IgA Vasculitis and IgAV Nephritis in Children: Based on a National Survey and Guidelines in Japan

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IgA Vasculitis (IgAV) and IgAV Nephritis in Children

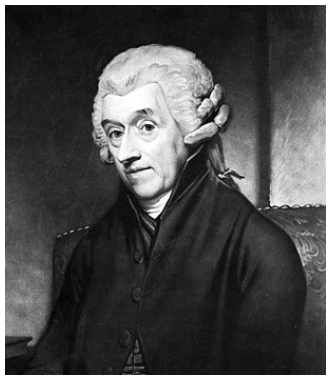
- History of IgA Vasculitis and IgAV Nephritis
- Classification, Epidemiology, Clinical presentations, and Pathogenesis of IgA Vasculitis and IgAV Nephritis
- National Survey of IgAV Nephritis in Japan
- Clinical Guidelines for IgAV and IgAV nephritis in Japan
- Future Prospects of IgAV and IgAV nephritis

History of IgAV and IgAVN

- In 1801, William Heberden described the first case of a 5-year-old boy with pains and swellings in various parts, his belly, urine tinged with blood, and the skin of his legs covered in bloody spots.
- In 1837, Johann Lukas Schönlein first described the clinical association of purpura, arthralgia, and arthritis.
- In 1874, Eduard Henoch, reported cases of children with purpura, abdominal pain, bloody diarrhea, and joint pain.

↓

Henoch-Schönlein purpura



William Heberden

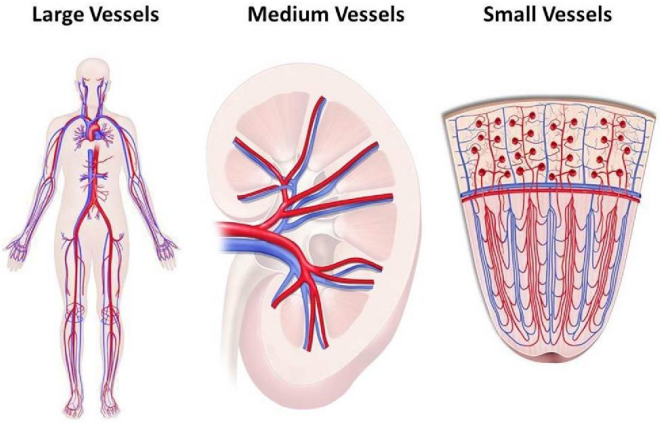
Johann Lukas Schönlein

Eduard Henoch

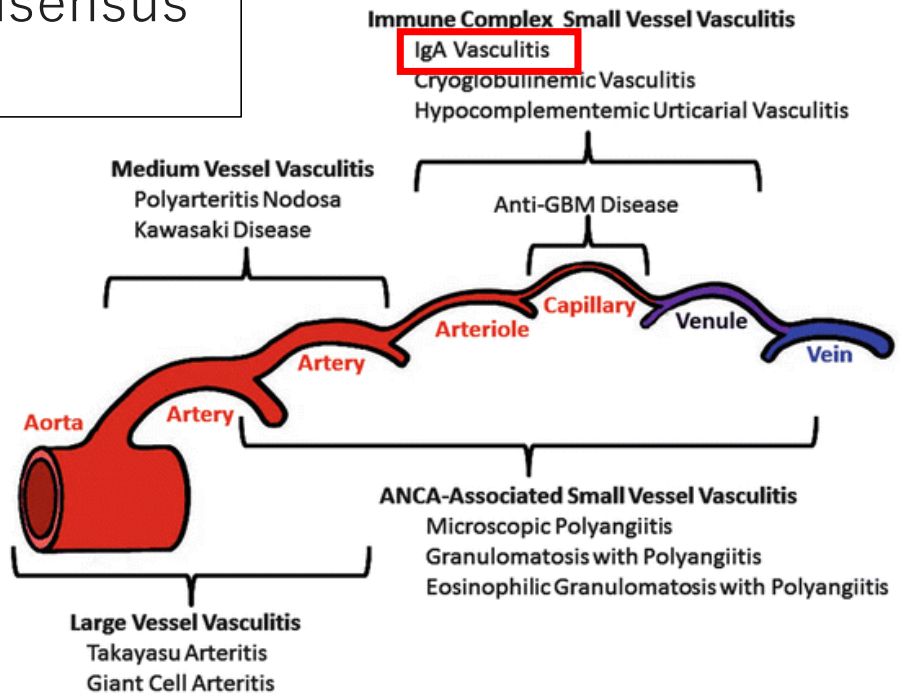
(Parums DV, Med Sci Monit. 2024., https://www.hopkinsvasculitis.org/types-vasculitis/henochschnlein-purpura/Image source: Wikipedia)

Classification of IgAV

- The American College of Rheumatology 1990 criteria for the classification of vasculitis.
- 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides



Large vessel vasculitis (LVV), Medium vessel vasculitis (MVV), Small vessel vasculitis (SVV), Variable vessel vasculitis (VVV), Single-organ vasculitis (SOV), Vasculitis associated with systemic disease, Vasculitis associated with probable etiology



(Fries JF,et al. Arthritis Rheum. 1990., Jennette JC, et al. Arthritis Rheum. 2013)

Epidemiology and Clinical Presentations of IgA Vasculitis

◆Epidemiology

- IgA vasculitis in children is typically self-limited.
- Approximately 90% of IgAV occur in children between 3-15 years of age, with a mean age of 6 years.
- An estimated global incidence in 2019 of between 3-27 per 100,000.
- In Asia, the annual incidence in children is 70 cases per 100,000.
- Gene polymorphisms involve genes encoding endothelial nitric oxide synthase (eNOS), interleukin-18 (IL-18), and angiotensin-converting enzyme (ACE).

◆Clinical Presentations

- The clinical signs and symptoms may develop in children over days or weeks, usually including purpura and joint pain.
- Up to 50% of children have gastrointestinal symptoms that can be mild (abdominal pain, nausea, vomiting) to gastrointestinal hemorrhage, obstruction, or perforation due to the effects of small vessel vasculitis.
- IgAV nephritis is reported in between 20% and 54% of children with IgA vasculitis and is more common in older children and adults.

(Parums DV, Med Sci Monit. 2024)

Diagnosis of IgA Vasculitis

■ EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008.

Table 1 Final EULAR/PRINTO/PRES HSP criteria (with glossary) and classification definition (sample 973)

Criterion	Glossary	Sensitivity (%)	Specificity (%)	AUC (%)
Purpura (mandatory criterion)	Purpura (commonly palpable and in crops) or petechiae, with lower limb predominance, * not related to thrombocytopenia	89	86	87.5
1. Abdominal pain	Diffuse abdominal colicky pain with acute onset assessed by history and physical examination. May include intussusception and gastrointestinal bleeding	61	64	62.2
2. Histopathology	Typically leucocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit	93	89	91.1
3. Arthritis or arthralgias	Arthritis of acute onset defined as joint swelling or joint pain with limitation on motion Arthralgia of acute onset defined as joint pain without joint swelling or limitation on motion	78	42	59.9
4. Renal involvement	Proteinuria >0.3 g/24 h or >30 mmol/mg of urine albumin/creatinine ratio on a spot morning sample Haematuria or red blood cell casts: >5 red blood cells/high power field or red blood cells casts in the urinary sediment or ≥2+ on dipstick	33	70	51.4
HSP EULAR/PRINTO/PRES Ankara 2008 classification definition: κ 0.90 (95% CI 0.84 to 0.96)	Purpura or petechiae (mandatory) with lower limb predominance* and at least one of the four following criteria: Abdominal pain Histopathology Arthritis or arthralgia Renal involvement	100	87	93.5

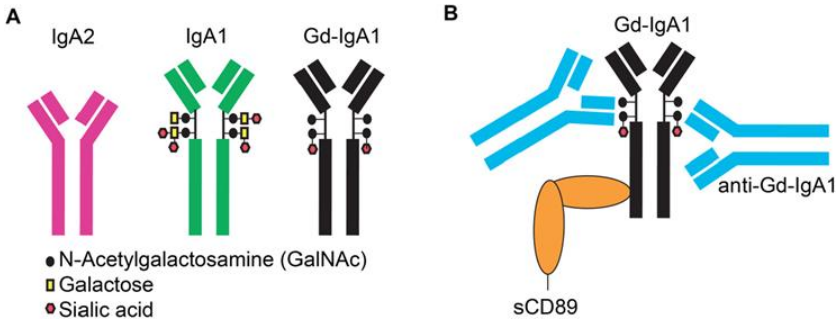
*For purpura with atypical distribution a demonstration of an IgA deposit in a biopsy is required.
AUC, area under the curve; EULAR, European League Against Rheumatism; HSP, Henoch–Schönlein purpura; PRES, Paediatric Rheumatology European Society, PRINTO, Paediatric Rheumatology International Trials Organisation.

- No specific diagnostic serological laboratory tests or biomarkers for IgA vasculitis exist.
- purpura with atypical distribution a demonstration of an IgA deposit in a biopsy is required.

(Seza Ozen, et al. Ann Rheum Dis 2010., Parums DV, Med Sci Monit. 2024.)

Pathogenesis of IgAV and IgAVN

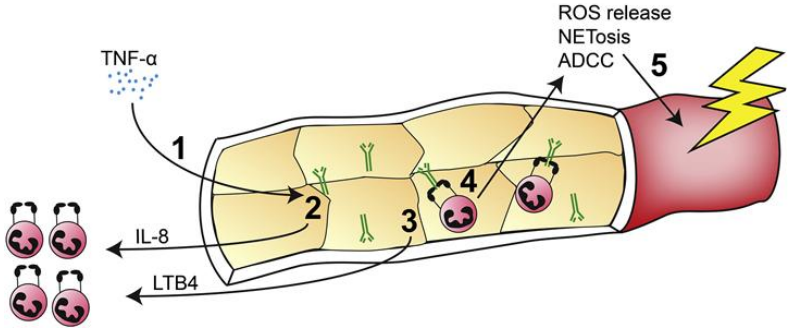
◆ IgAV is characterized by
- IgA1 immune deposits
- complement factors and neutrophil infiltration
- with vascular inflammation



➢ IgA can activate the mannan-binding lectin and alternative complement pathways and multiple receptors such as CD71 and Fc α RI(sCD89).
→ complements activation and mesangial IgA deposition

➢ In IgAVN, Gd-IgA1, autoantibodies and sCD89 form large immune complexes.
→ Gd-IgA1 immune complexes and deposition of immune complexes in the glomerulus.

➢ Serum-derived IgA from IgAV patients to a specific antigen, β 2-glycoprotein I (β 2GPI).
→ anti-endothelial cell antibodies (AECA), targeting β 2GPI, activate endothelial cells and induce inflammation through cytokines.



(Heineke et al. Autoimmunity Reviews 2017)

Guidelines of childhood IgAV/IgAV nephritis in worldwide

◆KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases: IMMUNOGLOBULIN A VASCULITIS, 2.8.1 IgAV-associated nephritis in children
(Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. Kidney Int. 2021)

◆European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis-the SHARE initiative.
(Ozen S, et al. Rheumatology. 2019)

◆ UK Kidney Association guideline review: 'The initial management of IgA vasculitis (Henoch-Schönlein purpura) in children and young people' in conjunction with 'The management of complications-associated IgA vasculitis (Henoch-Schönlein purpura) in children and young people'.
(Day C, et al. *Arch Dis Child Educ Pract Ed*. 2024)

◆ Consensus evidence-based recommendations for treat-to-target management of immunoglobulin A vasculitis.
(Abu-Zaid MH, et al. Ther Adv Musculoskelet Dis. 2021)

Survey of IgAV nephritis in Japan

RESEARCH ARTICLE

Epidemiology of biopsy-proven Henoch–Schönlein purpura nephritis in children: A nationwide survey in Japan

Chikako Terano[1,2¤], Riku Hamada[1]*, Ichiro Tatsuno[2,3,4], Yuko Hamasaki[5], Yoshinori Araki[6], Yoshimitsu Gotoh[7], Koichi Nakanishi[8], Hitoshi Nakazato[9], Takeshi Matsuyama[10], Kazumoto Iijima[11], Norishige Yoshikawa[12], Tetsuji Kaneko[13], Shuichi Ito[14], Masataka Honda[1], Kenji Ishikura[15], on behalf of the Japanese Study Group of Renal Disease in Children

- Worldwide, there are limited data available from national epidemiological surveys on childhood IgAV.
- Uniform diagnostic criteria for the diagnosis of “nephritis” were lacking and the actual situation was unknown.
- The Japanese Study Group of Renal Disease in Children conducted a nationwide survey in 2018.
- The survey was conducted on newly diagnosed IgAV nephritis by kidney biopsy at the age of 1 year to 15 years between January 2013 and December 2015.

- ◆the estimated annual incidence of biopsy-proven IgAV nephritis is 1.32 per 100,000 population in Japan.
- ◆91.9% of facilities performed a biopsy within 1 month for patients with acute kidney injury (AKI).
- ◆66.9% of the patients without AKI but with hypo-albuminemia (serum Alb <3.0 g/dL), underwent biopsy within 1 month, and 94.3% within 3 months.
- ◆patients showing uTP/Cr >1.0 g/gCr, 23.0% of facilities reported performing a renal biopsy only after 6 months, suggesting that many facilities preferred to monitor the condition before proceeding with a biopsy.

(Terano C, et al. PLoS One. 2022)

Survey of IgAV nephritis in Japan

◆Treatment The treatment approach for IgAV nephritis also varied across facilities.

Table 4. Treatment protocols for HSPN in individual institutions.

	Severe	Moderately severe	Mild
With MPT	75.5%	26.2%	5.9%
With PSL	94.3%	90.5%	43.6%
With immunosuppressants	87.0%	77.6%	25.0%
Only RAS inhibitors	0.0%	6.2%	47.7%

Methylprednisolone pulse therapy and prednisolone combined with immunosuppressants were common for severe cases (ISKDC class IV or V). For mild cases (ISKDC class I, II, or IIIa and uTP/Cr <1.0 g/gCr), approximately half of the facilities used prednisolone and one-quarter used immunosuppressants, while around half treated only with RAS inhibitors.

◆ Re-biopsy after treatment
17.8% of institutions performed a re-biopsy for patients achieved remission.
If abnormal urinary findings remained, 77.4% of institutions performed a re-biopsy.

➡ The Japanese Society of Pediatric Nephrology published the guidelines for the management and treatment of IgA vasculitis, encompassing IgAV nephritis, in 2023.

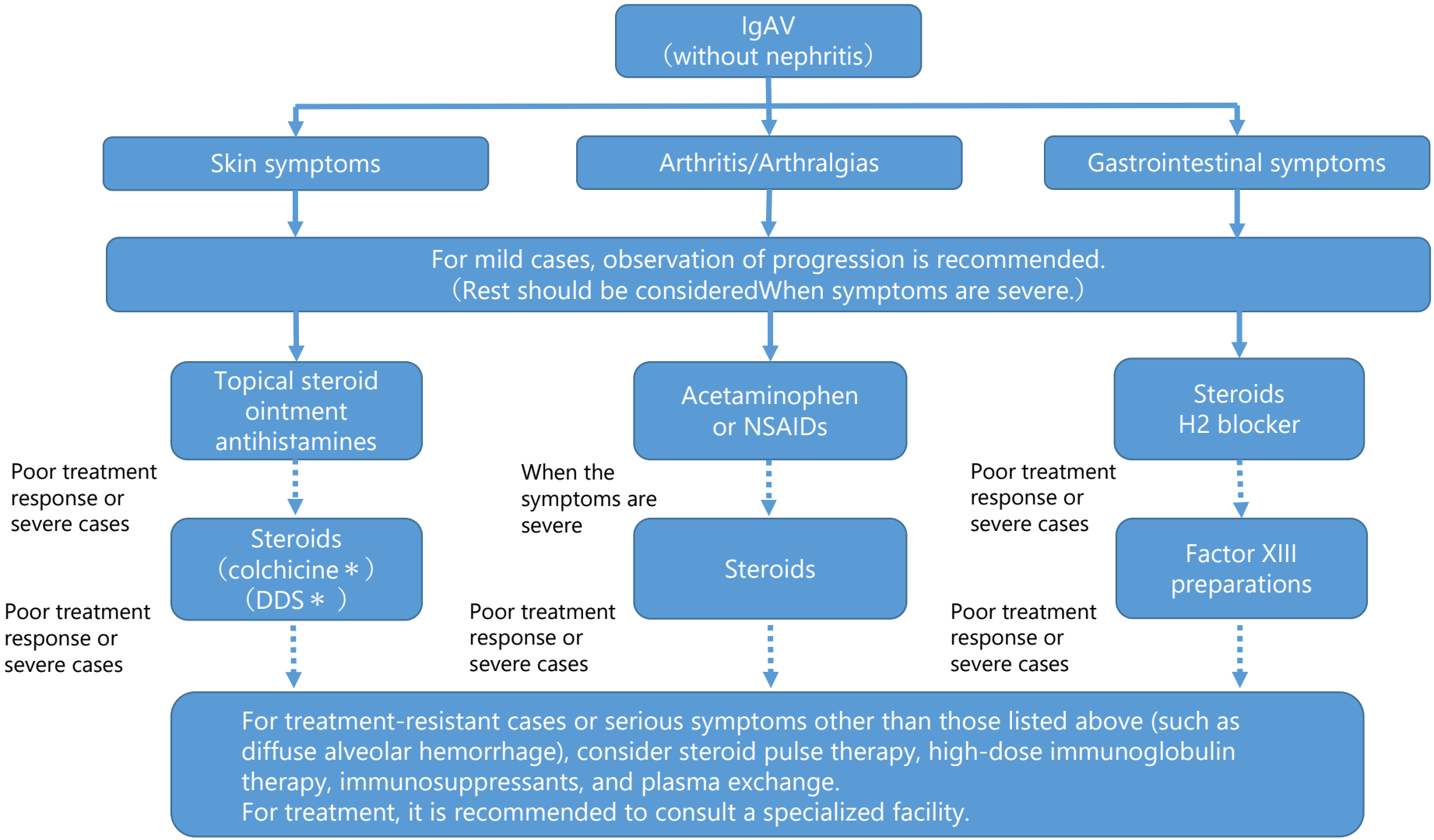
(Terano C, et al. PLoS One. 2022)

Guidelines for IgAV and IgAV nephritis in Japan

- Introduction
- Clinical Questions 1-14
  - CQ 1-7: Management and Treatment for IgAV (excluding IgAV nephritis)
  - CQ 8: Is steroid therapy recommended for preventing the development of pediatric IgAV nephritis?
  - CQ 9: Are renin-angiotensin system (RAS) inhibitors recommended for pediatric IgAV nephritis?
  - CQ 10: Are steroids and immunosuppressive agents recommended for severe pediatric IgAV nephritis?
  - CQ 11: Is steroid pulse therapy recommended for severe pediatric IgAV nephritis?
  - CQ 12: Is pulse urokinase therapy recommended for severe pediatric IgAV nephritis?
  - CQ 13: Is plasma exchange therapy recommended for severe pediatric IgAV nephritis?
  - CQ 14: Is plasma exchange therapy recommended for severe pediatric IgAV nephritis?

(Pediatric IgA vasculitis clinical practice guidelines in Japan. 2023)

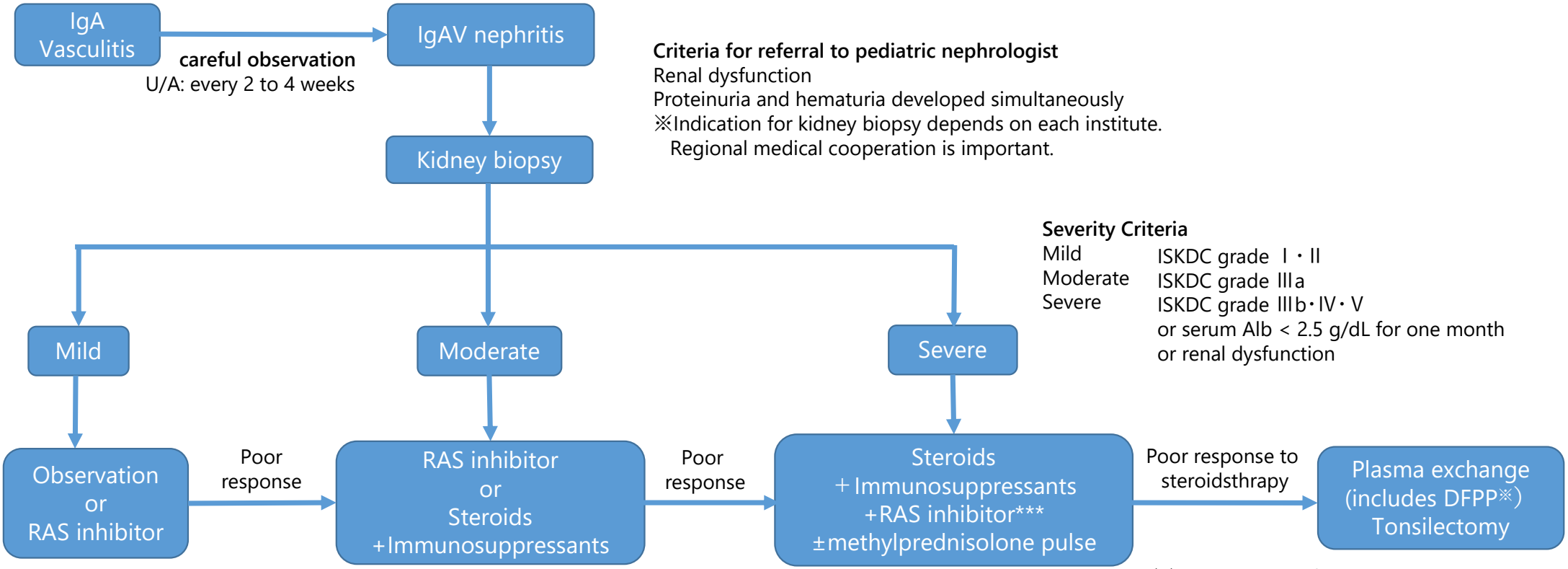
Outlines of the Treatment for Pediatric IgA vasculitis



DDS: Diaphenylsulfone, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

＊ Not covered by insurance; recommended to consult a specialized facility

Outlines of the Treatment for Pediatric IgAV nephritis



Criteria for referral to pediatric nephrologist
Renal dysfunction
Proteinuria and hematuria developed simultaneously
※Indication for kidney biopsy depends on each institute.
Regional medical cooperation is important.

Severity Criteria

Mild	ISKDC grade Ⅰ・Ⅱ
Moderate	ISKDC grade Ⅲa
Severe	ISKDC grade Ⅲb・Ⅳ・Ⅴ or serum Alb < 2.5 g/dL for one month or renal dysfunction

*** Caution is required when renal function declines

※DFPP：Double filtration plasmapheresis

Immunosuppressants

Mizoribine*	Cyclophosphamide
Cyclosporine*	Tacrolimus**
Azathioprine	Mycophenolate mofetil**

* Insurance coverage for nephrotic syndrome
** Not covered by insurance

The timing for evaluating treatment efficacy
Asymptomatic hematuria/proteinuria → after 6 to 12 months
Exacerbation of hematuria and proteinuria → after 3 to 6 months
※ Rapidly progressive glomerulonephritis should be treated promptly

U/A: Urinalysis

Guidelines for IgAV and IgAV nephritis in Japan

CQ8: Is steroid therapy recommended for preventing the development of pediatric IgAV nephritis?

Steroid therapy is NOT recommended for preventing the development of pediatric IgAV nephritis. (grade 1B)

- Three randomized controlled trials (RCTs) have been confirmed: there is no evidence that steroid therapy for pediatric IgAV patients prevent s the development of IgAV nephritis.

CQ9: Are renin-angiotensin system (RAS) inhibitors recommended for pediatric IgAV nephritis?

No recommendation.

- Although RAS inhibitors are broadly used for IgAV nephritis, there is no RCT reported so far. Some reports said that early induction of RAS inhibitors are effective for amelioration of proteinuria and renal prognosis. KDIGO guidelines 2021 stated that RAS inhibitors should be used for IgAV nephritis presenting proteinuria for more than three months.
- There is a possibility that RAS inhibitors are effective for suppressing the progression of renal dysfunction and reducing proteinuria

(Pediatric IgA vasculitis clinical practice guidelines in Japan. 2023)

Guidelines for IgAV and IgAV nephritis in Japan

CQ 10: Are steroids and immunosuppressive agents recommended for severe pediatric IgAV nephritis?
CQ 11: Is steroid pulse therapy recommended for severe pediatric IgAV nephritis?

It is recommended to use steroids and immunosuppressive agents for severe cases of pediatric IgAV nephritis.
However, treatment with steroids alone lacks sufficient evidence, so combination therapy with steroids and immunosuppressive agents is suggested.

CQ10: recommendation grade for each agent;
No recommendation: steroids alone
grade 2B: tacrolimus
grade 2C: cyclophosphamide, azathioprine, cyclosporine, mycophenolate mofetil, combined therapy of steroids and immunosuppressants.
CQ11:
Steroid pulse therapy has the possibility of being effective for severe cases of pediatric IgAV nephritis, so it may be considered.

(Pediatric IgA vasculitis clinical practice guidelines in Japan. 2023)

Guidelines for IgAV and IgAV nephritis in Japan

CQ 12: Is pulse urokinase therapy recommended for severe pediatric IgAV nephritis?
CQ 13: Is plasma exchange therapy recommended for severe pediatric IgAV nephritis?
CQ 14: Is plasma exchange therapy recommended for severe pediatric IgAV nephritis?

No recommendation.

- These supplementary therapies may hold promise for severe cases of pediatric IgAV nephritis; however, due to the absence of RCTs, evidence supporting their efficacy is currently lacking.

(Pediatric IgA vasculitis clinical practice guidelines in Japan. 2023)

Future Prospects of IgAV and IgAV nephritis

- The pathogenesis and mechanisms of IgA vasculitis and IgAV nephritis remain unclear. Further elucidation is expected to advance in order to establish preventive measures and effective treatment strategies.
- Due to the lack of reliable randomized controlled trials (RCTs), there is an urgent need to generate evidence worldwide.
- To accumulate cases and facilitate research, it is necessary to develop management and treatment guidelines standardized globally.

Treatment of IgA nephropathy

Joo Hoon Lee

Asan Medical Center Children's Hospital,

University of Ulsan College of Medicine,

Seoul, Republic of Korea

Treatment of IgA nephropathy in **children**

- The **optimal approach** to therapy in **children with IgA nephr opathy (IgAN)** is uncertain, and **guidelines** are lacking.
- This lecture will mostly show RCT results from **adult** studies.
- Treatment can be divided into supportive care and immunosu ppressive therapy

Supportive Care in IgAN

IgAN with **asymptomatic hematuria (HU)**

- In pediatric patients with **asymptomatic HU**,
  we do not recommend
  - kidney biopsy to diagnose IgAN or
  - any treatment.

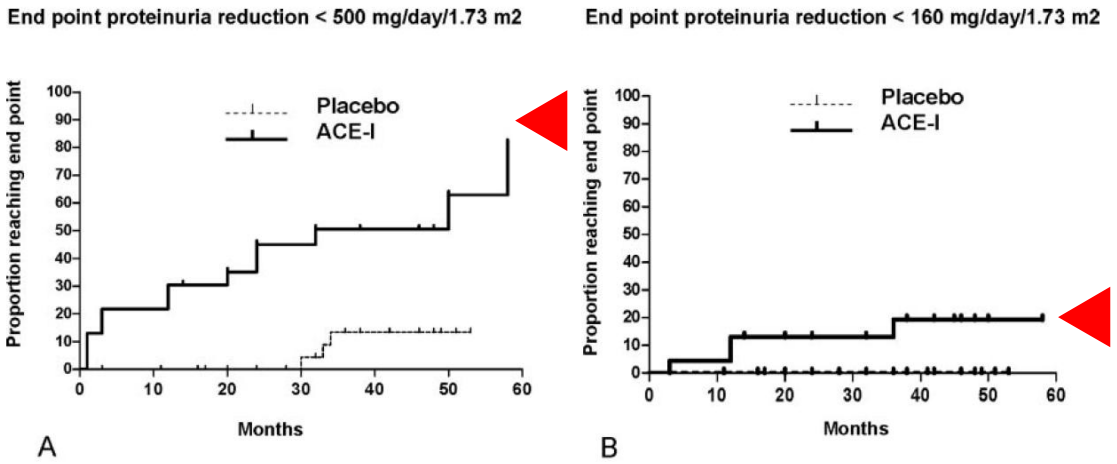
KSPN guideline for HU

RAS blockade in children

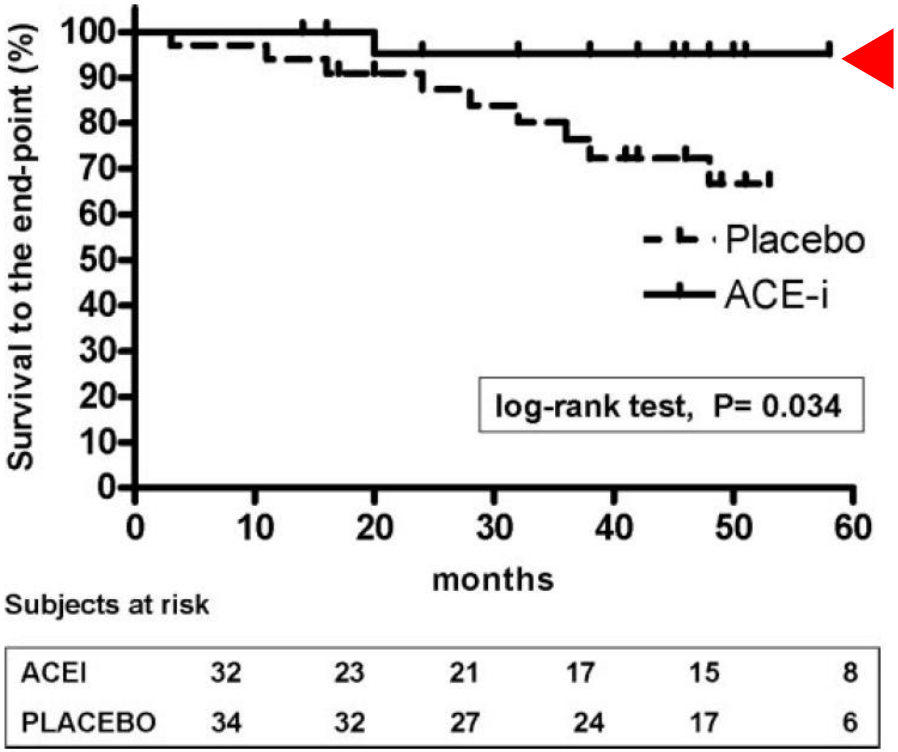
- In patients with **IgAN** who have HU and PU (PCR > 0.2),
  we recommend treatment with either
  - an **angiotensin-converting enzyme (ACE) inhibitor** or
  - an **angiotensin receptor blocker (ARB).**
- **RAS blockade** reduces systemic and intraglomerular hydrosta tic pressures by inhibiting angiotensin II-mediated efferent art eriolar vasoconstriction.

KDIGO guideline 2021

IgACE study (Europe): 32 Benazepril vs 34 Placebo (RCT. Age 3~35 yr)



There were statistically more patients in **ACE-I group** with stable decrease in PU and complete remission of PU compared to placebo gro up ($p < 0.05$).



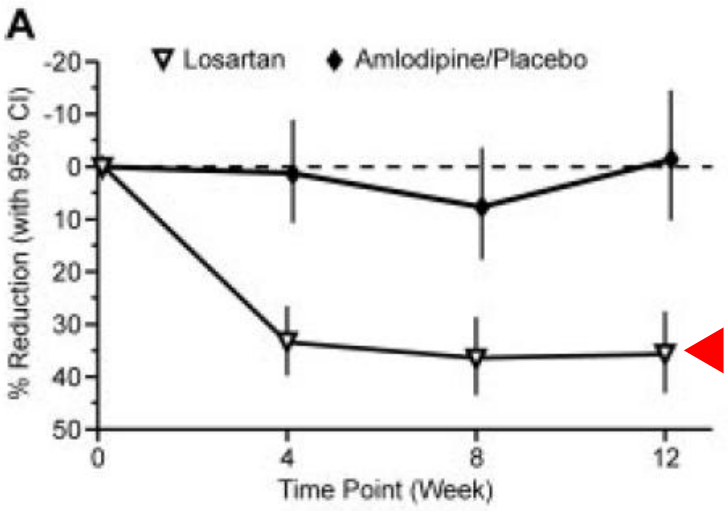
Composite end point of decrease in CrCl by 30% and/or increase of PU up to the nephrotic range was significantly lower in the **ACE-I group** compared to the placebo group

JASN 2007;18:1880-8

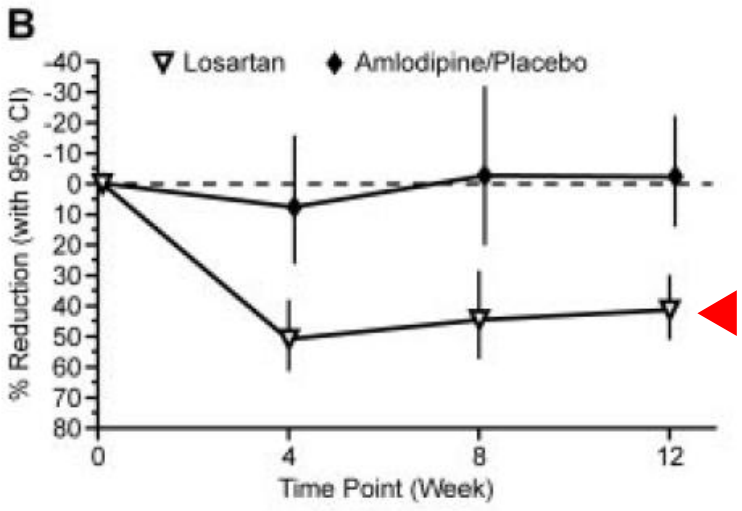
ESCAPE study (19 countries): children, CKD and PU

Normotensive: 116 **losartan** vs 118 placebo, **hypertensive**: 29 **losartan** vs 25 placebo

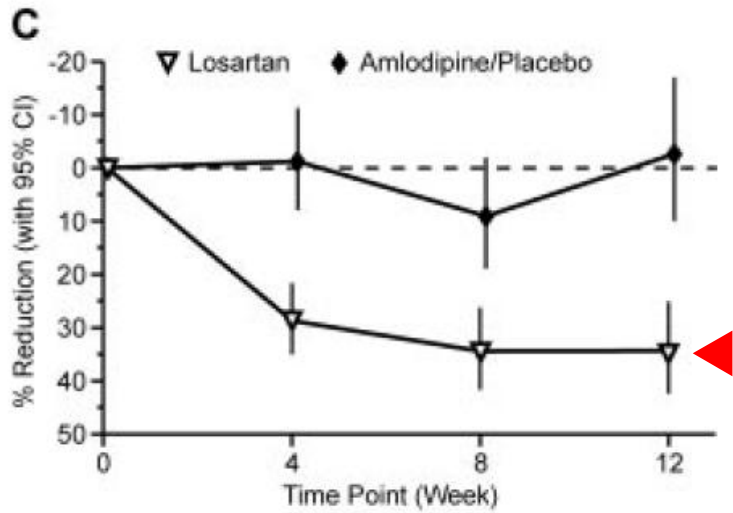
Total



Hypertensive



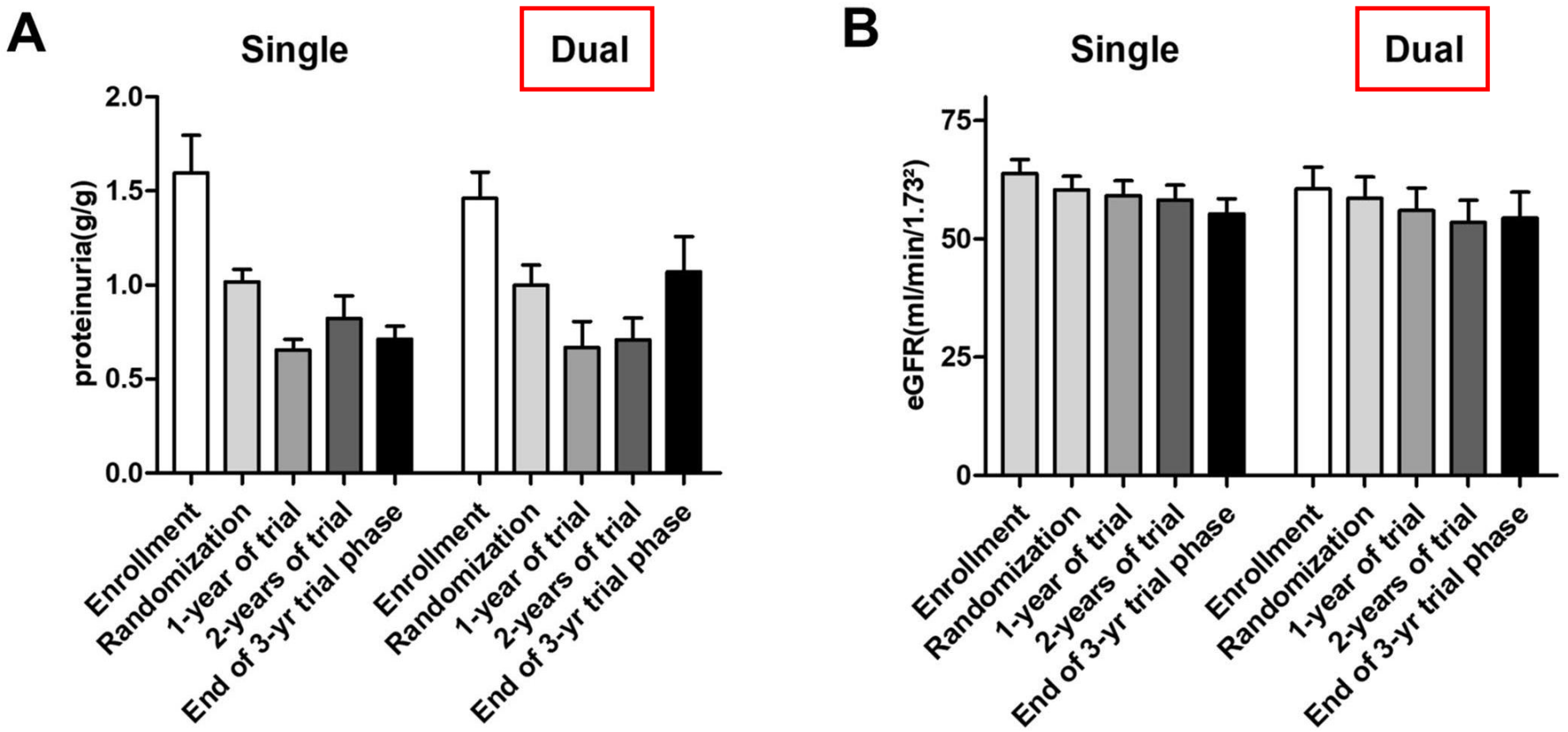
Normotensive



In **losartan** group, **PU reduction** was consistently observed in the hypertensive and normotensive patients c ompared with amlodipine/placebo group.

CJASN 2010;5:417-24

STOP-IgAN study (Germany): 112 adults with PU



No additional benefit was found with **dual blockade of RAS** compared to single blockade.

J Nephrol 2020;33:1231-9

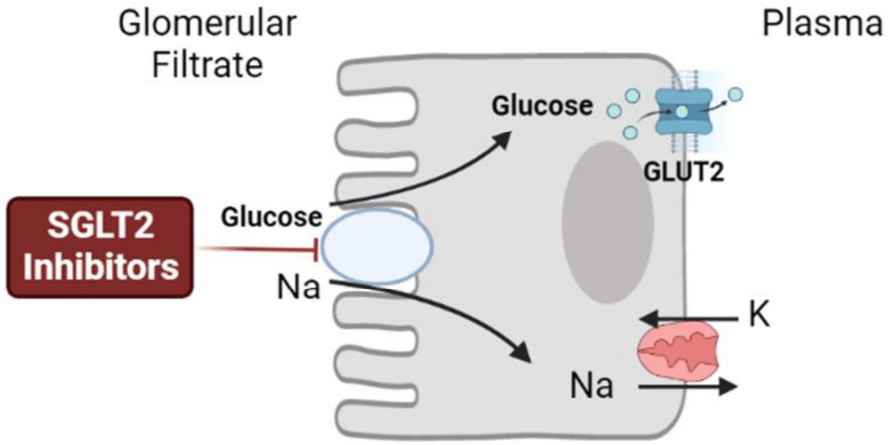
Supportive care in IgAN

- Supportive care such as **optimal lifestyle modification** (including smoking cessation, maintaining a healthy weight, and regular exercises) is needed.
- **Blood pressure** should be controlled (targeting systolic blood pressure <90th percentile for age, sex, and height).

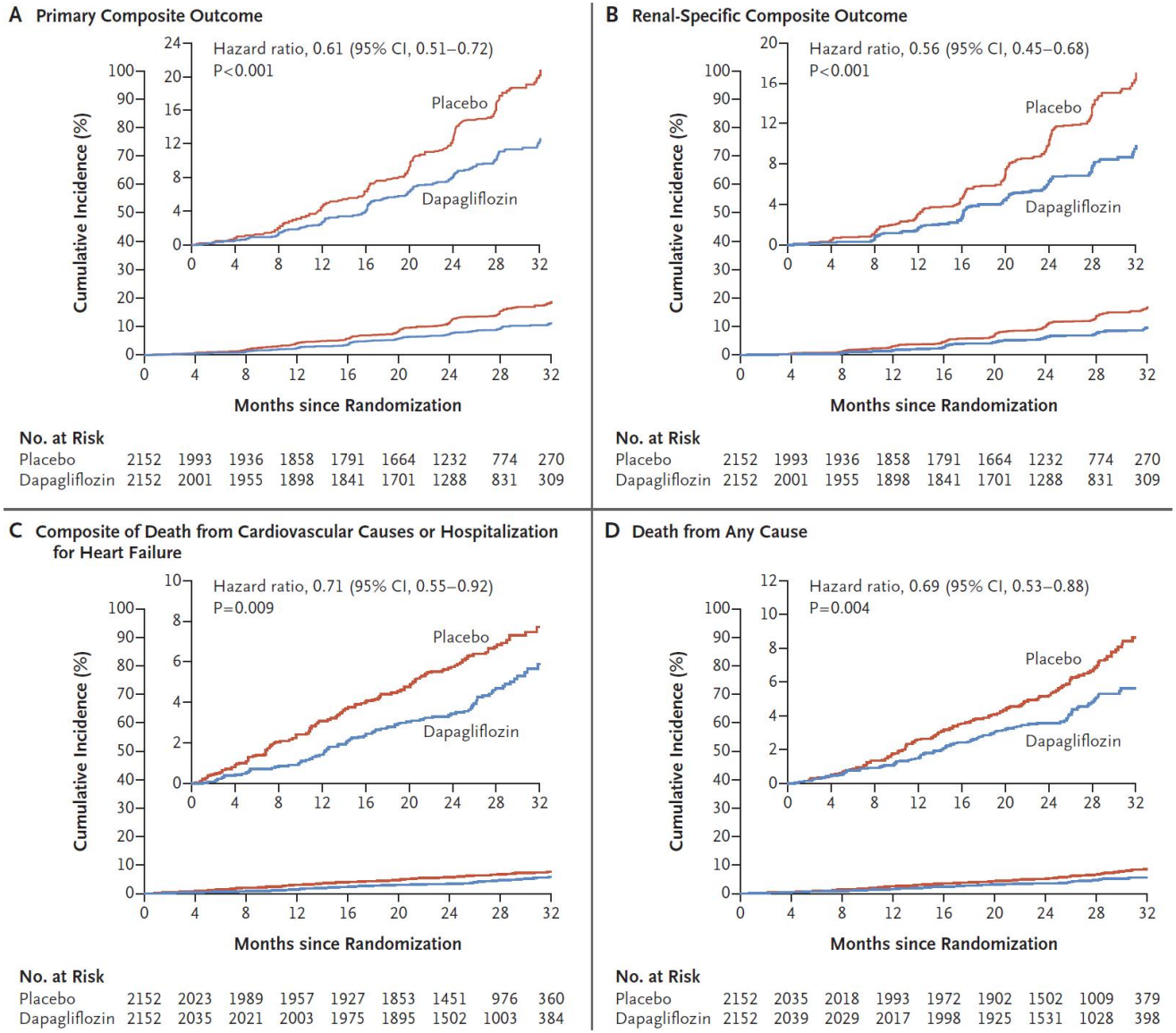
KDIGO guideline 2021

Sodium-glucose cotransporter 2 (SGLT2) inhibitor

- **SGLT2 inhibitors** inhibit **SGLT2**, which is expressed in the **proximal tubule** and mediates reabsorption of approximately 90 percent of the filtered **glucose** load.
- If **PU persists** despite the above measures for mor e than 3 months, we may add a **SGLT2 inhibitor**.
- The benefits of **SGLT2 inhibitors** appear to be ind ependent of their blood glucose–lowering effects a nd may be mediated by **natriuresis and glucose-i nduced osmotic diuresis**, leading to a **reduction i n intraglomerular pressure**.



DAPA-CKD (21 countries): 4304 adults (GFR 25~75 ml/min/1.73m^2)



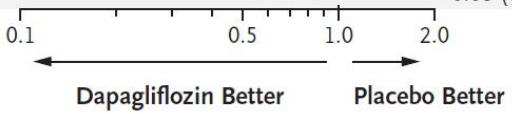
Dapagliflozin = SGLT2 inhibitor

The **primary** composite **outcome** (A), **renal**-specific composite **outcome** (B), composite of **death** from **cardiovascular causes** or hospitalization for **heart failure** (C), **death** from **any cause** (D) were all statistically favoring **dapagliflozin group**.

NEJM 2020;383:1436-46

DAPA-CKD (21 countries): 4304 adults (GFR 25~75 ml/min/1.73m^2)

Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of participants/total no.		
All participants	197/2152	312/2152	0.61 (0.51–0.72)
Age			
≤65 yr	122/1247	191/1239	0.64 (0.51–0.80)
>65 yr	75/905	121/913	0.58 (0.43–0.77)
Sex			
Male	126/1443	209/1436	0.57 (0.46–0.72)
Female	71/709	103/716	0.65 (0.48–0.88)
Race			
White	110/1124	174/1166	0.62 (0.49–0.79)
Black	7/104	14/87	0.33 (0.13–0.81)
Asian	53/749	77/718	0.66 (0.46–0.93)
Other	27/175	47/181	0.54 (0.33–0.86)
Geographic region			
Asia	50/692	69/654	0.70 (0.48–1.00)
Europe	57/610	89/623	0.60 (0.43–0.85)
North America	35/401	69/412	0.51 (0.34–0.76)
Latin America	55/449	85/463	0.61 (0.43–0.86)
Type 2 diabetes			
Yes	152/1455	229/1451	0.64 (0.52–0.79)
No	45/697	83/701	0.50 (0.35–0.72)
Estimated GFR			
<45 ml/min/1.73 m^2	152/1272	217/1250	0.63 (0.51–0.78)
≥45 ml/min/1.73 m^2	45/880	95/902	0.49 (0.34–0.69)
Urinary albumin-to-creatinine ratio			
≤1000	44/1104	84/1121	0.54 (0.37–0.77)
>1000	153/1048	228/1031	0.62 (0.50–0.76)
Systolic blood pressure			
≤130 mm Hg	46/793	96/749	0.44 (0.31–0.63)
>130 mm Hg	151/1359	216/1403	0.68 (0.56–0.84)



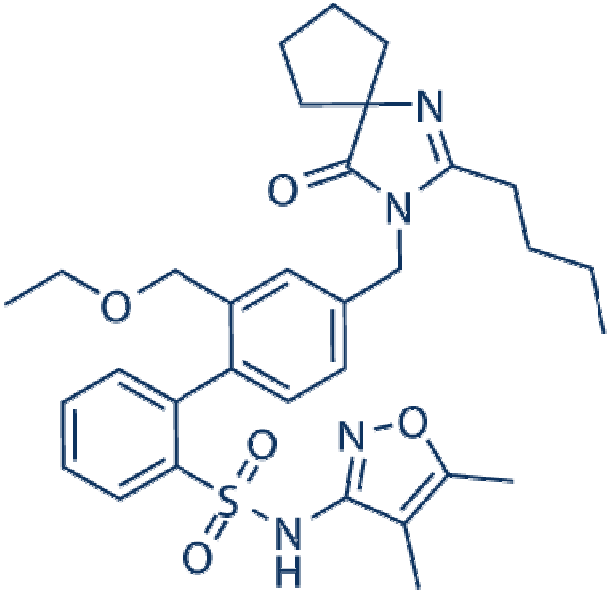
Dapagliflozin = SGLT2 inhibitor

The effect of **dapagliflozin** on the primary outcome was generally **consistent** across prespe cified subgroups including **non-DM** patients.

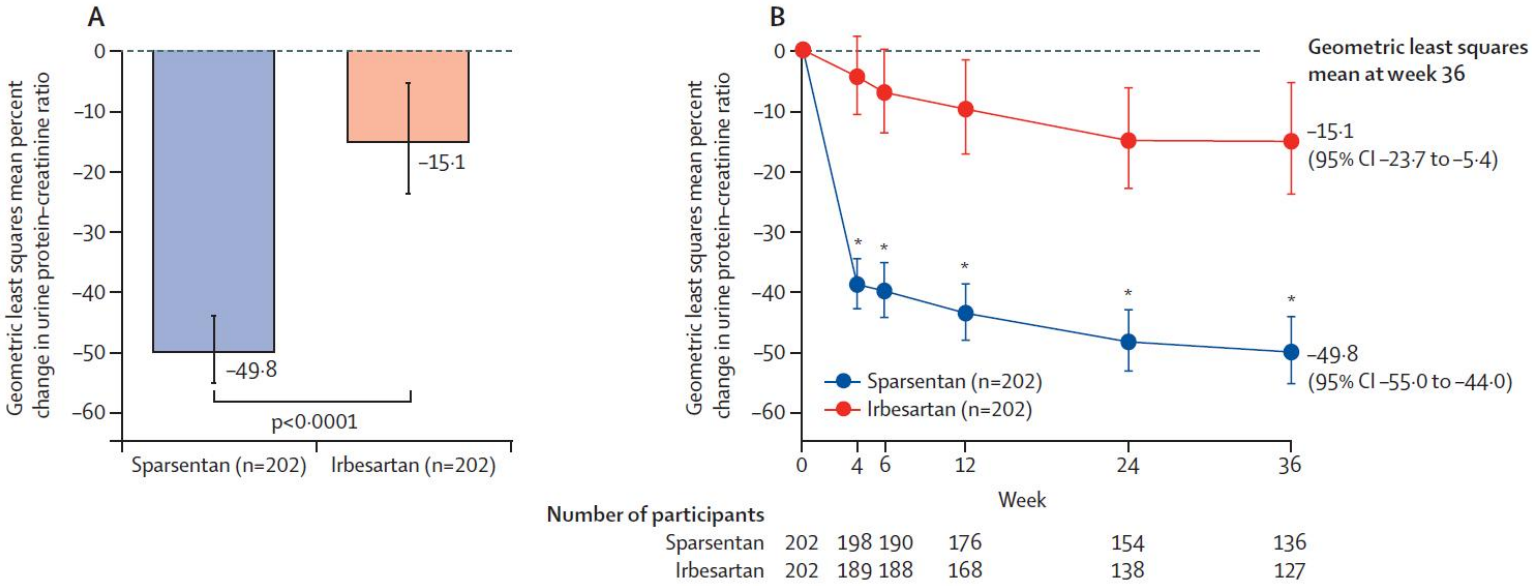
NEJM 2020;383:1436-46

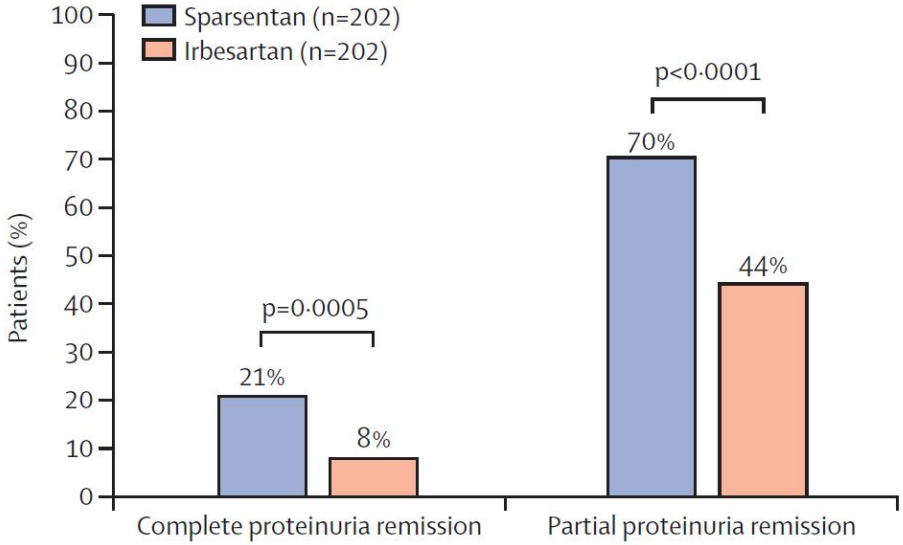
Sparsentan

- **Endothelin-1** contributes to the pathophysiology of IgAN via activation of **ET_A receptors**, leading to a variety of effects including vasoconstriction, pod ocyte dysfunction, tubular injury, inflammation, an d fibrosis.
- **Sparsentan** is a novel, non-immunosuppressive, si ngle-molecule, **dual endothelin and angiotensin receptor antagonist**.
- **Sparsentan** received conditional approval by the F DA for reduction of PU in patients with IgAN at ris k of rapid disease progression.



Phase 3 PROTECT study (18 countries): IgAN, PU > 1g/d, 202 irbesartan vs 202 **sparsentan** (RCT)





Reduction of PU and the rate of **complete remission** was statistically greater in the **sparsentan** group compared to irbesartan group.

Lancet 2023;401:1584-94

Fish oil?

- The rationale for using **fish oil** in patients with IgAN is based on the premise that n-3 fatty acids may limit the production or action of cytokines and eicosanoids evoked by the initial i mmunologic renal injury.
- A benefit from **fish oil** has not been clearly established, and r andomized trials evaluating fish oil in patients with IgAN have reported conflicting results.

Donadio et al. (Mayo clinic) IgA adult patients, 55 fish-oil vs 51 placebo

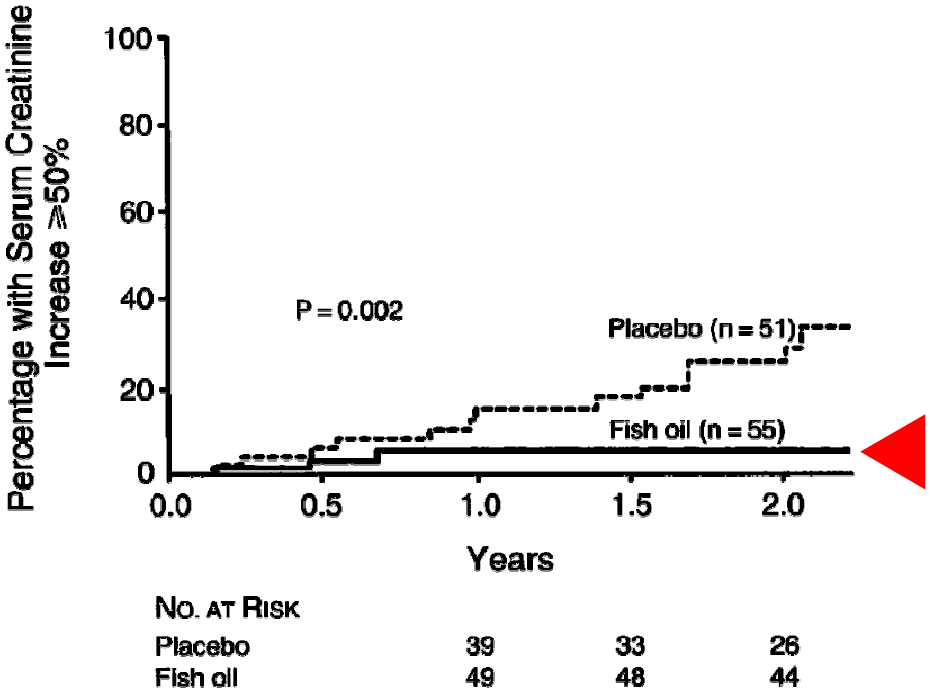


Table 2. Effect of Two Years of Treatment with Fish Oil or Placebo on the Occurrence of the Primary End Point in Patients with IgA Nephropathy, According to the Stratification Factors.*

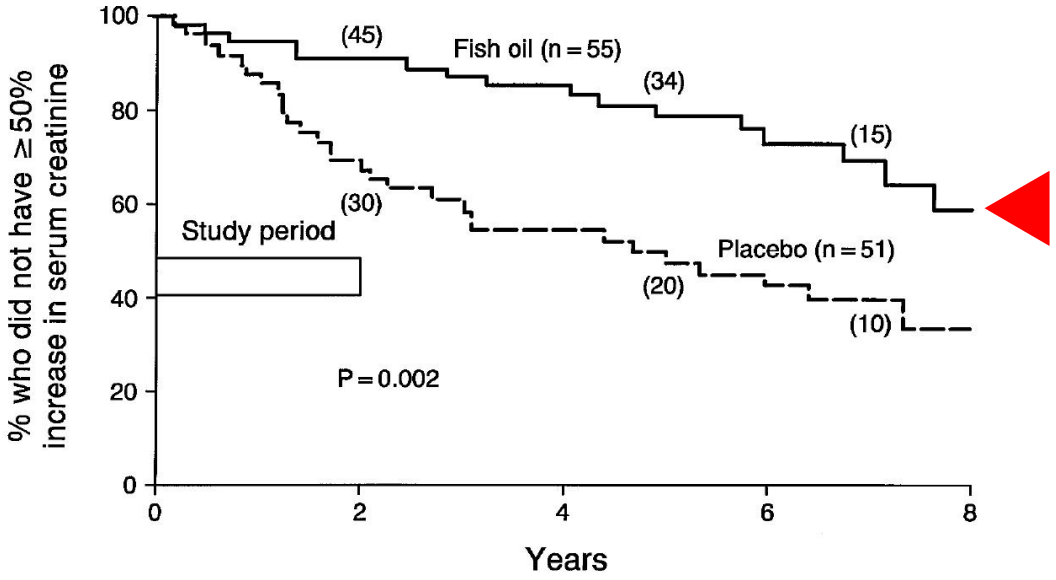
Factor†	Fish-Oil Group		Placebo Group		P Value
	Total No.	% Reaching End Point‡	Total No.	% Reaching End Point‡	
Hypertension					
Present	31	3	31	35	0.010
Absent	24	9	20	34	0.045
Elevated serum creatinine					
Present	36	9	32	42	0.010
Absent	19	0	19	19	0.035
Urinary protein excretion					
≥3.5 g/24 hr	15	14	15	65	0.030
1.0–3.4 g/24 hr	40	3	36	20	0.035

Fish-oil group showed less cumulative percentage of creatinine increase by 50% compared to placebo group

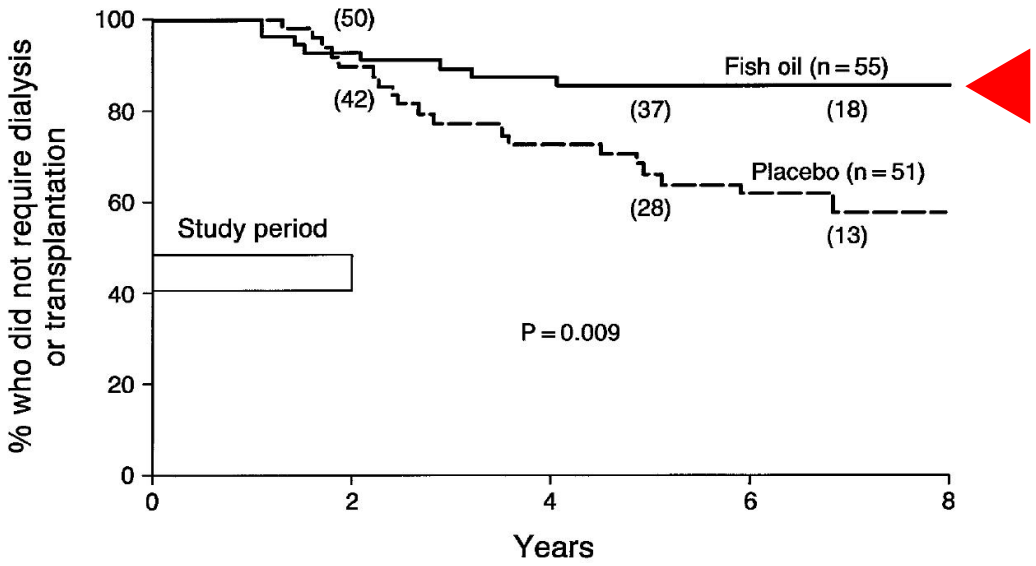
Hypertension, elevated serum creatinine, and nephrotic range PU occurred significantly **less frequently** in the **fish-oil group**.

NEJM 1994;331:1194-9

Donadio et al. (Mayo clinic)



There were **more** cumulative percentage of patients wit h IgAN treated with **fish oil** whose **sCr** did **not** increase by 50% or more to last follow-up compared to **placebo group**.



There were **more** cumulative percentage of patients with IgAN treated with **fish oil** who did **not** develop **ESRD** to last follow-up compared to **placebo group**.

JASN 1999;10:1772-7

Hogg et al. (north America, network of 37 adult and pediatric nephrology centers): age ≤40yr
33 prednisone, 32 O3FA, 31 placebo

Table 3. Proportional hazards model for time to failure

Effect	Hazard Ratio	95% Confidence Interval
Analysis of treatment		
prednisone group	0.551	(0.101 to 3.009)
O3FA group	2.031	(0.611 to 6.751)
Analysis of treatment and proteinuria		
prednisone group	0.308	(0.053 to 1.798)
O3FA group	1.348	(0.400 to 4.546)
UP/C ratio	2.694	(1.299 to 5.586)

Superiority of **prednisone** or **O3FA** over **placebo** in slowing progression of renal disease was **not** demonstrated.

CJASN 2006;1:467-74

Ferraro et al. (Italy): adult with PU. 15 PUFA vs 15 control

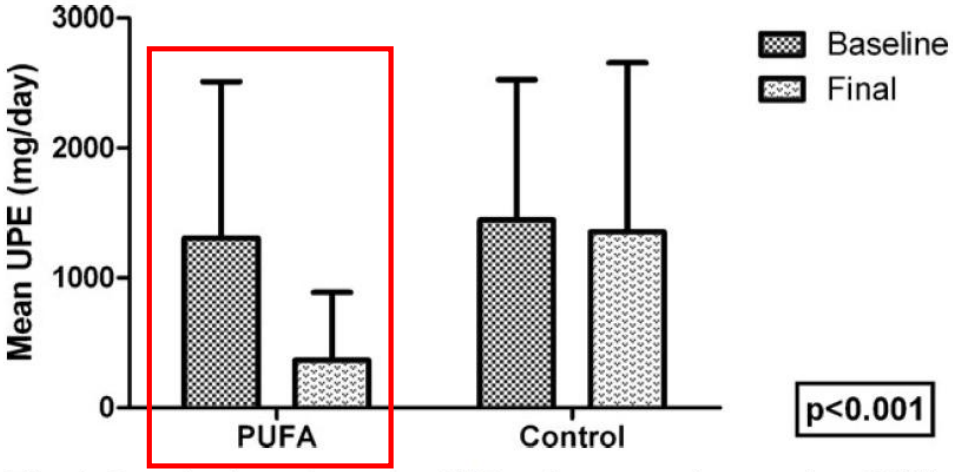


Fig. 1. Proteinuria at 6 months. UPE, urinary protein excretion; PUFA, polyunsaturated fatty acids.

Table 4. Stepwise multivariate regression model for UPE reduction

	B (SEB)	Beta	Adjusted R^2	*P*-value
Treatment group	57.6 (13.2)	0.62	0.46	<0.001
Gender				0.72
Body weight				0.12

UPE, urinary protein excretion; SEB, standard error of B.

Patients treated with **PUFA** showed a more significant **reduction in PU** compared with the control group.

PUFA: polyunsaturated fatty acids

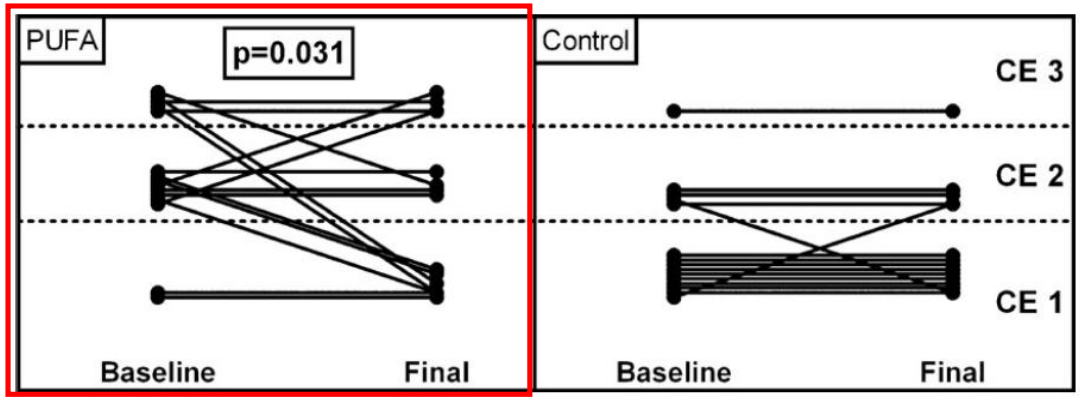


Fig. 2. Erythrocyturia at 6 months. CE, class of erythrocyturia; PUFA, polyunsaturated fatty acids.

Patients treated with **PUFA** showed a more significant **reduction in HU** compared with the control group.

NDT 2009;24:156-60

Immunosuppressive therapy in IgAN

Indications for immunosuppressive therapy

- **Immunosuppressive therapy** is considered in patients with **high risk of disease progression**.
- **Risk assessment** using **International IgA Nephropathy Prediction Tool (IIgAN-PT)** can be made using following parameters: estimated GFR, BP, PU, age, race/ethnicity (White, Japanese, Chinese, or other), prior use of ACE inhibitor or ARB, Oxford classification of IgAN MEST histology scores, immunosuppression use at or prior to biopsy

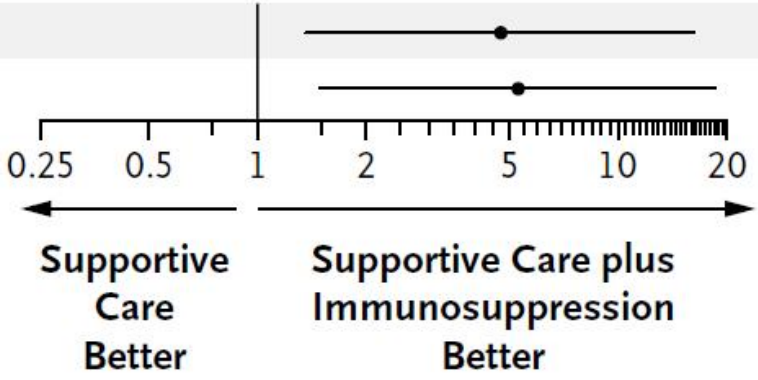
KI 2020;98:1009-19

STOP-IgAN study (Germany): adult IgAN → PU + HT, GFR 30~90 ml/min/1.73m^2

80 supportive care vs 82 supportive care + immunosuppression

A In Full Clinical Remission

Subgroup	Supportive Care	Supportive Care plus Immunosuppression	Odds Ratio (95% CI)	P Value
	no. of events/total no.			
Full-analysis set	4/80	14/82	4.82 (1.43–16.30)	0.01
Available-case analysis	4/72	14/71	5.38 (1.55–18.66)	0.008



Treatment with **supportive care plus immunosuppression** was better in achieving **full clinical remission**.

NEJM 2015;373:2225-36

Systemic glucocorticoids

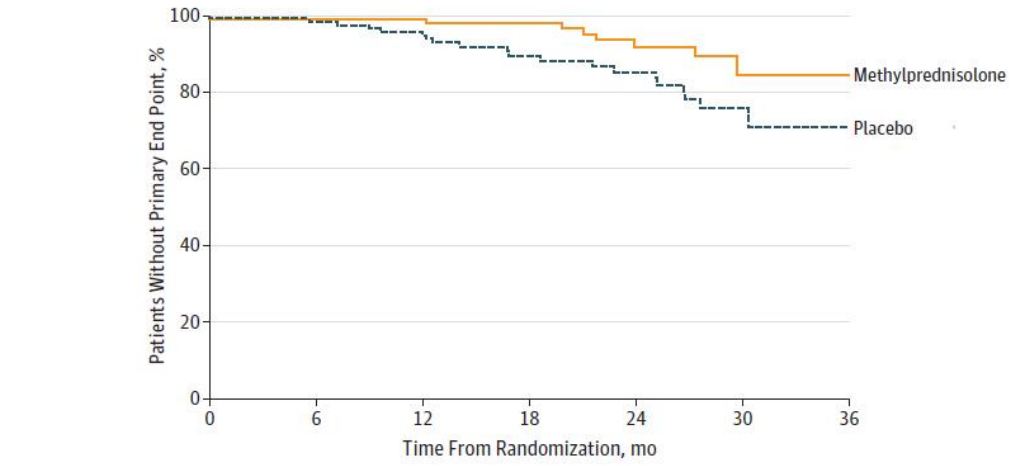
- **Systemic glucocorticoids** can be used in IgAN patients with a **high risk of disease progression**.

TESTING study (China, Australia, India, Canada, Malaysia): PU>1g/d, GFR 20~120 ml/min/1.73m^2,

134 **methylprednisolone** vs 126 placebo

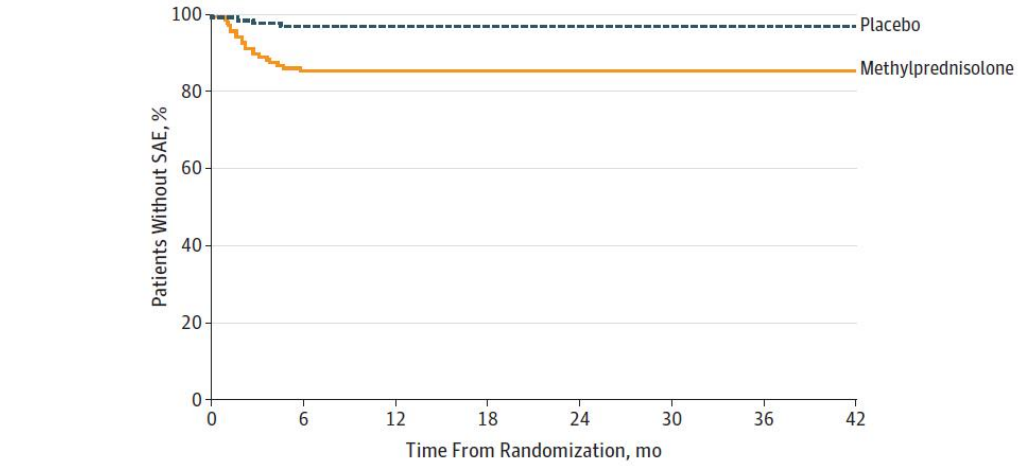
(0.6-0.8 mg/kg/d)

Figure 3. Time From Randomization to First Primary Composite Outcome of 40% eGFR Decrease, ESKD, or Death Due to Kidney Failure, by Treatment Group



Methylprednisolone group showed statistically **less** occurrence of a **50% decrease in eGFR**, development of **ESKD**, or **death** due to kidney disease (p=0.02).

Figure 2. Time From Randomization to First Serious Adverse Event, by Treatment Group



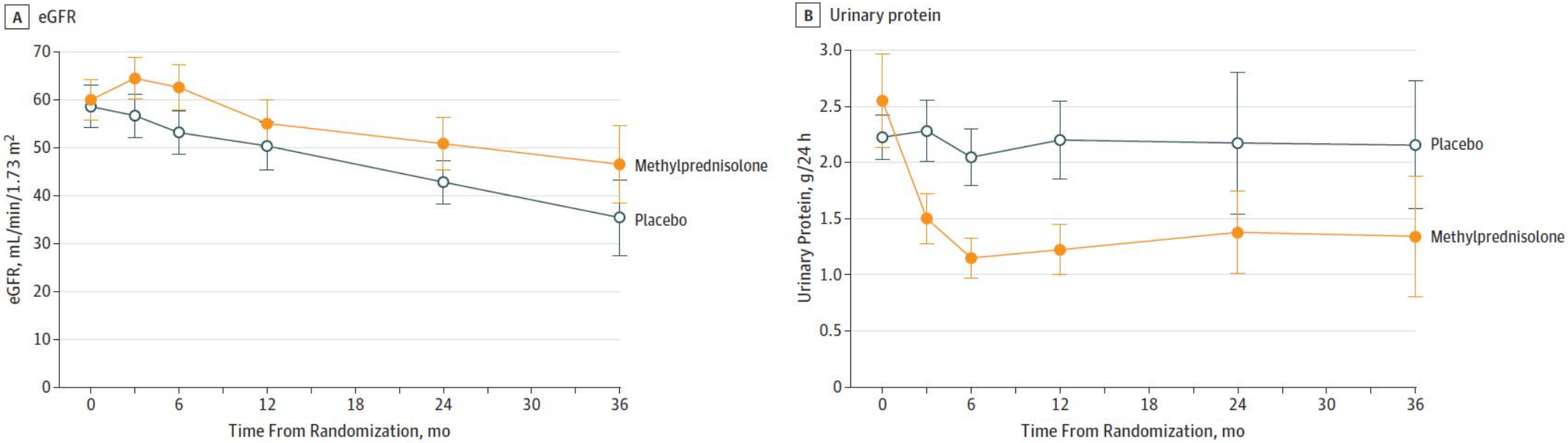
Methylprednisolone group showed statistically **more serious adverse events** (p=0.001).

JAMA 2017;318:423-42

TESTING study (China, Australia, India, Canada, Malaysia): PU>1g/d, GFR 20~120 ml/min/1.73m^2,

134 **methylprednisolone** vs 126 placebo

(0.6-0.8 mg/kg/d)



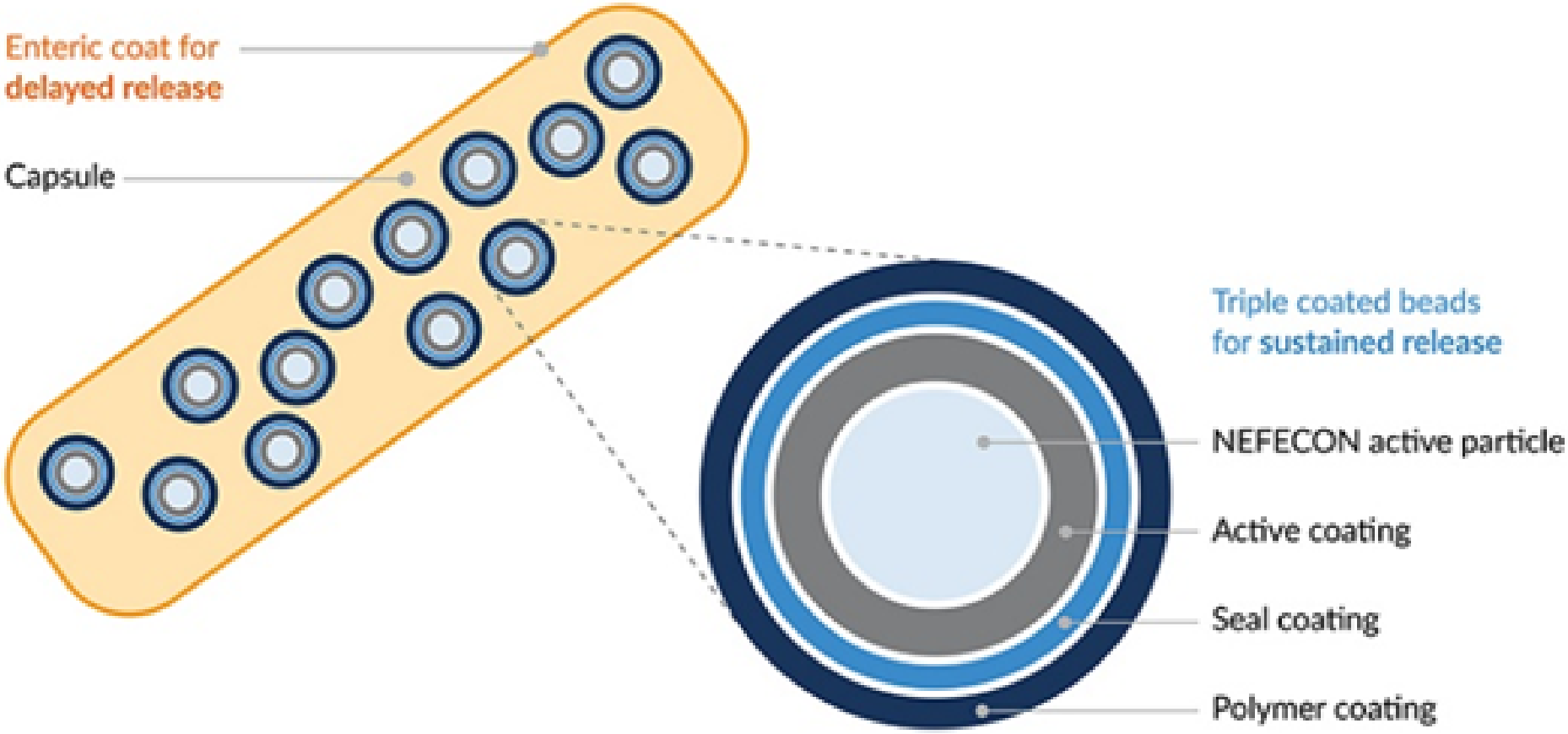
The annual rate of **eGFR decline** and time-averaged **PU** was **lower** in the **methylprednisolone** group

JAMA 2017;318:423-42

Targeted-release formulation (TRF) budesonide

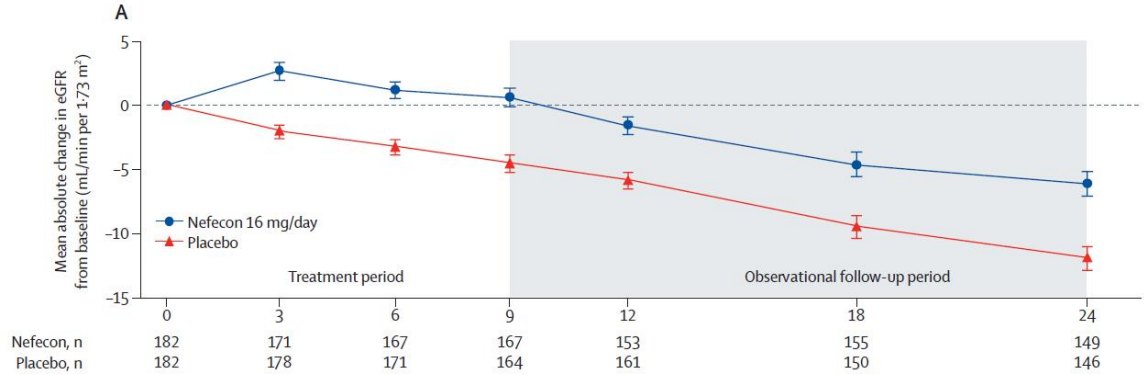
- **Mucosal B lymphocytes** localized within **Peyer patches** are postulated to be a source to produce **poorly galactosylated immunoglobulin A1 (IgA1)**.
- **TRF-budesonide** is designed to be released in the **distal ileum** (ileocecal region), where most **Peyer patches** are located.
- **Budesonide** has a 90% hepatic clearance at first liver passage, **limiting its systemic circulation**.

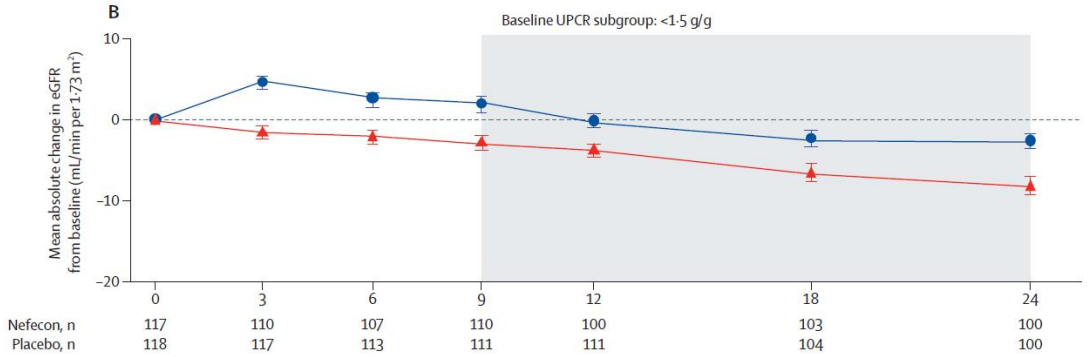
Targeted-release formulation (TRF) budesonide

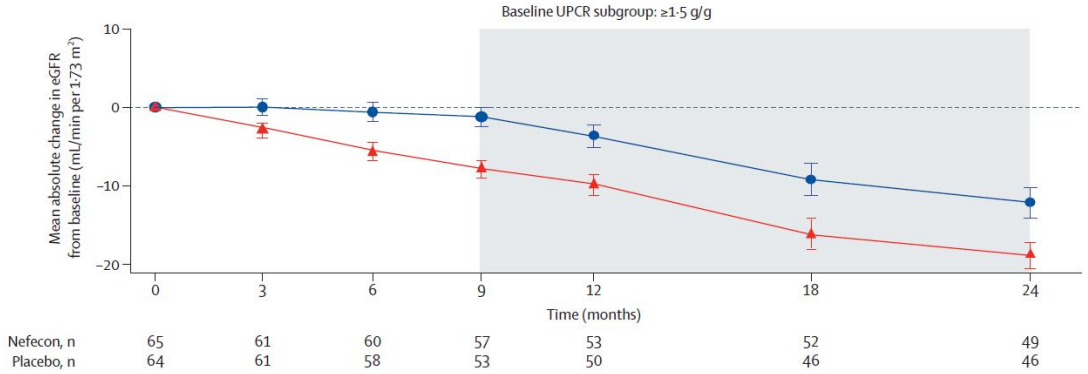


phase 3 NEFIGAN trial (20 countries): persistent PU≥1g/d, eGFR 35~90 ml/min/1.73m^2,

182 **Nefecon** vs 182 placebo **Nefecon**: TRF budesonide





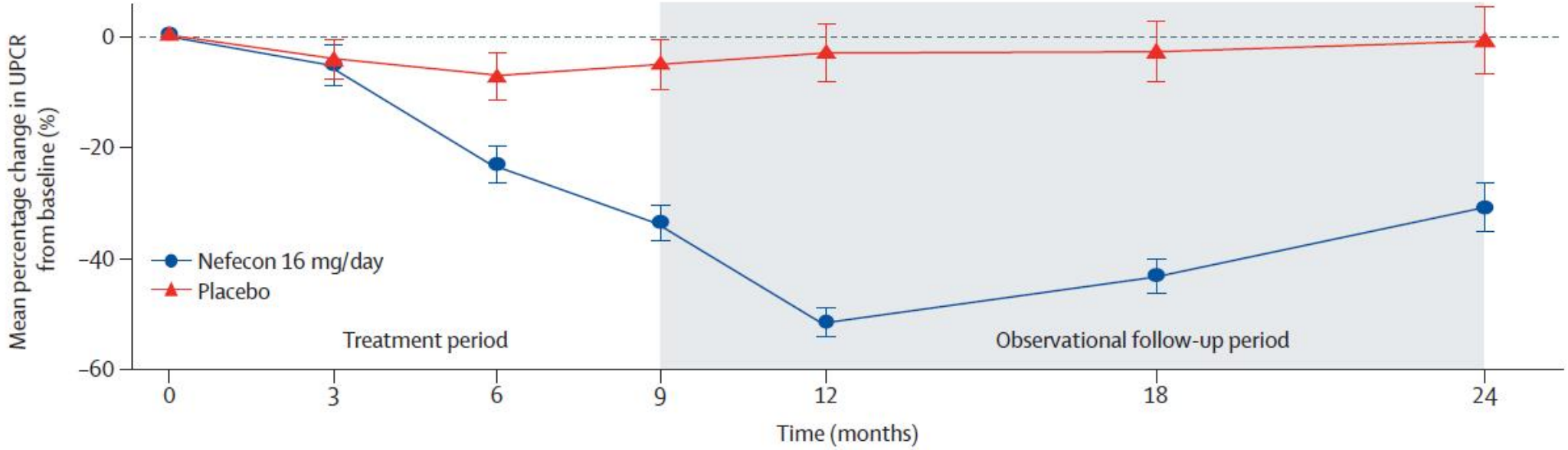


eGFR was more preserved in **Nefecon** group compared with placebo.

Lancet 2023;402:859-70

phase 3 NEFIGAN trial (20 countries): persistent PU≥1g/d, eGFR 35~90 ml/min/1.73m^2,

182 **Nefecon** vs 182 placebo **Nefecon**: TRF budesonide



PU decreased significantly in **Nefecon** group compared with placebo.

Lancet 2023;402:859-70

phase 3 NEFIGAN trial (20 countries): persistent PU≥1g/d, eGFR 35~90 ml/min/1.73m^2,

182 **Nefecon** vs 182 placebo **Nefecon**: TRF budesonide

Supplementary Table S8. Summary of TEAEs during treatment period* (≥5% in the Nefecon 16-mg/day arm)

Adverse events, n (%)	Nefecon 16 mg/day (n=182)	Placebo (n=182)
Peripheral oedema[†,‡]	31 (17)	7 (4)
Hypertension[§]	22 (12)	6 (3)
Muscle spasms	22 (12)	7 (4)
Acne	20 (11)	2 (1)
Headache	19 (10)	14 (8)
Nasopharyngitis	17 (9)	19 (10)
Face oedema[‡]	14 (8)	1 (0·5)
Dyspepsia	13 (7)	4 (2)
Arthralgia	12 (7)	4 (2)
Upper respiratory tract infection	10 (5)	10 (5)
Insomnia	10 (5)	7 (4)
Fatigue	10 (5)	7 (4)
Rash	10 (5)	7 (4)
Increase in weight	10 (5)	5 (3)

Nefecon group had generally **non-serious adverse events** and were of mild severity, and reversible during or after treatment.

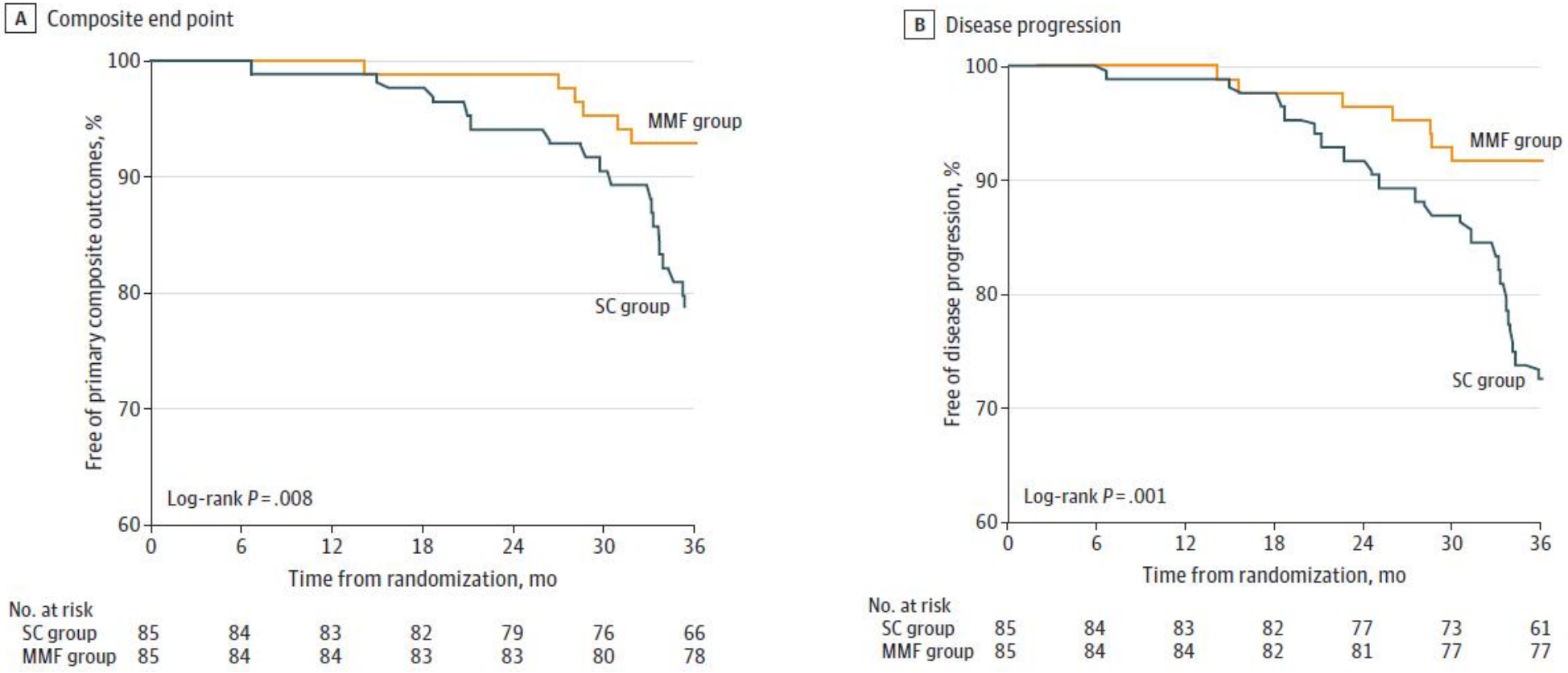
Lancet 2023;402:859-70

Mycophenolate mofetil (MMF)

- **MMF** is an alternative option for high-risk patients who are u nable to tolerate or do not wish to receive oral glucocorticoid s.
- Dosing: 300-600/m^2/dose twice daily. (Max. 3,000 mg/day)

MAIN study (China): adult IgAN, PU > 1g/d, eGFR < 60 ml/min/1.73m^2 or HT

80 MMF vs 77 supportive care

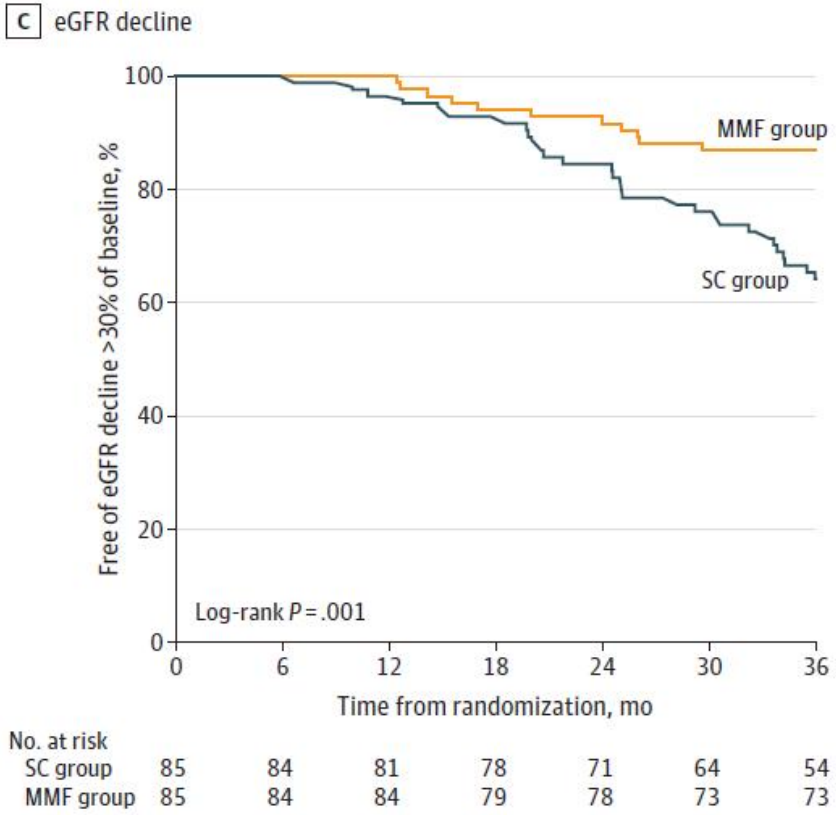


MMF treatment reduced **risk of the composite outcome** and **disease progression** by 77%.

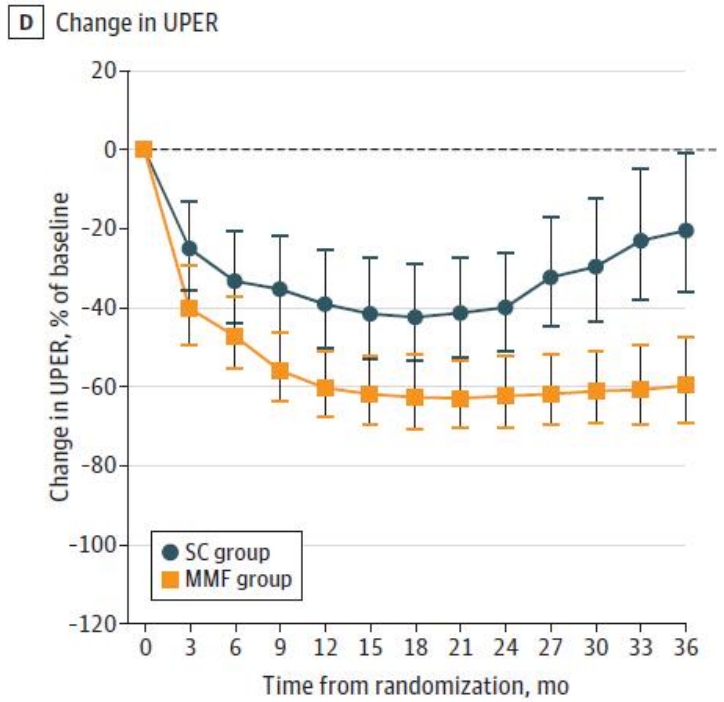
JAMA Network Open. 2023;6(2):e2254054.

MAIN study (China): adult IgAN, PU > 1g/d, eGFR < 60 ml/min/1.73m^2 or HT

80 MMF vs 77 supportive care



MMF treatment reduced the **risk of a 30% reduction in eGFR** by 72%



The MMF group had a significantly higher rate of **reduction in PU** from baseline compared with the SC group

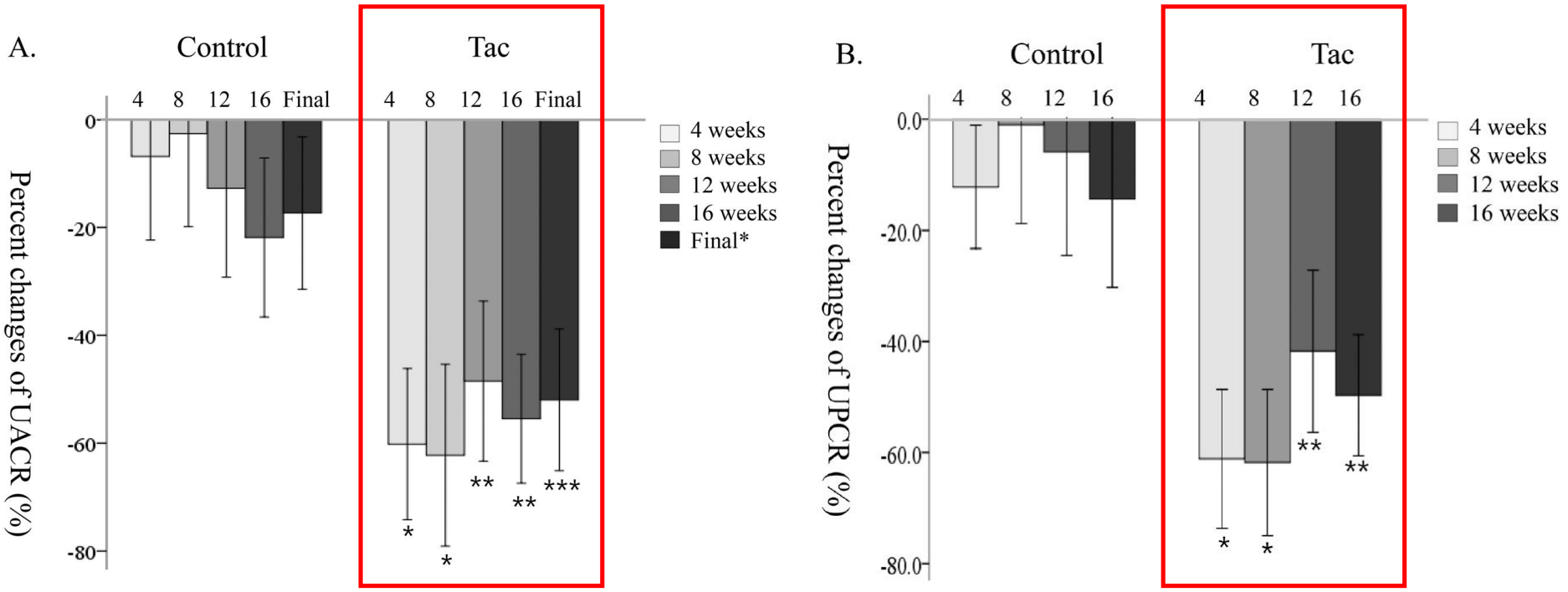
JAMA Network Open. 2023;6(2):e2254054.

Other immunosuppressive regimens

- Other immunosuppressive regimens below lack clear evidenc e supporting their efficacy in IgAN patient.
  - Calcineurin inhibitors
  - Rituximab
  - Cyclophosphamide
  - Azathioprine
  - Leflunomide
  - Hydroxychloroquine

Kim et al. (Korea): 18~69 yr, PU 0.3~2.9 g/g, GFR ≥ 45 ml/min/1.73m^2,

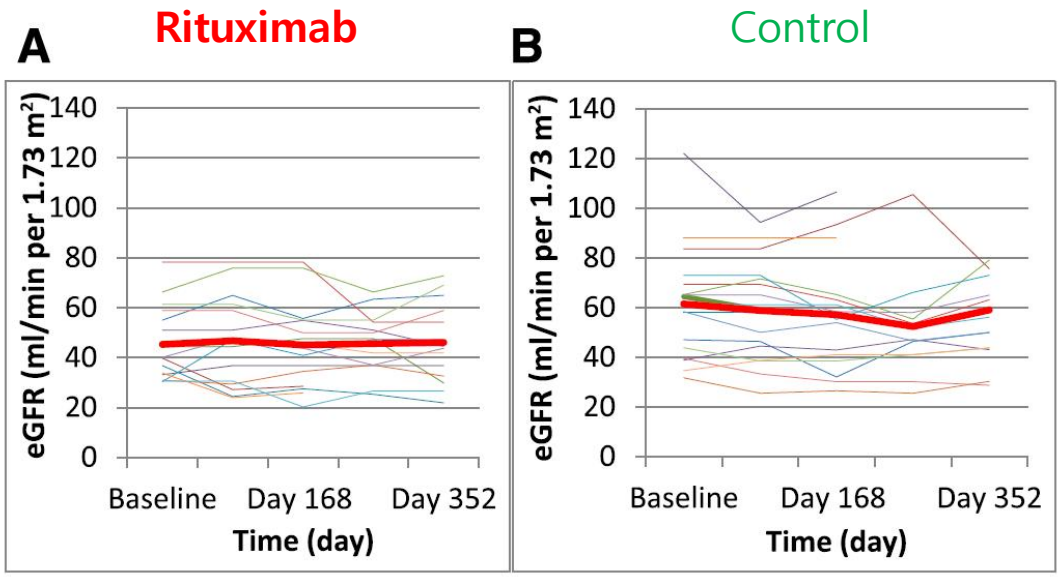
20 **Tacrolimus** vs 20 control



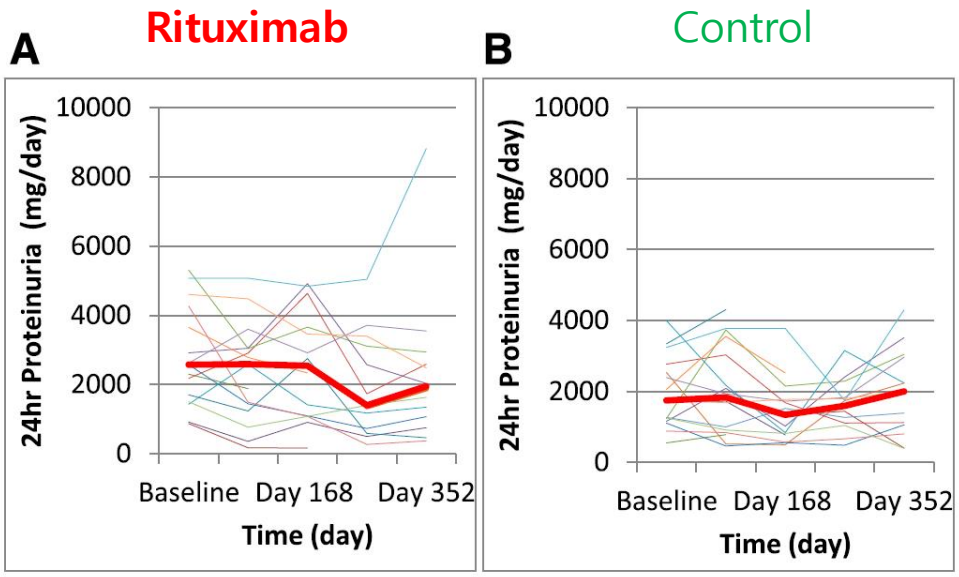
Albuminuria and **PU** decreased significantly in **tacrolimus** group

Lafayette et al. (USA): 18~70 yr, PU > 1g/d

15 **rituximab** vs 15 control



eGFR did not change in either gro up.

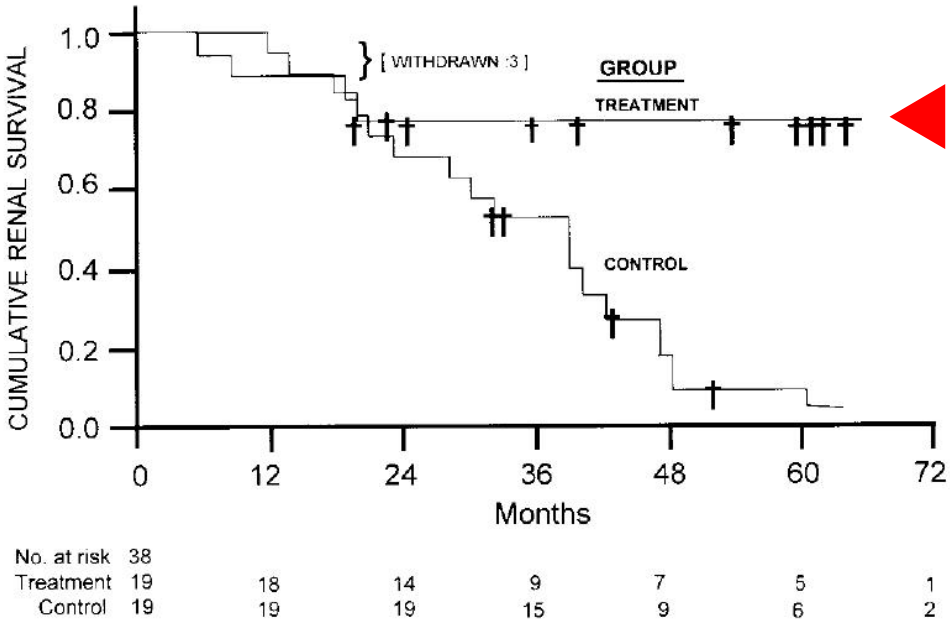


Rituximab did not alter
the level of **PU** compared with
that at baseline or in the control group

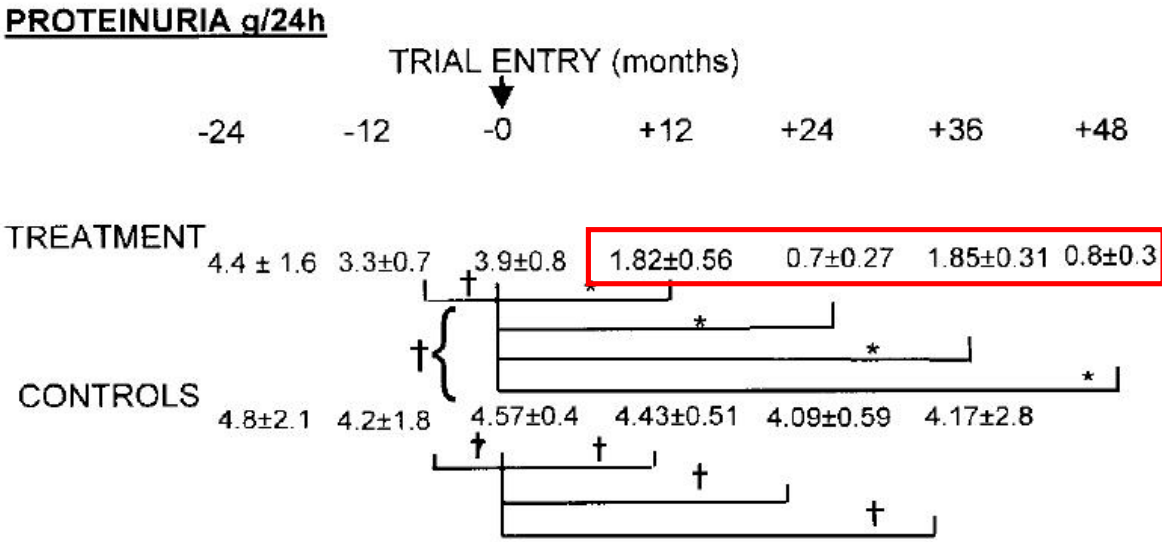
JASN 2017;28:1306-13

Ballardie et al. (UK): 18~54 yr,

19 **cyclophosphamide** + **prednisolone** vs 19 control



Cumulative **renal survival** after 2 yr
in the **cyclophosphamide** treatment group was
significantly **improved** (P 0.05, log rank)

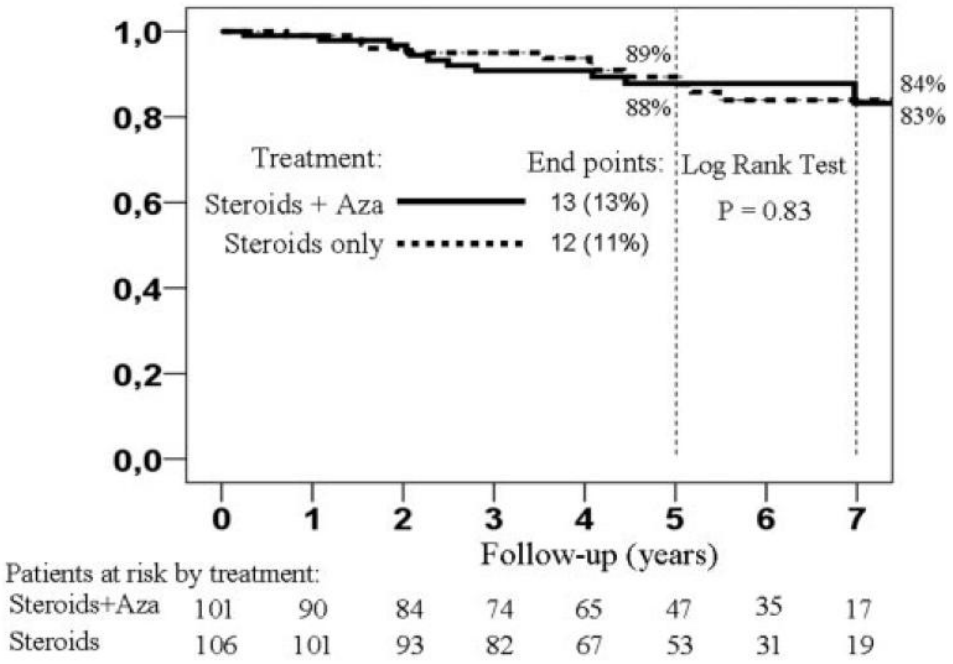


Cyclophosphamide treatment **reduced PU** from 12 mo
and was sustained in the treatment group
compared with pretrial values, or
compared with controls, who showed no significant cha
nges throughout.

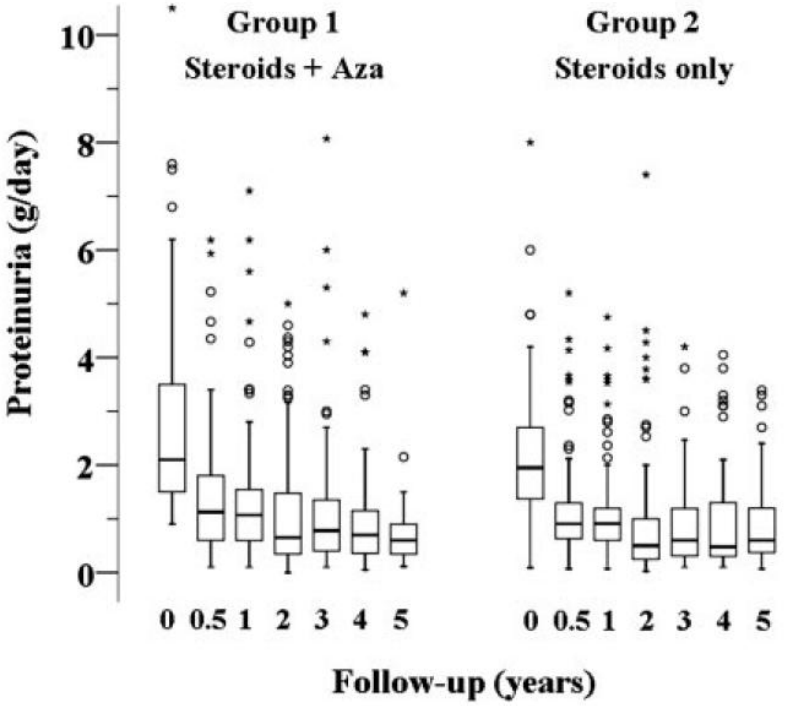
JASN 2002;13:142-8

Pozzi et al. (Italy): 27~51 yr, Cr ≤2.0 mg/dL, PU ≥1.0 g/d

82 **steroid + azathioprine** vs 98 steroid



Renal survival was <u>similar</u> in both treatment groups.



There were <u>similar</u> decrease in **PU** during follow-up in both treatment groups.

JASN 2010;21:1783-90

Tonsillectomy

- Tonsillectomy is not routinely recommended.

Table 2. Logistic regression analysis of the impact of tonsillectomy, renal function, blood pressure and urinary protein excretion at baseline and after disappearance of proteinuria, hematuria or both at study completion

	Odds ratio	95% CI	P-value
Disappearance of proteinuria			
Assigned treatment	2.98	1.01–8.83	0.049
eGFR (baseline)	0.99	0.97–1.02	0.560
Mean blood pressure (baseline)	1.04	0.97–1.11	0.297
Proteinuria (baseline)	0.61	0.33–1.13	0.115
RASi (baseline)	0.51	0.16–1.68	0.270
Disappearance of hematuria			
Assigned treatment	1.23	0.43–3.55	0.697
eGFR (baseline)	0.99	0.97–1.01	0.304
Mean blood pressure (baseline)	0.97	0.91–1.04	0.450
Proteinuria (baseline)	0.91	0.54–1.54	0.737
RASi (baseline)	0.95	0.29–3.13	0.930
Clinical remission			
Assigned treatment	2.24	0.77–6.51	0.140
eGFR (baseline)	0.99	0.97–1.02	0.554
Mean blood pressure (baseline)	1.01	0.94–1.08	0.858
Proteinuria (baseline)	0.75	0.41–1.38	0.348
RASi (baseline)	0.63	0.19–2.06	0.445

Kawamura et al. 10~69 years, PU 1.0~3.5 g/day, sCr≤1.5 mg/dL

33 **tonsillectomy** + steroid pulse *vs* 39 steroid pulse

Tonsillectomy combined with steroid pulse therapy had sig nificantly but marginally greater **antiproteinuric effect** but had no beneficial effect to attenuate **hematuria** and to in crease the incidence of **clinical remission** over steroid pulses alone .

NDT 2014;29:1546-53

Treatment of IgAN

Supportive care

- We do **not recommend** **kidney biopsy** or any **treatment** in patients with **asymptomatic HU**.
- We recommend **ACE inhibitor** or **ARB** in patients with **PU**.
- **BP control** and **lifestyle modification** is needed.
- If **PU** persists, we may consider **SGLT2 inhibitor** or switch from the ACE inhibitor or ARB to **sparsentan**.
- **Fish-oil** seems to have a limited role.

Immunosuppressive therapy

- We add **systemic glucocorticoids** in patients with a **high risk of disease progression**.
- Alternative options are **targeted-release budesonide** and **mycophenolate mofetil**.
- Other immunosuppressive agents, such as **calcineurin inhibitors, rituximab, cyclophosphamide, azathioprine** are less selected for first-line therapy.
- **Tonsillectomy** is not routinely recommended.

The 20th China-Japan-Korea Pediatric Nephrology Seminar
IPNA Teaching Course Fuzhou, China, April 13, 2024

Pediatric Acute Kidney Injury in China

Aihua Zhang

Children's Hospital of Nanjing Medical University
Jiangsu Children's Medical Center

Contents

- The epidemiology of pediatric AKI in the worldwide and in China
- The evolution of the diagnosis of pediatric AKI
- The etiology and risk factors of pediatric AKI in China

The epidemiology of pediatric AKI: challenge and advances

Epidemiology of acute kidney injury in children: a report from the 26th Acute Disease Quality Initiative (ADQI) consensus conference

Scott M. Sutherland[1] · Rashid Alobaidi[2] · Stephen M. Gorga[3] · Arpana Iyengar[4] · Catherine Morgan[2] · Emma Heydari[2] · A. Ayse Akcan Arikan[5] · Raj K. Basu[6] · Stuart L. Goldstein[7] · Michael Zappitelli[8] · the ADQI 26 Workgroup

- **Challenge:** Well-described in ICU or high-income countries **VS.** Inadequate data in non-ICU or middle-low income countries
- **Challenge:** Distinguishing AKI characteristics (or sub-categories or phenotypes)
- **Challenge:** The socioeconomic impact and long-term outcomes of AKI remain poorly understood

Scott M. Sutherland, et al. Pediatric Nephrology (2024) 39:919–928

The epidemiology of pediatric AKI: challenge and advances

Epidemiology of acute kidney injury in children: a report from the 26th Acute Disease Quality Initiative (ADQI) consensus conference

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- **Advances:** Standardized consensus criteria (KDIGO definition) in recent studies
- **Challenge:** Lack of real-time biomarkers, difficulty in application of urine output or baseline serum creatinine, lack of different definition of AKI phenotypes

Scott M. Sutherland, et al. Pediatric Nephrology (2024) 39:919–928

The incidence of pediatric AKI in worldwide

REVIEW ARTICLE

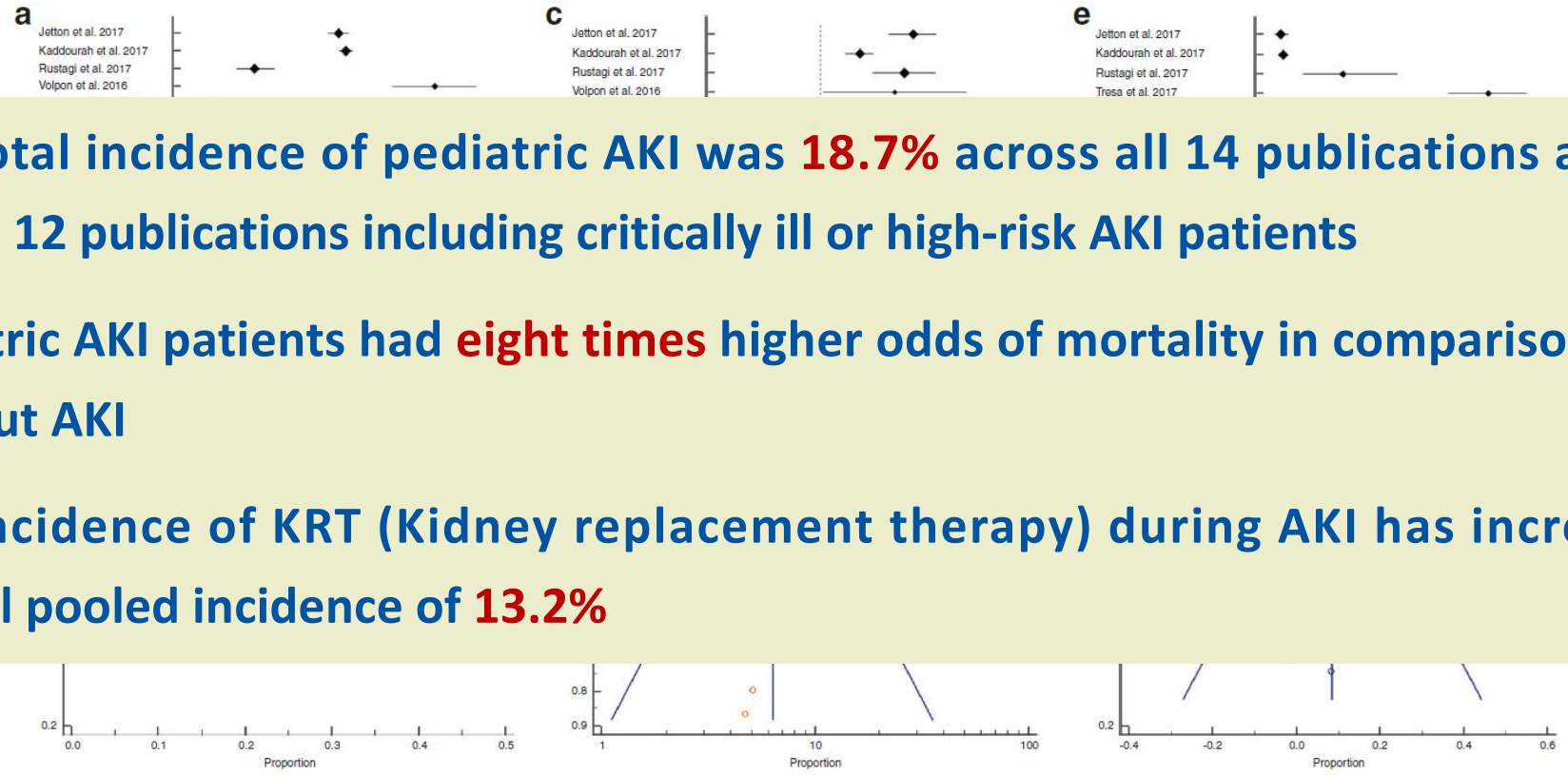
Advances in pediatric acute kidney injury

Rupesh Raina[1,2], Ronith Chakraborty[1,2], Abhishek Tibrewal[2], Sidharth K. Sethi[3] and Timothy Bunchman[4]

- **Meta-analyses of global burden of pediatric AKI (3,067,636 children from 14 studies from 2000 to 2020)**
- **12 publications included critically ill or high-risk AKI population from pediatric ICU or neonatal intensive care unit (NICU) or with baseline and follow-up creatinine level, while two publications had pediatric inpatient population.**

R Raina et al. Pediatric Research (2022) 91:44–55;

The incidence of pediatric AKI in worldwide



- The total incidence of pediatric AKI was **18.7%** across all 14 publications and **24.4%** across 12 publications including critically ill or high-risk AKI patients
- Pediatric AKI patients had **eight times** higher odds of mortality in comparison to those without AKI
- The incidence of KRT (Kidney replacement therapy) during AKI has increased the overall pooled incidence of **13.2%**

R Raina et al. Pediatric Research (2022) 91:44–55;

AWARE study

The NEW ENGLAND JOURNAL of MEDICINE

Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults

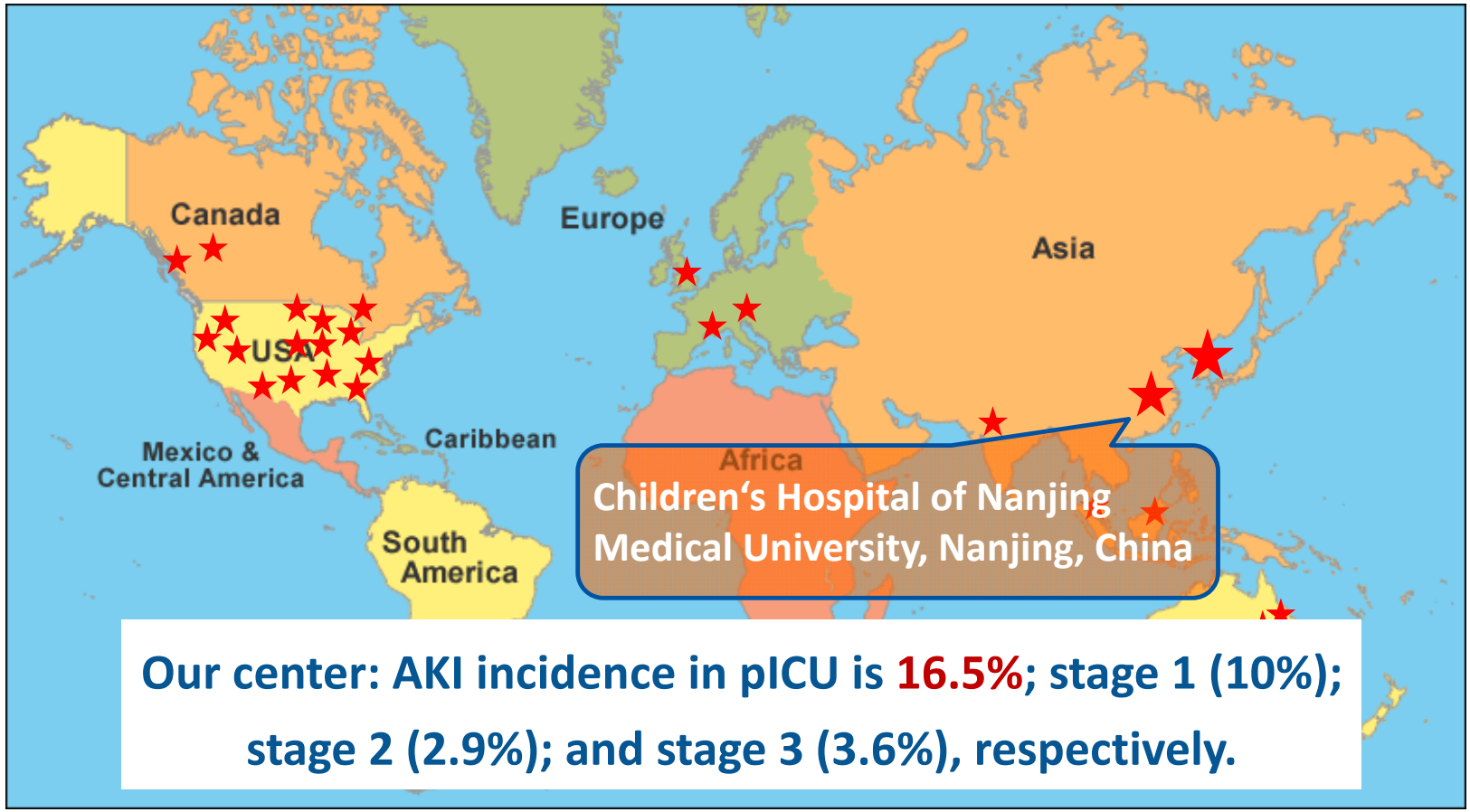
Ahmad Kaddourah, M.D., Rajit K. Basu, M.D., Sean M. Bagshaw, M.D., and Stuart L. Goldstein, M.D.,
for the AWARE Investigators*

JANUARY 5, 2017

- Prospective study
- 4483 critically ill
- 3 months to 25 years old
- Exculded CKD stage 5
- KDIGO criteria

- AKI incidence in ICU is high (27%); stage 1 (15.3%), stage 2 (6.3%), and stage 3 (5.3%)
- The daily prevalence of AKI on day 1 (14.5%) and day 7 (20.4%)
- Mortality rate in severe AKI is 11%
- Severe AKI is an independent risk factor for death

AWARE study



Our center: AKI incidence in pICU is 16.5%; stage 1 (10%); stage 2 (2.9%); and stage 3 (3.6%), respectively.

Kaddourah A, et al. N Engl J Med. 2017;376:11-20

The incidence of pediatric AKI in China

Multicenter Study > Pediatr Crit Care Med. 2022 Dec 1;23(12):e574-e582.
doi: 10.1097/PCC.0000000000003085. Epub 2022 Oct 10.

Pediatric Reference Change Value Optimized for Acute Kidney Injury: Multicenter Retrospective Study in China

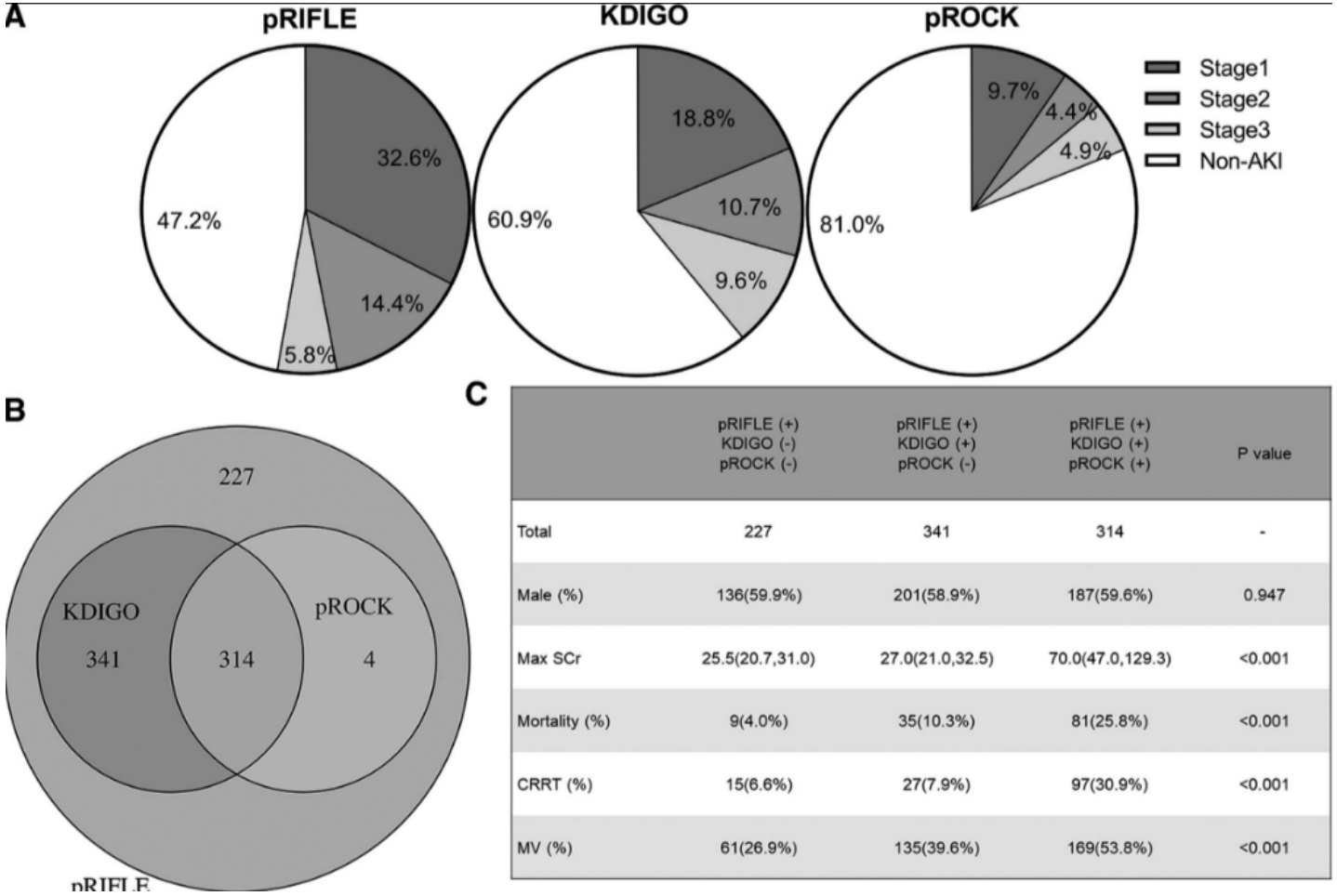
Jingxia Zeng [1], Hongjun Miao [1], Zhen Jiang [2], Yong Zhang [3], Xiaoli Guo [4], Qing Chen [5], Yu Wan [6], Peng Ji [6], Guojin Xie [7], Han Li [1], Xuejian Mei [1], Jinsu Zhou [1], Haisheng Xu [1], Jie Gu [1], Jun Cheng [3], Jianli Chen [5], Aihua Zhang [8], Xuhua Ge [1]

- **Design:** Multicenter retrospective study.
- **Setting:** Six PICUs in mainland China.
- **Patients:** One thousand six hundred seventy-eight hospitalized children admitted to the PICU with at least two creatinine values within 7 days.

Pediatr Crit Care Med. 2022 Dec 1;23(12):e574-e582.

. 2022 Dec 1;23(12):e574-e582.

The incidence of pediatric AKI in China



C

	pRIFLE (+) KDIGO (-) pROCK (-)	pRIFLE (+) KDIGO (+) pROCK (-)	pRIFLE (+) KDIGO (+) pROCK (+)	P value
Total	227	341	314	-
Male (%)	136(59.9%)	201(58.9%)	187(59.6%)	0.947
Max SCr	25.5(20.7,31.0)	27.0(21.0,32.5)	70.0(47.0,129.3)	<0.001
Mortality (%)	9(4.0%)	35(10.3%)	81(25.8%)	<0.001
CRRT (%)	15(6.6%)	27(7.9%)	97(30.9%)	<0.001
MV (%)	61(26.9%)	135(39.6%)	169(53.8%)	<0.001

- According to the definitions of **pRIFLE, KDIGO, and pROCK**, the prevalence of AKI in our cohort of 1,678 cases was **52.8%** (886), **39.0%** (655), and **19.0%** (318), respectively.

Pediatr Crit Care Med. 2022 Dec 1;23(12):e574-e582.

The incidence of pediatric AKI in China

Acute Kidney Injury among Hospitalized Children in China

Xin Xu,[1] Sheng Nie,[1] Aihua Zhang,[2] Jianhua Mao,[3] Hai-Peng Liu,[4] Huimin Xia,[5] Hong Xu,[6] Zhangsuo Liu,[7] Shipin Feng,[8] Wei Zhou,[9] Xuemei Liu,[10] Yonghong Yang,[11] Yuhong Tao,[12] Yunlin Feng,[13] Chunbo Chen,[14] Mo Wang,[15] Yan Zha,[16] Jian-Hua Feng,[17] Qingchu Li,[18] Shuwang Ge,[19] Jianghua Chen,[20] Yongcheng He,[21] Siyuan Teng,[22] Chuanming Hao,[23] Bi-Cheng Liu,[24] Ying Tang,[25] Wenjuan He,[1] Pinghong He,[1] and Fan Fan Hou[1]

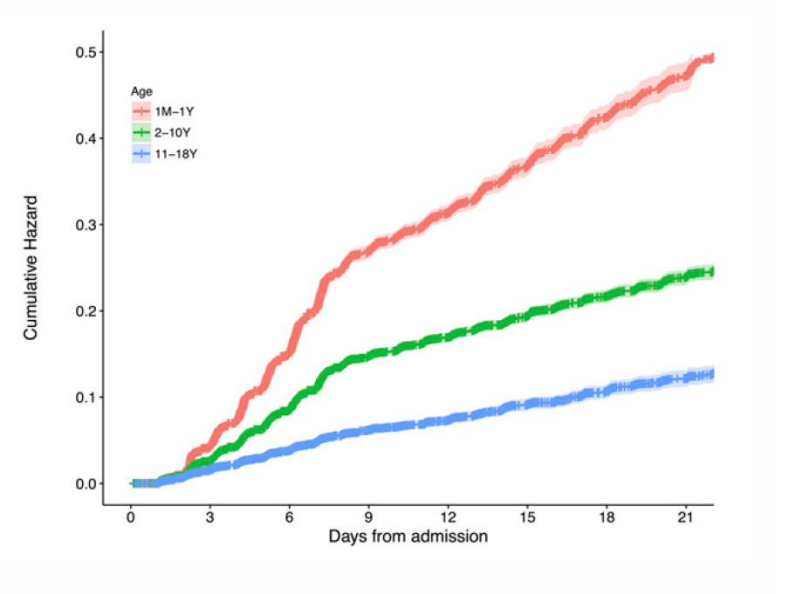
Clin J Am Soc Nephrol 13, 2018.

- **3,044,224 hospitalized children aged 1 month to 18 years, from 25 general and children's hospitals in China during 2013–2015.**
- **Identifying AKI according to the creatinine criteria of KDIGO.**
- **The in-hospital outcomes of AKI, including mortality, kidney recovery, and length of stay, were assessed.**

Xu X, et al. Clin J Am Soc Nephrol. 2018;13:1791–1800

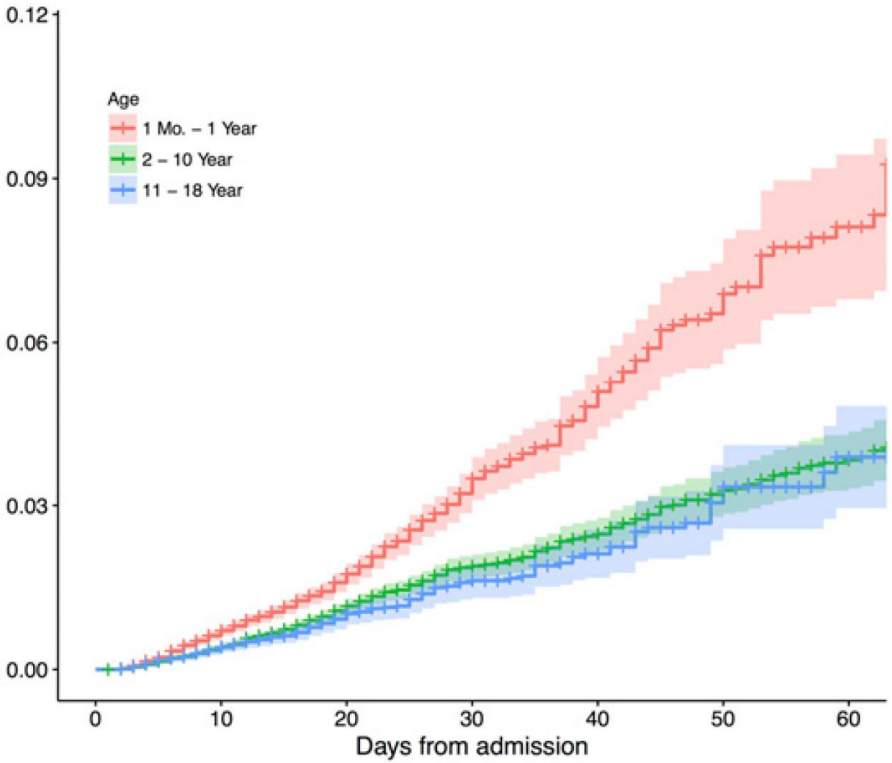
The incidence of pediatric AKI in China

- Incidence of AKI: 20%; 7% of community-acquired AKI and 13% of hospital-acquired AKI.
- The incidence of AKI were higher in children with younger age. AKI in infants (28%) was twice that in adolescents (12%).
- The incidence of hospital acquired AKI was higher with increasing number of days from admission. The cumulative incidence of hospital acquired AKI in the analysis set was 12%, 19%, 25%, and 29% on day 7, 14, 21, and 28, respectively.



Xu X, et al. Clin J Am Soc Nephrol. 2018;13:1791–1800

The prognosis of pediatric AKI in China



- The mortality among children with community-acquired AKI and with hospital-acquired AKI was 2.3%, and 5.3%, much lower than that in adult.
- The mortality was higher with greater severity of hospital acquired AKI and lower with age.

Xu X, et al. Clin J Am Soc Nephrol. 2018;13:1791–1800

AKI is substantially underdiagnosed in China

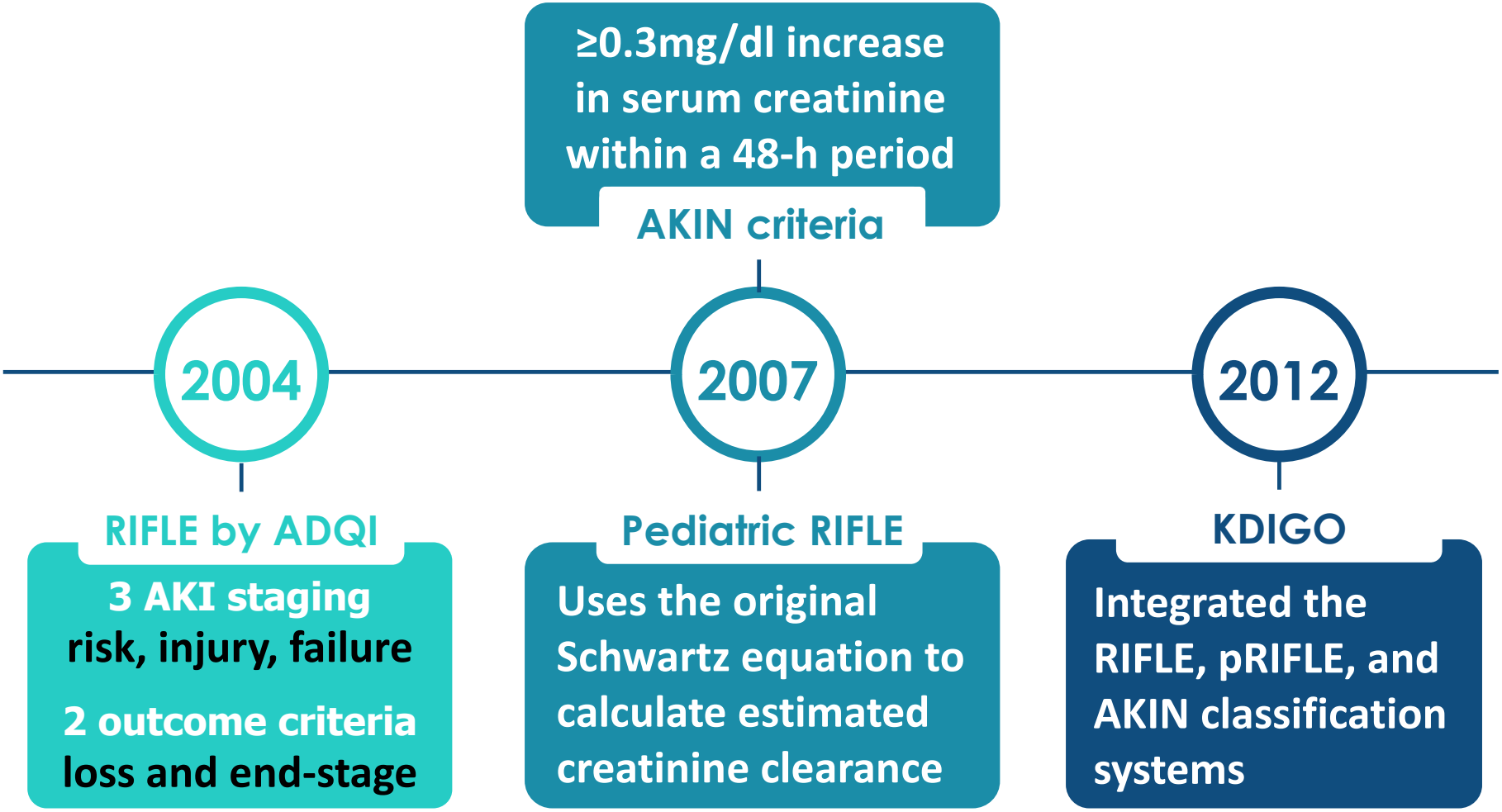
- Only 4% of the patients were diagnosed as AKI on discharge records, suggesting that the vast majority of AKI events were not recognized by clinicians.
- The physician-diagnosis rate of AKI was particularly lower among children in infancy (1%) and childhood (4%) compared with those in adolescence (11%), as well as those previously reported in the Chinese adults (26%).

Xu X, et al. Clin J Am Soc Nephrol. 2018;13:1791–1800

Contents

- The incidence of pediatric AKI in the worldwide and in China
- **The evolution of the diagnosis of pediatric AKI**
- The etiology and risk factors of pediatric AKI in China

Evolution of definition for pediatric AKI



pRIFLE, AKIN, KDIGO criteria for AKI

System	SCr criteria	UOP criteria
pRIFLE criteria		
Risk	eCCl decrease by 25%	<0.5 mL/kg/h for 8 h
Injury	eCCl decrease by 50%	<0.5 mL/kg/h for 16 h
Failure	eCCl decrease by 75% or eCCl <35 mL/min/1.73 m^2	≤0.3 mL/kg/h × 24 h or anuria × 12 h
Loss	Persistent complete loss of kidney function >4 weeks	
End-stage renal disease	End stage kidney disease (>3 months)	
AKIN criteria		
Stage 1	SCr increase ≥0.3 mg/dL (≥26.5 µmol/L) or increase to 1.5- to 2.0-fold from Baseline	<0.5 ml/kg/h for 6 h
Stage 2	SCr increase >2.0- to 3.0-fold from baseline	<0.5 mL/kg/h for 12 h
Stage 3	SCr increase >3.0-fold from baseline or serum creatinine ≥4.0 mg/dL (≥354 µmol/L) with an acute increase of at least 0.5 mg/dL (44 µmol/L) or need for RRT	<0.3 mL/kg/h for 24 h or anuria for 12 h or need for RRT
KDIGO criteria		
Stage 1	SCr increase ≥0.3 mg/dL (≥26.5 µmol/L)* or increase to 1.5- to 2.0-fold from baseline§	<0.5 mL/kg/h for 6–12 h
Stage 2	SCr increase >2.0- to 2.9-fold from baseline	<0.5 mL/kg/h for ≥12 h
Stage 3	SCr increase >3.0-fold from baseline or serum creatinine ≥4.0 mg/dL (≥354 µmol/L) with an acute increase of at least 0.5 mg/dL (44 µmol/L) or initiation of RRT or, in patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 mL/kg/h for 24 h Anuria for ≥12 h

Ding X, et al. Contrib Nephrol. 2018;193:1–12

KDIGO vs. pROCK

Multicenter Study > Zhonghua Er Ke Za Zhi. 2023 Nov 2;61(11):1011-1017.

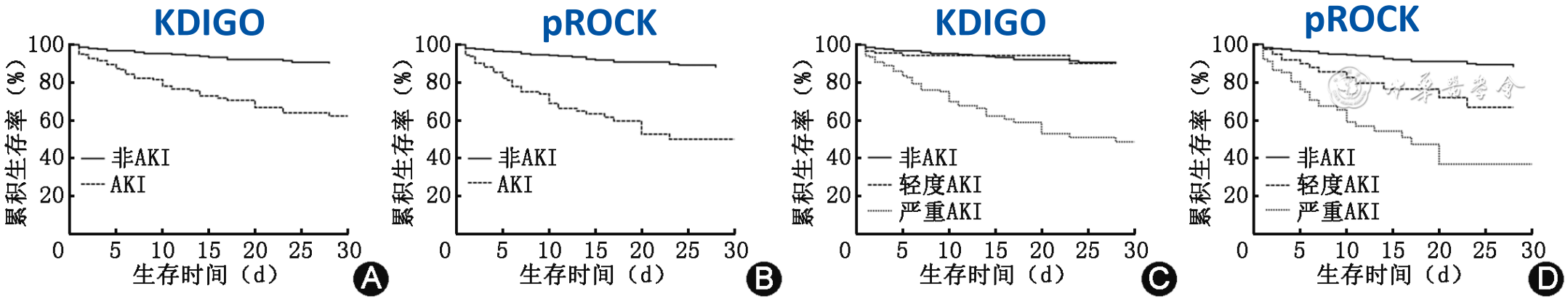
doi: 10.3760/cma.j.cn112140-20230623-00418.

[Comparison of diagnostic criteria for acute kidney injury in critically ill children]

- A multicenter prospective clinical cohort study
- 1,120 children admitted to 4 PICUs of tertiary children medical centers from September 2019 to February 2021
- 668 boys and 452 girls were included, with an age of 33 (10, 84) months

Zhonghua Er Ke Za Zhi. 2023 Nov 2;61(11):1011-1017.

KDIGO vs. pROCK



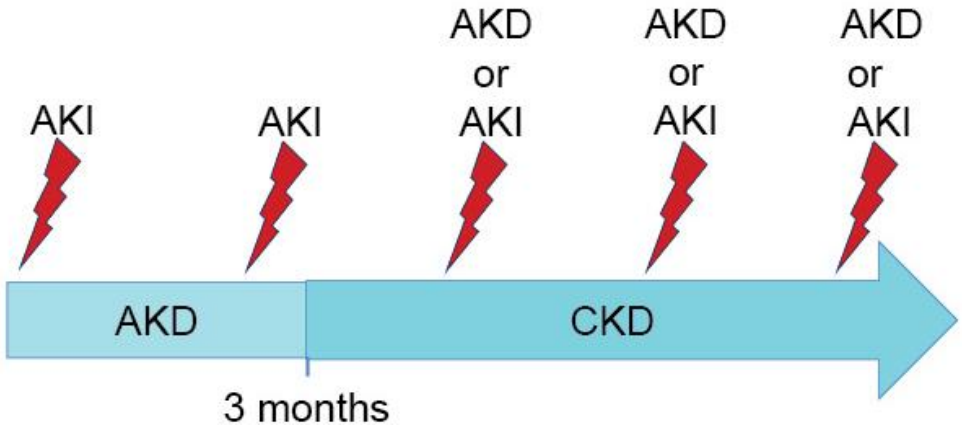
- The AKI incidence and staging varied depending on the used diagnostic criteria

The KDIGO definition is more sensitive, while the pROCK-defined AKI is more strongly associated with high mortality rate.

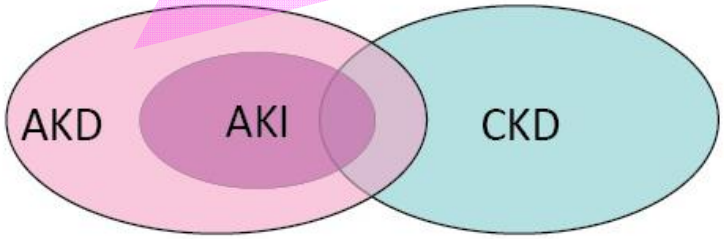
children

Zhonghua Er Ke Za Zhi. 2023 Nov 2;61(11):1011-1017.

KDIGO 2020 update: AKI-AKD-CKD



Abnormalities in kidney function that are not as severe as AKI
That develop over a period of >7 days.



AKD is defined by abnormalities of kidney function and/or structure with implications for health and with a duration of ≤3 months.

	AKI	AKD	CKD	NKD*
Duration	Within 7 days	≤3 months	>3 months	
Functional Criteria	Increase in Scr by ≥50% within 7 days, OR Increase in SCr by ≥0.3mg/dL (26.5µmol/L) within 2 days, OR Oliguria for ≥4 hours	AKI, OR GFR<60 mL/min/1.73m², OR Decrease in GFR by ≥35% times baseline, OR Increase in SCr by ≥50% times baseline	GFR <60 ml/min/1.73m²	GFR ≥60 ml/min/1.73m²
Structural Criteria	Not defined	Marker of kidney damage (albuminuria, hematuria, or pyuria are most common)	Marker of kidney damage (albuminuria is most common)	No marker of kidney damage

AKI, acute kidney injury; AKD, acute kidney diseases and disorders; CKD, chronic kidney disease; NKD, no kidney disease. *NKD implies no functional or structural criteria according to the definitions for AKI, AKD, or CKD. Clinical judgment required for individual patient decision making.

Nephron. 2021;146(3):302-305. doi:10.1159/000516647

KDIGO 2023 update: coming soon

Global Action. Local Change.

Scope of Work

KDIGO Clinical Practice Guideline for
Acute Kidney Injury (AKI) and Acute Kidney Disease (AKD)
Update 2023

Contents

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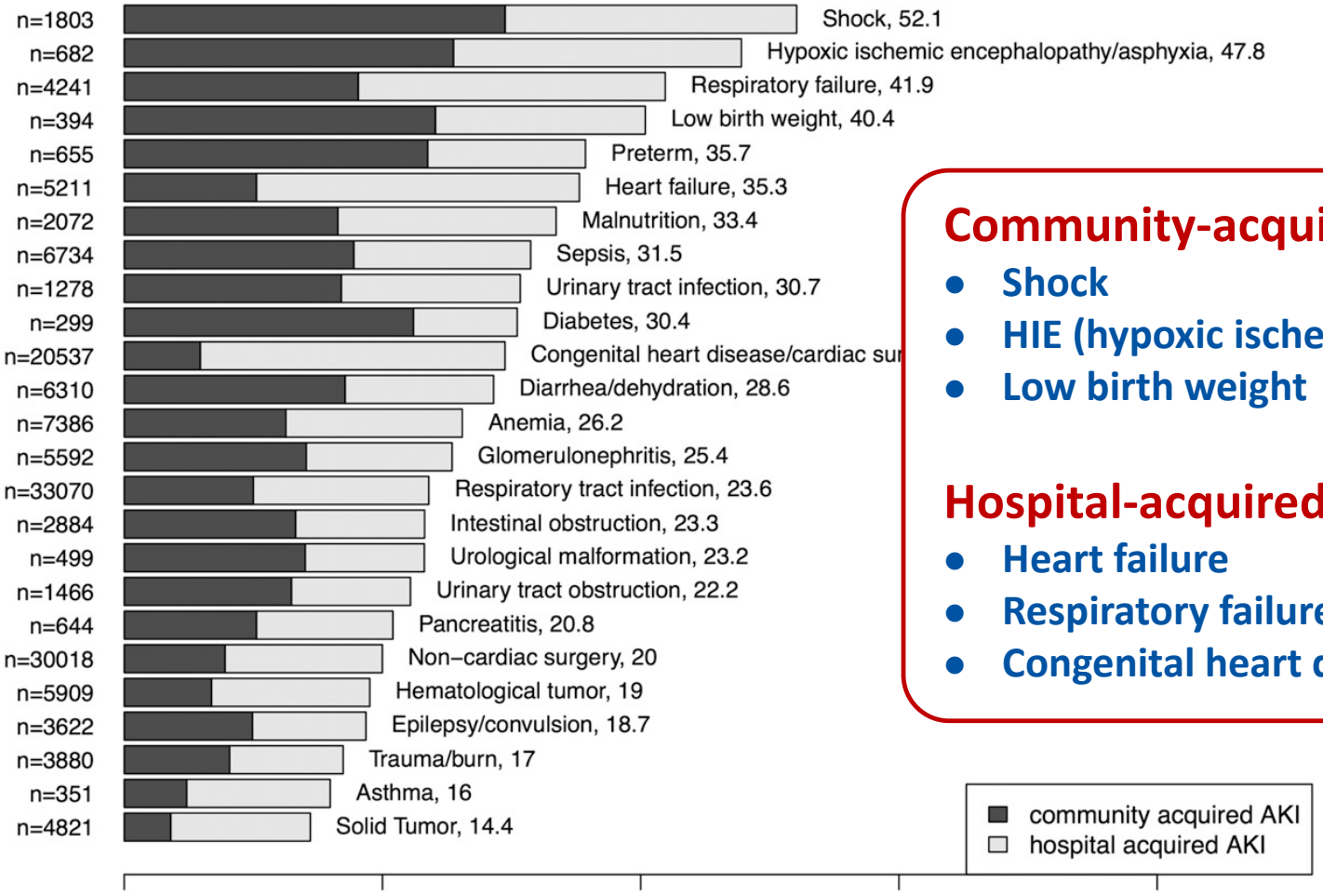
Etiology of pediatric AKI in China



Community-acquired AKI:

- Shock 30%
- HIE (hypoxic ischemic encephalopathy) 26%
- Low birth weight 24%

Hospital-acquired AKI:

- Heart failure 25%
- Respiratory failure 24%
- Congenital heart disease/cardiac surgery 24%

Xu X, et al. Clin J Am Soc Nephrol. 2018;13:1791–1800

The risk factors of pediatric AKI in China

The community-acquired AKI

Infant

GN and respiratory infection

Diarrhea/dehydration and sepsis

Shock, GN, and respiratory failure

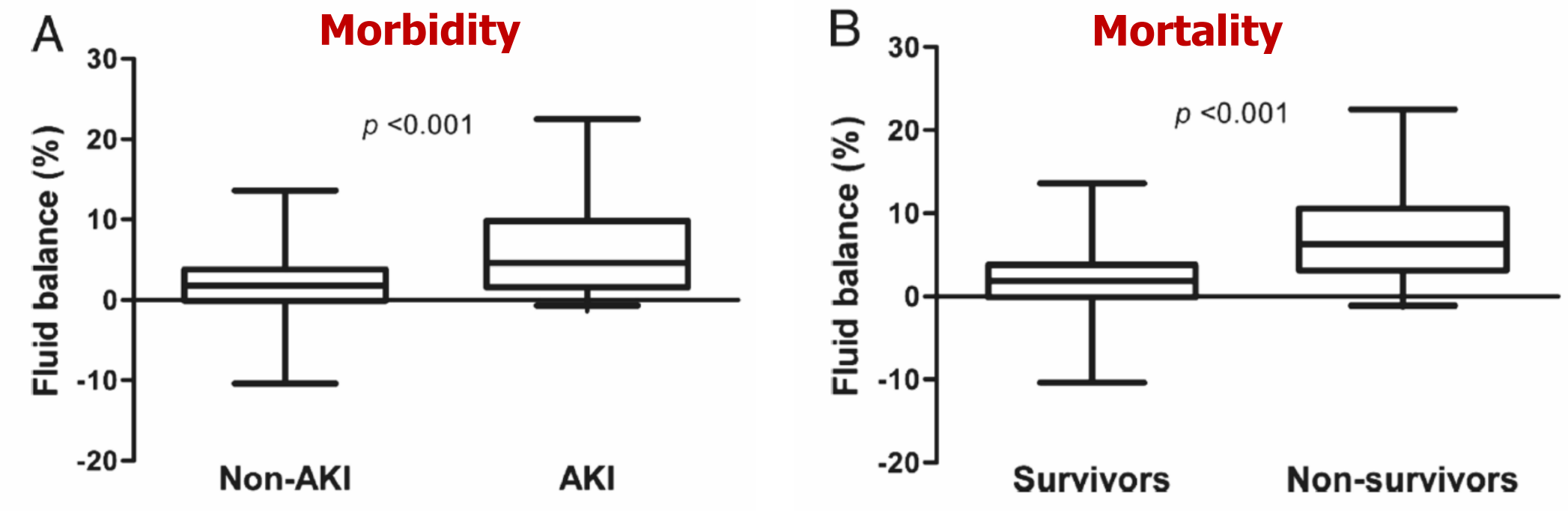
Congenital heart disease/cardiac surgery

Adolescent

The hospital-acquired AKI

Xu X, et al. Clin J Am Soc Nephrol. 2018;13:1791–1800

Early fluid overload is associated with AKI



Early fluid overload is also crucial for the occurrence of AKI and prognosis in pediatric patients.

Li Y, et al. Eur J Pediatr 2015

Nephrotoxic drugs contributed to hospital-acquired AKI

Drug	Frequency in All Patients (%)	Frequency in Patients with AKI (%)
Nonsteroidal anti-inflammatory drugs	23	32
Proton pump inhibitors	27	30
Antimycotics	4	8
Contrast media	4	7
Aminoglycoside antibiotics	4	5
Chemotherapeutic drugs	3	4

OR, odds ratio; 95% CI, 95% confidence interval; PAF, population attributable fraction.

- More than 30% of AKI was attributable to exposure of nephrotoxic drugs.
- Exposure of NSAIDs (nonsteroidal anti-inflammatory drugs) and PPIs (proton pump inhibitors) were the most important risk factors, contributing to 11% and 9% of risk for hospital-acquired AKI, respectively.

Xu X, et al. Clin J Am Soc Nephrol. 2018;13:1791–1800

Take home message

- Pediatric AKI has become a public health problem. The incidence in children is higher than that in adult, representing a big economic burden in China and in the worldwide.
- Pediatric AKI is substantially underdiagnosed in China, and the disease burden is significantly underestimated.
- There currently is a general consensus to apply KDIGO classification for pediatric AKI，but prediction tools are developing, such as biomarkers-guided and e-learning diagnosis
- Raising the awareness of pediatric AKI and its risk factors among physicians, especially primary care providers, will improve health care in children worldwide.

Thank you for your attention!





The 20th China-Japan-Korea Pediatric Nephrology Seminar
IPNA Teaching Course Fuzhou, China, April 13, 2024

Are children with IgA nephropathy different from adult patients?

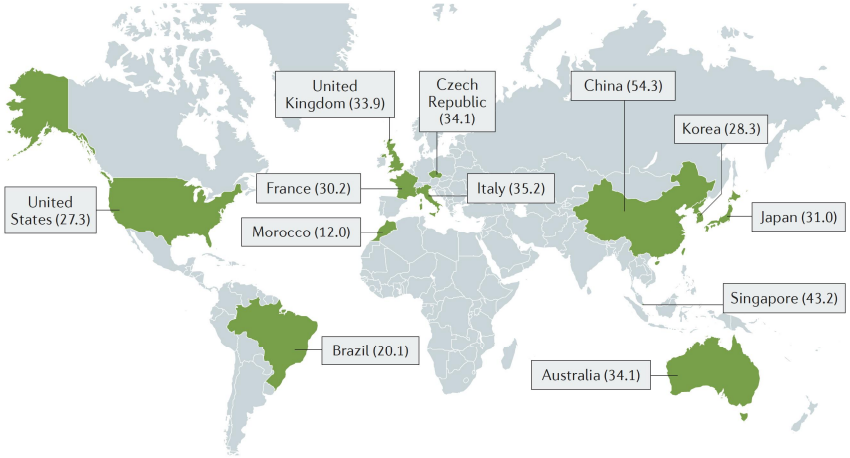
Xuhui Zhong

Department of Pediatric Nephrology

Peking University First Hospital, Beijing, China

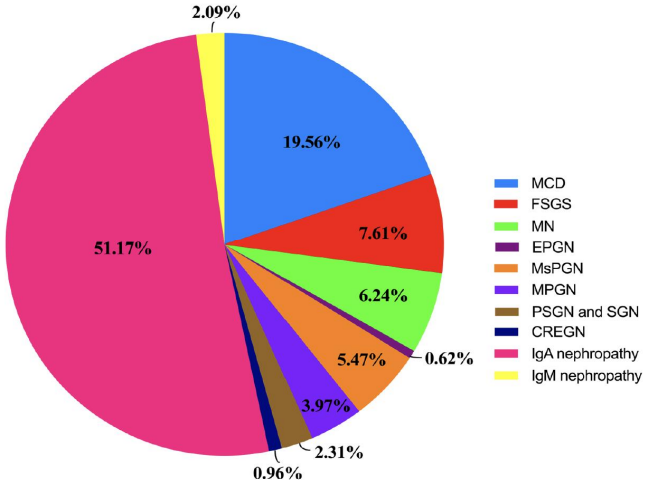
IgA nephropathy (IgAN) is one of the most common primary glomerular diseases in the world.

IgAN is the highest in developed countries in Asia.

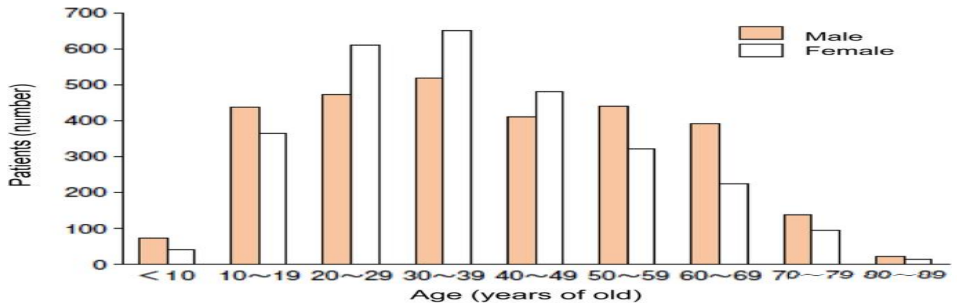


Nat Rev Dis Primers 2, 16001 (2016).

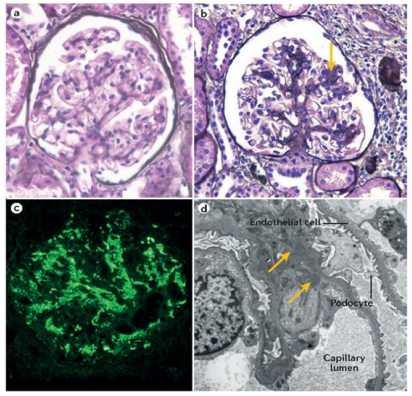
IgAN is the leading diagnosis of kidney biopsies among children with CKD in China.



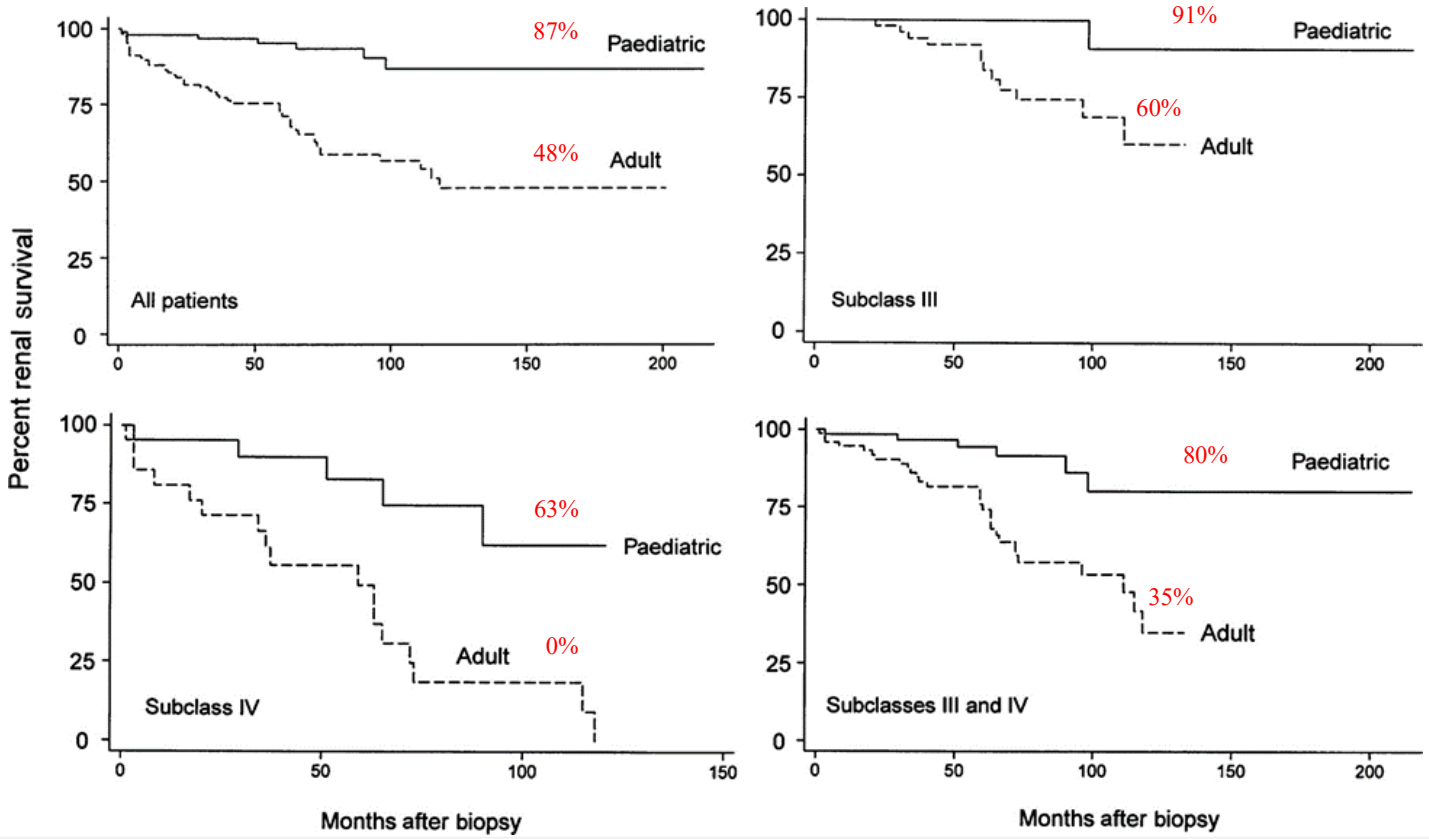
BMC Nephrology (2021) 22:195



Pediatric IgAN **Adult IgAN**



In 2008, a retrospective cohort study of 99 children and 125 adults in USA



The overall 10-year kidney survival among children diagnosed with IgAN was superior to that in adults.

Haas, M. et al. *Nephrol Dial Transplant*. 2008

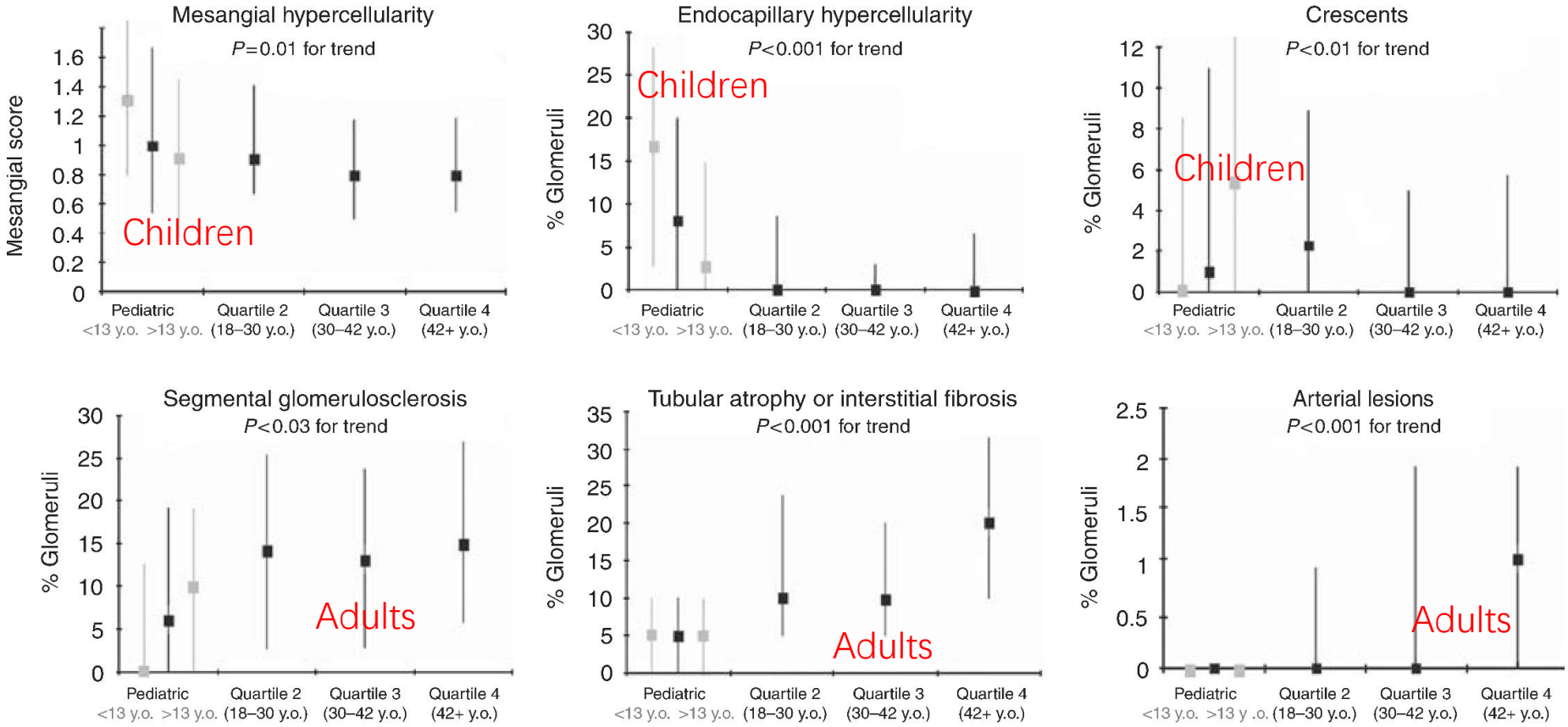
In 2010, International IgA Nephropathy Network and the Renal Pathology Society

Table 1 | Clinical findings according to age group

	Children (*n*=59)	Adults (*n*=206)	*P*-value
At time of biopsy			
Median age (years)	13 (4–17.9)	35 (19–73)	
Female	25%	28%	>0.1
MAP (mm Hg)[a]	84 ± 10	102 ± 17	<0.001
eGFR (ml/min/1.73 m^2)[b]	120 ± 43	73 ± 27	<0.001
Proteinuria (g/day)[c]	2 (0.5–7.8)	1.7 (0.5–18.5)	>0.1
% Nephrotic	27%	30%	>0.1
Previous macroscopic hematuria	60%	28%	<0.001
Follow-up			
Duration of follow-up (months)	62 (20–268)	77 (12–231)	0.02
MAP (mm Hg)[a]	86 ± 8	97 ± 10	<0.001
Proteinuria (g/day)[c]	0.9 (0.1–7.0)	1.2 (0.2–9.3)	0.006
Treated with RAS blockade (ACEi, ARB)	56%	80%	<0.001
Any immunosuppression	48%	24%	0.001
Prednisone	48%	24%	0.001
Other	17%	7%	0.02
Fish oil	25%	14%	0.03
Rate of decline in renal function (ml/min/1.73 m^2/year)	−2.7 ± 11	−3.7 ± 7.6	>0.1

Compared with adults, children had a more frequent history of macroscopic hematuria, lower adjusted blood pressure, and higher eGFR but similar proteinuria.

Coppo, R. et al. *Kidney Int.* 2010



Children had significantly more mesangial and endocapillary hypercellularity, and less segmental glomerulosclerosis and tubulointerstitial damage.

Coppo, R. et al. *Kidney Int.* 2010

In 2020, reviewing 82 children and 129 adults from two different centers in Paris

Variable[a]	Adult (n = 129)	Children (n = 82)	P value
Age at diagnosis (years)	39 .1 ± 1.1	10.6 ± 0.4	0.0001
Familial IgAN history	11 (9.6)	15 (18.3)	0.07
Male	99 (73.8)	54 (65.8)	0.2
Systolic BP (mmHg)	136.46 ± 19.7	115.55 ± 15.5	
Diastolic BP (mmHg)	80.6 ± 13.2	67.6 ± 11.6	
eGFR (ml/min/1.73m^2)	64 ± 29.1	89.5 ± 31.8	0.0001
Serum albumin (g/dl)	3.8 ± 0.6	3.4 ± 0.7	0.0001
Proteinuria (g/g of creatinuria)	1.8 ± 1.6	2.1 ± 2.7	0.25
Pathological findings			
Glomerulus count	15.1 ± 7.9	15.9 ± 8.2	0.5
• M1	36 (27.9)	63 (80.7) (n = 78)	0.0001
• E1	39 (30)	57 (71.3) (n = 80)	0.0001

They reported higher eGFR at diagnosis in children compared to adults, but no difference in proteinuria.

Pediatr Nephrol 35:1897-1905.

In 2020, reviewing 82 children and 129 adults from two different centers in Paris

Variable[a]	Adult (n = 129)	Children (n = 82)	P value
Age at diagnosis (years)	39 .1 ± 1.1	10.6 ± 0.4	0.0001
• M1	36 (27.9)	63 (80.7) (n = 78)	0.0001
• E1	39 (30)	57 (71.3) (n = 80)	0.0001
• C1/C2	43 (33.3)/3 (2.3)	26 (33.7)/8 (10.3) (n = 77)	0.11
• S1	106 (81.5)	49 (61.3) (n = 80)	0.0012
• P 1	44 (33.8)	12 (16.4) (n = 73)	0.0077
• T1	63 (49.5)	1 (1.35) (n = 74)	0.0001

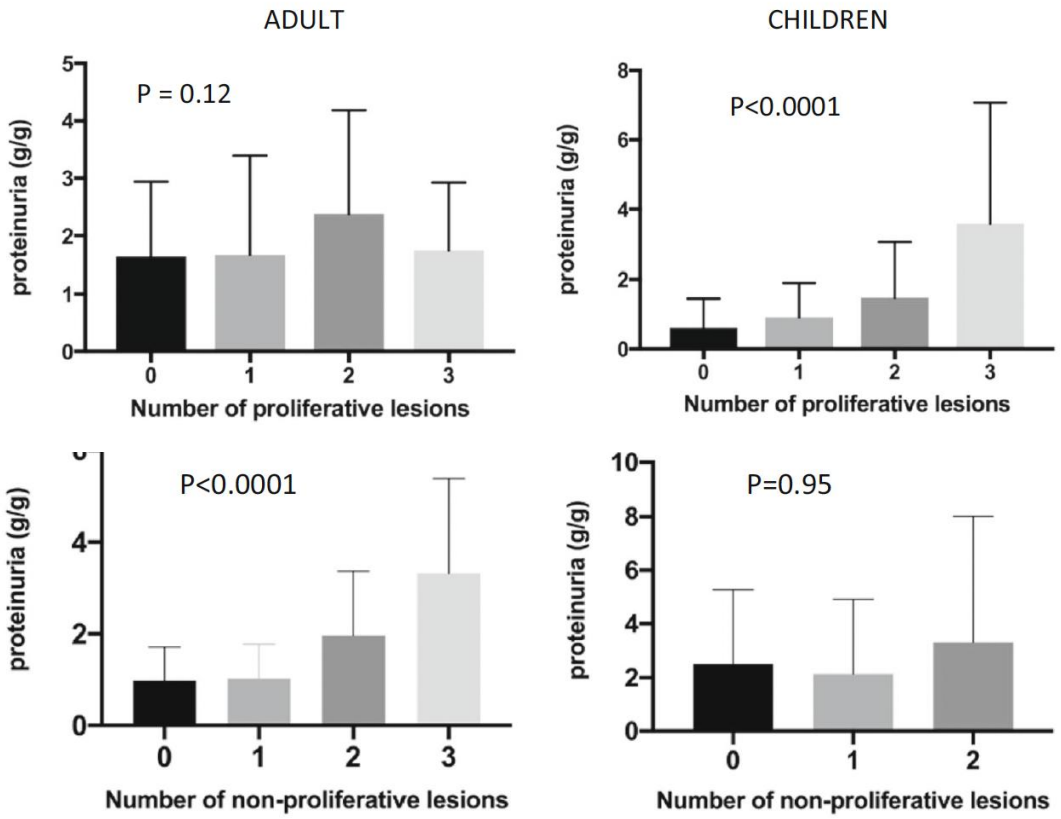
Higher proportions of mesangial and endocapillary hypercellularity in children, focal glomerulosclerosis, tubular atrophy/interstitial fibrosis, and podocytopathy were more frequent in adults.

Pediatr Nephrol 35:1897-1905.

In 2020, reviewing 82 children and 129 adults from two different centers in Paris

Proliferative lesions

Non-proliferative lesions



Proteinuria in children with IgAN is a marker of glomerular proliferative lesions whereas its presence in adults often reflects the presence of chronic lesions.

Pediatric IgAN

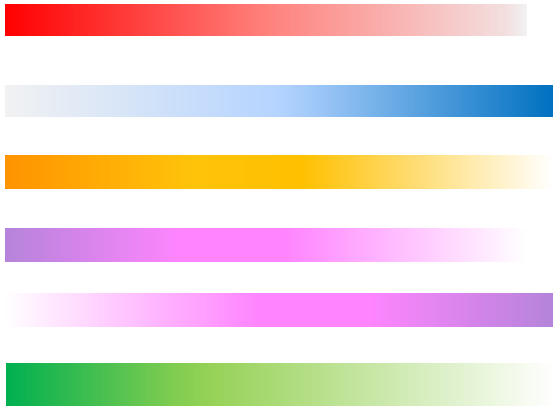
Adult IgAN

Gross hematuria

Kidney function

Acute lesion

Survival



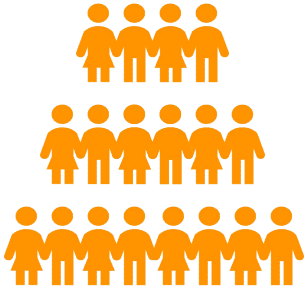
Hypertension

Chronic lesion

Proteinuria?

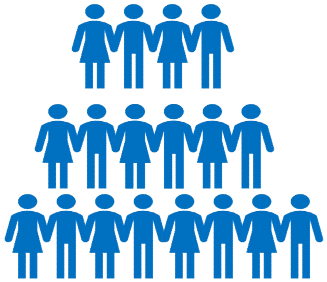
Treatment?
Response?

Pediatric cohort



Registry of IgA Nephropathy in Chinese Children, RACC

Adult cohort



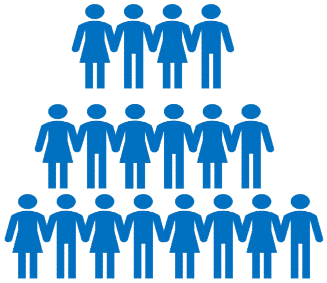
A single-center cohort of IgAN patients, by Department of Nephrology

Pediatric cohort

Pediatric Group

N=1015

Adult cohort



Adult Group

N=1911

1. **Are children different from adults, in clinical and pathological manifestation?**

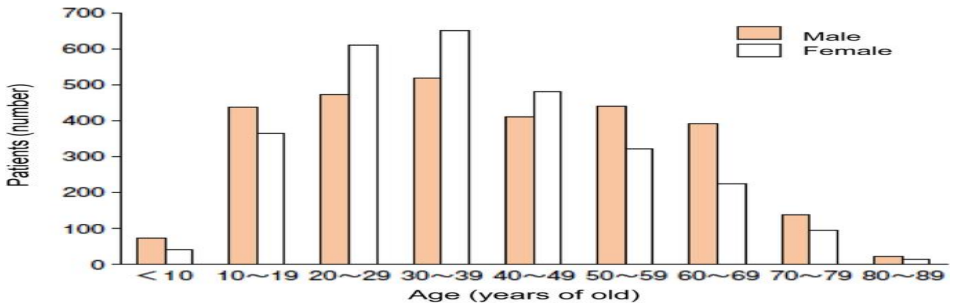
Clinical characteristics at biopsy between pediatric and adult IgAN

	Pediatric IgAN (N = 1015)	Adult IgAN (N = 1911)	*P* value
Onset age (y)	9 (7, 11)	32 (26, 41)	
Disease duration (m)	1.0 (1.0, 3.0)	16.0 (8.0, 34.0)	<.0001
Gender (male, %)	68	50	<.0001
History of gross hematuria (%)	88	20	<.0001
Hypertension (%)	9	29	<.0001
eGFR (ml/min/1.73 m^2)	163.0 (125.2, 204.1)	80.4 (53.4, 103.6)	<.0001
ALB (g/L)	33.1 (24.5, 39.4)	38.7 (35.3, 41.7)	<.0001
ALB <30 g/L (%)	40	9	<.0001
ALB<25 g/L (%)	26	5	<.0001
Serum IgA (g/L)	2.1 (1.5, 2.9)	3.2 (2.5, 4.0)	<.0001
Serum C3 (g/L)	1.1 (0.9, 1.3)	1.0 (0.9, 1.2)	<.0001
Urine red blood cell count (/μl)	499.5 (110.0, 2045.0)	12.5 (4.0, 42.5)	<.0001
Daily proteinuria (g/24 h/1.73m^2)	1.8 (0.8, 3.2)	1.3 (0.7, 2.5)	<.0001
Nephrotic proteinuria (%)	55	16	<.0001
Nephrotic syndrome (%)	35	6	<.0001

Pathological characteristics between pediatric and adult IgAN

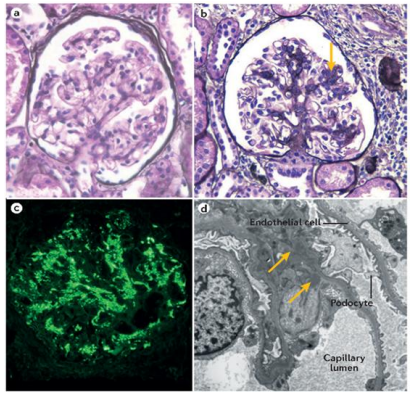
	Pediatric IgAN (N = 1015)	Adult IgAN (N = 1911)	*P* value
Disease duration (m)	1.0 (1.0, 3.0)	16.0 (8.0, 34.0)	<.0001
Age at biopsy (y)	10 (7, 12)	34 (28, 43)	
MEST-C score *			
M1 (%)	62	39	<.0001
E1 (%)	42	34	0.0002
S1 (%)	28	62	<.0001
T1-2 (%)	8	34	<.0001
C1-2 (%)	52	59	0.0017

*Pathological Oxford classification was available for 788 children and 1389 adults.



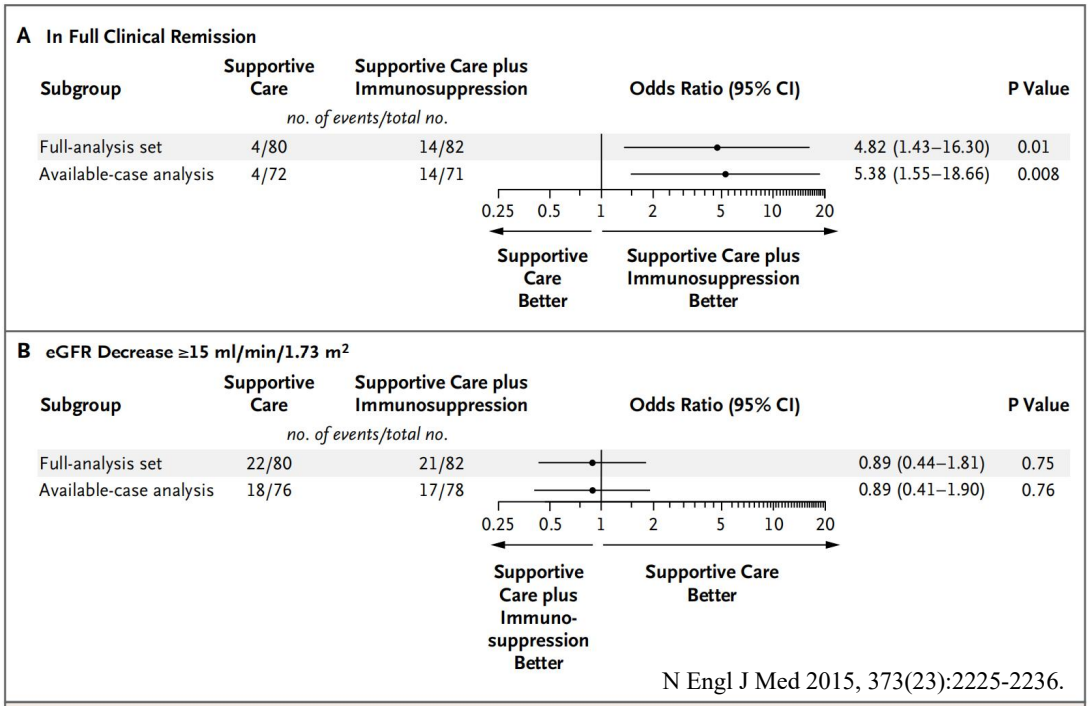
Pediatric IgAN

Adult IgAN



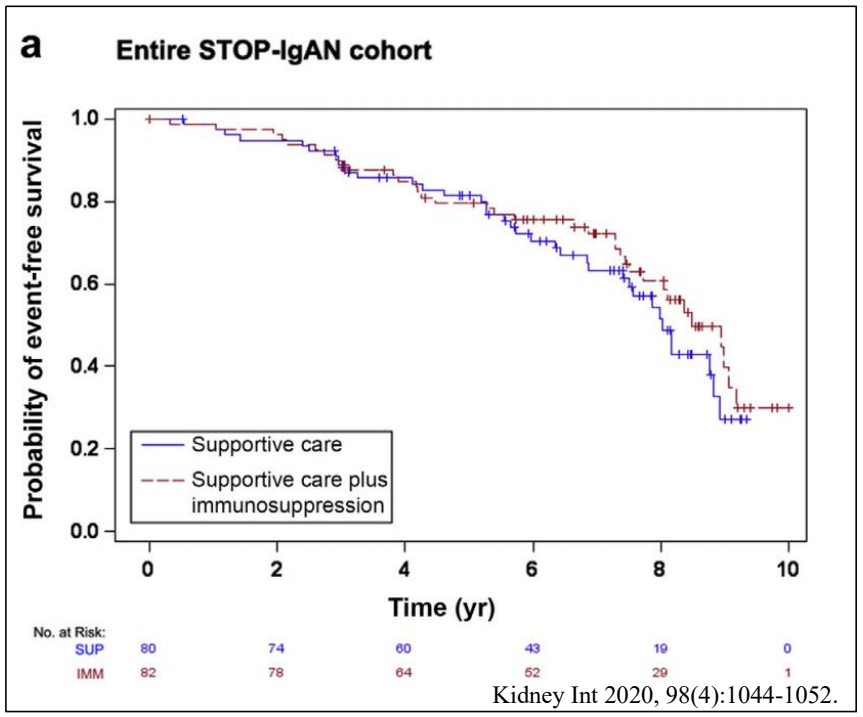
STOP-IgAN, a multicenter, open-label, RCT of adult IgAN

At the end of the 3-year trial phase



N Engl J Med 2015, 373(23):2225-2236.

After ten years...



Kidney Int 2020, 98(4):1044-1052.

The addition of immunosuppressive therapy to intensive supportive care in patients with high-risk IgAN did not significantly improve the outcome.

TESTING study, multicenter, double-blind, RCT, oral methylprednisolone in adult IgAN and proteinuria ≥1g/d

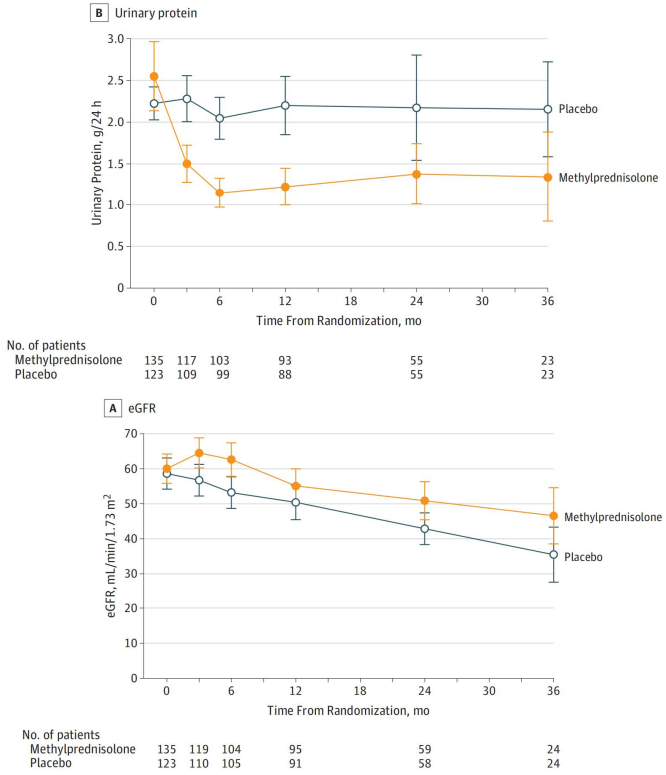
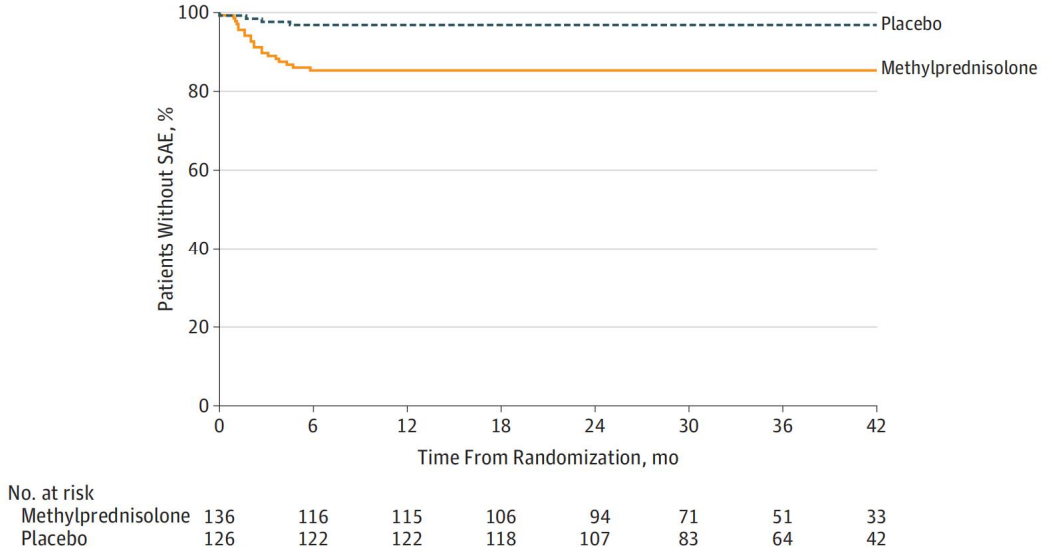
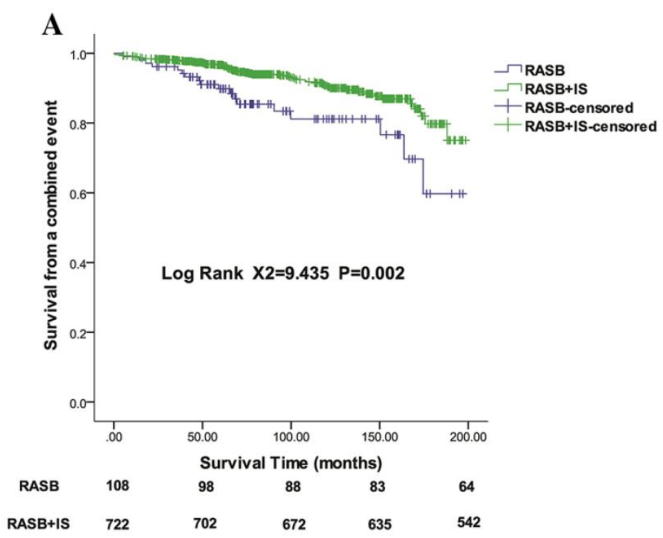


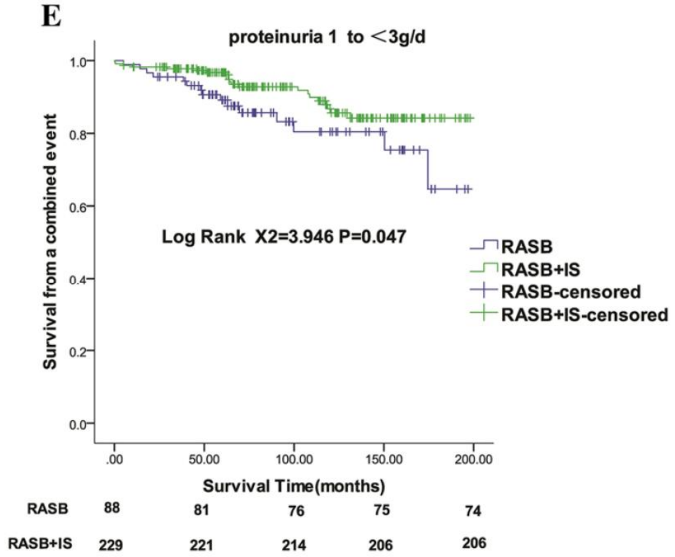
Figure 2. Time From Randomization to First Serious Adverse Event, by Treatment Group

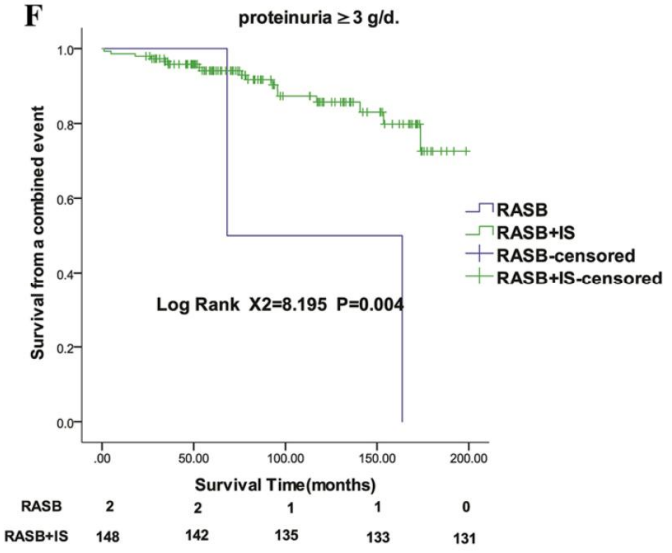


Although the efficacy of glucocorticoids in Asian adults was demonstrated, there has also been increased consideration of their safety.

From 2000 to 2017, 1243 Chinese children with IgAN were enrolled and a follow-up of at least 1 year after a biopsy

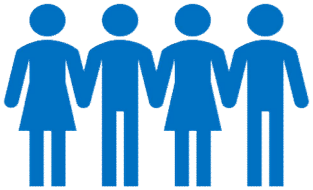






The study suggested that immunosuppressive therapy may reduce the risk of progression in IgAN children had both eGFR > 50 ml/min/1.73m² and proteinuria of at least 1 g/day.

J Nephrol 2020, **33**(6):1263-1273.



KDIGO 2021 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF GLOMERULAR DISEASES

Kidney International (2021) 100, S1-S276 S1

Expert opinion as practice points

Glucocorticoids could be prescribed

- Proteinuria>1 g/d, or
- Protein-to-creatinine ratio (PCR)>1 g/g, and/or
- Mesangial hypercellularity

A 6-month course of glucocorticoid therapy is suggested only for

- At high risk of progressive CKD despite maximal supportive care

1. **Are children different from adults, in clinical and pathological manifestation?**
2. **Do pediatric nephrologists practice differently from adult nephrologists, when facing IgAN?**

Comparison of treatment pattern between children and adults

	Pediatric IgAN (N = 1015)	Adult IgAN (N = 1911)	*P* value
CSs (%)	74	40	<.0001
Only CSs (%)	21	14	<.0001
CSs+CTX (%)	13	7	<.0001
CSs+MMF (%)	10	1	<.0001
CSs+TAC (%)	6	0	<.0001
CSs+etc.* (%)	7	7	0.6295
RAS blockers (%)	49	94	<.0001

The proportion of patients prescribed with corticosteroids alone or in combination with other immunosuppressants was significantly greater in children than in adults with IgAN.

Pediatr Nephrol 2024.

Baseline characteristics and medications prescribed for pediatric and adult IgAN after propensity score matching

	Pediatric IgAN(N=93)	Adult IgAN(N=93)	*P* value
Hypertension (%)	13 (14)	18 (19)	0.33
eGFR (ml/min/1.73 m^2)	119.9 (94.0, 136.0)	116.3 (104.8, 125.7)	0.16
Proteinuria (g/24 h/1.73m^2)	2.2 (1.5, 3.8)	2.1 (1.4, 2.9)	0.52
M1, N (%)	45 (48)	44 (47)	0.88
E1, N (%)	41 (44)	39 (42)	0.77
S1, N (%)	42 (45)	47 (51)	0.46
T1-2, N (%)	15(16)	15(16)	1.00
C1-2, N (%)	60(65)	62(67)	0.29
Medication prescribed			
CSs (%)	81 (87)	42 (45)	<.0001
Only CSs (%)	31 (33)	18 (19)	0.03
CSs+CTX (%)	9 (10)	9 (10)	1.00
CSs+MMF (%)	6 (6)	0 (0)	0.03
CSs+TAC (%)	6 (6)	1 (1)	0.12
CSs+etc.# (%)	13 (14)	4 (4)	0.02
RAS blockers (%)	67 (72)	87 (94)	<.001

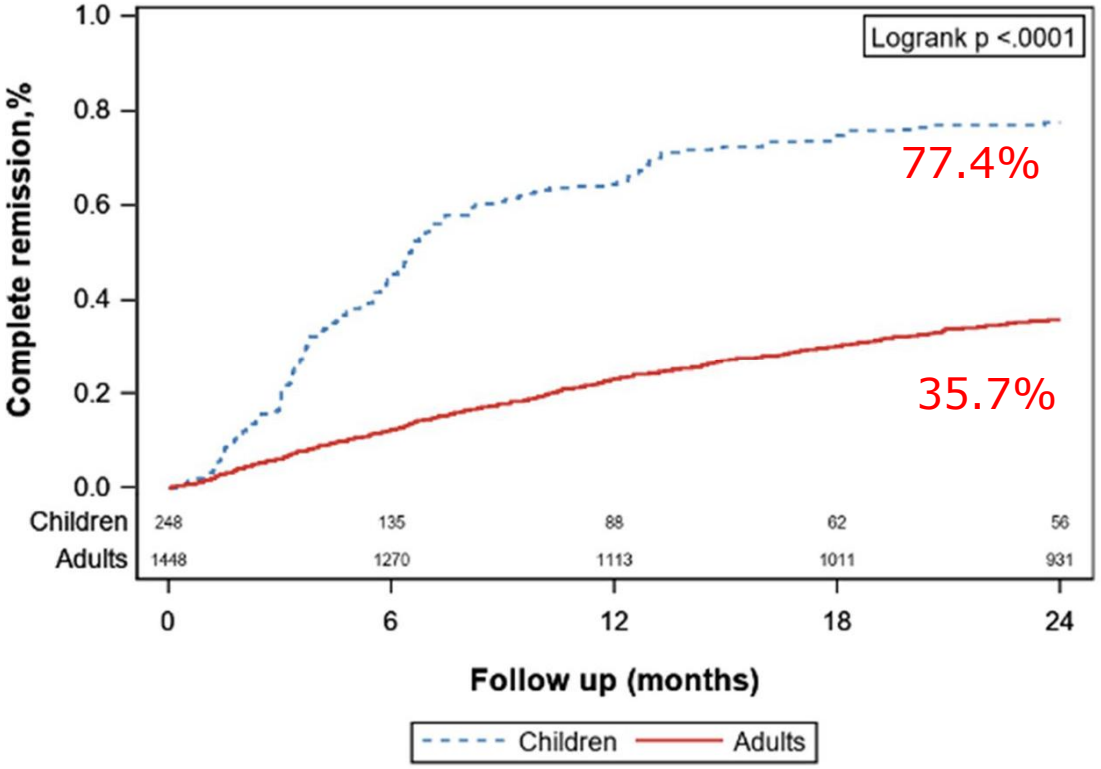
Medications prescribed for pediatric and adult IgAN after propensity score matching

	Pediatric IgAN(N=93)	Adult IgAN(N=93)	*P* value
Hypertension (%)	13 (14)	18 (19)	0.33
eGFR (ml/min/1.73 m^2)	119.9 (94.0, 136.0)	116.3 (104.8, 125.7)	0.16
Proteinuria (g/24 h/1.73m^2)	2.2 (1.5, 3.8)	2.1 (1.4, 2.9)	0.52
Medication prescribed			
CSs (%)	81 (87)	42 (45)	<.0001
Only CSs (%)	31 (33)	18 (19)	0.03
CSs+CTX (%)	9 (10)	9 (10)	1.00
CSs+MMF (%)	6 (6)	0 (0)	0.03
CSs+TAC (%)	6 (6)	1 (1)	0.12
CSs+etc.# (%)	13 (14)	4 (4)	0.02
RAS blockers (%)	67 (72)	87 (94)	<.001

Adjusted by multivariable, among the patients presented with proteinuria >1 g/d at baseline, children were more likely to be treated with glucocorticoids than adults.

1. **Are children different from adults, in clinical and pathological manifestation?**
2. **Do pediatric nephrologists practice differently from adult nephrologists, when facing IgAN?**
3. **Does pediatric IgAN progress differently from adult patients?**

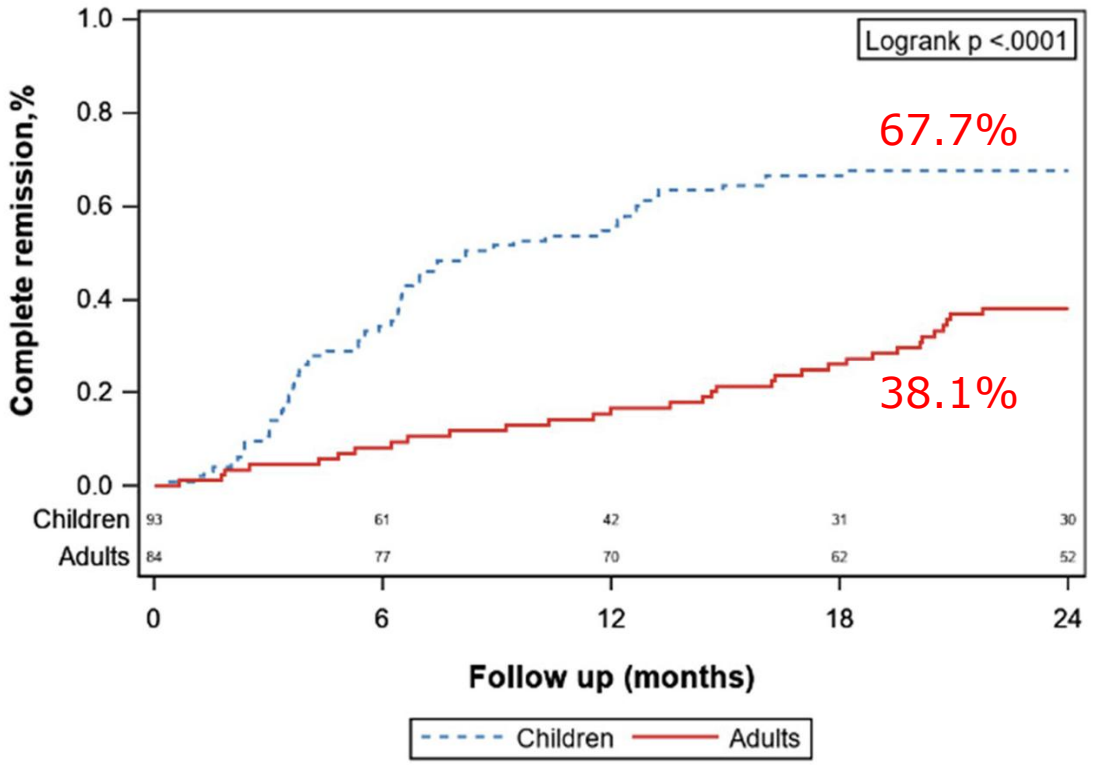
Comparison of complete remission of proteinuria between children and adults



Pediatr Nephrol 2024.

After multivariate analysis, the probability of complete remission of proteinuria in pediatric IgAN was still significantly greater than that in adult IgAN.

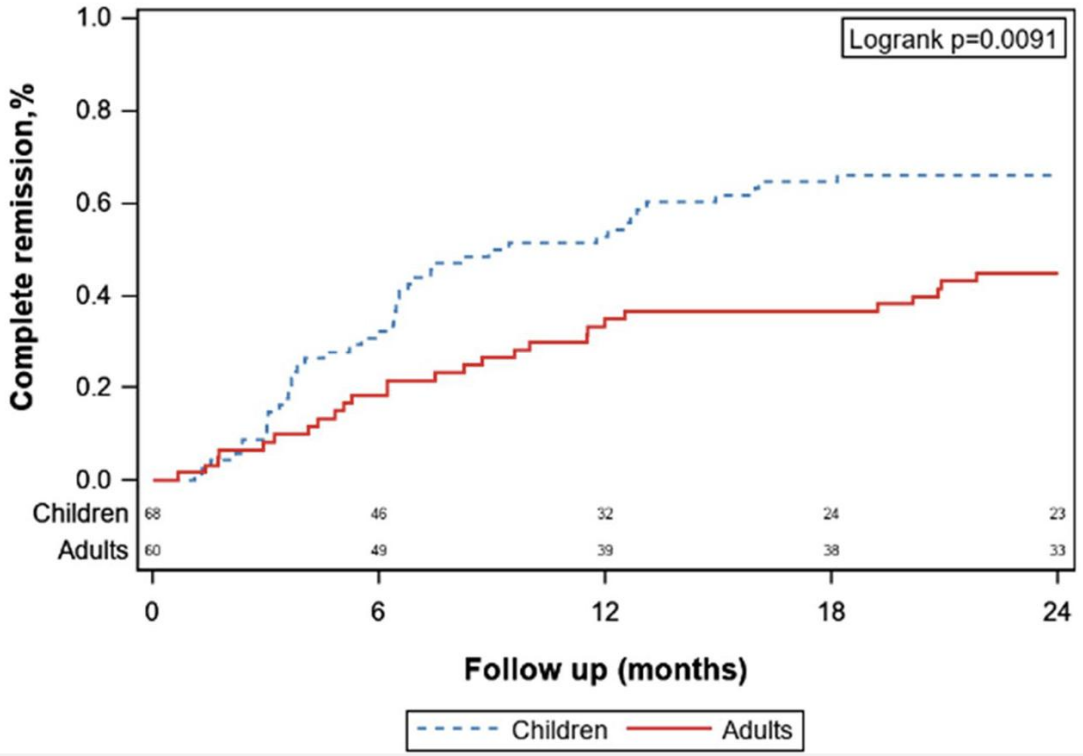
Comparison of complete remission of proteinuria between children and adults, with proteinuria >1g/d



Pediatr Nephrol 2024.

The percentage of patients in complete remission of proteinuria was significantly greater in the pediatric group than in the adult group.

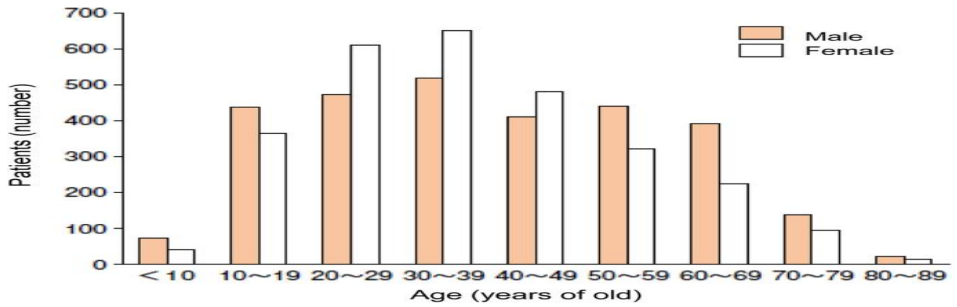
Comparison of complete remission of proteinuria between children and adults with proteinuria >1g/d, prescribed with steroids



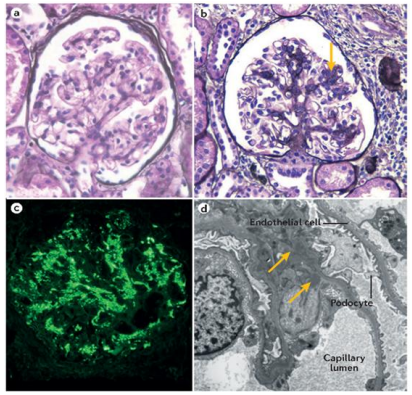
Pediatr Nephrol 2024.

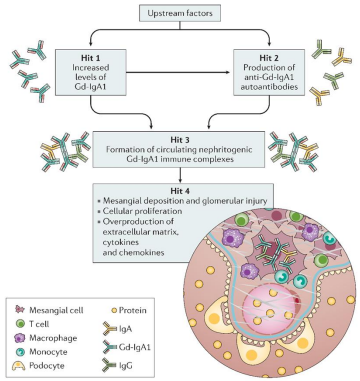
Children treated with steroids were more likely to reach complete remission of proteinuria than adults were (HR, 1.87; 95%CI, 1.16 to 3.02; p=0.01)

1. **Are children different from adults, in clinical and pathological manifestation?**
2. **Do pediatric nephrologists practice differently from adult nephrologists, when facing IgAN?**
3. **Does pediatric IgAN progress differently from adult patients?**
4. **Why does pediatric IgAN present differently from adult IgAN?**



Pediatric IgAN **Adult IgAN**



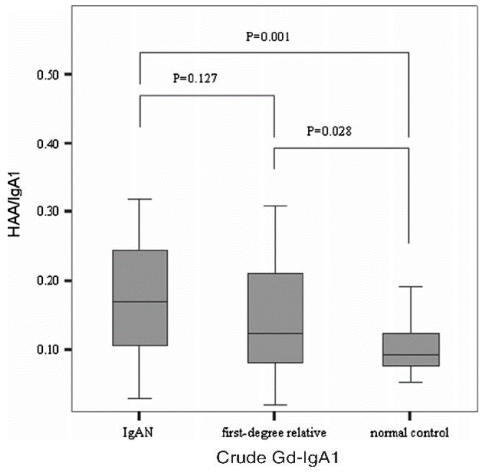


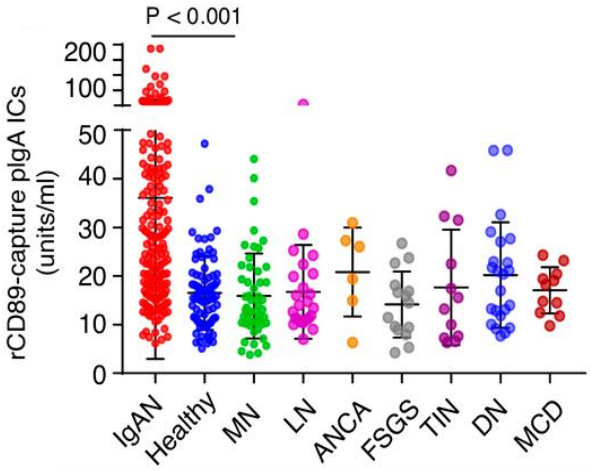
Lai, KN et al. *Nat Rev Dis Primers.* 2016

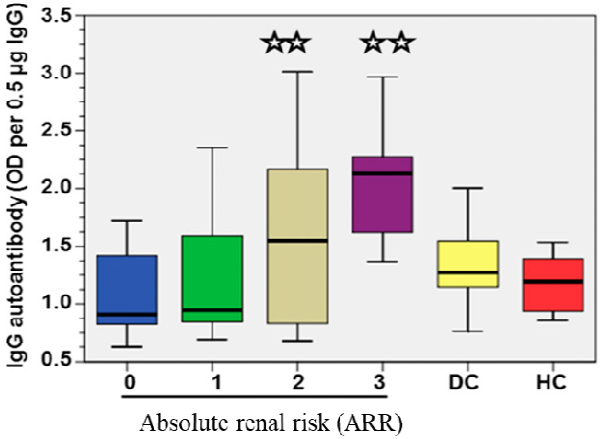
‘Four-hits’ hypothesis in children and adults

Gd-IgA1 | ICs | IgG autoantibody

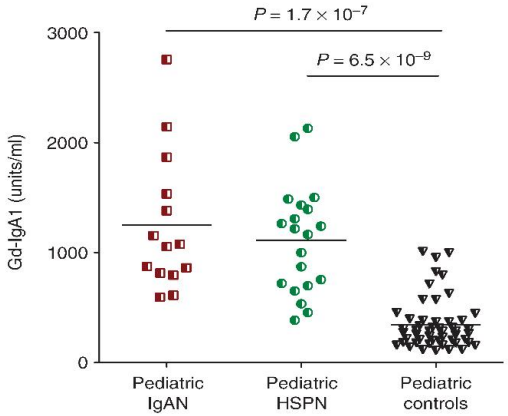
Adults

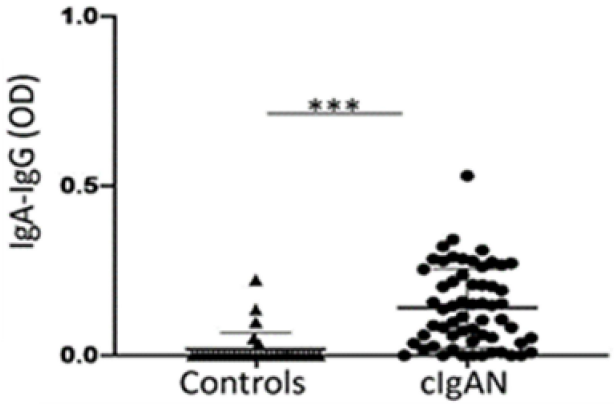






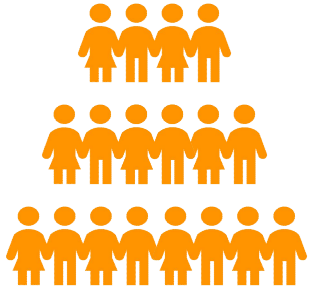
Children



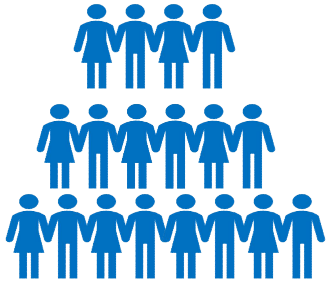


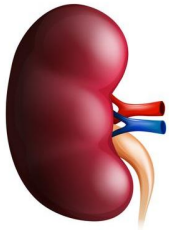
Lin, X. et al. *Nephrol Dial Transplant*. 2009
Kiryluk, K. et al. *Kidney Int.* 2011

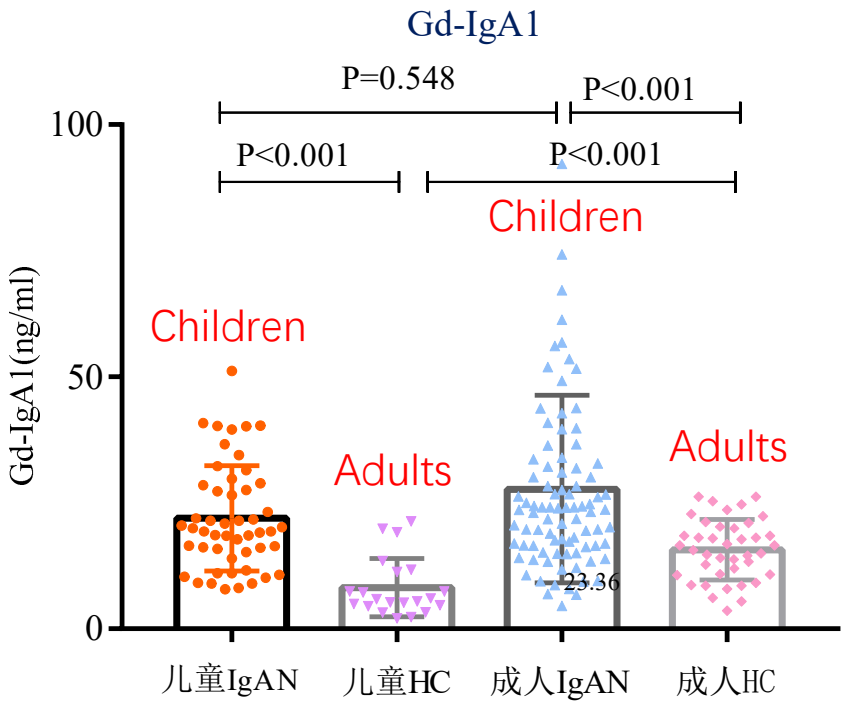
Pediatric cohort

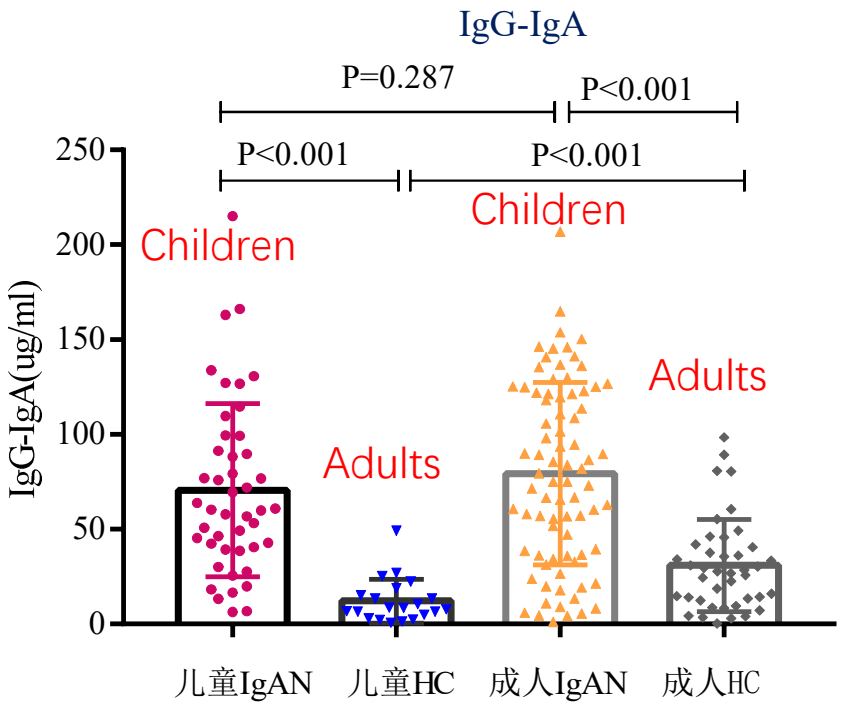


Adult cohort

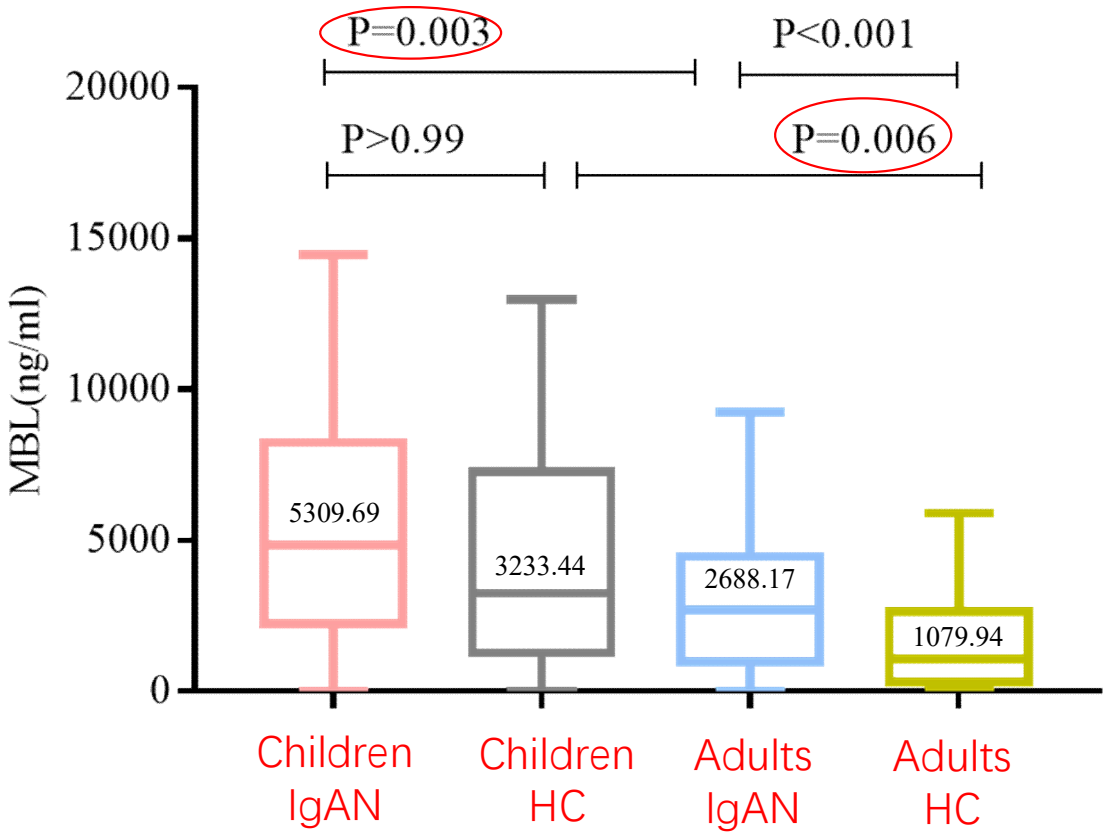








- **Gd-IgA1 was significantly higher in both children and adults than in healthy controls.**
- **There were no significant differences in Gd-IgA1 and IgG-IgA complexes levels between children and adults with IgAN**



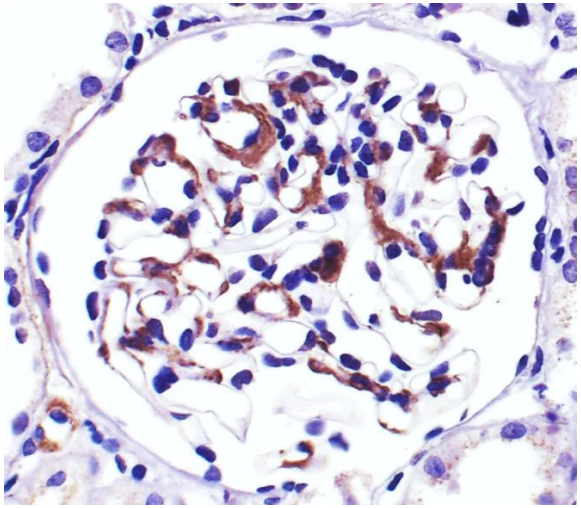
Children with IgAN have higher circulating MBL levels than adults with IgAN

Patients with higher circulating MBL levels have higher protein and more crescents

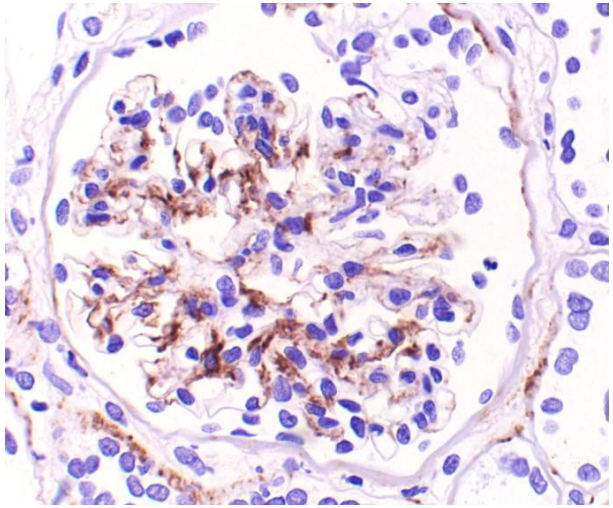
Table 1. Demographic, clinical, and histologic characteristics of patients with IgAN

Characteristic	Mean±SD or Median (IQR), *n*=749		Deficiency Group, *n*=39		Sufficiency Group, *n*=437		High Group, *n*=273		*P* Value[a]	*P* Value[b]
Baseline										
Age, yr	34.7±12.1		38.4±11.4		35.1±11.9		33.3±12.3		0.10	0.052
Sex (% men)	362 (48.3)		13 (33.3)		193 (44.2)		156 (57.1)		0.19	0.001
Initial proteinuria, g/d	1.29 (0.69, 2.51)		1.73 (0.64, 2.43)		1.15 (0.67, 2.28)		1.50 (0.84, 3.25)		0.31	<0.001
Prodromic infection (%)	256 (34.2)		26 (66.7)		138 (31.6)		92 (33.7)		<0.001	0.56
Gross hematuria (%)	213 (28.4)		16 (41.0)		115 (26.3)		82 (30.0)		0.049	0.28
eGFR, ml/min per 1.73 m^2	83.89±30.64		88.52±30.46		82.95±30.24		84.72±31.34		0.27	0.46
CKD stages 1/2/3/4–5[c] (%)	345 (47.4)/231 (30.8)/141 (18.8)/32 (4.3)		20 (51.3)/12 (30.8)/5 (12.8)/2 (5.1)		197 (45.1)/136 (31.1)/87 (19.9)/17 (3.9)		128 (46.9)/83 (30.4)/49 (17.9)/13 (4.8)		0.71	0.85
HBP, mmHg (%)	369 (49.3)		19 (48.7)		211 (48.3)		139 (50.9)		0.96	0.50
Oxford classification[d] (%)										
M1	609 (82.4)		31 (79.5)		357 (82.8)		221 (82.2)		0.60	0.82
E1	368 (49.8)		22 (56.4)		211 (49.0)		135 (50.2)		0.37	0.75
S1	481 (65.1)		28 (71.8)		277 (64.3)		176 (65.4)		0.35	0.76
T1/T2	220 (29.8)/123 (16.6)		6 (15.4)/7 (17.9)		132 (30.6)/72 (16.7)		82 (30.5)/44 (16.4)		0.31	0.89
C1/C2	334 (45.2)/68 (9.2)		19 (48.7)/1 (2.6)		192 (44.5)/34 (7.9)		123 (45.7)/33 (12.3)		0.54	0.05
Follow-up										
Follow-up interval, mo	47.0 (26.0, 81.0)		38.0 (19.0, 69.0)		44.0 (25.0, 84.0)		52.0 (27.5, 80.0)		0.31	0.31
Treated with immunosuppressive agents or prednisone (%)	353 (47.1)		13 (33.3)		192 (43.9)		148 (54.2)		0.20	0.01
RAS blocker (%)	713 (95.2)		38 (97.4)		414 (94.7)		261 (95.6)		0.46	0.60
Slope, ml/min per 1.73 m^2 per year	−2.91 (−5.22, −1.25)		−4.28 (−5.84, −2.24)		−2.85 (−5.13, −1.19)		−2.89 (−5.72, −1.25)		0.03	0.42
Outcome	No. (%)	Per 100 Patient-yr	No. (%)	Per 100 Patient-yr	No. (%)	Per 100 Patient-yr	No. (%)	Per 100 Patient-yr		
50% Decline in eGFR	102 (13.6)	3.47	8 (20.5)	6.47	47 (10.8)	2.95	47 (17.2)	3.97	0.07	0.01
ESRD	67 (8.9)	2.27	9 (23.1)	7.29	38 (8.7)	2.37	32 (11.7)	2.70	0.04	0.19
Composite[e]	112 (15.0)	3.83	10 (25.6)	8.08	51 (11.7)	3.19	51 (18.7)	4.32	0.01	0.01

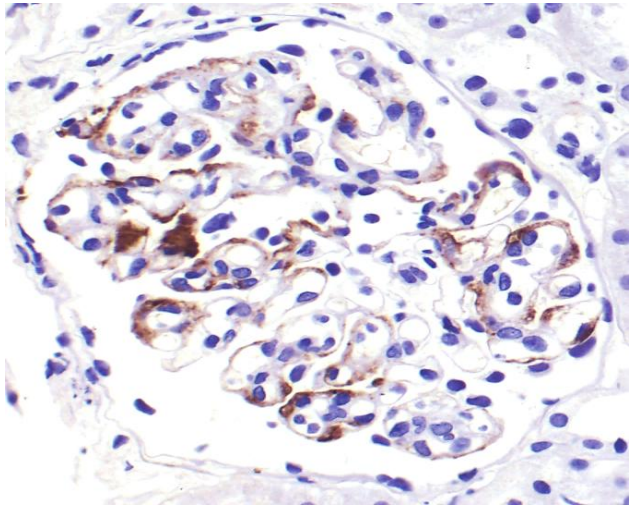
Guo, W. Y.et al. *J Am Soc Nephrol*. 2017



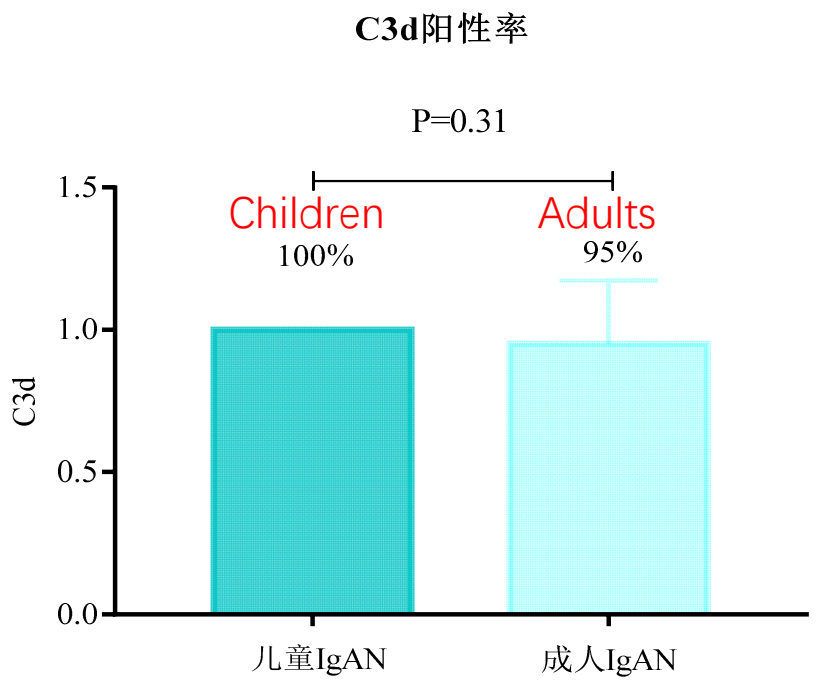
C3d

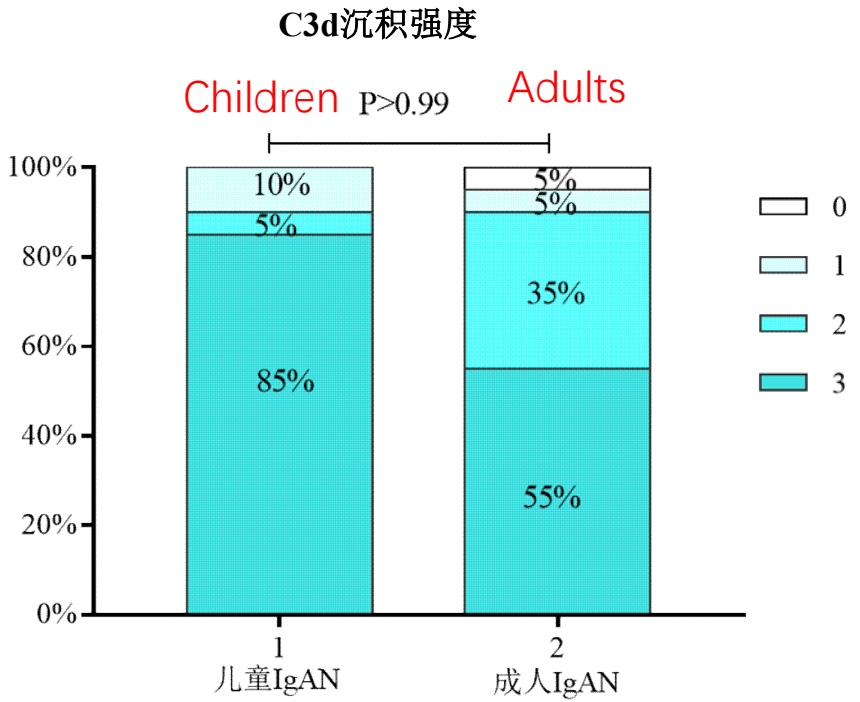


C5b-9

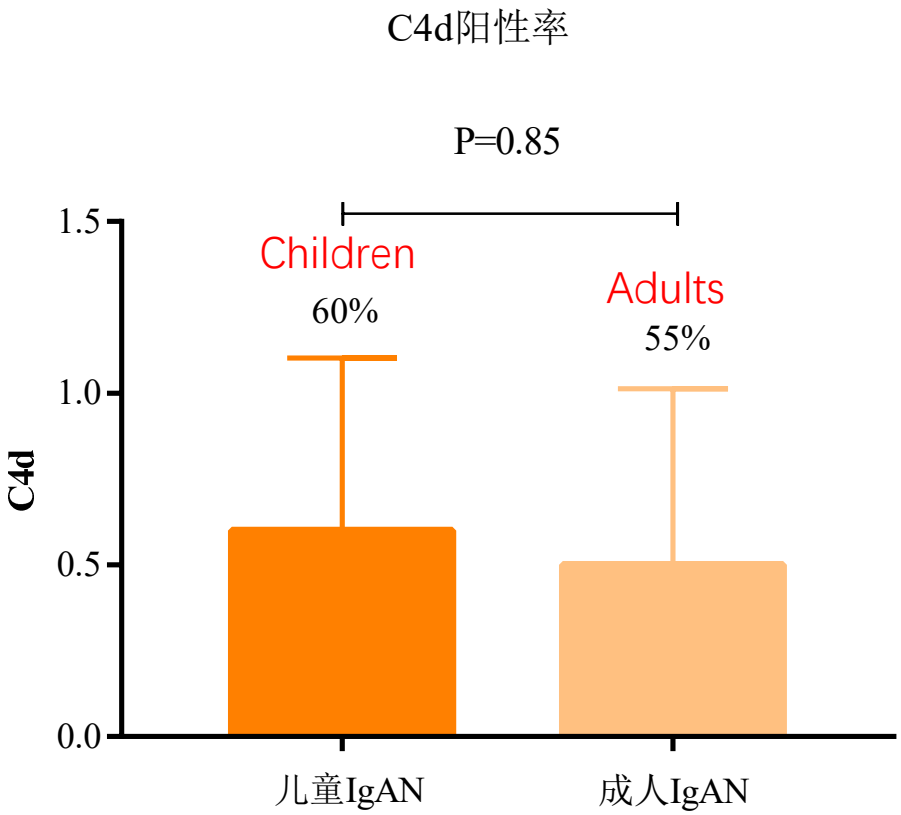


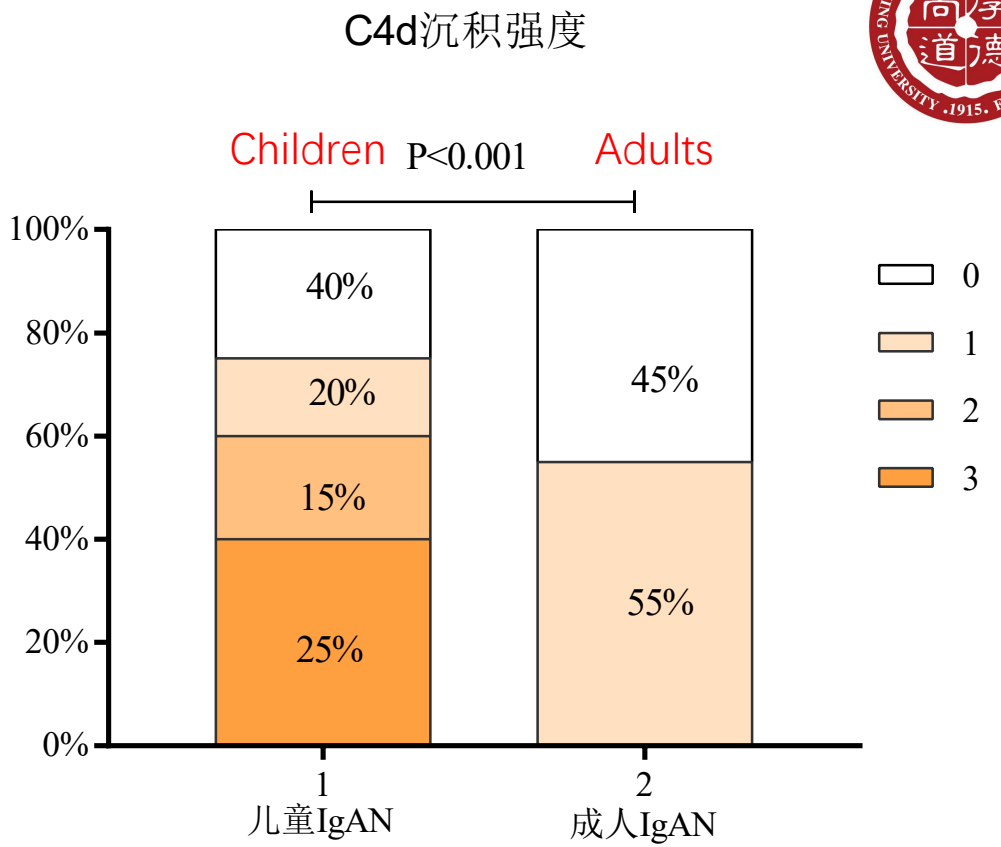
C4d



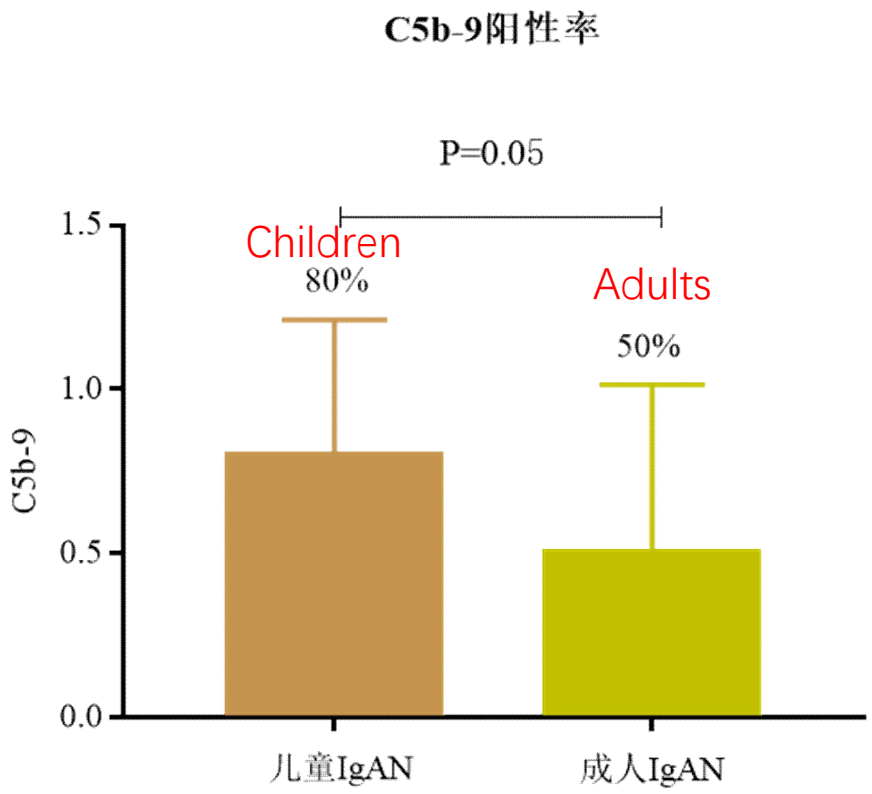


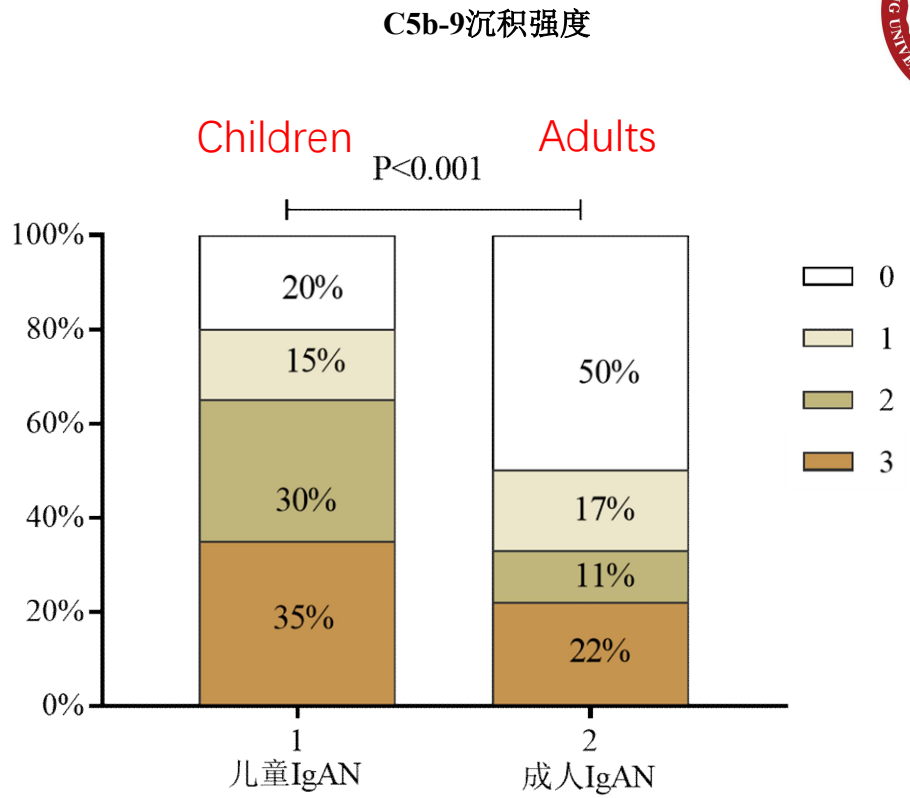
No difference of the prevalence of C3d and intensity of staining on the kidney tissues.



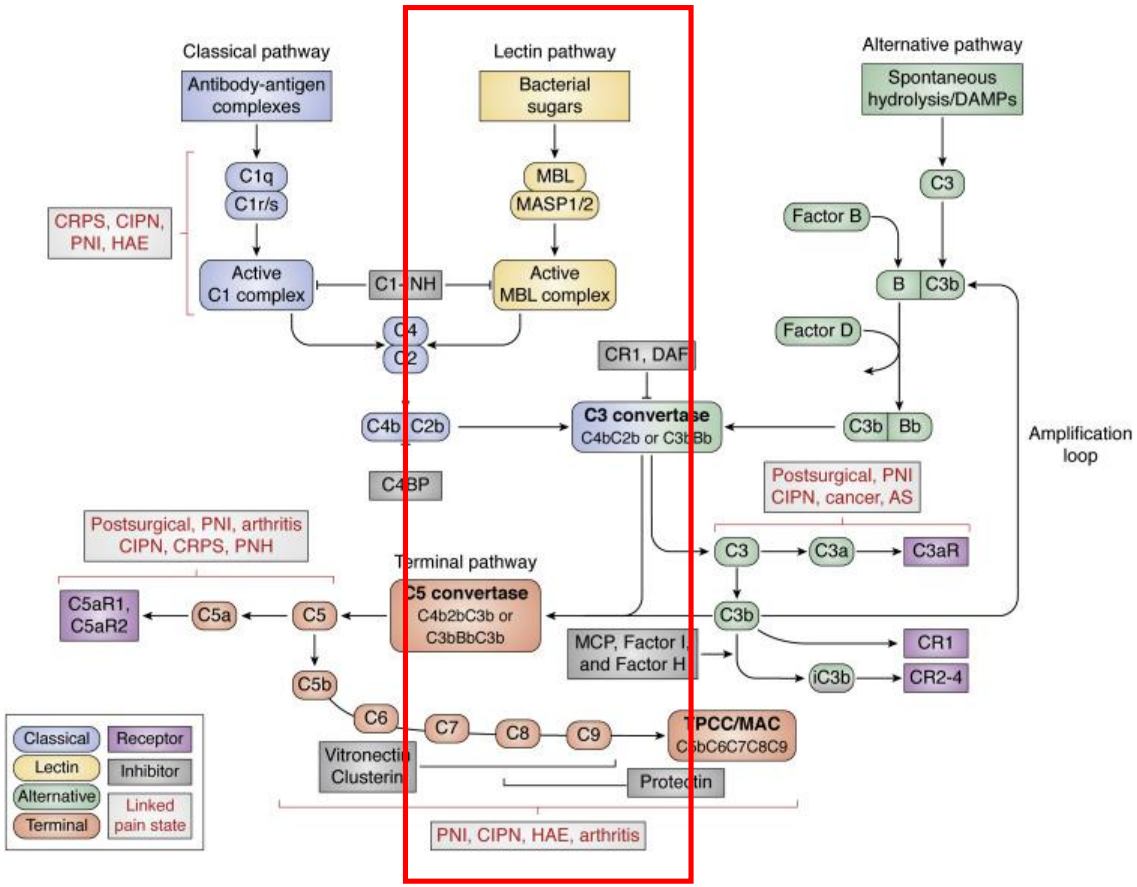


The deposition intensity of glomerular deposition of C4d in children with IgAN was higher than that in adults.





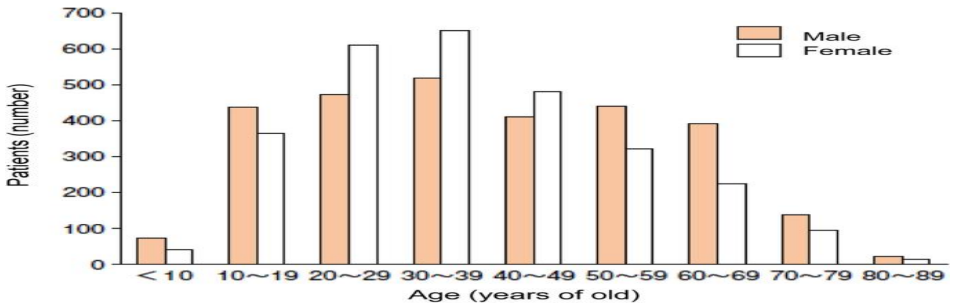
The prevalence and the deposition intensity of glomerular deposition of terminal complement complex C5b-9 in children with IgAN was higher than that in adults.



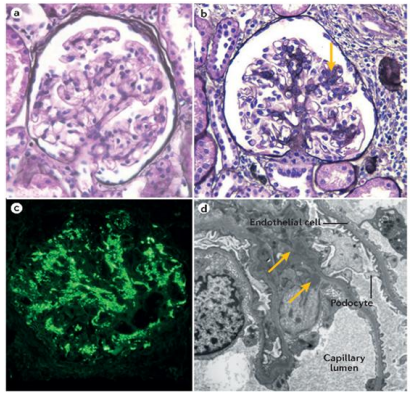
The level of complement activation, especially the level of lectin pathway activation, was significantly higher in children with IgAN than in adults.

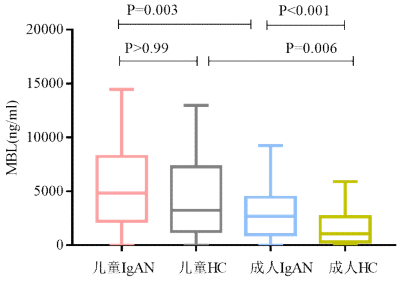
Roos. et al. *JASN*. 2006
Miyazaki, R.et al. *Clinical nephrology*. 1984

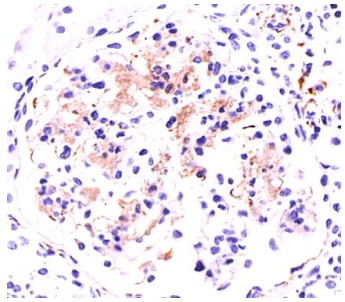
Are children with IgA nephropathy different from adult patients?



Pediatric IgAN **Adult IgAN**







Are children with IgA nephropathy different from adult patients?

1. Are children different from adults, in clinical and pathological manifestation? **YES**
2. Do pediatric nephrologists practice differently from adult nephrologists, when facing IgAN? **YES**
3. Does pediatric IgAN progress differently from adult patients? **YES**
4. Why are children with IgAN different from adult patients? **Maybe**

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- Chengdu Women and Children's Central Hospital
- Children's Hospital Affiliated to Chongqing Medical University
- Children's Hospital Affiliated to Capital Institute of Pediatrics
- Children's Hospital Affiliated to Zhejiang University School of Medicine
- Fuzhou General Hospital of Nanjing Military Region
- Guangzhou First People's Hospital
- Guangzhou Women and Children's Medical Center
- Hebei Provincial Children's Hospital
- Huazhong University of Science Tongji Hospital, Tongji Medical College
- Hunan Provincial Children's Hospital
- Jiangxi Children's Hospital
- Jilin University First Hospital
- Nanjing Children's Hospital Affiliated to Nanjing Medical University
- Nanjing General Hospital of Nanjing Military Region
- Peking University First Hospital
- Second Xiangya Hospital of Central South University
- Shandong Provincial Hospital
- Shanghai Children's Hospital
- The First Affiliated Hospital of Anhui Medical University
- The First Affiliated Hospital of Sun Yat-sen University
- Tianjin Children's Hospital
- Wuhan Women and Children's Medical Care Center
- Xi'an Children's Hospital
- Xuzhou Children's Hospital
- Yunnan First People's Hospital
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