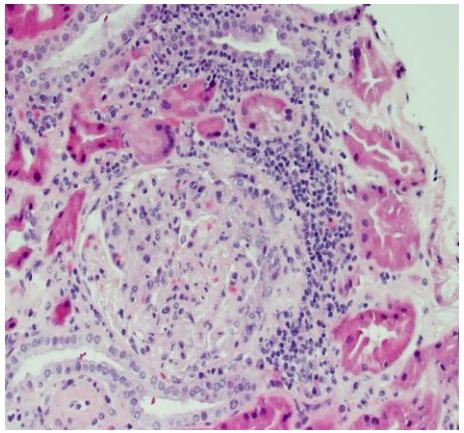
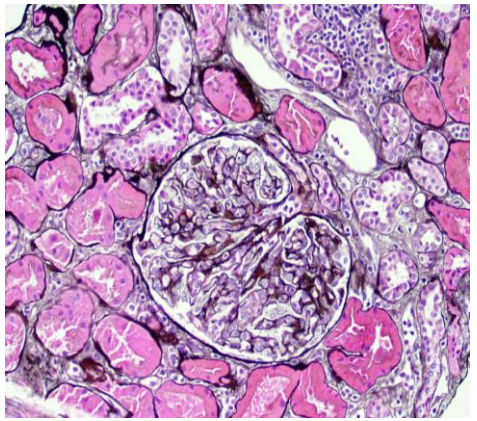
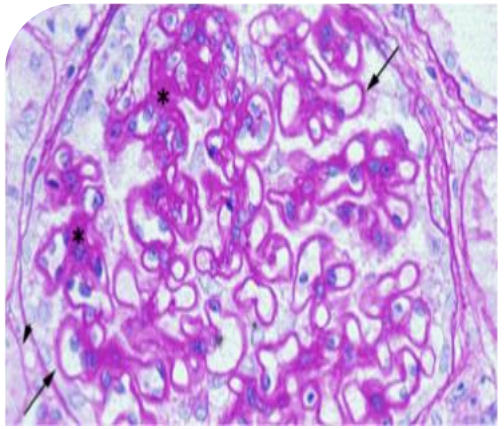
OBJECTIVES

- Significance of recurrent GN in the transplanted kidney
- Goal of the GN working group
- Structure of the work
- Brief highlights
- Preliminary data
- Future work



Significance of GN recurrence

- All primary GN recur highly post transplant
- Recurrence rate is different for each type
- Second most common cause of allograft failure after rejection
- Limited data on the pathology and its significance in the outcome
- Limited data on de novo GN

Goals of this work

Establish pathology guidelines in GN diagnosis for pathologists/ clinicians

Early signs of recurrence

Late manifestation

Understanding GN changes

when combined with other pathological changes

SAVE “GLOMERULUS”

BANFF GN

Correlations & predictions

pathology with clinical manifestation & outcome

Genetic variations

biomarkers

correlation with pathology

GN Banff Working Group

Aula Magna Room: March 29th, 2017; 18:30-20:30

- Chairs: Nada Alachkar & Serena Bagnasco
- Multi international centers; **~ 30 centers**: pathology/nephrology/immunology/surgery members
- Each center: pathologist + clinician
- Members: **54** showed interest

MEMBERS

Member	Title	Institution
Alexandre Loupy	Nephrology	Necker hospital, France
Michael Mengel	Pathology	University of Alberta, Canada
Surya V Seshan	Pathology	Weill Cornell Medicine, USA
Darshana Dadhania	Nephrology	Weill Cornell Medicine, USA
Ibrahim Batal	Pathology	Columbia University, USA
Marian C Clahsen-van Groningen	Pathology	Erasmus University Rotterdam, Netherlands
Patricia Campbell	Immunology	University of Alberta, Edmonton, Canada
Davis Massey	Pathology	Virginia Commonwealth University, USA
Alton B. "Brad" Farris	Pathology	Emory University Hospital, USA
Maarten Naesens	Nephrology	University Hospitals Leuven, Belgium
Adnan Sharif	Nephrology	University Hospitals Birmingham, UK
Ajda T Rowshani	Nephrology	Erasmus University Medical, Netherlands
Dana Baran	Nephrology	McGill University Hospital Centre, Canada
Maha Mohamed	Nephrology	Univ. of Wisconsin, USA
Bassam Abu Jawdeh	Nephrology	Univ. of Cincinnati, USA
Gaurav Gupta	Nephrology	Virginia Commonwealth University, USA
Marco Delsante	Pathology	Johns Hopkins, USA
Lorraine Racusen	Pathology	Johns Hopkins, USA
Anke Schwarz	Pathology	Hannover Medical School, Germany
Michael Stokes	Pathology	Columbia University, USA
Nithya Krishnan	Nephrology	University Hospital (Coventry), UK
Nasreen Hasan Mohamed	Pathology	King Fahad Specialist Hospital-Dammam, Saudi Arabia
Emanuele Cozzi	Immunology	University of Padua, Italy
David Rush	Nephrology	University of Manitoba, Winnipeg, Canada
Mark Haas	Pathology	Cedar s Sinai, USA
Ruth Sapir-Pichhadze	Nephrology	McGill University, Canada
Laurine Bow	Immunology	Yale, USA
Diana Taheri	Pathology	Isfahan University , Iran
Jason Kidd	Nephrology	Virginia Commonwealth University, USA
Lynn D Cornell	Pathology	Mayo Clinic, USA
Tarek Alhamad	Nephrology	Wash. Univ. St. Louis, USA
Kevin Wen	Nephrology	University of Alberta, Canada
Cuong Nguyen	Nephrology	Oklahoma, USA

Previous meetings

- Kickoff meeting: June 13, 2016; Boston, MA (ATC)
  - Starting with IgA in native and transplant; followed by other GN
  - Multi-centers' registry
  - Reports of the bx
- Second meeting: November 17th, 2017; Chicago, IL (ASN)
  - Share single center's data in redcap/other data entry system
  - Grants for data entry and analysis
  - Each center will have internal IRB

Main Questions

??????

- **Recurrence rate of GN /Frequency of de novo GN?**
- **Manifestations/characteristics of recurrence /de novo in the allograft in each of these glomerulopathies?**
- **Clinical and pathological characteristics of "NATIVE" GN that can predict recurrence in the transplanted kidney?**
- **Characteristics of the histological /clinical manifestation in "ALLOGRAFT" with predictive value for progression/graft survival?**
- **What do we need for diagnosis: Light microscopy/IF/EM/Markers?**

GN in Native Kidney

	Characterization	Clinical
Glomerulopathy	PATHOLOGY	CLINICAL FINDINGS
Native disease	Light Microscopy: Global glomerulosclerosis (%) Segmental glomerulosclerosis (%) Hyalinosis Podocyte changes Glomerular capillary walls Mesangial matrix expansion Mesangial hypercellularity Endocapillary proliferation Crescents Karyorrhexis/ segmental necrotizing lesions Tubular injury Tubulitis Interstitial inflammation % interstitial fibrosis % Tubular atrophy Arteriosclerosis (cv) Arteriolar hyalinosis (ah) IF: EM: presence of deposits and distribution, Substructures % of podocyte foot process effacement	Demographics Age of onset Renal manifestations at onset Renal function eGFR Hematuria Proteinuria, UPCR at time of onset Co-morbidities Diabetes, Hypertension at onset Progression of the disease, time from onset to ESRD (eGFR, UPCR others) Therapy for glomerulopathy

GN in Transplanted Kidney

	Characterization	Clinical
Glomerulopathy	PATHOLOGY	CLINICAL FINDINGS
Post Transplant	Light Microscopy: Global glomerulosclerosis (%) Segmental glomerulosclerosis (%) Hyalinosis Podocyte changes Glomerular capillary walls Mesangial matrix expansion Mesangial hypercellularity Endocapillary proliferation Crescents Karyorrhexis/ segmental necrotizing lesions Tubular injury Tubulitis Interstitial inflammation % interstitial fibrosis % Tubular atrophy Arteriosclerosis (cv) Arteriolar hyalinosis (ah) IF: EM: presence of deposits and distribution, Substructures % of podocyte foot process effacement	Type of donor (Live, Deceased, cPRA, HLA mismatches) Desensitization Induction Maintenance immunosuppression Rejection episodes and type of rejections pre- post recurrence Infections pre-post recurrence Time of Onset of the pathological changes from transplantation Renal function at onset of recurrence Treatment of glomerulopathy Effect of treatment Resolution/persistence/progression in FU biopsies

Elements to be analyzed

Elements	Histology	Clinical
Frequency	Histological features at diagnosis	Time of onset post transplant
Predictors	Histological predictors	Clinical predictors: Demographics, Age, native dx, characteristics of the transplanted kidney (live/decease, HLA compatibility etc), eGFR, Hematuria, UPCR, therapy, episodes and types of rejection
Relation to native dx	Comparison with histological features in the native kidney	Demographics, Age, native dx, eGFR, Hematuria, UPCR, therapy, Progression of the native dx
WORKING GROUP		
	Copy of Bx Report/Shared scan slides	Clinical data of the center's cohort
Questionnaire		
Registry		

THE HISTORY OF RECURRENT GLOMERULONEPHRITIS

"glomerulonephritis" AND "kidney transplantation"
2737 publications

Earlier data--- recurrent MN 1960

AMERICAN JOURNAL OF CLINICAL PATHOLOGY
Vol. 34, No. 2, August, 1960, pp. 155-162
Printed in U.S.A.

MEMBRANOUS GLOMERULONEPHRITIS OCCURRING IN A HUMAN RENAL HOMOGRAFT

REPORT OF A CASE

ARTHUR F. KRIEG, M.D., ROBERT P. BOLANDE, M.D., WILLIAM D. HOLDEN, M.D., CHARLES A. HUBAY, M.D., AND LESTER PERSKY, M.D.
Departments of Pathology and Surgery, Western Reserve University, Cleveland, Ohio

Reported human renal homografts vary widely in survival time and function. Inasmuch as rejection of the homograft probably is on an immunologic basis,[8] one might expect histologic changes similar to hypersensitivity diseases, such as experimental glomerulonephritis. This type of reaction has been infrequent in reported human renal homografts.

REPORT OF CASE

Clinical Course

An 11-year-old white boy seemed to be well until 3 days prior to admission, when he first complained of abdominal pain, partially relieved by vomiting. After blood transfusion at another hospital, he was noted to be oliguric, and was transferred to Babies and Children's Hospital.

Physical examination revealed a lethargic, acutely ill child. Blood pressure was 180/110, pulse 100 per min., and respirations 34 per min. Eye grounds were normal, and the heart was not enlarged. There was moderate tenderness in the left costovertebral angle.

Laboratory data were as follows: urinalysis revealed 4+ albuminuria, 10 to 15 red blood cells, and 10 to 15 white blood cells per high-power field. The hemoglobin was 7.0 Gm. per 100 ml. Blood urea nitrogen was 228 mg. per 100 ml. and creatinine 17 mg. per 100 ml. Sodium was 135 mEq., potassium 9.2 mEq., and carbon dioxide 5.8 mEq. per l. Blood pH was 7.11.

Initial treatment included intravenous fluids, insulin, exchange resins, reserpine, and apresoline. On the third hospital day, hemodialysis with the artificial kidney was performed, and, on the fourth hospital day, cystotomy was performed, and suprapubic catheter drainage established. At operation, conspicuous hypertrophy of the urinary bladder was observed. Retrograde pyelograms revealed bilateral hydronephrosis and hydroureter. After operation, the output of urine increased to between 100 and 500 ml. per day. The patient's condition gradually became worse, however, and, on the fourteenth hospital day, a second hemodialysis was performed. Because of the grave prognosis, a human renal homotransplant was suggested.

On the twenty-first hospital day, a kidney was obtained from a 30-year-old woman, dead on arrival at the hospital. This kidney was kept sterile and packed in ice for a period of approximately 1 hr., while the patient's vessels were being prepared. This was performed because of experimental evidence that cooling of the kidney permits longer survival under anoxic conditions.[18] Between 2 and 3 hr. elapsed between the time of death and completion of transplantation. Autopsy of the donor revealed hepatic portal cirrhosis with diffuse, fatty metamorphosis. No other significant lesions were observed, and toxicologic studies were negative.

Transplantation was performed according to the technic of Hume and associates.[8] The renal artery was anastomosed end-to-end with the profunda femoris artery; the renal vein was anastomosed end-to-side with the femoral vein; the ureter was brought out through a separate skin incision laterally. The kidney was covered with a skin graft. At operation, no leakage was apparent at the anastomoses, and the patient tolerated the procedure well. Cysteine was administered orally, inasmuch as laboratory experiments at that time[17] suggested improved survival of renal homografts in dogs treated with cysteine.

After operation, the output of urine from

Received, January 28, 1960; revision received, March 31; accepted for publication April 13.

Dr. Krieg is Resident in Pathology; Dr. Bolande is Associate Professor of Pathology; Dr. Holden is Oliver H. Payne Professor of Surgery and Director, Department of Surgery; Dr. Hubay is Associate Professor of Surgery; and Dr. Persky is Associate Professor of Urology.

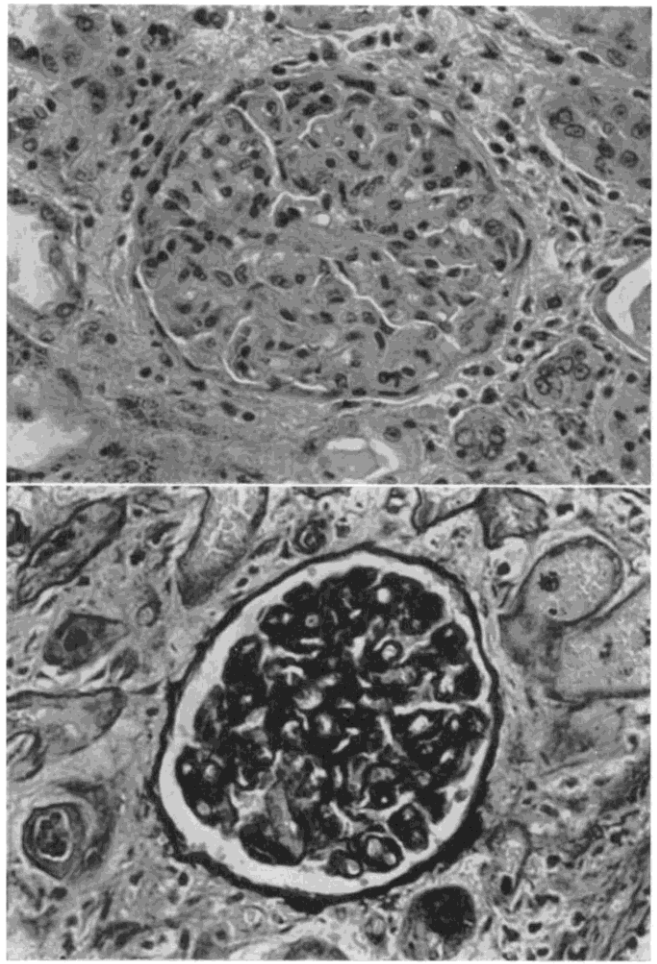


FIG. 1 (upper). Transplanted kidney. The glomerular tufts are larger than normal and ischemic, with thick eosinophilic basement membranes. The number of endothelial nuclei seems to be somewhat increased. There is renal tubular degeneration, with hemoglobin casts. In the interstitial tissue, edema and extravasated red blood cells are present. Hematoxylin and eosin. × 400.

FIG. 2 (lower). Transplanted kidney. The thick glomerular capillary basement membranes are intensely stained. The glomerulus is large and ischemic. This and Figure 1 are characteristic of membranous glomerulonephritis. Periodic acid-Schiff. × 400.

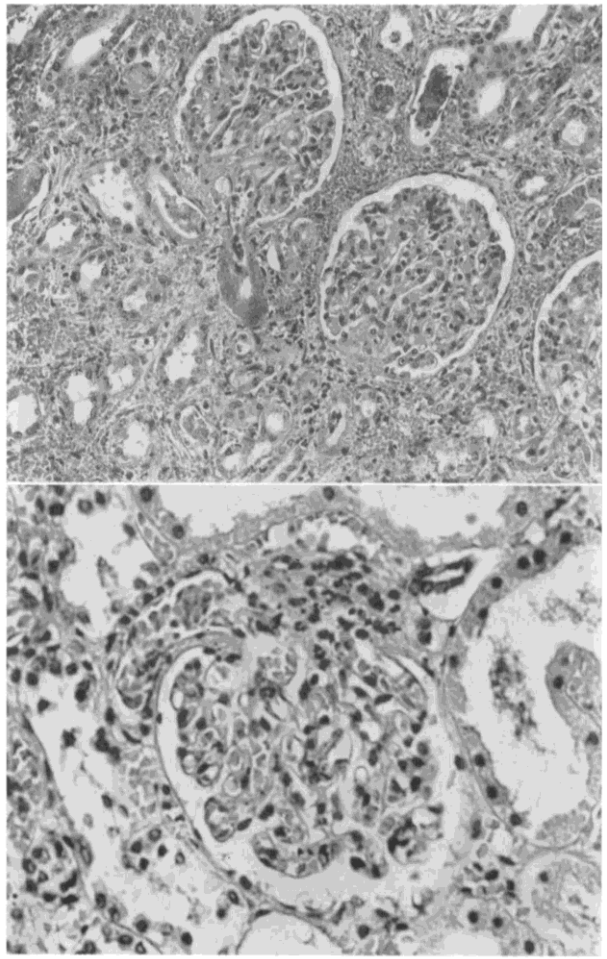


FIG. 3 (upper). Transplanted kidney. Arteriolar fibrinoid necrosis is prominent. Changes of membranous glomerulonephritis are present; also, tubular degeneration with casts and interstitial hemorrhage may be observed. Hematoxylin and eosin. × 200.

FIG. 4 (lower). Donor's second kidney, not transplanted. The thin, delicate glomerular capillaries, normal tubules, and lack of interstitial hemorrhage or infiltrate are conspicuously different from the transplanted kidney. Hematoxylin and eosin. × 400.

Earlier data--- recurrent MPGN 1970

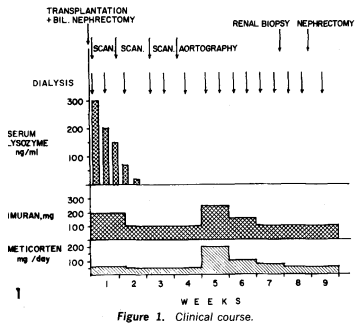


Figure 1. Clinical course.

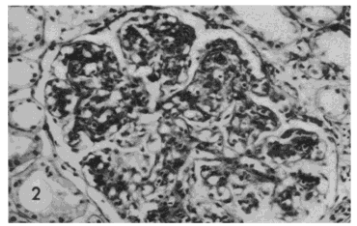


Figure 2. Glomerulus, showing accentuated lobulation, increased cellularity, with moderate numbers of polymorphonuclear leukocytes. Periodic acid-Schiff stain, original magnification × 450.

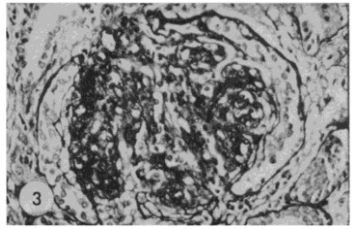


Figure 3. Marked proliferation of cells, lining Bowman's capsule. Glomerular scarring, involving only part of the tuft. Methenamine silver stain, original magnification × 250.

Postoperatively, 60 mg of Meticorten® and 200 mg of Imuran were given daily for the first ten days. Throughout this period and the subsequent fifty days, the patient remained anuric (Figure 1). On the second postoperative day, an I^{131} Hippuran® renal scan revealed good up-take, indicating vascularization, but no excretion of the dye. Identical findings were recorded in repeat scans on the eighth and seventeenth postoperative days. On the twenty-fourth postoperative day aortography was undertaken, which confirmed the patency of the main renal artery.

On the twenty-eighth day a therapeutic trial of increased immunosuppression was instituted, in the belief that the continuing anuria was caused by rejection. Despite the administration of Imuran in doses of 250 mg daily and Meticorten 200 mg daily, for seven days, the anuria persisted. The patient's general condition was maintained by intermittent dialysis.

On the fiftieth postoperative day, in the face of persisting anuria, a renal biopsy was performed. On the basis of the histopathologic findings, which showed diffuse proliferative glomerulonephritis, the grafted kidney was removed. Since then, the patient has been maintained in good general health by repeated hemodialysis.

PATHOLOGIC FINDINGS

The first biopsy specimen, obtained in 1966, showed the following features: All glomeruli were abnormal. They showed prominent lobulation (Figure 2) with marked increase in cellularity. In most of the glomeruli the hypercellularity was intracapillary, but in a few of them epithelial capsular crescents were seen (Figure 3). Capillary basement membrane thickening was noted. The glomerular capillary lumens contained a moderate number of leukocytes. Focal fibrinoid changes were noted in some capillary loops. Interstitial inflammation was seen and polymorphonuclear leukocytes were prominent, sometimes appearing as small interstitial abscesses.

The patient's kidneys, removed at the time of the transplantation, weighed 70 gm each, and the histologic findings were compatible with a diagnosis of chronic sclerosing glomerulonephritis.

The biopsy specimen obtained on the fiftieth post-transplantation day of the grafted kidney contained only 5 glomeruli. All showed proliferative changes, a slightly increased number of intracapillary cells and abundant cres-

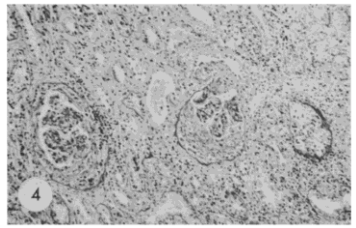


Figure 4. The renal allograft shows marked crescent formations. Periodic acid-Schiff stain, original magnification × 100.

Fulminatingly Progressive Recurrent Glomerulonephritis in a Renal Allograft

JOSEPH ROSENFELD, M.D.
JOSEPH LEVI, M.D.
MICHAEL ROBSON, M.D.
ALBERT PICK, M.D.
MINA BEN-BASSAT, M.D.
Tel-Aviv, Israel

The recurrence of glomerulonephritis in the transplanted kidney is one of the most serious hazards precluding viability of the graft. We describe a patient who received a kidney from his mother and in whom recurrent glomerulonephritis and persistent anuria rapidly developed in the postoperative period. Increased serum muramidase levels in the first two weeks suggested the possibility of acute tubular necrosis as a cause for the anuria. Subsequently, the return of the muramidase levels to those that existed before transplantation, accompanied by serum complement levels of zero and by "humps" observed in the electron microscopic picture of a biopsy specimen of the grafted kidney, made the diagnosis of recurrent glomerulonephritis the most likely explanation for the clinical evolution.

It is emphasized that, in the early post-transplantation period, in the differential diagnosis of anuria, the possibility of rapidly recurrent glomerulonephritis should be considered in addition to acute tubular necrosis and acute rejection.

The success of renal transplantation has been hampered on occasion by the recurrence of the recipient's original disease in the transplanted kidney, especially when the patient was suffering from glomerulonephritis [1]. Thus in a recent study Glassock et al. [2] reported that of twenty-two patients whose original disease has been glomerulonephritis, the disease recurred in eleven following the transplantation of an isograft. Porter et al. [3] reported the appearance of recurrent glomerulonephritis in three patients with renal allografts.

In most of the cases described the lesion of the transplanted kidney was a slowly progressive process. We describe another patient with rapidly developing recurrent glomerulonephritis, characterized by persistent anuria in the post-transplantation period.

CASE REPORT

This seventeen year old boy (Y.H.) was seen for the first time in our hospital in 1965 at the age of thirteen with an acute glomerulonephritis following follicular tonsillitis. At that time a renal biopsy specimen showed features compatible with a diagnosis of proliferative glomerulonephritis. Progressive deterioration in renal function followed his initial admission, and within two years his endogenous creatinine clearance decreased from 60 to 3 ml/minute. His clinical course was characterized by hypertension unresponsive to the usual drug therapy and by frequent attacks of left ventricular failure.

An indwelling Scribner shunt was inserted and hemodialysis was begun. Two months after institution of periodic hemodialysis his mother donated a kidney which was transplanted into the patient. Both were of blood group "A" and lymphocytotoxicity was negative. Removal of the donor kidney was difficult, owing to the extreme obesity of the mother, and the kidney was traumatized. Because of technical difficulties associated with the anastomosis, there was a prolonged cold ischemic time of seventy minutes. During the operation, bilateral nephrectomy was performed.

From the Department of Medicine and The Renal Unit, The Protein Laboratory and the Department of Pathology, Beilinson Medical Center, Tel-Aviv University Medical School, Tel-Aviv, Israel. Requests for reprints should be addressed to Dr. J. B. Rosenfeld, Beilinson Medical Center, P.O.B. 85, Petah-Tikvah, Israel. Manuscript received January 22, 1970.

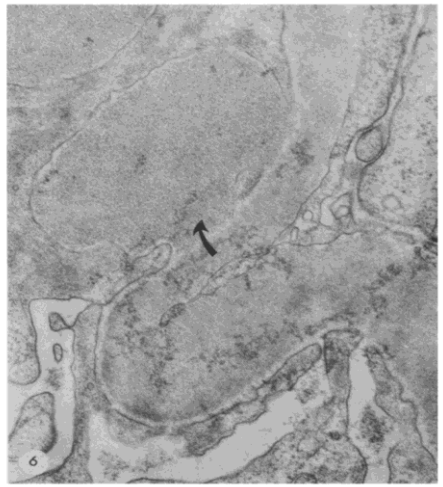


Figure 6. Electron micrograph of the renal allograft. Part of the glomerular capillary loop showing a "hump" (arrow) on the epithelial side of the capillary basement membrane. Uranyl acetate, lead citrate stain, original magnification × 10,000.

Figure 7. Immunofluorescent microscopy of the glomerulus showing lumpy-bumpy patterns of IgM and B,C globulin deposition within the glomerular capillaries of the removed kidney.

Recurrent Glomerulonephritis After Renal Transplantation 1978

J Hamburger, J Crosnier, and L H Noel

Annual Review of Medicine

Table 1 Incidence of recurrent glomerulonephritis (GN) in the series of Necker Hospital, Paris, France

Type of GN	No. of patients	No. of cases with recurrence
Focal and segmental glomerulosclerosis	14	4
Membranous GN	2	0
Membrano-proliferative GN with subendothelial deposits	23	2
Membrano-proliferative GN with isolated C_3 deposits	4	3
Membrano-proliferative GN, lobular form	13	2
Dense deposits disease	11	8
Rapidly progressive GN	1	0
IgA mesangial deposits	20	9
Schönlein-Henoch purpura	6	1
Unclassified GN	72	—
Total	166	29

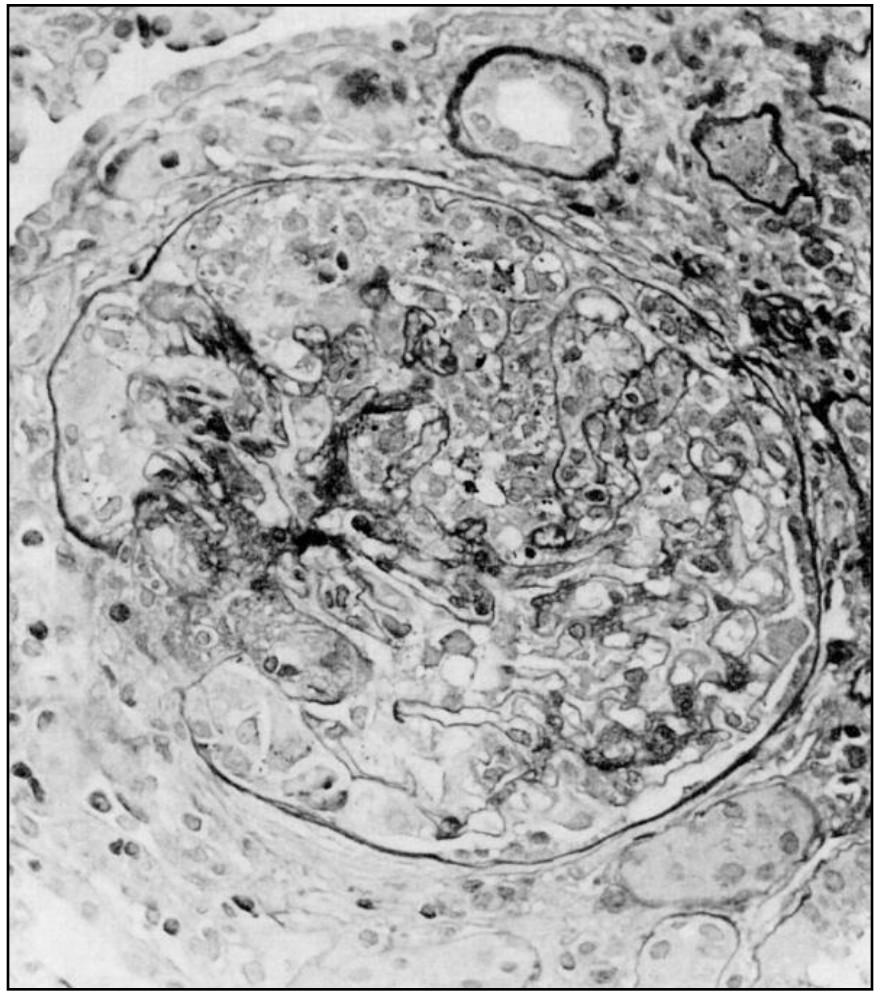
DE NOVO COLLAPSING GLOMERULOPATHY IN RENAL ALLOGRAFTS

Meehan, Shane; Pascual, Manuel; Williams, Winn; Tolkoff-Rubin, Nina; Delmonico, Francis; Cosimi, A; Colvin, Robert

Transplantation. 65(9):1192-1197, May 15, 1998

	CG de novo (n=5)	FSGS de novo (n=5)
Glomeruli		
Visceral epithelial cell swelling and hypercellularity (>1+)[a]	5[a]	0
PAS+ podocyte droplets	4	1
Capillary collapse		
Segmental	4	5[b]
Global	3	0
Foam cells	1	1
Hyaline accumulation	2	5
Adhesions	0	4
Ischemic wrinkling of the GBM[c]	4	2
GBM duplication	4	3
Mesangial matrix expansion	0	4
Mesangial hypercellularity	1	1
Blood vessels		
Hyaline arteriolosclerosis (>1+)	4	1
Arterial intimal fibrosis (>1+)	3	3
Interstitium		
Fibrosis		
Diffuse	4	1
Focal	1	4

[a] Grade: 0=none, 1+=mild, 2+=moderate, 3+=severe.
[b] Segmental collapse associated with capillary loop hyaline.
[c] Abbreviation used in table: GBM, glomerular basement membrane.



RECURRENT AND DE NOVO GLOMERULAR DISEASE AFTER RENAL TRANSPLANTATION: A Report from Renal Allograft Disease Registry (RADR) 1999

Center	Total no.	%	Recurrent/de novo disease no.	%
MCW[a]	1002	20.4	64	6.4
WU	784	15.9	16	2.0
UL	744	15.2	5	0.7
UCSF	1497	30.5	39	2.6
UC	429	8.7	26	6.0
UW	457	9.3	17	3.7
Total	4913	100	167	3.4

[a] MCW, Medical College of Wisconsin, Milwaukee, WI; WU, Washington University, St. Louis, MO; UL, University of Louisville, Louisville, KY; UCSF, University of California at San Francisco, San Francisco, CA; UC, University of Cincinnati, Cincinnati, OH; UW, University of Washington, Seattle, WA.

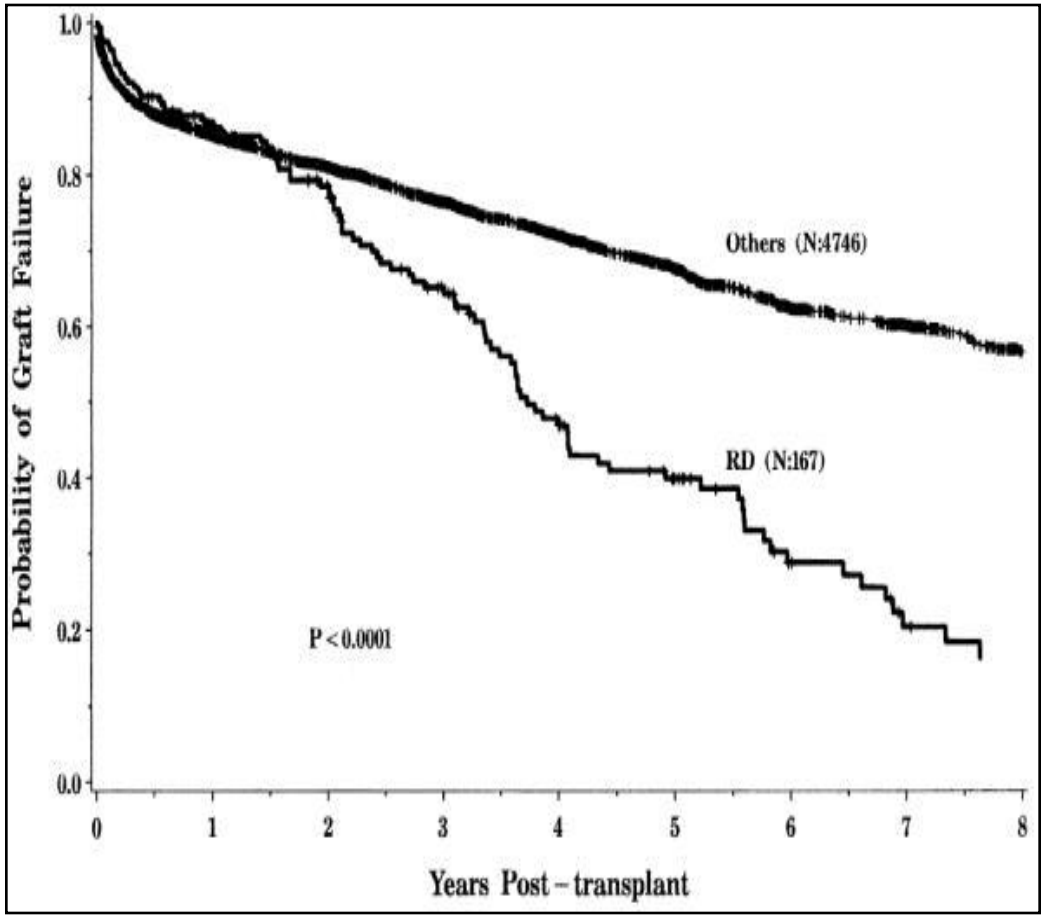
Disease Types (N=167)	%	Mean age (yr)	Male (gender) (%)	CAD transplant (%)
1) FSGS (57)	34.1	34.5	64.9	82.5
2) IgAN (22)	13.2	38.8	72.7	59
3) MPGN (18)	10.8	36.3	50	83.3
4) MN (16)	9.6	35.8	93.8	68.8
5) DN (19)	11.4	45.2	78.9	89.5
6) HUS/TTP (8)	4.8	32.9	50	50
7) Others (27)[a]	16.1	39.4	63	74
P value	NA	0.0585	0.104	0.099

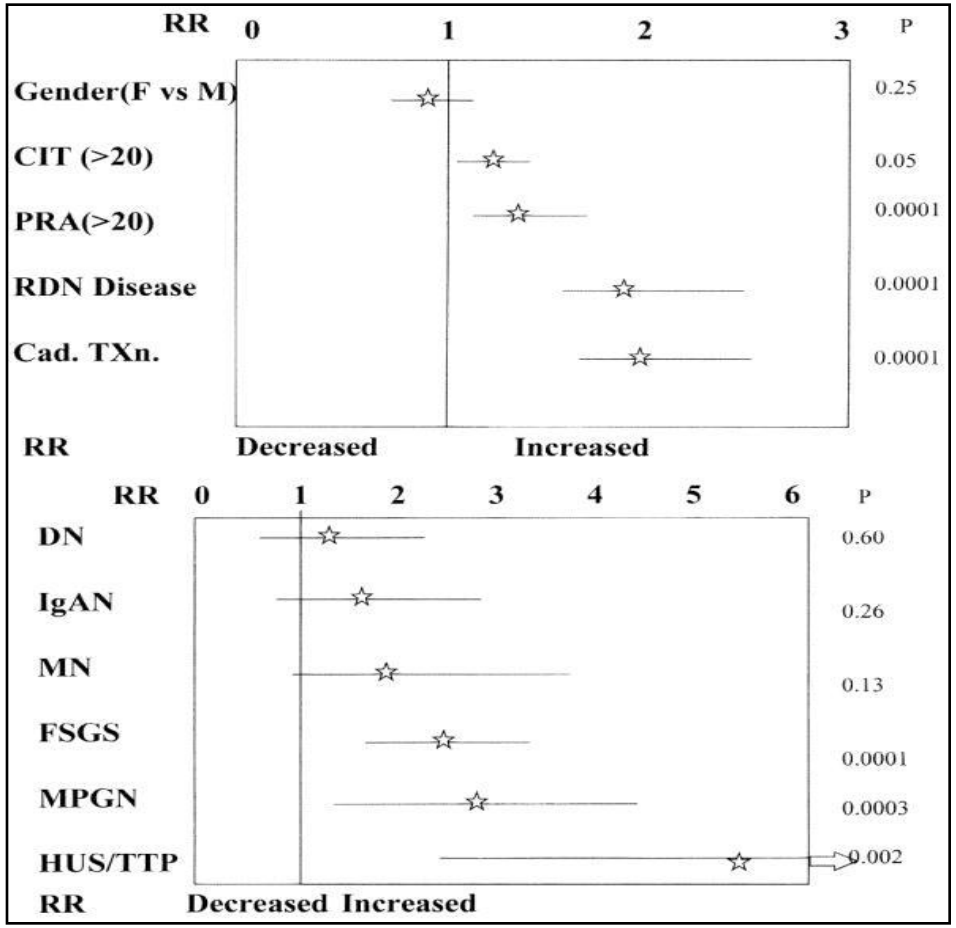
[a] Others are: immune complex GN, 12; vasculitis (crescentic GN), 6; SLE, 3; Anti-GBM, 2; oxalosis, 2; miscellaneous, 2.

	Graft failure N	Graft failure %	Kidney half-life (days)
FSGS (57)	37	65	1244
MPGN (18)	12	66	1330
MN (16)	7	44	1193
IgAN (22)	9	41	1619
DN (19)	10	53	2357
HUS/TTP (8)	5	63	215
Others (27)	12	44	1461
Total 167	92	55%	1360 (1229–1619)

Hariharan S et al. Transplantation 1999

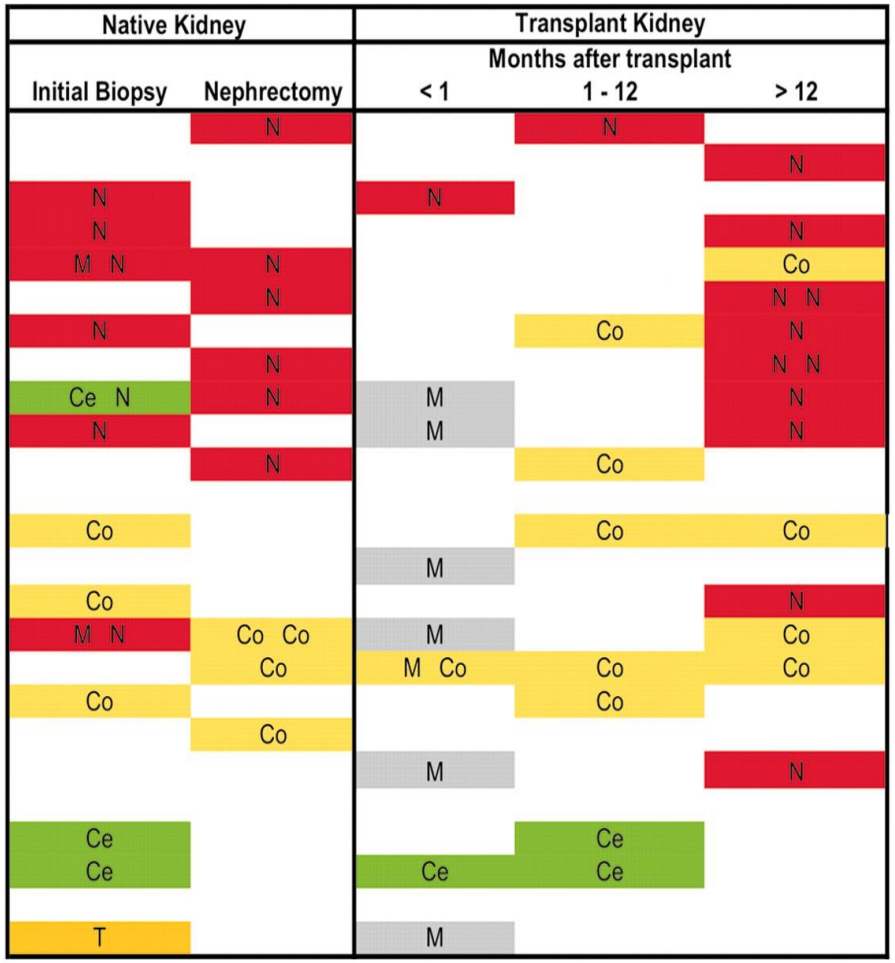
RECURRENT AND DE NOVO GLOMERULAR DISEASE AFTER RENAL TRANSPLANTATION: A Report from Renal Allograft Disease Registry (RADR)





Hariharan S et al. Transplantation 1999

FSGS variants in patients' native and transplant kidneys



[a]Second transplant

N: FSGS Not otherwise specified; Co: Collapsing FSGS; Ce: Cellular FSGS;
T: Tip lesion FSGS; M: Minimal change disease-like lesion

		Native Kidney							Transplant						
Patient	Gender	Age (yr)	Indication(s)	Proteinuria[b]	Variant	No. of glomeruli	IF	EM	Age at biopsy (yr)	Time to biopsy (d)	Indication(s)	Proteinuria[b]	Variant	No. of glomeruli	IF	EM
1	M	19	P/Cr	7.2	Collapsing	14	IgM, C3, C1q	NA	23	120	Np, Cr	NA	Collapsing	17	NA	NA
										425	Cr	8.9	Collapsing	10	IgM	FP
									26[c]	3[c]	Cr[c]	2[c]	MC[c]	42[c]	NA[c]	FP[c]
2	M	52	P	NA	Cellular	8	NA	NA	61	45	Cr	3.3	Cellular	17	IgM, IgA	NA
3	M	35	Np	24	Cellular	>25	IgA, IgM	NA	38	30	Cr	10	Cellular	6	No	FP
									39	150	Np/Cr	17	Cellular	Ne	NA	NA
4	F	27	Ne	NA	NOS	A	NA	NA	18	150	Np	NA	NOS	7	IgG, IgA, IgM	NA
									23[c]	1460[c]	Cr[c]	2[c]	NOS[c]	>25[c]	No[c]	NA[c]
5	F	24	Np	8.7	NOS	20	IgM	NA	31	10	Cr/P	9	NOS	17	NA	FP
6	M	36	P	NA	NOS	8	IgM, C3	NA	45	2555	P	2.3	NOS	5	No	NA
7	M	13	Np	NA	Collapsing	30	IgM, IgG, C3, C1q	NA	20	548	Np, Cr	6	NOS	5	IgM	NA
8	F	2	NA	10.4	MC	15	Neg	NA	16	4015	Cr	NA	Collapsing	13	Neg	NA
		2	NA	2.8	NOS	6	NA	NA								
		3	NA	3.24	NOS	Ne	NA	NA								
9[e]	M	45	NA	NA	Tip lesion	30	NA	NA	57	5	Np, Cr	6	MC	10	Neg	FP
10	F	39	Ne	3+	NOS	Ne	IgM, C3	NA	40	393	P, Cr	4.5	NOS	>25	IgM, C3	FP
									42	1043	Cr	3+	NOS	17	IgM, C3	FP
11	M	6	Np	3+	MC	12	IgM	FP	7	2	P, R	6.1	MC	>25	IgM, C3	FP
		6	Np	6.4	NOS	>25	NA	FP	8	389	Np	11.8	Collapsing	Ne	IgM, C3	FP
		7	Np	13.7	Collapsing	Ne	IgM, C3	FP								
		7	Np	8.4	Collapsing	Ne	IgM, C3	NA								
12	M	49	Ne	2.3	Collapsing	Ne	IgM, C3	FP	49	4	P	10.0	MC	13	IgM, C3	FP
									49	7	R	4.7	Collapsing	3	IgM, C3	FP
									49	63	P, R	20.0	Collapsing	8	NA	NA
									51	645	Np, Ne	10.3	Collapsing	Ne	NA	NA
13	M	37	P	NA	Collapsing	9	IgM, C3	FP	40	206	Cr	14.4	Collapsing	7	IgM, C3	FP
14	F	54	P	9.2	NOS	9	IgM, C3	FP	56	237	P, Cr, R	10.3	Collapsing	5	IgM, C3	FP
									58	824	R	15.7	NOS	4	NA	FP
15	M	25	NA	NA	Collapsing	Ne	NA	NA	25	16	NA	1+	Rejection	7	NA	NA
									25	255	NA	3+	Necrosis[d]	Ne	NA	NA
									25[c]	53[c]	NA[c]	NA[c]	MC[c]	8[c]	NA[c]	FP[c]
									26[c]	347[c]	NA[c]	4+[c]	NOS[c]	12[c]	NA[c]	NA[c]
16	M	45	NA	NA	NOS	Ne	C3	NA	55	354	R	3.8	NOS	5	IgM, C3	FP
									57	851	P, R	3.8	NOS	4	NA	FP
17	M	3	P	3.2	Cellular	>25	NA	NA	15	7	P, Cr	17.9	MC	12	NA	FP
		15	Ne	10.8	NOS	Ne	IgM, C3	FP	19	1183	Cr	13.9	NOS	15	IgM, C3	FP
		15	Ne	10.8	NOS	Ne	IgM, C3	FP								
18	M	3	NA	Y	NOS	>25	C3	NA	3	24	NA	2+	MC	>25	NA	FP
									7	1470	NA	1.0	NOS	2	NA	NA
19	M	59	Ne	2+	NOS	Ne	IgM, C3	NA	59	108	P	5.0	Collapsing	2	IgM, C3	FP

[a]C1q: segmental C1q; C3, segmental C3; Cr, elevated creatinine; EM, electron microscopy; F, female; FP, foot process effacement; IF, immunofluorescence; IgA, segmental IgA; IgG, segmental IgG; IgM, segmental IgM; M, male; NA, data not available; Ne, nephrectomy; Neg, no immune deposition in IF; Np, nephrotic syndrome; P, proteinuria; R, r/o rejection.
[b]Proteinuria measured in g/24 h or on a scale from 0 to 4+.
[c] Second transplant.
[d]Nephrectomy showed severe necrosis.
[e]First two grafts were lost as a result of primary nonfunction.

IJpelaar et al. JASN 2008;19:2219-2224

Kidney Transplantation Outcomes across GN Subtypes in the United States

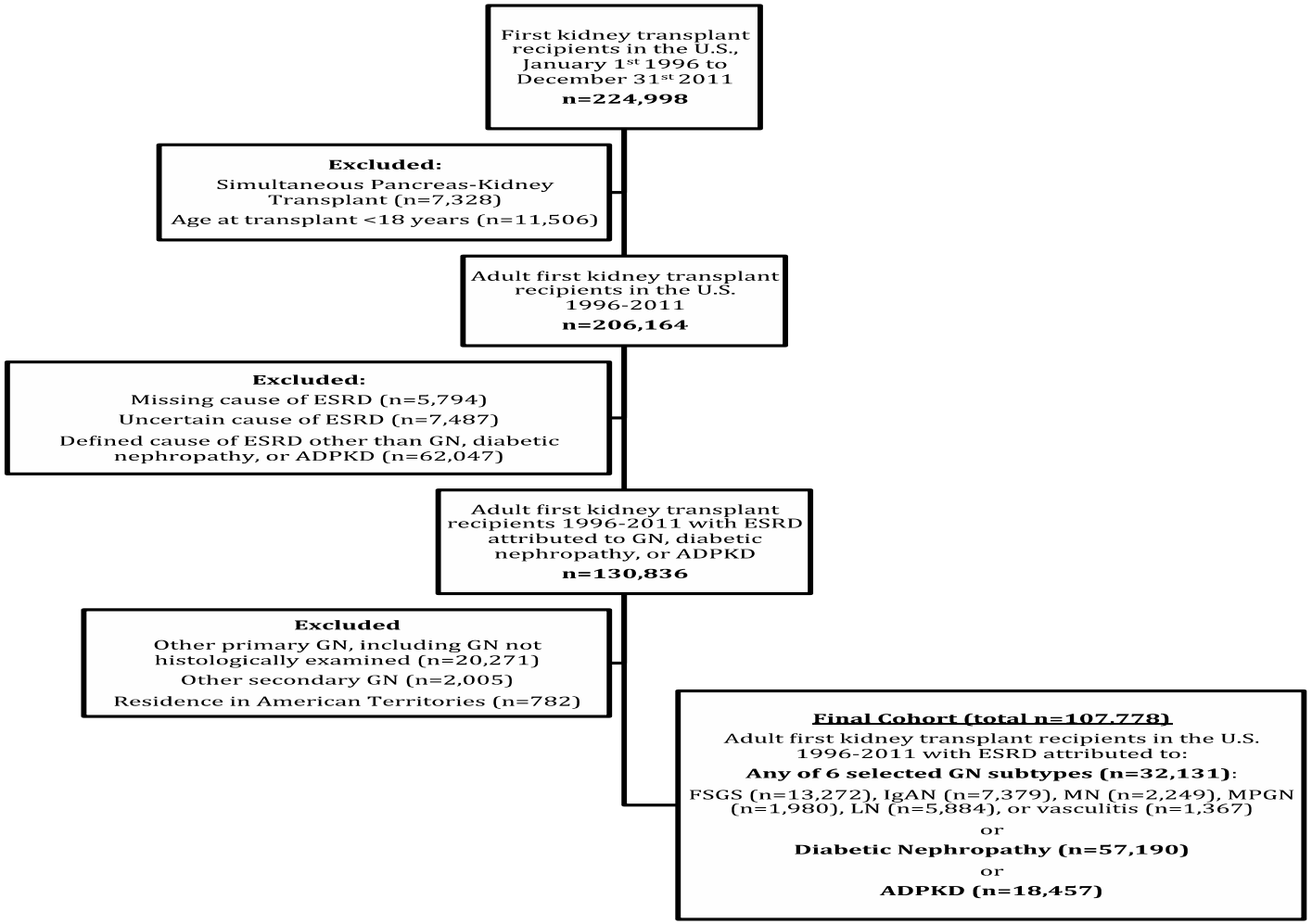
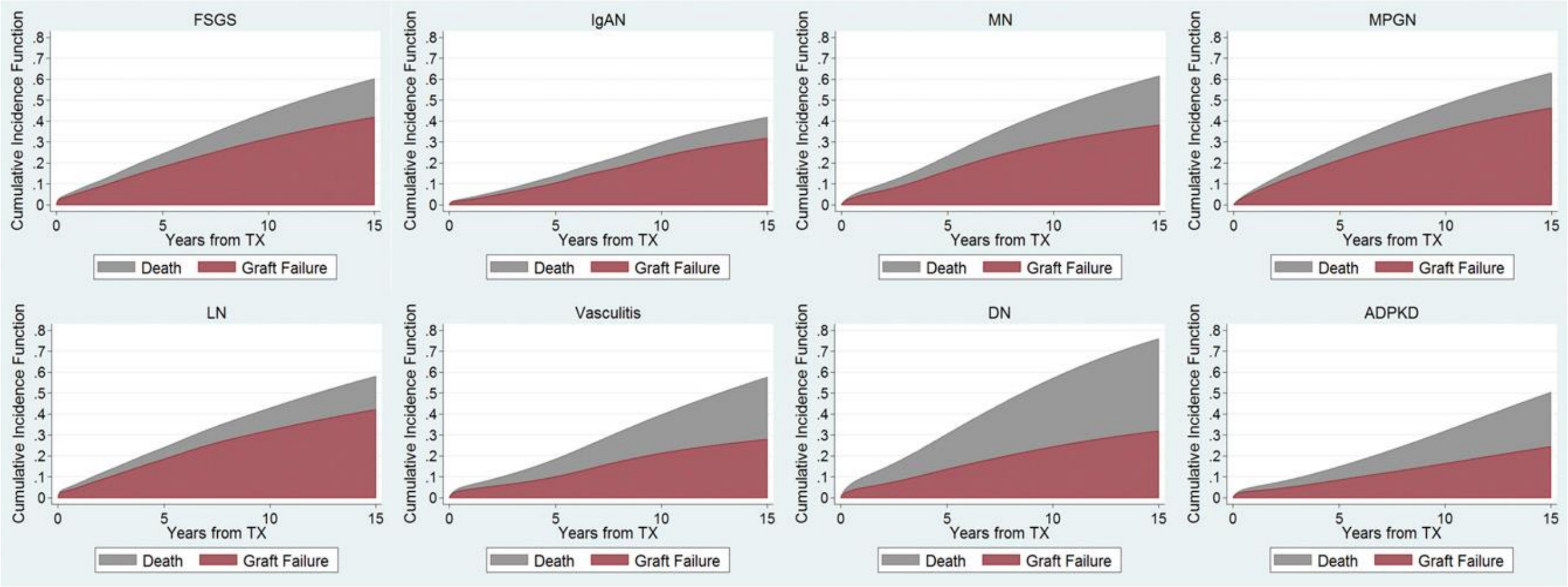


Figure 1. Assembly of the final study cohort of patients with ESRD due to GN, diabetic nephropathy, or autosomal dominant polycystic kidney disease (ADPKD).

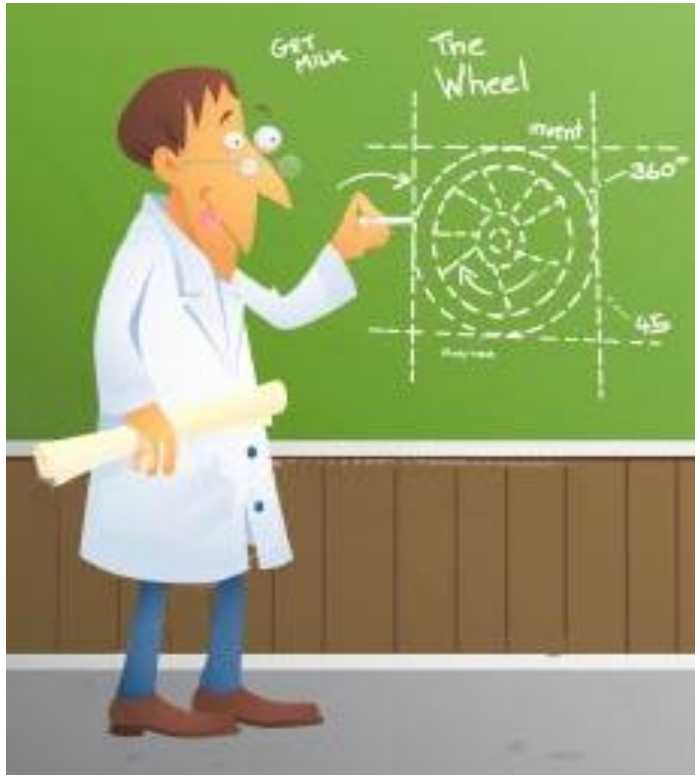
O'Shaughnessy et al. JASN 2016

Kidney Transplantation Outcomes across GN Subtypes in the United States



O'Shaughnessy et al. JASN 2016

THE GOAL IS



NOT to Reinvent GN recurrence

BUT To Connect ALL The Dots

Single Center’s Experience

- Johns Hopkins University: IgA, FSGS, MPGN, MN
- University of Alberta
- Virginia Commonwealth University
- Colombia
- Wisconsin University

IgA nephropathy--native

	Characterization	Clinical
IgA nephropathy	PATHOLOGY	CLINICAL FINDINGS
Native disease	IgA deposits with no histological glomerular changes IgA deposits with histological changes Light Microscopy: Global glomerulosclerosis (%) Segmental glomerulosclerosis (%) Hyalinosis Podocyte changes Glomerular capillary walls Mesangial matrix expansion Mesangial hypercellularity Endocapillary proliferation Crescents Karyorrhexis/ segmental necrotizing lesions Tubular injury Tubulitis Interstitial inflammation % interstitial fibrosis % Tubular atrophy Arteriosclerosis (cv) Arteriolar hyalinosis (ah) IF: EM: presence of deposits and distribution, Substructures % of podocyte foot process effacement	Demographics Age of onset Renal manifestations at onset Renal function eGFR Hematuria Proteinuria, UPCR at time of onset Co-morbidities Diabetes, Hypertension at onset Progression of the disease, time from onset to ESRD (eGFR, UPCR others) Therapy for glomerulopathy

IgA nephropathy--transplant

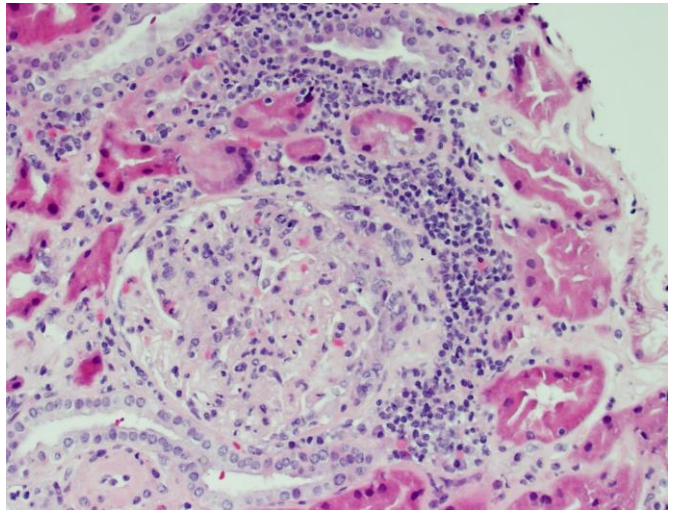
	Ch Characterization	Clinical
IgA nephropathy	PATHOLOGY	CLINICAL FINDINGS
Post Transplant	IgA deposits with no histological glomerular changes IgA deposits with histological changes Light Microscopy: Global glomerulosclerosis (%) Segmental glomerulosclerosis (%) Hyalinosis Podocyte changes Glomerular capillary walls Mesangial matrix expansion Mesangial hypercellularity Endocapillary proliferation Crescents Karyorrhexis/ segmental necrotizing lesions Tubular injury Tubulitis Interstitial inflammation % interstitial fibrosis % Tubular atrophy Arteriosclerosis (cv) Arteriolar hyalinosis (ah) IF: EM: presence of deposits and distribution, Substructures % of podocyte foot process effacement	Type of donor (Live, Deceased, cPRA, HLA mismatches) Desensitization Induction Maintenance immunosuppression Rejection episodes and type of rejections pre- post recurrence Infections pre-post recurrence Time of Onset of the pathological changes from transplantation Renal function at onset of recurrence Treatment of glomerulopathy Effect of treatment Resolution/persistence/progression in FU biopsies

IgA nephropathy--Elements to be analyzed

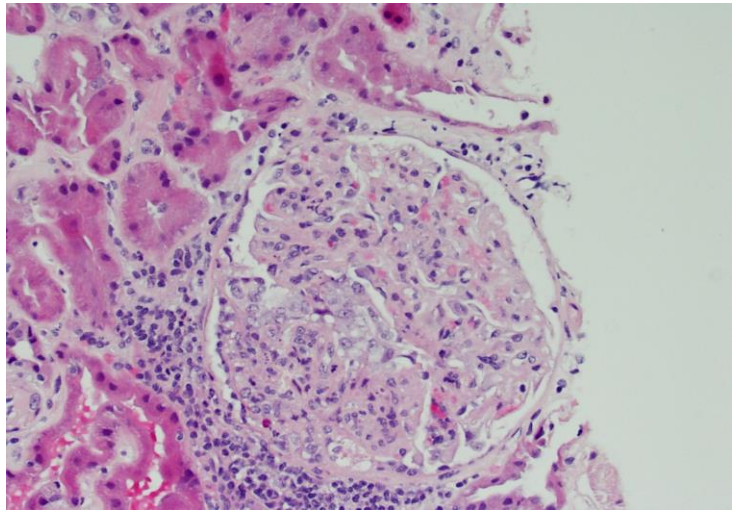
Frequency	Histological features at diagnosis	Time of onset post transplant
Predictors	Histological predictors	Clinical predictors: Demographics, Age, native dx, characteristics of the transplanted kidney (live/decease, HLA compatibility etc), eGFR, Hematuria, UPCR, therapy, episodes and types of rejection
Relation to native dx	Comparison with histological features in the native kidney	Demographics, Age, native dx, eGFR, Hematuria, UPCR, therapy, Progression of the native dx
Correlation with FSGS	FSGS associated with IgA; Podocyte injury	Effect on UPC: more if FSGS lesions
De Novo	IgA post transplant with no native IgA	Time/Lab changes

IgA Nephropathy

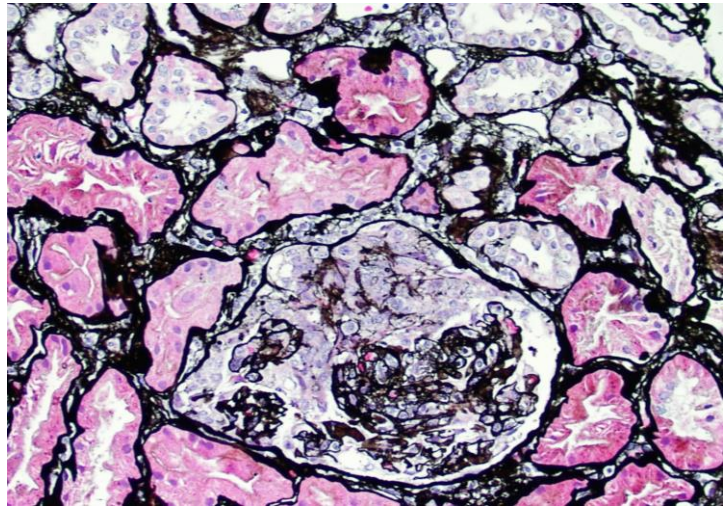
Focal proliferative with fibrocellular crescent

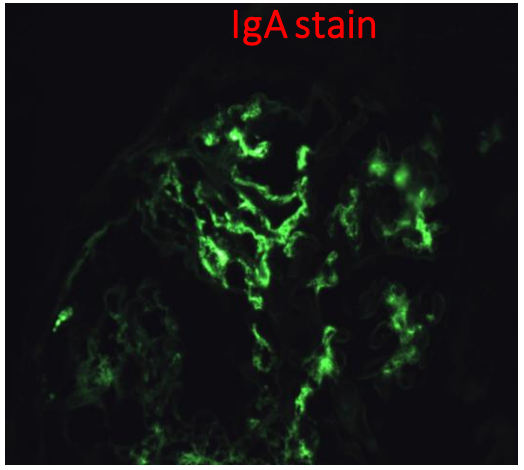


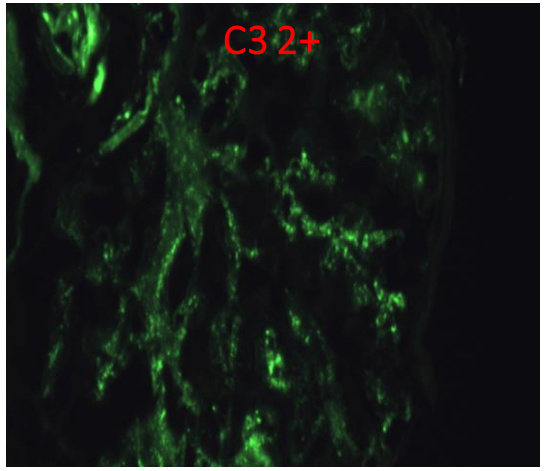
Focal proliferative GN with cellular crescent

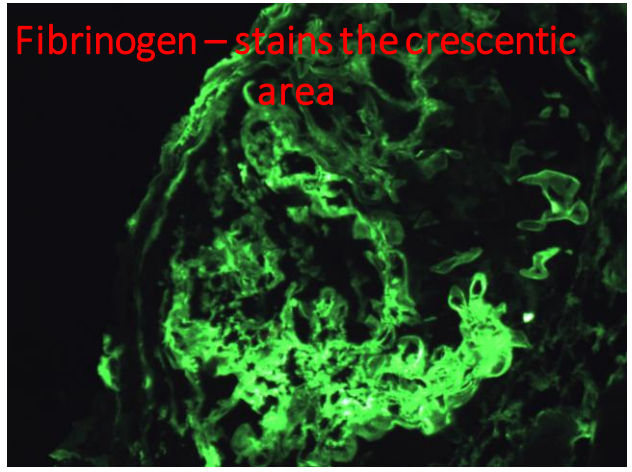


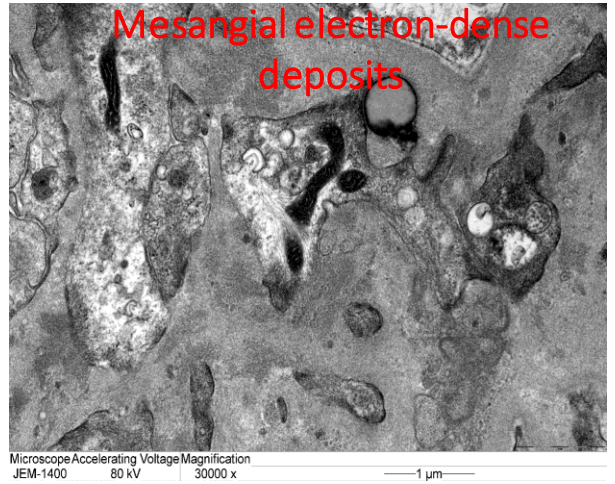
Crescent - silver stain







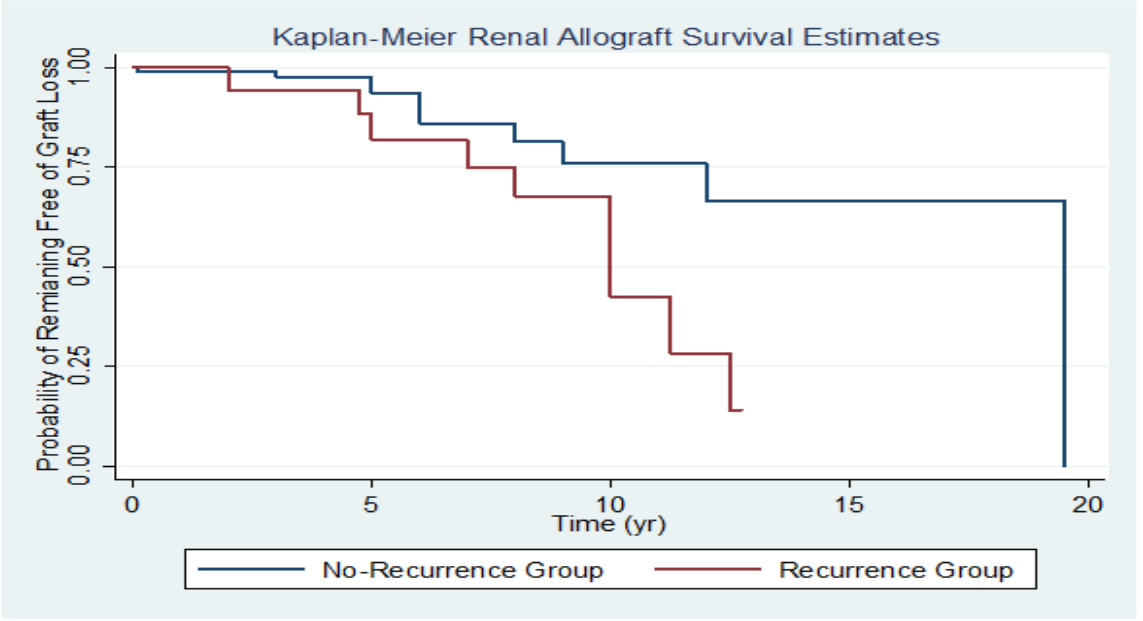




IgA Nephropathy, n=105 pts, 122 allografts

Clinical characteristic	Recurrent group (n=22) Allografts (n=23)	Non-recurrent group (n=82) Allografts (n=99)	P value
Male (%)	18 (82)	48 (58)	0.07
Mean age at diagnosis, years ± SD	29.4 ± 10.4	35.4 ± 14.3	0.11
Time from diagnosis to ESRD	2.4 ± 3.3	5.0 ± 0.9	0.32
Time from ESRD to transplant	1.4 ± 1.4	1.7 ± 1.6	0.64
UPC at diagnosis, g/g ± SD	4.4 ± 0.07	4.1 ± 6.7	0.17
Serum albumin at diagnosis, g/dL	4.3 ± 0.4	4.1 ± 0.6	NS
Mean age at transplant, years	37.7 ± 2.3	44 ± 1.3	0.05
Preemptive transplant (%)	4 (17)	26 (26)	0.53
Deceased	5	40	0.11
Living related	12	31	0.07
Living unrelated	6	28	0.78
Age at recurrence, years ± SD	44.3 ± 11.7	-	
Time to recurrence, years ± SD	6.75 ± 5.5	-	
Therapy after transplant			
ACEI/ARB (%)	14 (61)	31 (31)	0.002
Steroids (%)	17 (74)	84 (85)	NS
Cyclophosphamide (%)	2 (9)	1 (1)	NS
Rejections (%)	7 (30)	17 (17)	0.049
recent serum creatinine, mg/dL	2.7 ± 2.1	1.4 ± 0.8	0.0001
Mean most recent UPC ratio, g/g	1.6 ± 1.9	0.3 ± 0.8	0.0004
Graft failure (%)	13 (57)	10 (10)	0.0001
Time to Graft Failure, years ± SD	6.5 ± 5.1	10.4 ± 7.5	<0.0001

Parameters	Before recurrence	At recurrence	Most recent	p value
Mean RBC/ hpf ± SD	N/A	27 ± 50	3 ± 5	0.18
Mean UPC ratio, g/g ± SD	N/A	2 ± 2.2	1.6 ± 1.9	0.76
Mean serum creatinine, mg/dL ± SD	1.7 ± 0.8	2.9 ± 2.8	2.7 ± 2.1	0.06
Mean eGFR mL/min/1.73 m^2 ± SD	49 ± 20.5	37 ± 22	32 ± 25	0.04

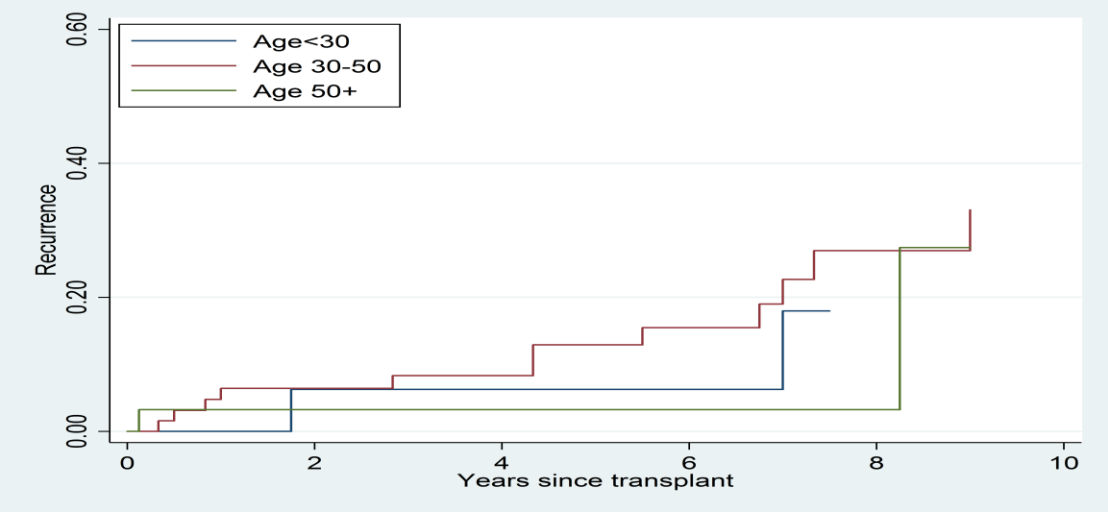


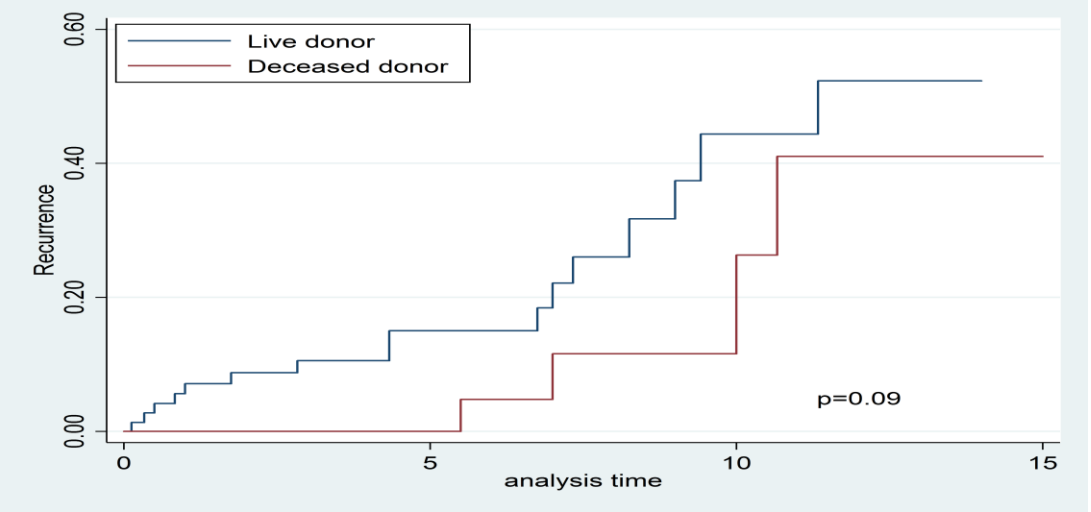
Nijim S & Alachkar N. Transplant Proc 2016

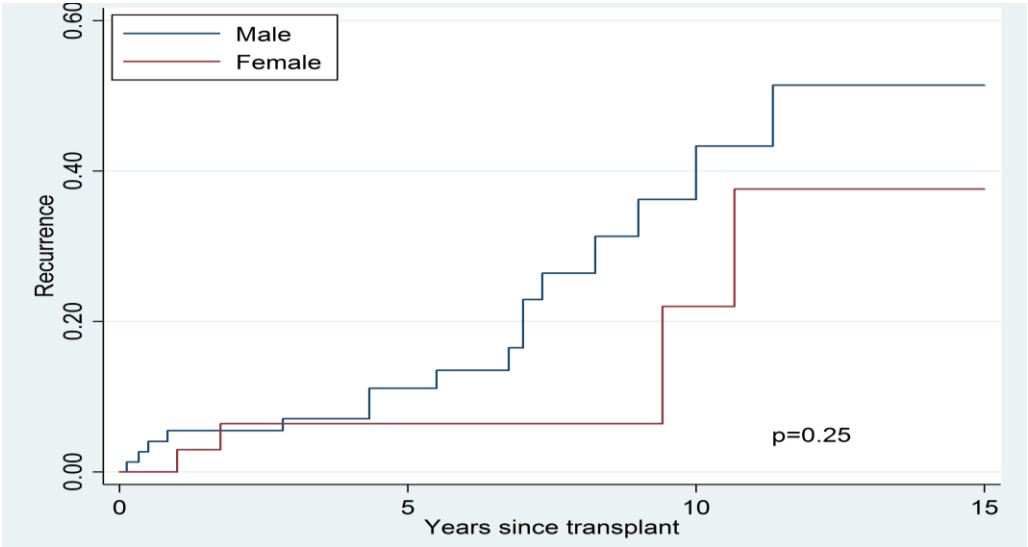
IgA Nephropathy, n=105 pts, 122 allografts

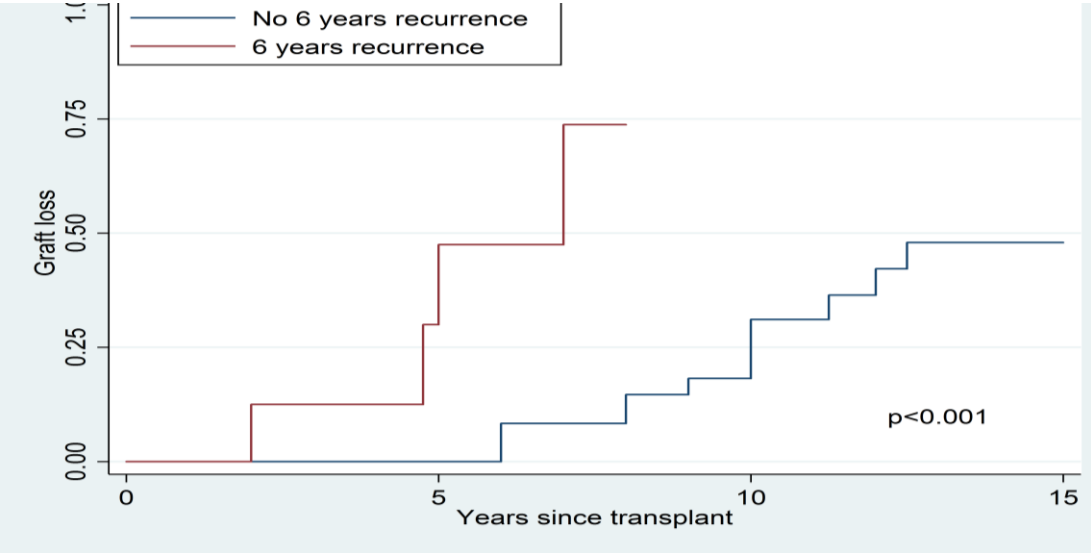
- Graft loss was attributed to recurrent IgA nephropathy if the renal allograft biopsy at the time of clinical graft failure demonstrated diffuse mesangial proliferation and glomerular sclerosis due to IgA deposits

RISK FACTORS OF RECURRENCE AND GRAFT SURVIVAL (n=62; with follow up of >6 years)









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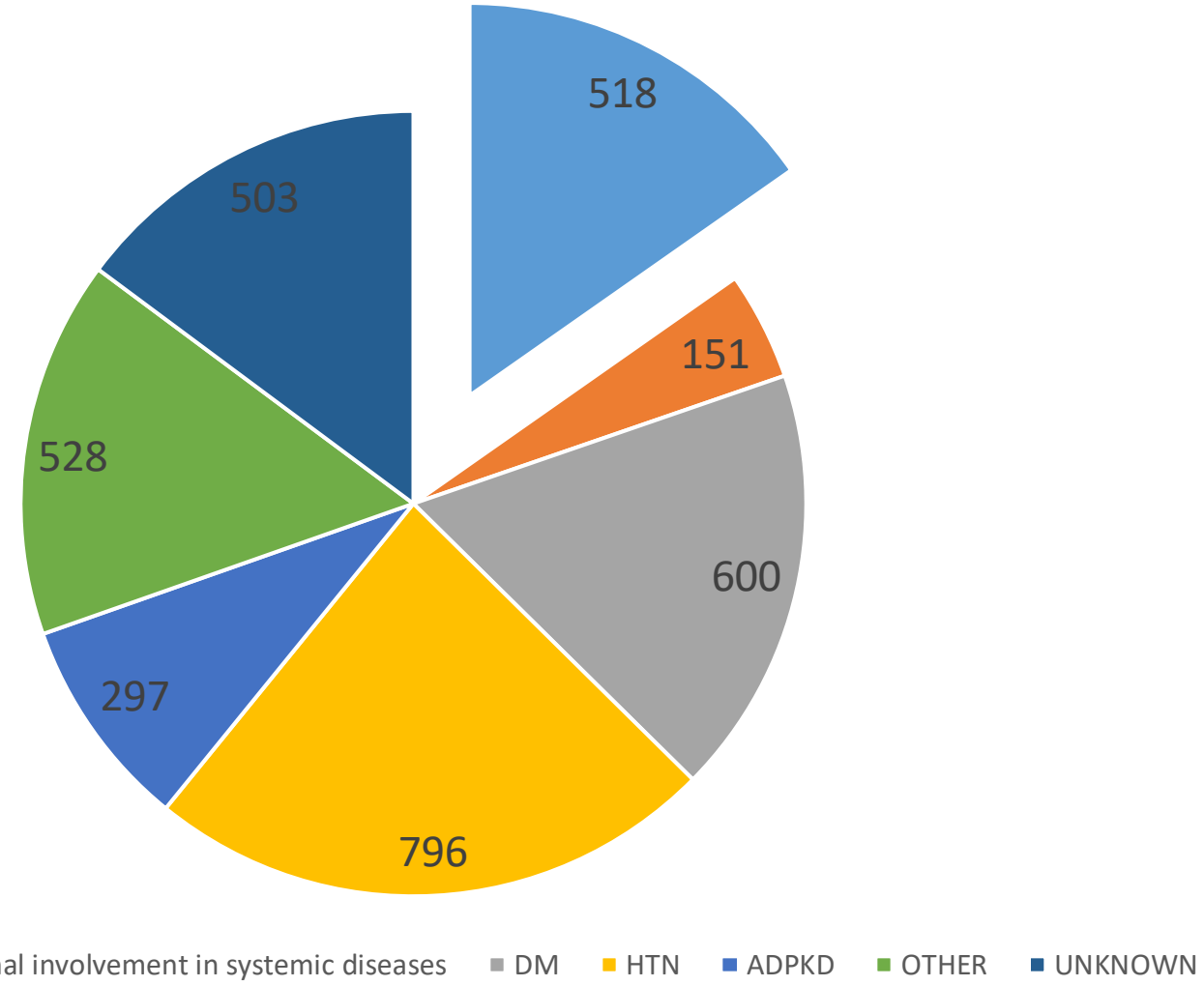
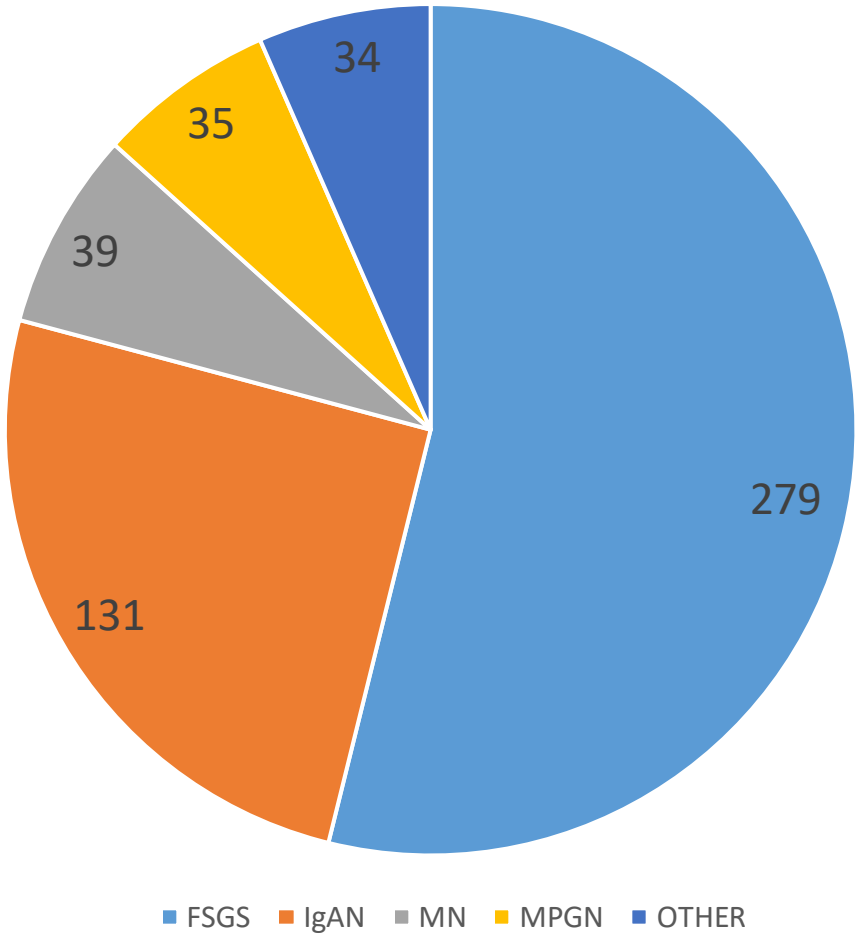
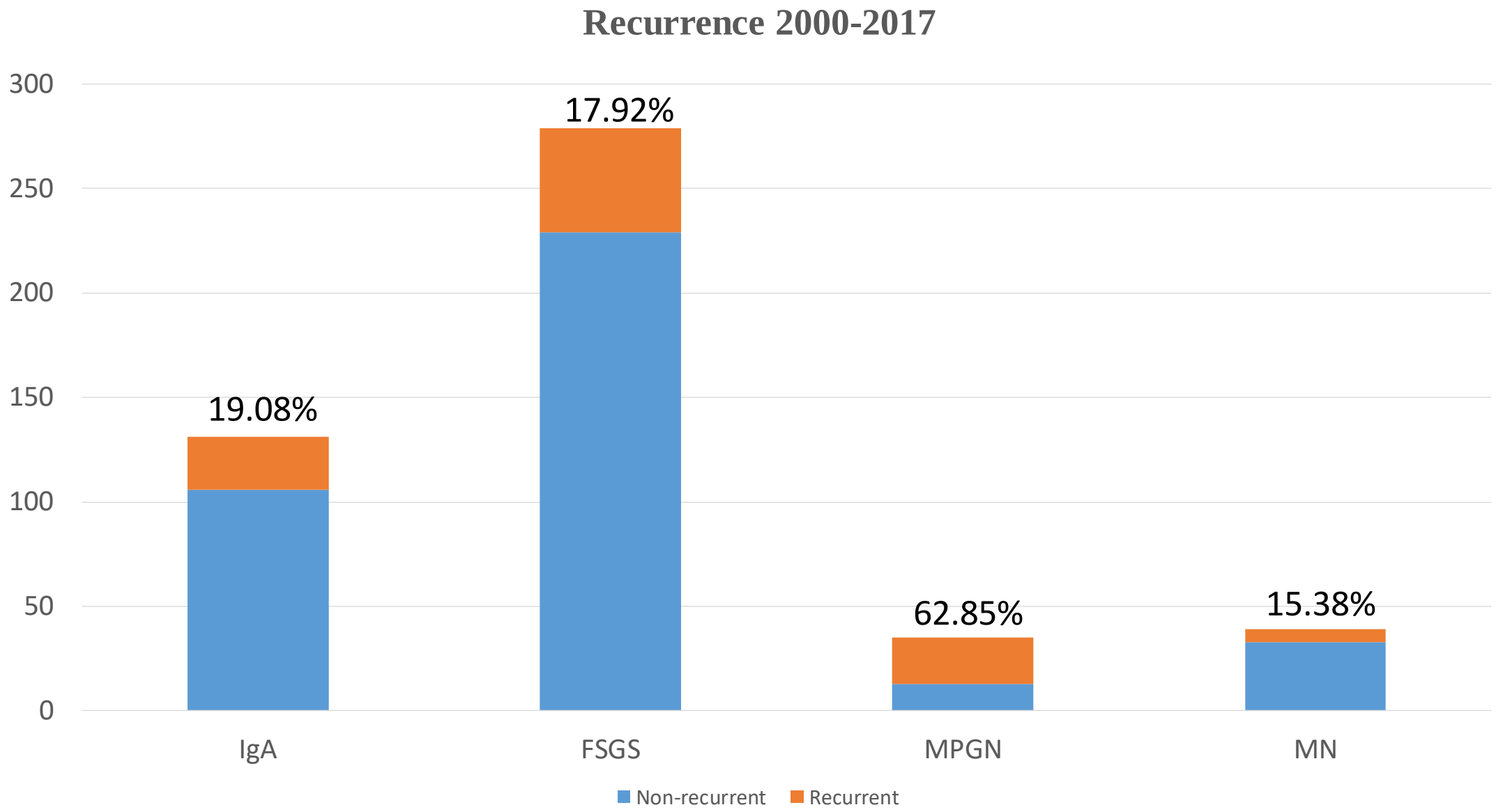
Causes of ESRD in transplanted patients from Jan 2000 to Nov 2016 (Total Tx 3393)

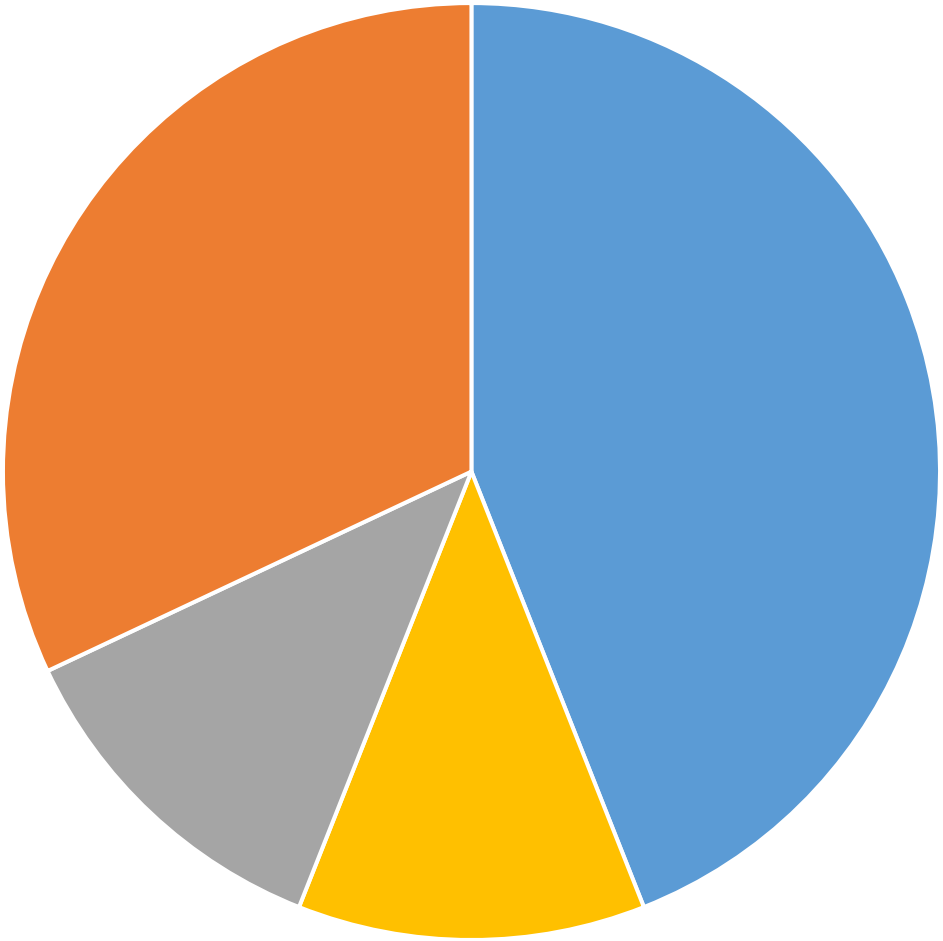


Primary GN (Total 518)

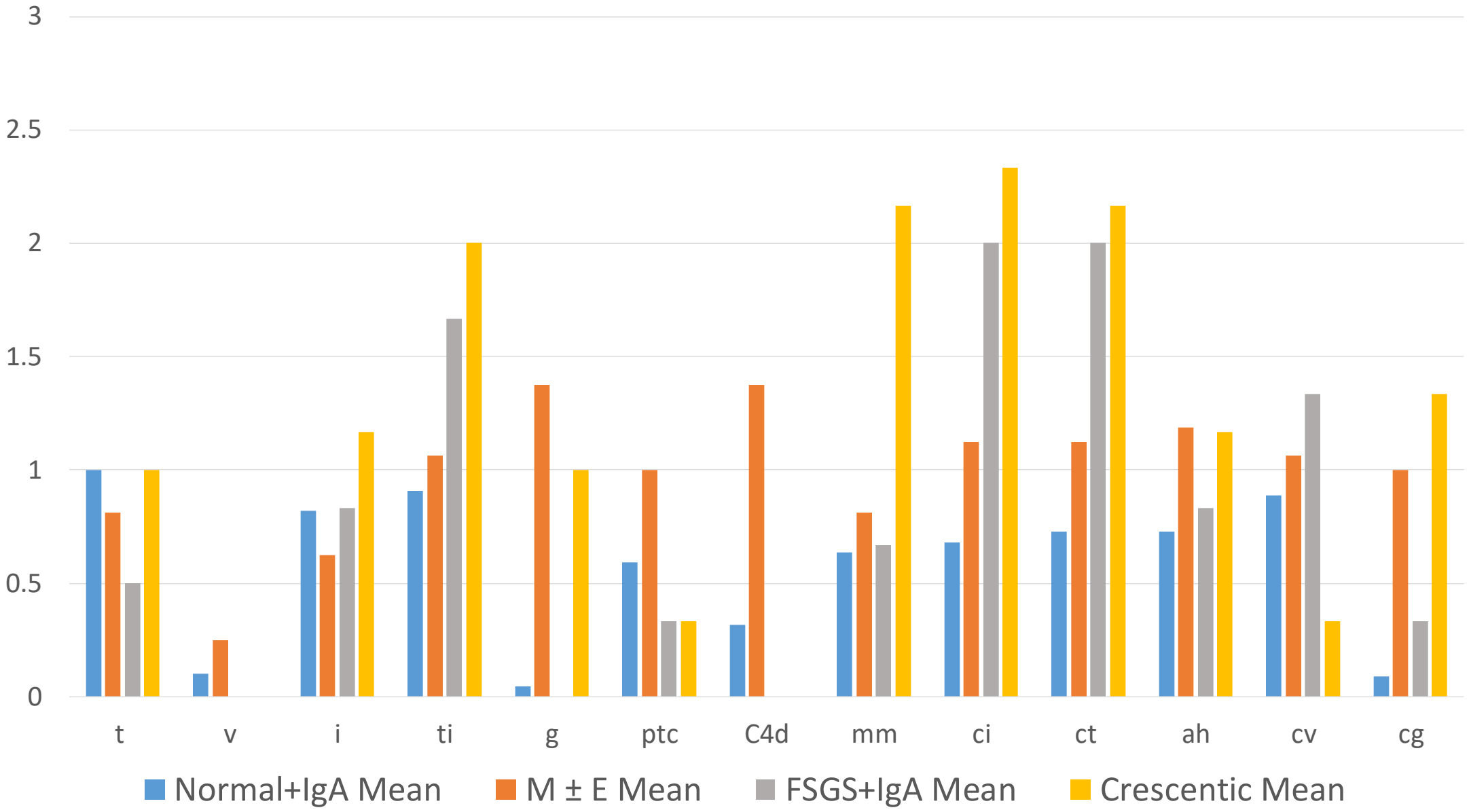


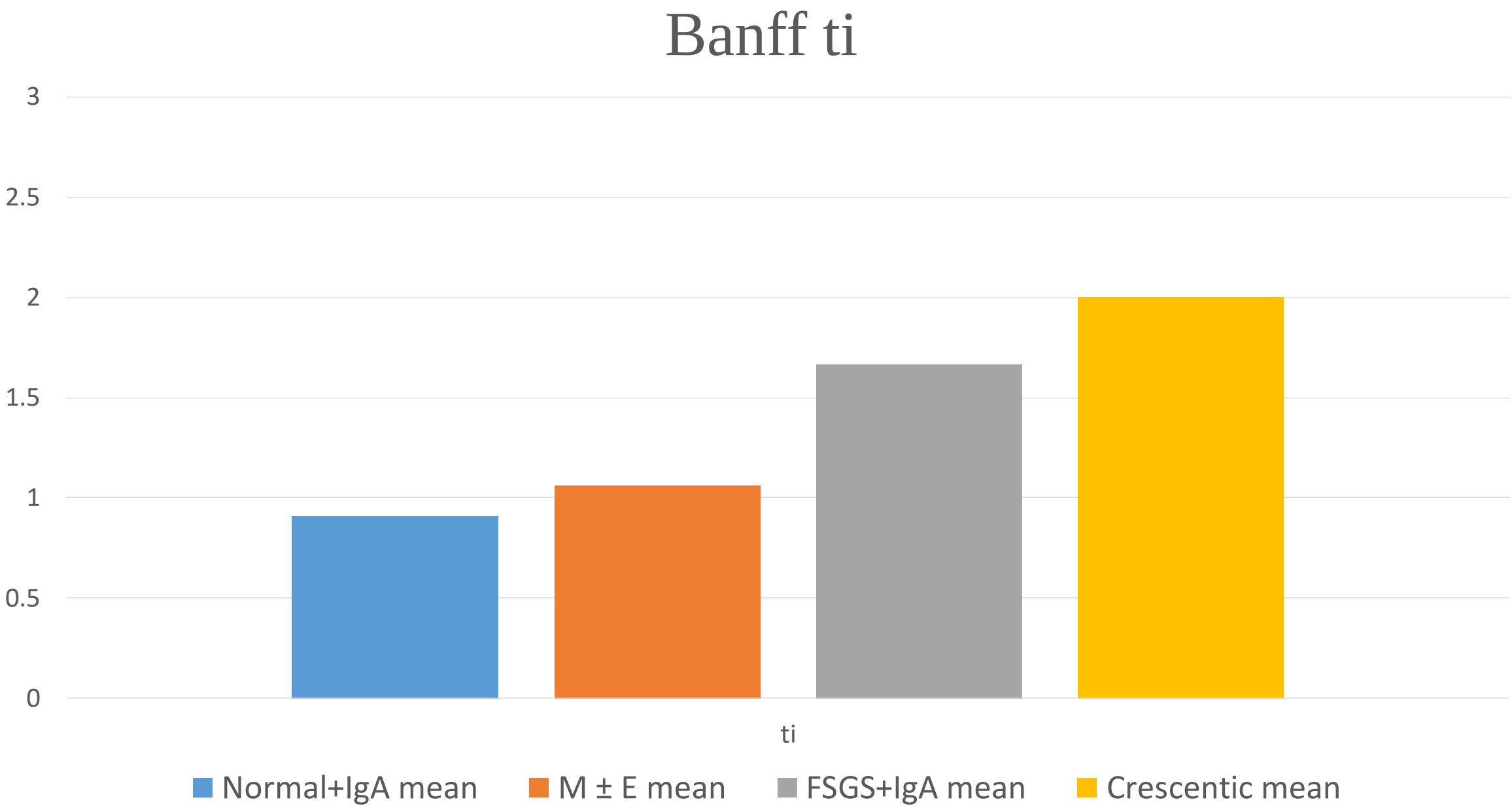

Recurrence 2000-2017
300
250
200
150
100
50
0
19.08%
17.92%
62.85%
15.38%
IgA
FSGS
MPGN
MN
Non-recurrent
Recurrent

Glomerular Changes IgA recurrence

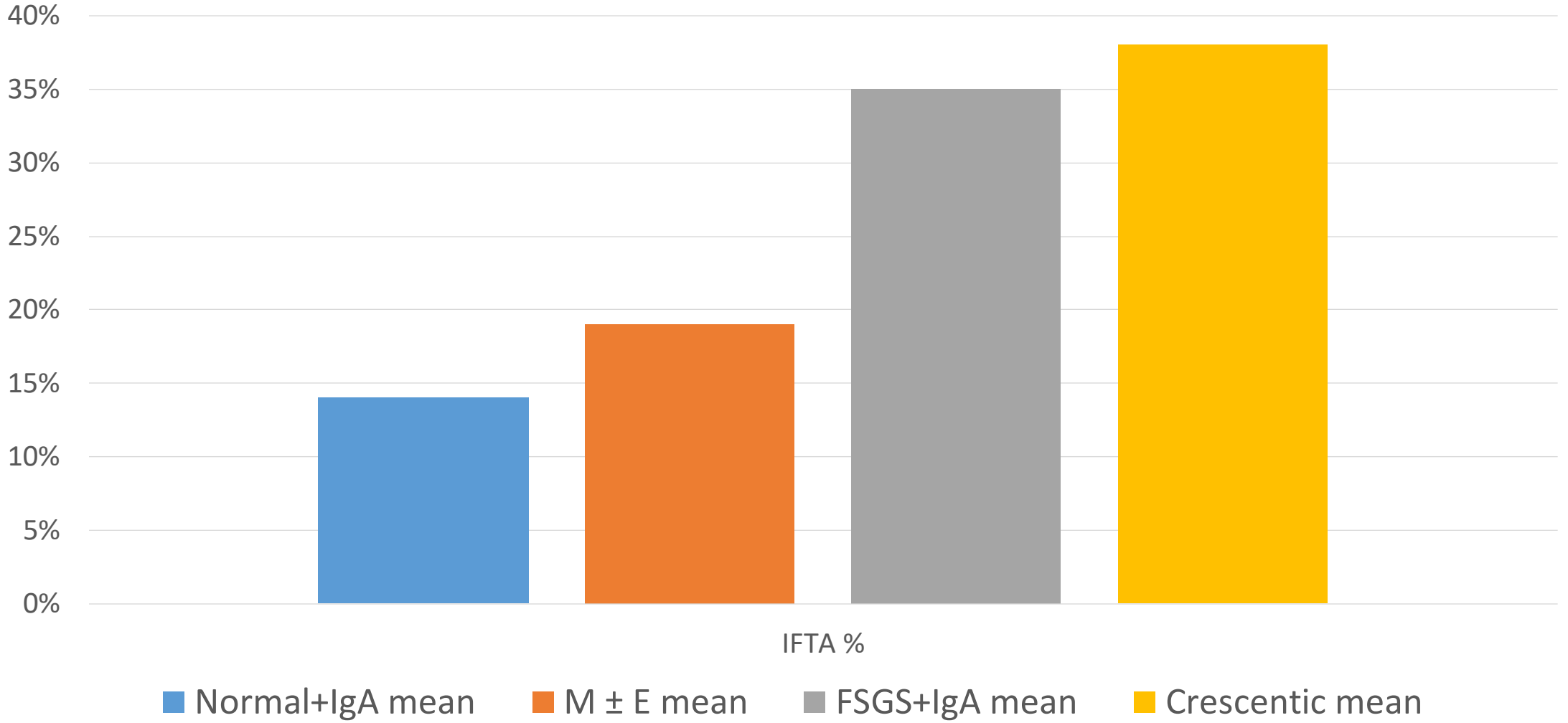


Banff

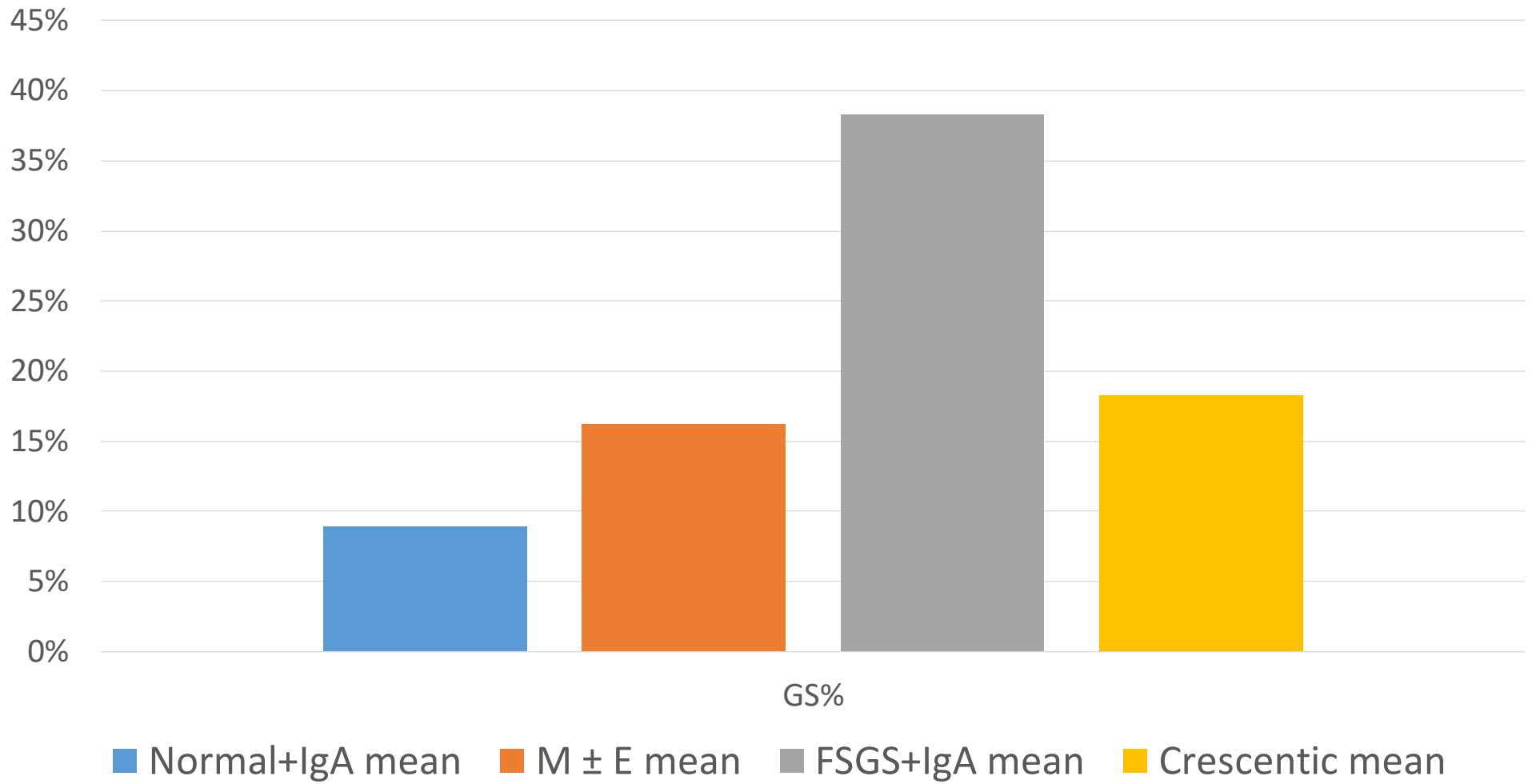

3
2.5
2
1.5
1
0.5
0
t
v
i
ti
g
ptc
C4d
mm
ci
ct
ah
cv
cg
Normal+IgA Mean
M ± E Mean
FSGS+IgA Mean
Crescentic Mean

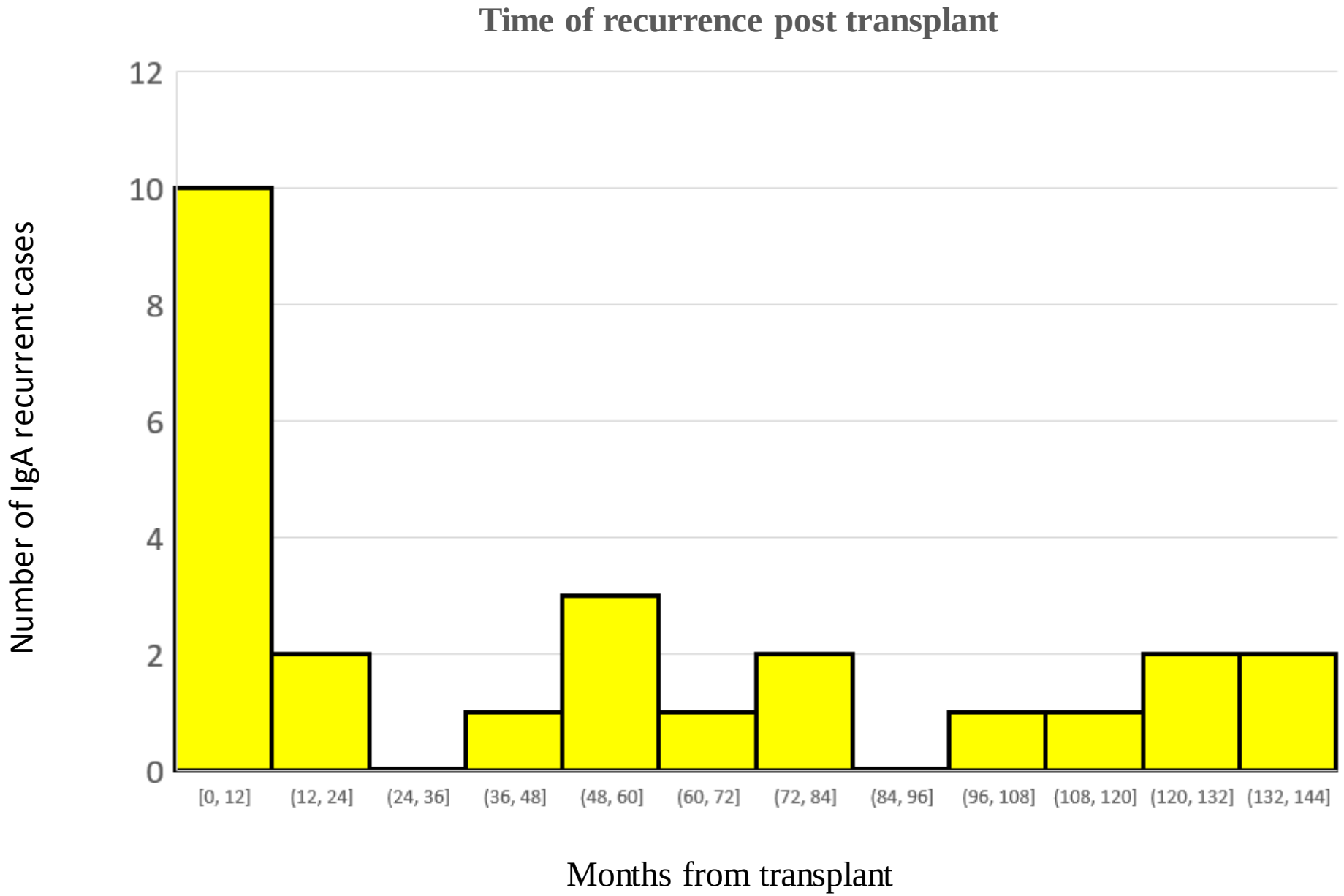

Banff ti
3
2.5
2
1.5
1
0.5
0
ti
Normal+IgA mean
M ± E mean
FSGS+IgA mean
Crescentic mean

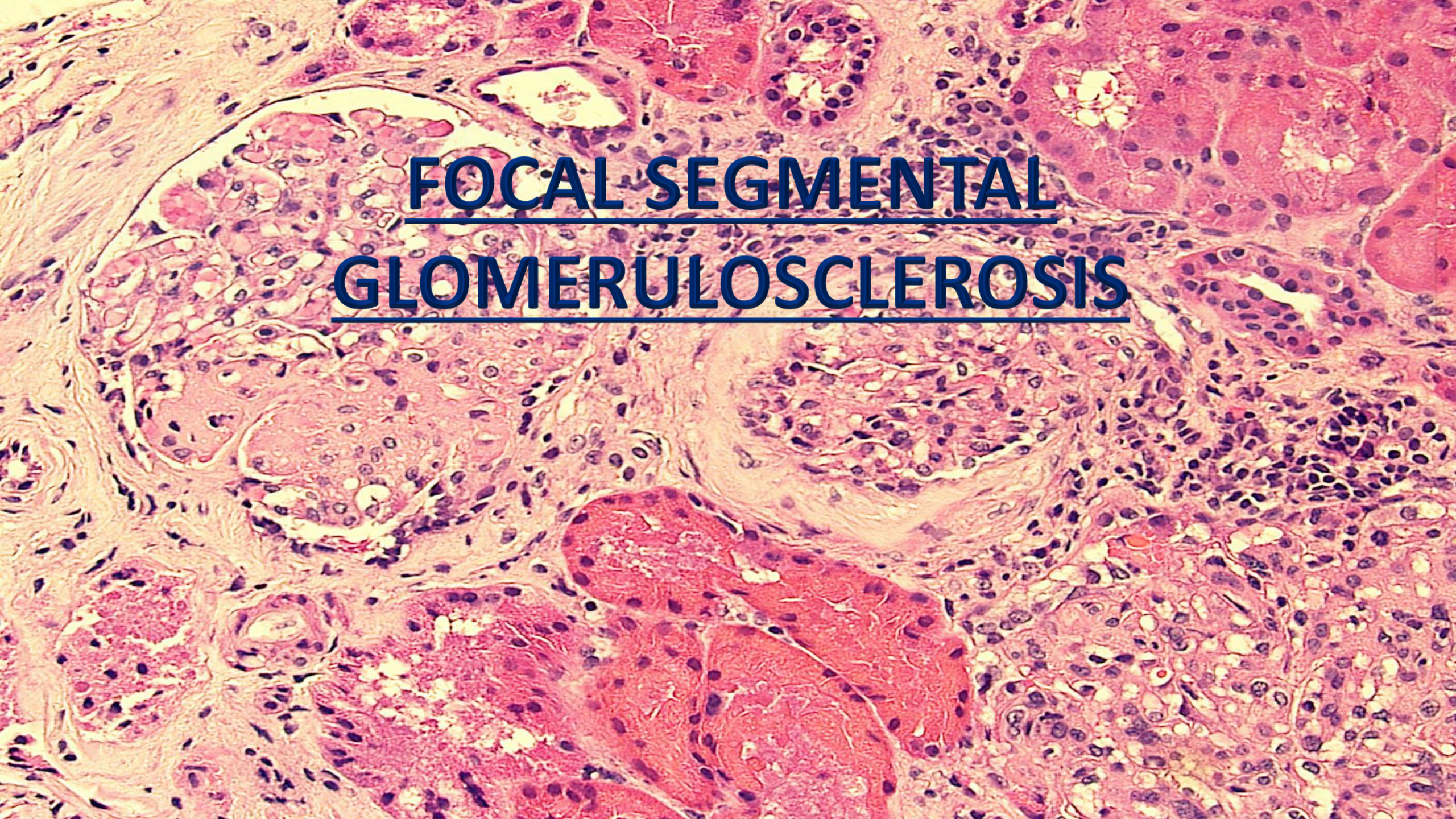
IFTA %


40%
35%
30%
25%
20%
15%
10%
5%
0%
IFTA %
Normal+IgA mean
M ± E mean
FSGS+IgA mean
Crescentic mean

Global Glomerulosclerosis (GS) %




Time of recurrence post transplant
Number of IgA recurrent cases
12
10
8
6
4
2
0
[0, 12]
(12, 24]
(24, 36]
(36, 48]
(48, 60]
(60, 72]
(72, 84]
(84, 96]
(96, 108]
(108, 120]
(120, 132]
(132, 144]
Months from transplant


FOCAL SEGMENTAL
GLOMERULOSCLEROSIS

Early findings of FSGS

- Podocytes injury: focal detachment from the GBM

- Podocytes loose their adhesive phenotype in early FSGS, which may contribute to the detachment of podocytes from the GBM

Kemeny E et al. Clin Nephrol. 1995 Feb;43(2):71-83

Retrospective Data, n=25

- 9 recurrent FSGS had histopathological data available on their primary FSGS:
- 3 had collapsing, 2 tip, and 4 classic (NOS)
- 4 had histopathological data also available at the time of recurrence: 3 had concordant FSGS variants, and 1 had primary classic FSGS, had recurrent collapsing FSGS post transplant

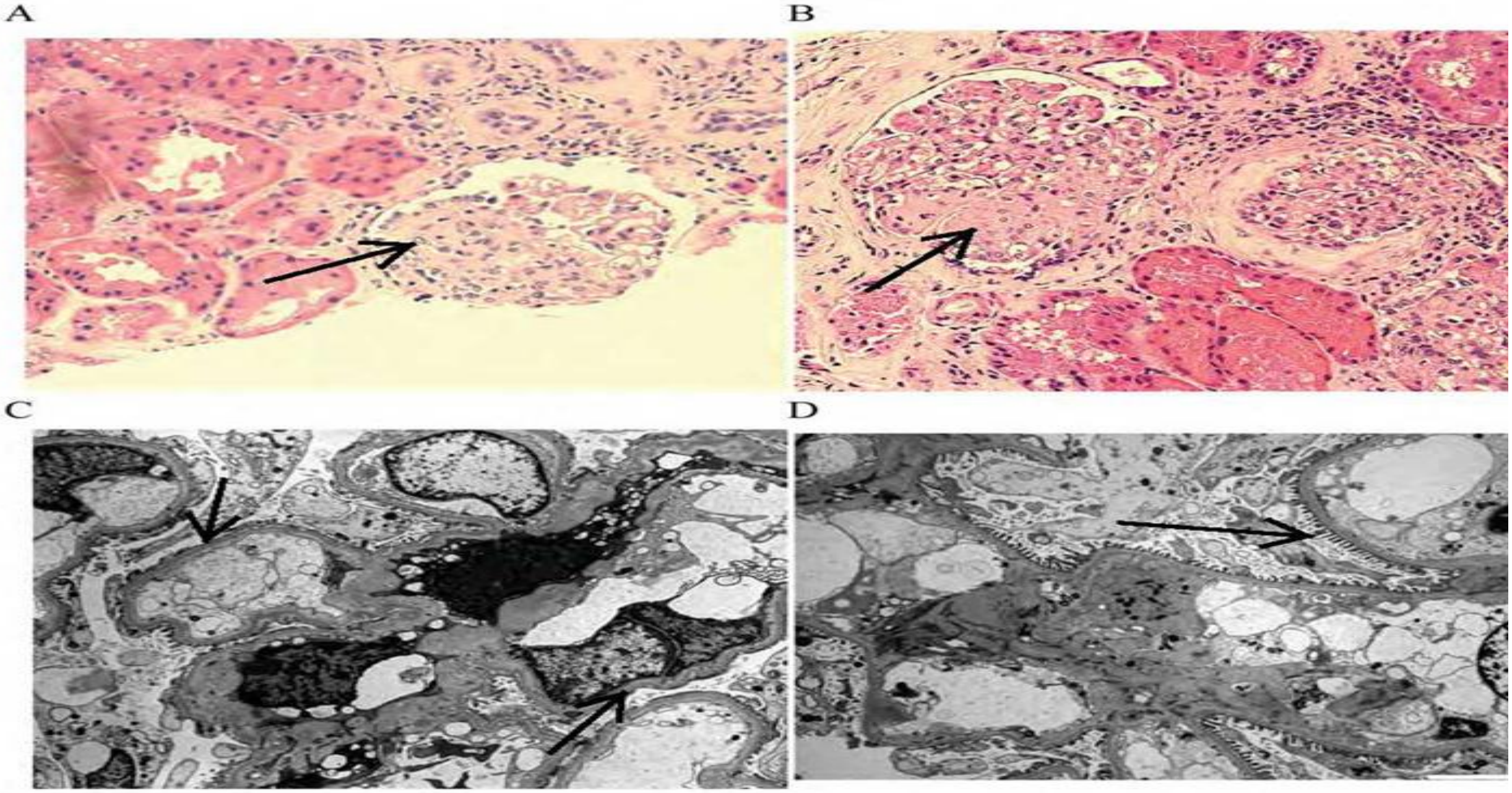
Alachkar et al. Transplantation 2013

Retrospective Data, n=25

- 24 had bx at time of post-transplant FSGS diagnosis
- 6 had histopathological changes consistent with FSGS on light microscopy (two with classic FSGS, one with tip and collapsing variant, two with collapsing variant and one with perihilar variants)
- 18 did not have any FSGS changes on light microscopy
- Foot process effacement 13% - 100%

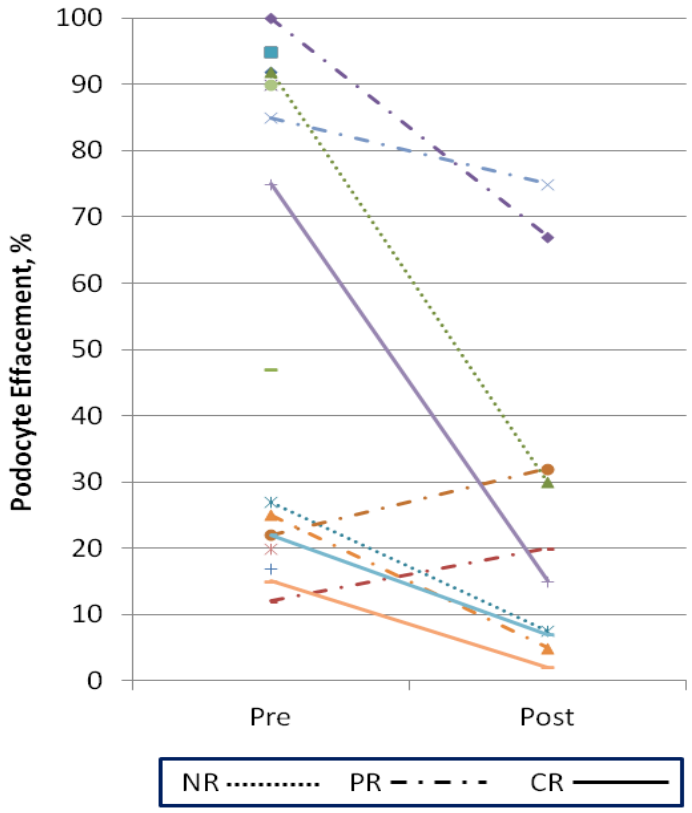
Alachkar et al. Transplantation 2013

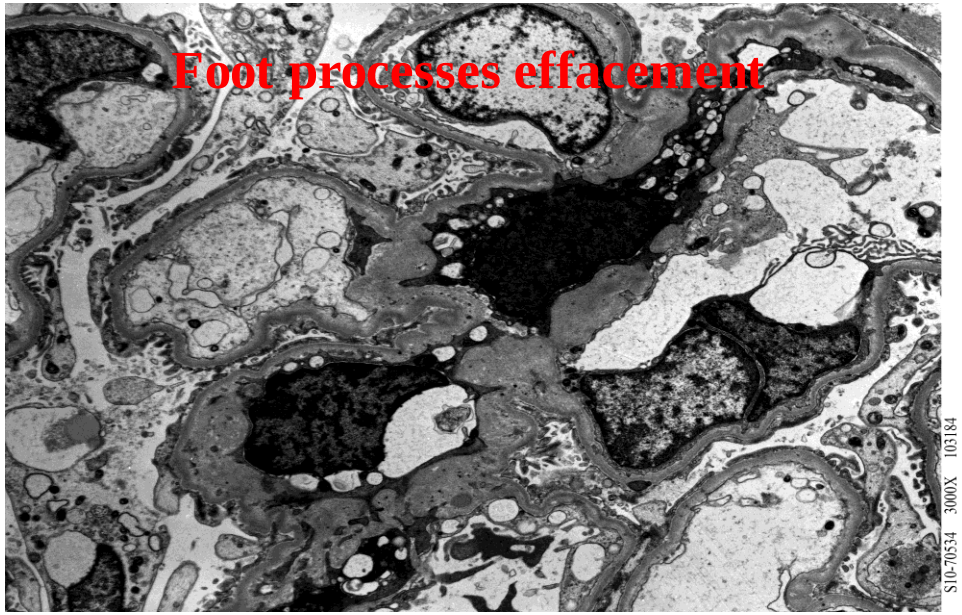
Pathological Changes of post transplant FSGS

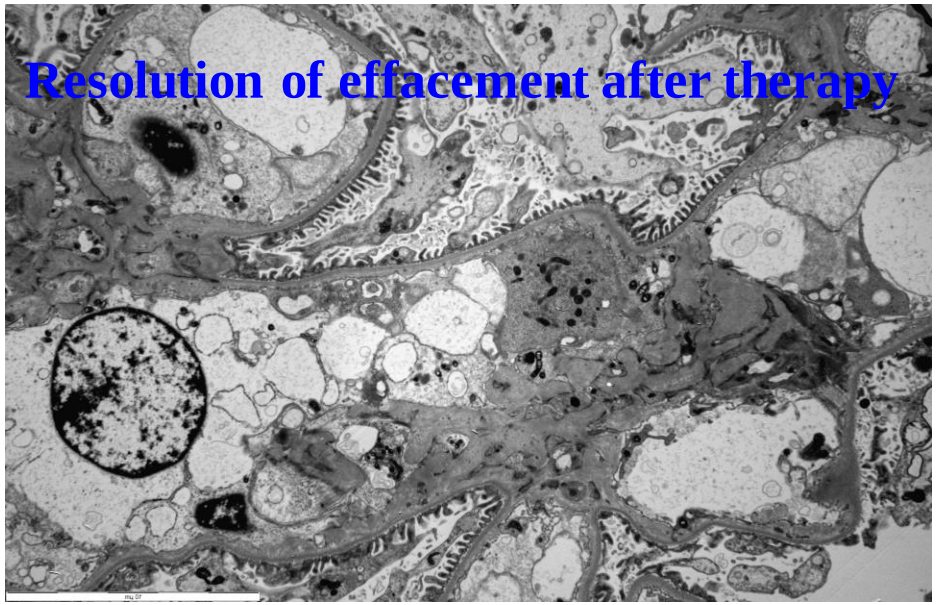


Changes in podocyte effacement after therapy with PP+Rituximab

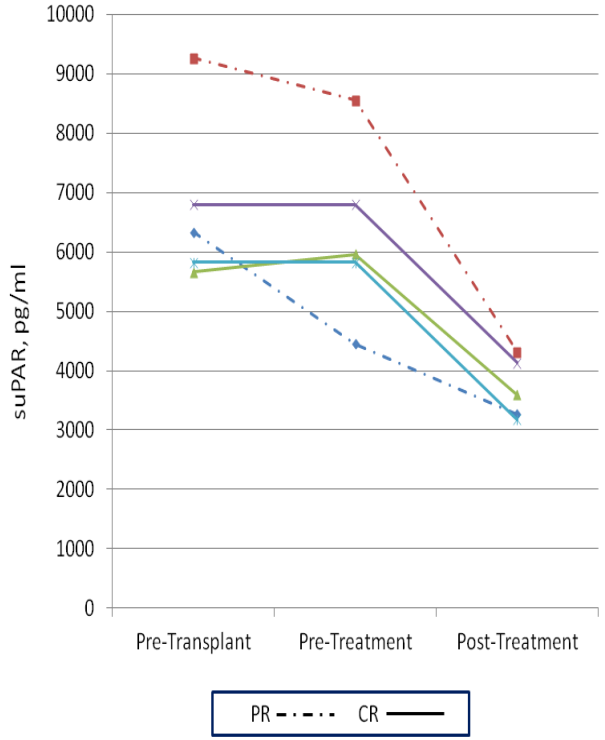
Recovery of podocyte effacement after therapy







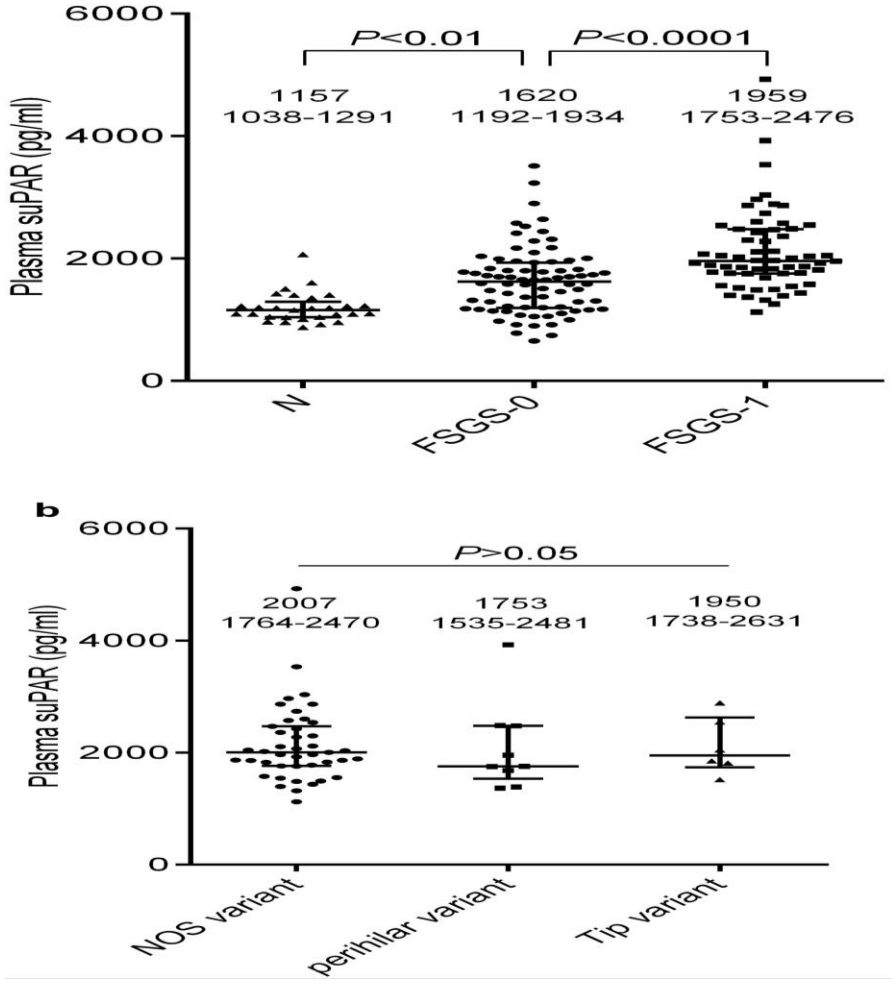
Decrease suPAR level after therapy



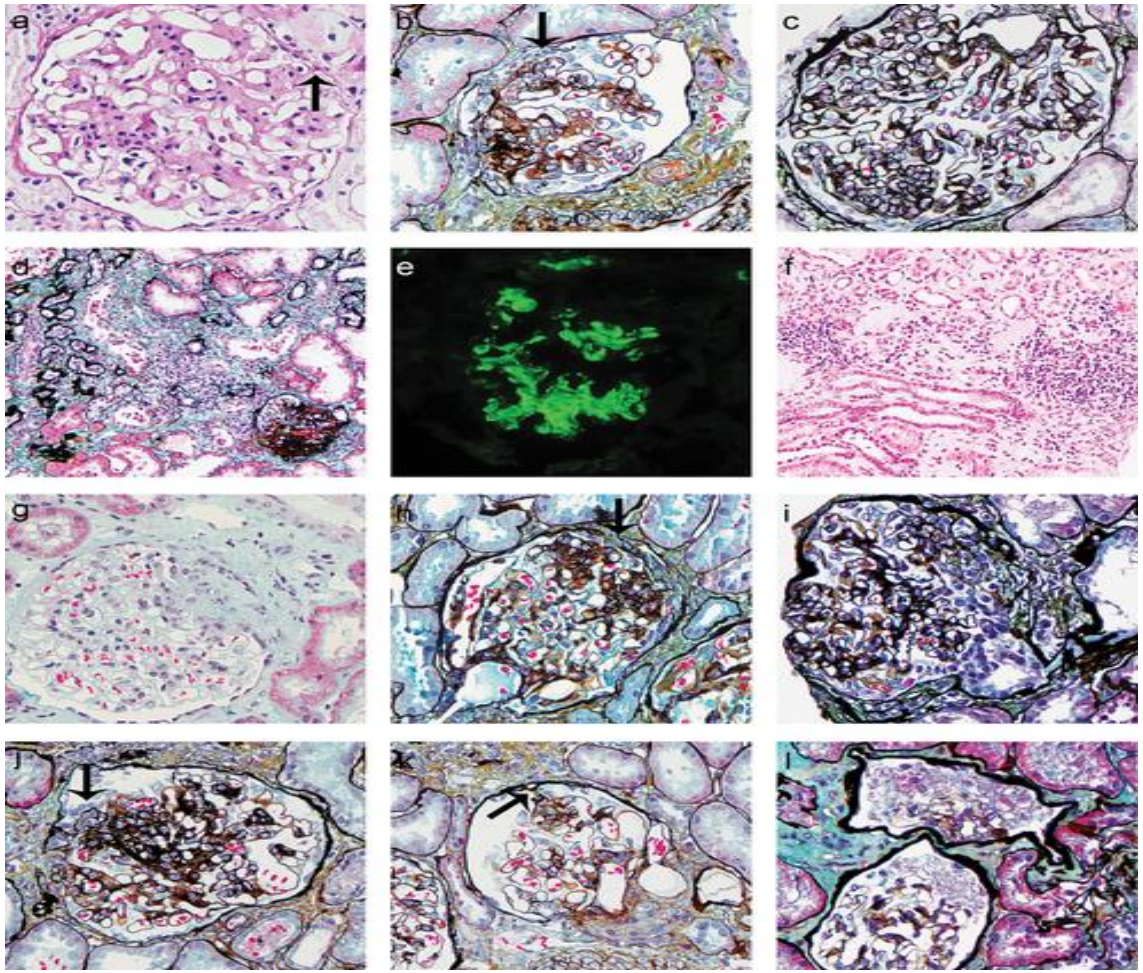
suPAR levels higher in severe (≥75%) vs mild (≤25%) podocyte effacement (13,030 vs. 4,806 pg/ml; P=0.03)

Alachkar et al. Transplantation 2013

Plasma suPAR correlations with FSGS lesions in IgA



FSGS lesions in IgA nephropathy



Guo et al. PLOS ONE.2015

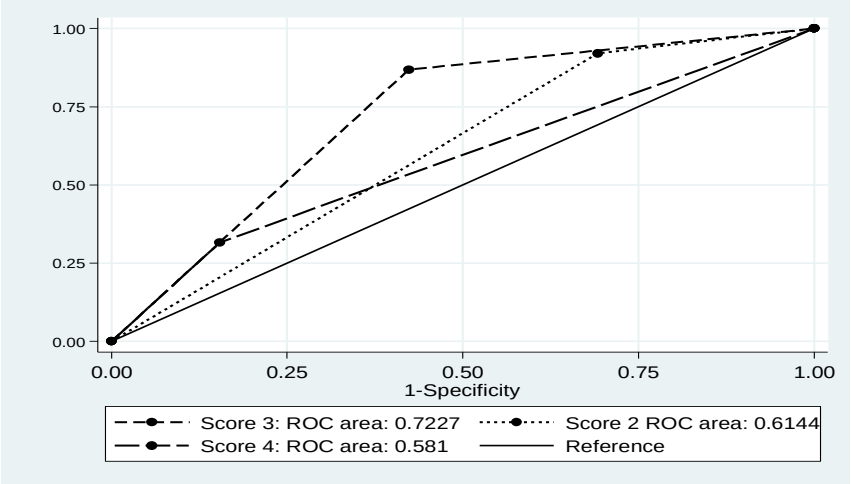
rFSGS prospective data, n=66

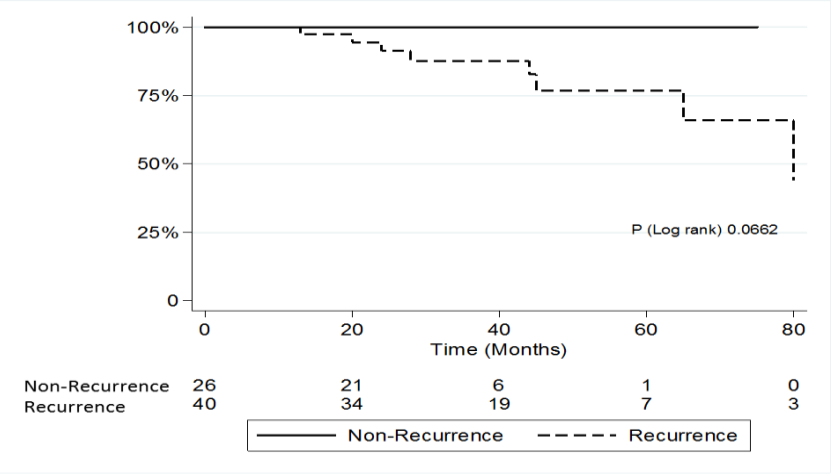
- Serum samples, clinical data and biopsy results
- Recurrence: 38 patients (59%), 2 de novo
- Median time to recurrence 1.25 mos (1 day- 30 mos)
- Mean UPC at recurrence: 5.81 g/g (2.1-17 g/g)

OUR OUTCOME

Table 3. Predictive values of clinical variables			
Variable	**Hazard Ratio**	**CI***	**P value**
White race	1.15	(0.4- 3.26)	0.787
Female gender	0.76	(0.27-2.08)	0.579
Age at diagnosis	0.99	(0.96- 1.02)	0.793
Time to ESRD†	1.04	(0.97-1.12)	0.201
Dialysis duration	1.01	(0.85-1.19)	0.883
Previous recurrence	0.92	(0.19-2.05)	0.107
Source of transplant (Living related)	0.88	(0.28-2.77)	0.83
Use of Rituximab	0.733	(0.29-1.26)	0.163
Use of Rituximab and TPE§	0.632	(0.18-1.15)	0.225
DGF¶ (In deceased donor)	1.42	(0.27-7.51)	0.67
Clinical score 3 and above	1.445	(1.16- 1.72)	0.009

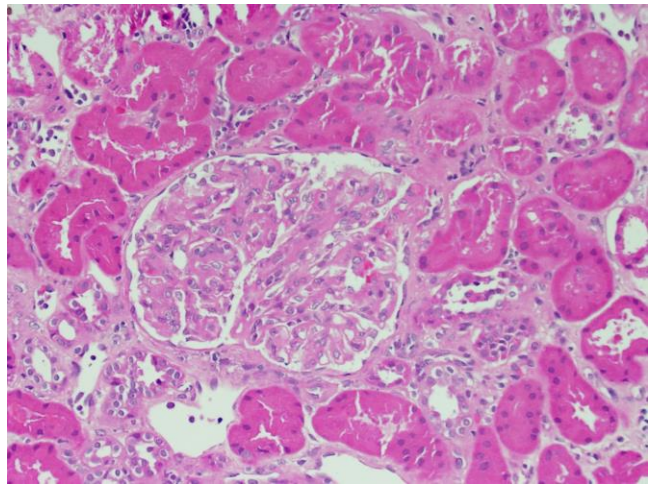
*CI: Confidence Interval; †ESRD: end stage renal disease; §TPE: therapeutic plasma exchange; ¶DGF: delayed graft function



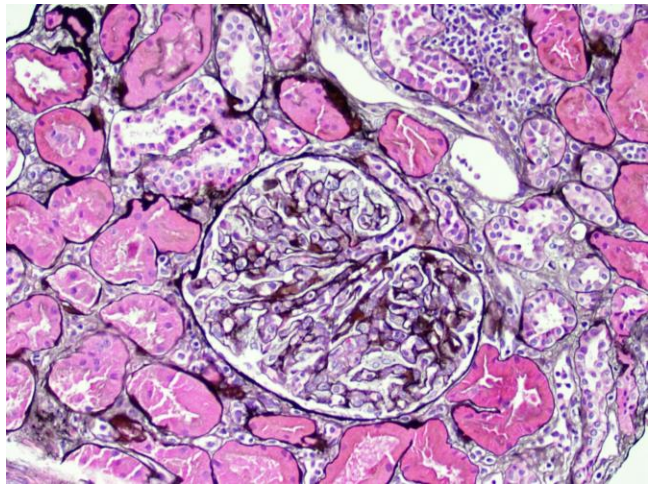


MPGN

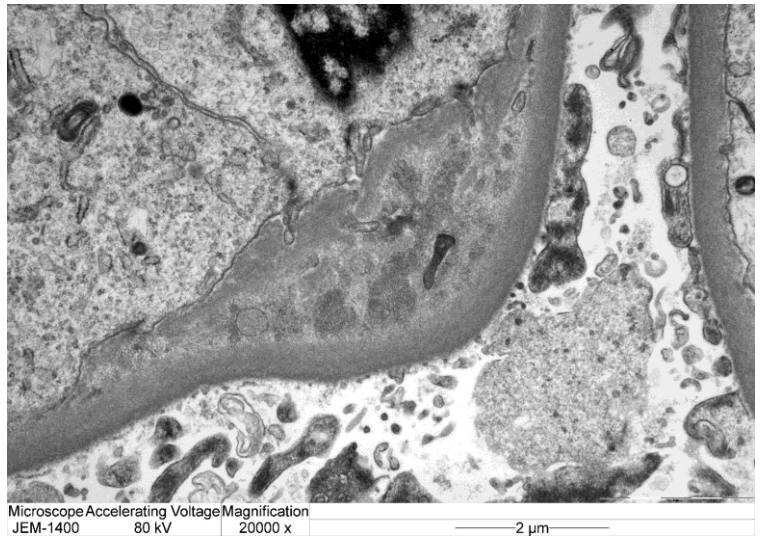
Segmental thickening + endocapillary proliferation with lobulated appearance

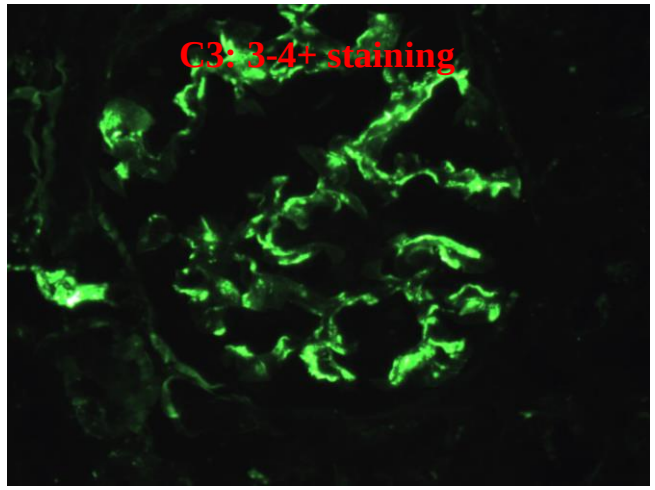


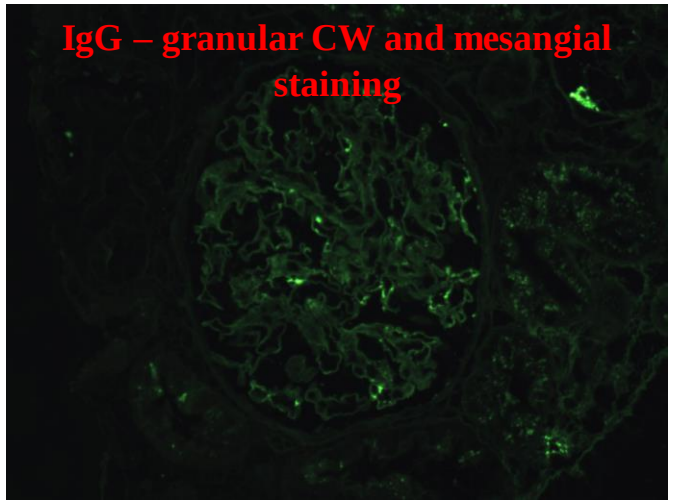
Double contours

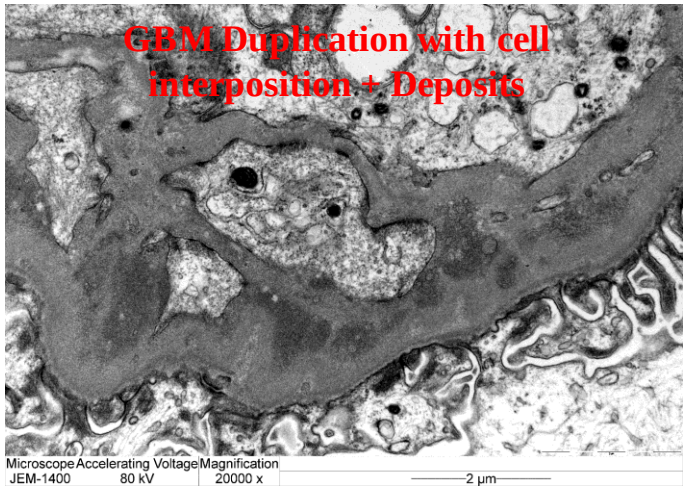


Duplication of GBM with immune-complex deposits in between









MPGN

n=34, recurrent n=18

Variable	Transplants (n=40)
Median age at transplantation- yr (range)	37.4 (15-59)
Gender (Male)	20 (50%)
Race: Caucasian African American Other	28 (70%) 7 (17%) 5 (13%)
MPGN type (Old classification*): Type I Type II Type III Mixed	65% 9% 21% 5%
MPGN type (New classification†): ICGN CGN	88% 12%
Donor source: Deceased Living unrelated Living related	10 (25%) 15 (37%) 15 (37%)
Number of mismatches 0 1 2 3 4 5 6	 1 (2%) 3 (7%) 5 (12%) 10 (25%) 7 (17%) 7 (17%) 6 (15%)
Preemptive kidney transplant	4 (10%)
Median cumulative ESRD duration for non-preemptive- yr (range)	5.2 (0.2-20)

Independent variable	Hazard Ratio (CI)	P-value
Age at transplantation	1.019 (0.937-1.018)	0.65
Gender (Male)	1.00 (0.118-8.420)	1
Race (Caucasian)	1.5 (0.120-18.411)	0.1
Allograft source (Living related)	10.19 (0.866-12.96)	0.045
Duration of dialysis	0.951 (0.775-1.167)	0.612
Preemptive transplantation	6.322 (1.455-12.411)	0.018
Previous failed transplantation	0.833 (0.098-7.026)	0.86
DGF (In deceased donor)	1.21 (0.158-9.508)	0.83
Development of rejection	3.148 (0.854-9.546)	0.25
Use of ACEi/ARB	1.312 (0.587-5.847)	0.658
Low complement level	5.522 (1.632-18.679)	0.006
Evidence of monoclonal gammopathy	5.606 (1.522-20.642)	0.010

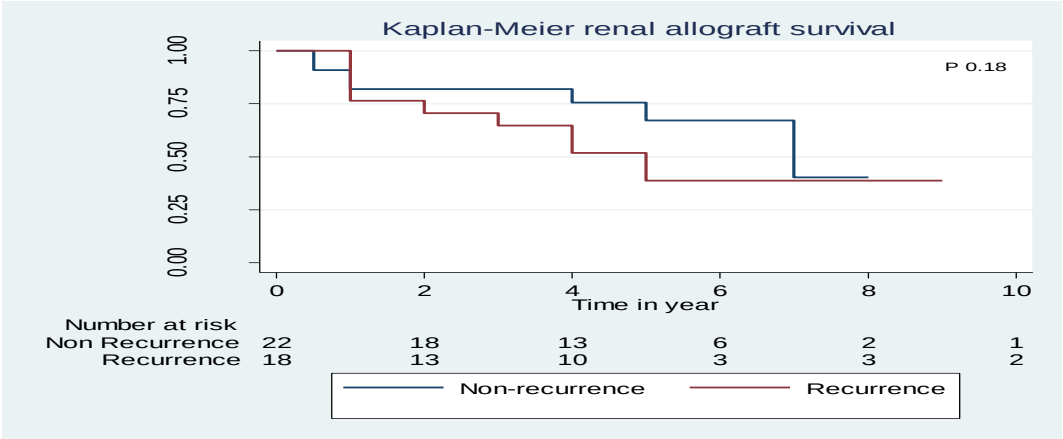
Alasfar S et al. BMC Nephrology 2016

MPGN, n=34

Reason for graft loss	Frequency
MPGN recurrence	6
Antibody-Medicated Rejection	2
Cell-Medicated rejection	2
MPGN recurrence & rejection*	3
ATN	2
Bleeding	1
Thrombosis	1

Recurrence type at time of diagnosis (new classification)	Number of cases	Recurrence type at time of diagnosis (old classification)
ICGN	15	Type I: 14, Type III:1
CGN	2	Type I: 1, Type II: 1
ICGN-IgA dominant	1	Type I

Treatment	Number of allografts	Response to therapy*
High dose steroids	4	1
Rituximab ± plasmapheresis	8	3
Plasmapheresis	1	1
Eculizumab	1	1
No change in therapy	4	3



Alasfar et al. Alachkar. BMC Nephrology 2016

Other centers' experience

- **University of Alberta (Dr. Wen):**
  - **182** cases of IgA (1st transplants only, living donor and decease donors) with 50 cases of recurrence, recurrence rate **27%**
  - All of these were biopsy proven native IgA nephropathy; able to find the native biopsy reports and/or pathology samples
  - Should be able to access the pathology for the **50** recurrence cases
- **Virginia Commonwealth University (Dr. Gupta):**
  1. FSGS **157**
  2. Membranous glomerulonephritis **29**/nephropathy **18** **(Total 47)**
  3. IgA nephropathy **59**

Other centers' experience

- **Colombia University (Dr. Batal):**
  - 3 years: 2006-2008
    - IgAN found in 538 native biopsies; of these **22** had transplant: at Columbia (n=19) or other hospitals (n=3), of these 22 , **6** show recurrent IgAN in allograft
  - Expect to have**~100** cases in Columbia from 2000-now; **~70** from 2005-2016.
- **Wisconsin University (Dr. Mohamed):**
  - Native kidney diagnosis and already transplanted
  - IgA nephropathy diagnosis: n=**306** (2000 to present)
  - Glomerulonephritis diagnosis: n=**341** (2000 to present)

SUMMARY

- Limited data on GN pathology: single center’s findings
- Recurrent GN is missing from Banff
- Unifying characterization of recurrent GN and de novo GN is crucial
- Identify early findings for therapies/response to therapies
- Histological prediction and correlation of clinical manifestation and outcome
- Understanding other glomerulopathies
- This work will potentially lead to guidelines for clinical practice

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- BANFF ORGANIZERS
- GN working group members
  - Serena Bagnasco
  - Marco Delsante