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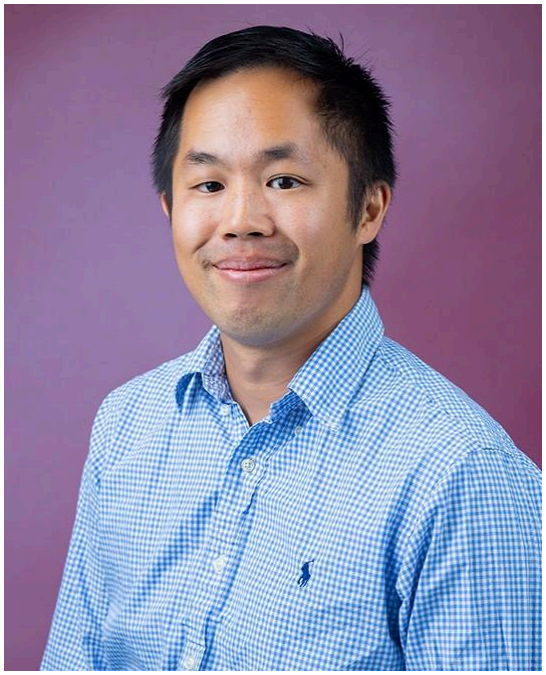
🧵Tweetorial Alert 🧵

1/
Hey #NephTwitter!
Welcome to a 🆕 #tweetorial #xtorial brought to you by @KIReports

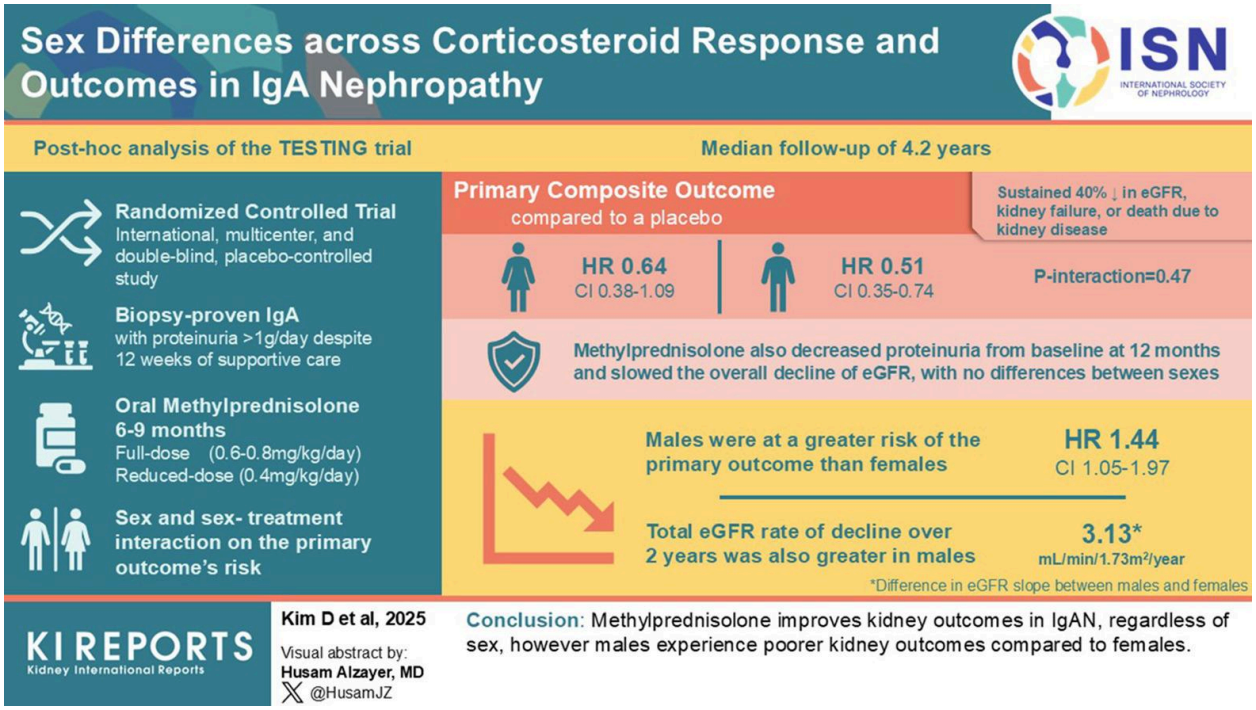
2/
Our author is Melvin @MChanMD (pediatric nephrologist)
Our topic: Sex Differences Across Corticosteroid Response and Outcomes in IgA Nephropathy

#MedTwitter #nephtwitter @ISNkidneycare #XTwitter



3/
There are no conflicts of interest. Please also check out #KIReportsCommunity educational #blogposts at https://www.kireportscommunity.org/. FOLLOW US at @KIReports for more expert #MedEd in #kidneydisease. #FOAMed @MedTweetorials

4/ Our #Tweetorial is based on a recent publication by Dr. Dana Kim and VA by @husamjz.bsky.social:
Sex Differences Across Corticosteroid Response and Outcomes in IgA Nephropathy
🔗https://www.sciencedirect.com/science/article/pii/S2468024925004851



5/ Intro

⚡ ⬆️ recognition that sex plays a role in predicting trajectory of CKD

⚡Traditionally, there is higher prevalence of CKD in ♀ whereas ♂ have more progressive CKD

⚡Little is known about how sex affects treatment responses in IgAN, specifically with steroids.

PMID: 32828189

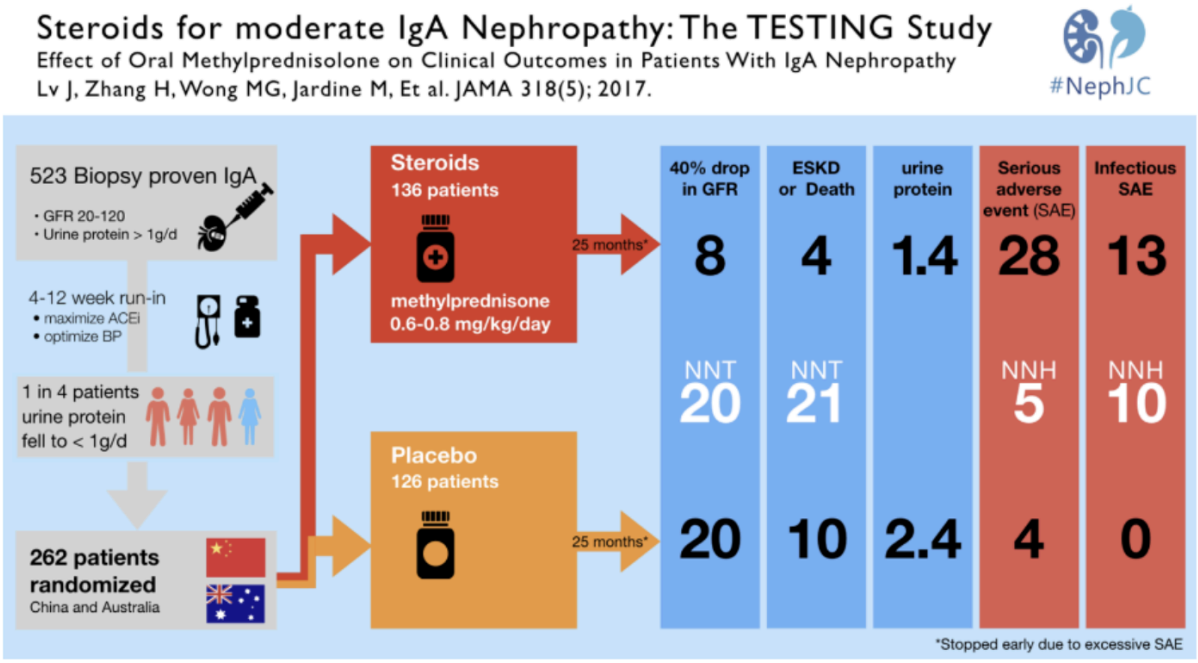
6/ Methods
🧱Post-hoc analysis of TESTING, which is a multi-site study (Australia, Canada, China, India, and Malaysia)

🎗️Inclusion: Biopsy proven IgAN with persistent proteinuria > 1g/day despite RAASi for minimum of 3 months, with eGFR >= 20mL/min/1.73m2

7/ Methods
🎗️Participants were randomized to 6-9 months of full dose or reduced dose of steroids

For a refresher 👉https://www.nephjc.com/news/2022/6/5/re-testing

🔭VA by @langoteamit.bsky.social



8/ Outcomes

🫘Primary Outcome: Major adverse kidney outcomes (40% reduction in eGFR from baseline, renal failure, or death from renal failure)

🫘Secondary Outcomes: ⏰ to renal failure, percentage change in proteinuria over 12 months, and eGFR 📉over 2 years

9/ Statistics

📌Treatment/Sex Interactions

👉Primary outcome via Cox hazard models*

👉Secondary outcome via mixed effect models*

*Models included interaction analysis via sex, treatment, & time; models adjusted for baseline data, including proteinuria, eGFR, endocapillary hypercellularity, & site

10/ Statistics

📌Kidney Outcomes

Primary Outcome: Kaplan Meier survival; confounders adjusted by Cox hazard models, including IgAN Risk Prediction Tool and baseline characteristics (age, Oxford score, proteinuria, eGFR, smoking, race, BMI, hypertension, systolic blood pressure)

11/ Clinical Characteristics

⚕ Significant differences include ♂ have higher levels of the following than ♀ : BMI, smoking, hypertension, systolic BPs, proteinuria, IFTAs

⚕ ♀ were older than ♂

Table 1. Baseline characteristics of participants in the TESTING trial by sex

Characteristics	Sex		*P*-Value
	Female (n = 198)	Male (n = 305)	
Randomized glucocorticoid dose, *n* (%)			0.23
Full dose	96 (48.5%)	166 (54.4%)	
Reduced dose	102 (51.5%)	139 (45.6%)	
Intervention, *n* (%)			0.95
Methylprednisolone	102 (51.5%)	155 (50.8%)	
Placebo	96 (48.5%)	150 (49.2%)	
Age, median (IQI), yr	37.6 (30.4–47.4)	35.1 (28.4–44.8)	0.02
Ethnicity, *n* (%)[a]			0.40
White	6 (3.0%)	19 (6.2%)	
Chinese	149 (75.3%)	230 (75.4%)	
South Asian	30 (15.2%)	33 (10.8%)	
South-East Asian	13 (6.6%)	20 (6.6%)	
Japanese	0 (0.0%)	1 (0.3%)	
Other Eastern Asian	0 (0.0%)	1 (0.3%)	
Mixed	0 (0.0%)	1 (0.3%)	
Body mass index, mean (SD), kg/m^2	24.5 (4.7)	25.3 (4.4)	0.05
Smoking history			< 0.001
Previous smoker	2 (1.0%)	64 (21.0%)	
Current smoker	1 (0.5%)	41 (13.4%)	
Medical history			
Macroscopic hematuria	35 (17.7%)	45 (14.8%)	0.38
Hypertension	83 (41.9%)	158 (51.8%)	0.03
Tonsillectomy	0 (0.0%)	3 (1.0%)	0.16
Previous corticosteroids	15 (7.6%)	13 (4.3%)	0.11
Previous other immunosuppressant	11 (5.6%)	18 (5.9%)	0.87
Family history of IgA nephropathy	6 (3.0%)	6 (2.0%)	0.45
Diabetes	8 (4.0%)	9 (3.0%)	0.51
Blood pressure, median (IQI), mmHg			
Systolic	122 (13.6)	126 (12.4)	0.007
Diastolic	79.7 (9.6)	81.0 (9.7)	0.03
Laboratory findings, median (IQI)			
Urine protein, g/d	1.9 (1.4–2.8)	2.1 (1.5–3.1)	0.05
eGFR, ml/min per 1.73 m^2	58.2 (42.0–75.7)	58.2 (43.4–77.4)	0.73
Time since kidney biopsy, median (IQI), mo	5.0 (3.0–13.0)	5.0 (4.0–12.5)	0.47
Histology on kidney biopsy, *n* (%)[b]			
M1	119 (62.0%)	176 (58.5%)	0.44
E1	49 (24.7%)	78 (25.6%)	0.83
S1	134 (69.8%)	202 (67.1%)	0.53
Tubular atrophy/interstitial fibrosis (T)			0.03
T0: 0%–25%	105 (54.7%)	136 (45.2%)	
T1: 26%–50%	70 (36.5%)	117 (38.9%)	
T2: > 50%	17 (8.9%)	48 (15.9%)	

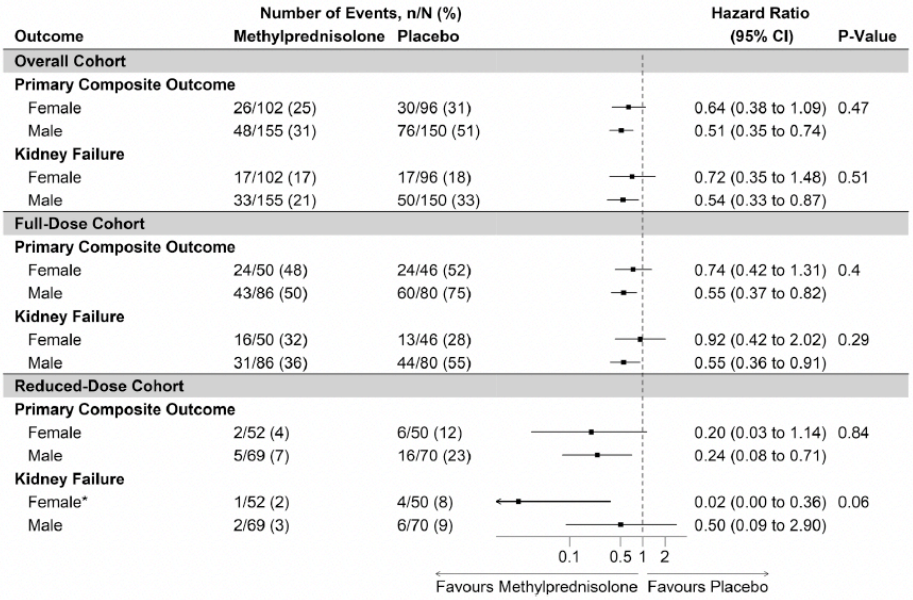
eGFR, estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration formula); IQI, interquartile interval.
[a]Ethnicity was self-reported by participants.
[b]Histological findings were scored as per the Oxford Classification MEST scoring system.
Normally distributed data are presented as mean (SD) and compared with *t* tests.
Nonnormally distributed data are expressed as median (IQI) and compared using Mann-Whitney U tests. Categorical data are presented as *n* (%) and compared using chi-square tests.

12/ Treatment Response by Sex

☝♂and ♀both appear to have non-significant improvements in composite primary outcome

☝♂had 59.4% and ♀a 47.2% reduction in proteinuria over 12 months

☝♂had an eGFR decline of 3.73mL/min/1.73m2/year vs 3.21 in ♀over 2 years



Outcome	Number of Events, n/N (%) Methylprednisolone	Placebo	Hazard Ratio (95% CI)	P-Value
Overall Cohort				
Primary Composite Outcome				
Female	26/102 (25)	30/96 (31)	0.64 (0.38 to 1.09)	0.47
Male	48/155 (31)	76/150 (51)	0.51 (0.35 to 0.74)	
Kidney Failure				
Female	17/102 (17)	17/96 (18)	0.72 (0.35 to 1.48)	0.51
Male	33/155 (21)	50/150 (33)	0.54 (0.33 to 0.87)	
Full-Dose Cohort				
Primary Composite Outcome				
Female	24/50 (48)	24/46 (52)	0.74 (0.42 to 1.31)	0.4
Male	43/86 (50)	60/80 (75)	0.55 (0.37 to 0.82)	
Kidney Failure				
Female	16/50 (32)	13/46 (28)	0.92 (0.42 to 2.02)	0.29
Male	31/86 (36)	44/80 (55)	0.55 (0.36 to 0.91)	
Reduced-Dose Cohort				
Primary Composite Outcome				
Female	2/52 (4)	6/50 (12)	0.20 (0.03 to 1.14)	0.84
Male	5/69 (7)	16/70 (23)	0.24 (0.08 to 0.71)	
Kidney Failure				
Female*	1/52 (2)	4/50 (8)	0.02 (0.00 to 0.36)	0.06
Male	2/69 (3)	6/70 (9)	0.50 (0.09 to 2.90)	

Figure 1. Effect of methylprednisolone compared with placebo on kidney outcomes in the TESTING trial by sex. Effect of methylprednisolone versus placebo on the primary composite outcome (40% eGFR decline, kidney failure, or death because of kidney disease) and kidney failure by sex subgroups for the overall TESTING cohort, and the full- and reduced-dose methylprednisolone cohorts. Hazard ratios obtained from a Cox proportional hazards model, with corresponding 95% confidence intervals and *P*-value for heterogeneity conducted using likelihood ratio test. *Lower limit of 95% confidence interval = 0.0008. eGFR, estimated glomerular filtration rate.

13/ Kidney Outcomes by Sex

☝♂had a 44% higher risk of primary outcome than ♀, even after adjusting for baseline covariates

☝♂had greater decline in eGFR than ♀when on full vs reduced dose steroid treatment

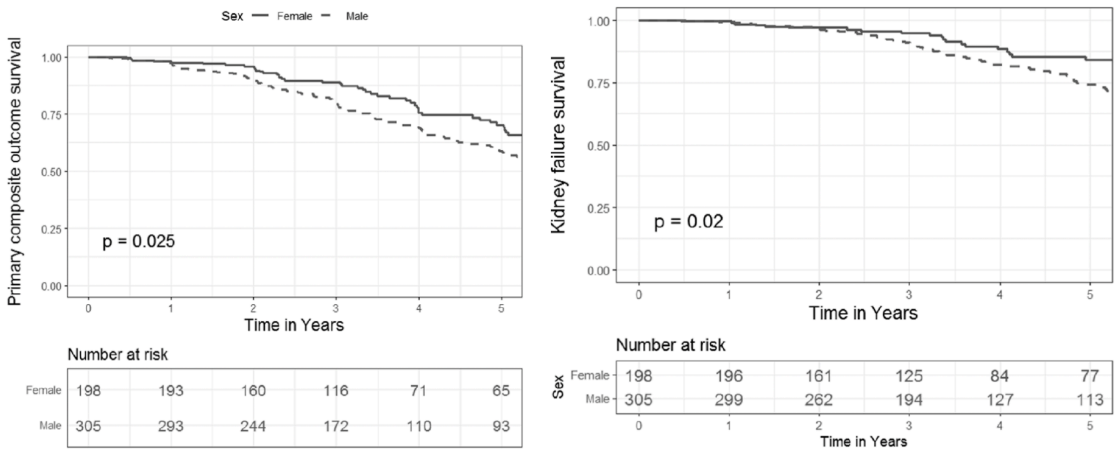


Figure 2. Kidney survival in the TESTING trial by sex. Kaplan-Meier curves for time to the primary composite outcome and kidney failures for males and females with corresponding log-rank *P*-values.

Total annual eGFR Slope, mL/min/1.73m2 per year (95% CI)

Cohort	Male	Female	Difference	P-Value
Overall	-3.08 (-4.50 to -1.67)	0.05 (-1.65 to 1.75)	3.13 (0.92 to 5.34)	0.006
Full-Dose	-4.51 (-6.34 to -2.68)	-2.28 (-4.63 to 0.06)	2.23 (-0.75 to 5.20)	0.140
Reduced-Dose	-1.67 (-3.79 to 0.45)	1.79 (-0.60 to 4.18)	3.46 (0.26 to 6.66)	0.030

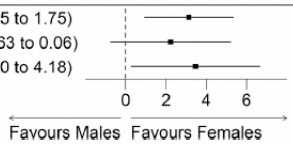


Figure 3. Difference in total eGFR slope over 2 years in IgA nephropathy by sex. The difference in total annualized eGFR slope over 2 years in males versus females in the overall TESTING cohort, and the reduced-dose and full-dose cohorts separately. A 2-slope, mixed-effects, linear spline model was used with an unstructured residual variance-covariance matrix and a knot at month 3. Fixed effects included treatment arm, baseline eGFR and baseline proteinuria. CI, confidence interval; eGFR, estimated glomerular filtration rate.

14/ Insights

🔑Steroids improve kidney outcomes (delays dialysis initiation, slows eGFR decline, reduces proteinuria) regardless of sex

🔑Males have higher likelihood of renal failure and steep eGFR decline

15/ Strengths

💪First to look at sex differences in treatment and outcomes

💪Large international data from largest steroid trial in IgAN

💪Comparable representation from females and males

16a/ Limitations

👎Small when cohort was split into female/male so unable to make broader conclusions

👎Post-hoc retrospective study rather than prospective

👎External validity

16b/ Limitations Continued

💡Large portion of this cohort is southeast Asian

💡Studies have shown that IgA in SE Asians tend to be more aggressive than Europeans and Africans

https://pubmed.ncbi.nlm.nih.gov/40975564/

17/ Now let's see if you have learned something!

Do you think sex makes a difference in IgAN? Feel free to write a commentary!
1. Yes
2. No
3. More data please!

18/ The topic remains controversial. We hope this #tweetorial has improved your knowledge on the effects of sex on IgAN. Please share this #tweetorial with your followers and friends! Thanks to @MChanMD for authoring & *** for great feedback! @ISNkidneycare @KIReports