Supplementary appendix

This supplementary appendix provides:

1. Search equation via PubMed, EMBASE, and Cochrane library
2. Quality assessment of the included studies.
3. Summary of the associated factors for adverse renal outcome.
4. Trial sequential analysis comparing patients with hematuria or not.
5. Subgroup analysis
6. Funnel plot
7. Publication bias assessed by Egger test and Begg test
8.Sensitivity analyses by omitting the studies with high risk of bias
9. Quality assessment of the GRADE results.
10. Summary of contextual factor data.
11. Meta-regression
12. PROSPERO protocol registration.

1.Supplementary material 1: Search strategy used in the current systematic review and meta-analysis

Keywords for researching and screening

Exposure

1. Hematuria [MeSH]
2. Haematuria [MeSH]
3. Urin* red blood cell
4. Urin* erythrocyte

Outcomes

5. Kidney disease [MeSH]
6. End-stage renal disease[MESH]
7. Chronic kidney disease [MeSH]
8. End?stage kidney disease
9. Renal?deterioration
10. Renal*
11. Disease?progress*
12. Outcome

Study designs

13. Cohort stud*
14. Cohort studies [MeSH]
15. Longitudinal stud*
16. Longitudinal studies [MeSH]
17. Follow?up

18. Follow-up studies [MeSH]
19. Population stud*
20. Population-based stud*

limit
21. Article or article in press
22. 2010.1.1-2022.12.20

Not
23. Animal$
24. Reviews
25. Correspondence
26. Case reports
27. Expert opinions
28. Editorials

***PUBMED* Web of Sci EMBASE**

#1
(hematuria [MeSH]) OR (haematuria [MeSH]) OR (urin* red blood cell [Title/Abstract]
) OR (urin* erythrocyte [Title/Abstract])

#2
(kidney disease [MeSH]) OR (chronic kidney disease [MeSH]) OR (end-stage renal disease [MESH]) OR (end?stage kidney disease [Title/Abstract]) OR (renal?deterioration [Title/Abstract]) OR (renal* [Title/Abstract]) OR (disease?progress* [Title/Abstract]) OR (outcome [Title/Abstract])

#3
(cohort studies[MeSH Terms]) OR (longitudinal studies[MeSH Terms]) OR (follow up studies[MeSH Terms]) OR (cohort stud*[Title/Abstract]) OR (longitudinal stud*[Title/Abstract]) OR (population stud*[Title/Abstract]) OR (population-based stud*[Title/Abstract]) OR (follow?up[Title/Abstract])

#4

(“journal article” [Publication Type])

#5

(animal$ [Title/Abstract])

#1 and #2 and #3 and #4 NOT #5

Year: 2010.01.01-2022.12.20

Language: English

Species: humans

N=695

Web of Sci

#1

(TS=(hematuria) or TS=(haematuria) or TS=(urin* red blood cell) or TS=(urin* erythrocyte)

and

(TS=(kidney disease) or TS=(chronic kidney disease) or TS=(end-stage renal disease) or TS=(end?stage kidney disease) or TS=(renal?deterioration) or TS=(renal*) or TS=(outcome) or TS=(disease?progress*)

and

(TS=(cohort stud*) or TS=(longitudinal stud*) or TS=(population stud*) or TS=(population-based stud*) or TS=(follow?up*)

#1 AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article) AND Time: (2010-2022)

n=2006

EMBASE

#1

hematuria/ or haematuria or urin*red blood cell.mp. or urin*erythrocyte.mp.

#2

kidney disease.mp. or chronic kidney disease.mp. or end-stage renal disease.mp. or end?stage kidney disease.mp. or renal?deterioration.mp. or renal*.mp. or renal*.mp. or disease?progress*.mp. or outcome.mp.

#3

exp cohort analysis/ or exp Longitudinal study/ or exp population research/ or population-based study.mp. or exp follow up

#4

1 and 2 and 3

#5 limit 4 to (human and English language and yr="2010 - 2022" and (article or article in press)

N=4031

2.Supplementary material S2: Table S1.NOS scores for each of the included articles

First author (year of publishment)	Selection					Comparability		Outcomes				Total score	Risk of bias in total	Associated Factors
Item number of NOS	1	2	3	4	Risk of bias	5	Risk of bias	6	7	8	Risk of bias			
Bjørneklett（2011）	1	1	0	1	Low	0	Median	1	1	1	Low	6	Low	
Baek（2012）	1	1	1	1	Low	0	Median	1	1	1	Low	7	Low	macroalbuminuria, microalbuminuria, hypertension, diabetes
Lin（2015）	1	1	1	1	Low	0	Median	1	0	1	Low	6	Median	
Lv（2017）	0	1	1	1	Low	0	Median	1	0	1	Low	5	Median	
Mashitani（2017）	1	1	1	1	Low	0	Median	1	1	1	Low	7	Low	
Orlandi（2018）	1	1	1	1	Median	0	Median	1	0	1	Low	6	Median	following period
Lin（2018）	1	1	1	1	Low	0	Median	1	1	1	Low	7	Low	
Bobart（2019）	0	1	1	1	Median	1	Low	1	0	1	Median	6	Median	time, estimated proteinuria, MEST-C score, RASB, immunosuppression
Vandenbussche（2019）	0	1	1	1	Median	0	Median	1	0	1	Low	5	High	
Wu (2012)	1	1	1	1	Low	0	Median	1	0	0	Median	5	High	eGFR < 60 ml/min/1.73 m^2
Okada (2020)	1	1	0	1	Low	0	Median	1	0	1	Low	5	High	men, proteinuria ≥0.5 g/day and sbp⩾132 mm Hg
Precil（2020）	0	1	1	1	Median	0	Median	1	1	1	Low	6	Low	
Yoshida (2020)	1	1	1	1	Low	0	Low	1	1	0	Low	6	Low	without albuminuria
Okada (2020)	1	1	0	1	Low	0	Median	0	1	0	Low	4	High	men, proteinuria ≥0.5 g/day and sbp⩾132 mm Hg
Yoshida (2020)	1	1	1	1	Low	0	Low	1	0	0	Low	6	High	
Fogh (2021)	1	1	1	1	Low	1	Low	1	1	1	Low	8	Low	age, type of hospital care, comorbidity, hematuria type
He（2021）	1	1	1	1	Low	1	Low	1	0	1	Low	6	Median	

Ebbestad (2022)	1	1	1	1	Low	0	Median	1	1	0	Low	6	Median	
Sevillano (2017)	1	1	1	1	Median	1	Low	1	1	1	Low	7	Low	TA-P
														age, renal function at baseline IS treatment
Yu (2020)	1	1	1	1	Median	1	Low	1	1	1	Low	7	Low	
Weng（2022）	1	1	1	1	Low	0	Median	1	0	1	Median	6	Median	

Abbreviations: MEST-C, M：Mesangial hypercellularity; E：Endocapillary hypercellularity; S：Segmental glomerulosclerosis; T：Tubular atrophy/ interstitial fibrosis; C：Cellular or fibrocellular crescents; eGFR, Estimated glomerular filtration rate; RASB：Renin–angiotensin–system blockers; SBP：Systolic Blood Pressure; IS：immunosuppression

Table S1.NOS scores for each of the included articles

3.Supplementary material S3: Table S2. Summary of the associated factors of included studies.

Associated factors	**Risk Ratio (95%CI)**	**Study**
Sociodemographic factors		
Gender		
Female		
	1.38 (0.97–1.96), p = 0.151	Lin (2015)
	1.39 (0.96–2.01), p = 0.151	Lin (2018)
	1.14 (0.570–2.281), p = 0.711	Wu (2020)
	1.16 (0.52-2.59), p=0.100	Okada (2020)
	2.57 (2.25–2.93)	Fogh (2021)
Male		
	0.90 (0.67–1.21), p=0.482	Baek (2012)
	1.38 (0.97–1.96), p = 0.151	Lin (2015)
	1.25 (0.45-3.46), p=0.670	Lv (2017)
	1.39 (0.96–2.01), p = 0.151	Lin (2018)
	2.008 (1.15–3.50), p < 0.001	Wu (2020)

	2.14 (1.21-3.78), p=0.100	Okada (2020)
	2.29 (2.12–2.48)	Fogh (2021)
	0.89 (0.360–2.185), p=0.794	Weng (2022)
Age		
	0.99 (0.98–1.00), p=0.200	Baek (2012)
<65 years old	1.73 (1.25-2.39), p=0.016	Lin (2015)
⩾65 years old	0.71 (0.44-1.14), p=0.016	
	1.31 (0.87-1.96), p=0.190	Lv (2017)
<65 years old	1.31 (0.96-1.80), p=0.190	Lin (2018)
⩾65 years old	1.25 (0.86-1.82), p=0.125	
per year	1.038 (0.996-1.081), p=0.078	Bobart (2019)
<59 years old	1.79 (0.87-3.65), p=0.700	Okada (2020)
⩾59 years old	1.59 (0.83-3.02), p=0.700	
	0.982 (0.938–1.026), p=0.436	Weng (2022)
	1.02 (1.01-1.05), p=0.050	Sevillano (2017)
Body Mass Index		
	2.01 (1.20–3.35), p=0.009	Baek (2012)
< 25 kg/m^2	1.93 (1.30–2.86), p=0.531	Lin (2015)
>25 kg/m^2	1.14 (0.84–1.54), p=0.531	Lin (2015)
< 25 kg/m^2	1.08 (0.83–1.68), p=0.163	Lin (2018)
>25 kg/m^2	1.67 (1.22–2.30), p=0.163	Lin (2018)
⩾23.6 kg/m^2	1.60(0.88-2.92), p=0.4	Okada (2020)
<23.6 kg/m^2	1.75 (0.80-3.83), p=0.4	Okada (2020)
Clinical factors		
Hypertension		
	2.01 (1.03–3.93), p=0.041	Baek (2012)

	1.40(0.50-3.91), p=0.52	Lv (2017)
	1.55(1.36-1.76)	Fogh (2021)
	0.292 (0.116–0.731), p=0.009	Weng (2022)
Cardiovascular disease (CVD)		
	1.65 (0.93–2.94), p=0.088	Baek (2012)
Without CVD	1.39 (1.05–1.85), p=0.289	Lin (2015)
With CVD	0.97 (0.49–1.90) p=0.289	Lin (2015)
	1.81(0.56-5.93), p=0.33	Lv (2017)
Without CVD	1.51 (1.13–2.01), p=0.234	Lin (2018)
With CVD	1.29 (0.84–1.99) p=0.234	Lin (2018)
Diabetes mellitus		
	1.48 (1.04–2.10), p=0.029	Baek (2012)
	0.38 (0.07-2.00), p=0.25	Lv (2017)
	1.68 (1.44–1.91)	Fogh (2021)
Proteinuria		
0.5-1.0 (g/24 h)	0.49 (0.09-2.81), p=0.43	Lv (2017)
>1.0 (g/24 h)	1.56 (0.51-4.73), p=0.44	Lv (2017)
per 0.5 g	1.375 (1.154-1.639), p<0.001	Bobart (2019)
⩾0.5g/24h	1.85 (1.12-3.04), p=0.03	Okada (2020)
<0.5 g/24h	0.36 (0.04-3.09), p=0.03	Okada (2020)
Albuminuria		
Microalbuminuria	2.86 (1.50–5.44), p=0.001	Baek (2012)
Macroalbuminuria	3.87 (2.46–6.06), p< 0.001	Baek (2012)
Without albuminuria	0.99 (0.62–1.57), p < 0.001	Yoshida (2020)
With albuminuria	1.14 (0.76–1.70), p < 0.001	Yoshida (2020)
eGFR		

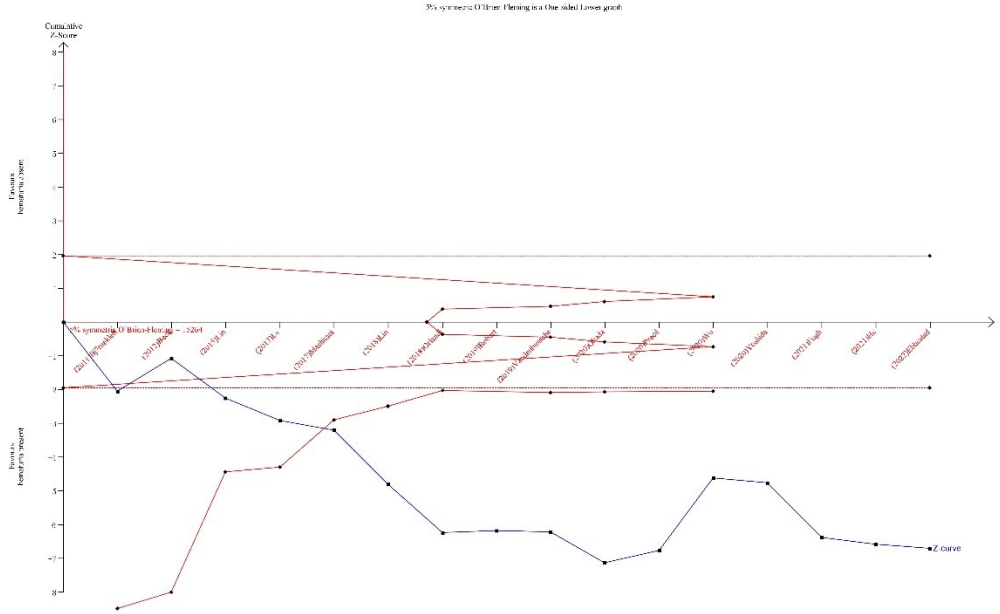
per 10 mL/min/1.73 m^2	0.294 (0.127-0.680)	
≥ 60 ml/min/1.73m^2	4.395 (1.998–9.668), p=0.014	
	0.961 (0.946–0.977), p< 0.001	Weng (2022)
Blood pressure		
Systolic blood pressure		
per 10 mmHg	1.726 (1.294-2.303), p<0.001	Bobart (2019)
	1.01 (1.01-1.02), p=0.02	Sevillano (2017)
>140mmHg	1.58 (1.16-2.16), p=0.359	Lin (2018)
<140mmHg	1.19 (0.82-1.72), p=0.359	Lin (2018)
⩾132mmHg	2.08 (1.15-3.76), p=0.07	Okada (2020)
<132mmHg	0.85 (0.35-2.05), p=0.07	Okada (2020)
Diastolic blood pressure		
per 10 mmHg	0.928 (0.480-1.796), p=0.83	Bobart (2019)
	1.01 (1-1.03),p=0.03	Sevillano (2017)
Histology at biopsy (IgAN)		
M (1 versus 0)		
	1.368 (0.171-10.971), p=0.77	Bobart (2019)
	0.667 (0.252–1.764), p=0.414	Weng (2022)
	2.67 (1.11-6.45), p=0.030	Sevillano (2017)
E (1 versus 0)		
	0.761 (0.158-3.768), p=0.73	Bobart (2019)
	1.342 (0.545–3.305), p=0.522	Weng (2022)
	2.16 (0.62-7.43), p=0.220	Sevillano (2017)
S (1 versus 0)		
	4.643 (0.578-37.287), p=0.15	Bobart (2019)
	3.674 (0.847–15.929), p=0.082	Weng (2022)

	2.45 (0.98 to 6.09), p=0.06	Sevillano (2017)
T (≥1 versus 0)		
	12.208 (1.525-97.707), p=0.018	Bobart (2019)
	12.676 (4.690–34.260), p< 0.001	Weng (2022)
	5.550 (2.29-13.33), p=0.030	Sevillano (2017)
Microscopic hematuria		
	1.90 (1.56–2.31)	Fogh (2021)
	1.001 (1.000–1.001), p=0.003	Weng (2022)
	1.37 (1.08–1.74), p=0.009	He (2021)
Macroscopic hematuria	2.55(2.16–3.01)	Fogh (2021)
	0.285 (0.083–0.981), p=0.047	Weng (2022)
Albumin		
	0.79 (0.65-0.96), p=0.019	Baek (2012)
<3.5 g/dL	1.30 (0.77–2.19), p=0.896	Lin (2015)
>3.5 g/dL	1.41 (1.03–1.94), p=0.896	Lin (2015)
<3.5 g/dL	1.21 (0.88–1.67), p=0.062	Lin (2018)
>3.5 g/dL	1.79 (1.25–2.56), p=0.062	Lin (2018)
	0.954 (0.904–1.007), p=0.086	Weng (2022)
Hemoglobin (HGB)		
	0.86 (0.80–0.92), p< 0.001	Baek (2012)
	0.960 (0.937–0.983), p=0.001	Weng (2022)
HGB<10g/dL	2.20 (1.27–3.80), p=0.013	Lin (2015)
HGB>10g/dL	1.09 (0.80–1.47), p=0.013	Lin (2015)
HGB<10g/dL	1.75 (1.13–2.72), p=0.012	Lin (2018)
HGB>10g/dL	1.19 (0.89–1.58), p=0.012	Lin (2018)

Time-averaged hematuria (TA-H)		
	1.002 (1.001–1.003) p<0.001	Weng (2022)
	4.210 (1.66–10.64) p=0.02	Sevillano (2017)
	1.510 (1.27–1.80) p<0.001	Yu (2020)
	1.450 (1.23–1.69) p< 0.001	He (2021)
Urine protein-to-creatinine ratio (UPCR)		
< 0.5	4.19 (1.44–12.2), p=0.048	Lin (2015)
0.5-1.5	0.86 (0.51–1.46), p=0.048	Lin (2015)
>1.5	1.25 (0.94–1.65), p=0.048	Lin (2015)
< 0.5	4.41 (1.17–16.7), p=0.048	Lin (2018)
0.5-1.5	1.16 (0.87–1.72), p=0.048	Lin (2018)
>1.5	1.32 (0.91–1.91), p=0.048	Lin (2018)
C-reactive protein (CRP)		
<3 mg/L	1.24 (0.86–1.80), p=0.701	Lin (2015)
>3 mg/L	1.63 (1.19–2.23), p=0.701	Lin (2015)
<3 mg/L	1.78 (1.28–2.49), p=0.163	Lin (2018)
>3 mg/L	1.20 (0.85–1.68), p=0.163	Lin (2018)

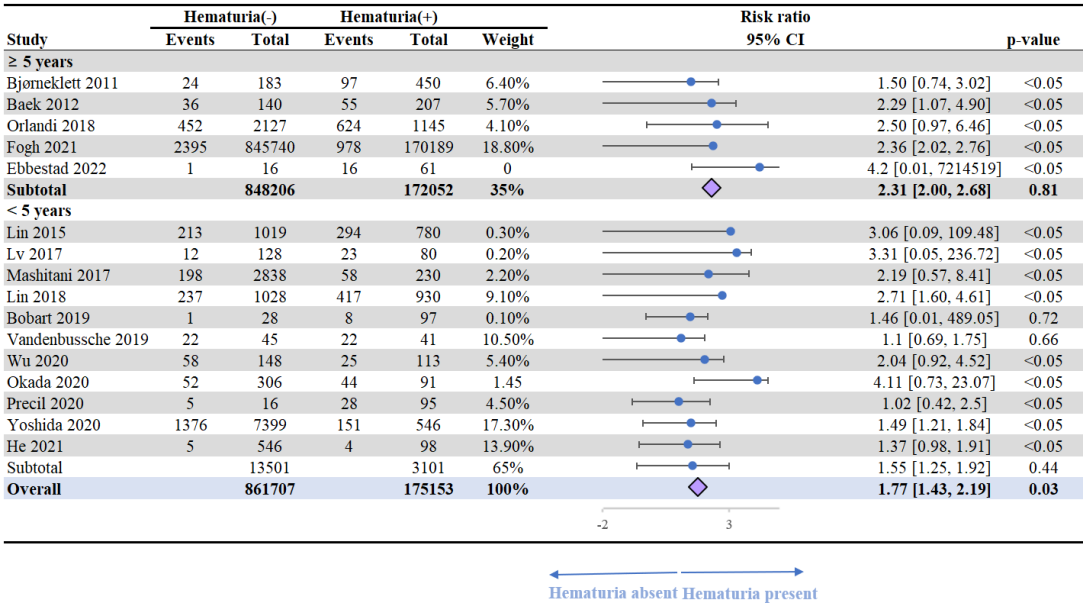
Table S2. Summary of the associated factors of included studies.

5.Supplementary material S4: Trial sequential analysis comparing patients with hematuria or without hematuria

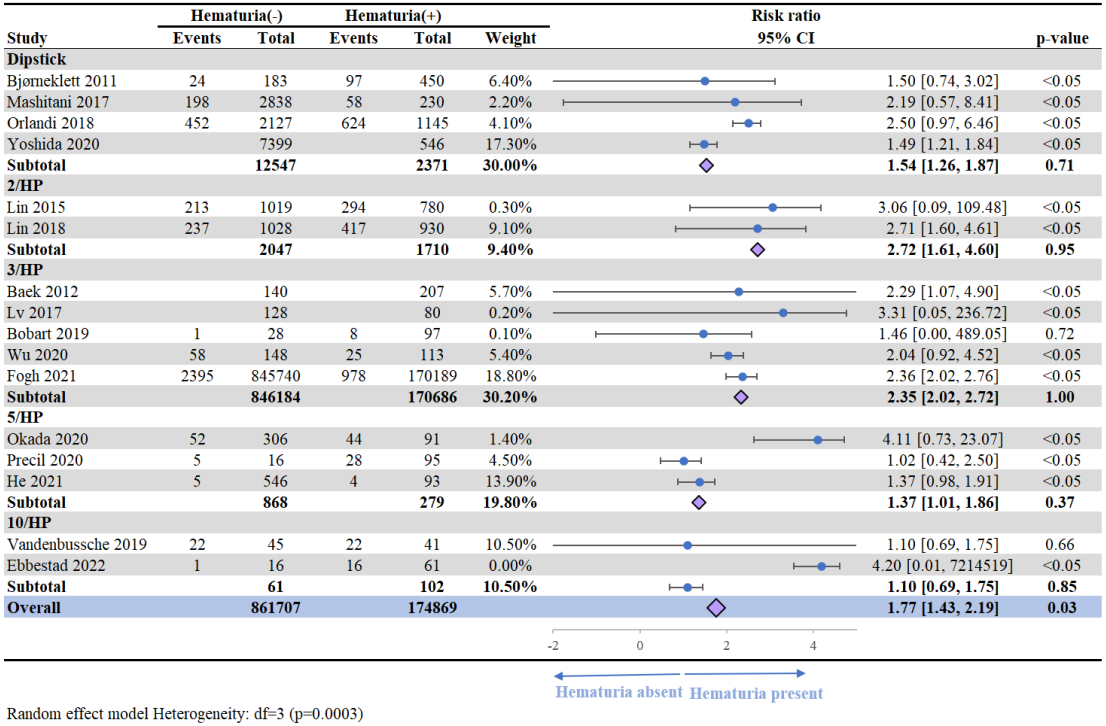


Supplementary Figure S1. The TSA demonstrated that the adverse renal outcome has been consistently higher in patients with hematuria compared to that of those without.

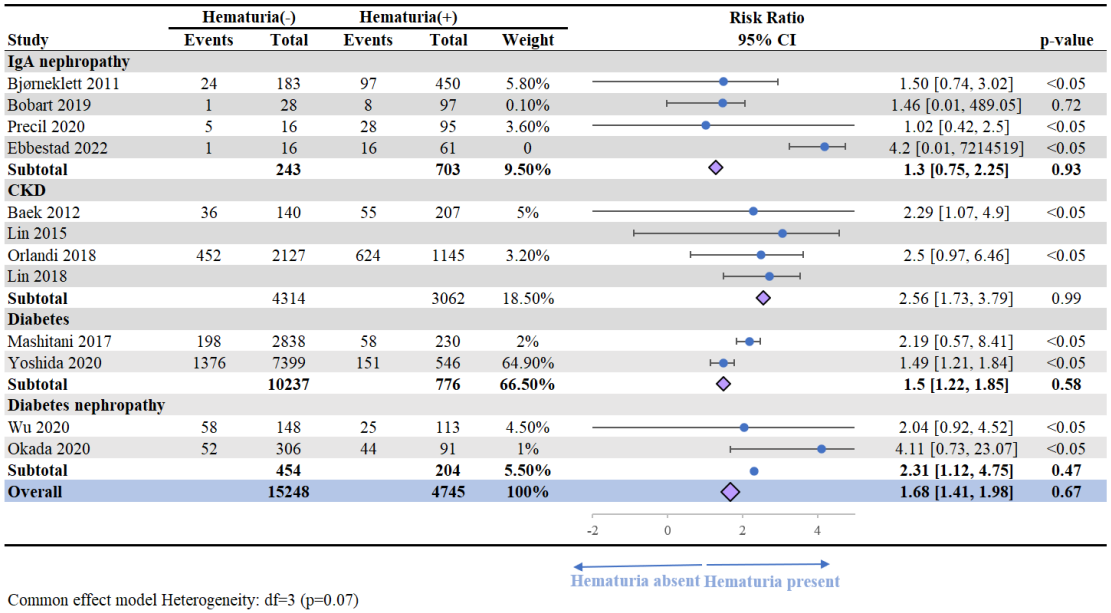
5.Supplementary material S5: Subgroup analysis



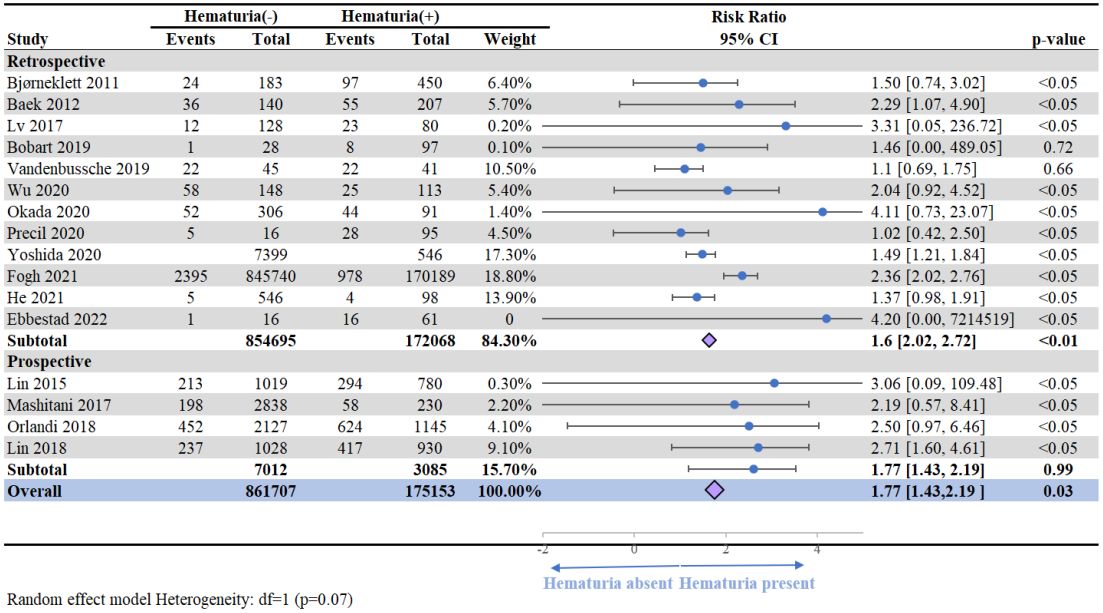
Supplementary Figure S2a. Forest plots depicting adverse renal outcome comparing hematuria group versus the non-hematuria group by following up period.



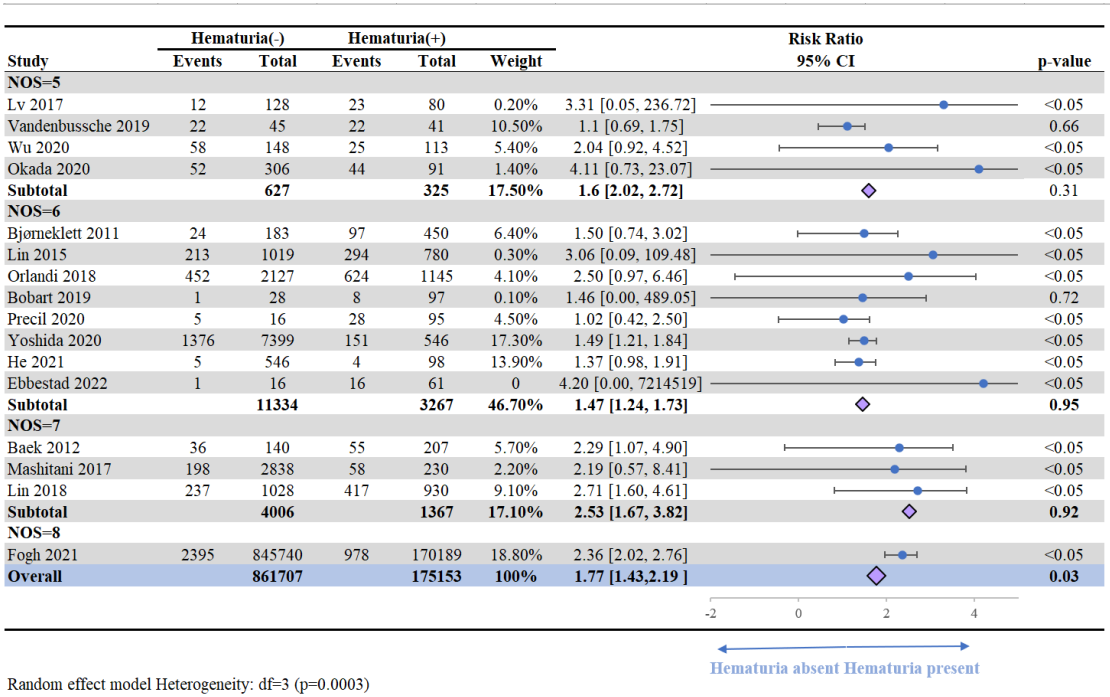
Supplementary Figure S2b. Forest plots depicting adverse renal outcome comparing hematuria group versus the non-hematuria group by hematuria measurement.



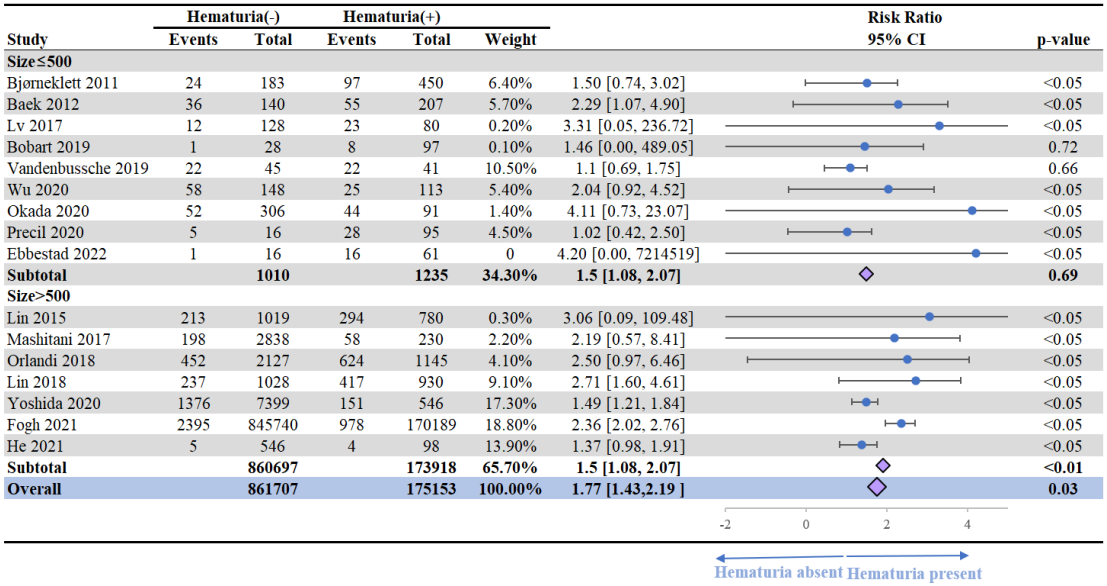
Supplementary Figure S2c. Forest plots depicting adverse renal outcome comparing hematuria group versus the non-hematuria group by setting.



Supplementary Figure S2d. Forest plots depicting adverse renal outcome comparing hematuria group versus the non-hematuria group by study design.

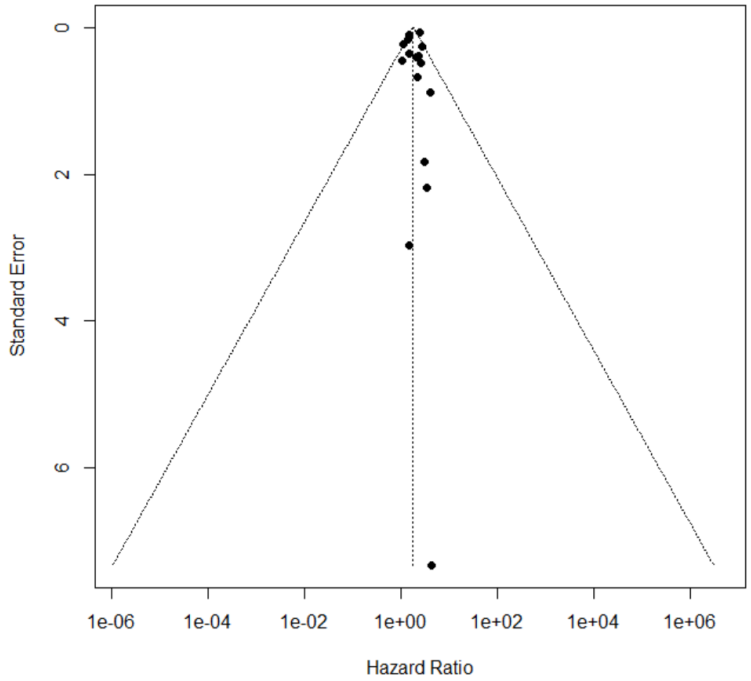


Supplementary Figure S2e. Forest plots depicting adverse renal outcome comparing hematuria group versus the non-hematuria group by NOS.



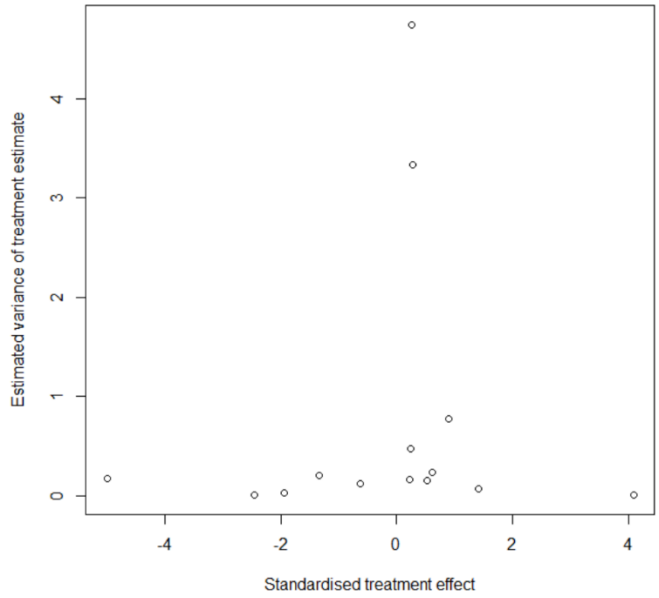
Supplementary Figure S2f. Forest plots depicting adverse renal outcome comparing hematuria group versus the non-hematuria group by size.

6.Supplementary Figure S3: Funnel plot

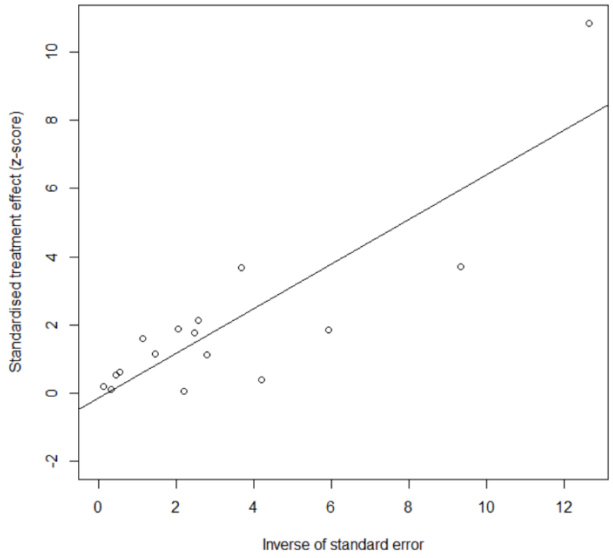


Supplementary Figure S3a. The funnel plot showed no publication bias on the risk of adverse renal outcome by pooling the hazard ratios.

7.Supplementary material S4: Publication bias assessed by Begg's test and Egger test

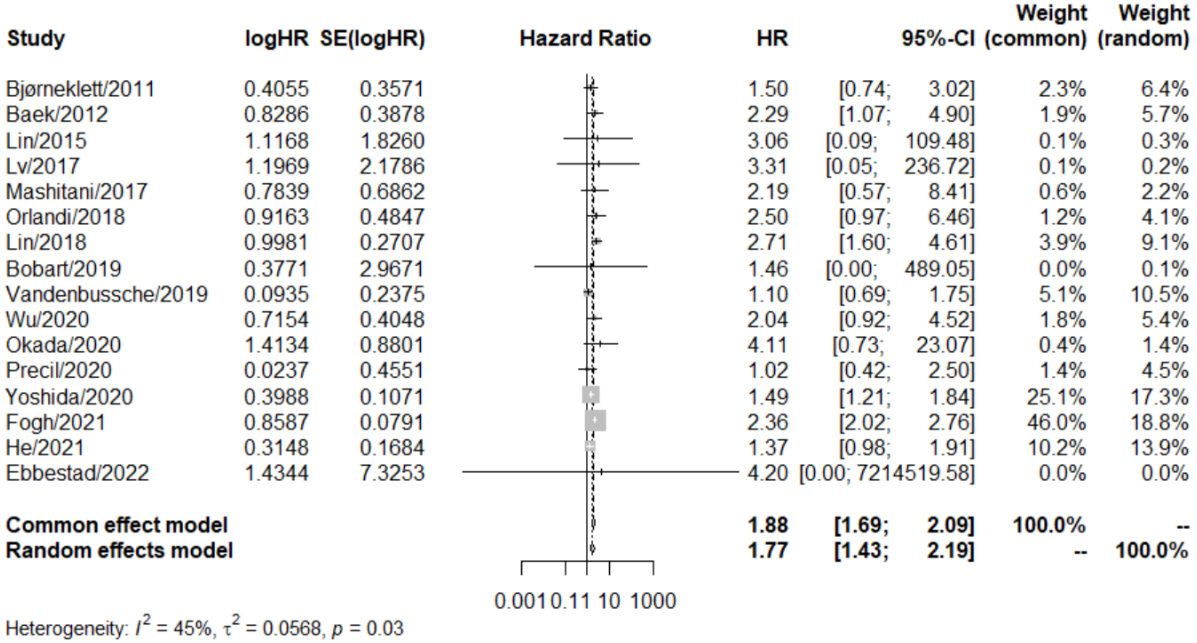


Supplementary Figure S4a. Begg's plot of included studies



Supplementary Figure S4b. Eagger test of included studies

8. Supplementary material S5: Sensitivity analyses by omitting the studies with high risk of bias



Supplementary Figure S5. Sensitivity analyses by omitting the studies with high risk of bias.

9. Supplementary material S6: Table S3. Quality assessment the GRADE results of hematuria at baseline.

Summary of findings:

Hematuria compared to non-hematuria for adverse renal outcome

Setting:

Intervention: hematuria at baseline

Comparison: no hematuria at baseline

№ of patients		Effect		Certainty	Importance
hematuria present	hematuria absent	Relative (95% CI)	Absolute (95% CI)		
2844/175153 (1.6%)	5087/861707 (0.6%)	**RR 1.77** (1.43 to 2.19)	**13 more per 1,000** (from 7 more to 19 more)	⊕⊕⊕◯ Moderate	IMPORTANT

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group **and the relative effect** of the intervention (and its 95% CI)

CI: confidence interval; **RR:** risk ratio

GRADE Working grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.is a possibility that it is substantially different.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table S3. Quality assessment the GRADE results of hematuria at baseline.

Table S4. Quality assessment the GRADE results of hematuria remission.

Summary of findings:

Hematuria remission compared to hematuria permission for adverse renal outcome

Setting:

Intervention: hematuria remission

Comparison: hematuria permission

№ of patients		Effect		Certainty	Importance
hematuria remission	hematuria permission	Relative (95% CI)	Absolute (95% CI)		
86/921 (9.3%)	234/1315 (17.8%)	**RR 0.37** (0.24 to 0.55)	**108 fewer per 1,000 (from 132 fewer to 76 fewer)**	⨁⨁◯◯ Low	IMPORTANT

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group **and the relative effect** of the intervention (and its 95% CI)

CI: confidence interval; **RR:** risk ratio

GRADE Working grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.is a possibility that it is substantially different.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table S4. Quality assessment the GRADE results of hematuria remission.

10.Supplementary Material S7: Summary of contextual factor data

In the study, we included a total of 20 cohort studies, and 1,047,171 participants were analyzed. In the part of baseline hematuria, Bjørneklett (2011) et al. tested the applicability of the Japanese model in predicting 10- to 20-year risk of ESRD and all-cause mortality in a cohort of 633 Norwegian IgAN patients who were known to have hematuria bouts or not. Patients with hematuria measured by dipstick had significantly worse prognosis (the measured risk of ESRD) than patients without hematuria (RR (risk ratio) 1.5, 95% CI (confidence interval) 1.0−2.4, $p<0.05$).

Baek (2012) et al. conducted a retrospective cohort study and followed up for at least 10 years of 347 patients diagnosed with stage 3 CKD. Outcomes included progression to stage 4 or 5 over a 10-year period. Progression of chronic kidney disease were more severe for patients with microscopic hematuria (RR 2.29, 95% CI 1.65−3.17, $p<0.001$).

Lin (2015) et al. included 3303 patients with stage 3–5 nondiabetic CKD in the prospective study. Microscopic hematuria in patients with stage 3–5 nondiabetic CKD is associated with increased risks of ESRD (RR 3.06, 95% CI 1.13−8.28, $P < 0.05$).

Lv (2017) et al. retrospectively analyzed the long-term outcomes of enrolled 208 AAV patients with persistent hematuria during clinical remission (stabilization or decrease of the serum creatinine concentration, concurrent with gradual tapering of immunosuppressive medications), had a significantly higher risk of ESRD (RR 3.31, 95% CI 1.13−9.67, $P < 0.05$) compared with patients without hematuria.

Mashitani (2017) et al. included 3068 patients with type 2 diabetes and there was significantly higher incidence of ESRD (RR 2.19, 95% CI 1.22−3.91, $P < 0.05$) among patients with dipstick hematuria.

Orlandi (2018) conducted a prospective cohort study involving 3272 CKD patients (eGFR of 20 to 70 ml/min/1.73m^2 at baseline). Individuals with hematuria had a greater risk for ESRD (RR 2.50, 95% CI 1.73−3.63, $P < 0.05$) in the first 2 years of follow-up but did not improve risk prediction.

Lin (2018) et al. had 1799 stage 3-5 CKD patients included in prospective research. Hematuria was significantly associated with an increased risk (RR 2.71, 95% CI 2.23−3.30, $P < 0.05$) of end-stage renal disease.

Bobart (2020) et al. enrolled 125 patients with IgA nephropathy. An increase in the degree of microhematuria was significantly associated with an eGFR decline of -0.81 mL/min/1.73 m^2 (RR 2.71, 95% CI -1.44 to -0.19, P=0.01), after adjusting for follow-up time, proteinuria and T score. However, baseline microhematuria was not found to be significantly associated with ESRD (RR 1.458, 95% CI 0.18−11.811, P =0.72).

Vandenbussche (2019) et al. had 78 patients with histologically proven PIGN who presented a first renal flare of AAV in remission after conventional induction treatment with corticosteroids and cyclophosphamide and/or rituximab. Patients in hematuria group were more likely to develop ESRD than in the other groups (RR 1.10, 95% CI 0.73−1.66, P =0.66).

Wu (2020) et al. had 261 patients with diabetic nephropathy included. The hematuria (+) group showed higher risk for progressing to ESRD (RR 2.05, 95% CI 1.40−2.99, $P < 0.05$).

Okada (2020) et al. recruited 397 patients with diabetic nephropathy. Microscopic hematuria is a risk factor for ESRD in diabetic nephropathy, independent of proteinuria and renal pathology (RR 4.11, 95% CI 2.73−6.18, P < 0.05).

Precil (2020) et al. enrolled 111 patients with IgA nephropathy. Patients with hematuria had higher possibility of ESRD (RR 1.02, 95% CI 0.47−2.25, P < 0.05).

Yoshida (2020) et al. had 7945 patients with type 2 diabetes and there was significantly higher possibility of faster decline in kidney function but not higher risk of development or progression of albuminuria (RR 1.49, 95% CI 1.30−1.72, P < 0.05).

Fogh (2021) et al. had 1,015,929 patients with a hospital-based hematuria diagnosis and no apparent underlying cause included in their study to assess the long-term risk of ESRD. 170,189 patients in hematuria group show higher possibility of ESRD (RR 2.36, 95% CI 2.21−2.52, P < 0.05). Hematuria also increased the risk of ESRD in patients with pre-existing comorbidities like diabetes (adjusted RR: 1.3 [95%CI: 1.1–1.5]) and urogenital cancer (adjusted RR: 1.4, 95%CI: 1.1–1.9), whereas no association was observed in patients with previous kidney disease (adjusted HR: 0.9, 95%CI: 0.8–1.0).

He (2021) et al. enrolled 644 patients with primary membranous nephropathy into their initial hematuria prognosis study. Hematuria group increased the risk of ESRD (RR 1.37, 95% CI 1.08−1.74, P < 0.05).

Ebbestad (2021) et al. included 77 patients with IgA nephropathy from the IgAN-RPT cohort and there was no statistical significance in the risk of ESRD between hematuria group and non-hematuria group (RR 4.20, 95% CI 0.60−29.32, P =0.086).

In the part of hematuria remission, Sevillano (2017) et al. included 112 patients with renal biopsy–proven IgAN. Patients were divided in two groups according to the magnitude of TA-hematuria. They found patients in hematuria remission group had lower incidence of ESRD (RR 0.382, 95% CI 0.242−0.603, P <0.05).

Yu (2020) et al. enrolled 1333 patients with IgA patients and showed hematuria remission is associated with a lower incidence of ESRD (RR 0.245, 95% CI 0.058−1.038, P <0.05).

He (2021) et al. had 639 patients with primary membranous nephropathy and there was less likely to develop ESRD in hematuria remission group (RR 0.61, 95% CI 0.4−0.93, P =0.001).

Weng (2022) et al. had 152 patients with IgA nephropathy and there showed lower incidences of ESRD in hematuria remission group (RR 0.264, 95% CI 0.062−1.126, P <0.05).

11.Supplementary Material S8: List of excluded

Ineligible population (n= 11)

1. Bellincioni C, Garigali G, Fogazzi GB. Glomerular isolated microscopic hematuria: urinary features and long term follow-up of a selected cohort of patients. J Nephrol. 2019 Apr;32(2):253-258. doi:10.1007/s40620-018-0560-9. (Classification of hematuria as persistent isolated microscopic hematuria and intermittent isolated microscopic

hematuria)

2. Vivante A, Afek A, Frenkel-Nir Y, Tzur D, Farfel A, Golan E, Chaiter Y, Shohat T, Skorecki K, Calderon-Margalit R. Persistent asymptomatic isolated microscopic hematuria in Israeli adolescents and young adults and risk for end-stage renal disease. JAMA. 2011 Aug 17;306(7):729-36. doi: 10.1001/jama.2011.1141. (Specific participants of 1203626 persons aged 16 through 25 years (60% male) examined for fitness for military service between 1975 and 1997)

3. Ishida M, Matsuzaki K, Suzuki H, Suzuki Y, Kawamura T, Marunaka Y, Iwami T. Association between 3-Year Repetitive Isolated Hematuria and eGFR Deterioration in an Apparently Healthy Population: A Retrospective Cohort Study. Int J Environ Res Public Health. 2022 Sep 12;19(18):11466. doi: 10.3390/ijerph191811466. (Classification the study participants into two groups as per the consistency of hematuria; three or more consecutive hematuria vs. the others)

4. Nakagawa K, Tanaka S, Tsuruya K, Kitazono T, Nakano T. Association between microscopic hematuria and albuminuria in patients with chronic kidney disease caused by diabetes and hypertension: the Fukuoka Kidney disease Registry Study. Clin Exp Nephrol. 2023 Mar;27(3):227-235. doi: 10.1007/s10157-022-02298-7. (Patients were divided into three groups according to erythrocyte count in urine sediment [T1: < 5/high power feld (HPF); T2: 5–9/HPF; T3: ≥ 10/HPF].)

5. Yuste C, Rubio-Navarro A, Barraca D, Aragoncillo I, Vega A, Abad S, Santos A, Macias N, Mahillo I, Gutiérrez E, Praga M, Egido J, López-Gómez JM, Moreno JA. Haematuria increases progression of advanced proteinuric kidney disease. PLoS One. 2015 May 27;10(5):e0128575. doi: 10.1371/journal.pone.0128575. (Patients were categorized in 2 groups according to the presence of hematuria. Patients were considered hemoproteinuric (HP) when presented both hematuria and proteinuria, whereas proteinuric patients (P) presented proteinuria alone.)

6. Le W, Liang S, Chen H, Wang S, Zhang W, Wang X, Wang J, Zeng CH, Liu ZH. Long-term outcome of IgA nephropathy patients with recurrent macroscopic hematuria. Am J Nephrol. 2014;40(1):43-50. doi: 10.1159/000364954. (Patients with biopsy-proven primary IgAN in Jinling Hospital were divided into three groups according to different patterns of macroscopic hematuria (MH): RMH, isolated MH (IMH), and those without a history of MH (NMH).)

7. Tanaka K, Moriyama T, Iwasaki C, Takei T, Nitta K. Effect of hematuria on the outcome of IgA nephropathy with mild proteinuria. Clin Exp Nephrol. 2015 Oct;19(5):815-21. doi: 10.1007/s10157-014-1068-9. (Patients were divided into two groups: (1) patients with low (<20/high-power field [HPF]) urinary red blood cell (U-RBC) counts (L-RBC group) and (2) patients with high (≥20/HPF) U-RBC counts (H-RBC group).)

8. Chen TK, Murakami C, Manno RL, Geetha D. Hematuria duration does not predict kidney function at 1 year in ANCA-associated glomerulonephritis. Semin Arthritis Rheum. 2014 Oct;44(2):198-201. doi: 10.1016/j.semarthrit.2014.03.008. Epub 2014 Mar 28. (Patients were classified as hematuria duration <90 days vs. ≥90 days following renal biopsy.)

9. Tan M, Li W, Zou G, Zhang C, Fang J. Clinicopathological features and outcomes of IgA nephropathy with hematuria and/or minimal proteinuria. Kidney Blood Press Res. 2015;40(2):200-6. doi: 10.1159/000368495. (Patients were classified as (1) only hematuria (2) only proteinuria (3) hematuria and proteinuria (4) macroscopic hematuria.)

10. Kwon H, Lee DG, Kang HC, Lee JH. Incidence of isolated dipstick hematuria and its association with the glomerular filtration rate: a cross-sectional study from the

Korean National Health and Nutrition Examination Survey V (2010-2012). Int Urol Nephrol. 2016 Apr;48(4):451-6. doi: 10.1007/s11255-016-1215-1. (Isolated hematuria is classified as negative, grade 1, grade 2, or grade 3+ (grades 3, 4, 5) according to the results of a dipstick urine test.)

11.Iwasaki C, Moriyama T, Tanaka K, Takei T, Nitta K. Effect of hematuria on the outcome of immunoglobulin A nephropathy with proteinuria. J Nephropathol. 2016 Apr;5(2):72-8. doi: 10.15171/jnp.2016.12. (Patients were divided into two groups: (1) patients with low (<20/high-power field [HPF]) urinary red blood cell (U-RBC) counts (L-RBC group) and (2) patients with high (≥20/HPF) U-RBC counts (H-RBC group).)

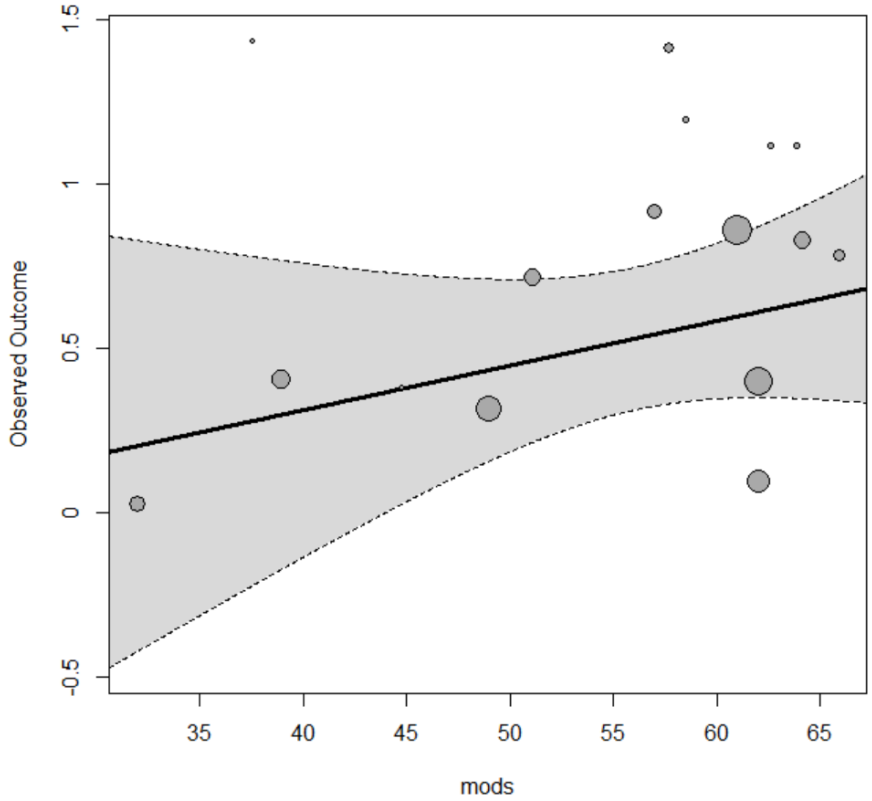
Cross-sectional study (n= 1)

1. Shan Y, Zhang Q, Liu Z, Hu X, Liu D. Prevalence and risk factors associated with chronic kidney disease in adults over 40 years: a population study from Central China. Nephrology (Carlton). 2010 Apr;15(3):354-61. doi: 10.1111/j.1440-1797.2009.01249.x. The primary outcome was defined as the appearance of proteinuria.

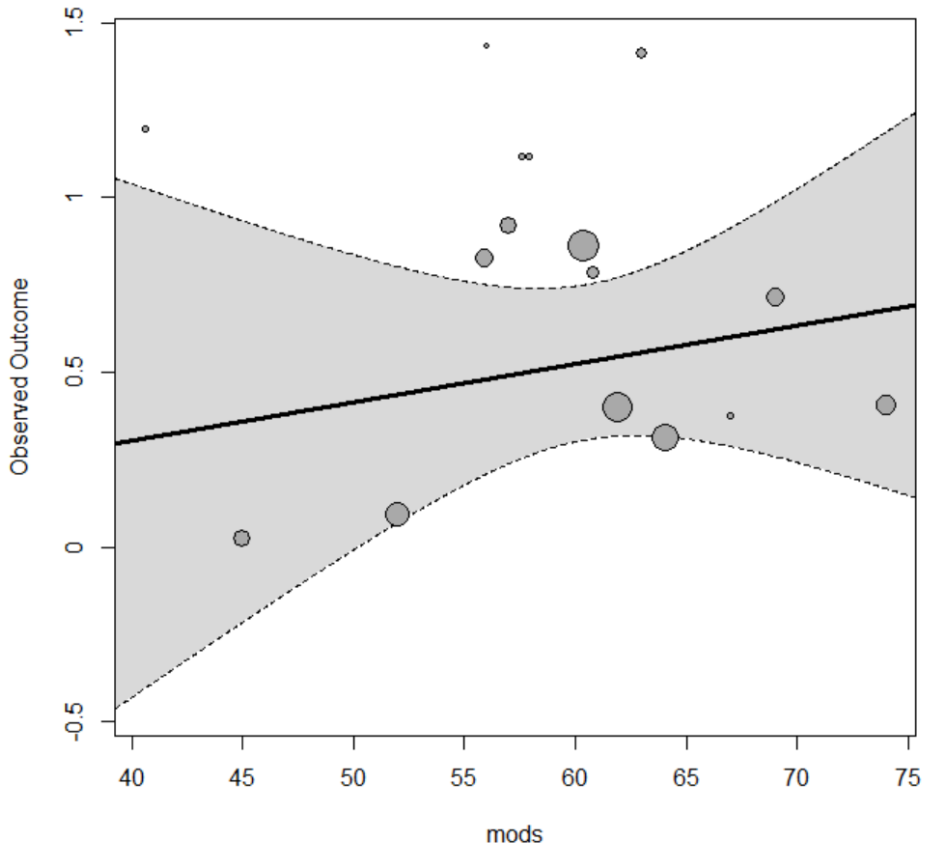
No outcome of interest (n= 1)

1. Chen J, Liu S, Xu H, Wang W, Xie Y, Tang W, Yuan Q, Zheng L, Lin L, Fu S, Shen J. Retrospective Analysis of Clinical Outcomes in Patients with Immunoglobulin A Nephropathy and Persistent Hematuria Following Renin-Angiotensin System Blockade. Med Sci Monit. 2020 Aug 21;26:e922839. doi: 10.12659/MSM.922839. (The secondary outcomes were the decreased percentage of hematuria, the rate of eGFR decline during follow-up and final blood pressure.)

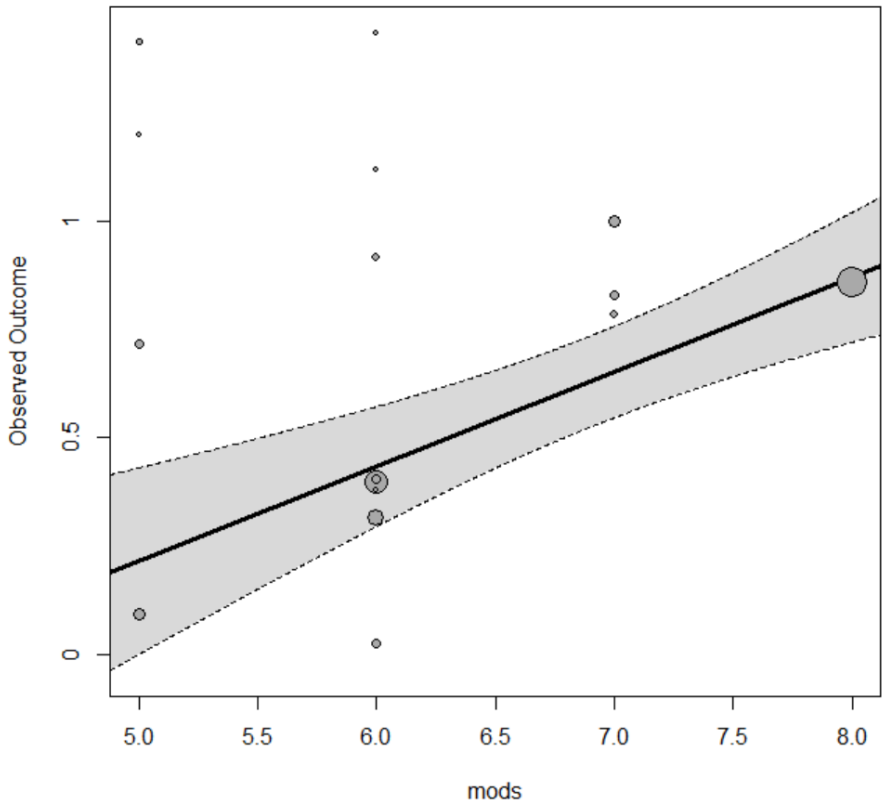
12.Supplementary Material S9: Meta-regression



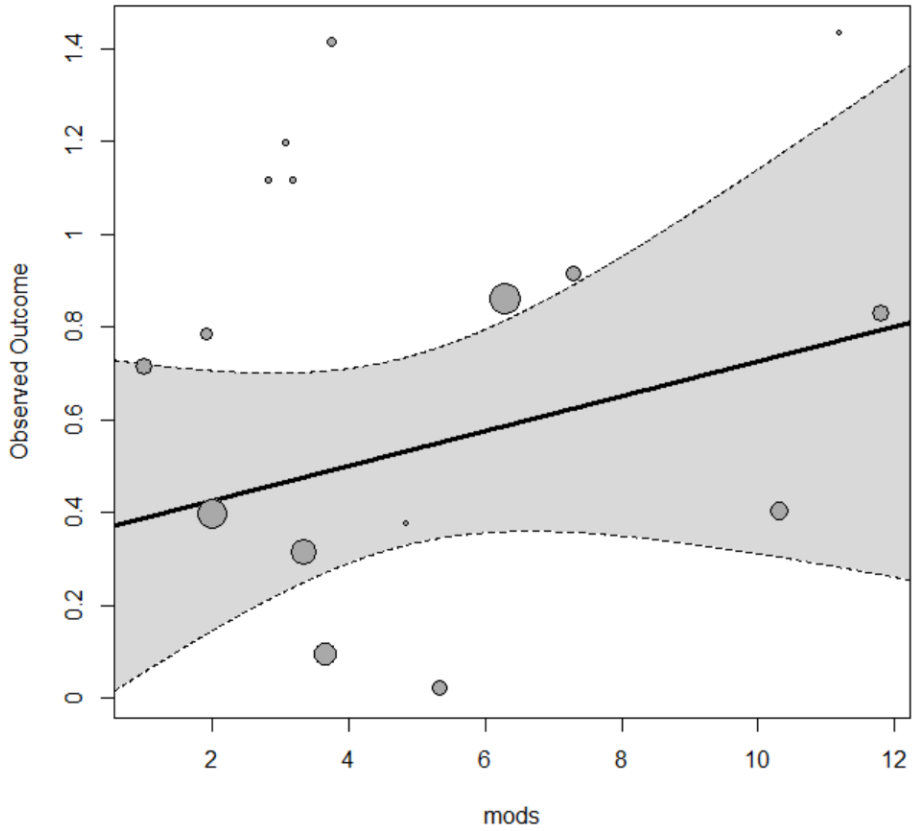
Supplementary Figure S6a. The meta-regression bubble plot showing the effect modification of age on the risk of adverse renal outcome comparing hematuria versus hematuria absent groups.



Supplementary Figure S6b. The meta-regression bubble plot showing the effect modification of continuous percentage of male on the risk of adverse renal outcome comparing hematuria versus hematuria-absent groups.



Supplementary Figure S6c. The meta-regression bubble plot showing the effect modification of NOS score on the risk of adverse kidney events comparing hematuria versus hematuria absent groups.



Supplementary Figure S6d. The meta-regression bubble plot showing the effect modification of following up period on the risk of adverse kidney events comparing hematuria versus hematuria absent groups.

13. Supplementary Material S10: PROSPERO protocol registration.

Review question

Do patients with hematuria or associated factors have higher risk for kidney disease progression？ P：Patients underwent urinary examinations with hematuria

I：Longitudinal follow-up

C：none

O: the development of incident CKD or renal deterioration

Searches

PubMed Web of Sci EMBASE (Year: 2010.01.01-2022.12.20 Language: English Species: humans)

Types of study to be included

inclusion: retrospective cohort study; RCT; prospective studies, clinical trials exclusion : Animal experiments, reviews, correspondences, case reports, expert opinions and editorials

Condition or domain being studied

Hematuria, defined by the presence of red blood cell in urine, was considered as the commonest clue of chronic kidney disease(CKD).As an accepted measurement of hematuria diagnosis, urinary red blood cell(URBC) examination was commonly achieved in clinical laboratories by urine strip results, microscopic examination and urine flow cytometer. CKD is a progressive disease that is defined by structural and functional changes to the kidney.

Participants/population

Inclusion: patients had hematuria whose urinalyses data are available Exclusion : transplant recipients, pregnant women, female patients who were menstruating, patients with active tuberculosis, malignancy, acute hemorrhage, an indwelling urinary catheter, infection, or urolithiasis.

Intervention(s), exposure(s)

Inclusion : patients underwent urinary examination and were followed up

Comparator(s)/control

inclusion：patients with no hematuria；patients with hematuria only

Main outcome(s)

The outcome was 1.renal deterioration, i.e., reduction in eGFR 5 years later. 2. incidence of CKD (eGFR < 60 mL/min/1.73 m2), , and newly developed glomerulonephritis confirmed by renal biopsy 3.Rapid renal function progression was defined when the eGFR slope was less than −5mL/ min/1.73m2/year. The eGFR was defined by using the simplified MDRD equation 4.initiation of renal replacement therapy 5.preceding creatinine or eGFR it is the review inclusion criteira

Measures of effect

odds ratios；risk difference

Additional outcome(s)

none

Data extraction (selection and coding)

The search identified all eligible studies. The titles and abstracts were screened by two investigators (Yingxiang Li and Yang Li) who independently assessed the abstracts, and if necessary the full texts, to determine whether the studies satisfied the inclusion criteria. If these two investigators differed in their views, a third investigator (Yi Fang) would read the study in question, all three investigators then engaged in discussion. The study was included only if consensus was achieved. The search contained the following medical subject headings and key text words: hematuria, haematuria, chronic kidney disease（CKD）, renal deterioration, haemorrhagic, bleeding, erythrocyte count, red blood cell, renal disease, urinalysis

Risk of bias (quality) assessment

Two investigators（Yingxiang Li and Yang Li）independently evaluated the study quality of the included studies using Newcastle-Ottawa Scale (NOS) . NOS included 8 items assessing the selection (4 items, 4 points), comparability (1 item, 2 points), and outcomes (3 items, 3 points) of every included study with the total scores of 9 points. A total score of 9 points for included studies were deemed to have a low risk of bias. The studies with two or three points for selection, one for comparability, and two for outcomes were considered to have medium risk of bias.The studies scored of zero or one point for selection or outcomes, and zero point for comparability were deemed to have a high risk of bias. Besides, a total score lower than 6 points for included studies were also deemed to have a high risk of bias in this meta-analysis.

Strategy for data synthesis

This study will be performed using R version 4.2.0..A random-effects model will be used to compare the outcomes of interest between patients with hematuria and patients with no hematuria quantitatively.The raw data was used from included studies to calculate the outcomes. A meta-regression will be used to evaluate possible reasons for the differences in the patients with hematuria and patients with no hematuria or across studies. We will apply Funnel plots to examine potential publication bias. The included studies'statistical heterogeneity was calculated using the $\chi 2$ test and the I^2 statistic. Meta-regression was also performed to examine the potential sources of heterogeneity between studies according to sample and study characteristics such as risk of bias, sample size, follow-up time, and definition of hematuria. To examine the stability of the pooled results, sensitivity analysis by leave-one-out methods (i.e., exclusion of one study at a time) was performed. Sensitivity analysis was also performed by omitting low-

quality studies and to observe the effect by study quality . Begg's test and Egger's test were used to examine publication bias. Funnel plot was also used to detect publication bias.

Analysis of subgroups or subsets

Subgroup analyses will be conducted using the baseline characteristics, e.g., diabetic mellitus(DM) or hypertensive population, hematuria stage, isolated hematuria or hematuria with proteinuria，persistent or single episodes of hematuria, follow-up period. Random effect model (REM) with Dersimonian and Laird method will be used to calculate the estimates

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Type and method of review

Individual patient data (IPD) meta-analysis, Meta-analysis, Prognostic, Systematic review

Anticipated or actual start date

01 January 2023

Anticipated completion date

01 October 2023

Funding sources/sponsors

The science and Technology Committee of the Shanghai Municipal

Grant number(s)

State the funder, grant or award number and the date of award

Key Laboratory Project 14DZ2260200，20DZ2271600 and Medical guidance support project 18411960800

Conflicts of interest

Language

English

Country

China

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Disease Progression; Follow-Up Studies; Hematuria; Humans; Kidney; Renal Insufficiency, Chronic

Date of registration in PROSPERO

14 January 2023

Date of first submission

04 January 2023