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Hematuria and subsequent long-term risk of end-stage kidney disease: a systematic review and meta-analysis of cohort study

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 June 2023 and was last updated on 14 June 2023.

INTRODUCTION

Review question / Objective Is isolated hematuria a risk factor for chronic kidney disease and end-stage renal disease?
P : Patients underwent urinary examinations and without proteinuria or chronic kidney disease
E : isolated hematuria patients
C : non-hematuria patients
O : diagnosis of chronic kidney disease, renal dysfunction or failure, end-stage renal disease.

Condition being studied Chronic kidney disease (CKD) constitutes a major global public health challenge, with a prevalence rate ranging from 11%-13% worldwide, and is anticipated to generate significant societal and economic burden, while adversely impacting the quality of life for affected individuals. Concurrently, CKD increases the risk of developing cardiovascular disease (CVD) and mortality. The asymptomatic onset of CKD, characteristic of the early stages, leads to a low disease awareness among patients, reinforcing the paramount importance of identifying and intervening in risk factors in a timely manner to delay the progression of CKD.
At present, the presence of urinary albumin, proteinuria, and dyslipidemia has been validated as early indicators of CKD progression and mortality risk, while the association between polyclonal serum free light chains (sFLC) and hematuria in relation to CKD constitutes a controversial risk factor. Nonetheless, there is insufficient evidence regarding asymptomatic isolated hematuria as a potential biomarker for future CKD progression.
Emerging clinical and medical research information emphasizes the salience of hematuria as a prominent topic in nephrology. The increasing body of evidence linking isolated hematuria to

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adverse renal outcomes underlines hematuria as a risk factor for CKD progression and death. Nevertheless, the published research findings have been inconsistent, with non-uniform adjustment for confounding factors, resulting in an inconclusive relationship between isolated hematuria and the risk of developing CKD or end-stage renal disease (ESRD).

METHODS

Search strategy Take Pubmed for example: ("prospective STUDY" OR "cohort STUDY" OR "longitudinal STUDY" OR "follow-up STUDY") AND (’renal impairment’ or ‘renal dysfunction’ or ‘chronic kidney disease’ or ‘chronic kidney failure’ or “renal function decline ” or “renal insufficiency” or “decline in renal function ” or “decline in kidney function ” or “ decline of function in renal ” or “loss of kidney function ” or “worsening renal function ” or ‘ESKD’ or ‘ESRD’ or ‘end-stage disease’ or ‘end-stage-kidney disease’ or ‘acute kidney injury’ or ‘renal deterioration’ or ‘Chronic glomerulonephritis renal deterioration’ or ‘worsening renal function’ or “estimated glomerular filtration rate” or “ glomerular filtration rate ” or ‘GFR’ or ‘eGFR’ or ”serum creatinine” “creatinine” ; “blood urea nitrogen” or “cystatin C” or ” albuminuria” or “proteinuria” or “CKD progression” or “ ESRD progression” or “lower eGFR” or “high risk of ESRD” or “fast eGFR decline” or “advancing CKD stages” or “rapidly declining kidney function” or “CKD development” or “incident end-stage kidney disease” or “eGFR and slope”) AND (“hematuria” or “Hematuresis” or ” asymptomatic hematuria” or ” persistent microscopic hematuria” or ” dipstick hematuria” or ” Persistent Isolated Hematuria”).

Participant or population Patients underwent urinary examinations and without chronic kidney disease.

Intervention Exposure: isolated hematuria patients.

Comparator Non-hematuria Patients.

Study designs to be included Cohort Study.

Eligibility criteria Study/cohort for evaluation or follow-up for persistent, isolated microscopic hematuria. Persistent isolated microscopic hematuria was defined as microscopic hematuria detected by urinalysis on at least two occasions (at least 6 months apart), but in the absence of other signs of kidney disease. Exclusion criteria were pathologic proteinuria (defined as urine protein/creatinine ratio > 0.2), hypertension, estimated glomerular filtration rate (< 90 mL/min/1.73 m2), abnormal kidney ultrasound, or a known diagnosis of kidney disease.

Information sources Databases that will be searched for the systematic review , such as MEDLINE, EMBASE, WEB of SCIENCE, CHKD-CNKI,CHONGIQNG VIP, WANFANG, etc. Additional sources, including USA Clinical Trial Registry (ClinicalTrials.gov) and Chinese Clinical Trial Registry(chictr.org.cn).

Main outcome(s) Incidence of end-stage renal disease; incidence of chronic kidney disease**.**

Additional outcome(s) New-onset proteinuria; glomerular filtration rate decrease: eGFR <60 mL/min per 1.73 m2; New-onset abnormal serum creatinine; New-onset abnormal cystatin C**.**

Quality assessment / Risk of bias analysis In order to assess the methodological quality of the studies included, we shall employ an adapted version of the Newcastle-Ottawa Scale (NOS), which holds significant academic repute. The NOS comprises eight rigorous criteria, designed to evaluate three key domains – selection of study groups, ascertainment of exposure and outcome, and comparability of said groups. Each criterion will be rated using a star system, with a maximum rating of nine stars. The ratings shall be conducted by two authors, namely CJH and CZX, and any discrepancies shall be meticulously resolved via discussion with a third author, HM, thereby ensuring rigorous evaluation standards.

Strategy of data synthesis Our meta-analysis was conducted using the DerSimonian-Laird random effects model. The effect sizes from the final model that adjusted for the maximum covariates were used from the eligible studies. For studies that reported RRs/HRs/ORs, the effect size and 95% CIs were extracted directly using participants with outcomes of interest without hematuria as the reference group. HRs were assumed to be numerically the same as the RRs. The between-study heterogeneity was examined with Cochran’s Q test. Significant heterogeneity was defined as a value of p<0.10. The I2-statistic was used to quantify the heterogeneity. A two-tailed p<0.05 was considered statistically significant. Statistical analyses were performed in RevMan5.3 software.R 4.1.1 Our meta-analysis was conducted using the DerSimonian-Laird random effects model. The effect sizes from the final model that adjusted for the maximum covariates were used from the eligible studies. For

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studies that reported RRs, the RRs and 95% CIs were extracted directly using participants with outcomes of interest without hematuria as the reference group. HRs were assumed to be numerically the same as the RRs. For studies that did not report HRs, the estimated HRs and 95% CIs were computed by the available Kaplan–Meier curves using the Engauge Digitizer software, version 4.10 and the method of Tierney et al. [20]. If the effect sizes could not be obtained, the crude RRs were calculated by the chisquare test. Pooled estimates were calculated on the logarithm of the RR from the individual studies. The results were then transformed back to the RR scale. The between-study heterogeneity was examined with Cochran's Q test. Significant heterogeneity was defined as a value of $p < .10$. The I2-statistic was used to quantify the heterogeneity. A twotailed $p < .05$ was considered statistically significant. Statistical analyses were performed in Stata software, version 15.0(StataCorp).

Subgroup analysis Considering the significant heterogeneity observed in the clinical presentation of hematuria, this study aims to conduct a subgroup analysis of patients based on the frequency and diagnostic method of hematuria. Specifically, the frequency of hematuria will be partitioned into categories of persistence and transient phenotypes, for a precise evaluation of disease progression. Moreover, the diagnostic method will be sub-divided into two distinct frameworks of microscopic and macroscopic diagnosis, allowing for a more detailed and thorough evaluation of clinical features and disease characteristics.
The implementation of this subgrouping approach has the potential to deepen and enhance the description of clinical phenotypes and help provide essential insights into the pathogenic mechanisms associated with isolated hematuria-associated renal diseases. Furthermore, the implementation of this stratification technique may facilitate the optimization of disease management strategies specific to varying subgroups, ultimately resulting in improved clinical outcomes for those affected.

Sensitivity analysis: Sensitivity analyses were performed by omitting 1 study at a time and repeating the meta-analysis.

Language restriction No.

Country(ies) involved China, UK.

Keywords Isolated hematuria; Chronic kidney disease ; End-stage renal disease; Meta-analysis; Cohort Study.

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