IgA Nephropathy – Prognostic Considerations & Nanjing Jinling Hospital Studies

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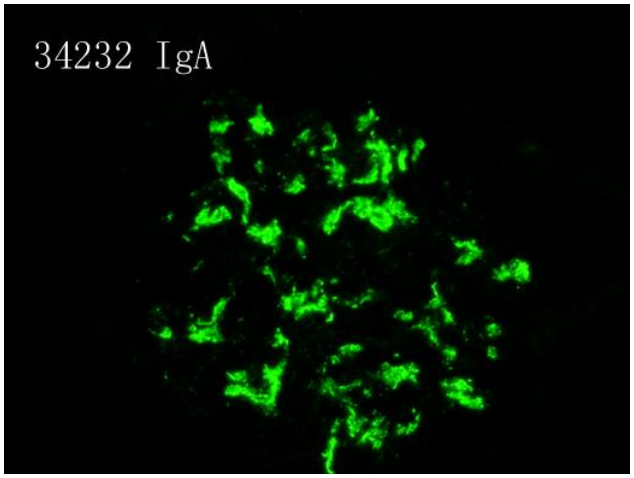
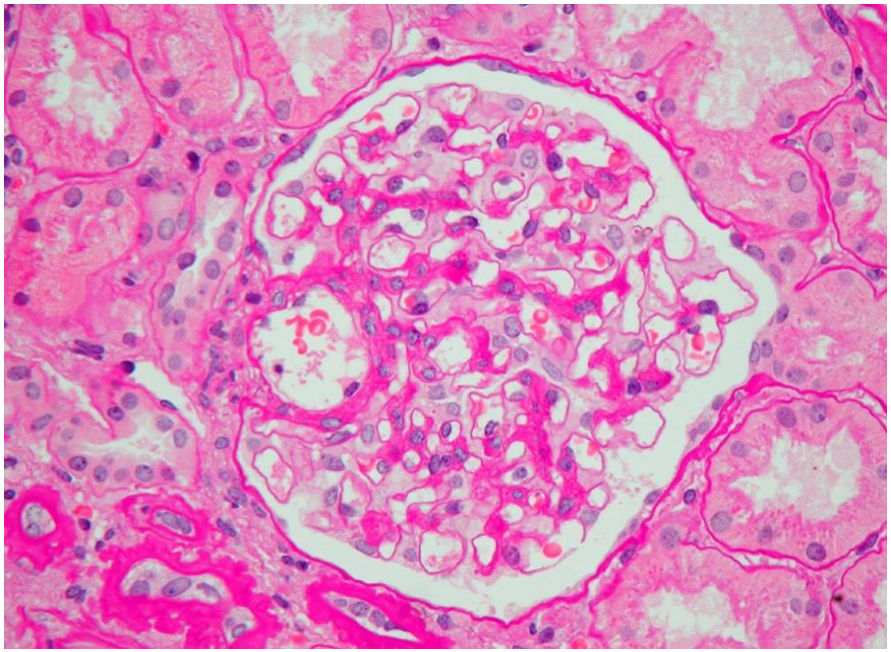
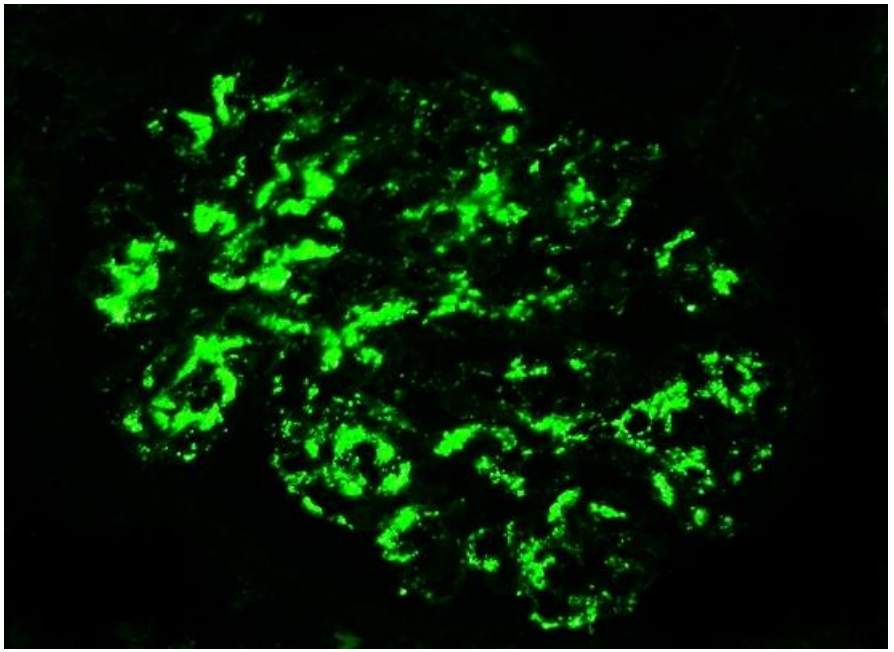
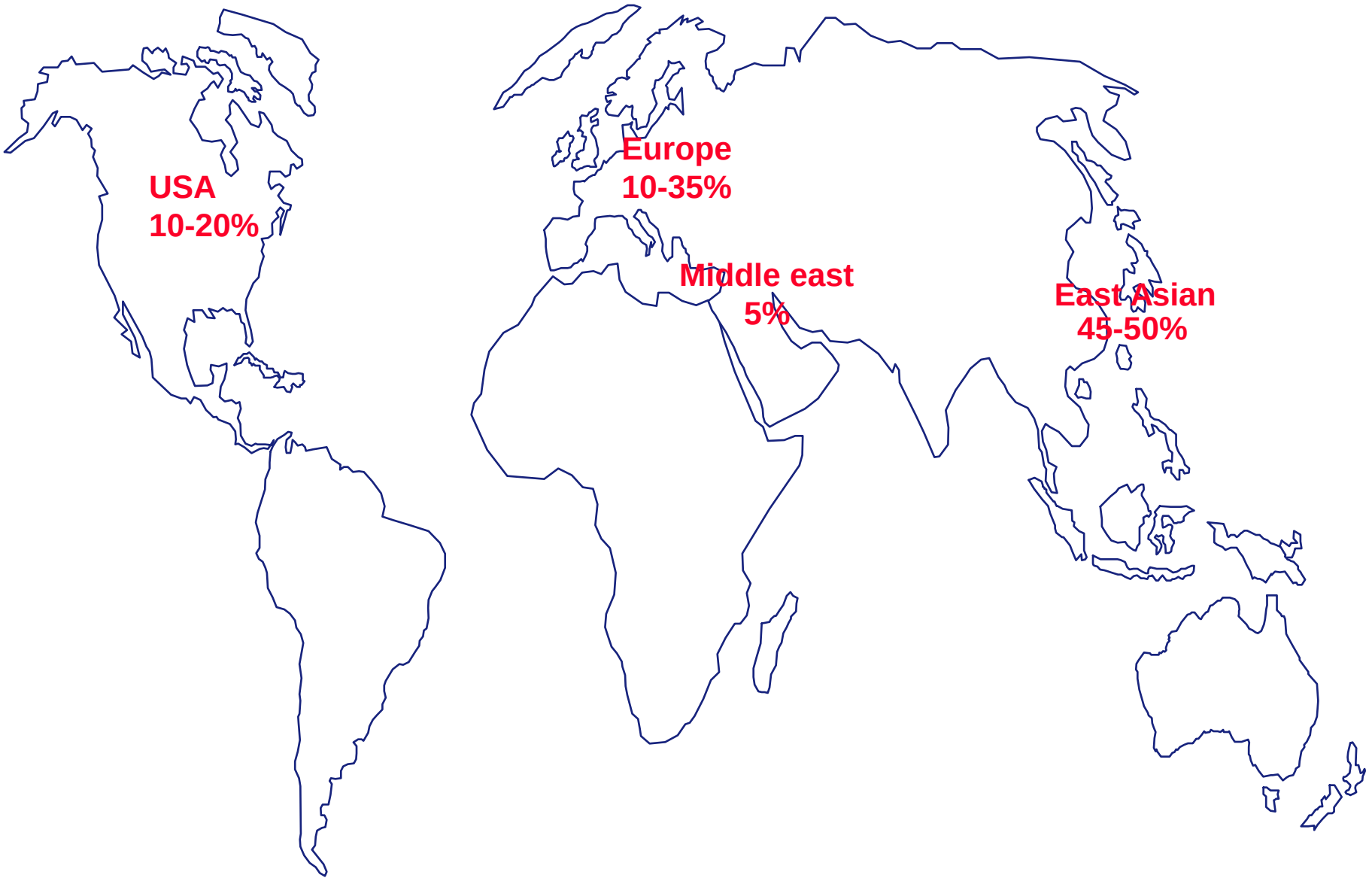


- **IgAN is the most common form of primary glomerulonephritis worldwide**
- **The hallmark of IgAN is the mesangial dominant or codominant deposition of IgA by IF with mesangial proliferation.**





Geographic variability in the prevalence of IgAN



The clinical presentation of primary IgAN is variable

- Microscopic hematuria without proteinuria ;
- Isolated or Recurrent macroscopic hematuria;
- Asymptomatic microscopic hematuria with proteinuria ;
- Nephrotic proteinuria or Nephrotic syndrome;
- Hypertension;
- Acute renal failure;
- Chronic renal failure.

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Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population

WeiBo Le, ShaoShan Liang, YangLin Hu, KangPing Deng, Hao Bao, CaiHong Zeng and ZhiHong Liu

1989 to 2005

Table 1. Demographic and clinical features at biopsy[a]

Items	Values	Items	Values
Female (%)	50.3%	Urinary protein (g/day)	0.89 (0.51–1.59) g/day
Age at onset (years)	31 ± 9	<1.0 (%)	55.7%
Age at biopsy (years)	34 ± 9	≥1.0 (%)	44.3%
BMI (Kg/m^2)	22.8 ± 3.3	>3.5 (%)	7.0%
Family history of kidney disease (%)	6.8%	Urinary microscopic hematuria (1000 cells/mL)	400 (60–1380)
Initial presenting clinical features (%)		Serum albumin (g/L)	38.3 ± 6.0
By chance in a health check-up	19.5%	Total cholesterol (mmol/L)	4.9 ± 1.8
Macroscopic hematuria	30.0%	Triglyceride (mmol/L)	1.8 ± 1.3
Edema	23.4%	Serum uric acid (μmmol/L)	369 ± 110
Hypertension	11.2%	eGFR (mL/min/1.73m^2)	89 ± 33
Others	15.2%	SCr (mg/dL)	1.06 ± 0.55
Previous macroscopic hematuria	35.9%	CKD Stage 1 (%)	47.6%
Isolated macroscopic hematuria	22.2%	CKD Stage 2 (%)	31.6%
Recurrent macroscopic hematuria	13.7%	CKD Stage 3 (%)	18.3%
Persistent hypertension (%)	31.0%	CKD Stage 4 (%)	1.9%
		CKD Stage 5 (%)	0.6%

[a]CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; ESRD, end-stage of renal disease. Values are expressed as mean ± SD or median (interquartile range). Categorical variables are expressed in percentages. Calculation of MAP and eGFR is detailed in the text.

Nephrology American Journal of

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Long-Term Outcome of IgA Nephropathy Patients with Recurrent Macroscopic Hematuria

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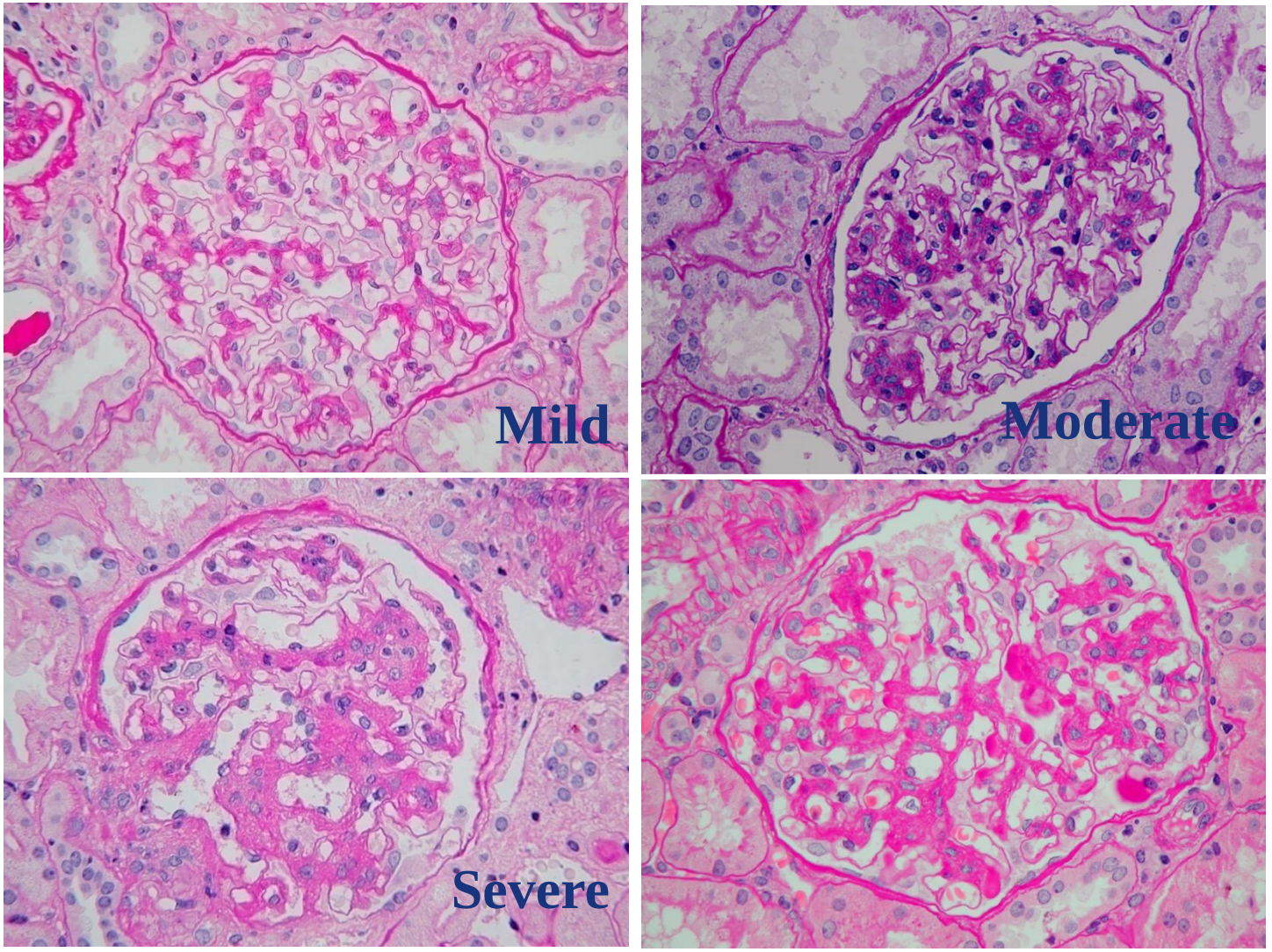
Nanjing,

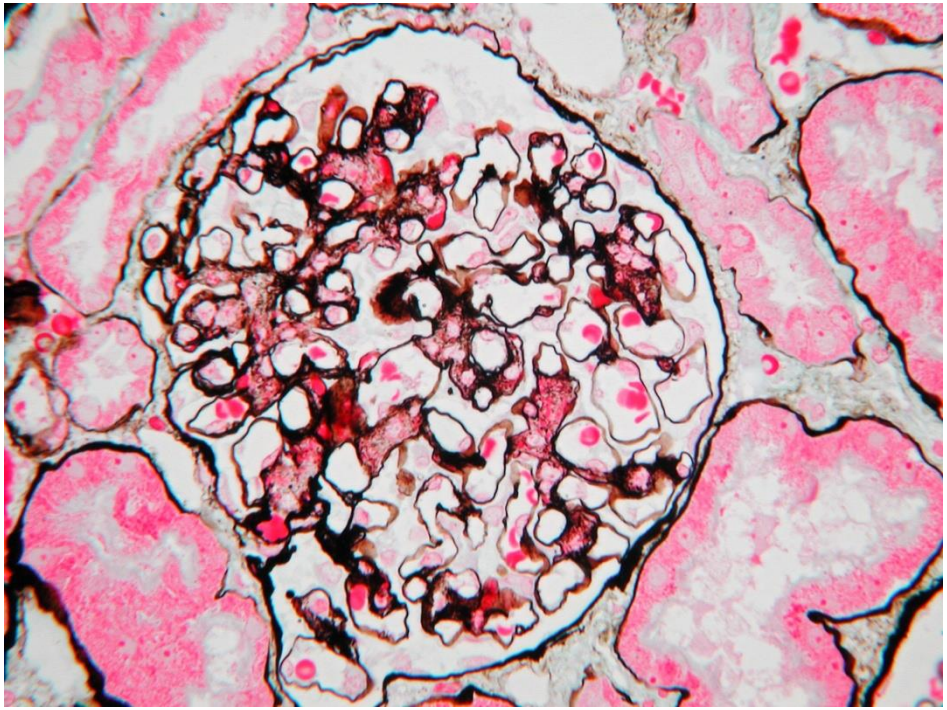
Table 1. Demographic and clinical features at biopsy

Item	RMH (n = 158)	IMH (n = 256)	NMH (n = 741)	p value
Female, %	59.5	58.2	45.6[a, e]	<0.001
Age at onset, years	26±9	29±9[c]	32±9[a, e]	<0.001
Age at biopsy, years	30±9	32±9[c]	35±9[a, e]	<0.001
Body mass index, kg/m^2	21.5±2.9	22.5±3.0[c]	23.1±3.4[a, e]	<0.001
Family history of CKD, %	11.1	4.8[d]	6.7	0.05
Hypertension ≥140/90 mm Hg, %	14.0	14.8	40.3[a, e]	<0.001
Proteinuria at biopsy, g/day	0.66 (0.38–1.52)	0.78 (0.41–1.42)	0.97 (0.58–1.65)[a, e]	<0.001
Proteinuria at biopsy (categorical)				<0.001
<0.5 g/24 h, %	38.1	31.5	19.1	
0.5–1.0 g/24 h, %	25.8	29.5	33.1	
≥1.0 g/24 h, %	36.1	38.9	47.8	
Urinary microscopic hematuria, log cells/μl	6.6±2.1	6.6±2.1	5.1±2.0[a, e]	<0.001
Serum albumin, g/l	39.4±5.4	38.9±5.1	37.8±6.4[a, f]	<0.001
Total cholesterol, mmol/l	4.5±1.3	4.4±1.1	5.2±2.1[a, e]	<0.001
Triglyceride, mmol/l	1.5±1.0	1.6±1.3	1.9±1.4[a, e]	<0.001
Serum uric acid, mmol/l	324±84	336±95	390±114[a, e]	<0.001
Serum creatinine, mg/dl	0.89±0.34	0.95±0.49	1.13±0.59[a, e]	<0.001
eGFR, ml/min/1.73 m^2	103±26	98±35	84±32[a]	<0.001
CKD stage (KDOQI), %				<0.001
CKD stage 1	71.5	65.2	47.6	
CKD stage 2	20.9	23.8	29.8	
CKD stage 3	7.0	9.7	19.3	
CKD stage 4	0.6	0	2.7	
CKD stage 5	0	1.2	0.5	

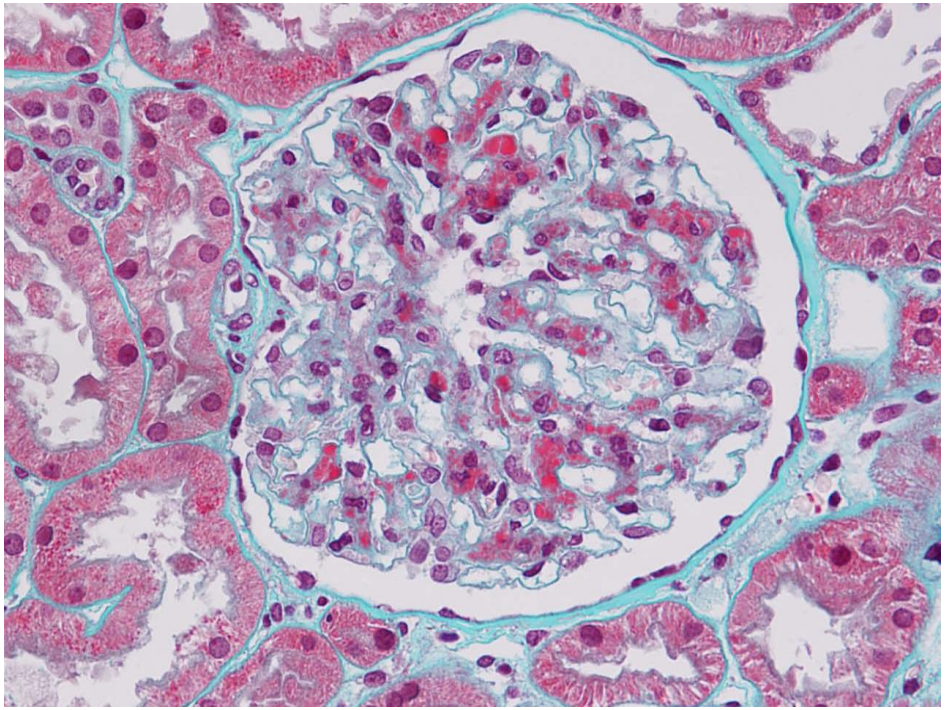
[a] $p < 0.01$ RMH vs. NMH; [b] $p < 0.05$ RMH vs. NMH; [c] $p < 0.01$ RMH vs. IMH; [d] $p < 0.05$ RMH vs. IMH; [e] $p < 0.01$ IMH vs. NMH; [f] $p < 0.05$ IMH vs. NMH.

IgAN light microscopy



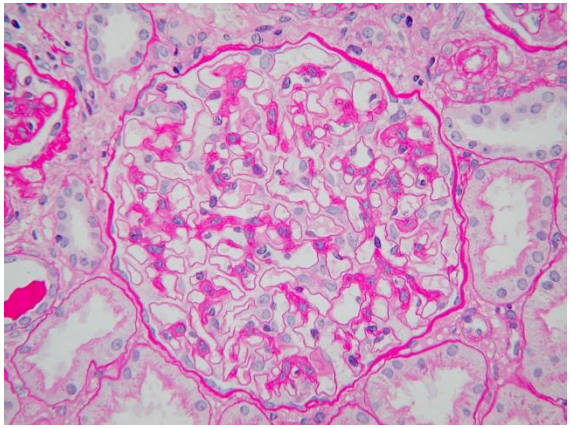
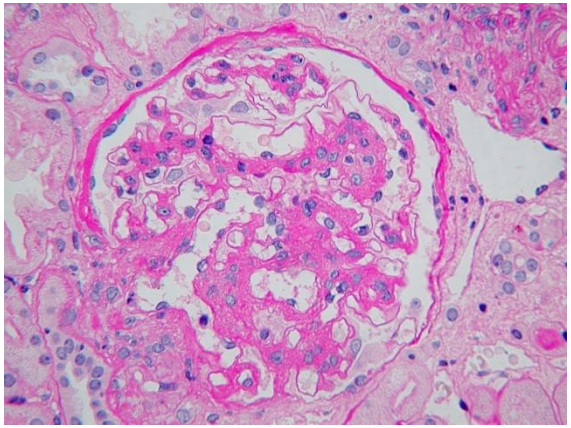
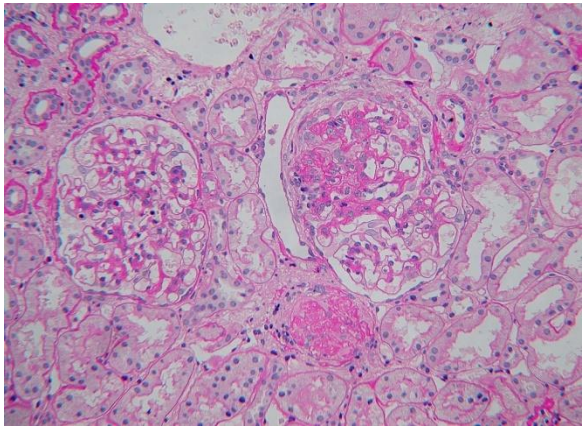


PASM-Masson trichrome



Masson trichrome

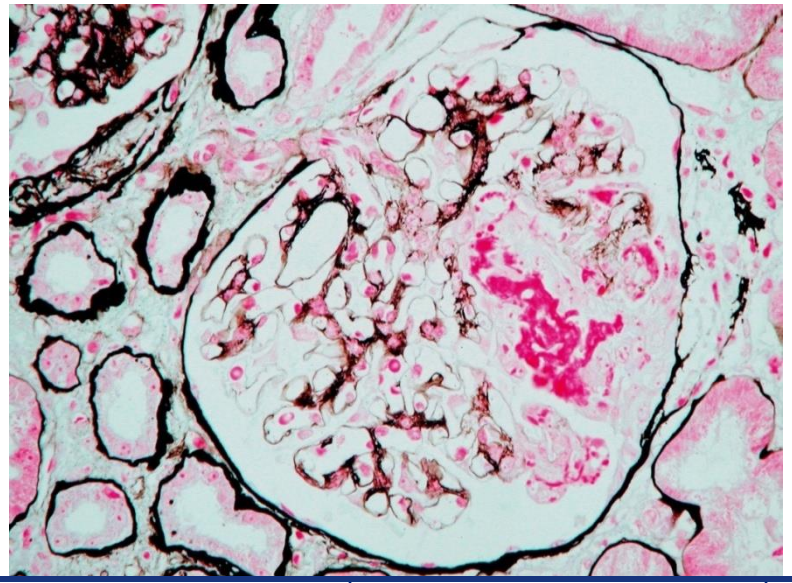
The histologic lesions of IgAN are not uniform

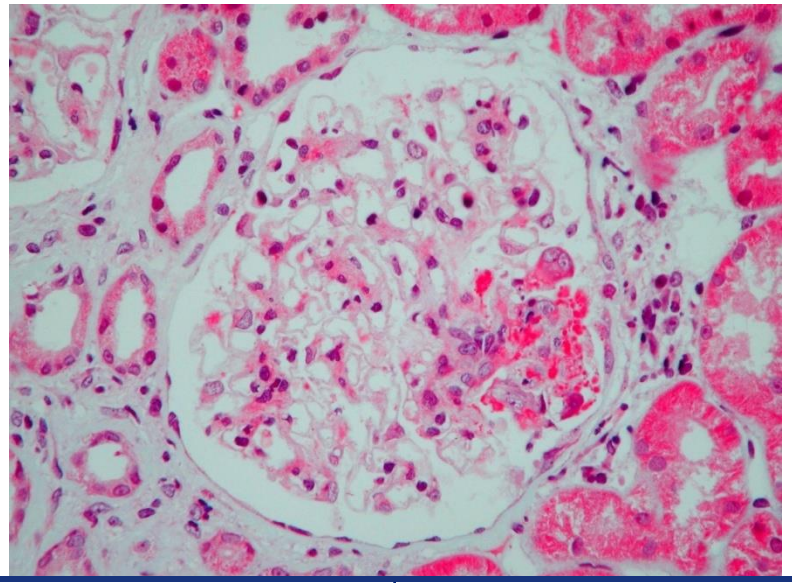




Active lesions in IgAN

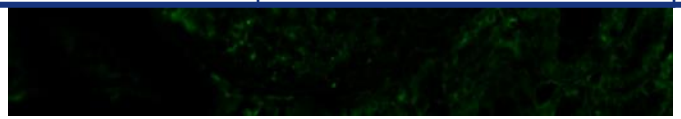
- Mesangial hypercellularity
- Endocapillary proliferation
- Necrosis, karyorrhexis,
- Cellular and fibrocellular crescents,
- Macrophage infiltration/mesangiolysis
- Tubulo-interstitial inflammation in non-scarred cortex
- Acute tubular injury

Necrotizing lesion: fibrinoid necrosis

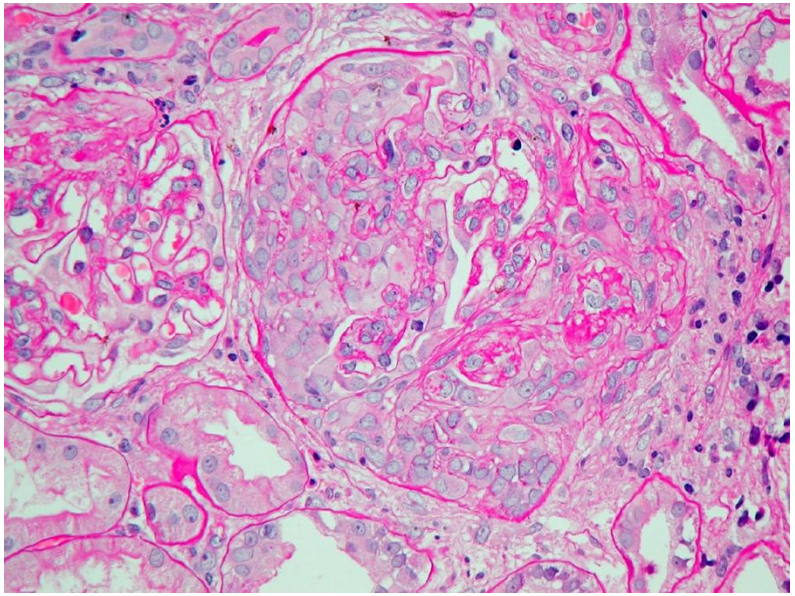


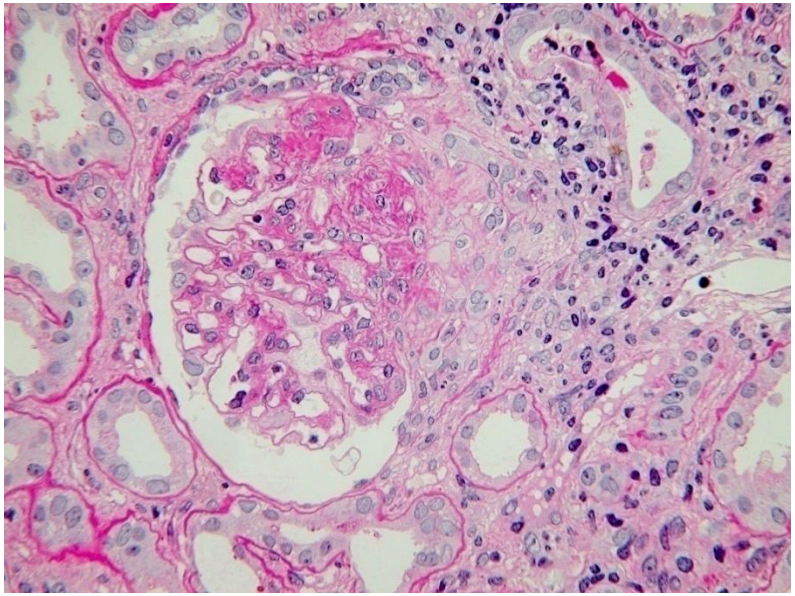


Study	Patients	Necrosis	prevalence %
Oxford	265	6	2.3
Nanjing	1026	117	15



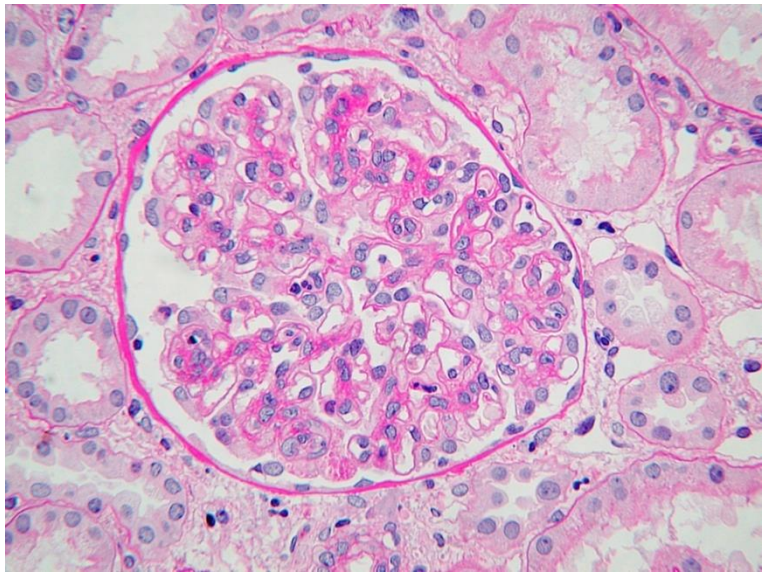
Cellular and fibrocellular crescents

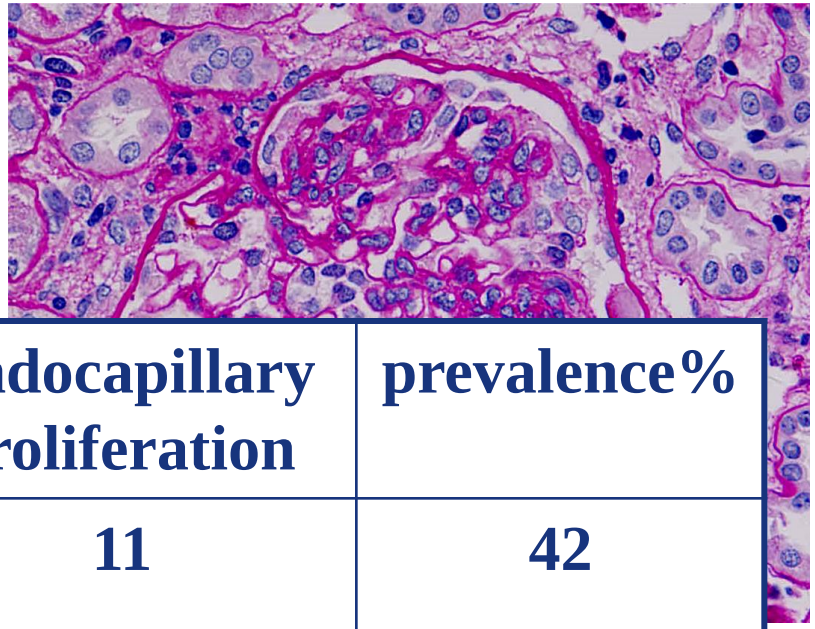




Study	Patients	crescents	prevalence %
Oxford	265	119	45
Nanjing	1026	492	48

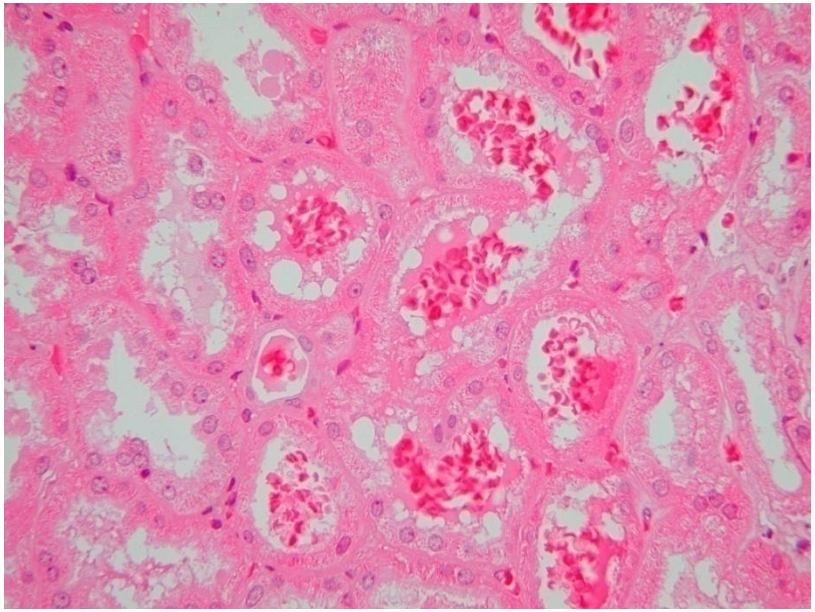
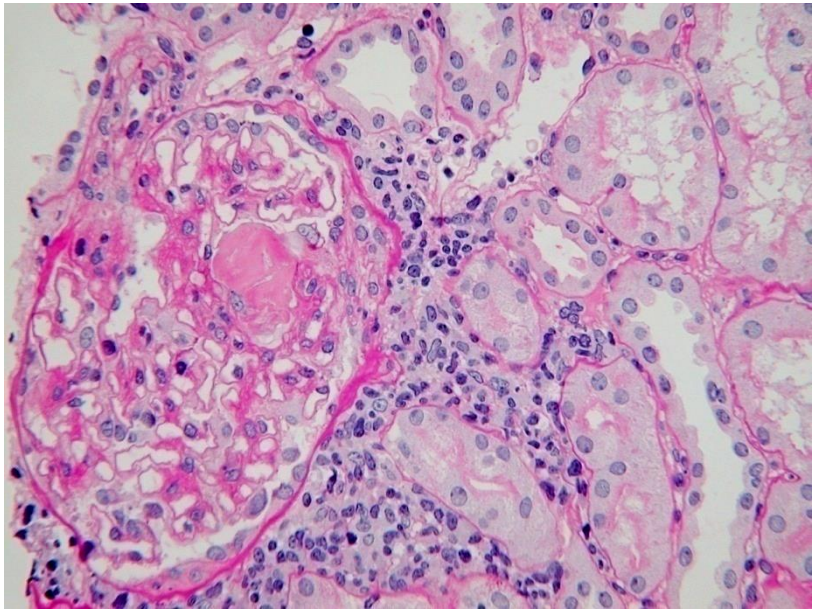
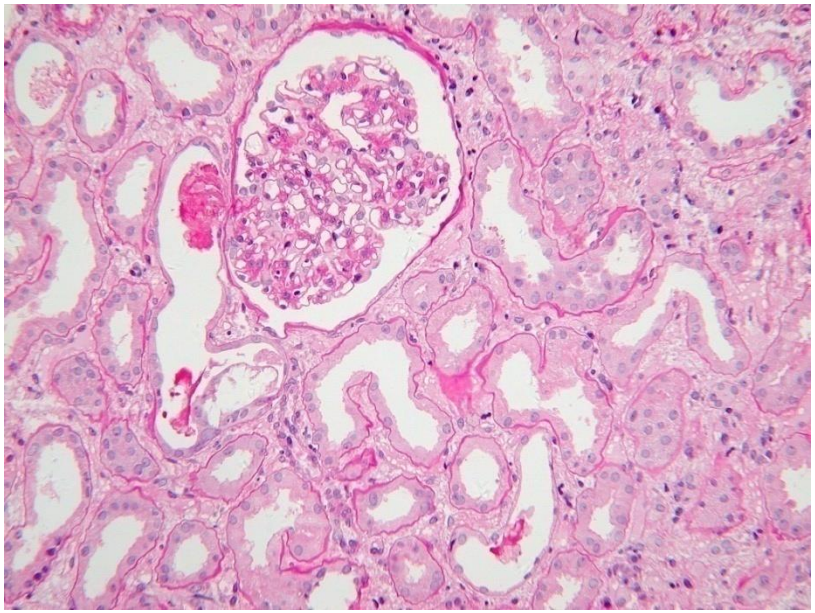
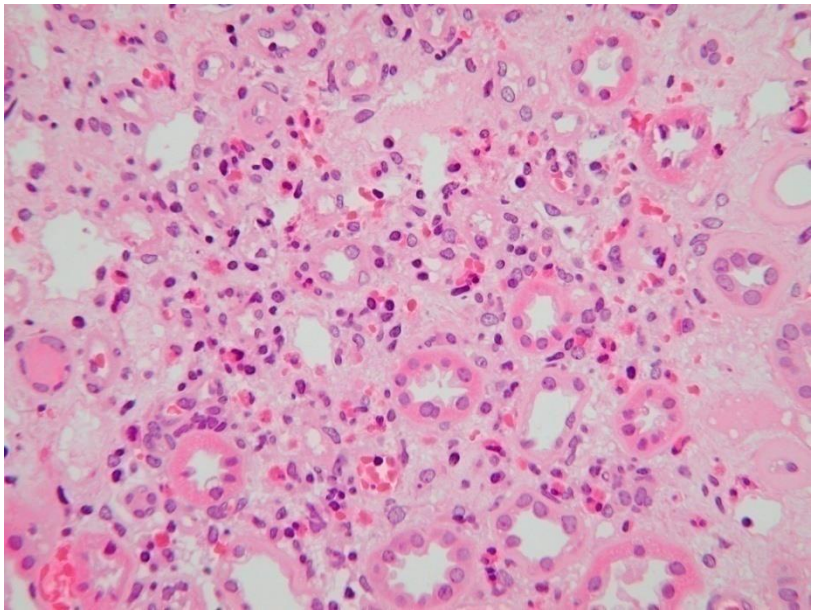
Endocapillary proliferation





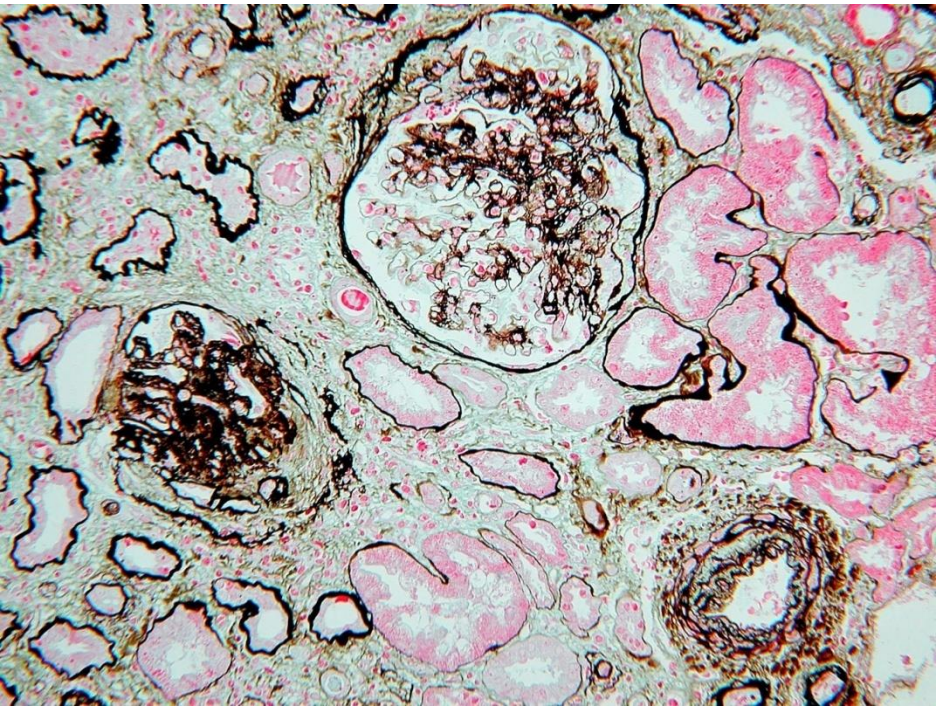
Study	Patients	Endocapillary proliferation	prevalence%
Oxford	265	11	42
Nanjing	1026	113	11

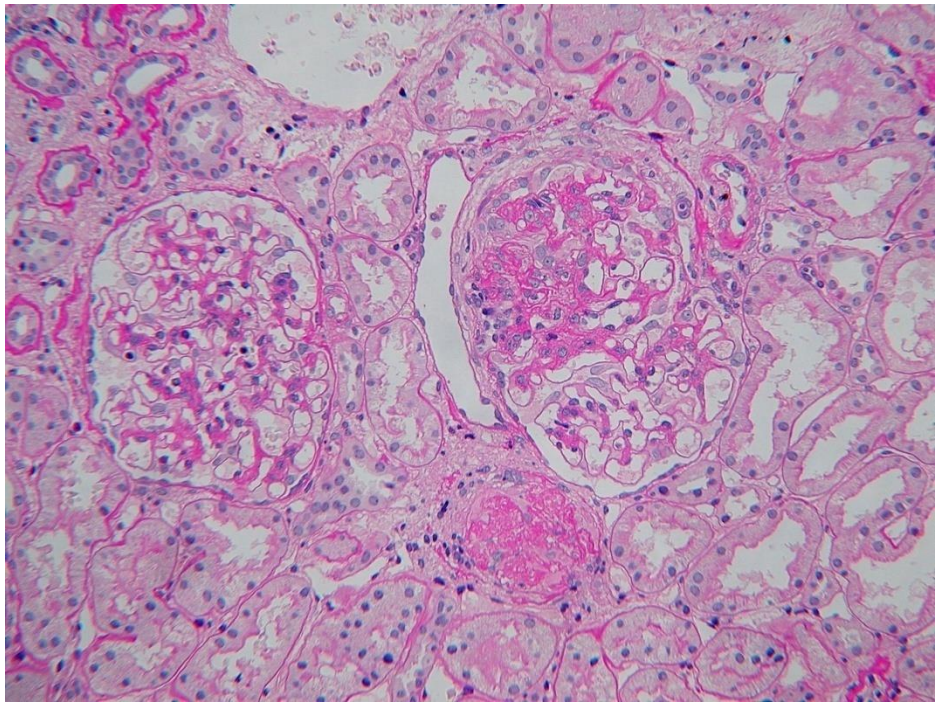
Acute tubular interstitial injury

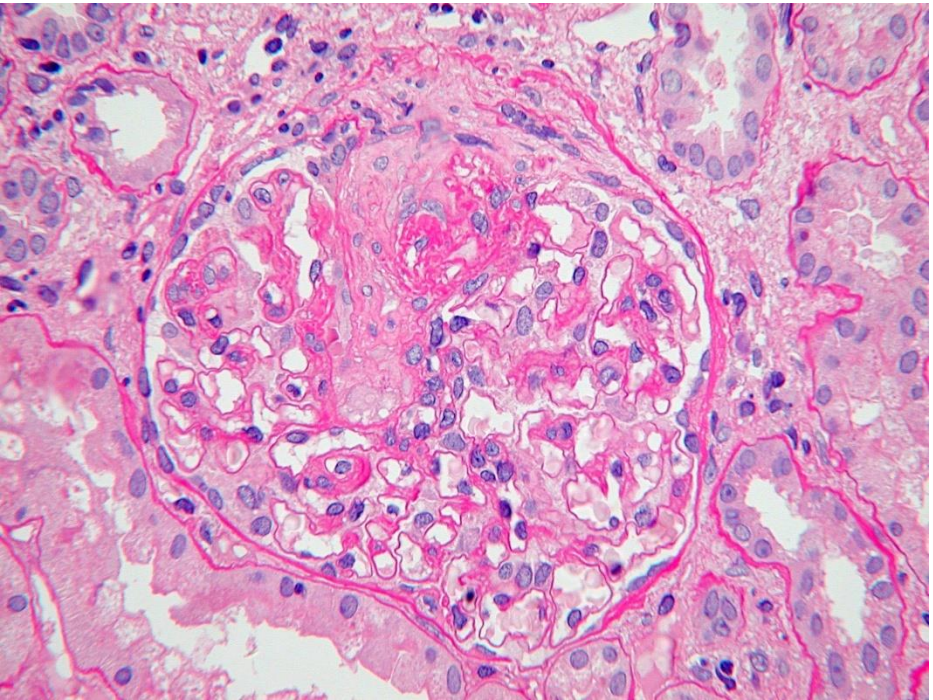





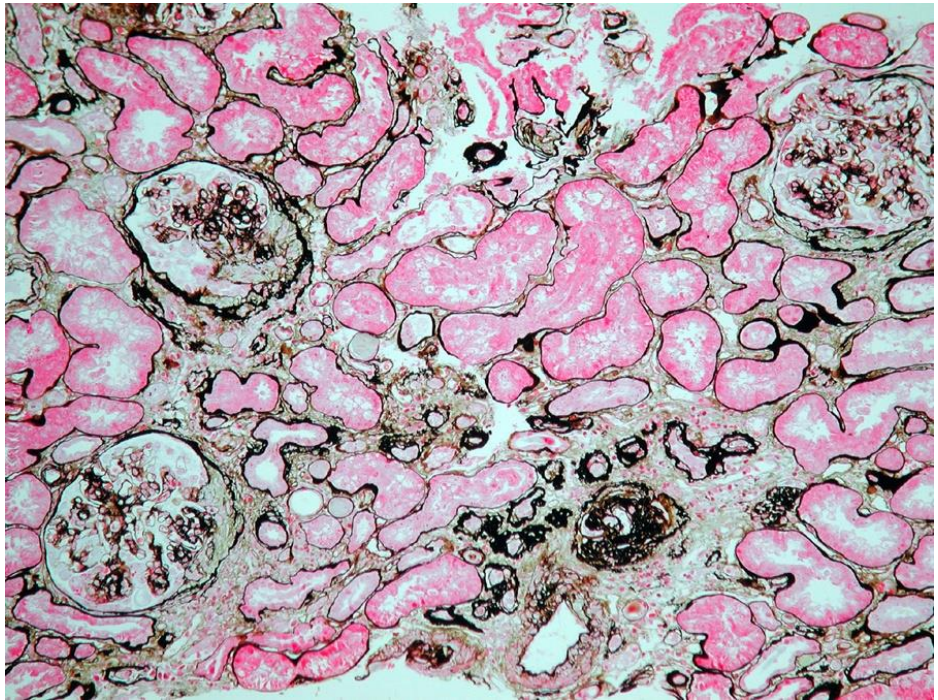
Chronic lesions In IgAN

- Global glomerulosclerosis
- Segmental glomerulosclerosis
- Fibrous crescents/ tuft adhesions/scar
- Tubular atrophy
- Interstitial fibrosis

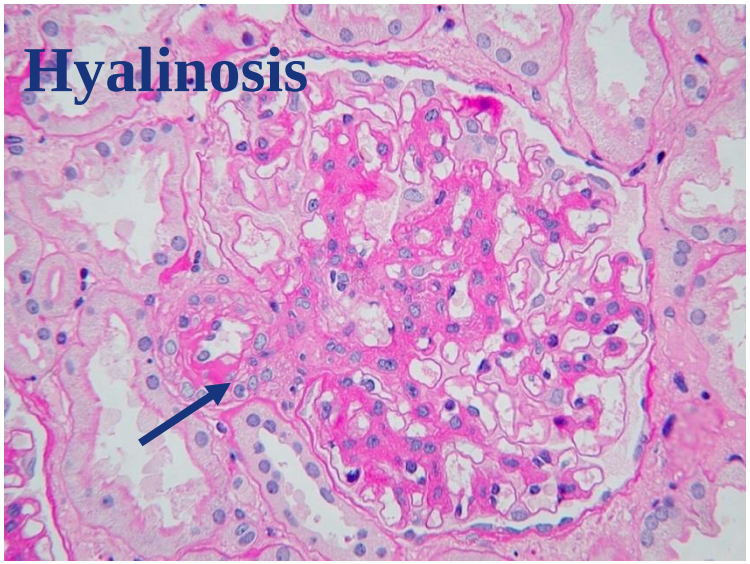


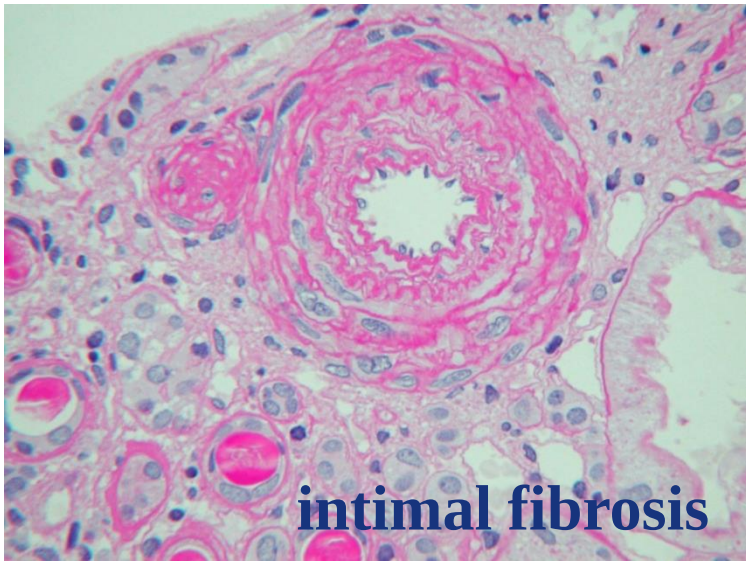


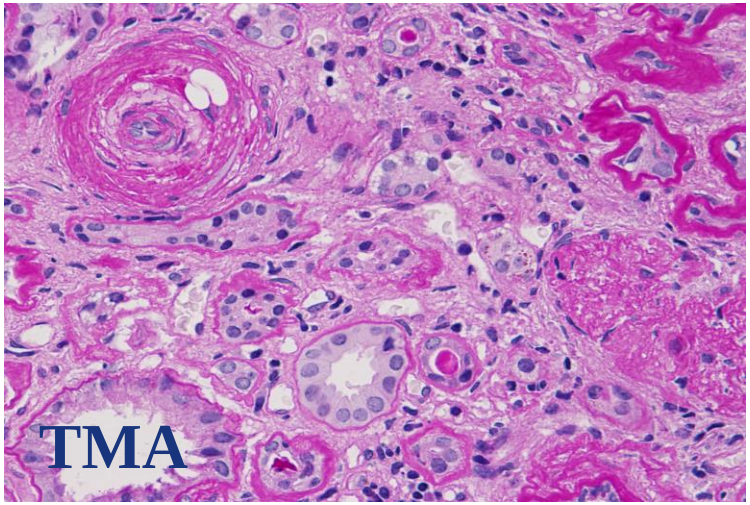


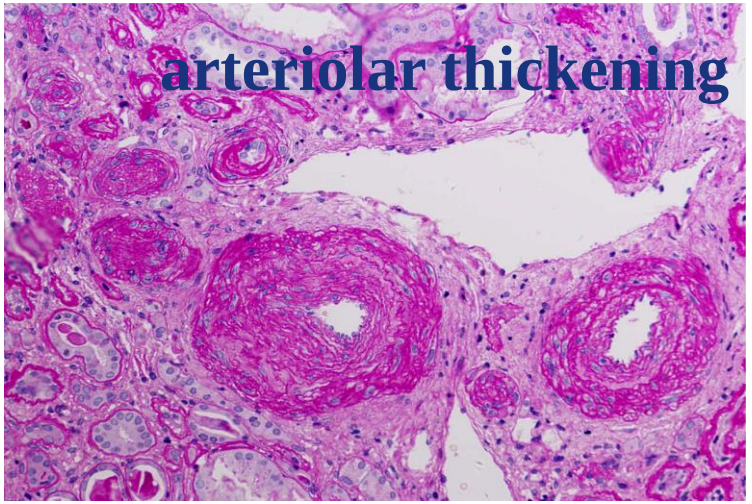


IgAN vasclular lesions

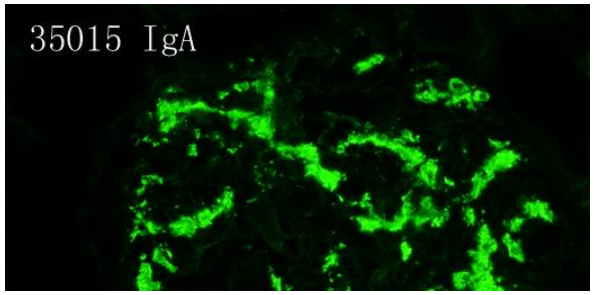


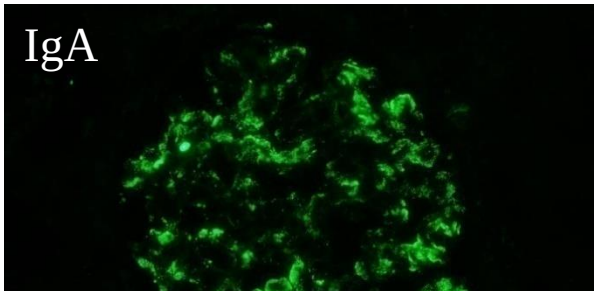






IF of IgAN





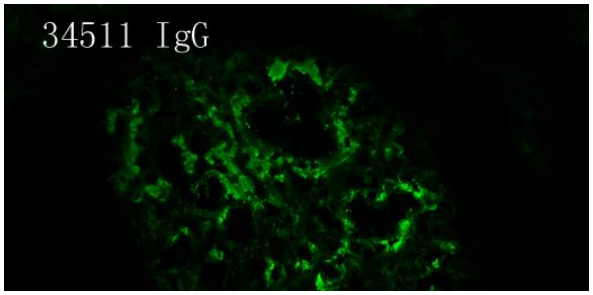


Table 1. Correlation of histological features with immunostaining patterns[a]

	Mesangial-only IgA ($n = 149$)	Capillary wall IgA ($n = 26$)	P-value	No/trace IgG ($n = 119$)	IgG > trace ($n = 30$)	P-value
Mesangial cellularity score	0.9 ± 0.5	1.3 ± 0.6	0.007	0.9 ± 0.5	1.2 ± 0.6	0.03
% Glomeruli global glomerulosclerosis	8 (0–82)	11 (0–55)	>0.1	11 (0–82)	8 (0–63)	>0.1
% Glomeruli segmental glomerulosclerosis	6 (0–44)	5 (0–33)	>0.1	4 (0–38)	9 (0–38)	>0.1
% Glomeruli endocapillary proliferation	0 (0–54)	6 (0–47)	0.003	0 (0–50)	4 (0–47)	0.005
% Glomeruli cellular + fibrocellular crescents	0 (0–55)	0 (0–39)	>0.1	0 (0–55)	0 (0–39)	>0.1
% Tubular atrophy	10 (0–70)	10 (0–30)	>0.1	10 (0–70)	10 (0–60)	>0.1
% Interstitial fibrosis	10 (0–70)	10 (0–30)	>0.1	10 (0–70)	10 (0–60)	>0.1
Arteriosclerosis score	0 (0–2)	0 (0–2)	>0.1	0 (0–2)	0 (0–2)	>0.1
Arteriolar hyalinosis score	0 (0–3)	0 (0–3)	>0.1	0 (0–3)	0 (0–3)	>0.1

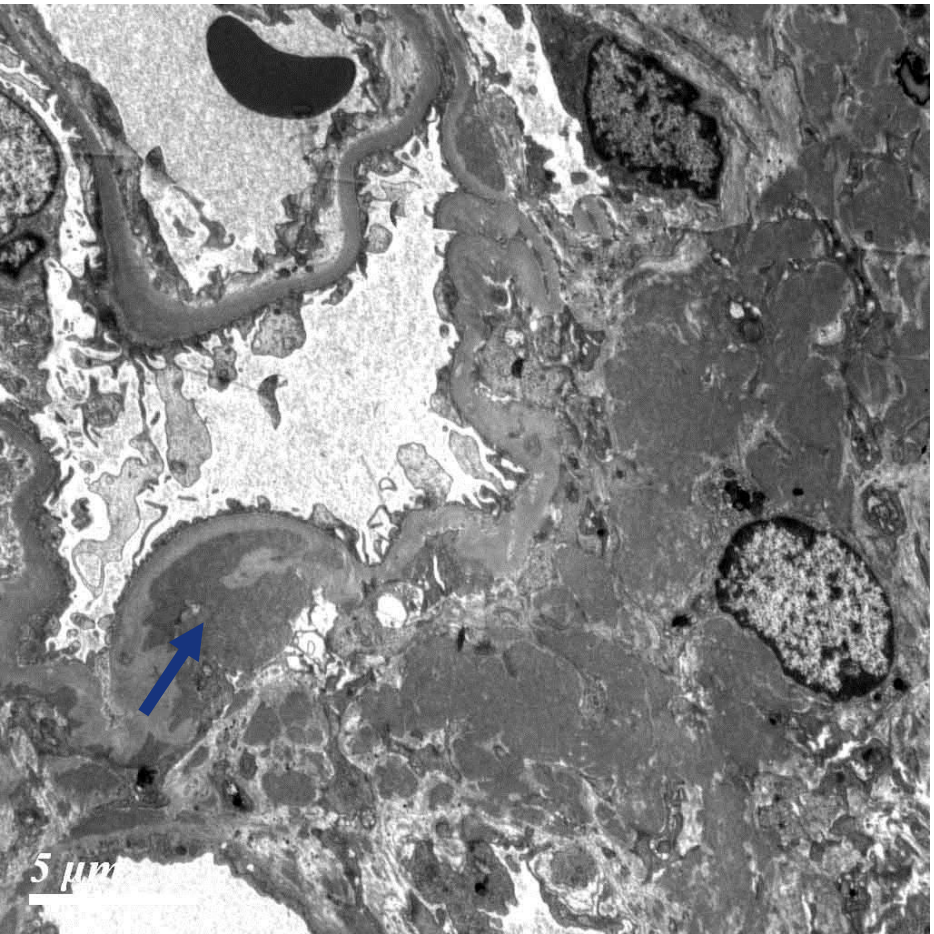
[a]Data are presented as mean ± SD for normally distributed data or median (range) for non-parametric distributions. **NDT (2011) 26: 2533–2536**

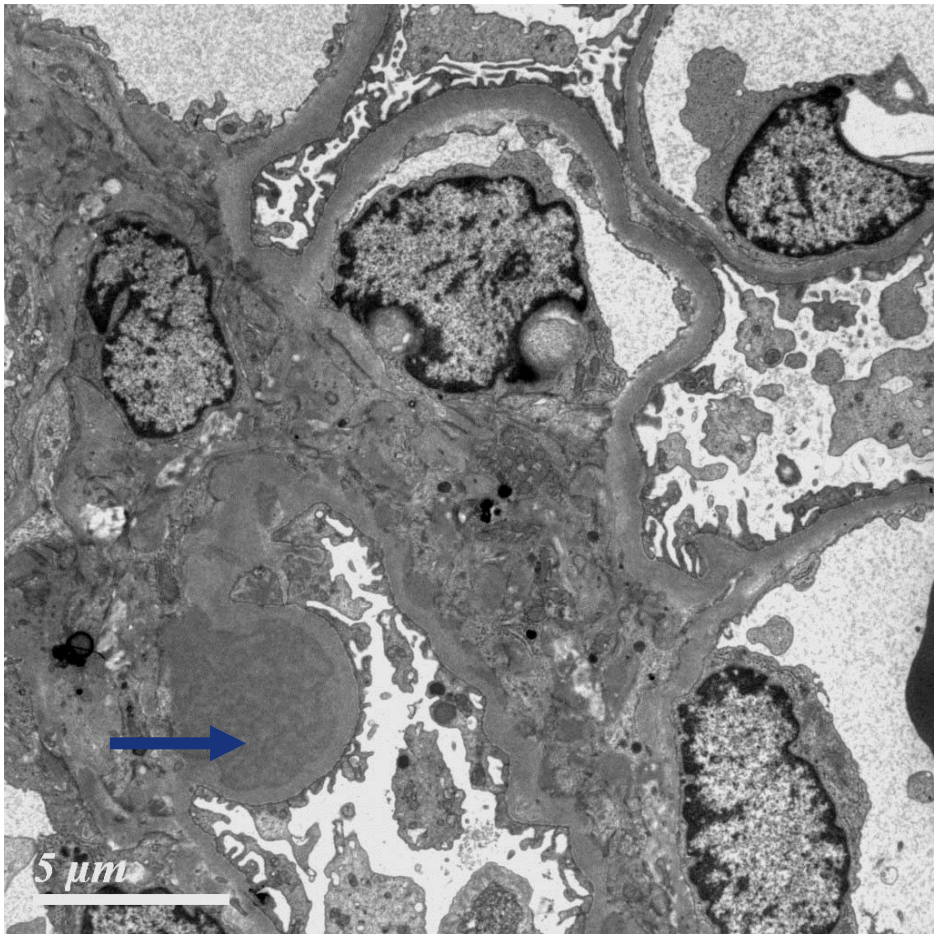
- **Co-deposition of C3 is common with IgG, and less common with IgM. Only IgA deposition: 15%**
- **Predominant IgA1 subclass**
- **λ more brightly than κ light chains**

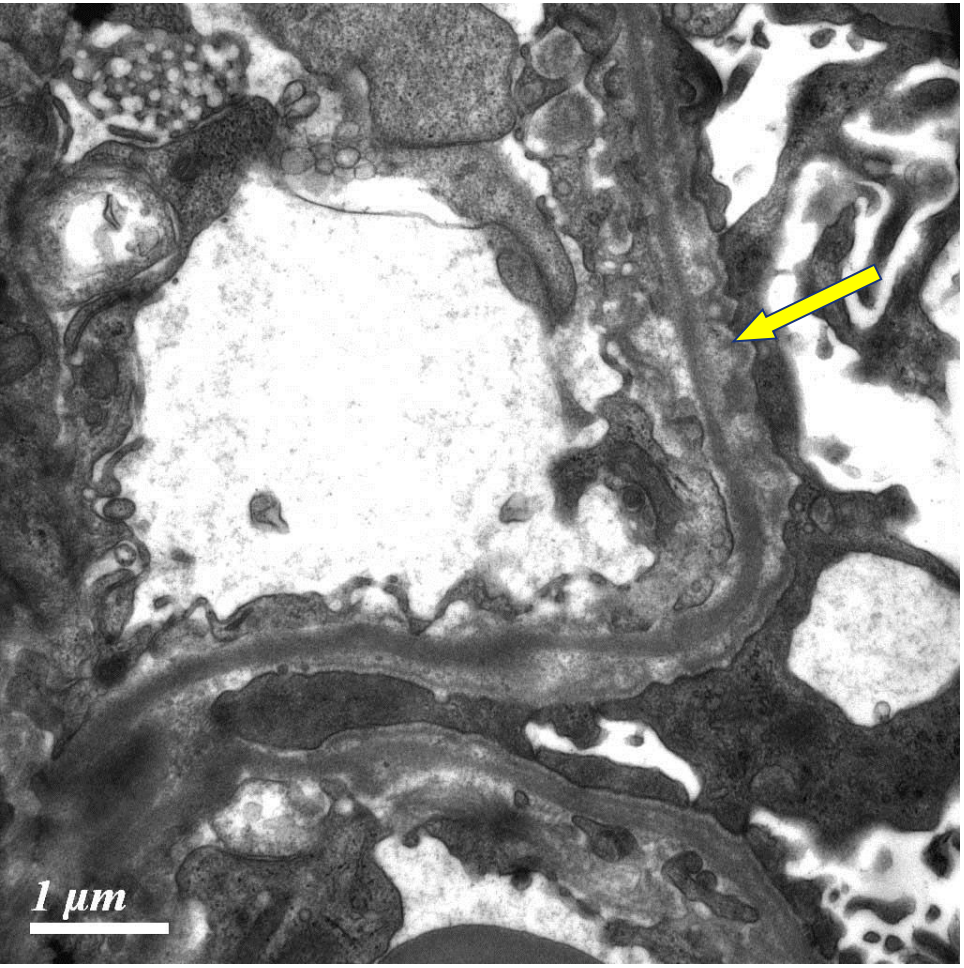
Am J Kidney Dis 1988;11:425
Am J Clin Pathol 1986;85:548

IgAN Electron Microscopy

- Granular electron-dense immune deposits in the mesangium and paramesangium



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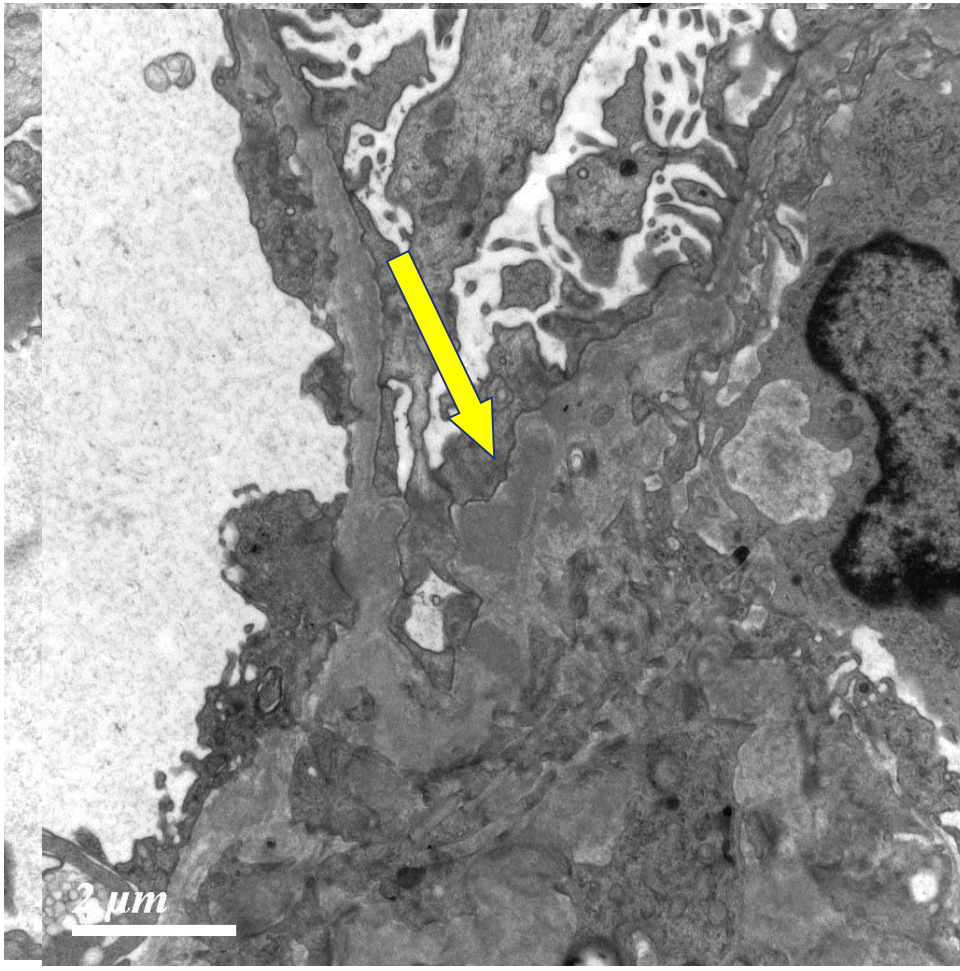
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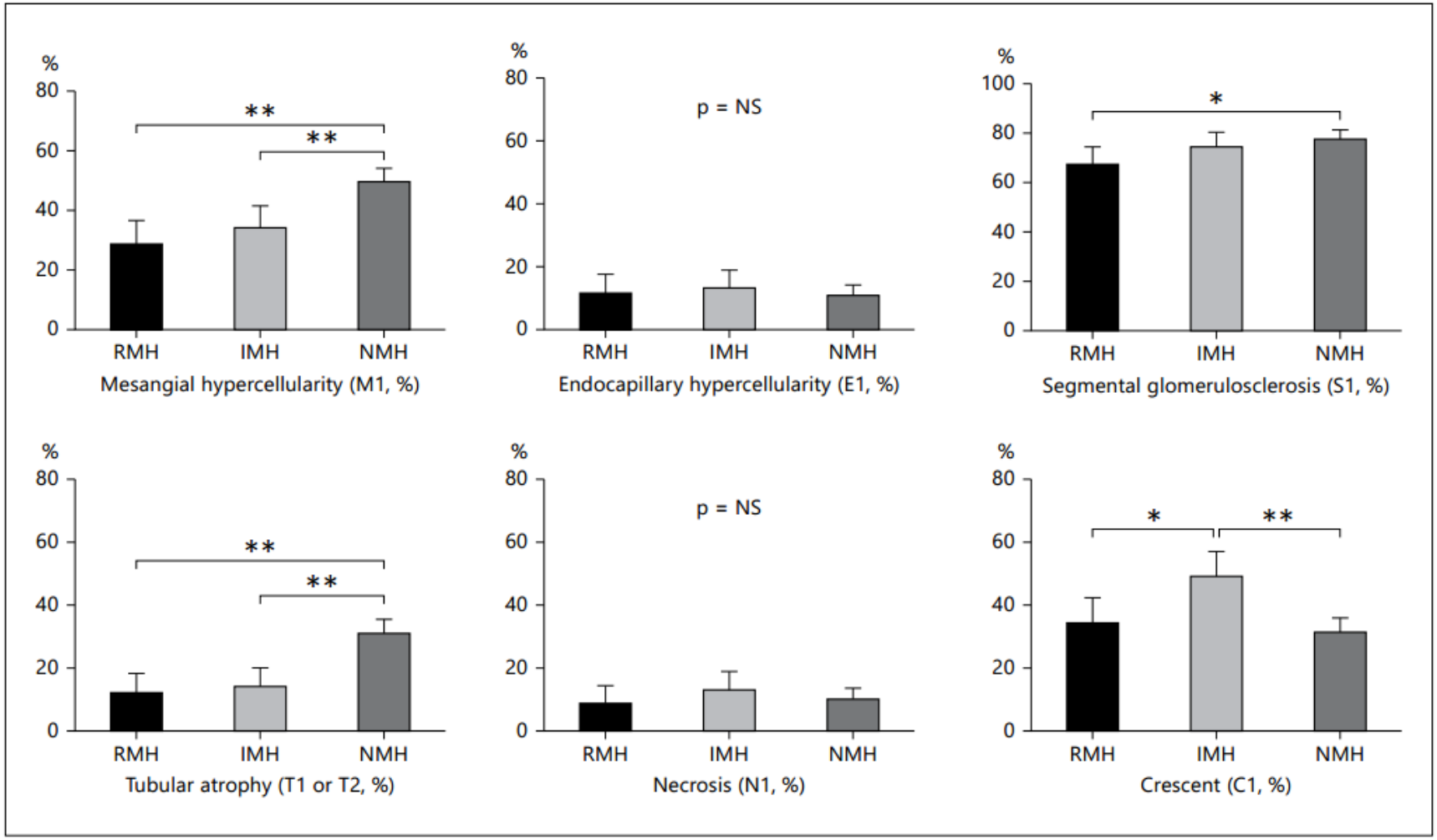
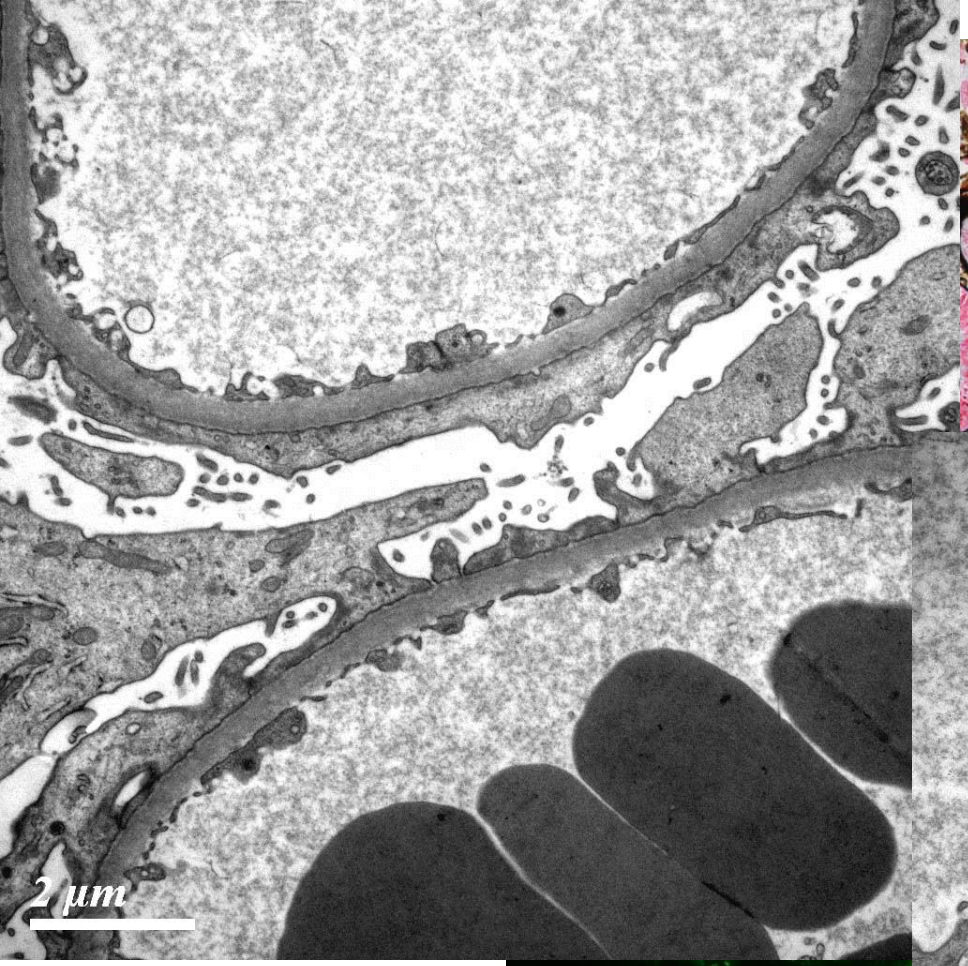
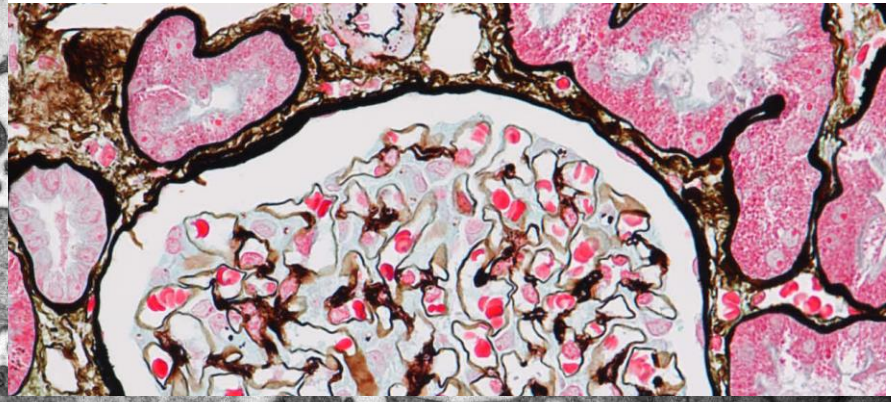


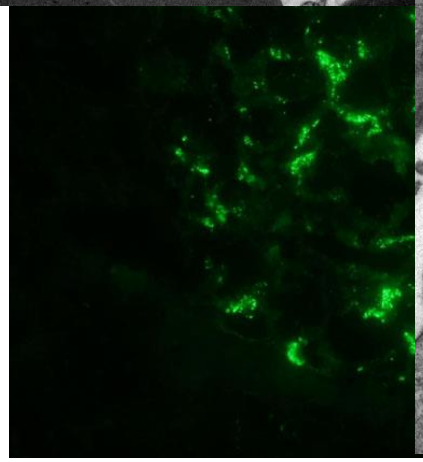
Fig. 1. Pathological features at biopsy among different MH patterns. * $p < 0.05$, ** $p < 0.01$; NS = not significant.

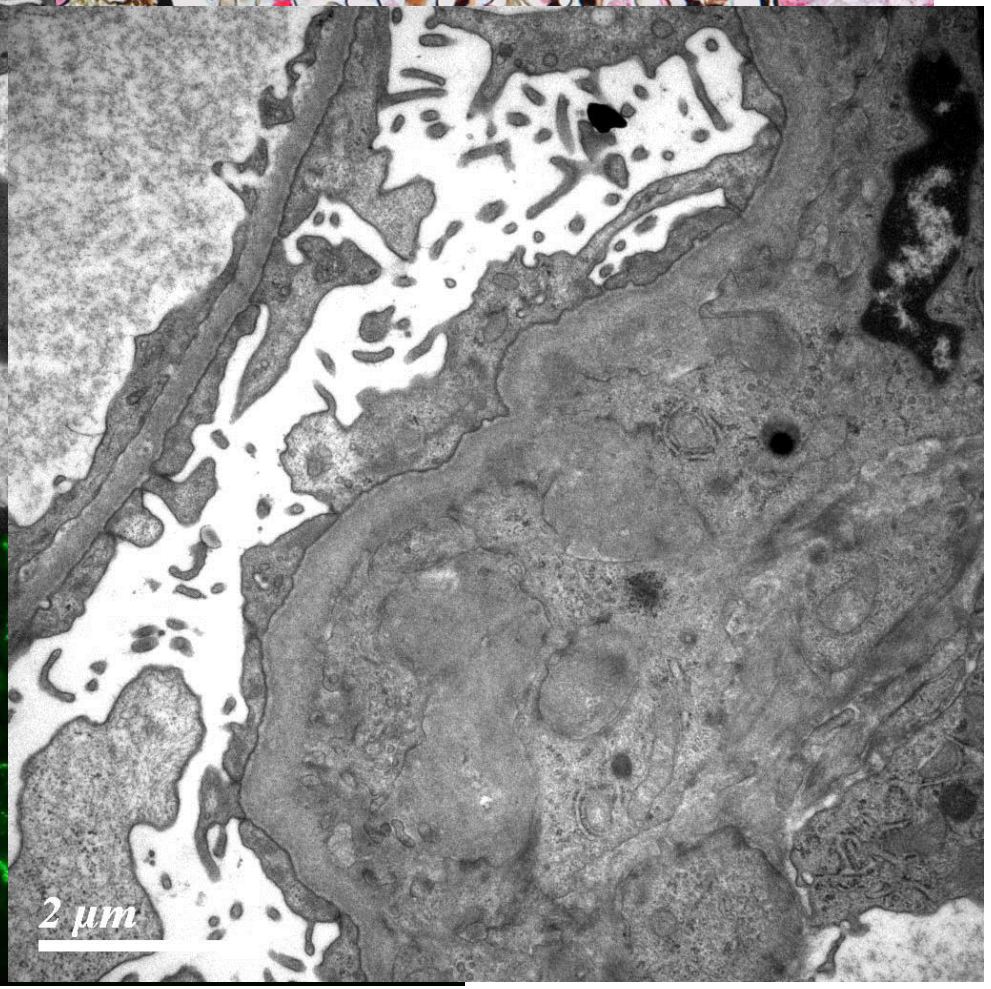
Minimal change disease like IgAN （MCD-IgAN）

- **Clinical features：NS，responsive to steroids**
- **Pathological features:**
  - **LM：Normal or minimal change**
  - **IF：IgA，with or without IgM、C3**
  - **EM：Electron dense deposits in mesangium，diffuse footprocess effacement**


2 µm






2 µm

Comparison of demographic , clinical and pathological characteristics

J Nephrol2015 Nov 4. [Epub ahead of print]

Items	MCD-IgAN (n = 247)	Non-MCD-IgAN	p
Male, %	67.6		
Interval between presentation and biopsy (months)	1 (0.1–40		
Age (years)	27.05 ± 1		
Initial symptom, %			
Edema	91.9		
Gastrointestinal discomfort	6.1		
Hypertension	0		
Gross hematuria	0		
Health examination	0.8		
Others	1.2		
Hypertension history, %	3.2		
Hypertension, %	19.0		
Urinary protein (g/day)	6.33 ± 3.8		
Grade of urinary protein (g/day), %			
<1.0	5.3		
1–3.5	11.3		
>3.5	83.4		
Urinary microscopic hematuria (10^4/ml)	1 (0–1100		
Grade of urinary microscopic hematuria (10^4/ml), %			
<10	81.4		
10–100	13.8		
>100	4.9		
Serum albumin (g/l)	23.39 ± 5		
Total cholesterol (mmol/l)	10.77 ± 3		
Triglyceride (mmol/l)	2.69 ± 1.1		
Serum uric acid (μmol/l)	380.53 ±		
SCr (mg/dl)	0.93 ± 0.1		
eGFR (ml/min/1.73 m^2)	109.48 ±		

MCD-IgAN immunoglobulin (Ig)A nephropathy with minir
estimated glomerular filtration rate

Items	MCD-IgAN (n = 247)	Non-MCD-IgAN (n = 1121)	p
Glomeruli, median (range)	24 (8–72)	21 (8–61)	0.168
Global glomerulosclerosis %, median (range)	0 (0–22.2)	13.6 (0–90.0)	<0.001
Oxford classification of IgAN, n (%)			
M1	27 (10.9)	408 (36.4)	<0.001
E1	0 (0)	105 (9.4)	<0.001
S1	0 (0)	754 (67.3)	<0.001
T1/T2	12 (4.9)	225 (20.1)	<0.001
N1	0 (0)	106 (9.5)	<0.001
C1	0 (0)	357 (31.8)	<0.001
Interstitial inflammation, n (%)			<0.001
0	106 (42.9)	72 (6.4)	
1	138 (55.9)	757 (67.6)	
2	3 (1.2)	212 (18.9)	
3	0 (0)	80 (7.1)	
Vascular lesion, n (%)			
Intimal thickening	35 (14.2)	430 (38.4)	<0.001
Hyaline degeneration	82 (33.2)	754 (67.3)	<0.001

M mesangial hypercellularity, *E* endocapillary proliferation, *S* segmental sclerosis or adhesion, *T* tubular atrophy/interstitial fibrosis, *N* glomerulus necrosis, *C* crescents. For other abbreviations, see Table 1

Nephrol Dial Transplant (2013) 28: 2339–2345
doi: 10.1093/ndt/gft211
Advance Access publication 19 June 2013

Corticosteroid therapy in IgA nephropathy with minimal change-like lesions: a single-centre cohort study

Jinquan Wang | Research Institute of Nephrology, Jinling Hospital, Nanjing

- **27 biopsy-proven adult MCD-IgAN, 15 males and 12 females**
- **Prednisone:1 mg/kg(maximum 60 mg/day) for 6 weeks or until 2 weeks after CR**
- **Reduced by 10 mg, followed by tapering 5 mg every 2 weeks down to 30 mg/day, and then 2.5 mg every 2 weeks down to 15 mg/every-other-day,**

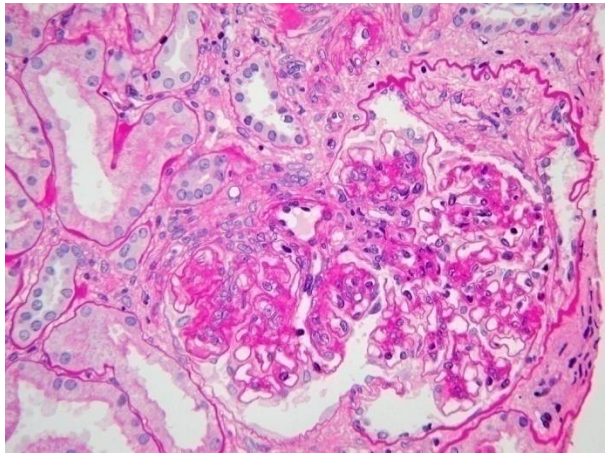
Week after treatment	1	2	4	8	12
complete remission rate(%)	3.7	48.1	92.6	100	100

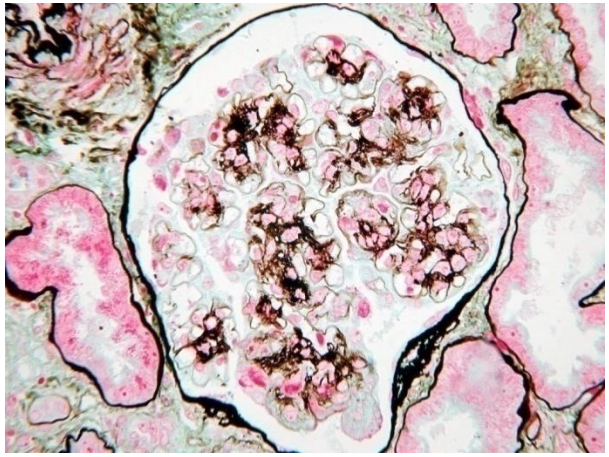
complication	Infection	alanine aminotransferase elevation	FBG elevation	K<3.5 mmol/L
Cases	2	5	2	5

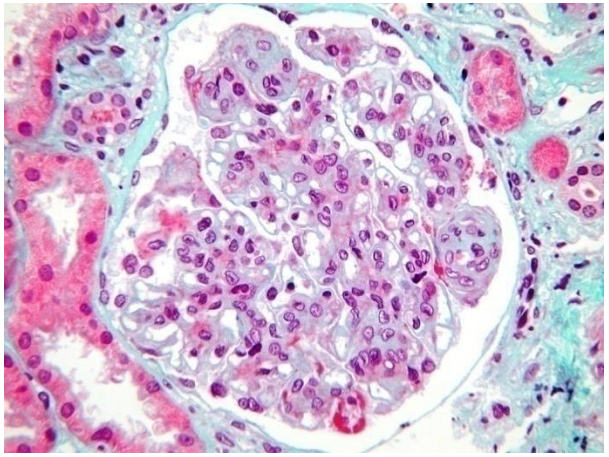
Differential Diagnosis

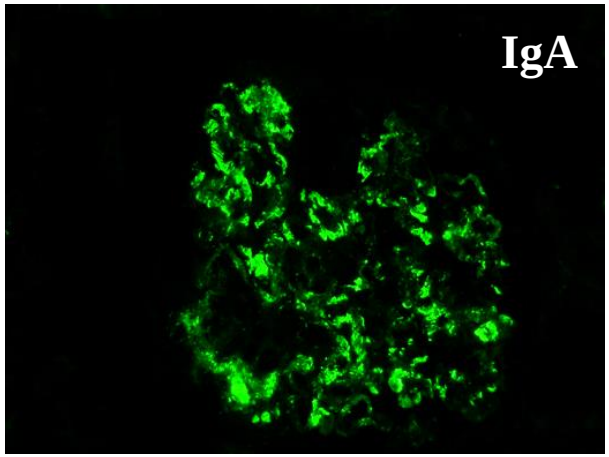
- **Secondary IgAN**
  - **Hepatobiliary diseases**
  - **Rheumatologic diseases**
- **Henoch-Schönlein purpura(HSP)**
- **IgA-dominant postinfectious glomerulonephritis**

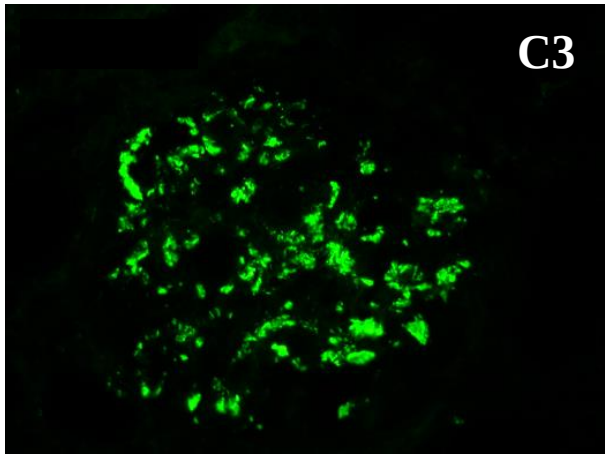
HBV related IgAN

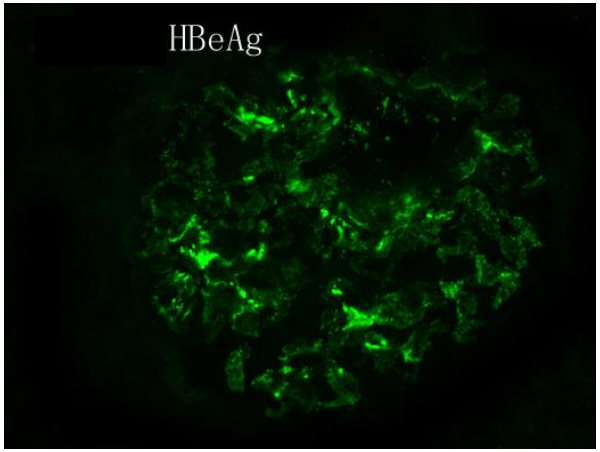






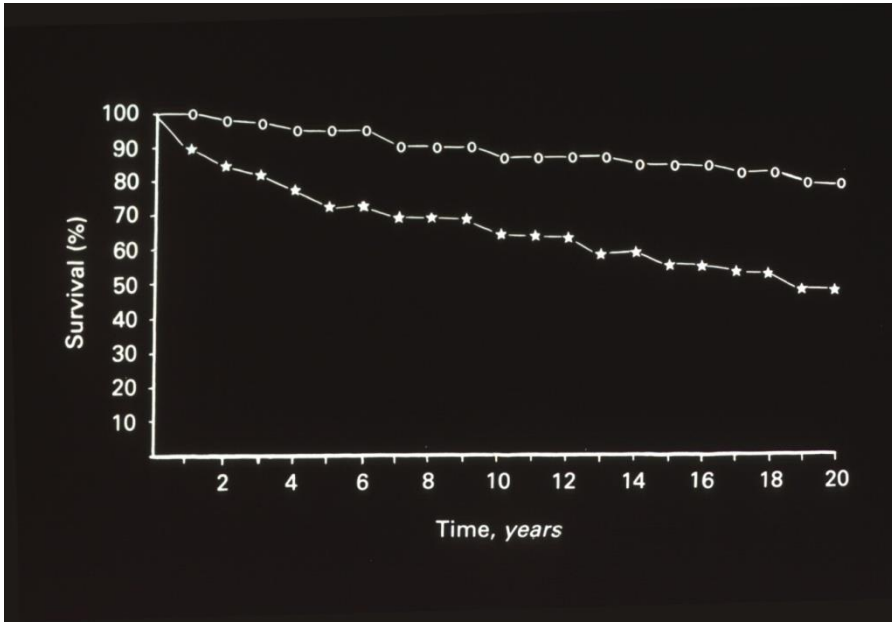




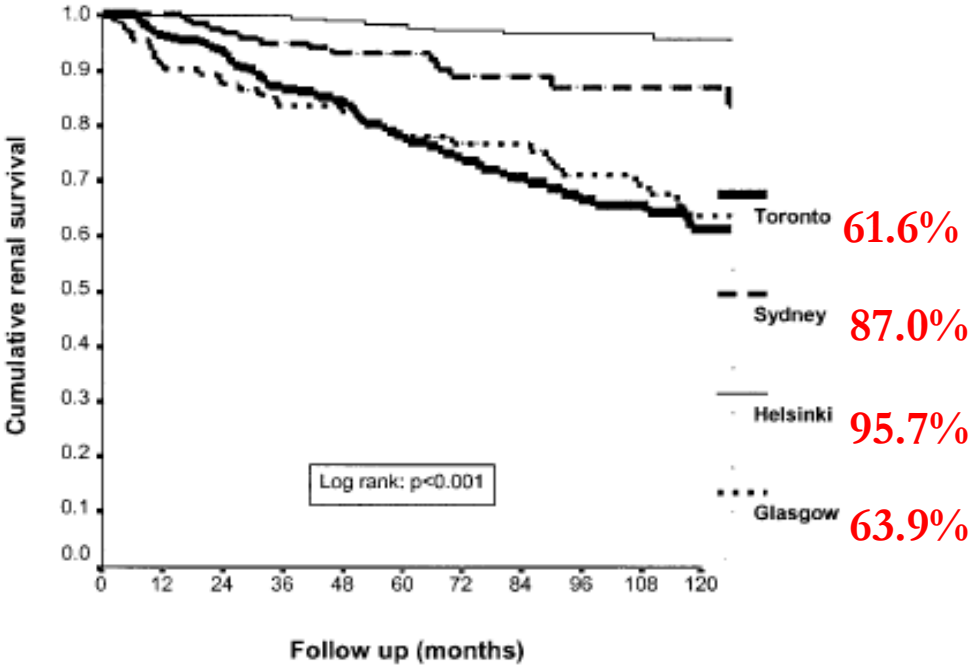


Prognosis in IgA Nephropathy

- 10 years 10 - 25% to ESRD
- 20 years 25 - 50% to ESRD



Rodicio 1982

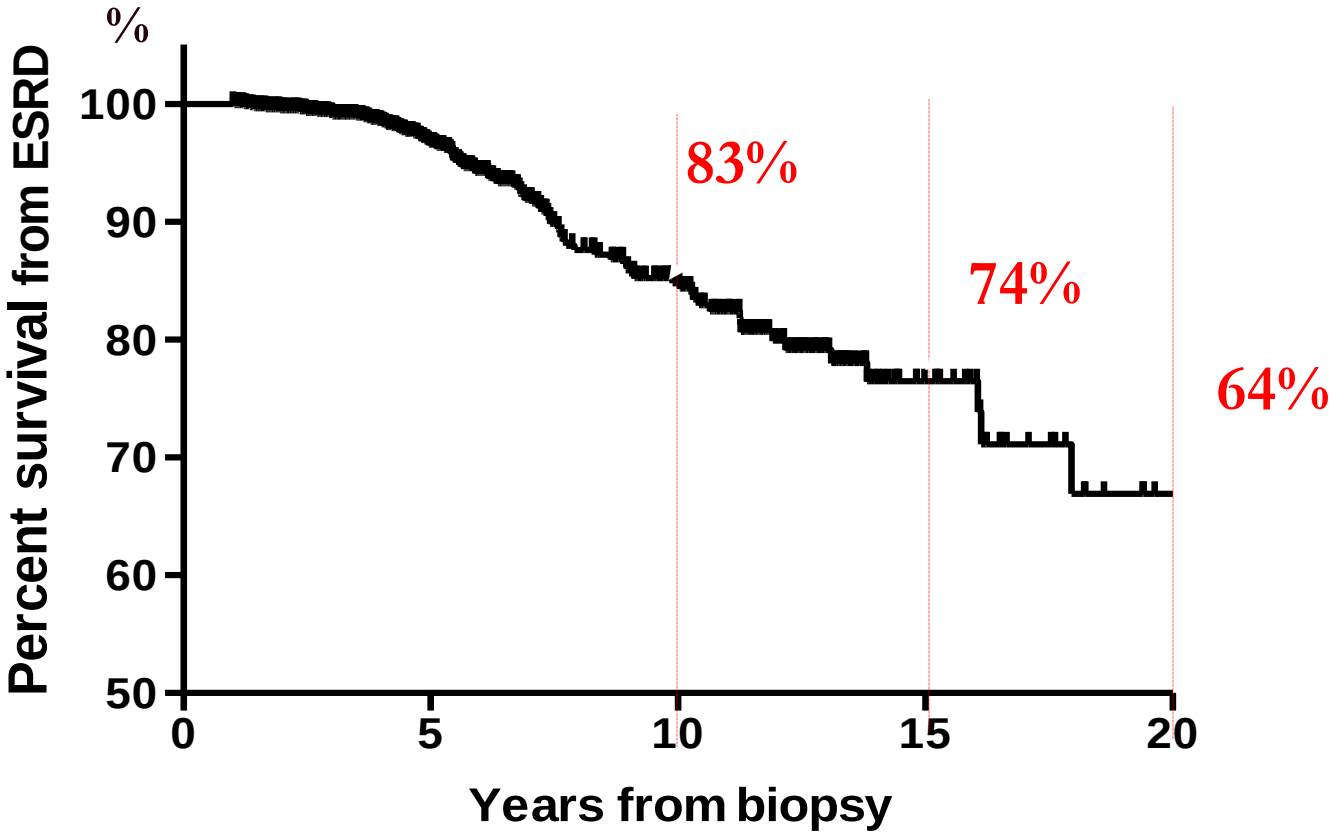


Geddes et al, NDT 2003

Nephrol Dial Transplant (2012) 27: 1479–1485
doi: 10.1093/ndt/gfr527
Advance Access publication 29 September 2011

Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population

WeiBo Le, ShaoShan Liang, YangLin Hu, KangPing Deng, Hao Bao, CaiHong Zeng and ZhiHong Liu



Clinical risk factors for progression

- **Poor prognosis**
  - **Older age**
  - **Severity of proteinuria**
  - **Renal impairment**
  - **Hypertension**
  - **Increased BMI**
- **Good prognosis**
  - **Recurrent macroscopic hematuria**
- **No impact on prognosis**
  - **Sex**
  - **Ethnicity**
  - **Serum IgA levels**

Barrat J et al. JASN. 2005.16:2088-2097

Nephrol Dial Transplant (2012) 27: 1479–1485
doi: 10.1093/ndt/gfr527
Advance Access publication 29 September 2011

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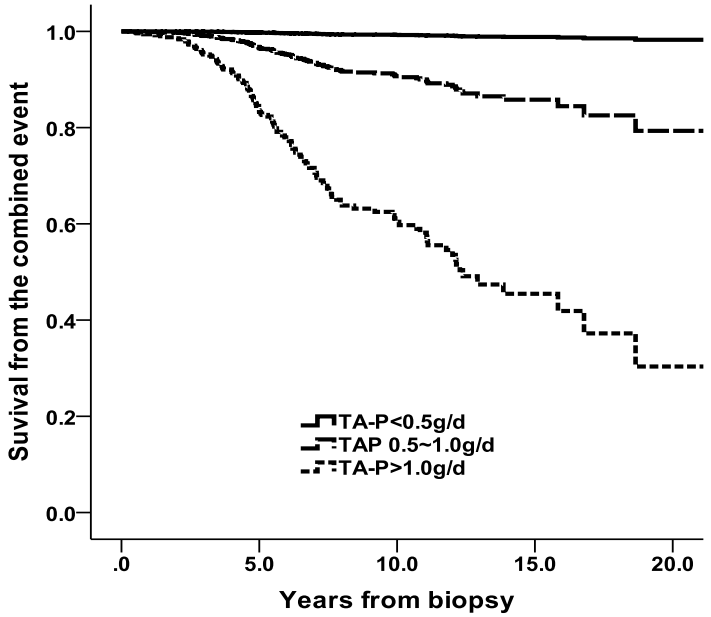

- **Higher level of proteinuria, hypertension, impaired renal function, and hyperuricemia are independent predictors of worse prognosis.**
- **Sustained proteinuria >1.0g/day was the strongest predictor of renal failure.**

TA-Proteinuria, TA-P, Time-average Proteinuria

Combined event: 50% reduction in renal function, or ESRD

Original Report: Patient-Oriented, Translational Research

American Journal of Nephrology

Am J Nephrol 2014;40:43–50
DOI: 10.1159/000364935

Received: February 27, 2014
Accepted: May 29, 2014
Published online: July 2, 2014

Long-Term Outcome of IgA Nephropathy Patients with Recurrent Macroscopic Hematuria

hen Zhang

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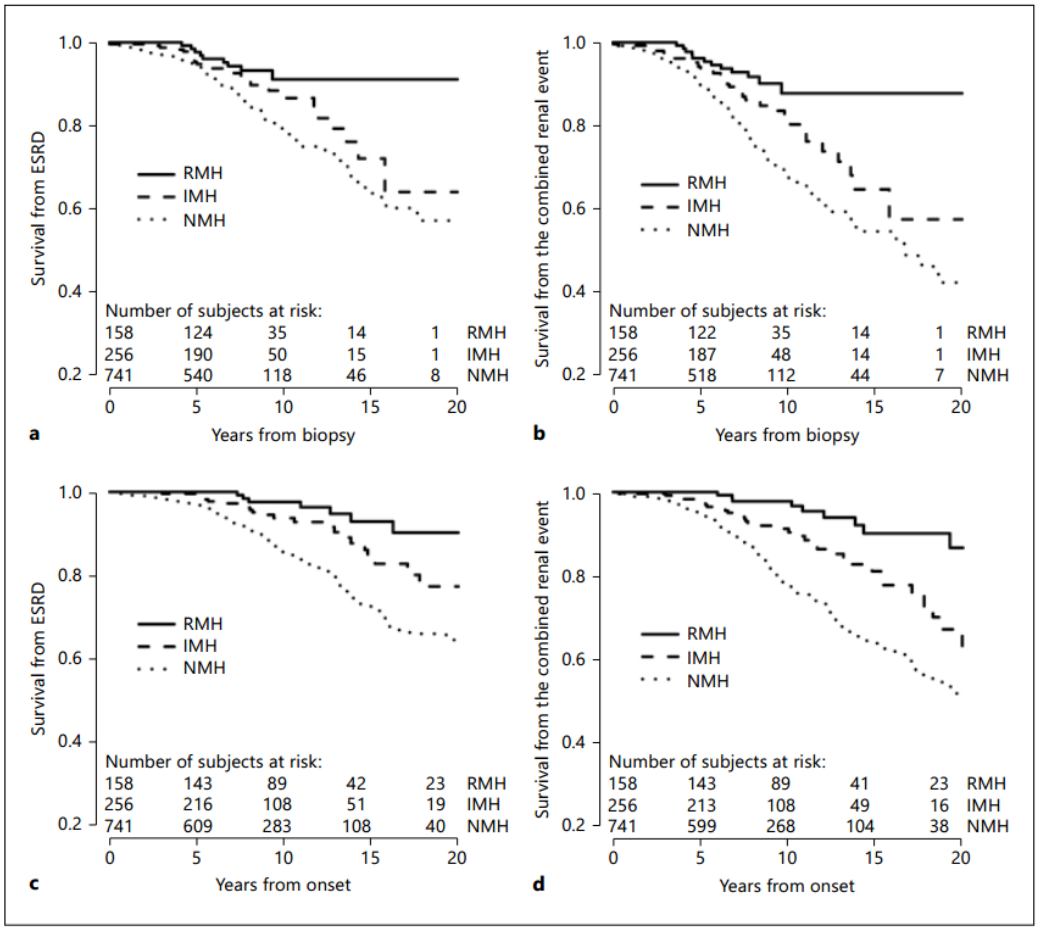


Fig. 2. a–d Kaplan-Meier renal survival curve of IgAN patients with different MH patterns.

ESRD

	5Y(%)	10Y(%)	20Y(%)
RMH	98	91	91
IMH	95	89	64
NMH	95	79	57

Combined renal event

	5Y(%)	10Y(%)	20Y(%)
RMH	96	90	90
IMH	94	83	55
NMH	89	71	41

The strongest independent predictors of poor outcome in adult and pediatric IgAN

- **Extensive interstitial fibrosis and tubular atrophy,**
- **High index scores for glomerular and/or tubulointerstitial damage (based on semiquantitative scales),**
- **Higher class designations, as per the Lee and Haas classification systems.**

D'Amico G. (2004). Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. Semin Nephrol 24:179–96.

Weaker predictors of poor outcome in adult and pediatric IgAN

- **Extensive segmental to global glomerulosclerosis,**
- **Cellular crescents,**
- **Prominent hyaline arteriolosclerosis, and**
- **Immune deposits extending into glomerular capillary loops.**

D'Amico G. (2004). Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. Semin Nephrol 24:179–96.

Proposed histologic features for progression

- Poor prognosis
  - LM
    - Capsular Adhesions & crescents
    - glomerulosclerosis,
    - Tubular atrophy
    - interstitial fibrosis
    - Vascular wall Thickening
  - IF
    - Capillary loop IgA Deposits
    - Only IgA deposit
  - EM
    - Mesangiolysis
    - mesangial hypercellularity
- Good prognosis
  - Minimal light microscopic abnormalities
- No impact on prognosis
  - Intensity of IgA deposits
  - Co-deposition of IgG, IgM or C3

Barrat J et al. JASN. 2005.16:2088-2097

Prognostic studies of extracapillary proliferation in primary IgAN

References	Year	Cases	Predicting value	Inclusion criteria
Boyce et. al	1986	112	●	At least one year of further observation since the apparent onset.
Freese et. al	1998	67	●	Kidney transplant patients with native IgAN.
Hogg et. al	1994	80	●	Follow up>4 years
Bitencourt et. al	2004	56	●	Patients with one or more crescents.
El Karoui	2010	121	●	Adults
D'Amico et. al	1986	292	●□	Follow up>1 year since the apparent onset.
Edstrom Halling et. al	2012	127	●□	Patients with IgAN.
Alamartine et. al	1993	510	○	All primary IgAN patients.
Chacko et. al	2005	374	□	All primary IgAN patients.
Pankhurst et. al	2009	363	○	Patients with IgAN or HSPN.
Cattran DC et. al	2009	256	○, □	Patients with IgAN.
Zeng et. al	2012	1026	○, □	Patients with IgAN

Univariate ●= significant, ○= not significant; Multivariate ■= significant, □= not significant

J Nephrol
DOI 10.1007/s40620-015-0242-9

ORIGINAL ARTICLE

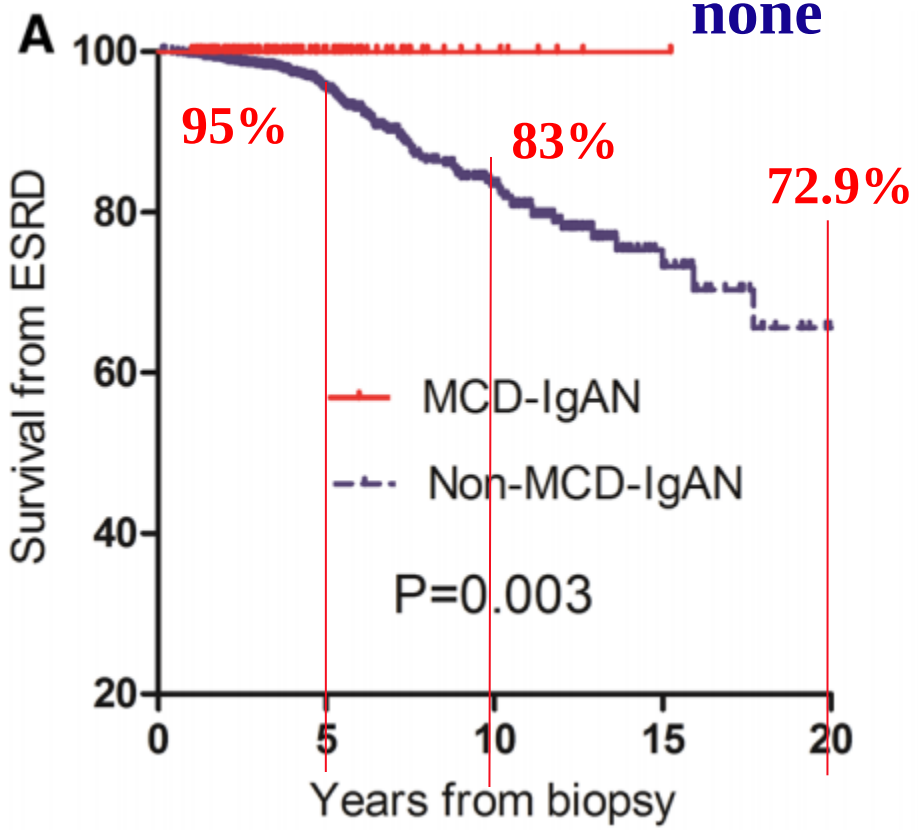
Long-term outcome of IgA nephropathy with minimal change disease: a comparison between patients with and without minimal change disease

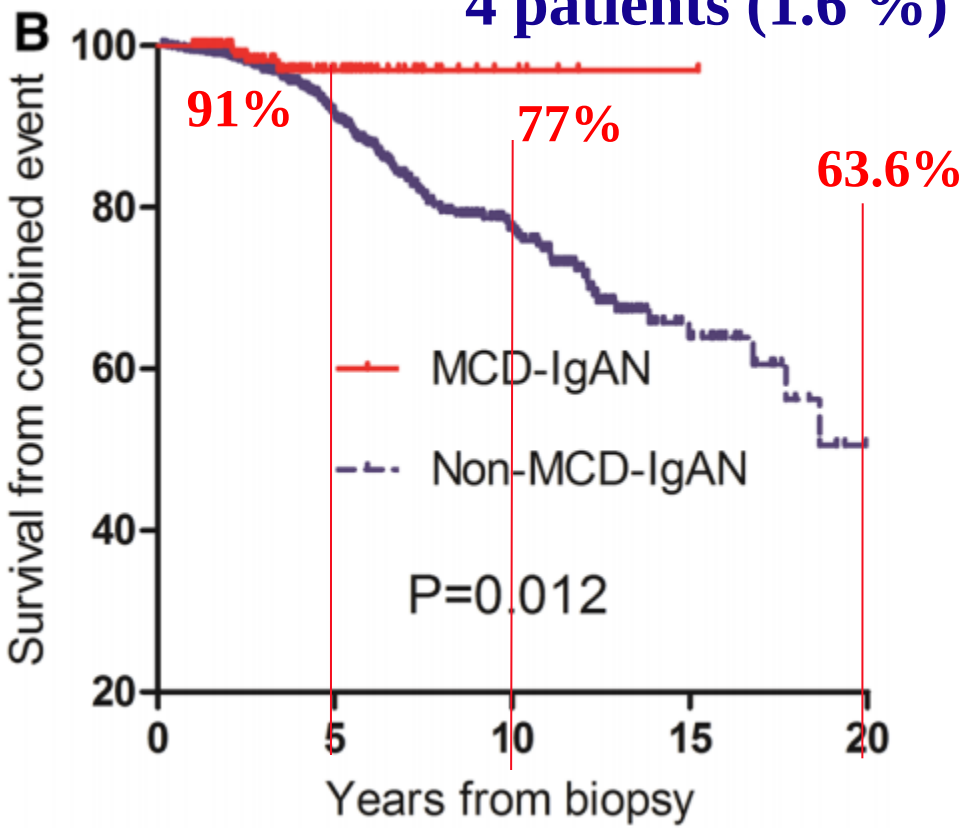
247 MCD-IgAN , 1121 Non-MCD-IgAN

Xiao-Wei Li[1,2] · Shao-Shan Liang[2] · Wei-Bo Le[2] · Shui-Qin Cheng[2] · Cai-Hong Zeng[2] · Jin-Quan Wang[2] · Zhi-Hong Liu[2]

none

4 patients (1.6 %)





follow-up of 2.6 years (range 1.0–15.2)

The Oxford Classification of IgA nephropathy

RPS

Pathology variables that were independently predictive of clinical outcome

- **Mesangial hypercellularity**
- **Segmental glomerulosclerosis/adhesion**
- **Endocapillary hypercellularity (segmental or global)**
- **Tubular atrophy/interstitial fibrosis**

Kidney International (2009) 76, 546–556;

Kidney International (2009) 76, 534–545

Curr Opin Nephrol Hypertens. 2013 Mar 20

Table 1. Summary of the published validation studies of the Oxford Classification of immunoglobulin A nephropathy

Reference	Centre	Patients: Adults A		% steroid	Steroid /	Antihypertensive	Renal outcome, MV inc.	Rate of loss of renal function, MV	Interaction with IS	Other
Oxford Classification study [1,2]	Multicentre, Europe, A							M, T	E	
Alamartine *et al.* [11]	Single centre							—	—	E, S, T predict outcome in UV analysis
El Karoui *et al.* [10▪]	Single centre							E, S, T	—	
Edström Halling *et al.* [12]	Single centre paediatric							—	—	M, E, T, Crescents predict outcome in UV
Herzenberg *et al.* [13]	Multicentre, Canada							S, T	Crescents, E	
Kang *et al.* [14]	Single centre							—	—	
Katafuchi *et al.* [9▪]	Single centre							—	Crescents, S	Optimal cut-off for crescents 6.8%
Kataoka *et al.* [15]	Single centre impact of							—	—	BMI
Lee *et al.* [16]	Single centre								—	
Moriyama *et al.* [17]	Single centre impact of syndrome							—	low T predicts response to steroids	
Shi *et al.* [18]	Single centre							—	E	
Shima *et al.* [19]	Japan, paed			proteinuria)			ts / inc. proteinuria, not eGFR)	—	—	7 reached end-point
Yau *et al.* [20]	Single centre, US	54 A	All IgAN	35%	78%	—	T	—	—	
Zeng *et al.* [5]	Multicentre, China	1026 A	All IgAN	31%	89%	E, Crescents, necrosis	M, T	M, T		S without adhesion in UV analysis

	Predicted outcome **13 studies**
M	**4**
E	**2** **indirect evidence :E is responsive to immunosuppressive therapy**
S	**4**
T	**10**

Clin Exp Nephrol
DOI 10.1007/s10157-015-1185-0

ORIGINAL ARTICLE

Extracapillary proliferation and arteriolar hyalinosis are associated with long-term kidney survival in IgA nephropathy

Yoshikatsu Kaneko[1] · Kazuhiro Yoshita[1] · Emiko Kono[1] · Yumi Ito[1] · Naofumi Imai[1] · Suguru Yamamoto[1] · Shin Goto[1] · Ichiei Narita[1]

- **Extracapillary proliferation and arteriolar hyalinosis were independently associated with renal outcome in patients with UPC≥0.5 g/day.**
- **Arteriolar sclerosis was significantly associated with higher UP, higher MAP, and lower eGFR at the diagnosis.**

Nephrol Dial Transplant (2009) 24: 886–891
doi: 10.1093/ndt/gfn563
Advance Access publication 8 October 2008

Original Article

NDT
Nephrology Dialysis Transplantation

Mesangial C4d deposition: a new prognostic factor in IgA nephropathy

Table 2. Clinical and pathological data of the patients at the time of renal biopsy and evolution to ESRD in the follow-up according to the C4d staining

Clinical and pathological data	C4d+ ($N = 19$)	C4d− ($N = 40$)	P-value
Age (year)	39.4 ± 12	27.9 ± 12	0.002
Gender male (%)	57.9%	82.5%	0.058
Macroscopic haematuria	44.4%	71.8%	0.04
Hypertension	57.9%	17.5%	0.003
Henoch-Schönlein purpura (%)	10.5%	15%	0.4
Urinary protein excretion (g/day)	3.0 ± 1.9	2.1 ± 2.2	0.1
Serum creatinine (mg/dl)	2.6 ± 1.5	1.3 ± 0.8	0.004
eGFR (ml/min/1.73 m^2)	44 ± 33	80 ± 33	0.001
Glomeruli showing sclerosis (%)	35 ± 30	13.3 ± 22	0.01
Glomeruli showing crescents (%)	4.9 ± 9.8	1.4 ± 4.2	0.1
Mesangial proliferation moderate–severe	26.3%	17.5%	0.4
Interstitial fibrosis moderate–severe	52.6%	10%	0.001
Evolution to ESRD in the follow-up	42.1%	7.5%	0.003

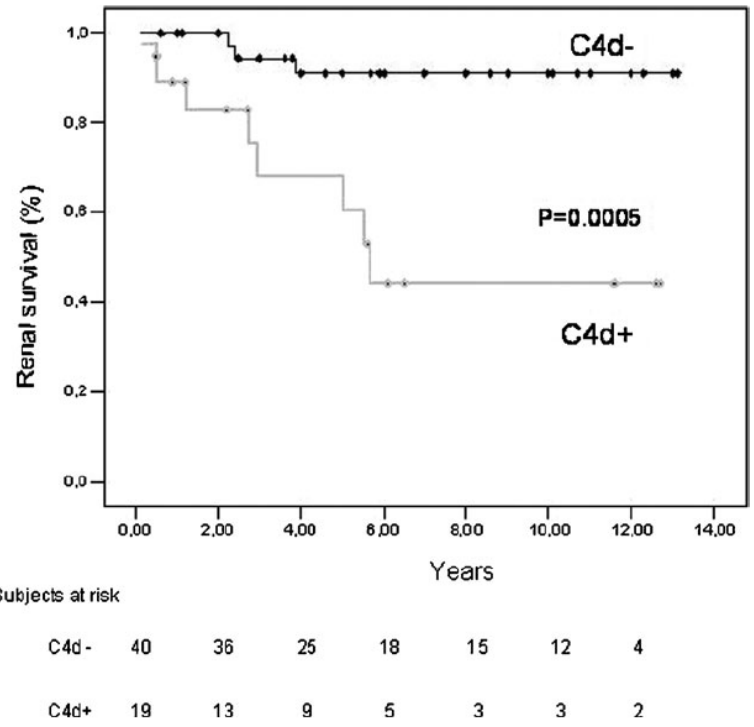


Fig. 3. Kaplan–Meier renal survival according to C4d positive (+) and negative (−) staining.

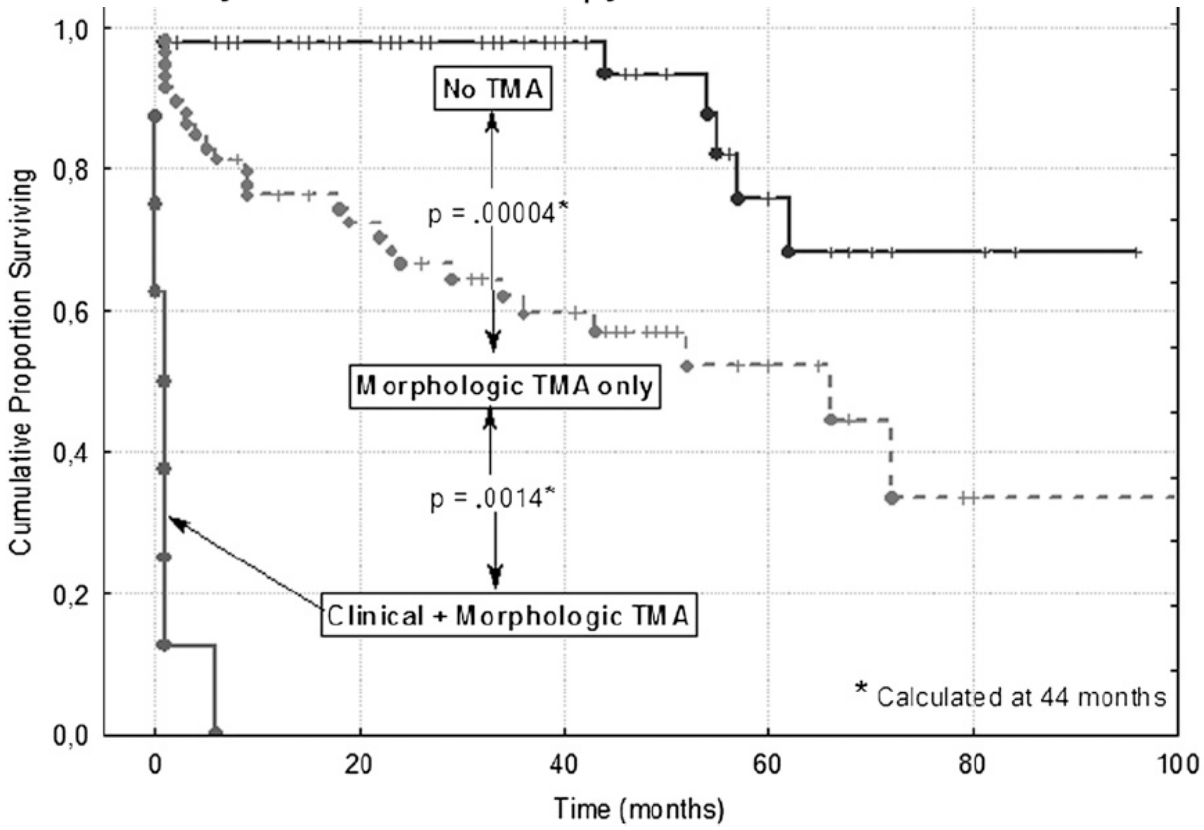
CLINICAL RESEARCH www.jasn.org

J Am Soc Nephrol 23: 137–148, 2012.

A Clinicopathologic Study of Thrombotic Microangiopathy in IgA Nephropathy

Khalil El Karoui,*† Gary S. Hill,* Alexandre Karras,‡ Christian Jacquot,‡ Luc Moulonguet,§ Olivier Kourilsky,‖ Véronique Frémeaux-Bacchi,¶ Michel Delahousse,** Jean-Paul Duong Van Huyen,* Alexandre Loupy,* Patrick Bruneval,* and Dominique Nochy*

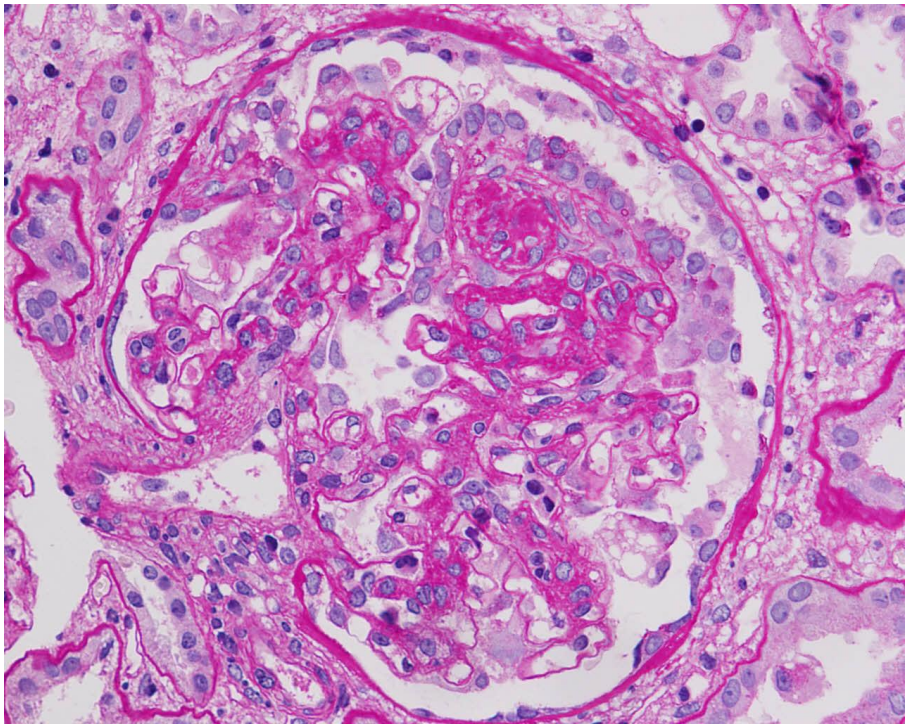
que Nochy*



- **128 patients**
- **53% with TMA,**
- **Normotensive 4%**
- **Controled HT 25%**
- **Uncontroled HT 71%**

Focal segmental glomerulosclerosis plays a major role in the progression of IgAN

KI(2011) 79, 635–642;
KI(2011) 79, 643–654;



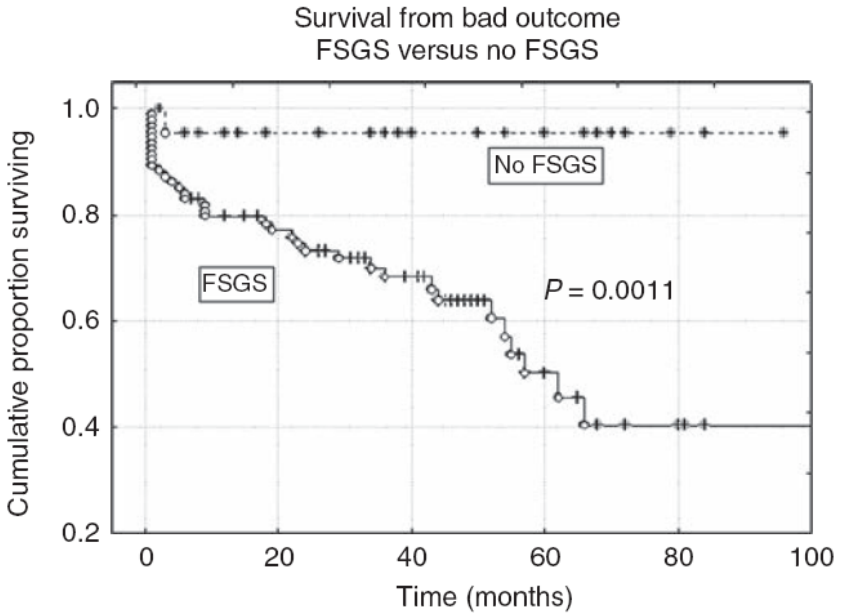


Figure 3 | Survival from bad outcome—all cases. Kaplan–Meier survival curves, comparing survival from bad outcome for all cases with focal segmental glomerulosclerosis (FSGS) compared with those without FSGS. Bad outcome is defined as doubling of serum creatinine (SCr) or need for dialysis.

- **with the cellular and collapsing forms having particularly bad outcomes, using modified Columbia criteria.**

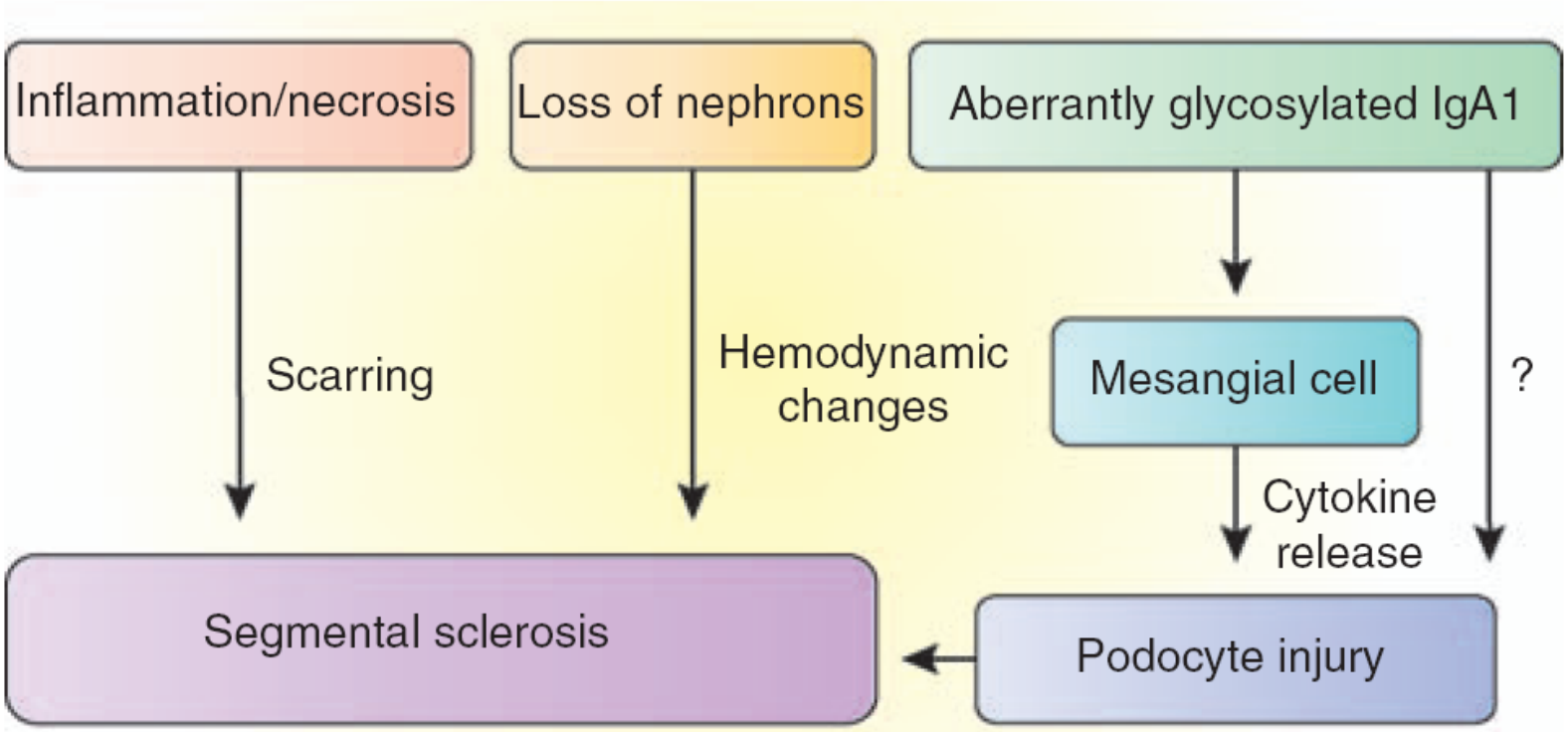
- **The interesting glomerular epithelial cell proliferation is not sufficient to classify these as typical collapsing lesions.**

- **These lesions are linked to a poor prognosis is important**

- **Perhaps ‘active proliferative sclerosis’ or ‘sclerosis with epithelial reactivity’ would come closest to capturing the essence of the lesions as described.**

Kidney International (2011) 80, 319;

Possible pathways by which segmental glomerulosclerosis develops in IgA nephropathy.



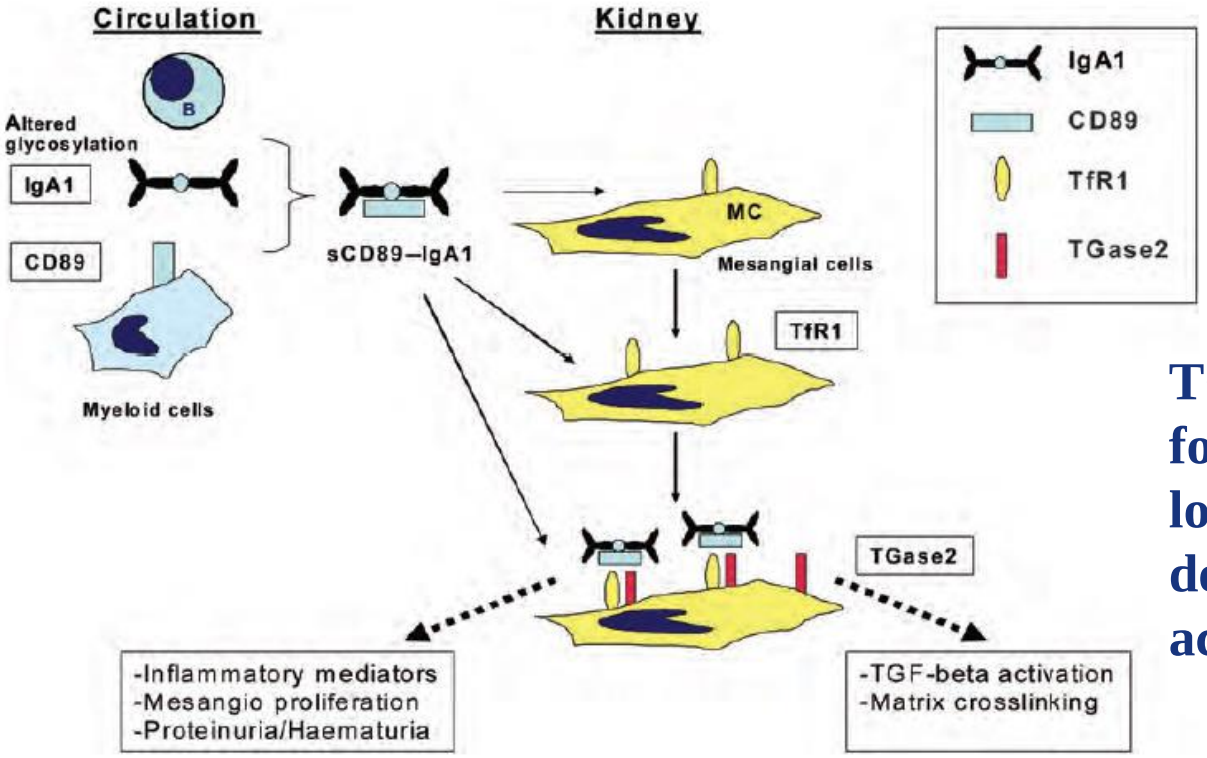
Kidney International (2011) **79,** 581 – 583.

Possible Pathogenesis of IgAN

- Abnormal glycosylation of IgA
- Ab against abnormally glycosylated IgA
- Defective clearance of circulating IgA complexes
- Increased affinity for IgA deposits in mesangium
- Mucosal excess Ab reaction in response to Ag exposure
- Increased mucosal permeability to Ag
- Genetic susceptibility

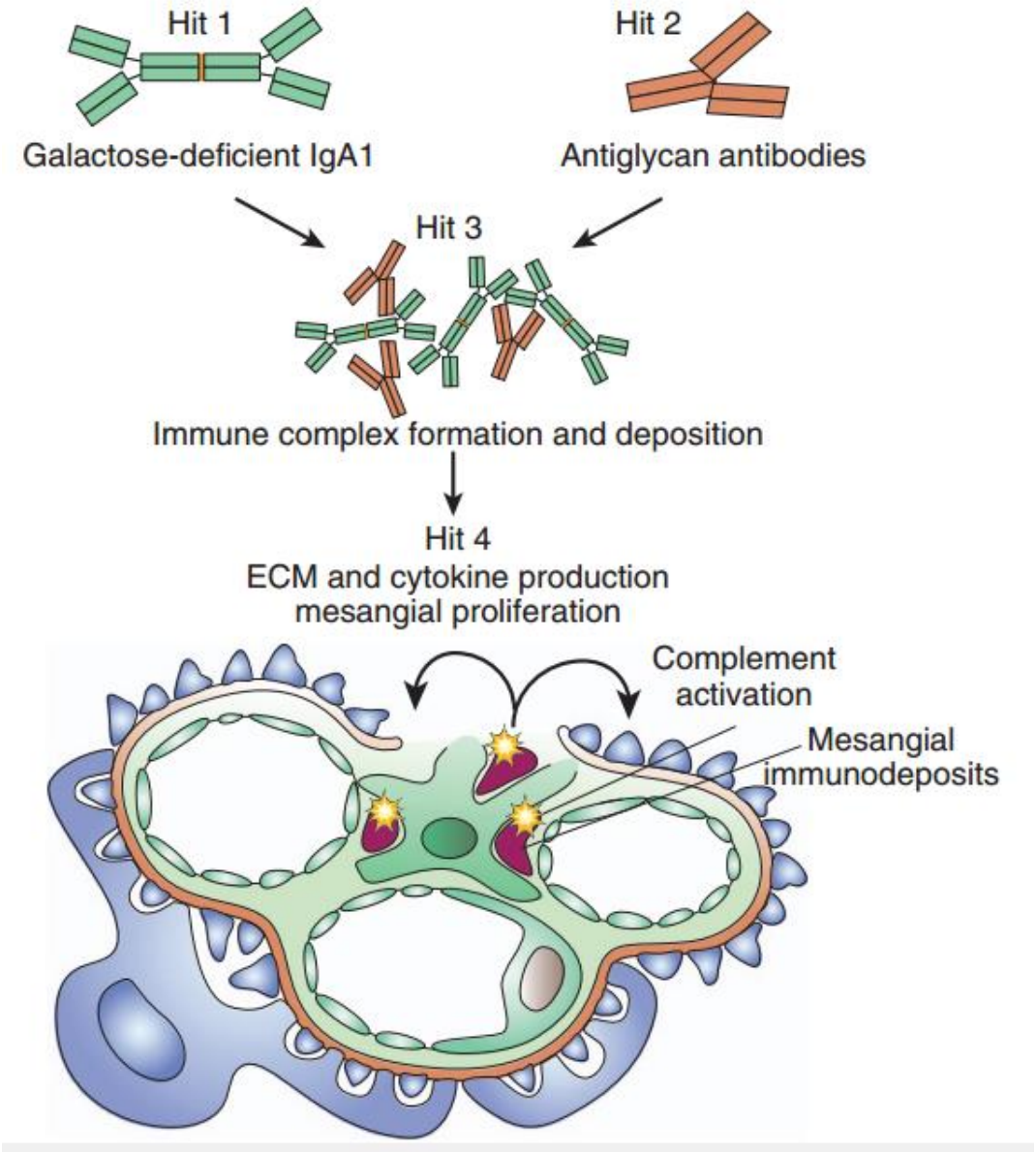
Kidney Dis 2015;1:8–18

- **Soluble CD89 as a new ligand of CD71 expressed on mesangial cells of IgAN patients and as inducers of transglutaminase 2 in their mesangium.**



TGase2 is responsible for a pathogenic amplification loop facilitating IgA1–sCD89 deposition and mesangial cell activation

J. Exp. Med.2012 Vol. 209 No. 4 793-806
Nephrol Dial Transplant (2013) 28: 794–797



The multihit pathogenesis model of IgA nephropathy

Kidney Int. 2015 Nov;88(5):974-89

BASIC RESEARCH www.jasn.org J Am Soc Nephrol 23: 814–824, 2012.

Abnormal miR-148b Expression Promotes Aberrant Glycosylation of IgA1 in IgA Nephropathy

Grazia Serino,*† Fabio Sallustio,*† Sharon N. Cox,* Francesco Pesce,* and Francesco P. Schena*†

*Nephrology, Dialysis and Transplantation Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy; and †Centro Addestramento Ricerca Scientifica in Oncologia (C.A.R.S.O.) Consortium, Valenzano, Italy

- **Upregulation of miR-148b directly correlated with levels of galactose-deficient IgA1.**
- **MiR-148b modulates IgA1 O-glycosylation and the levels of secreted galactose-deficient IgA1.**
- **Abnormal expression of miR-148b may explain the aberrant glycosylation of IgA1.**

Nephrol Dial Transplant (2015) 0: 1–8
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Original Article

Role of let-7b in the regulation of *N*-acetylgalactosaminyltransferase 2 in IgA nephropathy

Grazia Serino[1,2], Fabio Sallustio[2,3], Claudia Curci[2], Sharon N. Cox[1], Francesco Pesce[1,4], Giuseppe De Palma[2] and Francesco P. Schena[2,5]

- **Let-7b expression levels were higher in IgAN patients**
- **GALNT2 levels were significantly lower in IgAN patients**
- **Let-7b targets GALNT2, responsible for a decreased GALNT2 expression in IgAN**

Kidney Int. 2015 Nov 18. doi: 10.1038/ki.2015.333.

In a retrospective international study, circulating miR-148b and let-7b were found to be serum markers for detecting primary IgA nephropathy

Grazia Serino[1,2,3,12], Francesco Pesce[4,12], Fabio Sallustio[1,5], Giuseppe De Palma[1], Sharon N. Cox[1,2], Claudia Curci[1], Gianluigi Zaza[6], Kar N. Lai[7], Joseph C.K. Leung[7], Sydney C.W. Tang[7], Aikaterini Papagianni[8], Maria Stangou[8], Dimitrios Goumenos[9], Miltiadis Gerolymos[9], Kazuo Takahashi[10], Yukio Yuzawa[10], Shoichi Maruyama[11], Enyu Imai[11] and Francesco P. Schena[1]

- **Serum levels of the combined miRNA biomarker, let-7b and miR-148b，appears to be a novel, reliable, and noninvasive test to predict the probability of having IgAN**

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Increased miR-374b promotes cell proliferation and the production of aberrant glycosylated IgA1 in B cells of IgA nephropathy

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- **miR-374b up expression promotes B cell proliferation and aberrant glycosylation of IgA1 by targeting PTEN and Cosmc in B cells of IgA nephropathy.**
- **Inhibition of miR-374b prevents the B cell proliferation and aberrant glycosylation of IgA1**
- **It might represent a new therapeutic approach for IgAN**

Kidney Int2014 Mar;85(3):624-35.

MiR-223 downregulation promotes glomerular endothelial cell activation by upregulating importin α4 and α5 in IgA nephropathy

Hao Bao[1], Hao Chen[1], Xiaodong Zhu[1], Minchao Zhang[1], Genhong Yao[1], Yusheng Yu[1], Weisong Qin[1], Caihong Zeng[1], Ke Zen[1] and Zhihong Liu[1]

- **miR-223 downregulation promotes glomerular endothelial cell activation by upregulating importin α4 and α5 in IgAN.**
- **Monitoring the level of miR-223 in circulating endothelial cells may provide a noninvasive method for evaluating the severity of IgAN**

Thank you !