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The Role of Uromodulin in Chronic Kidney Disease – A Systematic Review and Meta-Analysis

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***Abstract*— Background:** Numerous studies have investigated the function of the biomarker uromodulin (UMD), which has shown promise in the diagnosis and severity assessment of chronic kidney disease (CKD). However, the results continue to be contradictory and inconclusive. Consequently, our goal was to investigate the connection between UMD and CKD patients, with a focus on their diagnostic utility and association with the severity of CKD based on the Kidney Disease Improving Global Outcomes (KDIGO) classification. **Methods:** We systematically searched PubMed, EMBASE, and Scopus using a predefined string to identify relevant studies. Included studies diagnosed CKD based on GFR according to Kidney Disease Outcomes Quality Initiative KDOQI guidelines or by calculating eGFR using the MDRD formula, meeting predefined criteria. Quality assessment was conducted using the Newcastle Ottawa Scale (NOS). The main outcome was the mean difference (MD) in serum UMD levels across CKD stages. **Results:** A total of 5 articles involving 1,094 subjects fulfilled our inclusion criteria and were included in our systematic review and meta-analysis. Significant differences in UMD levels were observed across multiple comparisons. When comparing CKD patients to controls, UMD levels showed a substantial MD of –115.719 (95% CI –163.297, -68.141). Similarly, UMD levels exhibited significant MDs when comparing controls vs. CKD 1 71.185 (95% CI 39.572, 102.798), controls vs. CKD 2 81.531 (95% CI 40.570, 122.491), controls vs. CKD 3 130.886 (95% CI 99.095, 162.677), controls vs. CKD 4 180.317 (95% CI 141.373, 219.262), controls vs. CKD 5 198.033 (95% CI 155.573, 240.494) and CKD 1-2-3 vs. CKD 4-5 89.540 (95% CI 47.561, 131.518). **Conclusions:** In conclusion, our systematic review and meta-analysis highlights pronounced differences in UMD levels across multiple comparisons in CKD. When comparing CKD patients with controls, a significant decrease in UMD levels is evident, indicative of potential implications in renal pathology. Moreover, the observed variations in UMD levels between different CKD stages underscore its potential utility as a biomarker for disease severity and progression. These findings contribute to our understanding of UMD dynamics in CKD and suggest avenues for further research into its diagnostic and prognostic significance in clinical practice.

Keywords: Biomarker, Chronic Kidney Disease, Uromodulin, Glomerular Filtration Rate.

1. Introduction

Chronic kidney disease (CKD) stands as a significant public health concern globally, characterized by the progressive decline of renal function over time. Its prevalence has been steadily rising, with estimates suggesting that millions of individuals worldwide are affected. CKD poses a substantial burden on healthcare systems due to its association with increased morbidity, mortality, and healthcare costs. Moreover, CKD is often accompanied by various complications, including cardiovascular disease, anemia, and bone disorders, further exacerbating the disease's impact on individuals' quality of life (1).

In clinical practice, the timely and accurate diagnosis of CKD is paramount for effective management and intervention strategies. Currently, diagnosis primarily relies on assessing kidney function through measurements of serum creatinine and estimated glomerular filtration rate (eGFR) (2). However, these conventional biomarkers may not fully capture the intricacies of renal function and the underlying pathophysiological processes in CKD. Consequently, there is a growing interest in exploring novel biomarkers that could enhance early detection, risk stratification, and monitoring of CKD progression.

Uromodulin (UMD), also called Tamm-Horsfall protein, is a glycoprotein primarily expressed in kidney epithelial cells. Rare mutations in the UMOD gene, which encodes UMD, have been linked to autosomal dominant tubulo-interstitial kidney disease (ADTKD). Recent genome-wide association

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studies (GWAS) have identified several genetic loci associated with renal function and the risk of chronic kidney disease (CKD) in various populations, including Europeans and Asians. Notably, the UMOD locus has shown a strong association with renal function. Studies have indicated that the influence of variations in the UMOD locus on CKD is more pronounced in older adults than in younger individuals. Additionally, the UMOD locus is linked to hypertension. Advances in understanding the role of UMD in kidney diseases have shifted our perspective from rare inherited diseases to more common forms of CKD. These findings suggest that UMD could provide insight into the mechanisms underlying CKD, particularly age-related or hypertensive nephrosclerosis, and may offer a new therapeutic target (3).

In the context of CKD, UMD has gained increasing attention as a potential prognostic marker and therapeutic target. Research has shown associations between altered UMD levels and adverse outcomes in CKD patients, including the progression to end-stage renal disease (ESRD), cardiovascular complications, and increased mortality (4). However, the current evidence regarding the relationship between UMD and CKD is not fully conclusive, with variations in findings across different studies. Consequently, there is a pressing need for a comprehensive review of the available literature to clarify the role of UMD in CKD and its implications for clinical practice. The aim of this systematic review and meta-analysis is to critically evaluate the current evidence regarding UMD levels in CKD patients. Specifically, we aim to assess the association between UMD levels and various stages of CKD. By synthesizing data from published studies, we seek to provide insights into the potential utility of UMD as a biomarker for monitoring CKD progression, ultimately informing clinical decision-making and guiding future research directions.

2. MATERIALS & METHODS

This systematic review and meta-analysis were written as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (5).

2.1. Data sources and Strategy

We conducted a computerized search using PubMed, Embase, and Scopus electronic databases, in order to identify observational studies assessing the UMD in CKD. The used search string is described in **Supplementary Material 1**. Moreover, we conducted a manual search for relevant missed publications through screening the references of included articles. The literature search was conducted from inception till the 15 July 2024 by two investigators (G.G. and R.C.C.) independently. In the case of discrepancies, a consensus was reached through discussion. We did not apply any filter or restrictions to duration, country, or language during the search. The titles and abstracts were then screened for eligibility, followed by full-text assessment of articles fulfilling our inclusion and exclusion criteria. Data extraction was performed by two investigators (G.G. and R.C.C) and verified by (A.I.), while any discrepancies were resolved by confronting the source article. The extracted data included author names, publication year, country, design of the study, studied population, total sample size, CKD percentage, mean age, sex distribution, body mass index (BMI), CKD diagnosis technique, mean ± SD or median (interquartile range), UMD levels and main study outcome, which were collated and presented in the manuscript text.

2.2. Eligibility Criteria

The inclusion criteria of original articles in our systematic review and meta-analysis were as follows: (1) observational cohort, cross-sectional, or case–control studies assessing the UMD in CKD; (2) CKD diagnosed according to each study criteria; (3) human studies with no restrictions to sex, race, or ethnicity; and (4) studies published in English, Swedish, German, French, or Romanian.

The exclusion criteria were as follows: (1) editorials, letters, short surveys, commentaries, case reports, conference abstracts, review articles, animal studies, pediatrics studies, practice guidelines, and abstracts published without a full article.

2.3 Risk of Bias Assessment in Individual studies

The investigators (G.G. and R.C.C) independently used the Newcastle-Ottawa Scale (NOS)(6), objectively evaluating the bias risk and internal validity of the studies included. Discrepancies between the two investigators regarding the quality assessment of the included studies were handled through discussion. Separate assessment forms were used for case-control studies and cross-sectional studies. All assessed studies were scored based on how many stars were obtained. The selection, comparability, and outcome section criteria were verified, and the study was subsequently graded with scores ranging between 0 to 10 stars. The number of stars were added up in each study in order to compare the quality of included studies in a quantitative manner. High-quality studies were considered to have received 7 stars or more. The methodological quality assessment did not affect the eligibility of the studies.

2.4 Summary Measures and Synthesis of Results

The data analyses of the systematic review and meta-analysis were performed using R with the Metafor package (OpenMeta Analyst) (7). The principal summary outcomes of UMD in CKD were the mean difference (MD). Between-study heterogeneity was evaluated by a χ^2-based Q-test and I^2. As per the recommendations of the Cochrane Handbook for identifying and measuring heterogeneity, we estimated I^2 values of 0 to 40% as not important; 30 to 60% as moderate heterogeneity; 50 to 90% as substantial heterogeneity; and 75 to 100% as considerable heterogeneity (8). In studies reporting medians and interquartile ranges (IQRs), we calculated the mean and standard deviation (SD) based on them. We combined the statistics (means and standard deviations) of the groups in studies with several subgroups of UMD patients or control subjects, to get the value for the entire set of subjects (when this was missing), according to the Cochrane Handbook recommendations. Subgroup analysis was conducted according to the severity of CKD using the KDIGO classification and depending on the available values from the extracted data from included studies. For all meta-analyses, we used restricted maximum likelihood random-effects

models. We reported the data from each study as the estimated MD with 95% CI, lower bound, upper bound, standard error, and *p*-value. Statistical significance was considered to be achieved if the *p*-value was <0.05 (9). The analyses were conducted if at least two studies reported the same outcome with available mean and SD, median (IQR).

3. Results

3.1 General Results

The initial search yielded six hundred and three articles (PubMed = 160 articles, EMBASE = 442 articles, and Scopus = 1 articles), as shown in **Figure 1**. A total of seventy-four studies were detected as duplicates and removed. After the removal of duplicates, five hundred twenty-nine articles were evaluated for inclusion and exclusion criteria fulfilment by assessing the titles and abstracts. After the first screening was performed, we excluded a total of 482 articles as follows: (1) two hundred and eighteen irrelevant studies, (2) ninety-nine reviews, (3) thirteen experimental studies, (4) one hundred and twenty conference abstracts, (5) eleven interventional studies, (6) ten pediatrics, (7) seven editorials & letters, (8) four other languages. We were not able to retrieve two articles. Subsequently, we performed a thorough reading and evaluation of the full texts for further eligibility assessment for the remaining thirty articles. Of these articles, forty were excluded with reasons that can be found in **Supplementary Material 2**. The total number of articles included in the qualitative synthesis was five studies, out of which all were included in the quantitative synthesis (10-14).

3.2 Study Characteristics

A summary of the main characteristics of the studies included is presented in **Supplementary Table 1**. This systematic review and meta-analysis included a total number of 1,094 individuals. According to studies that reported sex distribution excluding one study due to non-reported sex data, females presented a larger proportion of the included participants (females—441 [40,3%], males—653 [59,7%]). CKD was present in 865 subjects (79,1%) of the total study sample. Three studies were conducted in Asia (India $n = 2$, Japan $n = 1$), and two in Europe (Germany $n = 1$, Poland $n = 1$)

3.3 Definition of CKD

CKD was assessed using eGFR or GFR for diagnosing in all studies ($n = 5$).

3.4 UMD levels in CKD

3.4.1. UMD levels in CKD patients vs. controls

UMD levels were evaluated in a total of five studies comparing values in CKD patients with control subjects (10-14). **Figure 2** summarizes the obtained meta-analysis results. The pooled analysis that assessed UMD levels in adult CKD patients vs. control subjects showed an overall MD of -115.719 (95% CI -163.297, -68.141). Considerable heterogeneity was reported with an $I^2 = 97.595\%$ and a *p*-value <0.001.

3.4.2. Controls vs. CKD stages (1,2,3,4,5)

Moreover, subgroup analyses were further conducted in adults according UMD levels in each KDIGO CKD classification compared to controls as demonstrated in **Figure 3**.

The evaluation of UMD levels in controls vs. KDIGO stage 1 CKD patients was assessed in four studies (10, 12-14), with an MD of 71.185 (95% CI 39.572, 102.798) and considerable heterogeneity ($I^2 = 90.746\%$ and a *p*-value <0.001). UMD levels in controls vs. KDIGO stage 2 CKD was assessed in four studies (10, 12-14), with an MD of 81.531 (95% CI 40.570, 122.491) and considerable heterogeneity ($I^2 = 92.91\%$ and a *p*-value < 0.001). The UMD values in controls vs. KDIGO stage 3 CKD was evaluated in four studies (10, 12-14), with an MD of 130.886 (95% CI 99.095, 162.677) and considerable heterogeneity ($I^2 = 91.70\%$ and a *p*-value < 0.001). The UMD values in controls vs. KDIGO stage 4 CKD was evaluated in three studies (10, 12-14), with a MD of 180.317 (95% CI 141.372, 219.262) and considerable heterogeneity ($I^2 = 95.38\%$ and a *p*-value < 0.001) Moreover, UMD levels were assessed in controls vs. KDIGO stage 5 CKD in four studies (10, 12-14), with an MD of 198.033 (95% CI 155.573, 240.494) and considerable heterogeneity ($I^2 = 96.42\%$ and a *p*-value < 0.001).

3.4.3. UMD levels in stage 1 CKD patients compared to other KDIGO CKD stages

As demonstrated in **Figure 4**, we conducted a subgroup analysis according to UMD levels in each KDIGO CKD classification. UMD levels in CKD patients with CKD 1 vs. CKD 2 was evaluated in four studies (10, 12-14), with a MD of 13.189 (95% CI -1.314, 27.882) and considerable heterogeneity ($I^2 = 62.93\%$ and a *p*-value < 0.031); CKD 1 vs. CKD 3 in four studies (10, 12-14), with a MD of 54.223 (95% CI 26.285, 82.160) with considerable heterogeneity ($I^2 = 92.42\%$ and a *p*-value < 0.001); CKD 1 vs. CKD 4 in four studies (10, 12-14), with a MD of 108.068 (95% CI 51.877, 164.260) and considerable heterogeneity ($I^2 = 98.38\%$ and a *p*-value < 0.001); CKD 1 vs. CKD 5 in four studies (10, 12-14), with a MD of 126.628 (95% CI 66.033, 187.223) and considerable heterogeneity ($I^2 = 98.71\%$ and a *p*-value < 0.001).

3.4.4 UMD levels in stage 2 CKD patients compared to other KDIGO CKD stages

As demonstrated in **Figure 5**, we conducted another subgroup analysis according to UMD levels in each KDIGO CKD classification. UMD levels in CKD 2 vs. CKD 3 in four studies (10, 12-14), with a MD of 53.288 (95% CI 24.749, 81.826) and considerable heterogeneity ($I^2 = 93.32\%$ and a *p*-value < 0.001); CKD 2 vs. CKD 4 in four studies (10, 12-14), with a MD of 107.123 (95% CI 50.187, 164.058) and considerable heterogeneity ($I^2 = 98.56\%$ and a *p*-value < 0.001); CKD 2 vs. CKD 5 in four studies (10, 12-14), with a MD of 125.683 (95% CI 64.290, 187.076) and considerable heterogeneity ($I^2 = 98.86\%$ and a *p*-value < 0.001).

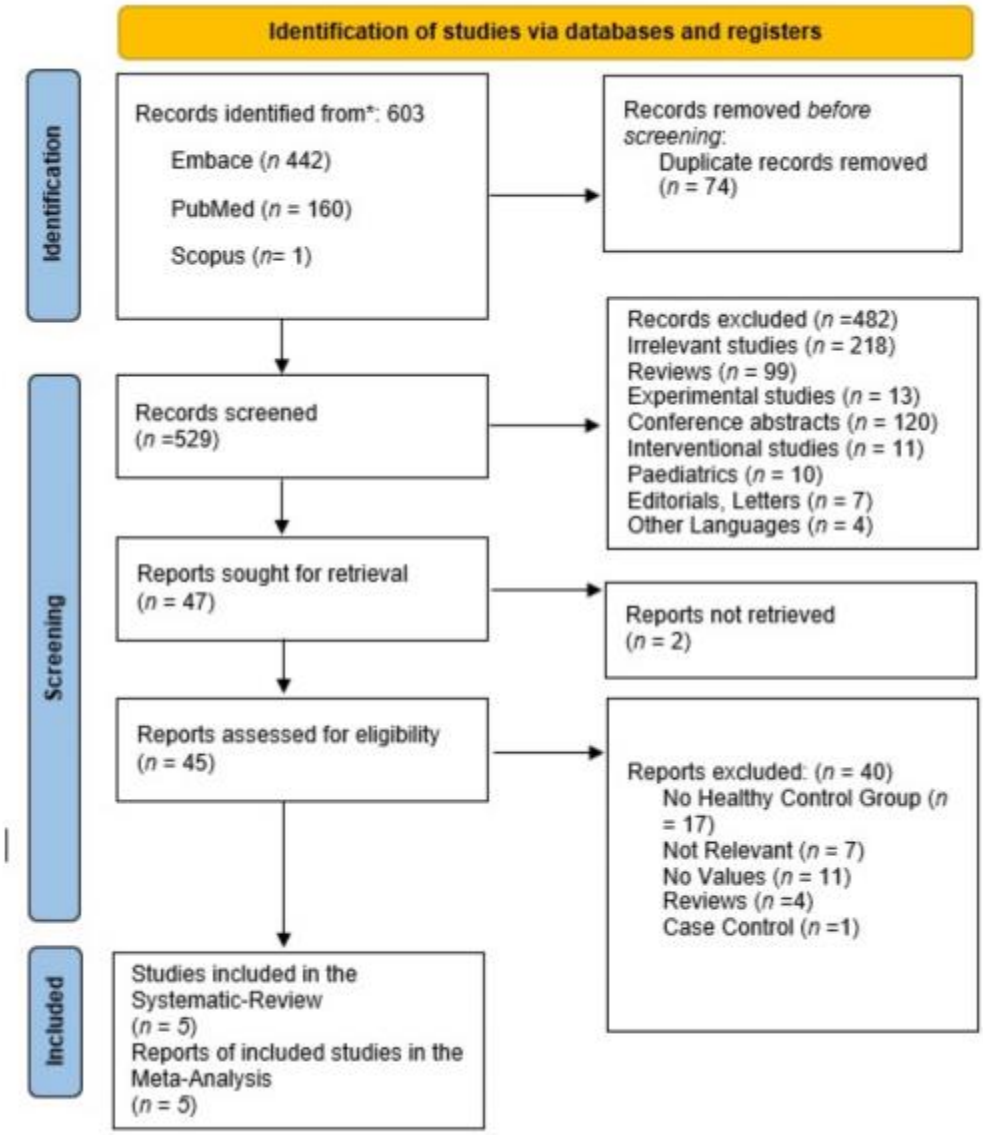

Figure 1. PRISMA flow diagram – identification, screening, and inclusion phases of our systematic review and meta-analysis

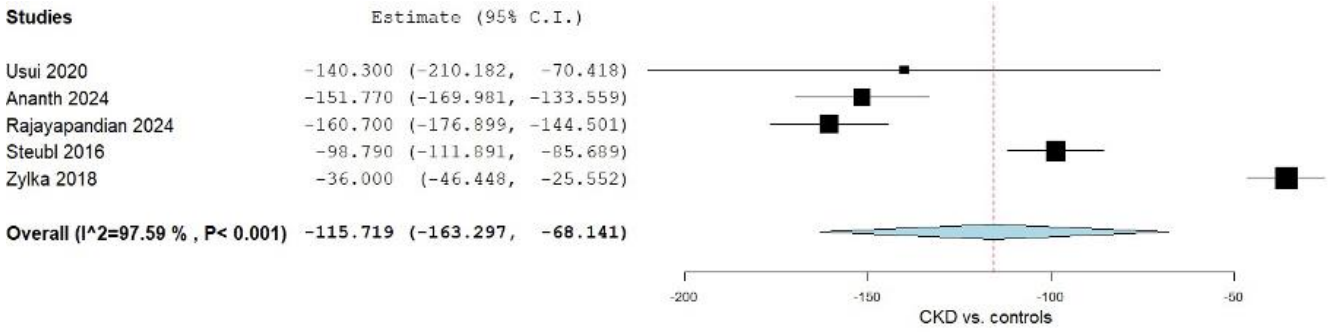

Figure 2. UMD levels in CKD patients vs. controls

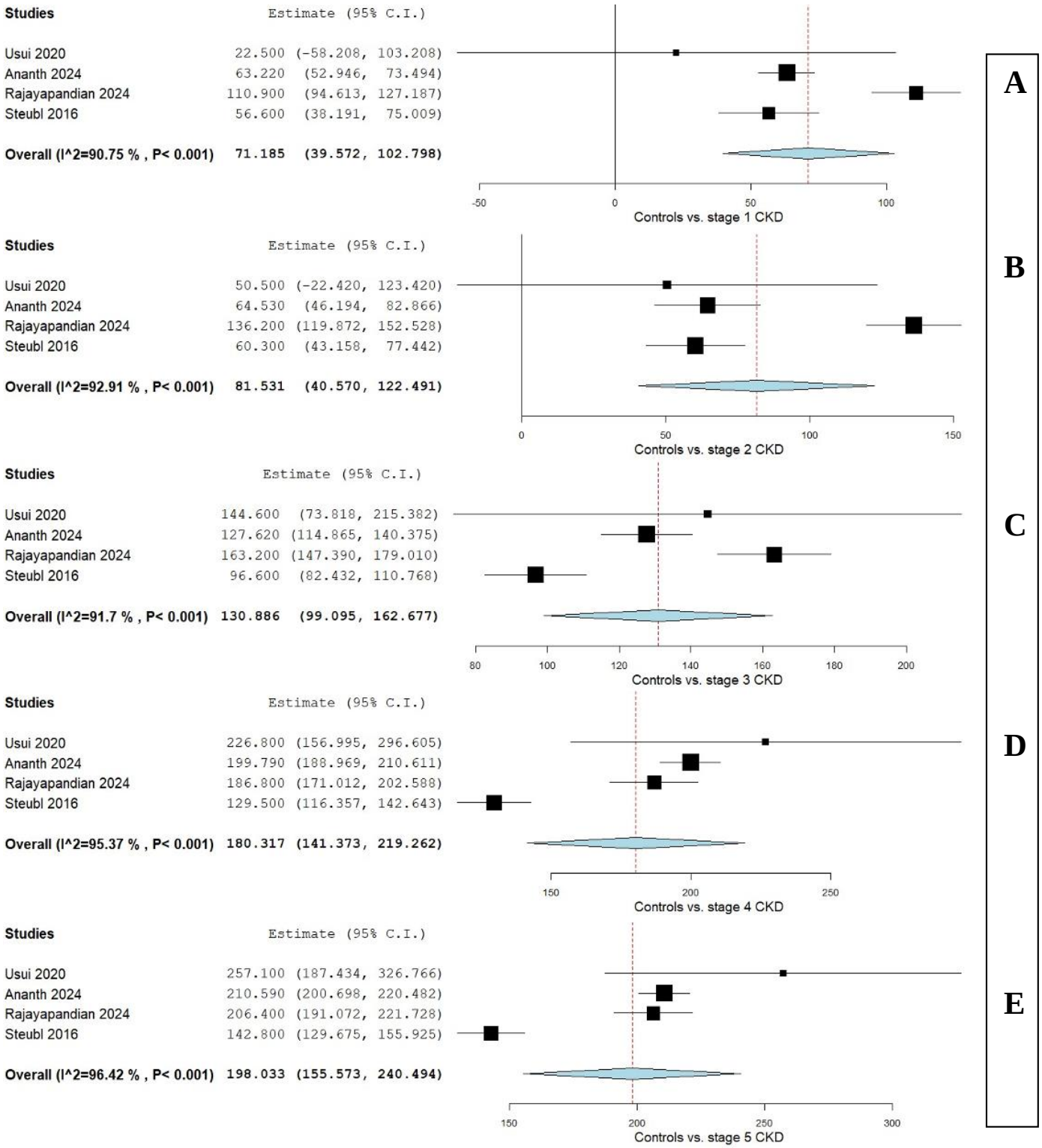

Figure 3. UMD levels in CKD patients according to controls vs. KDIGO CKD classification

(A) UMD levels in controls vs. KDIGO CKD 1; **(B)** UMD levels in controls vs. KDIGO CKD 2; **(C)** UMD levels in controls vs. KDIGO CKD 3; **(D)** UMD levels in controls vs. KDIGO CKD 4; **(E)** UMD levels in controls vs. KDIGO CKD 5.

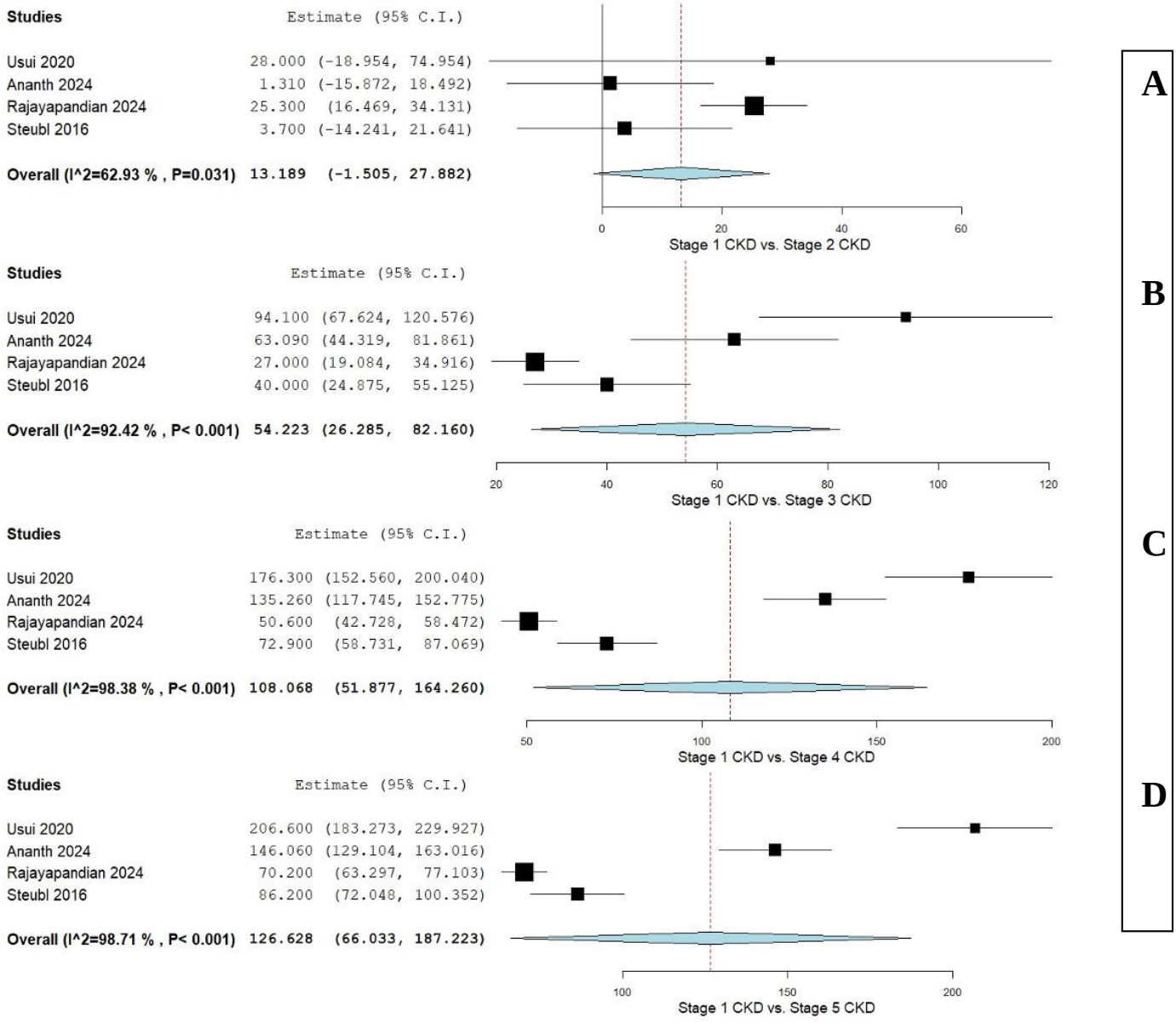

Figure 4. UMD levels in CKD patients according to KDIGO CKD classifications.

(A) UMD levels CKD Stage I vs. CKD Stage 2; **(B)** UMD levels in CKD Stage 1 vs. CKD Stage 3; **(C)** UMD levels in CKD Stage 1 vs. CKD Stage 4; **(D)** UMD levels in CKD Stage 1 vs. CKD Stage 5.

3.4.5. UMD levels in stage 3 CKD patients compared to other KDIGO CKD stages

As demonstrated in **Figure 6**, we conducted another subgroup analysis according to UMD levels in each KDIGO CKD classification. UMD levels in CKD 3 vs. CKD 4 in four studies (10, 12-14), with a MD of 52.124 (95% CI 24.001, 80.248) and considerable heterogeneity (I^2= 97.1% and a *p*-value < 0.001); CKD 3 vs. CKD 5 in four studies (10, 12-14), with a MD of 70.692 (95% CI 38.714, 102.670) and considerable heterogeneity (I^2= 98.09% and a *p*-value < 0.001).

3.4.6. UMD levels in stage 4 CKD patients compared to other KDIGO CKD stages

As demonstrated in **Figure 7**, we conducted another subgroup analysis according to UMD levels in each KDIGO CKD classification. UMD levels in CKD 4 vs. CKD 5 in four studies (10, 12-14), with a MD of 18.041 (95% CI 10.366, 25.718) and considerable heterogeneity (I^2= 78.59% and a *p*-value < 0.010).

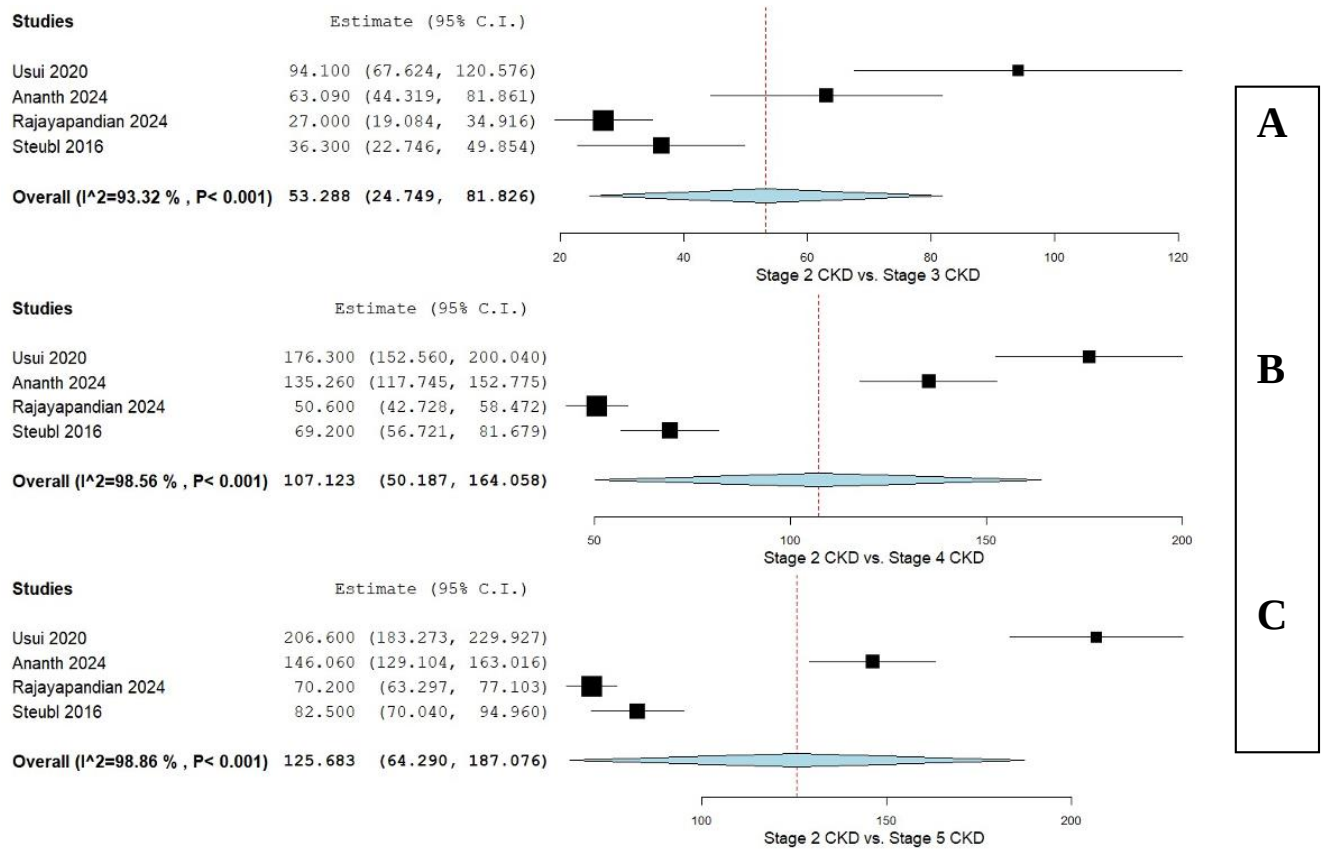

Figure 5. (A) UMD levels in CKD 2 vs. CKD 3; (B) UMD levels in CKD 2 vs. CKD 4; (C) UMD levels in CKD 2 vs. CKD 5.

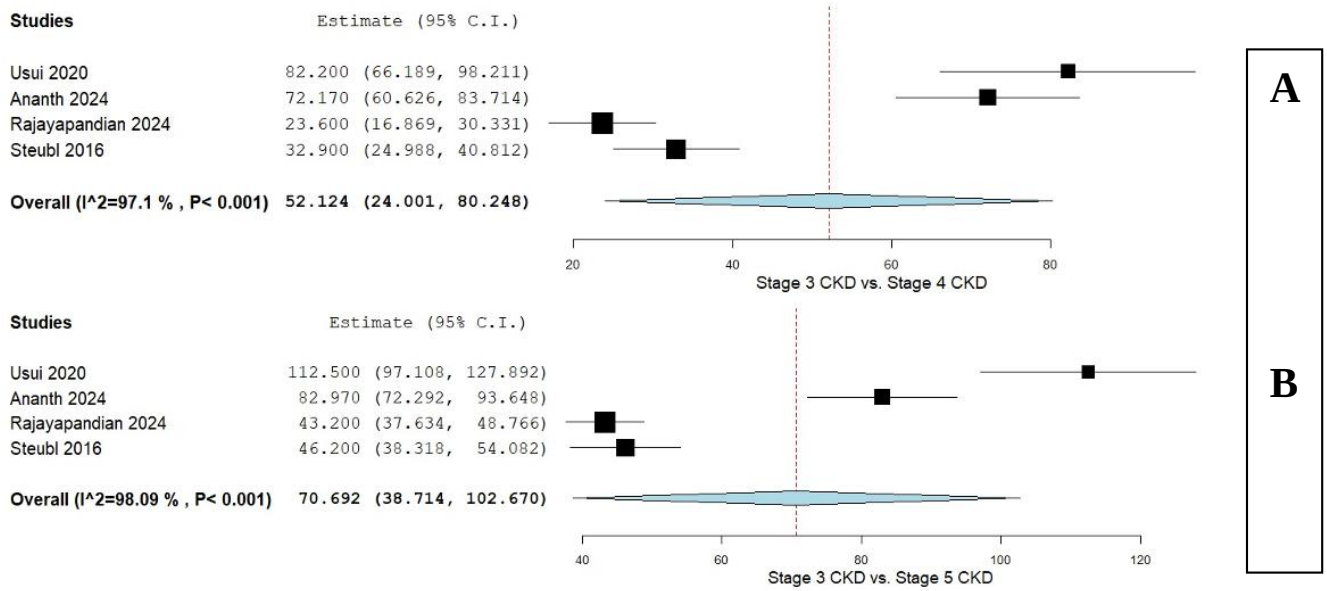

Figure 6. (A) UMD levels in CKD 2 vs. CKD 3; (B) UMD levels in CKD 2 vs. CKD 4; (C) UMD levels in CKD 2 vs. CKD 5.

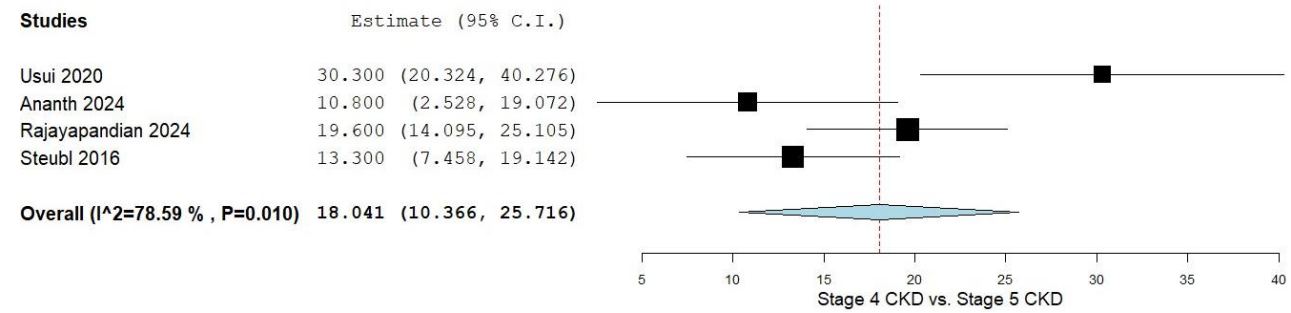

Figure 7. UMD levels in CKD 4 vs. CKD 5.

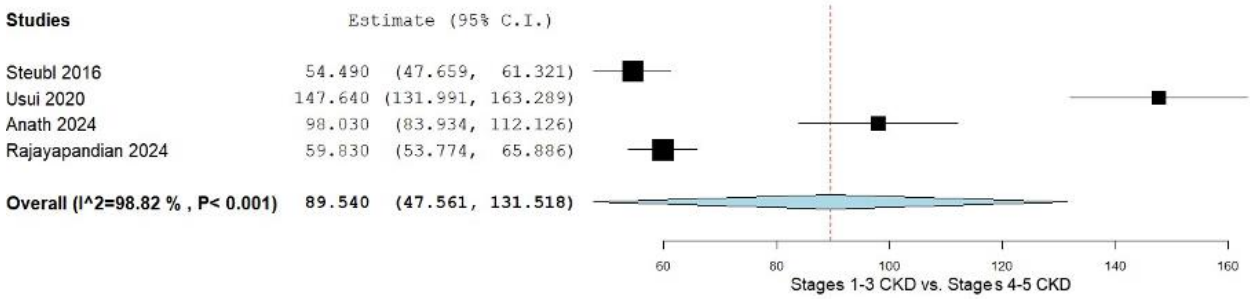

Figure 8. UMD levels in CKD 1-3 vs. CKD 4-5.

3.4.7. UMD levels in combined KDIGO CKD stages

As demonstrated in **Figure 8**, we conducted another subgroup analysis according to UMD levels in each KDIGO CKD classification. UMD levels in CKD patients with CKD 1-4 vs. CKD 4-5 was evaluated in four studies (10, 12-14), with a MD of 89.540 (95% CI 47.561, 131.518) and considerable heterogeneity (I^2 = 98.82% and a *p*-value < 0.001).

3.5. Bias Evaluation

We used the NOS quality assessment tool to evaluate the methodological quality of the studies included in our systematic review and meta-analysis, as shown in **Supplementary Table S2**. A total of seven articles were assessed using the NOS quality assessment tool for cross-sectional studies (6). Two articles received an overall rating of 8/10, one article received an overall rating of 7/10, one article received an overall rating of 7/10, and two articles received 6/10. Overall, all the studies had a clearly stated research objective or question. In almost half of the studies included, the population sample was truly or somewhat representative of the average in the target population, and the size of the population sample was satisfactory and justified. All the studies provided a validated measurement tool. Three controlled for the most important confounding factor and for at least one additional factor. All included studies assessed the outcome by record linkage, as well as employing an appropriate and clearly described statistical test and reported the results adequately.

4. DISCUSSION

Lately, several scores and biomarkers have been studied in CKD, more precisely to improve the accuracy of the current diagnostic methods as well as identify new biomarkers (1). In our systematic review and meta-analysis, we evaluated UMD levels in CKD patients and according to KDIGO CKD classification (15). We included five articles with a total population of 1,094 subjects in our quantitative and qualitative synthesis. We reported that the UMD is significantly decreased in adult CKD patients compared to controls, as well as significantly decreased the higher the CKD KDIGO stage is.

The diagnosis and classification of CKD are pivotal for effective management and prognostication. Conventionally, estimating glomerular filtration rate eGFR or directly measuring GFR serve as key diagnostic criteria (16). In recent research, the focus has intensified on refining these approaches through the exploration of novel scores and biomarkers. This heterogeneity in diagnostic approaches is crucial for understanding the applicability of the studied biomarkers in various clinical scenarios. Current guidelines recommend calculating eGFR or measuring GFR when the suspicion of CKD is raised. Diagnosing CKD entails a structured approach. Initially, assessing risk factors and symptoms can guide screening. Following this, calculating eGFR through equations like the Modification of Diet in Renal Disease (MDRD) (17) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is crucial (18). Additionally, evaluating urine albumin-to-creatinine ratio

aids in diagnosis. Subsequently, kidney imaging and biopsy may be warranted for further characterization. Integrating these steps facilitates timely and accurate diagnosis of CKD, enabling prompt intervention and improved patient outcomes (19).

The importance of uromodulin in the context of diabetes and diabetic kidney disease (DKD) is increasingly recognized due to its multifaceted role in renal health and disease progression. Uromodulin, a glycoprotein primarily produced by the epithelial cells of the thick ascending limb of the loop of Henle, serves several protective functions within the kidney, including modulation of immune responses, prevention of urinary tract infections, and inhibition of calcium oxalate crystallization. In patients with diabetes, elevated blood glucose levels lead to the formation of advanced glycation end-products (AGEs), which contribute to oxidative stress and inflammation, accelerating kidney damage. Recent findings suggest that uromodulin can undergo glycation in diabetic conditions, forming glycated uromodulin (glcUMOD), which may be linked to nephropathy. The decline in the normal function or production of uromodulin has been associated with impaired tubular recovery, chronic interstitial fibrosis, and eventual nephron loss. Thus, measuring levels of uromodulin, particularly its glycated form, could provide critical insights into the early detection of DKD and the extent of renal injury, offering a non-invasive biomarker for monitoring disease progression and potentially guiding therapeutic interventions in diabetic patients. This highlights the importance of uromodulin not only as a protective factor in kidney function but also as a valuable marker for identifying and managing kidney complications in diabetes (20).

In another study published study, serum uromodulin levels were found to be significantly and inversely correlated with fasting plasma glucose, plasma glucose measured two hours after a 75g oral glucose challenge, and HbA1c. Among the study participants, 27.6% had type 2 diabetes mellitus (T2DM). Analysis of covariance demonstrated that T2DM was an independent determinant of serum uromodulin levels, even after adjusting for factors such as hypertension and glomerular filtration rate. Prospectively, serum uromodulin levels were lowest in patients with T2DM at baseline, higher in initially nondiabetic individuals who developed diabetes during follow-up, and highest among those who remained non-diabetic. A similar trend was observed in relation to prediabetes. These findings suggest that serum uromodulin is significantly associated with impaired glucose metabolism and the development of both prediabetes and diabetes (21).

Based on our understanding of UMD's role in maintaining physiological balance and modulating inflammation and immune responses, it appears that UMD plays a protective role against chronic kidney disease (CKD). Elevated baseline levels of UMD are associated with a reduced risk of subsequent decline in glomerular filtration rate (GFR) (22-24). Furthermore, during CKD, the synthesis of UMD per functioning nephron increases, reflecting the kidney's response to injury. This was notably demonstrated by Thornley et al. (25) who found that THP excretion per milliliter of creatinine clearance was significantly higher in CKD patients compared to healthy individuals. (25). Despite this increased production by remaining nephrons, the progression of fibrosis leads to the loss of additional nephrons, resulting in an overall decrease in UMD production as CKD advances and GFR declines (10, 26). Conversely, in the early stages of CKD or in cases where kidney function has not yet significantly deteriorated, UMD production can be elevated. This phenomenon has been observed in early diabetes, even when GFR is normal, and in individuals before the onset of CKD. Notably, this increase in UMD production appears to be independent of renal mass (25, 27).

In our meta-analysis, we reported a significant decrease in UMD levels in CKD patients compared to the healthy controls. We have successfully demonstrated it again on a meta-analysis level combining the biggest 5 studies that compared serum UMD in healthy controls vs. CKD patients.

Moreover, another statistical comparison was conducted by comparing UMD values in CKD patients between CKD KDIGO stages vs. healthy controls, one stage at a time. By comparing stages CKD 1, CKD 2, CKD 3, CKD 4 and 5 separately against healthy controls, we observed a marked decrease in UMD values. The mean difference between healthy controls vs. CKD stages was increasing with each comparison, meaning that the higher the CKD stage the higher the mean difference between the healthy controls group and the CKD stage. In other words, when comparing the healthy controls vs. CKD 1 the MD was 71.91, with each comparison it kept rising until reaching healthy controls vs. CKD 5, the MD was 198. This shows that UMD can be used as a biomarker not only to assess the presence of CKD but also to assess the severity of CKD.

Additionally, a more detailed statistical analysis was performed to evaluate the differences in UMD levels across the different CKD stages, as classified by KDIGO guidelines. This analysis revealed significant variances in UMD concentrations between most CKD stages, with the notable exception of CKD Stage 1 compared to CKD Stage 2. The lack of a statistically significant difference in UMD values between these early stages can likely be attributed to the minimal extent of nephron fibrosis at these stages, which is insufficient to cause a marked decline in UMD that can be detected reliably. It is plausible that the initial stages of CKD are characterized by compensatory mechanisms in the renal tubules, which may maintain UMD secretion even when early renal impairment is present. This compensatory secretion potentially delays the onset of measurable decreases in UMD levels until more advanced fibrotic changes and tubular damage have occurred, as seen in later CKD stages. Such findings underscore the importance of considering the degree of renal fibrosis and tubular health when interpreting UMD levels as a biomarker in early CKD, that not enough fibrosis has set in to significantly impact the production and the release of UMD which is also significantly and statistically different in our analysis.

Another analytical approach involved combining CKD stages into broader groups to facilitate comparison based on the overall severity of chronic kidney disease. By grouping CKD stages 1 through 3 together and comparing them against stages 4-5, we aimed to elucidate differences in uromodulin levels reflective of disease progression. This combined analysis was instrumental in highlighting the significant disparity in UMD concentrations between early to moderate CKD (stages 1-3) and advanced CKD (stage 4-5) when treated as categorical blocks. The statistical difference observed underscores the extent to which UMD levels can differentiate between earlier stages of renal dysfunction, where nephron function is still relatively preserved, and later stages, characterized by extensive nephron loss and marked impairment of tubular function. Such stratified analysis not only reinforces the role of UMD as a potential biomarker for monitoring CKD progression but also suggests that UMD levels might serve as an indicator of cumulative renal damage, providing clinicians with a valuable tool to assess disease severity and adjust therapeutic interventions accordingly. This approach, by focusing on the aggregate differences across combined stages, offers a robust framework for understanding how UMD levels reflect underlying pathological changes associated with advancing CKD.

Moreover, In CKD, urinary biomarkers have also gained significant attention due to their potential in early diagnosis and disease monitoring. Various biomarkers, such as kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and alpha-1-microglobulin (α1M), have been widely studied for their roles in detecting renal dysfunction by assessing damage to different parts of the nephron. For instance, KIM-1 is linked with early proximal tubule damage and is shed into urine when injury occurs, making it a strong candidate for identifying initial stages of CKD. Similarly, NGAL correlates with a decline in GFR, making it useful for tracking disease progression. While these urinary markers are invaluable for detecting tubular injury, they often do not provide a comprehensive picture of systemic changes or inflammation (28, 29).

Nonetheless, several biomarkers can be studied in the urine, providing non-invasive methods to monitor kidney function. In addition to these urinary markers, urinary UMD has emerged as a promising biomarker with renoprotective effects, mainly produced in the thick ascending limb of Henle. Decreased urinary UMD levels have been associated with impaired kidney function and more severe CKD stages (28, 29). Despite its established role in urine, the exploration of UMD levels in serum is relatively novel. Measuring serum UMD could offer additional insights into systemic kidney function and inflammation, potentially providing a more holistic view of CKD progression. Our study's aim was to focus on serum UMD levels and their diagnostic utility across different CKD stages, evaluating its significance as a complementary biomarker to traditional urinary markers. In the future, urinary UMD also needs to be studied in greater depth, just as we have demonstrated with serum UMD, to establish its utility at a meta-analysis level and further validate its clinical application in CKD management.

Our study, while comprehensive, is not without limitations that warrant consideration. First and foremost, the diverse array of participant characteristics and the different etiologies of CKD in our review introduces variability. This diversity across methodologies, patient populations, and CKD diagnostic criteria may contribute to heterogeneity in our analysis, potentially impacting the coherence and generalizability of our findings. A subgroup analysis according to the etiology of CKD was not possible due to the limited number of studies that are currently published in the literature that evaluated this topic. Furthermore, the variability in diagnostic approaches for identifying CKD among the studies included in our review presents a challenge. Methods ranging from eGFR estimation to direct GFR measurement introduce complexity in ensuring uniformity and accuracy in CKD classification. Another consideration lies in the measurement of UMD levels, where differences in methodologies across studies, patient populations, and CKD diagnostic criteria may lead to measurement heterogeneity. Discrepancies in sample processing, assay techniques, and calibration protocols could influence the comparability of UMD measurements, potentially impacting the precision of our results. Variability in the extent and nature of covariate adjustments across studies may influence the accuracy and precision of our estimates pertaining to the association between UMD levels and CKD outcomes. Considering these limitations, cautious interpretation of our findings is essential. While our study provides valuable insights into the association between UMD levels and CKD outcomes, further research refinement is necessary to enhance the robustness and applicability of our findings.

Our study also presents several notable strengths that highlight the validity and significance of our findings. Firstly, our adherence to rigorous methodology ensures transparency and comprehensiveness in our approach, enhancing the reliability of our results. Moreover, the inclusion of a diverse range of studies spanning various geographic regions and populations enriches the breadth and applicability of our findings. This comprehensive approach allows for a nuanced understanding of the association between UMD levels and CKD across different contexts, strengthening the generalizability of our conclusions. By synthesizing data from multiple sources and employing standardized methodologies, we enhance the reliability and precision of our estimates, facilitating meaningful insights into the relationship between UMD and CKD. Additionally, our study benefits from a thorough evaluation of potential sources of bias and heterogeneity, including publication bias and methodological variability. By acknowledging and addressing these topics, we enhance the credibility and validity of our findings, ensuring a comprehensive and balanced interpretation of the data. Overall, our study represents a significant contribution to the existing literature on UMD and CKD, offering valuable insights that have implications for both research and clinical practice. The strengths outlined above underscore the robustness and significance of our findings, reinforcing the

importance of our study in advancing understanding and informing future research in this field.

5. CONCLUSIONS

In patients with CKD, UMD levels were significantly altered compared to healthy controls, with levels decreasing as CKD progressed. Lower uromodulin levels were more pronounced in advanced stages of CKD.

Authors contributions: G.G. and R.C.C. had the idea of the manuscript. G.G., R.C.C., and A.I. independently applied the search strategy and performed the study selection. R.C.C. and G.G., performed risk of bias assessment. R.C.C., G.G., and A.I. performed the data extraction. A.I. and D.C.L. conducted the statistical analysis. R.C.C. and G.G. drafted the manuscript. A.I., D.C.L, and S.L.P contributed to the writing of the manuscript. A.I. and D.C.L. made substantial contributions to the conception and critically revised the manuscript for important intellectual content. All authors revised the final manuscript and approved the final version.

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References:

1. Fassett RG, Venuthurupalli SK, Gobe GC, Coombes JS, Cooper MA, Hoy WE. Biomarkers in chronic kidney disease: a review. Kidney Int. 2011;80(8):806-21.
2. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Int. 2021;99(3s):S1-s87.
3. Takata T, Isomoto H. The Versatile Role of Uromodulin in Renal Homeostasis and Its Relevance in Chronic Kidney Disease. Intern Med. 2024;63(1):17-23.
4. Lhotta K. Uromodulin and chronic kidney disease. Kidney Blood Press Res. 2010;33(5):393-8.
5. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. 2021;372:n71.
6. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-5.
7. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software. 2010;36(3):1 - 48.
8. Akl E, Altman D, Aluko P, Askie L, Beaton D, Berlin J, et al. Cochrane Handbook for Systematic Reviews of Interventions2019.
9. Boscardin CK, Sewell JL, Tolsgaard MG, Pusic MV. How to Use and Report on p-values. Perspect Med Educ. 2024;13(1):250-4.
10. Steubl D, Block M, Herbst V, Nockher WA, Schlumberger W, Satanovskij R, et al. Plasma Uromodulin Correlates With Kidney Function and Identifies Early Stages in Chronic Kidney Disease Patients. Medicine (Baltimore). 2016;95(10):e3011.
11. Zyłka A, Dumnicka P, Kuśnierz-Cabala B, Gala-Błądzińska A, Ceranowicz P, Kucharz J, et al. Markers of Glomerular and Tubular Damage in the Early Stage of Kidney Disease in Type 2 Diabetic Patients. Mediators of Inflammation. 2018;2018.
12. Usui R, Ogawa T, Takahashi H, Iwasaki C, Koike M, Morito T, et al. Serum uromodulin is a novel renal function marker in the Japanese population. Clin Exp Nephrol. 2021;25(1):28-36.
13. Ananth S, Sreedhar Sharma M, Venkata Pakki Reddy PL, Umare M. ROLE OF SERUM UROMODULIN AS A BIOMARKER OF DECLINE IN RENAL FUNCTION IN CHRONIC KIDNEY DISEASE. International Journal of Medicine and Public Health. 2024;14(2):191-5.
14. Rajayapandian K, Singaravel VP, Natesan S. Study of Serum Uromodulin as A Biomarker of Kidney Function in Patients with CKD and to Identify Early Stages of Chronic Kidney Disease. European Journal of Cardiovascular Medicine. 2024;14(3):76-83.
15. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;105(4s):S117-s314.
16. Song L, Buggs V, Samara VA, Bahri S. Calculation of the estimated glomerular filtration rate using the 2021 CKD-EPI creatinine equation and whole blood creatinine values measured with Radiometer ABL 827 FLEX. Clin Chem Lab Med. 2022;60(6):867-76.
17. The Modification of Diet in Renal Disease Study: design, methods, and results from the feasibility study. Am J Kidney Dis. 1992;20(1):18-33.
18. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.
19. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. Jama. 2019;322(13):1294-304.
20. Chang CC, Chen CY, Huang CH, Wu CL, Wu HM, Chiu PF, et al. Urinary glycated uromodulin in diabetic kidney disease. Clin Sci (Lond). 2017;131(15):1815-29.

21. Leiherer A, Muendlein A, Saely CH, Kinz E, Brandtner EM, Fraunberger P, et al. Serum uromodulin is associated with impaired glucose metabolism. Medicine. 2017;96(5):e5798.
22. El-Achkar TM, Wu XR. Uromodulin in kidney injury: an instigator, bystander, or protector? Am J Kidney Dis. 2012;59(3):452-61.
23. Leiherer A, Muendlein A, Saely CH, Brandtner EM, Geiger K, Fraunberger P, et al. The value of uromodulin as a new serum marker to predict decline in renal function. J Hypertens. 2018;36(1):110-8.
24. Garimella PS, Biggs ML, Katz R, Ix JH, Bennett MR, Devarajan P, et al. Urinary uromodulin, kidney function, and cardiovascular disease in elderly adults. Kidney Int. 2015;88(5):1126-34.
25. Thornley C, Dawnay A, Cattell WR. Human Tamm-Horsfall glycoprotein: urinary and plasma levels in normal subjects and patients with renal disease determined by a fully validated radioimmunoassay. Clin Sci (Lond). 1985;68(5):529-35.
26. Risch L, Lhotta K, Meier D, Medina-Escobar P, Nydegger UE, Risch M. The serum uromodulin level is associated with kidney function. Clin Chem Lab Med. 2014;52(12):1755-61.
27. Thulesen J, Jørgensen PE, Torffvit O, Nexø E, Poulsen SS. Urinary excretion of epidermal growth factor and Tamm-Horsfall protein in three rat models with increased renal excretion of urine. Regul Pept. 1997;72(2-3):179-86.
28. Canki E, Kho E, Hoenderop JGJ. Urinary biomarkers in kidney disease. Clinica Chimica Acta. 2024;555:117798.
29. Benito S, Unceta N, Maciejczyk M, Sánchez-Ortega A, Taranta-Janusz K, Szulimowska J, et al. Revealing novel biomarkers for diagnosing chronic kidney disease in pediatric patients. Scientific Reports. 2024;14(1):11549