KDIGO-IACN symposium on IgA Nephropathy

Variable Clinical Features of IgAN: East vs West?

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Disclosures

- Scientific advice to companies:
  - Travere Therapeutics
  - Eledon Pharmaceuticals
  - Boehringer Ingelheim
- Honoraria and advisory fees received from:
  - AstraZeneca
  - Bayer
  - Boehringer Ingelheim
  - GSK
  - Novartis Pharma AG
- Local Lead of PROTECT and DUPLEX studies (Travere); ALIGN study (Chinook Therapeutics -> Novartis), BI690517 study (Boehringer Ingelheim) and DIMERIX study (Dimerix Bioscience)
- KDIGO Executive Committee 2020-2023
  - Core member of IgAN Clinical Practice Guideline Work Group 2024

IgA nephropathy: East vs West?

- Clinical Presentation
- Epidemiology
- Biopsy features
- Genetics
- Risk of kidney failure
- Unmet needs

Clinical Presentation

- Gross hematuria, often synpharyngitic (40-50%)
- Microscopic hematuria with or without proteinuria, often detected upon routine examination or evaluation of CKD (30-40%)
- Proteinuria, hypertension, or impaired kidney function (<10%)
- AKI or RPGN (rare)

Associated conditions

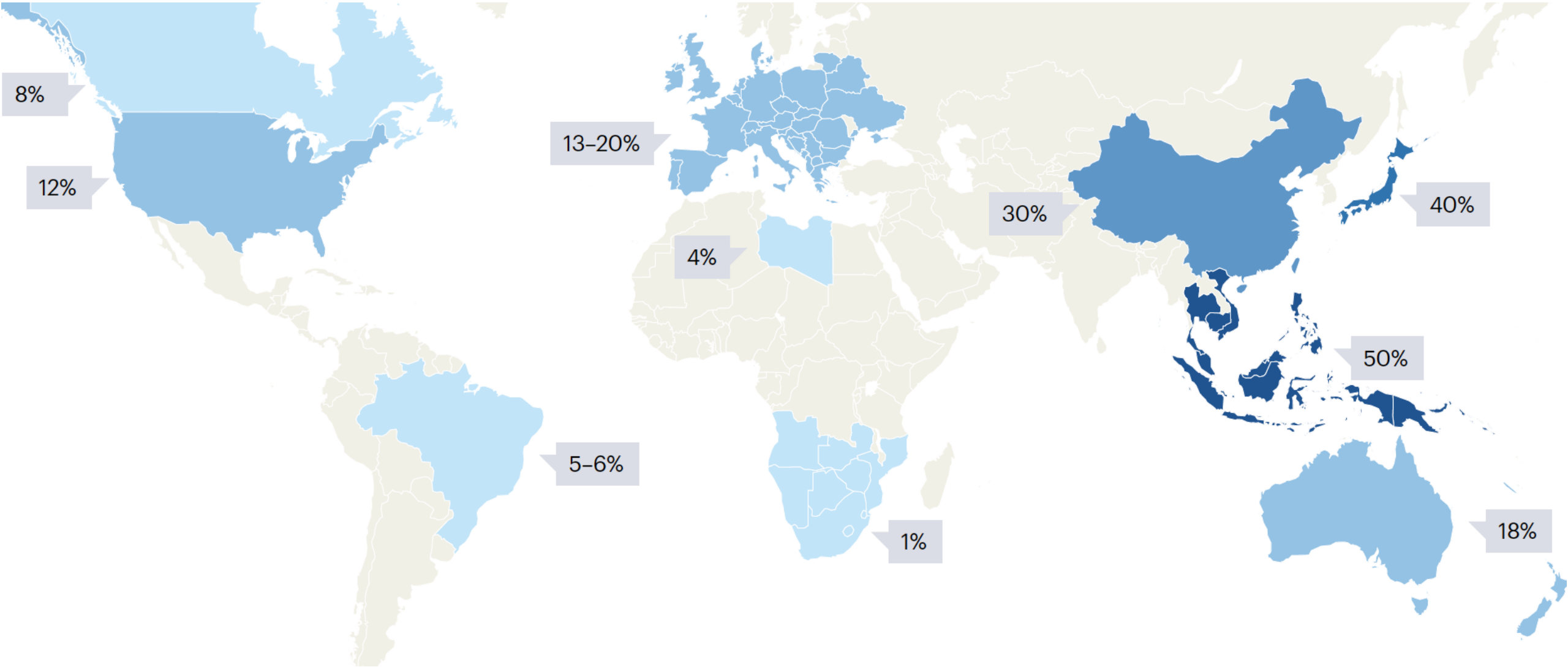
- Chronic liver disease – alcoholic cirrhosis, biliary atresia, alpha-1 antitrypsin deficiency esp in children
- Celiac disease
- HIV
- MRGS
- With other glomerular diseases
  - Minimal change disease (a variant of IgAN, behaving as MCD and should be treated as such)
  - GPA
- Other conditions – dermatitis herpetiformis, lymphoma, inflammatory bowel disease

Two patients with IgAN – one from Hong Kong (2024) and one from UK (2018)

Reason for presentation	Health checkup	Road accident
Age, gender	48 years old, female	28 years old, male
BMI, kg/m^2	21	31
Smoking status	Non-smoker	Non-smoker
Hematuria (dipstick)	+	+
Urine protein to creatinine ratio	1.7 mg/mg	1.69 mg/mg
Kidney function	> 90 ml/min/1.73 m^2	82 ml/min/1.73 m^2
Hypertension	–	+
Kidney biopsy	M1 E1 S1 T0–C1	M0 E0 S1 T0–C0

IgA nephropathy: East vs West

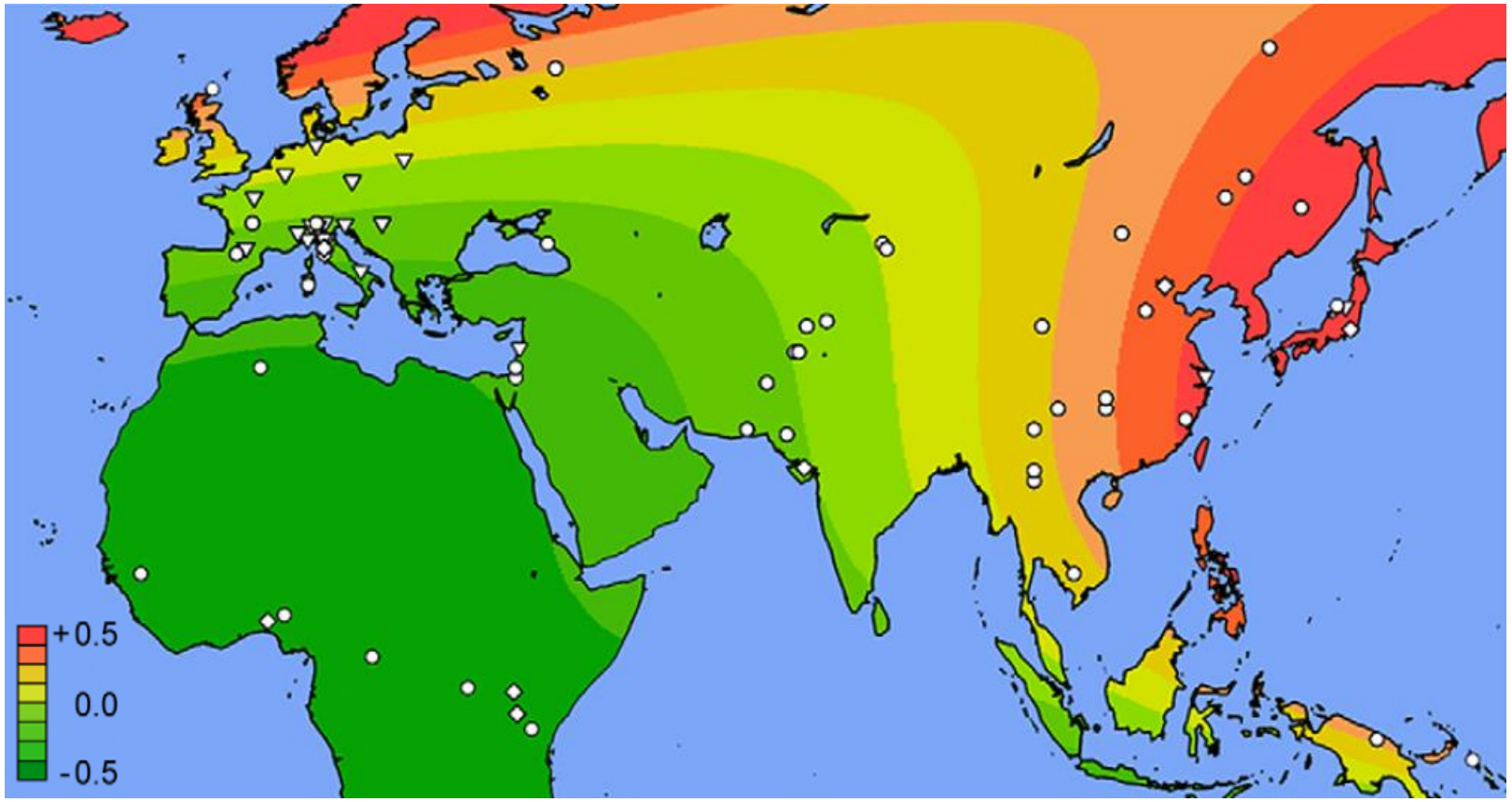
5 distinguishing features



Percentages of patients with glomerular disease who have IgAN

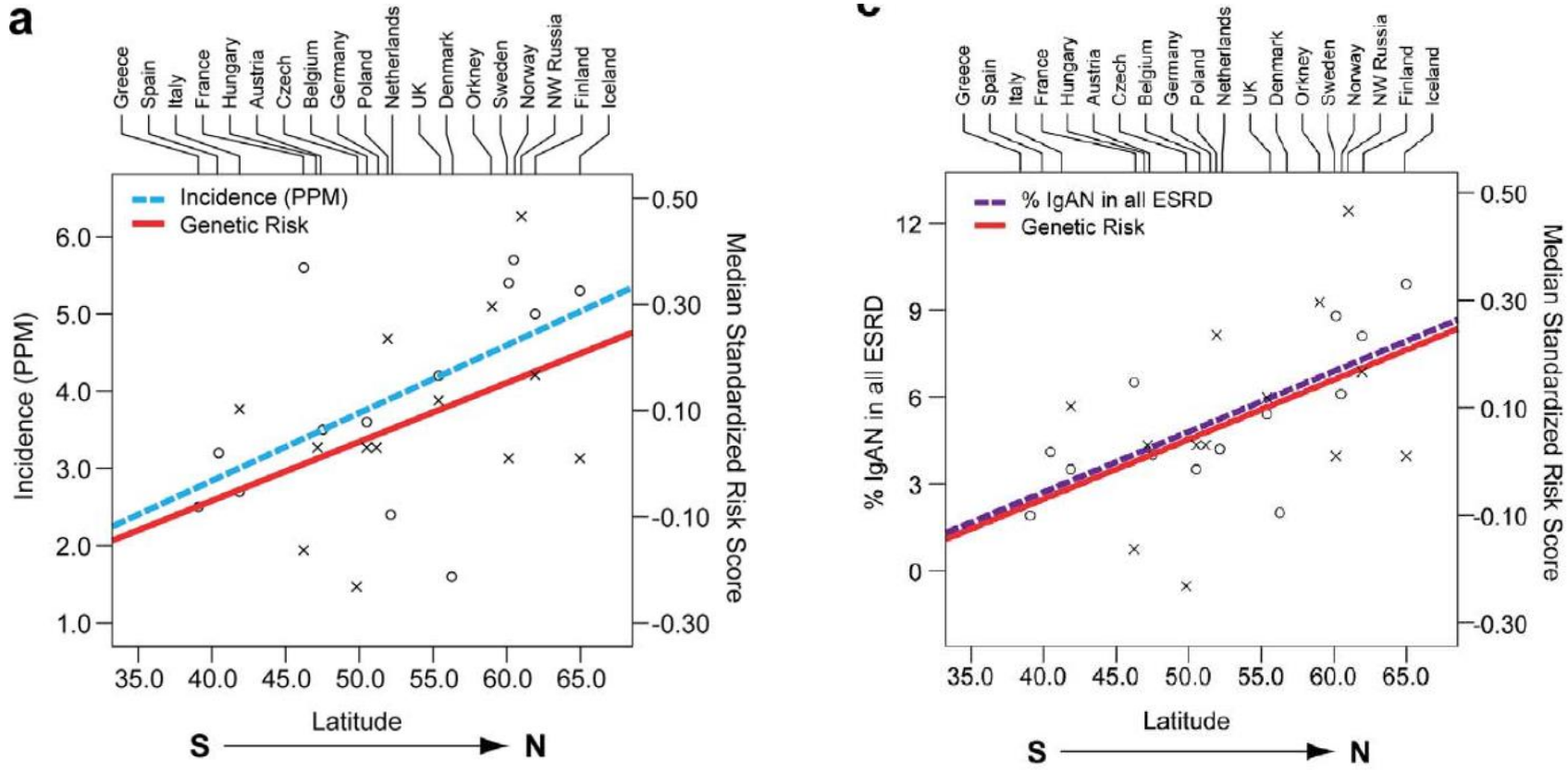
Stamellou E, Seikrit C, Tang SCW, et al. IgA nephropathy. Nat Rev Dis Primers. 2023

Worldwide geospatial risk differences in IgAN

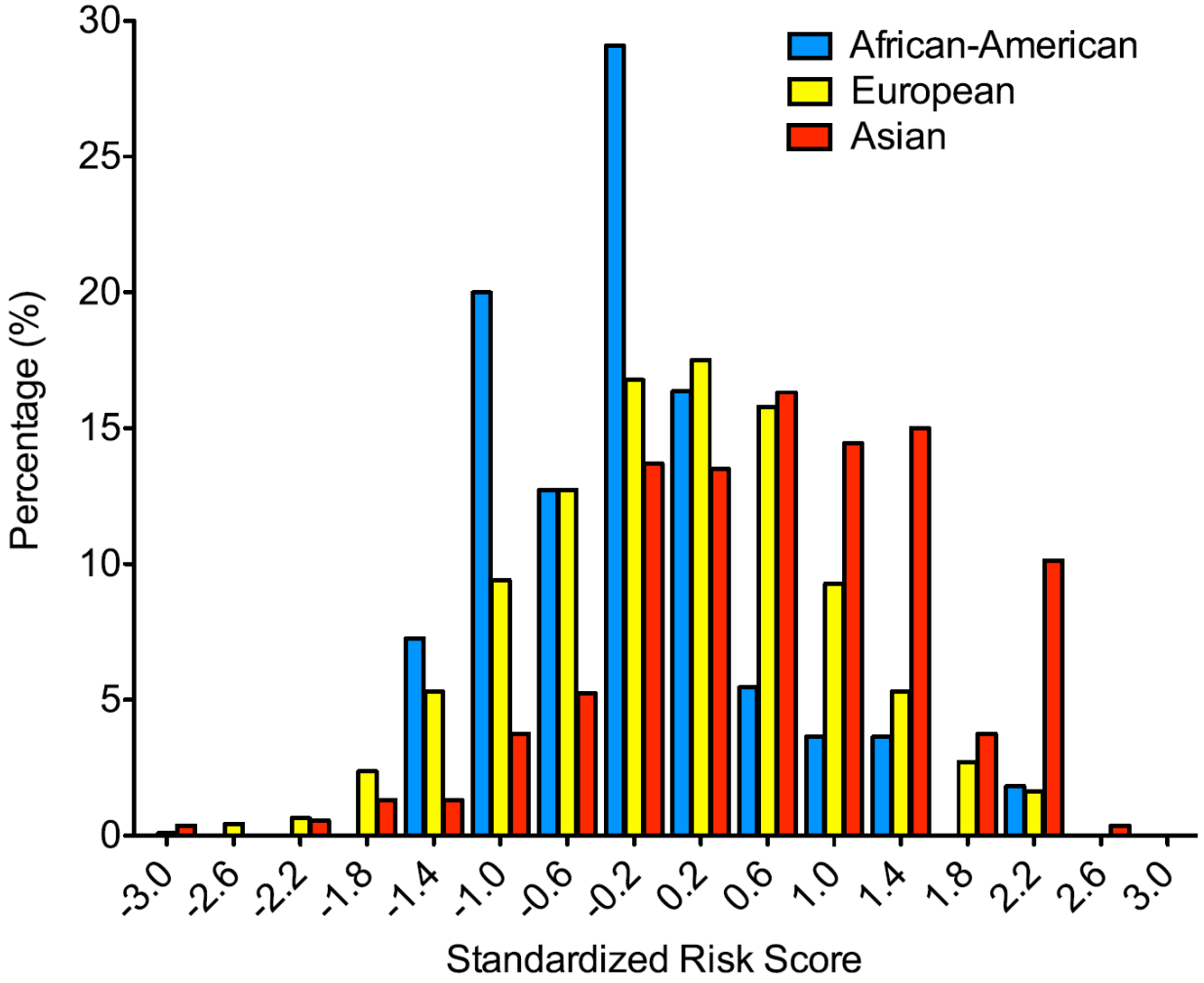


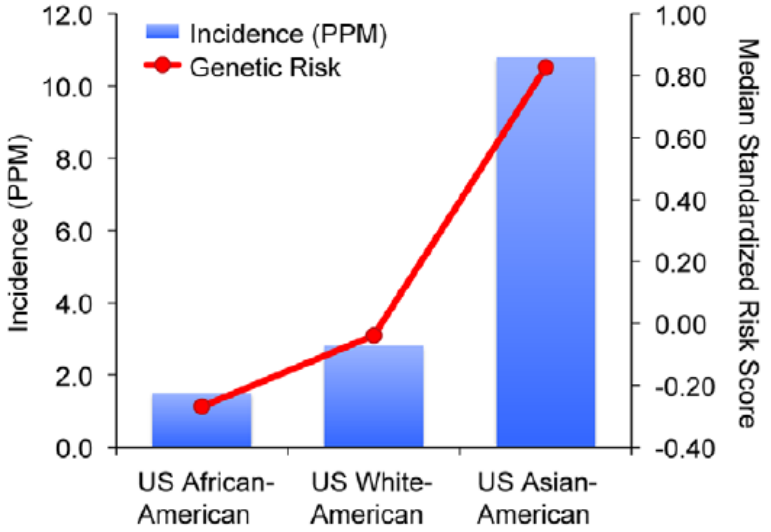
Kiryluk K, et al. PloS Gen 2012

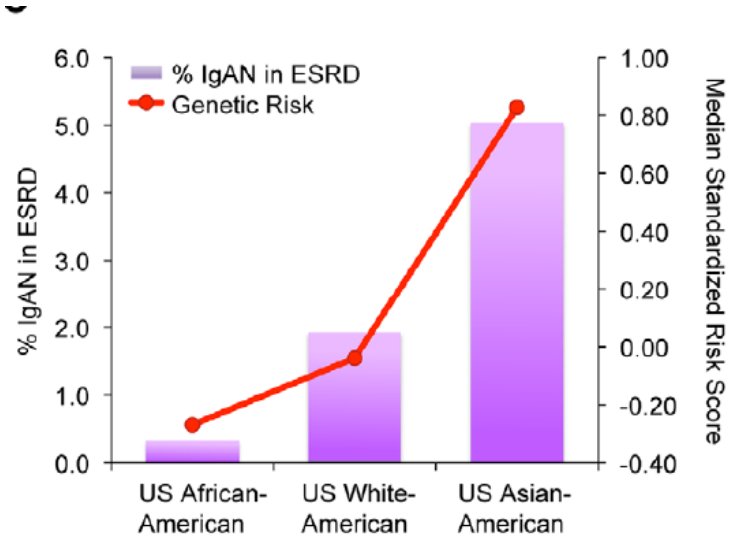
Correlation of average country latitude with country-specific genetic risk and IgAN–attributable kidney failure across Europe



Kiryluk K, et al. PloS Gen 2012







Kiryluk K, et al. PloS Gen 2012

3. Differences in actual gene loci: Insights from GWAS's from the East and the West

Genetic Determinants of IgA Nephropathy: Eastern Perspective

Ming Li, MD, PhD,[,†] and Xue-Qing Yu, MD, PhD[*,†,‡]*

ELSEVIER

Genetic Determinants of IgA Nephropathy: Western Perspective

Y. Dana Neugut, MS, and Krzysztof Kiryluk, MD, MS

Several of these loci encode proteins that modify activation of the alternative pathway of complement or the enzymatic *O*-glycosylation of IgA1

Megsin/Defensin/ April genes only seen in Chinese

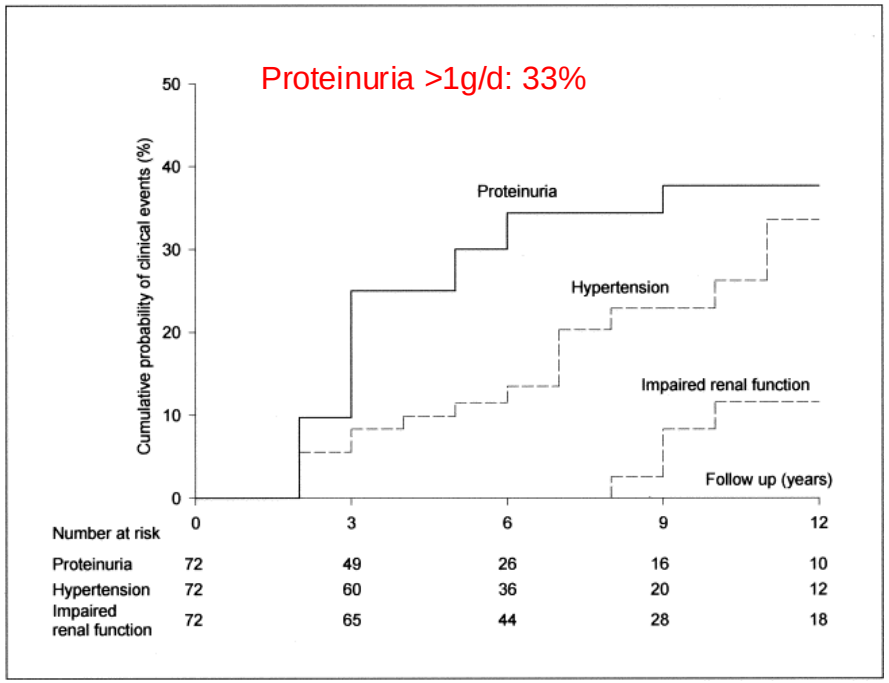
Locus	Notable genes at a locus	Number of risk alleles	Study Design	GWAS report of significant association
1p13	VAV3	1	Case-control	Kiryluk[67]
1q32	CFHR1, CFHR3	1	Case-control	Gharavi[65], Kiryluk[67]
3q27.3	ST6GAL1	1	Case-control	Li[68]
6p21	Multiple HLA genes	7	Case-control	Feehally[64], Gharavi[65], Kiryluk[67], Yu[66], Li[68]
8p23	DEFA1, DEFA3	3	Case-control	Yu[66], Kiryluk[67], Li[68]
8q22.3	ODF1-KLF10	1	Case-control	Li[68]
9q34	CARD9	1	Case-control	Kiryluk[67]
11p11.2	ACCS	1	Case-control	Li[68]
16p11	ITGAM, ITGAX	2	Case-control	Kiryluk[67], Li[68]
17p13	TNFSF13	1	Case-control	Yu[66], Kiryluk[67]
22q12	LIF, OSM	1	Case-control	Yu[66], Gharavi[65], Kiryluk[67]
7p21.3	C1GALT1	1	Serum Gd-IgA1 levels	Kiryluk[95], Gale[43]
Xq24	C1GALT1C1	1	Serum Gd-IgA1 levels	Kiryluk[95]

Chromosome 7

Feehally J, et al. J Am Soc Nephrol. 2010
Gharavi AG, Kiryluk K, et al. Nat Genet. 2011
Yu XQ, et al. Nat Genet. 2011
Kiryluk K, et al. Nat Genet. 2014
Li M, et al. Nat Commun. 2015

4. Difference in Clinical Course between Chinese and Europeans

The Natural History of Immunoglobulin A Nephropathy among Patients with Hematuria and Minimal Proteinuria



Szeto CC, et al. Am J Med 2001

Long-Term Outcomes of IgA Nephropathy Presenting with Minimal or No Proteinuria

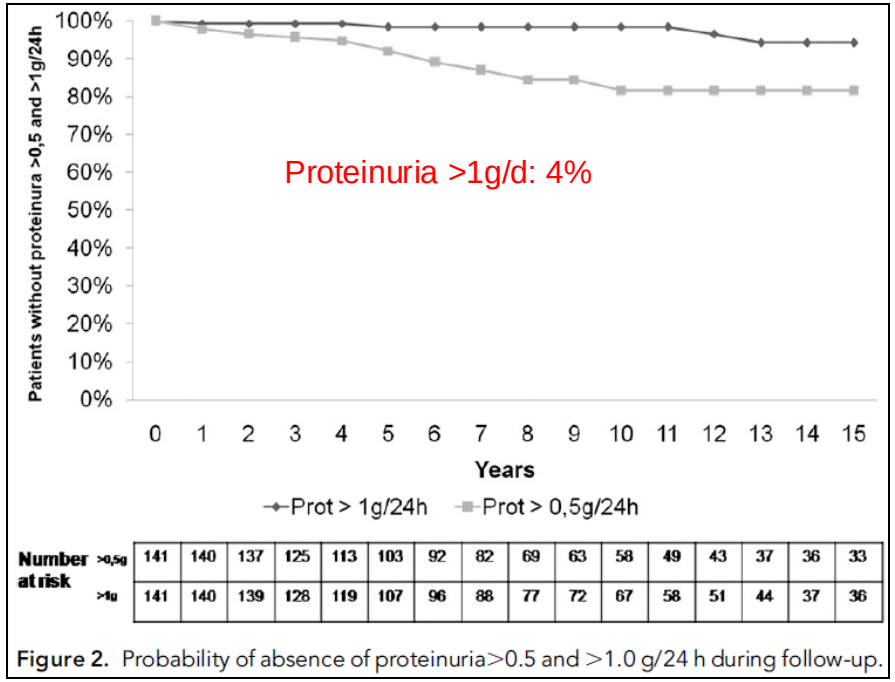


Figure 2. Probability of absence of proteinuria>0.5 and >1.0 g/24 h during follow-up.

Gutiérrez E, et al, JASN 2012

	STOP IgAN	TESTING
Intervention	**GFR > 60**: IV MP pulse x 3 for months 1/3/5 Oral MP 0.5 mg/kg/every other day **GFR < 60**: CYC for 3 months, AZA months 4 - 36, MP 40 mg/day tapered to 10 mg or lower subsequently	**Full dose:** Oral MP 0.6 - 0.8 mg/kg/day for 2 months, tapered 8 mg/month, 6-8 months total **Reduced dose:** Oral MP 0.4 mg/kg/day, tapered by 4 mg per month, 6-9 months total
Sample size	162	503
Age	**~ 44 years**	**~ 36 years**
Men	**~ 78%**	**~ 60%**
Ethnicity	**? 100% European/White**	**75% Chinese** **12% South Asian** **7% Southeast Asian**
Duration from biopsy to enrolment[1]	**Median 9.4 months**	**Median 5 months**
eGFR	~ 60 ml/min/1.73m^2	~ 57 ml/min/1.73m^2
Proteinuria	~ 1.7 g/day	~ 1.95 g/day
Blood Pressure	~ 125/77	~ 124/80
Biopsy Findings[1]	**M1 26%** **S1 91%** **E1 17%** **T0 59%** **T2 4%**	**M1 ~ 60%** **S1 68%** **E1 ~ 25%** **T0 ~ 49%** **T2 ~ 13%**
Total events	**43**	**180**
Slope of eGFR change in control arm	– 1.6 ml/min/1.73m^2	– 5 ml/min/1.73m^2

https://pmc.ncbi.nlm.nih.gov/articles/PMC9681628/figure/fig1/

Clin Kidney J. 2023 Dec 4;16(Suppl 2):ii1–ii8. doi: 10.1093/ckj/sfad199

Ethnicity and IgA nephropathy: worldwide differences in epidemiology, timing of diagnosis, clinical manifestations, management and prognosis

Mingfeng Lee [1], Hitoshi Suzuki [2,3,✉], Yoshihito Nihei [4], Keiichi Matsuzaki [5], Yusuke Suzuki [6,✉]

Author information Article notes Copyright and License information

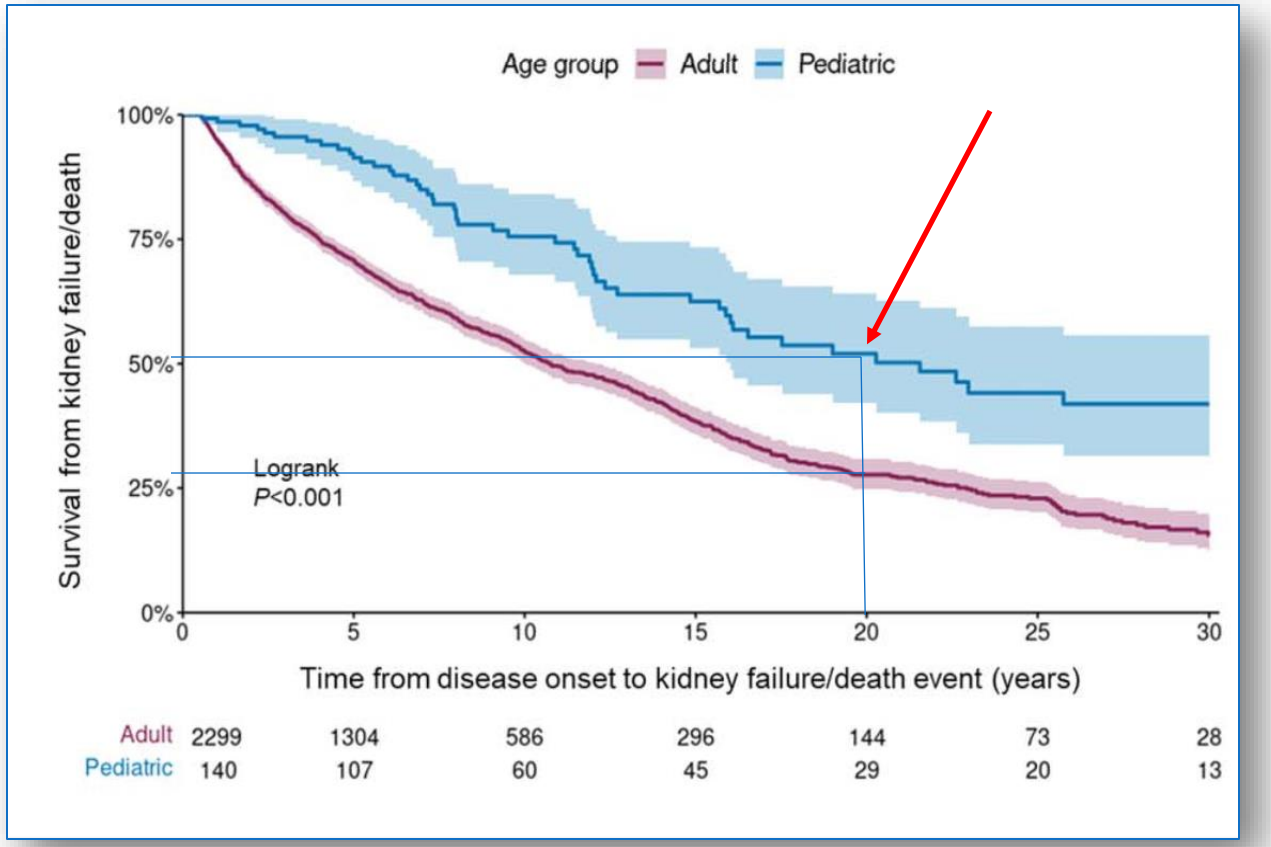
PMCID: PMC10695519 PMID: 38053973

ABSTRACT

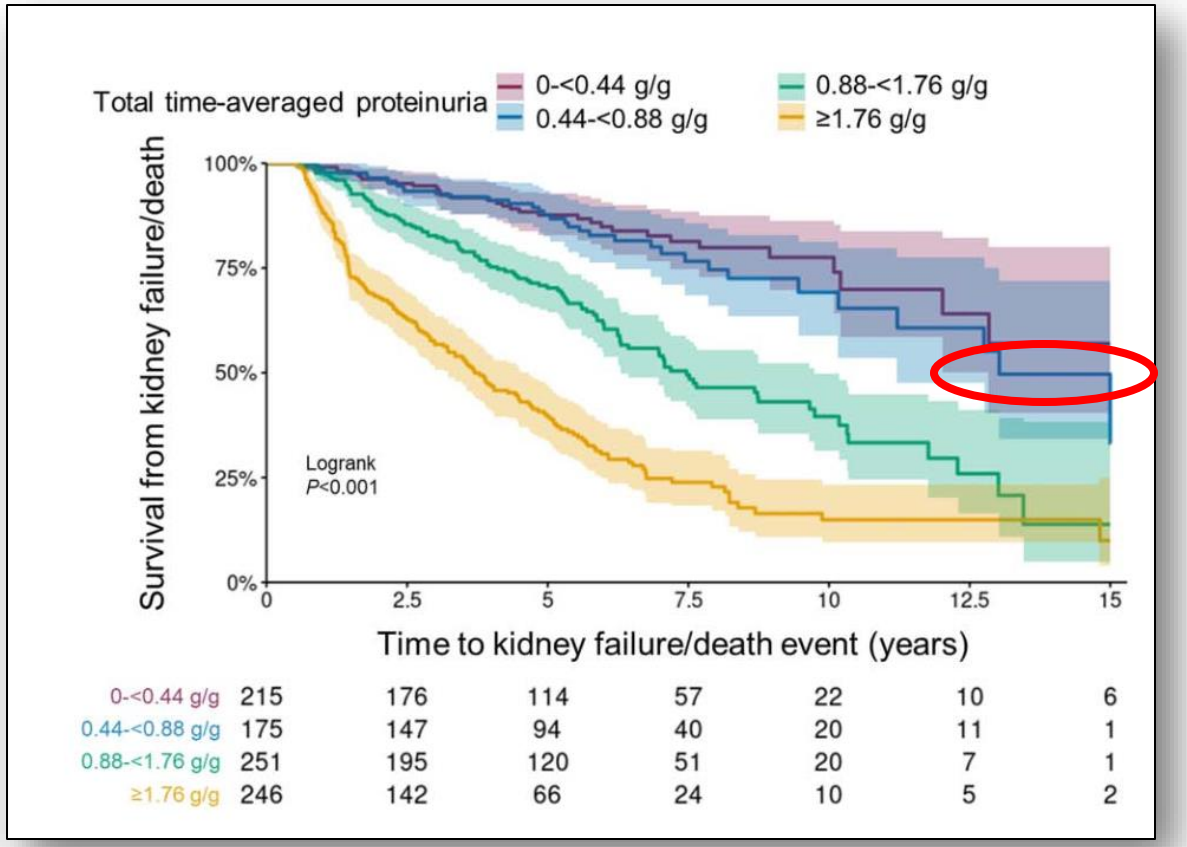
Immunoglobulin A nephropathy (IgAN), the most common primary glomerulonephritis, is one of the major causes of end-stage renal disease. Significant variances in epidemiology, clinical manifestation, timing of diagnosis, management and renal prognosis of IgAN have been reported worldwide. The incidence of IgAN is the most frequent in Asia, followed by Europe, and lower in Africa. Moreover, Asian patients show more frequent acute lesions in renal histology and present poorer renal outcomes compared with Caucasians. The comorbidities also show the difference between Asians and Caucasians. Although the frequency of gross hematuria with upper respiratory tract infection is not different,

IgA nephropathy is not a benign disease even if proteinuria is < 1g/day

Patients diagnosed < 18 years had significantly longer median kidney survival than adults (log-rank *P* < 0.001)



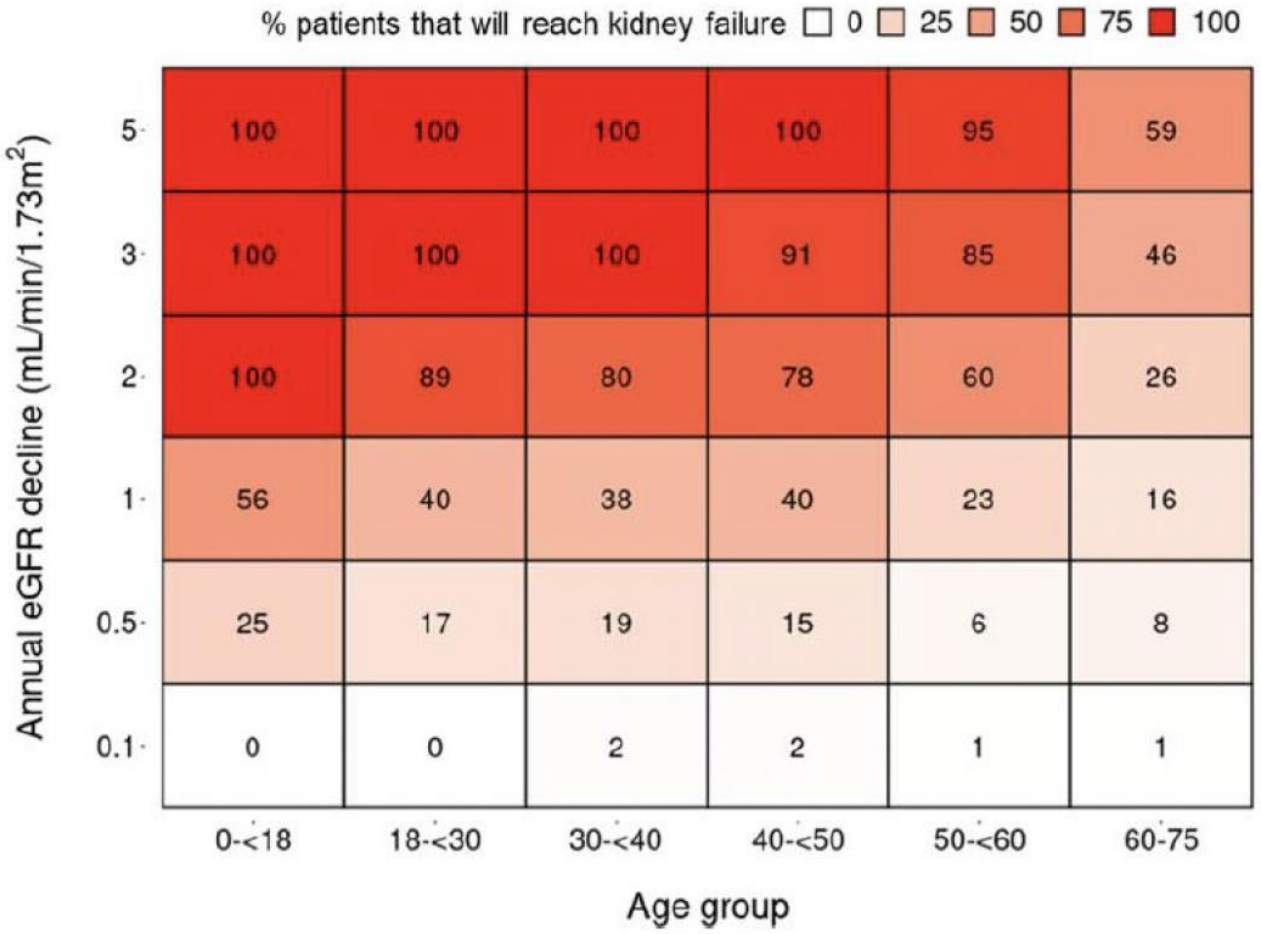
Patients with proteinuria >0.88 g/g were likely to progress to kidney failure or death more quickly than those <0.88 g/g



Pitcher, D et al; *C J Am Soc Nephrol* 2023 18:727-738

UK RaDaR Study

Almost all 2,299 adults and 140 adolescents with IgAN, UP >0.5g/d & eGFR <60 ml/min at diagnosis from RaDaR will develop kidney failure within their expected lifespan, unless eGFR attrition is < 1ml/min/year

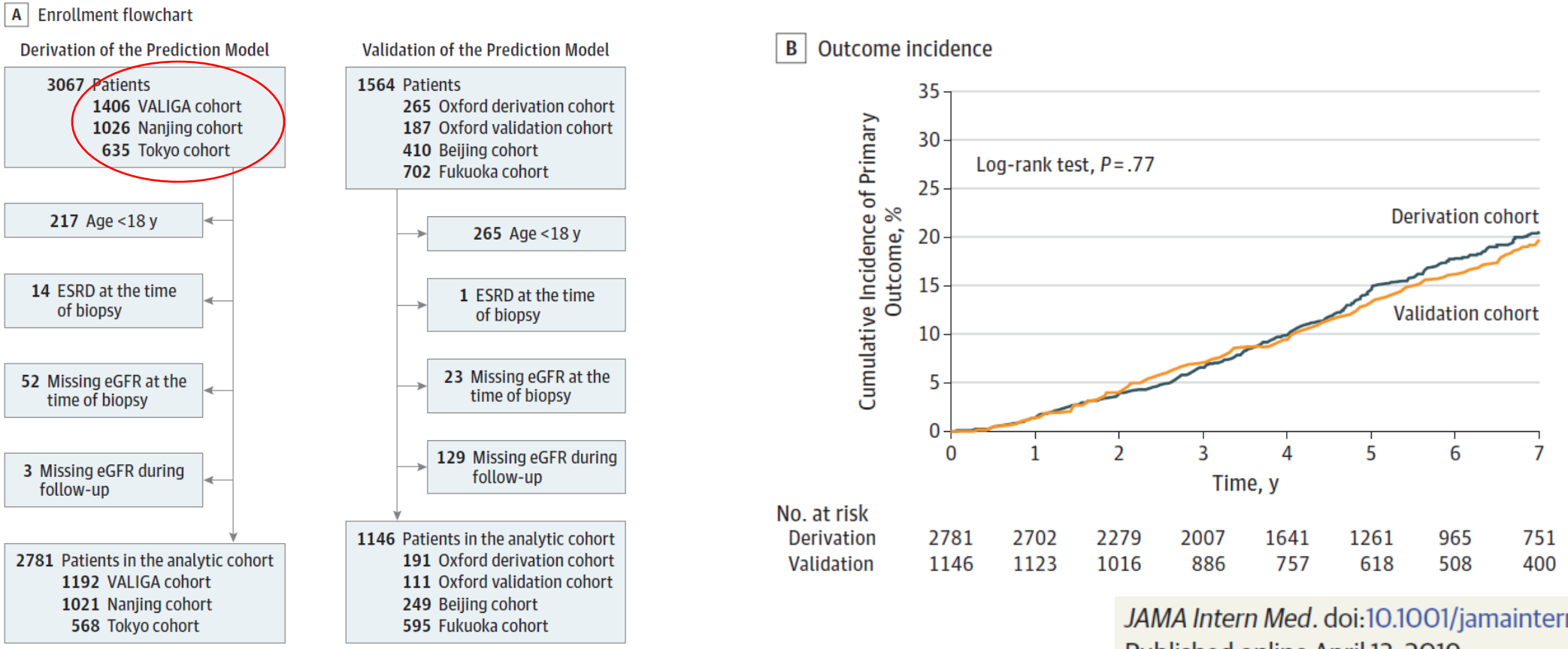


Pitcher, D et al; *C J Am Soc Nephrol* 2023 18:727-738

JAMA Internal Medicine | Original Investigation

Evaluating a New International Risk-Prediction Tool in IgA Nephropathy

Sean J. Barbour, MD, MSc; Rosanna Coppo, MD, FERA; Hong Zhang, MD, PhD; Zhi-Hong Liu, MD; Yusuke Suzuki, MD, PhD; Keiichi Matsuzaki, MD, PhD; Ritsuko Katafuchi, MD, PhD; Lee Er, MSc; Gabriela Espino-Hernandez, MSc; S. Joseph Kim, MD, PhD; Heather N. Reich, MD, PhD; John Feehally, FRCP; Daniel C. Cattran, MD, FRCPC; for the International IgA Nephropathy Network



JAMA Intern Med. doi:10.1001/jamainternmed.2019.0600
Published online April 13, 2019.

	Total	VALIGA[1]	Nanjing	Tokyo
Pathology				
M1	1057 (38%)	424 (35.5%)	435 (42.6%)	198 (34.8%)
E1	479 (17.2%)	159 (13.3%)	113 (11.1%)	207 (36.4%)
S1	2139 (76.8%)	875 (73.3%)	852 (83.4%)	412 (72.4%)
T1	688 (24.7%)	256 (21.4%)	247 (24.2%)	185 (32.5%)
T2	129 (4.6%)	68 (5.7%)	33 (3.2%)	28 (4.9%)
C	954 (34.3%)	155 (13%)	458 (44.9%)	341 (59.9%)

JAMA Intern Med. doi:10.1001/jamainternmed.2019.0600
Published online April 13, 2019.

*The data elements included in the International IgAN Prediction Tool**

Estimated GFR at biopsy.....ml/min/1.73m²

Systolic blood pressure at biopsy.....mmHg

Diastolic blood pressure at biopsy.....mmHg

Proteinuria at biopsy.....g/day

Age at biopsy.....years

Race
- Caucasian
- Chinese
- Japanese
- Other

Use of ACE inhibitor or ARB at the time of biopsy
- No
- Yes

MEST M-score
- 0
- 1

MEST E-score
- 0
- 1

MEST S-score
- 0
- 1

MEST T-score
- 0
- 1
- 2

Immunosuppression use at or prior to biopsy
- No
- Yes

*https://qxmd.com/calculate/calculator_499/international-igan-prediction-tool

Or simply type **QxMD IgAN** in your search engine

*The data elements included in the International IgAN Prediction Tool**

Estimated GFR at biopsy	90 ml/min/1.73m²
Systolic blood pressure at biopsy	120 mmHg
Diastolic blood pressure at biopsy	70 mmHg
Proteinuria at biopsy	1 g/day
Age at biopsy	21 years

Race
Caucasian
Chinese
Japanese
Other

Use of ACE inhibitor or ARB at the time of biopsy
No
Yes

MEST M-score
0
1

MEST E-score
0
1

MEST S-score
0
1

MEST T-score
0
1
2

Immunosuppression use at or prior to biopsy
No
Yes

Risk of Progression to ESKD 5 years later: 14.3%

If E and S lesions are present: 13.86%

If T1: 24%; If T2: 38%

Japanese: 28%

Caucasian: 20%

5. Difference in response to Therapy, e.g. Steroid/ MMF / CTX

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

Rauen T, et al. 2015

Baseline eGFR and proteinuria

eGFR — ml/min/1.73 m^2‡	61.5±27.3
Creatinine clearance — ml/min	76.0±34.7
Urinary protein excretion rate — g/day	2.2±1.8

CONCLUSIONS

The addition of immunosuppressive therapy to intensive supportive care in patients with high-risk IgA nephropathy did not significantly improve the outcome, and during the 3-year study phase, more adverse effects were observed among the patients who received immunosuppressive therapy, with no change in the rate of decrease in the eGFR. (Funded by the German Federal Ministry of Education and Research; STOP-IgAN ClinicalTrials.gov number, NCT00554502.)

Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy

The TESTING Randomized Clinical Trial

Jicheng Lv, MD[1,2]; Muh Geot Wong, PhD[2,3]; Michelle A. Hladunewich, MD[4]; et al JAMA 2022

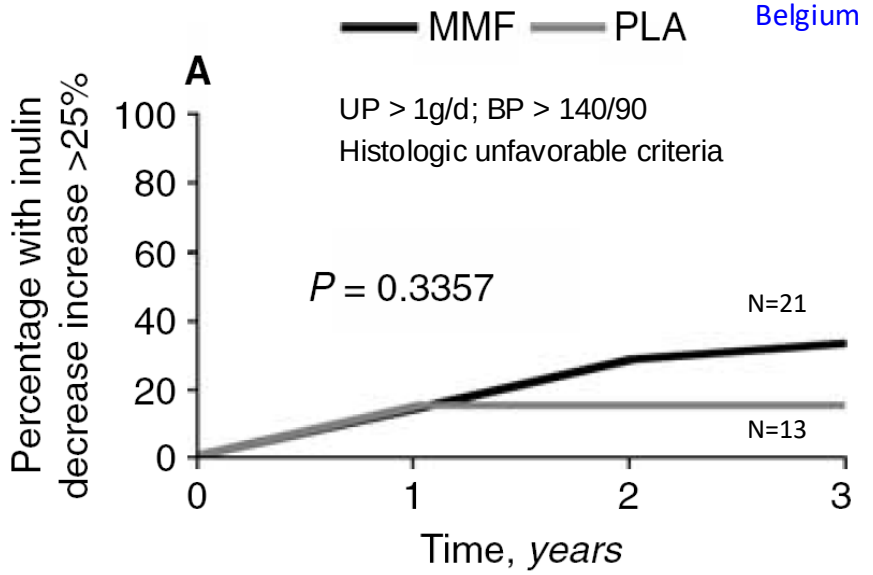
Baseline eGFR and proteinuria

eGFR, mL/min per 1.73 m^2[d]	56.1 (43.2-75.0)
Urine protein, g/d[e]	1.99 (1.36-3.09)

Conclusions and Relevance Among patients with IgA nephropathy at high risk of progression, treatment with oral methylprednisolone for 6 to 9 months, compared with placebo, significantly reduced the risk of the composite outcome of kidney function decline, kidney failure, or death due to kidney disease. However, the incidence of serious adverse events was increased with oral methylprednisolone, mainly with high-dose therapy.

Mycophenolate mofetil: Caucasian patients

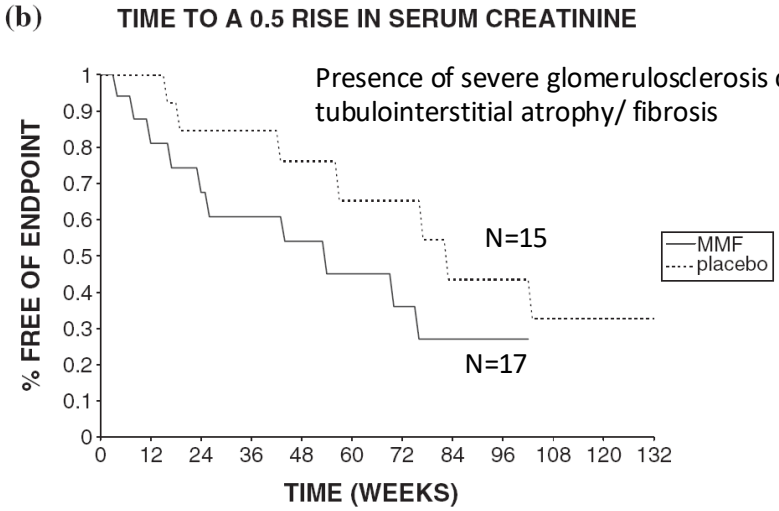
Belgium



UP > 1g/d; BP > 140/90
Histologic unfavorable criteria

Maes BD et al. Kidney Int 2004

USA

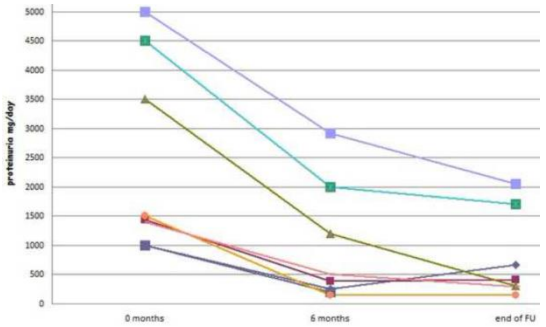


Presence of severe glomerulosclerosis or tubulointerstitial atrophy/ fibrosis

Frisch G, et al. *Nephrol Dial Transplant* 2005

Italy

UP > 2.4g/d; RBC > 76/HPF
Bx: 10% florid crescents
MPx3/Pred + MMF x 6m



Roccatello D, et al. J Nephrol 2012

USA
Canada

N=52→44 (7-70y); RASB+FOx3m→MMF vs pla if UP >0.6 – 0.8 g/g

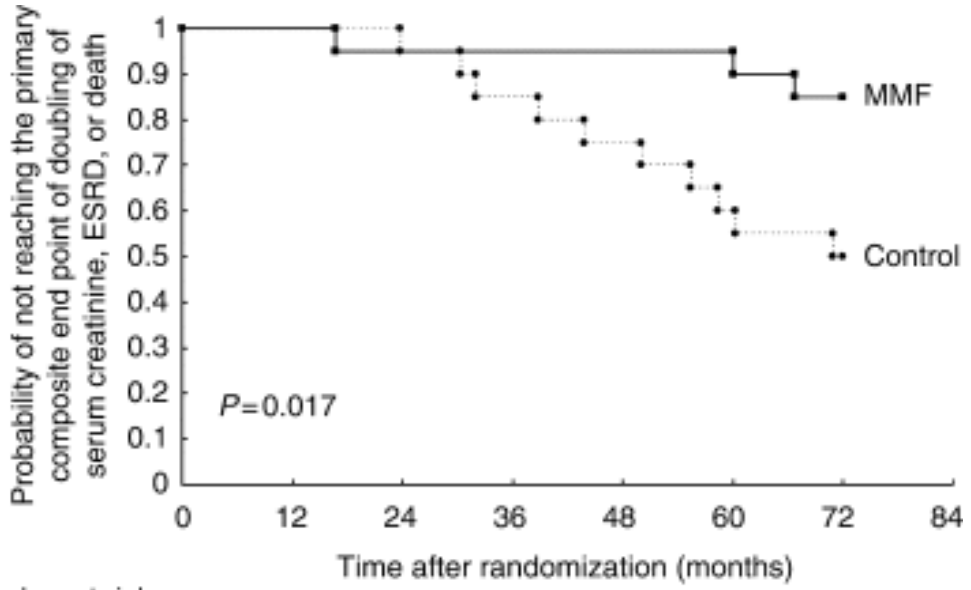
	MMF Group			Placebo Group		
	No.	Randomization Mean (95% CI)	Follow-up Mean (95% CI)	No.	Randomization Mean (95% CI)	Follow-up Mean (95% CI)
UPCR, in g/g						
Pts at randomization	25	1.59 (1.23 to 1.95)	—	27	1.40 (1.18 to 1.62)	—
Pts reaching 6 mo Rx	22	1.45 (1.16 to 1.75)	1.40 (1.09 to 1.70)	22	1.41 (1.17 to 1.65)	1.58 (1.13 to 2.04
Pts reaching 12 mo Rx	13	1.46 (1.00 to 1.92)	1.52 (0.94 to 2.11)	15	1.39 (1.09 to 1.70)	1.51 (0.79 to 2.22
Pts reaching 12 mo post-Rx	7	1.25 (0.94 to 1.55)	1.22 (0.70 to 1.74)	10	1.44 (1.00 to 1.88)	1.67 (0.53 to 2.82

Hogg R, et al. AJKD 2015

Kidney International (2010) **77,** 543–549

Long-term study of mycophenolate mofetil treatment in IgA nephropathy

Sydney C.W. Tang[1,2], Anthony W.C. Tang[2], Sunny S.H. Wong[2], Joseph C.K. Leung[1], Yiu Wing Ho[2] and Kar Neng Lai[1]



Number at risk

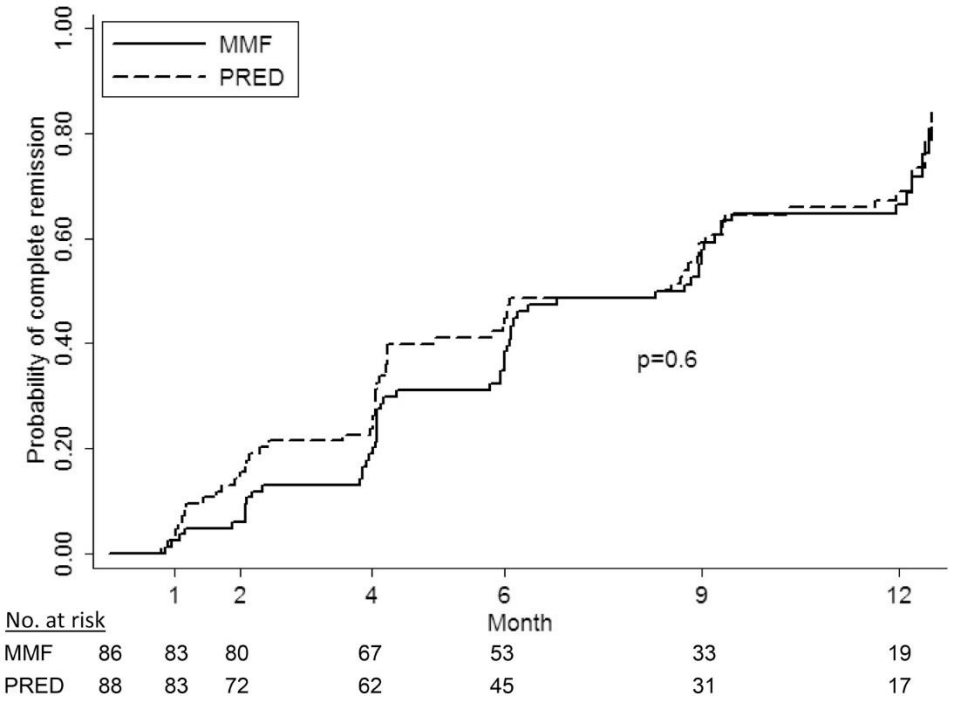
MMF group:	20	20	19	19	19	19	17
Ctl group:	20	20	19	17	15	12	10

AJKD 2017

Original Investigation

Mycophenolate Mofetil Combined With Prednisone Versus Full-Dose Prednisone in IgA Nephropathy With Active Proliferative Lesions: A Randomized Controlled Trial

Jin-Hua Hou, MD,[1,] Wei-Bo Le, PhD,[1,*] Nan Chen, MD,[2] Wei-Ming Wang, PhD,[2] Zhang-Suo Liu, MD,[3] Dong Liu, PhD,[3] Jiang-Hua Chen, MD,[4] Jiong Tian, PhD,[4] Ping Fu, MD, PhD,[5] Zhang-Xue Hu, MD,[5] Cai-Hong Zeng, PhD,[1] Shao-Shan Liang, MD,[1] Min-Lin Zhou, MD,[1] Hai-Tao Zhang, MD,[1] and Zhi-Hong Liu, MD[1]*



No. at risk

MMF	86	83	80	67	53	33	19
PRED	88	83	72	62	45	31	17

JAMA Network Open 2023

Original Investigation | Nephrology

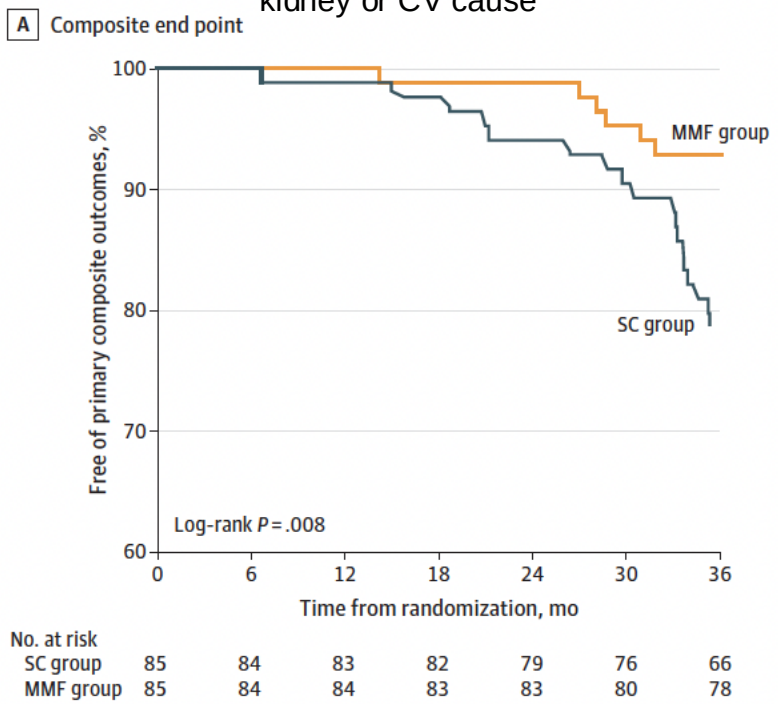
Effectiveness of Mycophenolate Mofetil Among Patients With Progressive IgA Nephropathy

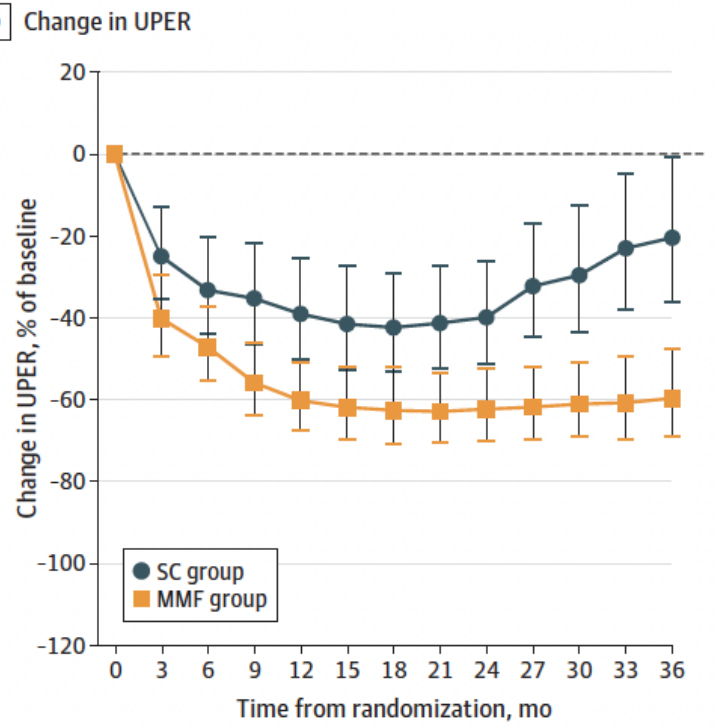
A Randomized Clinical Trial

Fan Fan Hou, MD, PhD; Di Xie, MD, PhD; Jun Wang, MD, PhD; Xin Xu, MD, PhD; Xiaobing Yang, MD, PhD; Jun Ai, MD, PhD; Sheng Nie, MD, PhD; Min Liang, MD, PhD; Guobao Wang, MD; Nan Jia, MD, PhD; for the MAIN Trial Investigators

170 participants (eGFR >30 and UPC>0.75g/d despite 3 months of SC with losartan) were randomized in a 1:1 ratio to: MMF (initially, 1.5 g/d for 12 m) plus SC or SC alone

2x sCr, kidney failure (dialysis, transplant, or kidney failure without KRT), or death due to kidney or CV cause





Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom glucocorticoids are being considered MMF may be used as a glucocorticoid-sparing agent	Three RCTs have been conducted in China: the first from Hong Kong (n=40, eGFR ~51 ml/min/1.73 m^2) showed a significant reduction in time-averaged proteinuria after MMF (1.5 to 2.0 g/day for 6 months) was added to SC in patients with proteinuria >1 g/d.[1] An extended 6-year follow-up showed a lesser slope of eGFR decline and lower probability of reaching kidney failure in MMF-treated patients;[2] the second from around Jiangsu (n=176, eGFR >90 ml/min/1.73 m^2) showed that MMF with low-dose glucocorticoids (0.4–0.6 mg/kg/d prednisone) for 6 months was non-inferior to standard-dose glucocorticoids (0.8–1.0 mg/kg/d) for the treatment of incident IgAN presenting with proliferative histologic lesions (E or C lesions with or without necrosis) on kidney biopsy and proteinuria >1.0 g/d.[3] There were significantly fewer glucocorticoid-related side-effects in the combination-therapy arm; the third from Guangdong (n=170, eGFR 50 ml/min/1.73 m^2) showed that MMF (initially, 1.5 g/d for 12 months, maintained at 0.75–1.0 g/d for at least 6 months) and SC reduced the frequency of the primary composite outcome (doubling of serum creatinine, kidney failure, or death due to kidney or cardiovascular causes, aHR 0.23; 95% CI, 0.09–0.63) and CKD progression (aHR 0.23; 95% CI, 0.1–0.57) compared to SC alone.[4] MMF was well tolerated in all the 3 trials.

F/48, Chinese, IgA nephropathy: M1E1S1T0

UPCR 1.7 mg/mg → 1.57 mg/mg after 7 weeks of MTD ARB

Patient was treated with MMF 750 mg bd and Prednisolone 20 mg/d

MMF
750mg bd

Protein/Cr, Urine, Ratio

Most recent from the left

Hospital	QMH	QMH	QMH	QMH	QMH	QMH	QMH	QMH	QMH
Case no.	ST 2410001Y	ST 2410001Y	ST 2410001Y	ST 2410001Y	ST 2410001Y	ST 2410001Y	ST 2410001Y	ST 2410001Y	ST 2410001Y
Request Date	19/09/24	01/08/24	20/06/24	09/05/24	11/04/24	11/04/24	07/03/24	05/02/24	05/02/24
Collect Date	31/10/24 09:06	16/09/24 09:11	26/07/24 09:51	13/06/24 09:35	02/05/24 09:45	11/04/24 15:44	21/03/24 09:54	20/02/24 09:15	05/02/24 11:47
Arrive Date	31/10/24 10:28	16/09/24 10:58	26/07/24 10:44	13/06/24 11:26	02/05/24 10:45	11/04/24 18:32	21/03/24 10:40	20/02/24 10:53	05/02/24 15:04
Result	0.56 H mg/mg Cr ↑	0.49 H mg/mg Cr ↑	0.61 H mg/mg Cr ↑	0.43 H mg/mg Cr ↑	0.40 H mg/mg Cr ↑	2.78 H mg/mg Cr ↑	0.76 H mg/mg Cr ↑	1.57 H mg/mg Cr ↑	1.57 H mg/mg Cr ↑
Reference Range	< 0.09	< 0.09	< 0.09	< 0.09	< 0.09	< 0.09	< 0.09	< 0.09	< 0.09

eGFR(CKD-EPI)

Most recent from the left

Hospital	QMH	QMH	QMH	QMH	QMH	QMH	QMH	QMH	QMH
Case no.	ST 2410001Y	ST 2410001Y	ST 2410001Y	ST 2410001Y	ST 2410001Y	ST 2410001Y	ST 2410001Y	ST 2410001Y	ST 2410001Y
Request Date	19/09/24	01/08/24	20/06/24	09/05/24	11/04/24	11/04/24	07/03/24	05/02/24	04/01/24
Collect Date	31/10/24 09:06	16/09/24 09:11	26/07/24 09:51	13/06/24 09:35	02/05/24 09:45	11/04/24 15:44	21/03/24 10:00	20/02/24 09:15	22/01/24 09:58
Arrive Date	31/10/24 09:58	16/09/24 10:46	26/07/24 10:53	13/06/24 10:11	02/05/24 10:41	11/04/24 17:05	21/03/24 10:34	20/02/24 10:19	22/01/24 11:15
Result	78 L unit ↓	85 L unit ↓	77 L unit ↓	78 L unit ↓	72 L unit ↓	75 L unit ↓	69 L unit ↓	85 L unit ↓	>90 unit
Reference Range	>90	>90	>90	>90	>90	>90	>90	>90	>90

CONCLUSION

- Although IgA nephropathy follows typical patterns of presentation, there are great variations which can range from isolated asymptomatic microscopic hematuria, gross hematuria, low-grade proteinuria, CKD, HT, to nephrotic syndrome, RPGN and AKI

- There are also distinct differences between patients from the East and the West
  - Epidemiology
  - Clinical course
  - Genetic risks and loci
  - Response to treatment

- **Unmet needs**
  - Is IgAN a different disease between Caucasians and Orientals
  - Should they be managed differently?
  - Lack of validated biomarkers to guide choice of treatment – precision medicine?

Thank You 谢谢

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