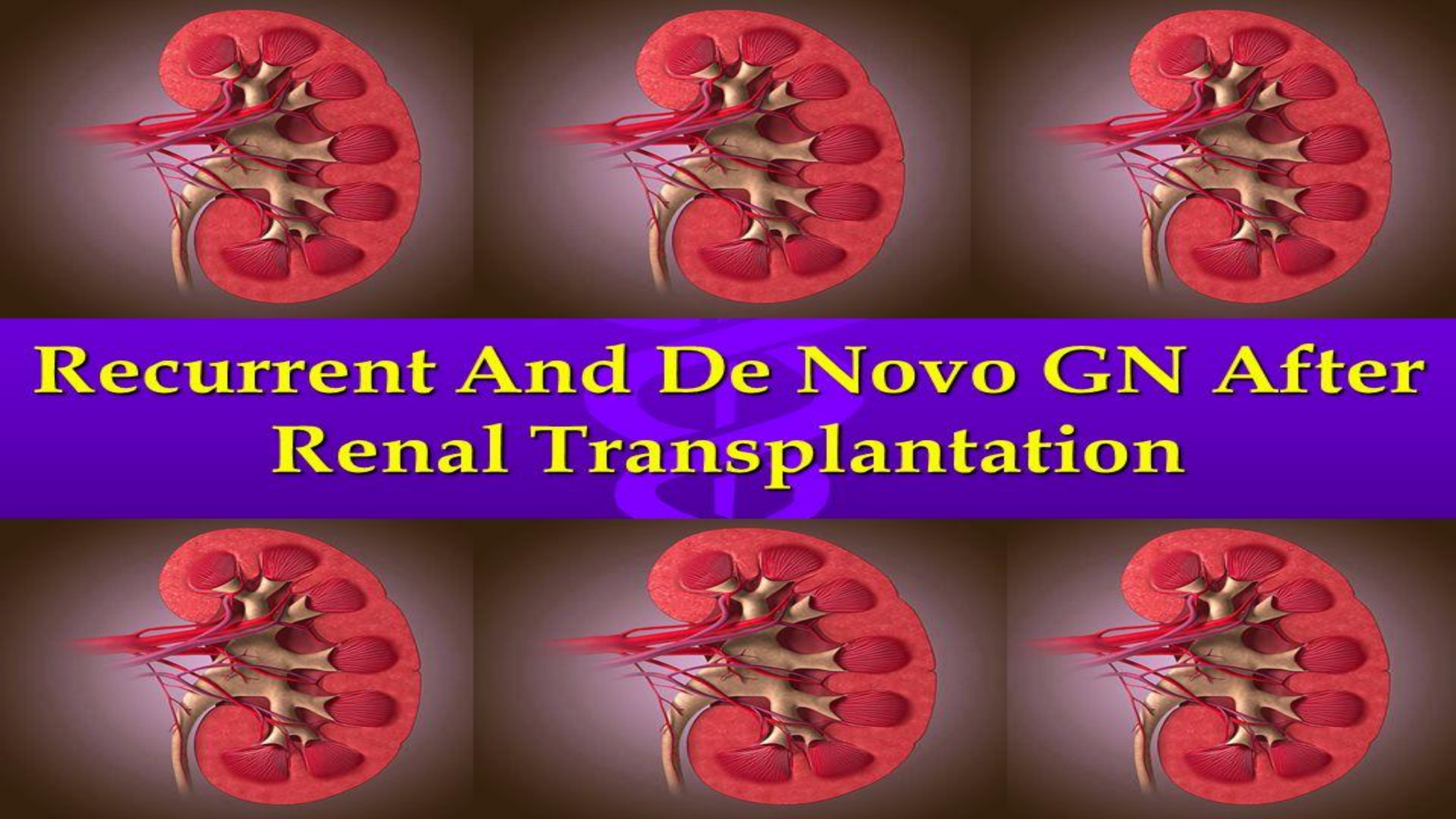

بسم الله الرحمن الرحيم



Recurrent And De Novo GN After Renal Transplantation

Dr F Pourrezagholi
SBMU
Shahid Labbafinejad Hospital

DENOVO OR Recurrence of glomerulopathies after kidney transplantation

- IgA glomerulopathy (GN)
- Membranous GN (MN)
- Membranoproliferative GN (MPGN)
- Focal and segmental glomerulosclerosis (FSGS)
- Hemolytic and uremic syndrome (HUS)
- SLE GN
- Diabetic GN
- Fribrillary GN

Morozumi K, et al. Nephrology. 2014;19 suppl 3:6-10

- GN recurrence rate is about 2.6% to 50% .
- The fourth most common cause of allograft loss after **acute rejection**, **chronic allograft nephropathy**, and **death with a functioning allograft**.

Predisposing factors :

- male gender
- younger recipient age
- living related donors
- closer HLA matching

Clin J Am Soc Nephrol. 2008;

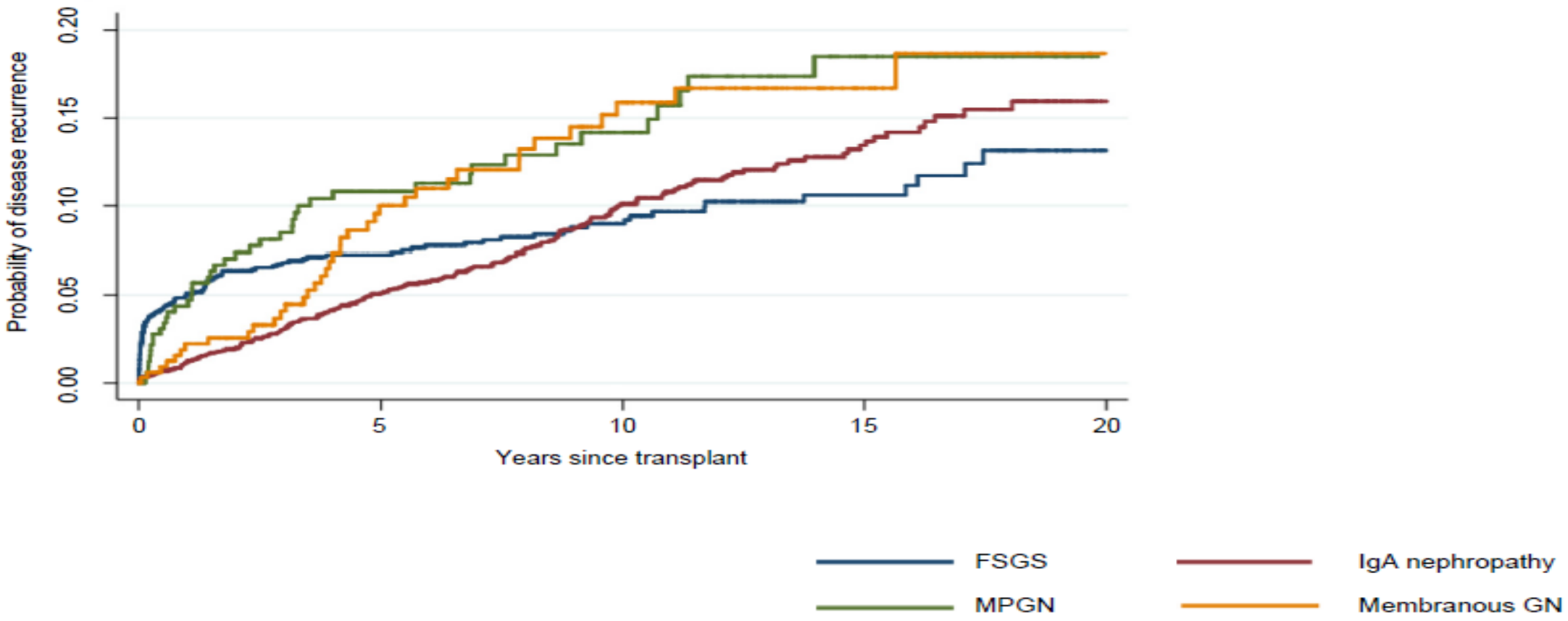
ANZDATA Registry. 2016, 38th Report.

Possible factors that influence the recurrence of glomerulonephritis

Focal segmental glomerulosclerosis
Age of onset
Interval to end-stage renal disease
History of graft loss due to recurrent FSGS
Circulating permeability factors
Circulating urokinase receptor
Membranous glomerulonephritis
Anti-phospholipase A2 receptor antibody
Anti-glomerular basement membrane (GBM) antibody glomerulonephritis
High titre of a-GBM antibody
Light chain deposition disease
AL-amyloidosis
Paraproteinaemic glomerulopathy
Free light chain detection, kappa/lambda ratio
Atypical HUS
Low ADMTS13 activity
Mutation of complement regulatory factor I, H
Some of MPGN-II (DDD)
Mutation of complement regulatory factor I, H, C3 NeF

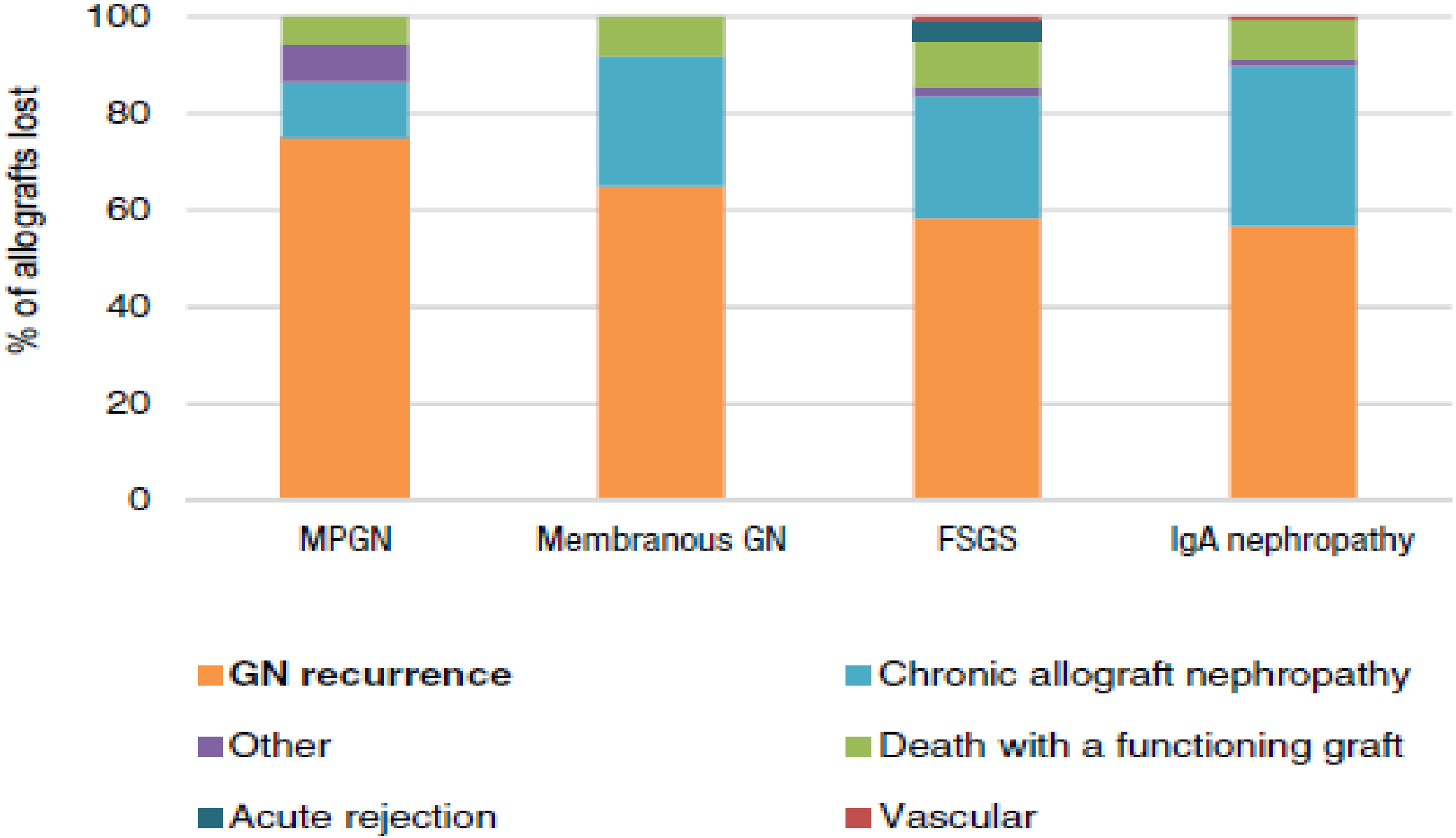
DDD, dense deposit disease; FSGS, focal segmental glomerulosclerosis; HUS, haemolytic uremic syndrome; MPGN, membranoproliferative glomerulonephritis.

Morozumi K, et al. Nephrology. 2014;19 suppl 3:6-10



Kidney International (2017)

PJ Allen et al.: Recurrent glomerulonephritis after transplantation



Kidney International (2017) 92,

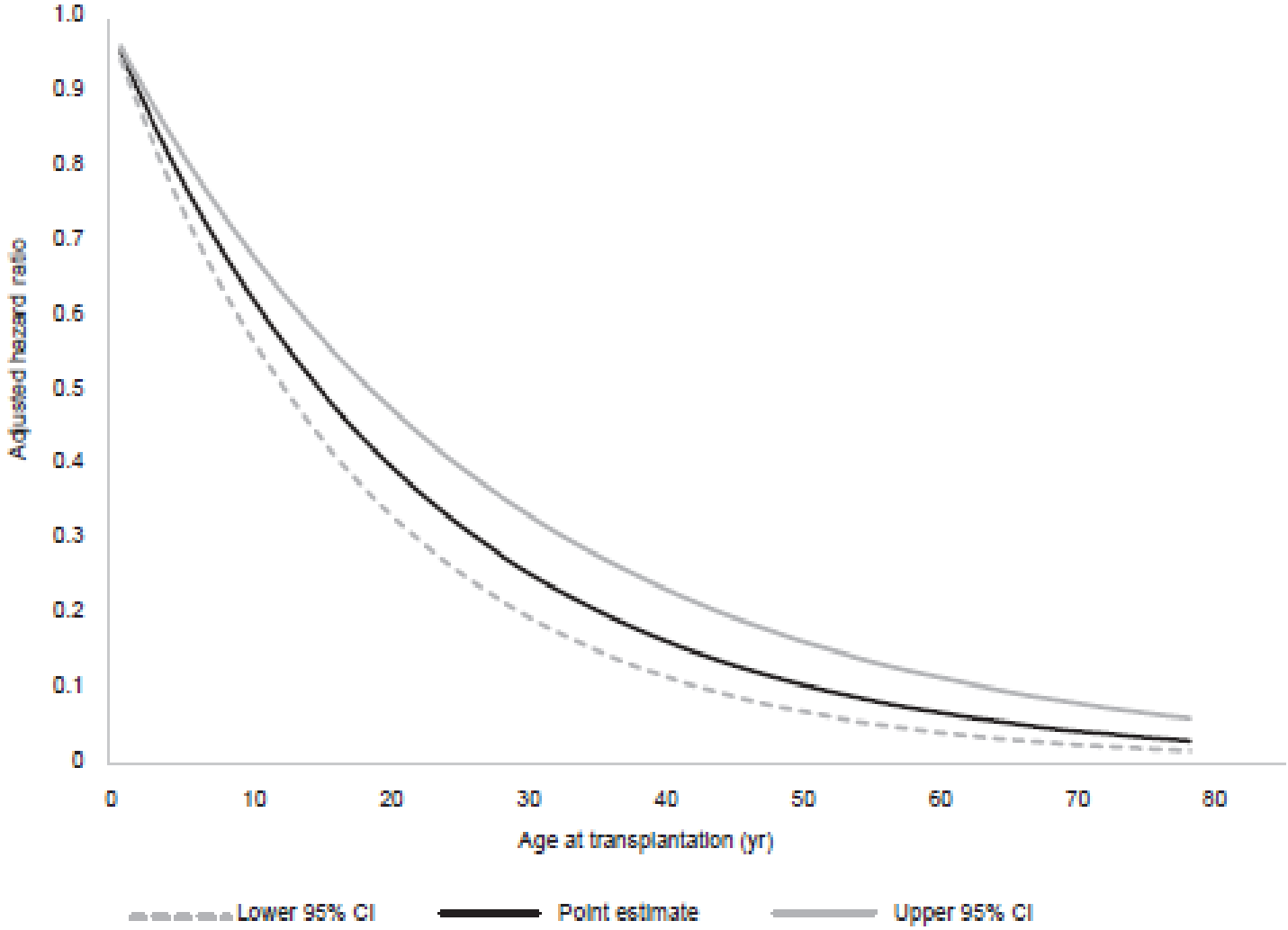
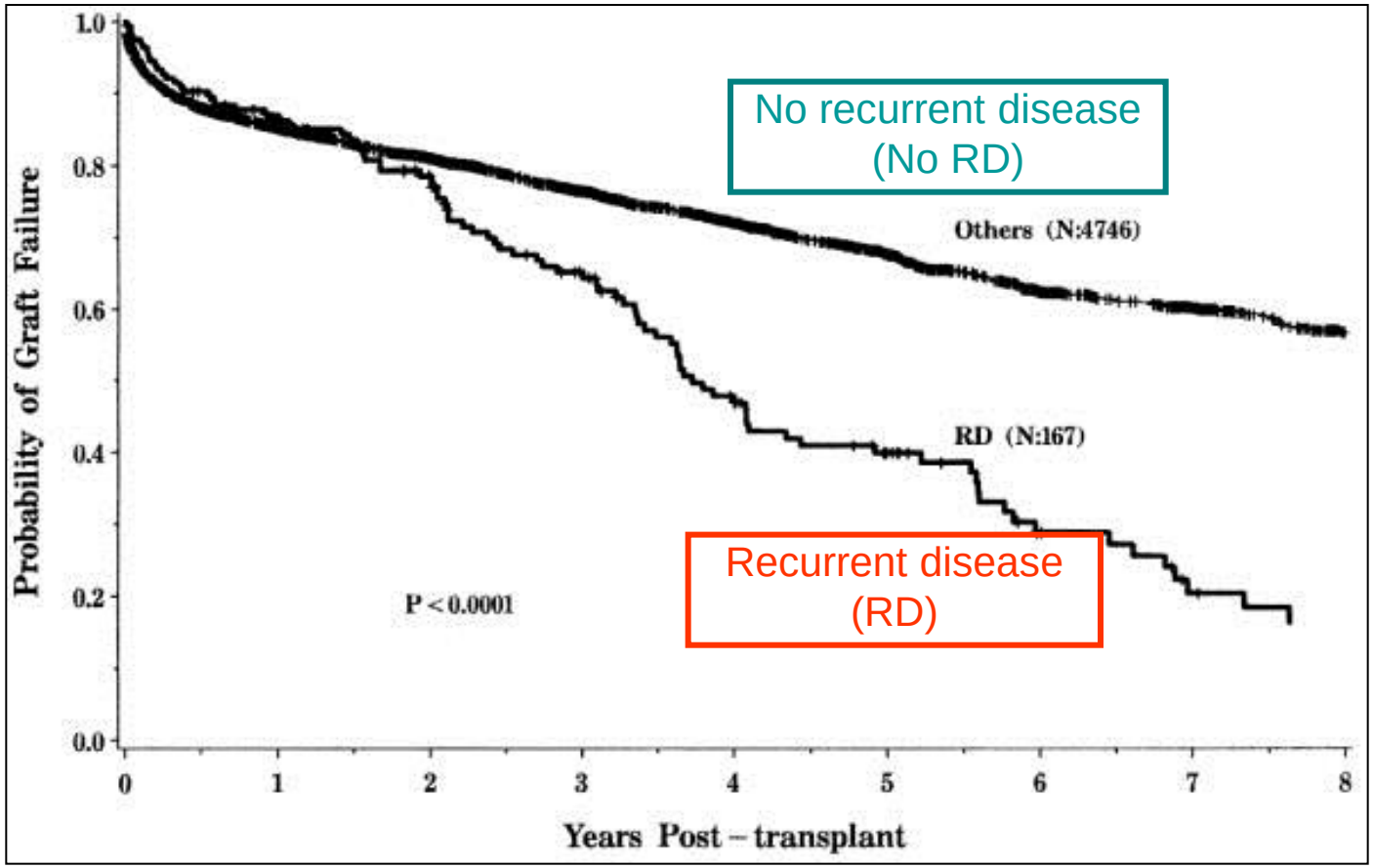


Figure 3 | Adjusted hazard ratios for disease recurrence according to age in recipients with recurrent glomerulonephritis as the primary cause of end-stage kidney disease. CI, confidence interval.

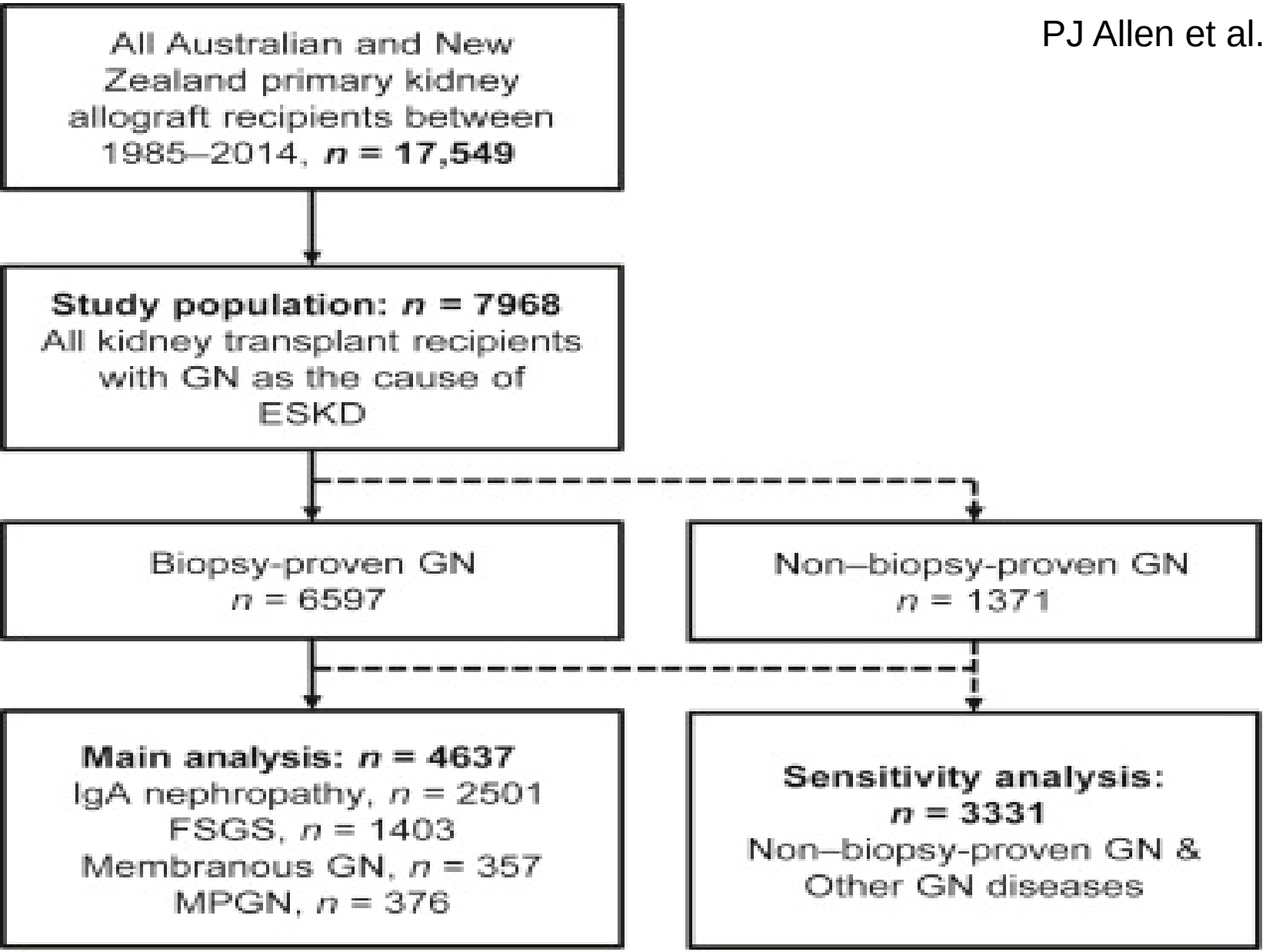
Outcome of kidney allograft with regards to recurrence



Hariharan S et al. Transplantation 1999


ANZ DATA
Australia & New Zealand
Dialysis & Transplant
Registry

PJ Allen et al.: Recurrent glomerulonephritis



- GN is the primary cause of ESKD in a large proportion of recipients, 50% in the Australian–New Zealand, 48% in China, and 30% in the US .
- Recipients with GN are generally younger than recipients with other diagnoses.
- 18% to 22% of kidney allografts are lost due to GN, **recurrent** or **de novo**.

Fernando G. Cosio1 and Daniel C. Cattran

Kidney International (2017)

Kidney International (2017)

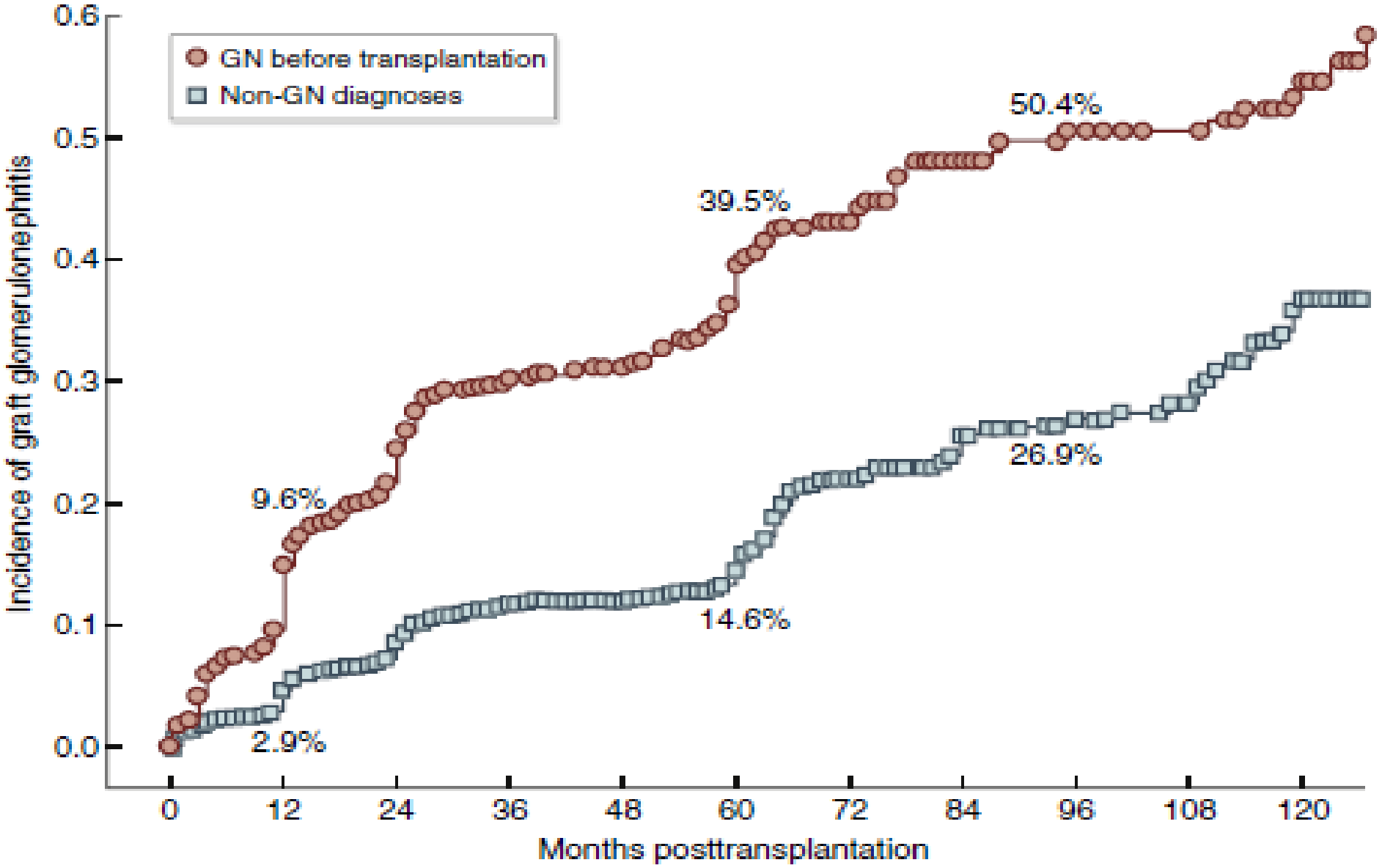
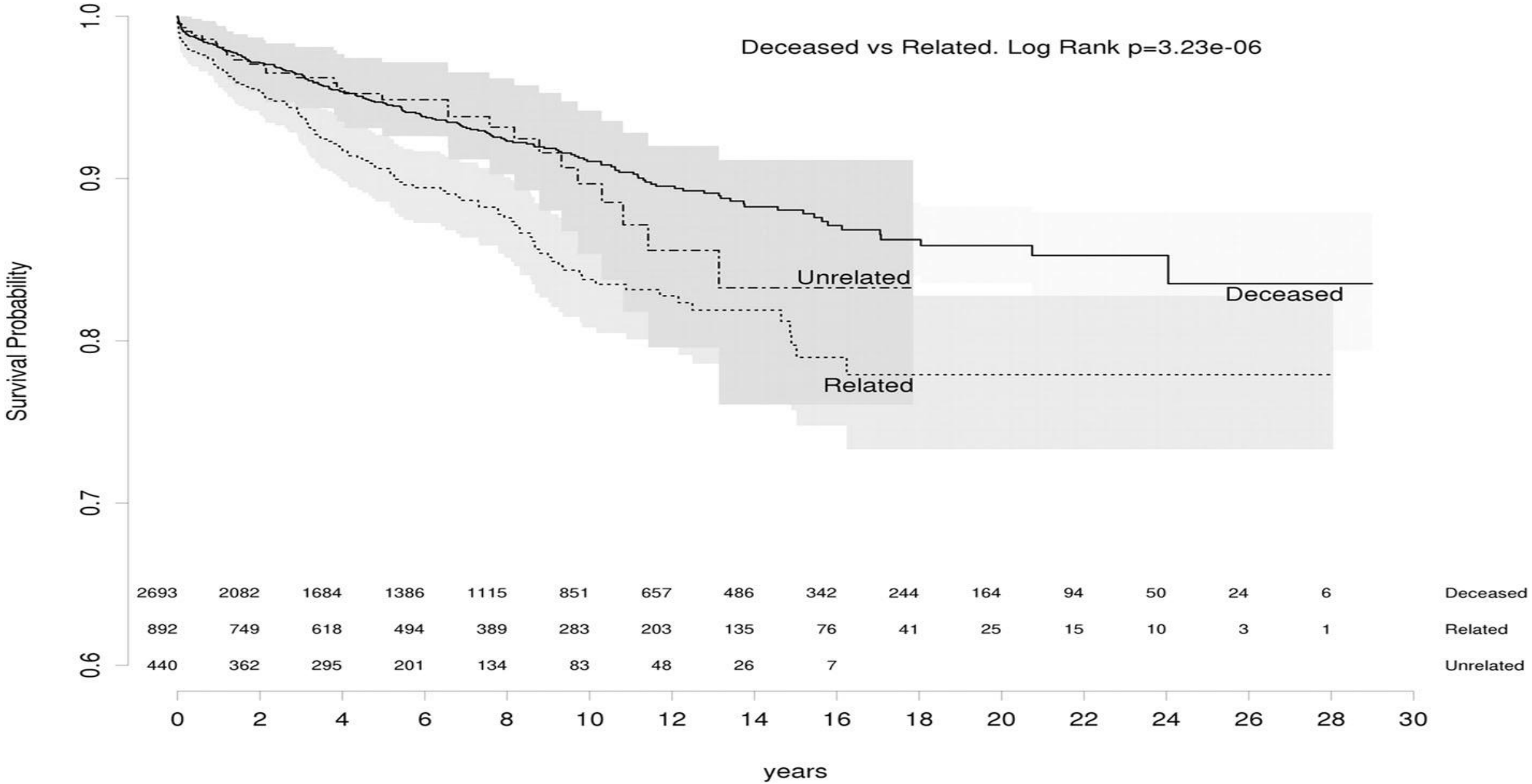


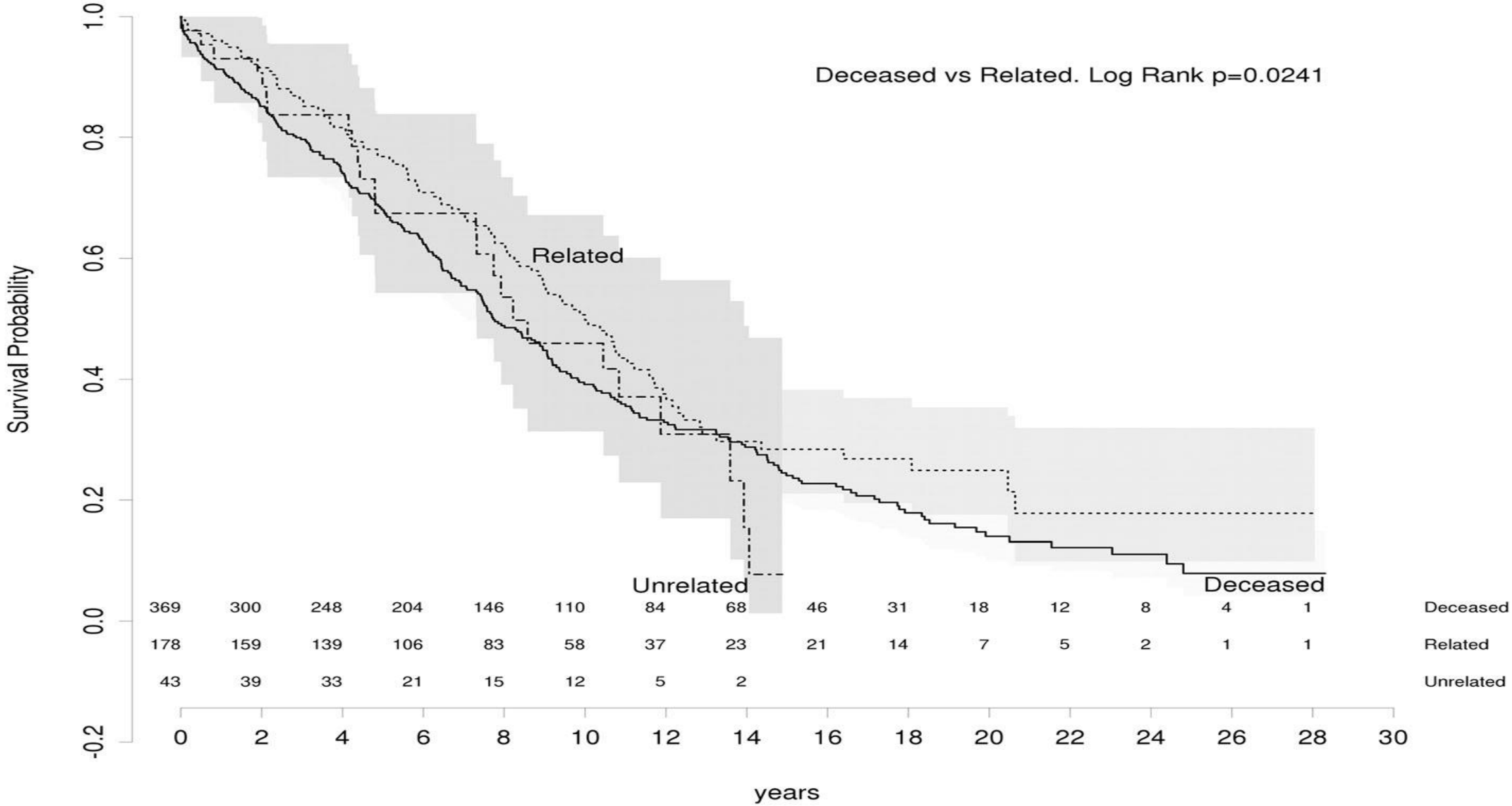
Table 1 Chracteristics of GN Patients by donor category

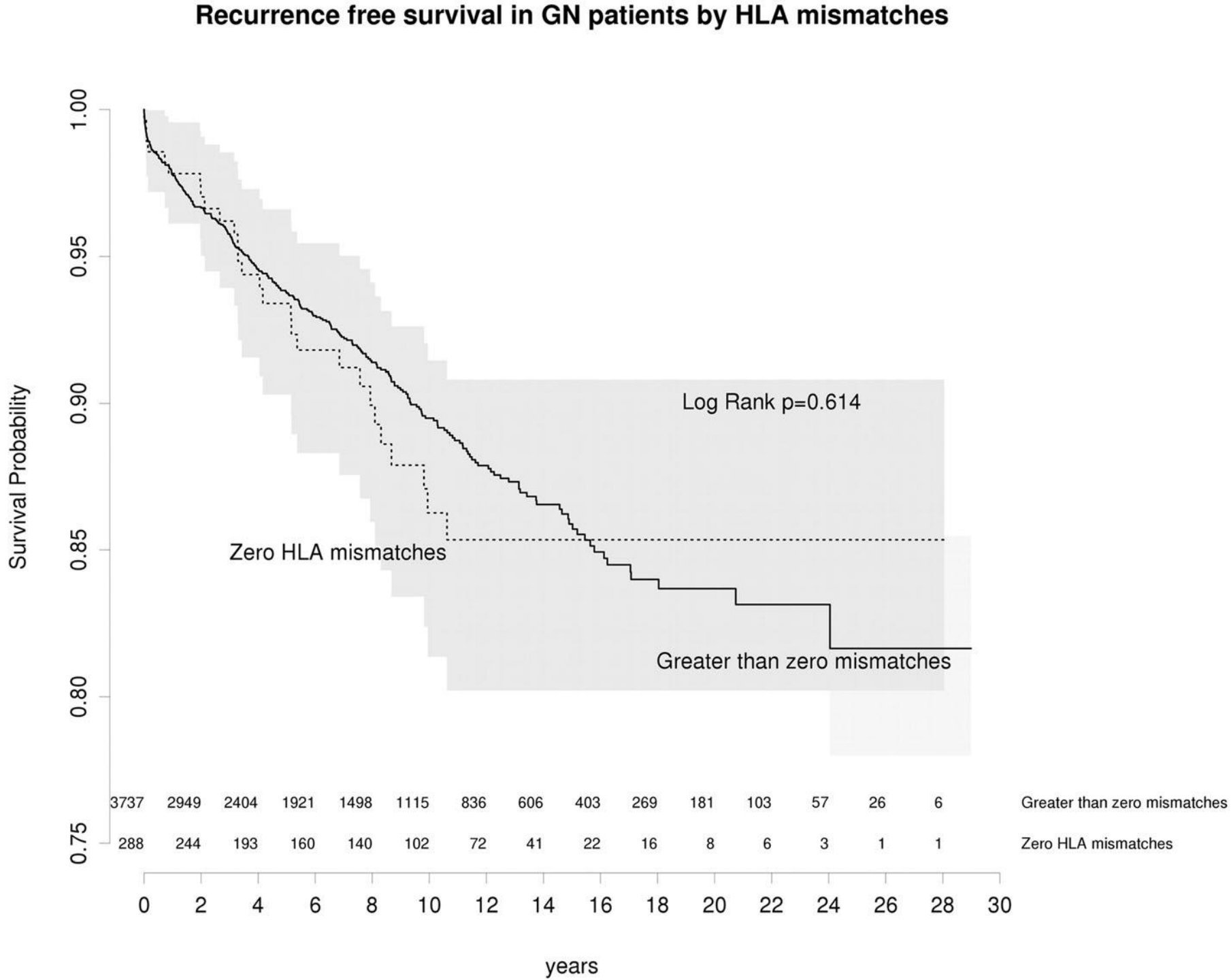
	Deceased	Related	Unrelated	Total	*P* value*
GN Patients	4956	1576	704	7236	0
Other Patients	6201	1686	900	8787	
Total	11157	3262	1604	16023	
GN patients					
Age (Mean, SD)	45.2 (13.4)	35.5 (13.7)	49.4 (12)*	43.6 (15.2)	<0.0001
GN Category					
FSGS	671 (13.5)	207 (13.1)	97 (13.7)	975 (13.4)	<0.0001
IgA	1552 (31.3)	557 (35.3)	284 (40.3)	2393 (33)	
MCGN	260 (5.2)	57 (3.6)	31 (4.4)	348 (4.8)	
MN	210 (4.2)	71 (4.5)	28 (3.9)	309 (4.2)	
Other GN	2263 (45.6)	684 (43.4)	264 (37.5)	3211 (44.3)	
Male Gender, n (%)	3311 (66.8)	994 (63)	487 (69.1)	4792 (66.2)	<0.005
Caucasian ethnicity, n (%)	4003 (80.7)	1283 (81.4)	586 (83.2)	5872 (81.1)	0.0006
Graft Number, n (%)					
Primary	4385 (88.4)	1464 (92.8)	626 (88.9)	6475 (89.4)	<0.0001
Secondary	514 (10.3)	100 (6.3)	72 (10.2)	686 (9.4)	
Subsequent	57 (1.1)	12 (0.7)	6 (0.8)	75 (1)	
Diabetes, n (%)	485 (9.7)	62 (3.9)	45 (6.3)	592 (8.1)	<0.0001
Peak panel reactive antibodies (%), Median (IQR)	5 (0–26)	1 (0–10)	0 (0–8)	3 (0–20)	<0.001
Total ischaemic time (hrs), Median (IQR)	14 (11–18)	2 (1–3)	2 (1–4)	11 (3–16)	<0.001
Zero HLA mismatches, n(%)	219 (4.4)	280 (17.7)	35 (4.9)	534 (7.4%)	<0.0001

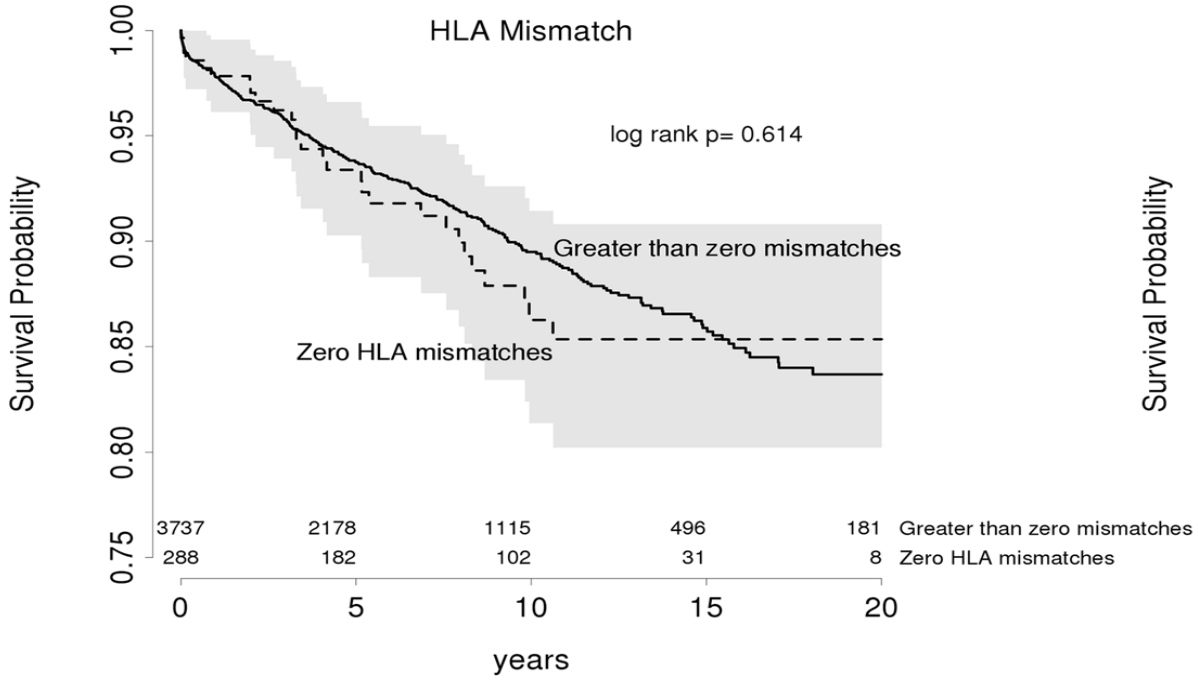


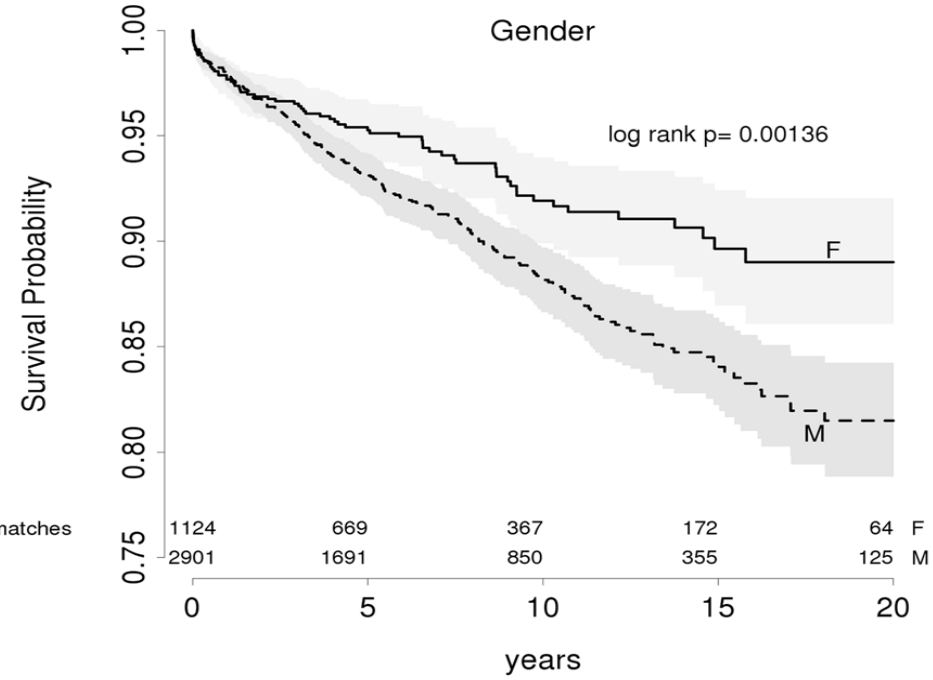
All GNs: recurrence free survival living related vs living unrelated vs deceased

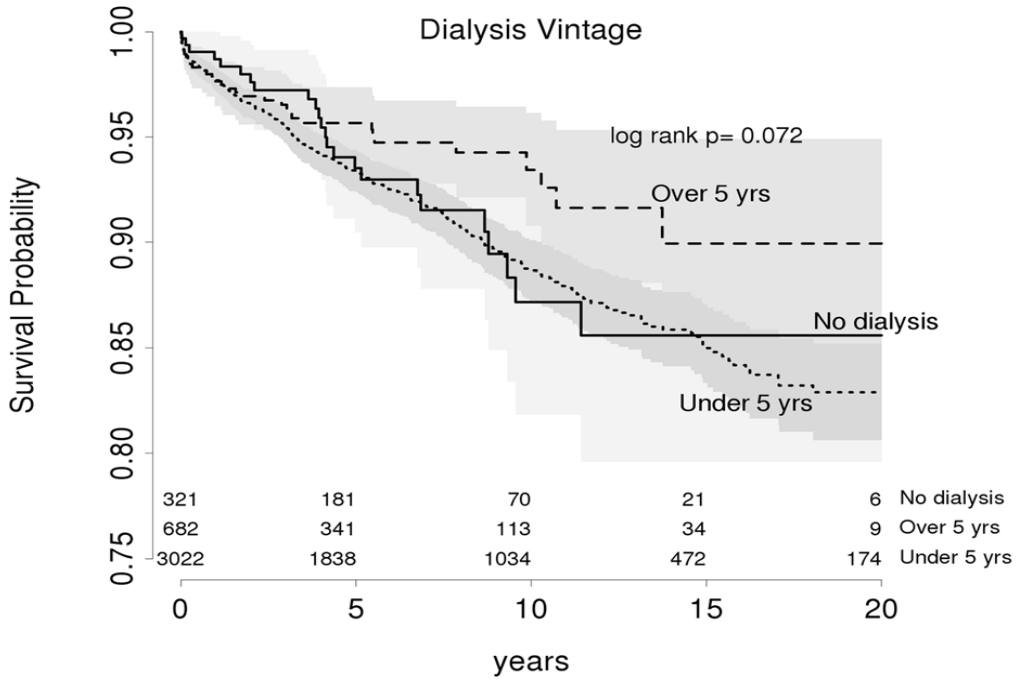
Death censored graft survival in GN patients with recurrence

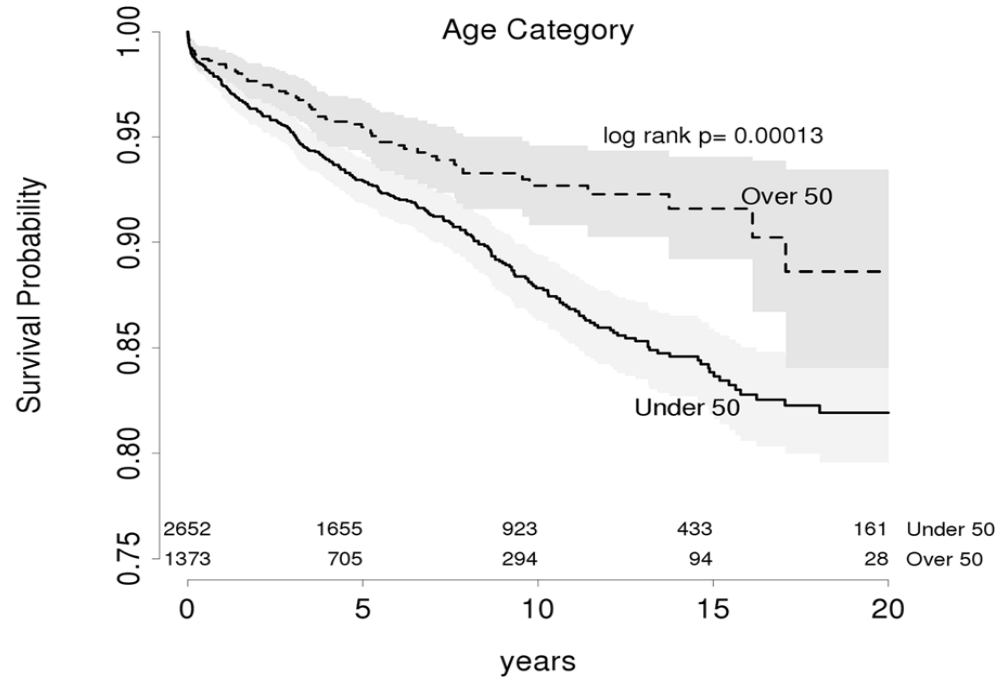



Recurrence free survival in GN patients by HLA mismatches
Survival Probability
1.00
0.95
0.90
0.85
0.80
0.75
Log Rank p=0.614
Zero HLA mismatches
Greater than zero mismatches
3737 2949 2404 1921 1498 1115 836 606 403 269 181 103 57 26 6
Greater than zero mismatches
288 244 193 160 140 102 72 41 22 16 8 6 3 1 1
Zero HLA mismatches
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
years


HLA Mismatch
log rank p= 0.614
Greater than zero mismatches
Zero HLA mismatches
Survival Probability
1.00
0.95
0.90
0.85
0.80
0.75
3737 2178 1115 496 181 Greater than zero mismatches
288 182 102 31 8 Zero HLA mismatches
0 5 10 15 20
years

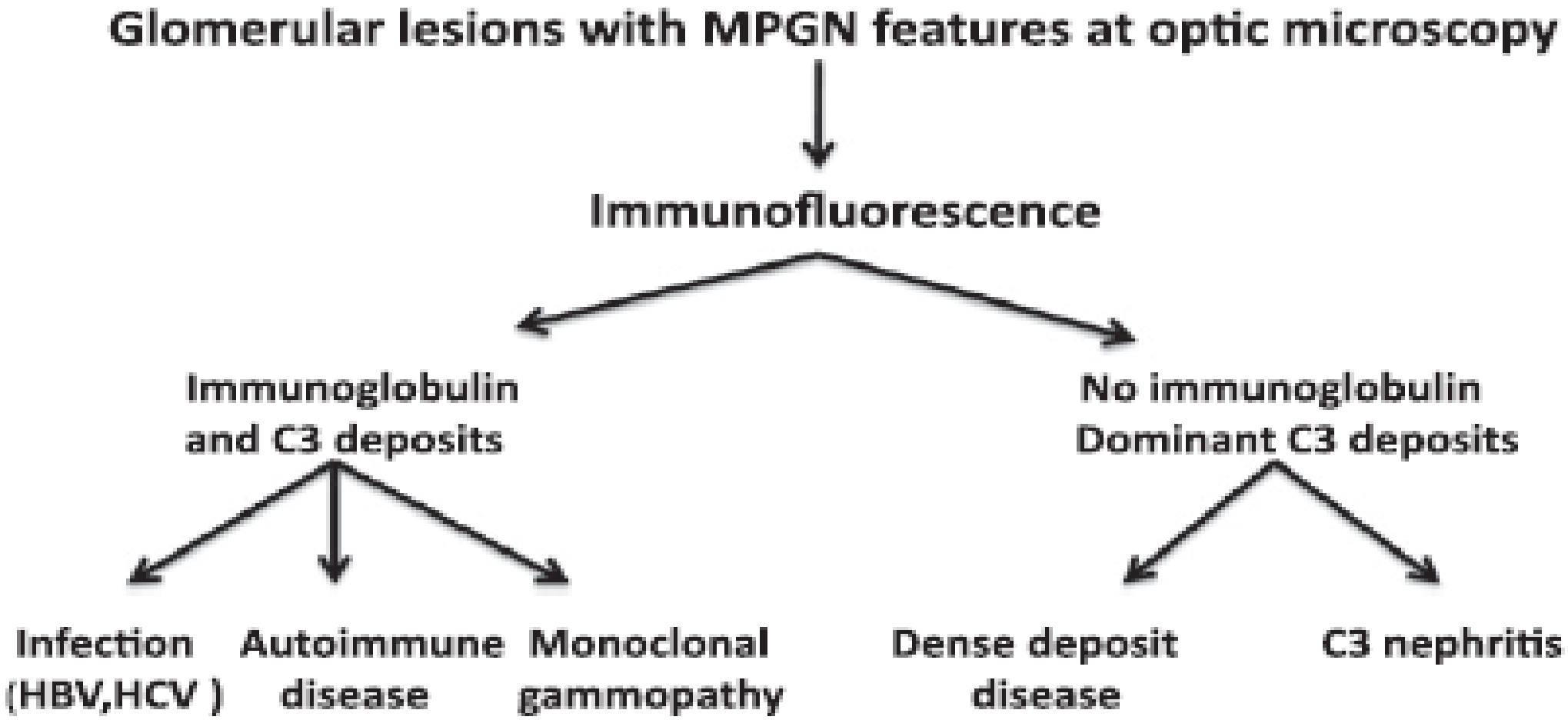

Gender
log rank p= 0.00136
F
M
Survival Probability
1.00
0.95
0.90
0.85
0.80
0.75
1124 669 367 172 64 F
2901 1691 850 355 125 M
0 5 10 15 20
years


Dialysis Vintage
log rank p= 0.072
Over 5 yrs
No dialysis
Under 5 yrs
Survival Probability
1.00
0.95
0.90
0.85
0.80
0.75
321 181 70 21 6 No dialysis
682 341 113 34 9 Over 5 yrs
3022 1838 1034 472 174 Under 5 yrs
0 5 10 15 20
years


Age Category
log rank p= 0.00013
Over 50
Under 50
Survival Probability
1.00
0.95
0.90
0.85
0.80
0.75
2652 1655 923 433 161 Under 50
1373 705 294 94 28 Over 50
0 5 10 15 20
years

MEMBRANOPROLIFERATIVE GN (MPGN)

- MPGN is a «pattern of injury» rather than a disease
  - Idiopathic MPGN is rare
- MPGN is a common feature of HCV-related glomerulopathy, with or without cryogobulinemia
- MGPN may be associated :
  - With complement pathway genetically-based dysfunction
  - Lupus
  - Monoclonal gammopathy
  - ➲ MGN recurrence varies according to the underlying disease



Post-Transplant De Novo Glomerular Diseases, Ponticelli Clin J Am Soc Nephrol , August, 2014

Glomerular deposits by immunofluorescence	Subtype	No. (%) (62)[a]	Recurrence risk (%)	Graft failure if recurrent
Igs	Polyclonal	24 (38.7)	30–35	10%
	Monoclonal	24 (38.7)	66	50%
Complement (C3)	C3GN	12 (19.3)	70	50%
	DDD	2 (3.2)	80–90	25%

Post-Transplant De Novo Glomerular Diseases, Ponticelli Clin J Am Soc Nephrol , August, 2014

MPGN with **monoclonal Ig deposits:**

- Recurrence 66%
- Very early posttransplantation
- Aggressive course leading to a graft failure
- Glomerular deposits IgG3-k+
- In 70% Monoclonal Ig in serum/urine in 70% negative
- No evidence of a plasma cell dyscrasia in the bone marrow
- Low risk of multiple myeloma developing.

MPGN with polyclonal Ig deposits

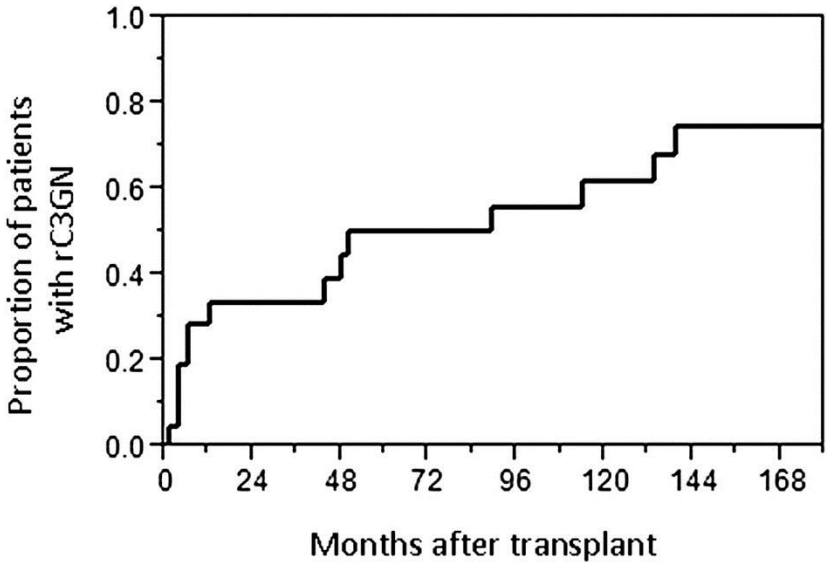
- Glomerular C4d deposits
- Low risk of recurrence
- late during the first 5 years
- Progressing relatively slowly
- Morphologically identical with denovo MPGN
- If complement levels (C3 and/or C4) is low risk of recurrenc is high.

C3GN

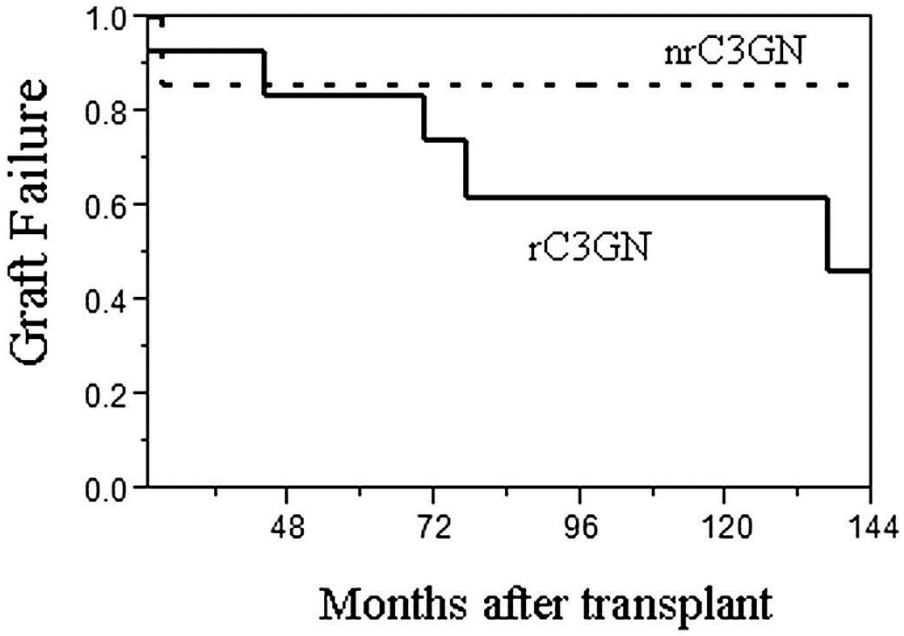
- Characterized by C3 deposits without Ig deposits
- Very high risk of recurrence 70%
- Clinically aggressive,
- Sometimes early recurrence
- Leading to graft failure (50%).
- In many case the outcome is ESRD

Zang L, et al. JASN 2014;25:1110-7

Clinical Findings, Pathology, and Outcomes of C3GN after Kidney Transplantation



Incidence of recurrent C3GN. Kaplan–Meier plot of the cumulative incidence of rC3GN after kidney transplantation.



Graft failure in rC3GN. Incidence of graft failure of rC3GN (solid line) and non-rC3GN (nrC3GN; dashed line) after kidney transplant (P=0.04, log rank). Median time to graft failure of rC3GN was 136 months, and median time to graft failure of nrC3GN was 330 months.

At the time of recurrence hematuria + proteinuria

Zang L, et al. JASN 2014;25:1110-7

- **Dense deposit disease :**

  - Electron dense transformation of the GBM and deposition of C3 (and other complement components with IgG deposition)

  - Very often :

    - Low C3 levels
    - 70 to 80% have a circulating autoantibody to C3Bb known as C3 nephritic factor (C3Nef)
    - Some of them may have factor H or I deficiency

  - Very high risk of recurrence (≈ 100%)

Glomerular deposits by immunofluorescence	Subtype	No. (%) (62)[a]	Recurrence risk (%)	Graft failure if recurrent
Igs	Polyclonal	24 (38.7)	30–35	10%
	Monoclonal	24 (38.7)	66	50%
Complement (C3)	C3GN	12 (19.3)	70	50%
	DDD	2 (3.2)	80–90	25%

Zand L, Lorenz EC, Cosio FG, et J Am Soc Nephrol. 2014;

Pre-transplantation studies	Lower risk of recurrence and progression	Higher risk of recurrence and progression
Native kidney biopsy Immunofluorescence (glomerular) Electron microscopy	Polyclonal Ig deposits[a]	Monoclonal Ig deposits[b] C3GN DDD, high risk of recurrence but often slow progression
Serum studies Complement levels (C3, C4) Monoclonal proteins	Normal Absent	Low C3 and/or C4 Present
Additional complement studies Alternative pathway activation? Classic/lectin pathway activation? Terminal pathway activation? C3Nef, C4Nef? Other autoantibodies? Genetic mutations?	Classic/lectin pathway activation (positive glomerular C4d) is associated with MPGN with polyclonal Ig deposits	Overactivation of alternative and/or terminal pathway Note: We do not know whether the mechanism of complement overactivation affects risk

Treatment :

- In case of factor H or I deficiency: prophylactic or therapeutic infusions of FFP
- In case of overt recurrence :
  - Plasmapheresis with FFP
  - Rituximab therapy ? Not sure..
  - Eculizumab therapy ? Certainly… but cost issue.

McCaughan JA, O'Rourke DMAm J Transplant. 2012

Response of post-transplant MPGN recurrence to different treatments

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

[a]Response to therapy defined by improvement in GFR and no subsequent graft loss
[b]The case was CGN

Alasfar S. et al. BMC Nephrol. 2016;17:7

FOCAL AND SEGMENTAL GLOMERULAR SCLEROSIS (FSGS)

Idiopathic FSGS :

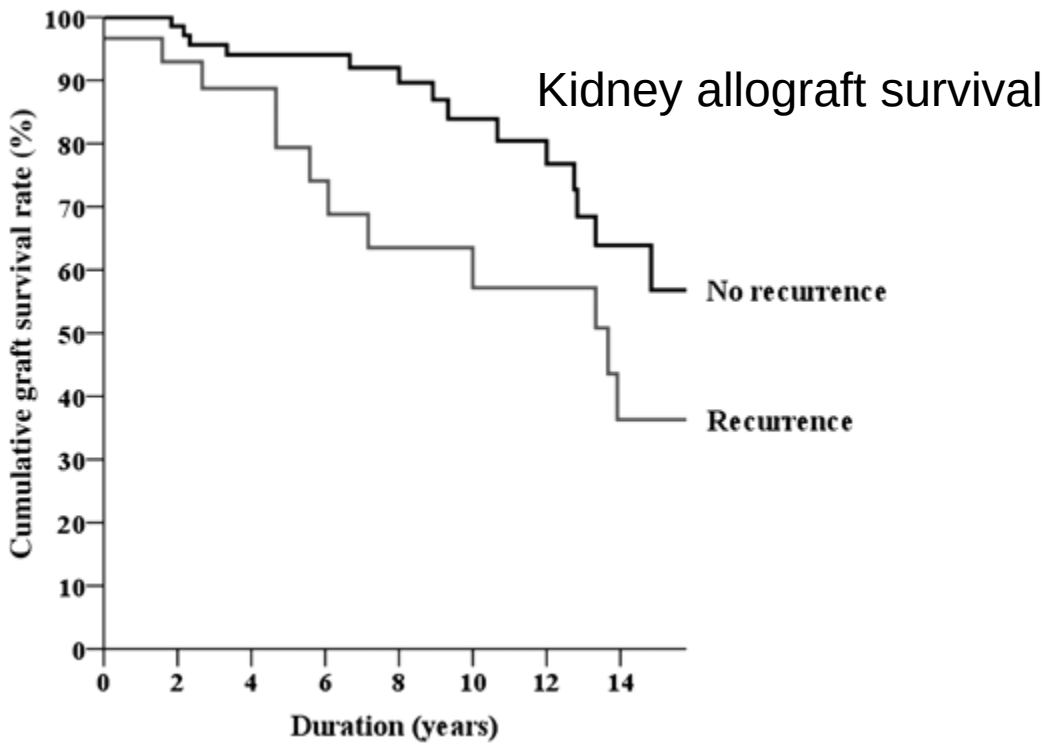
- Children and adults
- Recurrence rate :
  - Around 30- 50% on the first transplant
  - Around 80- 100% if it had already recurred on a previous graft
- 2 patterns posttransplant :
  - Immediate recurrence with heavy proteinuria as soon as the allograft recovers function
  - Late recurrence several months /years post KTx;
- Recurrence negatively affects allograft survival

Risk of FSGS recurrence is high:

- Younger patients(<15 years)
- Progress to ESRD within 3 years of diagnosis
- Higher levels of proteinuria
- Recurrence in previous allograft
- very low in genetic forms (related to high-risk APOL1 genotype)

Lee BT, Kumar V, Williams TA, et al ,Am J Transplant. 2012.

Multicentric study (South Korea); 47 FSGS adult pts and 60 FSGS paediatric pts

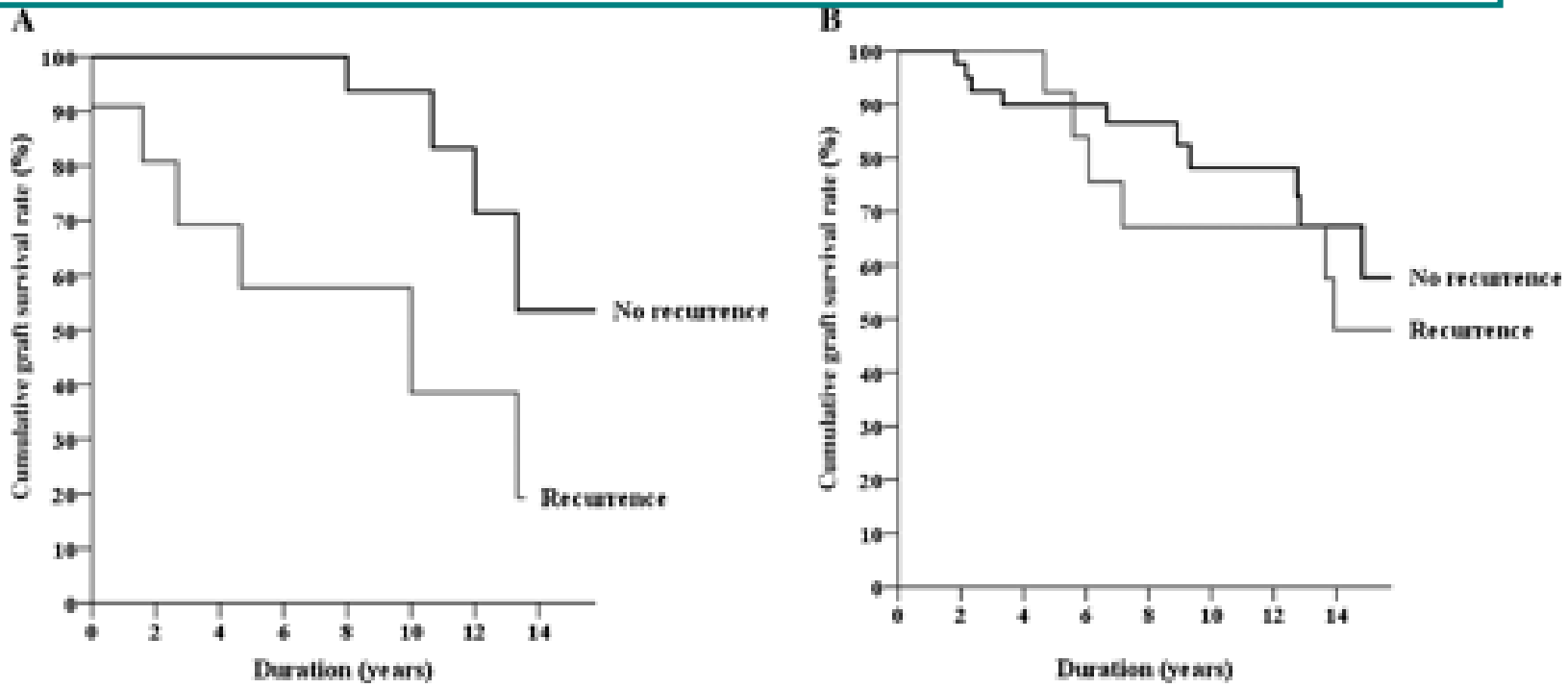


Kaplan–Meier curves of graft survival in recipients with and without recurrence of focal segmental glomerulosclerosis. The patients in the recurrence group have a poorer graft outcome than in the non-recurrence group (P = 0.037 by the log-rank test).

Hwang JH et al. NDT 2012;27:2559-65

FSGS in adults

FSGS in paediatrics



The impact of recurrent focal segmental glomerulosclerosis on the overall graft outcome in A-FSGS group (**A**) and C-FSGS group (**B**). While recurrence affected the graft outcome in the adulthood-onset group (P = 0.005), recurrence was not associated with the graft outcome in the childhood-onset group (P = 0.558 by the log-rank test).

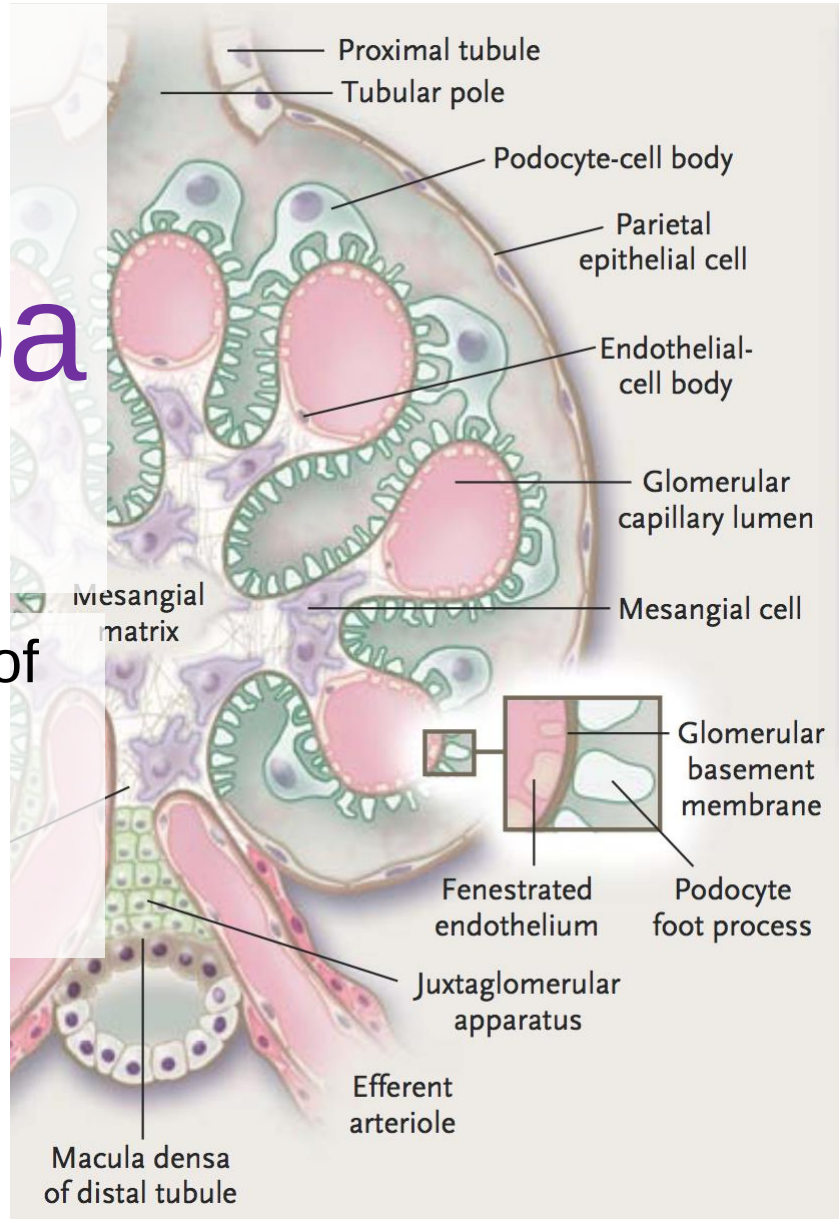
Hwang JH et al. NDT 2012;27:2559-65

Pathogenesis :

- **Unknown.**
- **Circulating factors:** soluble urokinase plasminogen activator receptors **(suPARs)**
- **B7-1 pathway**
- **podocytopathy**

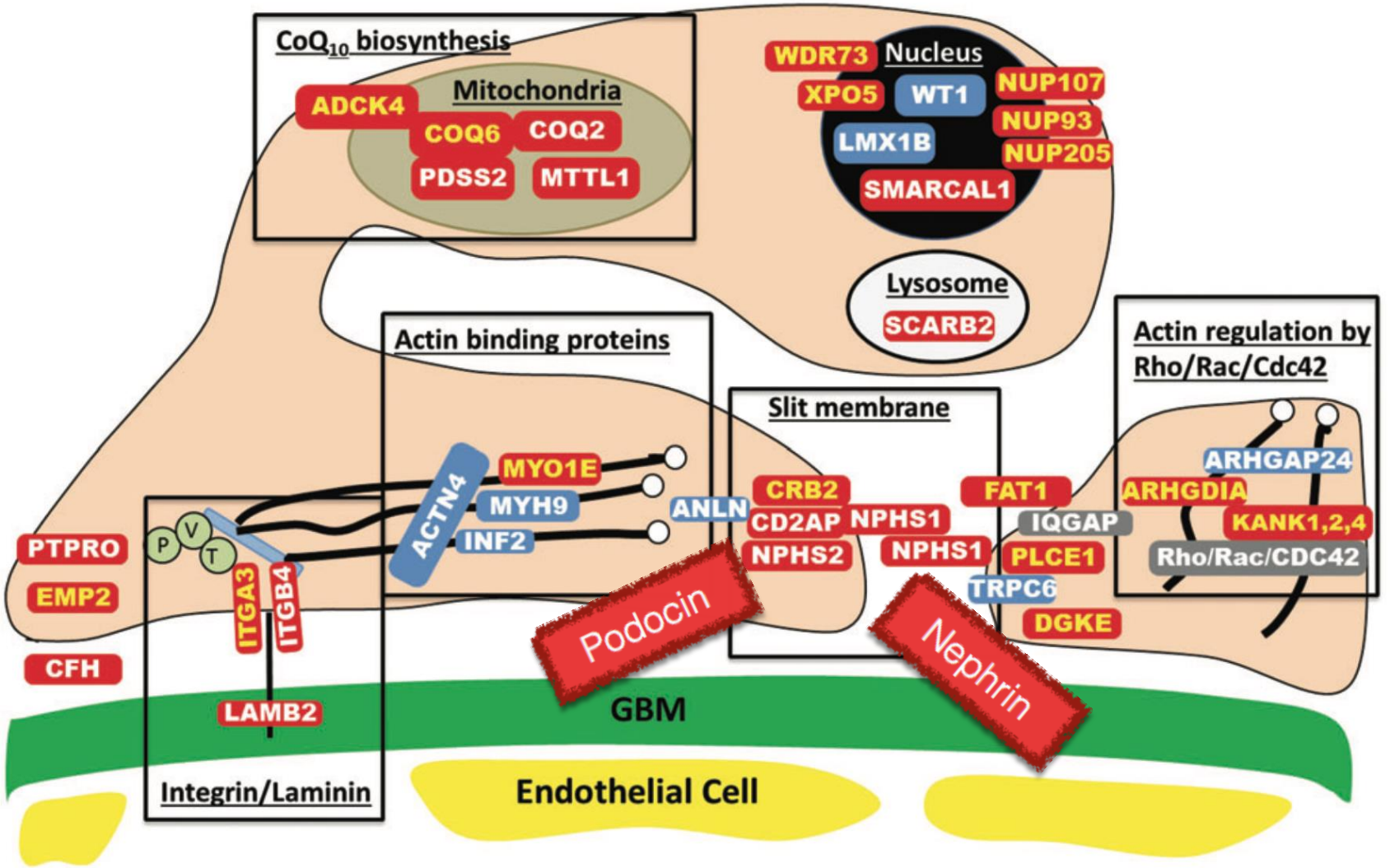
Podocytopathies

Podocytes are at the heart of FSGS



D'Agati 2011 NEJM

GENETIC CAUSES



Lovric 2016, Nephrol Dial Transplant 31: 1802–1813

FSGS TREATMENT

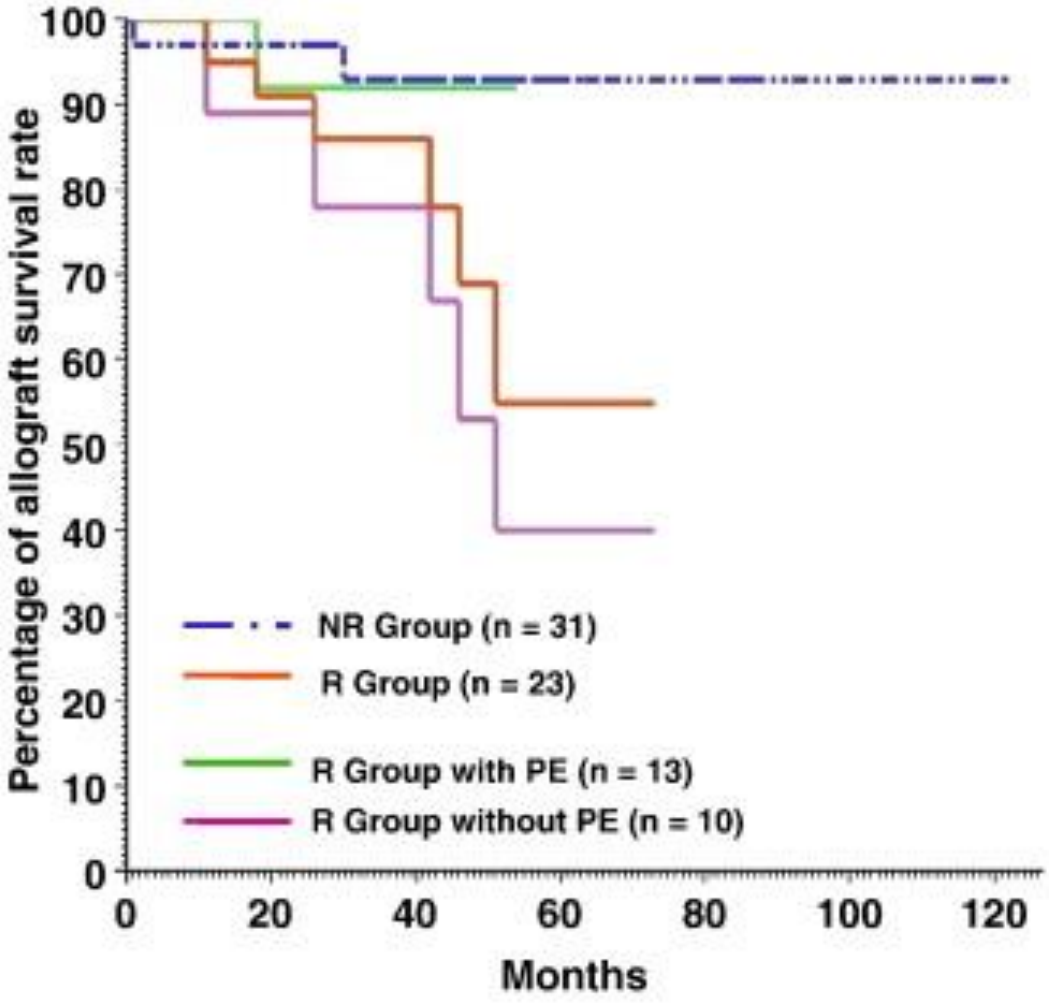
- Idiopathic FSGS: management
  - Prevention, i.e. to treat the recipient before transplantation
  1. ***Living donor :***
     - Start treatment around 10 days before KTx :
       - IV ciclosporine (« trough levels » at around 300 ng/mL)
       - Steroids (1 mg/kg/d)
       - Rituximab 375 mg/m² (D -10)

       Or Cyclophosphamide IV 1g (D -10)
       - 1 plasmapheresis (or immunoadsorption) session pre-KTx
     - Posttransplant immunosuppression : IV ciclosporine (10 days then orally), steroids, mycophenolate mofetil (MMF) or mycophenolic acid
       - Plasmapheresis : only when albuminuria > 500 mg/d

2. ***Deceased donor :***

- Start treatment as early as possible, i.e. a few hours pre-transplant:
  - IV cyclosporine
  - Steroids (1 mg/kg/d)
  - 1 plasmapheresis session
  - Then Rituximab IV 375 mg/m²
- Posttransplant immunosuppression : IV ciclosporine (10 days then orally), steroids, MMF or mycophenolic acid
- Plasmapheresis : only when albuminuria > 500 mg/d

Impact of plasma exchange on allograft survival rate: the Necker experience.



They retrospectively studied the allograft survival rate of patient with (R group) or without (NR group) FSGS recurrence from January 1994 to December 2004.
In case of recurrence, they separated patients according to PE status in their therapeutic approach.

Canaud G, et al. Transplant Rev, 2010

- Treatment of the recurrence of FSGS :

  - Rituximab infusion (375 mg/m²) or cyclophosphamide IV (1g) up to 4 times

  - Daily plasmapheresis (or daily immunoadsorption)

    - How many sessions ? It is guided by the albuminuria rate

    - ≈ 50% of remission

  - In case of no remission despite of the previous therapies try oral GALACTOSE

MGN

- The allograft may demonstrate :
- ***De novo*** **MN** :occurring more frequently than recurrent MN
  - ***Recurrence*** :
    - Between 6 to 36 months posttransplantation
    - May be silent (detected by protocol biopsies)
    - Is associated with a progressive increase rate of proteinuria
    - No predictive factors, except auto-antibodies to M type PLA2 receptors

Recurrent MGN

Recurrent rate :40% to 50%

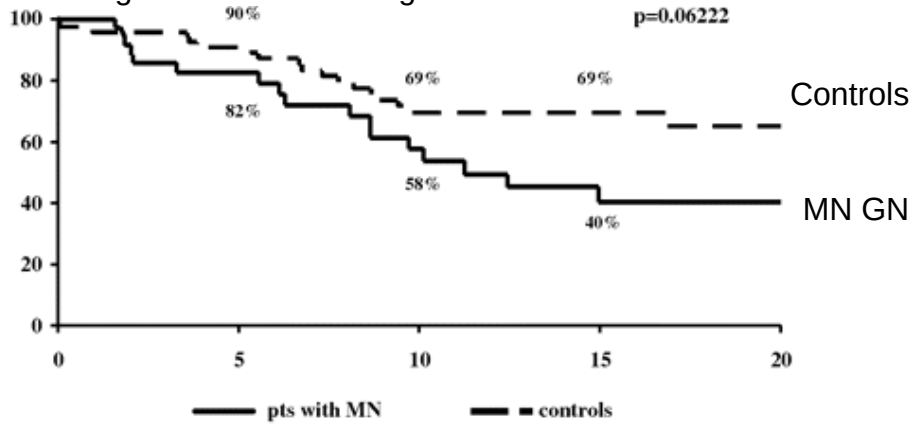
anti-PLA2R antibodies positive pre transplantation 60% to 76% risk of histologic recurrence

antibody negative patients 28%–30%.

Beck LH Jr, Fervenza FCJ, Am Soc Nephrol. 2011

Monocentric study; 35 first KT pts (1975-2008) matched with a controled group of 70 1st KT pts; posttransplant follow-up: 117 +/- 86 months

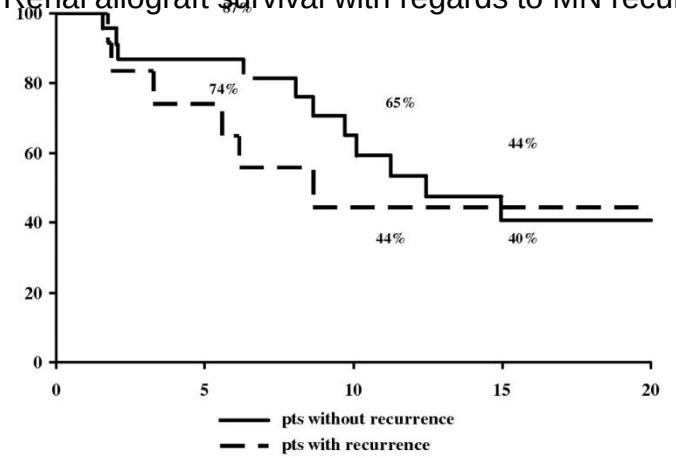
Renal allograft survival with regards to initial GN



Pts at risk	5 years	10 years	15 years	20 years
pts with MN	25	14	8	2
controls	52	34	19	6

Kaplan–Meier estimates of renal survival probability censored for death in renal transplanted patients with membranous nephropathy (solid line) and in controls (dashed line).

Renal allograft survival with regards to MN recurrence

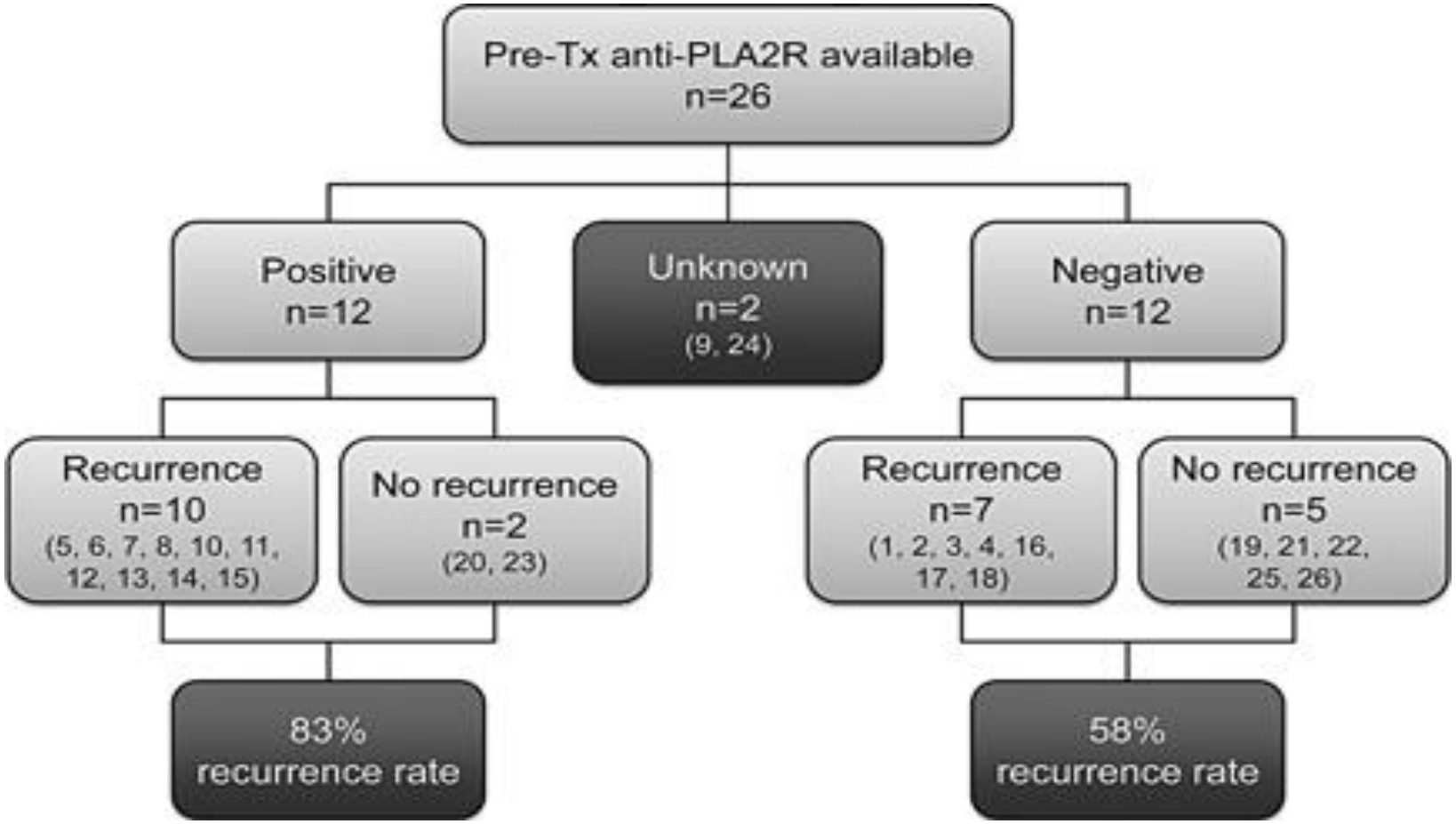


Pts at risk	5 years	10 years	15 years	20 years
pts without recurrence	16	11	6	2
pts with recurrence	8	3	2	0

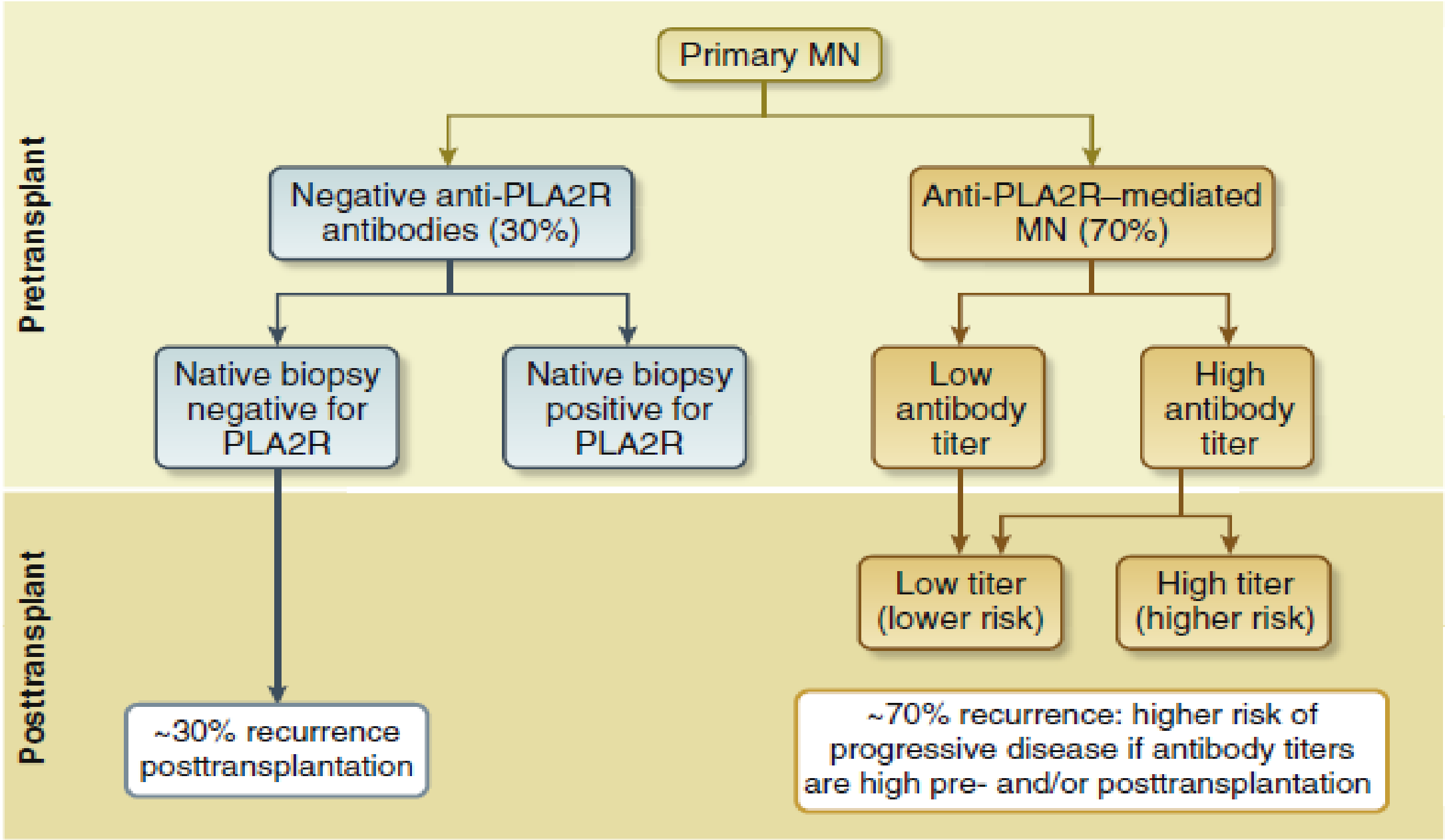
Kaplan–Meier estimates of renal survival probability censored for death in renal transplanted patients without recurrence (solid line) and in those with recurrence of membranous nephropathy (dashed line).

Moroni G, et al. NDT 2010;25(10):3408-15

Distribution of pre-Tx anti-PLA2R in those with and without MN recurrence



Kattah A, et al. AJT. 2015;15:1349-59



Assessment of risks of MN recurrence and progression posttransplantation

Kidney International (2017

TREATMENT

45% of death-censored graft losses in patients with primary MN are due to recurrent disease.

Early treatment when proteinuria reached 1000 mg/day has led to a very high percentage of therapeutic success.

TREATMENT

- Steroids and CNI are first line therapies
- ARB and / or ACEIs
- Combination of alkylating agents (cyclophosphamide or chlorambucil) and corticosteroids
- Rituximab therapy
  - 35% complete remission
  - 40% partial remission
  - Resorption of electron-dense immune deposits in many responders.

Transplantation ,December 30, 2015.

Rituximab therapy cotinue….

- no need to modify transplant immunosuppression.
- leads to progressive declines in anti-PLA2R antibody titers before the proteinuria declines.


jazzaab.ir