

The Analysis Study of Association of Intestinal Microbiota and Kidney Disease: A Comprehensive Systematic Review

^{1,2} Rachmad Alsy Setiafadi, ³ Nor Anisatun Nida, ³ Muhammad Naufal
Marom

¹ General Practitioner, PKU Muhammadiyah Mayong General Hospital,
Jepara Regency, Central Java, Indonesia

² Faculty of Medicine, Muhammadiyah University of Surakarta, Surakarta
City, Central Java, Indonesia

³ Faculty of Medicine, Sultan Agung Islamic University, Semarang City,
Central Java, Indonesia

Correspondence : alsysetiafadi47@gmail.com

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ABSTRACT

Background: Disruptions in gut microbiota composition (dysbiosis) in kidney diseases can lead to worsened kidney function. Dysbiosis may increase intestinal permeability and systemic inflammation, allowing bacterial toxins to enter the bloodstream and exacerbate CKD and its complications. This systematic review aims to evaluate the association of intestinal microbiota and kidney disease by analyzing available studies of the last 10 years.

Methods: The study adhered to PRISMA 2020 standards, examining English literature from 2014 to 2024. It excluded editorials, reviews from the same journal, and submissions without a DOI. PubMed, SagePub, SpringerLink, and Google Scholar were utilized as literature sources. **Result:** Initially retrieving 360 articles from online databases (PubMed, SagePub, SpringerLink and Google Scholar) eight relevant papers were selected after three rounds of screening for full-text analysis.

Conclusion: Gut microbiota alterations are closely linked to chronic kidney disease (CKD) and end-stage renal disease (ESRD), impacting inflammation and disease progression. Microbial shifts offer potential diagnostic and therapeutic insights, though further research is needed for clinical application.

Keyword: gut microbiota, chronic kidney disease, uremic toxins

INTRODUCTION

Chronic kidney disease (CKD) is a major global health concern, affecting 6-10% of the adult population across different countries. It encompasses a wide range of conditions, from mild kidney impairment to end-stage renal disease (ESRD). Cardiovascular disease (CVD) remains the leading cause of death in patients with CKD, with traditional risk factors such as hypertension, diabetes, and dyslipidemia playing significant roles. However, non-conventional factors, particularly chronic inflammation, have also emerged as major contributors to the increased cardiovascular risk seen in CKD patients.^{1,2}

In recent years, the concept of the gut-kidney axis has gained attention, highlighting the intricate relationship between gut microbiota and kidney health. The gut microbiota, which consists of trillions of microorganisms, is essential for maintaining host health through its role in immune regulation, energy

metabolism, and the production of short-chain fatty acids (SCFAs).^{3,4} However, in CKD, disruptions in the composition and function of the gut microbiota—known as dysbiosis—can lead to detrimental effects on kidney function. Dysbiosis can result in increased intestinal permeability, systemic inflammation, and the leakage of bacterial toxins into the bloodstream, further exacerbating CKD and its complications.^{5,6}

Gut dysbiosis in CKD is linked to the accumulation of uremic toxins such as indoxyl sulfate (IS), p-cresyl sulfate (PCS), and trimethylamine-N-oxide (TMAO), which contribute to oxidative stress, endotoxemia, and inflammation. These toxins not only worsen kidney function but also heighten the risk of cardiovascular diseases.^{7,8} Additionally, uremia-induced damage to the intestinal barrier weakens the structural integrity of the gut lining, facilitating the translocation of endotoxins and pro-inflammatory molecules into the

bloodstream, perpetuating a chronic inflammatory state in CKD patients.⁹

Short-chain fatty acids (SCFAs), which are produced by saccharolytic bacteria in the gut, have been recognized for their protective effects against kidney damage through anti-inflammatory and antioxidant mechanisms. However, in CKD, there is often a reduction in SCFA-producing bacteria and an increase in proteolytic bacteria that generate toxic metabolites. This microbial imbalance contributes to the overall progression of CKD and its associated complications. Therefore, understanding the gut-kidney axis is crucial, as it opens avenues for potential therapeutic interventions targeting gut dysbiosis, microbial metabolites, and the intestinal barrier in CKD management.¹⁰⁻¹² This systematic review aims to evaluate the association of intestinal microbiota and kidney disease by analyzing available studies of the last 10 years.

METHODS

Protocol

The author carefully followed the rules laid out in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. This was done to make sure the study met all its standards. The selection of this methodological approach was specifically aimed at ensuring the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic to to evaluate the association of intestinal microbiota and kidney based on literatures of the last 10 years. This study meticulously analyzed data on literatures to provide insights and enhance patient treatment strategies. The primary objective of this paper is to highlight the collective significance of the identified key points.

Inclusion criteria for this study entail: 1) Papers must be in English, and 2) Papers must have been published between 2014 and 2024. Exclusion criteria comprise: 1) Editorials; 2) Submissions without a

DOI; 3) Previously published review articles; and 4) Duplicate entries in journals.

Search Strategy

The keywords used for this research are gut microbiota, chronic kidney disease, uremic toxins. The Boolean MeSH keywords inputted on databases for this research are:

((("gastrointestinal microbiome"[MeSH Terms] OR ("gastrointestinal"[All Fields] AND "microbiome"[All Fields]) OR "gastrointestinal microbiome"[All Fields] OR ("gut"[All Fields] AND "microbiota"[All Fields]) OR "gut microbiota"[All Fields]) AND ("renal insufficiency, chronic"[MeSH Terms] OR ("renal"[All Fields] AND "insufficiency"[All Fields] AND "chronic"[All Fields]) OR "chronic renal insufficiency"[All Fields] OR ("chronic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "chronic kidney disease"[All Fields] AND ("uremic toxins"[MeSH Terms] OR ("uremic"[All Fields] AND "toxins"[All Fields]) OR "uremic toxins"[All Fields])) AND

((y_10[Filter]) AND (clinicaltrial[Filter]))).

Data retrieval

The authors assessed the studies by reviewing their abstracts and titles to determine their eligibility, selecting relevant ones based on their adherence to the inclusion criteria, which aligned with the article's objectives. A consistent trend observed across multiple studies led to a conclusive result. The chosen submissions had to meet the eligibility criteria of being in English and a full-text.

This systematic review exclusively incorporated literature that met all predefined inclusion criteria and directly pertained to the investigated topic. Studies failing to meet these criteria were systematically excluded, and their findings were not considered. Subsequent analysis examined various details uncovered during the research process, including titles, authors, publication dates, locations, study methodologies, and parameters.

Quality Assessment and Data Synthesis

Each author independently evaluated the research presented in the title and abstract of the publication to determine which ones merited further exploration. The subsequent

stage involved assessing all articles that met the predefined criteria for inclusion in the review. Decisions on including articles in the review were based on the findings uncovered during this evaluation process.

Table 1. Article Search Strategy

Database	Strategi Pencarian	Hits
Pubmed	<i>((("gastrointestinal microbiome"[MeSH Terms] OR ("gastrointestinal"[All Fields] AND "microbiome"[All Fields]) OR "gastrointestinal microbiome"[All Fields] OR ("gut"[All Fields] AND "microbiota"[All Fields]) OR "gut microbiota"[All Fields]) AND ("renal insufficiency, chronic"[MeSH Terms] OR ("renal"[All Fields] AND "insufficiency"[All Fields] AND "chronic"[All Fields]) OR "chronic renal insufficiency"[All Fields] OR ("chronic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "chronic kidney disease"[All Fields]) AND ("uremic toxins"[MeSH Terms] OR ("uremic"[All Fields] AND "toxins"[All Fields]) OR "uremic toxins"[All Fields])) AND ((y 10[Filter]) AND (clinicaltrial[Filter]))</i>	100
Science Direct	<i>((gut microbiota) AND (chronic kidney disease)) AND (uremic toxins)</i>	150
Sagepub	<i>((gut microbiota) AND (chronic kidney disease)) AND (uremic toxins)</i>	50
Google Scholar	<i>((gut microbiota) AND (chronic kidney disease)) AND (uremic toxins)</i>	160

Table 2. JBI *Critical appraisal of Study*

Parameters	Rossi (2014)	Wong (2014)	Jiang (2017)	Hu (2020)	Vaziri (2014)	Ren (2020)	Fukuhara (2024)	Derosa (2020)
1. Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation Was there a control group?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Bias related to confounding factors Were participants included in any comparisons similar?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	No.	No.	No.	No.	No.	No.	No.	No.
5. Bias related to assessment, detection, and measurement of the outcome Were there multiple measurements of the outcome, both pre and post the intervention/exposure? Were the outcomes of participants included in any comparisons measured in the same way? Were outcomes measured in a reliable	Yes No. Yes	Yes No. Yes	Yes No. Yes	Yes No. Yes	Yes No. Yes	Yes No. Yes	Yes No. Yes	Yes No. Yes

way?

6. Bias related to participant retention

Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?

Yes Yes Yes Yes Yes Yes Yes Yes

7. Statistical conclusion validity

Was appropriate statistical analysis used?

Yes Yes Yes Yes Yes Yes Yes Yes

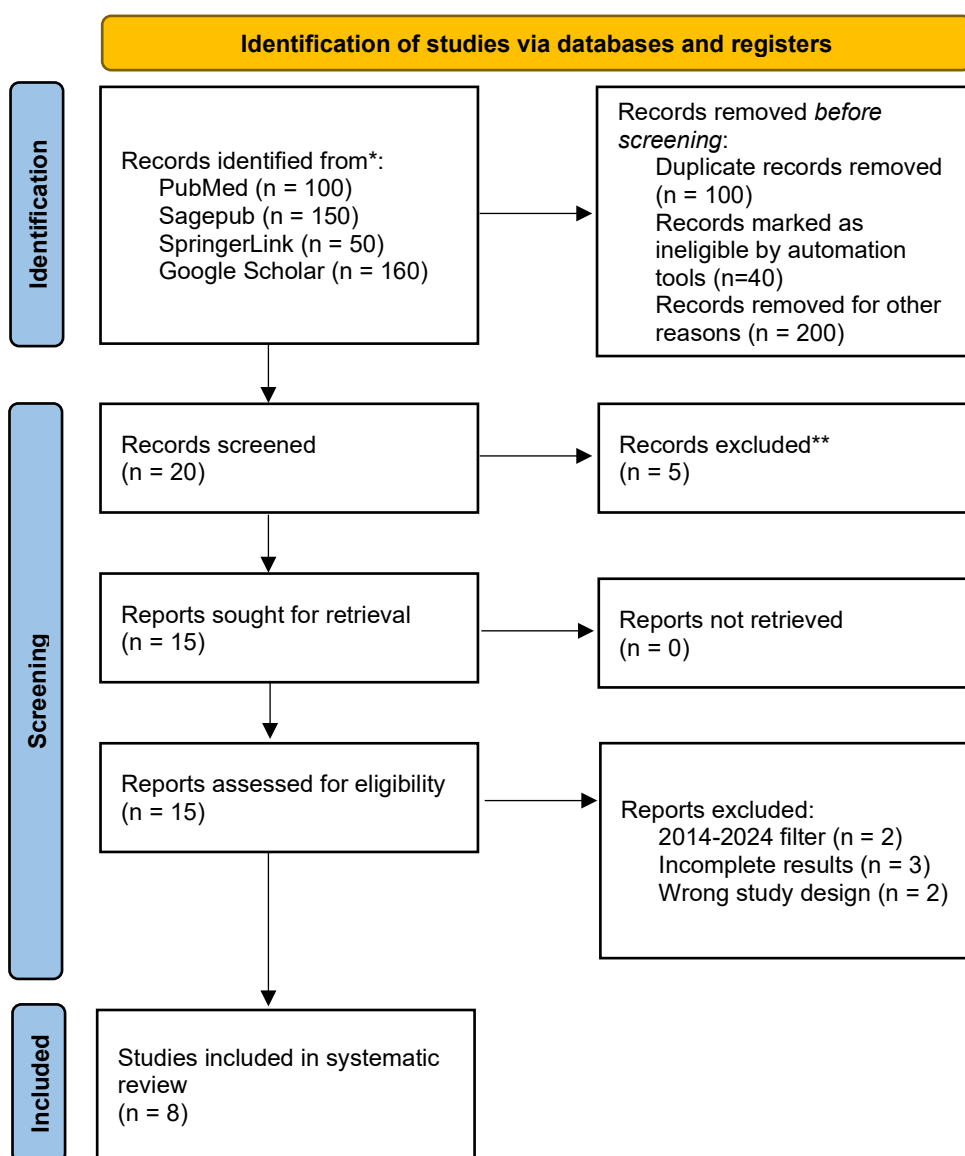


Figure 1. Article search flowchart

RESULT

The initial number of articles retrieved from online databases (PubMed, SagePub, SpringerLink, and Google Scholar) is 360 articles. After conducting three levels of screening, eight articles that directly relate to the current systematic review have been chosen for further assessment through full-text reading and analysis. Table 3 presents the selected literature included in this analysis.

Table 3. The literature included in this study

No	Author	Origin	Method	Sample	Result
1.	Rossi, et al. ¹³ (2014)	Australia	Cross sectional study	149 patients	In a study of 149 CKD patients (59% male; mean age 60 years; 44% diabetic; mean eGFR 40 mL/min/1.73 m ²), the uremic toxins indoxyl sulfate (IS) and p-cresyl sulfate (PCS) were found to be independently associated with inflammatory markers such as IL-6, TNF- α , and IFN- γ . PCS was also linked to increased arterial stiffness, measured by pulse wave velocity (PWV). Additionally, both IS and PCS were associated with an antioxidant enzyme, glutathione peroxidase (GPx). These findings suggest that inflammation and oxidative stress may contribute to the nephro- and cardiovascular

					toxicities of IS and PCS in CKD patients.
2.	Wong, et al. ¹⁴ (2014)	USA	Case control study	36 patients	In patients with end-stage renal disease (ESRD), 19 dominant microbial families were identified, with 12 families producing urease, 5 producing uricase, and 4 producing indole and p-cresol-forming enzymes. Conversely, among the 4 microbial families that were reduced in ESRD patients, 2 possessed butyrate-forming enzymes. These shifts in microbial composition are statistically significant ($p < 0.05$).
3.	Jiang, et al. ¹⁵ (2017)	China	Retrospective cohort study	112 patients	In a study comparing fecal microbiota between 52 end-stage renal disease (ESRD) patients and 60 healthy controls in southern China, significant differences in microbial composition were observed. ESRD patients had a lower total bacterial count ($p < 0.01$), with Bacteroides dominating, while the healthy group showed a higher prevalence of Prevotella. Additionally, 11 bacterial taxa were overrepresented in ESRD patients, while 22

					taxa were more abundant in healthy controls. Key butyrate-producing bacteria, including Roseburia, Faecalibacterium, Clostridium, Coprococcus, and Prevotella, were reduced in the ESRD group. Canonical correspondence analysis indicated that Cystatin C, creatinine, and eGFR were major environmental factors influencing microbial communities.
4.	Hu, et al. ¹⁶ (2020)	China	Retrospective cohort study	115 patients	Differences in gut microbiota composition and diversity were observed between CKD patients and healthy controls, with disease severity influencing these microbial shifts. CKD patients exhibited an increased abundance of Proteobacteria and decreased Synergistetes, particularly in advanced disease stages. There was a reduction in butyrate-producing bacteria and an increase in potential pathogens in CKD patients. Specific microbial genera, including Escherichia-Shigella,

					Parabacteroides, and Roseburia, were able to distinguish CKD patients from healthy controls with high accuracy using a random forest model. Functional analysis showed that fatty acid and inositol phosphate metabolism were enriched in CKD patients, while pathways involved in amino acid biosynthesis and energy metabolism were more prominent in healthy controls.
5.	Vaziri, et al. ¹⁷ (2014)	USA	Retrospective cohort study	36 objects	Significant differences were observed in the abundance of 190 bacterial operational taxonomic units (OTUs) between end-stage renal disease (ESRD) patients and healthy controls. Bacterial families such as Brachyobacterium, Catenibacterium, Enterobacteriaceae, and Pseudomonadaceae were notably increased in ESRD patients. To control for inter-individual variation, comorbidities, diet, and medications, a rat model was used, showing similar changes, with 175 bacterial OTUs differing between uremic

					and control animals. Specifically, uremic rats had a marked reduction in Lactobacillaceae and Prevotellaceae families.
6.	Ren, et al. ¹⁸ (2020)	China	Retrospective cohort study	520 patients	In a study analyzing 520 fecal samples from different regions of China, gut microbiome changes in chronic kidney disease (CKD) were characterized, and microbial markers were identified as potential diagnostic tools. Compared to healthy controls (n = 210), CKD patients (n = 110) exhibited significantly reduced gut microbial diversity, with increased levels of Klebsiella and Enterobacteriaceae and reduced Blautia and Roseburia. Functional analysis revealed an increase in tryptophan and phenylalanine metabolism and a decrease in arginine and proline metabolism in CKD. Five optimal microbial markers were identified using a random forest model, showing high diagnostic accuracy with area under the curve (AUC) values of 0.9887 in the discovery cohort and

					0.9512 in the validation cohort. Additionally, <i>Thalassospira</i> and <i>Akkermansia</i> were associated with CKD progression, and 13 operational taxonomy units correlated with six clinical indicators of CKD
7.	Fukuhara, et al. ¹⁹ (2024)	Japan	Retrospective cohort study	38 patients	This study involved 38 patients with moderate to severe frailty, divided into low-GNRI (n=18) and high-GNRI (n=20) groups. The low-GNRI group had more severely frail patients and exhibited significantly lower levels of serum transthyretin, cholinesterase, total cholesterol, and β2-microglobulin compared to the high-GNRI group. Differences in gut microbiota were noted, with lower abundances of Actinobacteria and Proteobacteria in the low-GNRI group. Specifically, the genus <i>Bifidobacterium</i>, including species <i>Bifidobacterium adolescentis</i> and <i>Bifidobacterium bifidum</i>, was significantly lower in the low-GNRI group.

8.	Derosa, et al. ²⁰ (2020)	France	Retrospective cohort study	69 patients	In this study, recent antibiotic (ATB) use (16% of patients) significantly reduced objective response rates to immunotherapy (from 28% to 9%) and altered gut microbiota composition, with species like <i>Clostridium hathewayi</i> becoming dominant in patients with renal cell carcinoma (RCC). Additionally, tyrosine kinase inhibitors (TKIs) taken prior to nivolumab also influenced microbiota shifts. Experiments using fecal microbiota transplantation (FMT) in mice demonstrated that gut bacteria from responding RCC patients or specific beneficial commensals (<i>Akkermansia muciniphila</i> and <i>Bacteroides salyersiae</i>) improved immune checkpoint blockade (ICB) efficacy.
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Rossi, et al.¹³ (2014) suggest that inflammation and oxidative stress may contribute to the nephro- and cardiovascular toxicities of IS and PCS in CKD patients. The study highlights the need for intervention trials aimed at reducing IS and PCS levels through dietary modifications and assessing their impact on cardiovascular outcomes in CKD.

Wong, et al.¹⁴ (2014) showed that the expansion of bacteria producing harmful compounds such as indoxyl sulfate, p-cresol sulfate, and urea-derived ammonia, coupled with a reduction in beneficial short-chain fatty acid (SCFA)-producing bacteria, may have negative implications for the health of ESRD patients.

Jiang, et al.¹⁵ (2017) showed that in ESRD patients, reduced butyrate-producing bacteria were negatively associated with inflammatory markers like CRP and Cystatin C, highlighting a link between gut microbiota and both inflammation and renal function in CKD.

Hu, et al.¹⁶ (2020) suggest that gut microbiota composition and function are linked to CKD severity, and specific microbes may serve as potential biomarkers for early diagnosis and monitoring of CKD progression.

Vaziri, et al.¹⁷ (2014) indicated that uremia significantly alters gut microbiome composition, though the biological implications of these changes require further study.

Ren, et al.¹⁸ (2020) showed that functional analysis revealed an increase in tryptophan and phenylalanine metabolism and a decrease in arginine and proline metabolism in CKD. Additionally, *Thalassospira* and *Akkermansia* were associated with CKD progression, and 13 operational taxonomy units correlated with six clinical indicators of CKD. The study highlights the potential of microbial markers as non-invasive diagnostic tools for CKD across different regions of China.

Fukuhara, et al.¹⁹ (2024) suggests that the GNRI is a valuable nutritional risk index in hemodialysis patients and highlights the strong association between deficiencies in *Bifidobacterium* species and increased nutritional risk.

Derosa, et al.²⁰ (2020) concluded that ATBs and TKIs impact gut microbiota composition, affecting the success of immunotherapy, with potential implications for identifying new bacterial biomarkers.

DISCUSSION

The association between intestinal microbiota and kidney disease has become increasingly evident, with recent studies revealing substantial insights into how gut microbiota alterations impact chronic kidney disease (CKD) and end-stage renal disease (ESRD). Research consistently demonstrates significant differences in gut microbiota composition between CKD or ESRD patients and healthy controls.²¹⁻²³

Rossi et al. (2014) found that uremic toxins like indoxyl sulfate (IS) and p-cresyl sulfate (PCS) were linked with inflammatory markers and arterial stiffness in CKD patients, suggesting that these toxins contribute to kidney and cardiovascular complications.¹³ Similarly, Wong et al. (2014) reported an increased prevalence of microbial families producing harmful compounds such as urease and indole in ESRD patients, coupled with a reduction in beneficial butyrate-producing bacteria.¹⁴ This reduction in butyrate-producing bacteria was further highlighted by Jiang et al.

(2017), who observed lower levels of key butyrate producers like *Roseburia* and *Faecalibacterium* in ESRD patients, suggesting a possible link between decreased butyrate production and renal inflammation.¹⁵

The impact of gut microbiota on disease severity and function is also evident from the studies reviewed. Hu et al. (2020) showed that CKD severity correlates with specific microbial shifts, including an increase in Proteobacteria and a decrease in Synergistetes, which reflect microbial dysbiosis in more advanced stages of the disease.¹⁶ Functional analysis indicated altered metabolic pathways, such as increased fatty acid and inositol phosphate metabolism in CKD patients, potentially contributing to disease progression. Similarly, Vaziri et al. (2014) and Ren et al. (2020) identified significant changes in bacterial operational taxonomic units (OTUs) in ESRD and CKD patients, suggesting these microbial shifts could serve as useful biomarkers for diagnosis and monitoring.^{17,18}

The potential of microbial markers for diagnosis and prognosis

is highlighted by several studies. Ren et al. (2020) identified microbial markers with high diagnostic accuracy, and Fukuhara et al. (2024) demonstrated the value of the GNRI as a nutritional risk index linked to gut microbiota composition in hemodialysis patients.^{18,19} Furthermore, Derosa et al. (2020) showed that beneficial bacteria like *Akkermansia muciniphila* and *Bacteroides salyersiae* could enhance immunotherapy outcomes in cancer patients, suggesting that similar microbial interventions might be beneficial for CKD management.²⁰

Despite promising progress, challenges remain in understanding the biological impact of microbiota changes on kidney disease. More research is needed to confirm findings, track microbiota changes over time, and assess the effects of interventions. Continued study may enable personalized, microbiota-based treatments for CKD and ESRD.²⁴

CONCLUSION

Gut microbiota alterations are closely linked to chronic kidney

disease (CKD) and end-stage renal disease (ESRD), impacting inflammation and disease progression. Microbial shifts offer potential diagnostic and therapeutic insights, though further research is needed for clinical application.

DISCLOSURE STATEMENT

Disclosure Statement : The authors have no conflicts of Interest to declare.

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