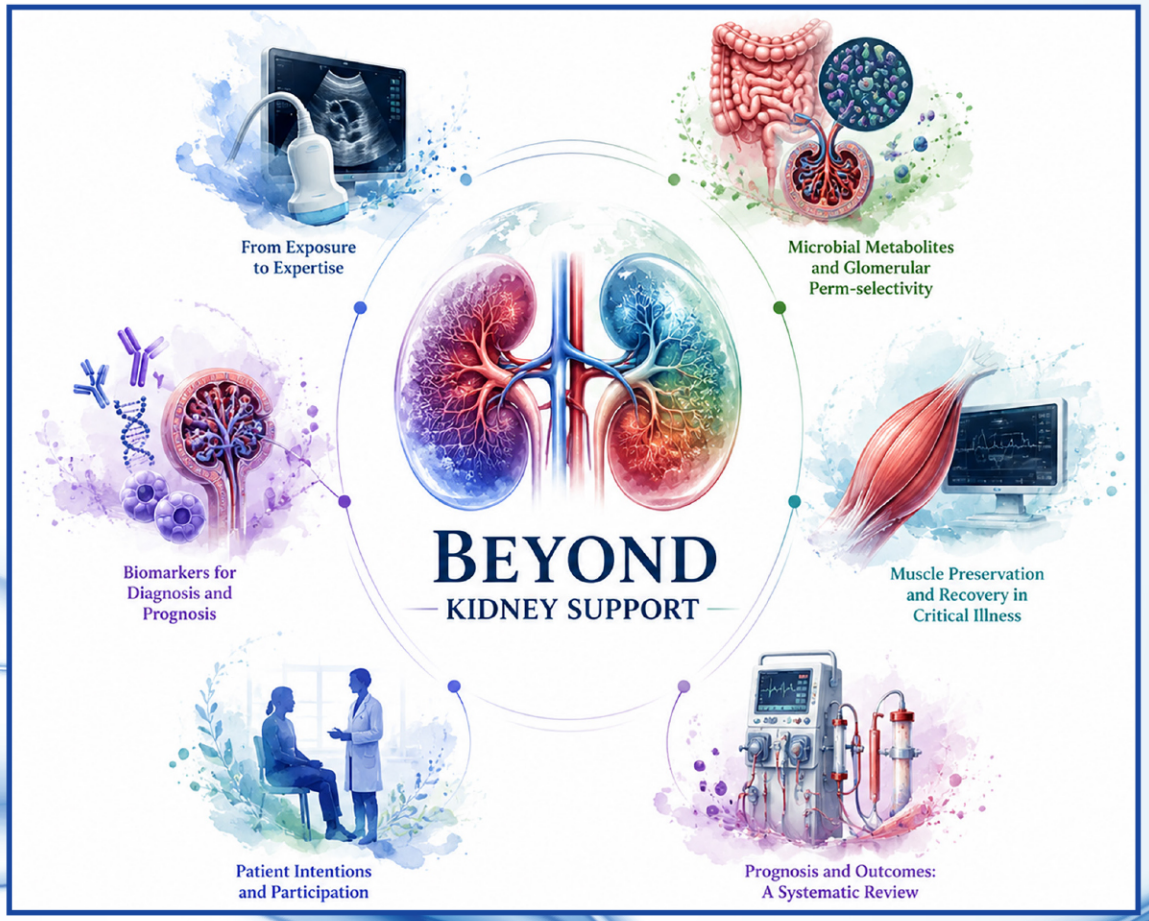
RJCCN

Research Journal of Critical Care Nephrology

Volume 2, Number 3, July 2026



RESEARCH JOURNAL OF CRITICAL CARE NEPHROLOGY

eISSN 3115-8463

Research Journal of Critical Care Nephrology Volume 2 Number 3 July 2026

RJCCN

Research Journal of Critical Care Nephrology

AIMS AND SCOPE

The *Research Journal of Critical Care Nephrology* (*RJCCN*), a peer-reviewed journal in English. The aim of the *RJCCN* is the worldwide reflection of the knowledge produced by the scientists and clinicians and nurses in nephrology especially critical care nephrology. It will be published quarterly since October 2025. The *RJCCN* provides a new platform for the advancement of the field. The journal's objective is to serve as a focal point for debates and exchange of knowledge and experience among researchers in a global context. Original papers, case reports, and invited reviews and editorial on all aspects of kidney diseases, Nephrology, Urology, Organ Transplantation, Intra-abdominal hypertension, CRRT, AKI, ICU care in Nephrology, Shock, Sepsis, ECMO, ARDS, and all topics in Anesthesiology, Vascular Surgery, Infectious Disease, Pediatrics, Pulmonology, Cardiology, Neurology, Cardiac Surgery, Toxicology, Oncology, Gynecology, and Forensic Medicine related to Nephrology and especially critical care nephrology will be covered by the *RJCCN*. Research on the basic science, clinical practice, and socio-economics of renal health are all welcomed by the journal editors.

DISCLAIMER

The statements and opinions expressed in the *RJCCN* reflect solely the views of the author(s) and contributor(s). The appearance of advertisements in the Journal does not reflect a warranty, endorsement, or approval of any of the products or services described.

eISSN. 3115-8463

Editorial Office.
Dialysis Department, Emam Hosein Hospital, Shahid Madani St, Postal Code: 1617763141, Tehran, Iran
Tel: +98 912 3834394
Website: www.rjccn.org
E-mail: info@rjccn.org, admin@rjccn.org, rjccn2024@gmail.com

Publisher. Self-published

Page Setter. Mahdi Akbarzadeh, graphicnegareh.group@gmail.com

Journal Subscription. The *RJCCN* is published every other season. It is free for subscription. To subscribe, please see the subscription form in *RJCCN* website. For more information you can contact the editorial office of the journal.

Manuscript Submission. Please prepare your manuscript according to the *Instructions to Authors* of the journal. You should send your manuscript via online submission system provided on www.rjccn.org.

Indexing/Abstracting. SID, Magiran, Sivilica (Local Indexing)

Cover: Advancing Scientific Knowledge and Clinical Practice. See page 161

RJCCN

Research Journal of Critical Care Nephrology

Volume 2, Number 3, July 2026

Table of Contents

RJCCN
Research Journal of Critical Care Nephrology

INSTRUCTIONS TO AUTHORS

*Summarized Version**
Updated June 2026

The *RJCCN* publishes manuscripts on nephrology especially critical care nephrology and related topics. Original research papers, case reports, and letters to the editor are considered for publication, all of which undergo extensive peer review prior to their acceptance. Review articles and Editorials are invited, but unsolicited reviews can be proposed to the editors by sending the title for initial consideration. Primarily, they are reviewed by the editors and biostatistical advisors. If extensive revision is not required, peer review will be done by at least 2 experts in the field. Otherwise the author(s) have to revise their manuscripts before the peer review process. Based on the comments of reviewers and the responses or revisions of the author(s), the Editorial Board either accepts or rejects the manuscripts. Reviewers' and authors' identities are kept confidential, and the existence of a submitted manuscript is not revealed to anyone other than the reviewers and editorial team.

Submission of Manuscripts

Manuscripts along with a covering letter and the signed Authors' Agreement Form (available from www.rjccn.org) should be submitted to the Editor-in-Chief of the *RJCCN* via the online submission system.

Electronic submission. The online submission is available on the journal's web site (www.rjccn.org) and is the only way of manuscript submission.

Identifiers

ORCID ID is essential for corresponding author.
The DOI will be gotten by journal after preparing the proof format.

Preparation of Manuscripts

General Instructions. Manuscripts should follow the stylistic conventions set forth in the *American Medical Association Manual of Style*, 10th edition. The Editors have the right to make editorial corrections and additional changes with the knowledge and approval of corresponding author. The preferred word processing format for the manuscript file is Microsoft Word. The main manuscript should carry the title page, abstract, main text, references, figures legends, and tables of the paper. Figures, including diagrams, photographs, etc, should be supplied separately and submitted as supplementary files. Please do not attach figures in the digital format of the main manuscript.
Manuscripts should be double-spaced, with 2.5-cm margins on all sides of the paper. All abbreviations must be spelled out the first time they are used, followed by the abbreviated form in parentheses. Units of measurement must be complied with the International System of Units (SI).

Original Research Papers. The journal considers Systematic Reviews and Meta-analysis as Original Articles provided that they are conducted using a rigorous, transparent, and reproducible methodology and comply with international reporting standards. Original papers should be arranged as: Title Page, Abstract, Introduction, Methods, Results, Discussion, Conclusions, Acknowledgements, References, Tables, and Legends. The title page must include the following: title; full first name; surname; affiliations of each contributor; each author's highest academic degree; the name, full postal address, telefax/telephone numbers of the contributor who will deal with correspondence; keywords; and the total number of pages and figures being submitted. A structured abstract (with the subheadings Introduction, Materials and Methods, Results, and Conclusions) should appear on the second page of the manuscript and should not exceed 250 words. The main text (excluding the abstract and references) should not exceed 3000 words.

Reports of Clinical Trials. Original research papers that report a randomized controlled trial, should comply with the guidelines provided by the Consolidated Standards of Reporting Trials (CONSORT) group. Also, supplying the manuscript with a CONSORT flowchart diagram is highly encouraged. Please refer to the CONSORT web site to see the guidelines and the flowchart template.
Although it is not obligatory yet, researchers who would like to publish reports of their clinical trial in *RJCCN* are strongly encouraged to register their studies in a registry of clinical trials proposed by the World Health Organization or the International Committee of Medical Journal Editors. As an option, the Iranian Registry of Clinical Trials is a registry suggested by the World Health Organization.

Reviews. Anyone wishing to write a review for the journal should first contact the editors. Review articles should be composed of systematic critical assessments of literature and data sources pertaining to clinical topics, emphasizing factors such as cause, diagnosis, prognosis, therapy, or prevention. They should have unstructured abstracts. All articles and data sources reviewed should include information about the specific type of study or analysis, population, intervention, exposure, and tests or outcomes. Authors of review articles should be experts and have contributions in the field of the addressed subject.

Special Reports. Manuscripts that cannot be considered as a review or original article, or those with special features, such as national reports, will be considered to be published in this section, upon the decision of the editor. An unstructured abstract not longer than 120 words is required for this section. The body of the manuscript should not exceed 1200 words. Tables and/or Figures should be limited to 2 ones and references to 15 in maximum.

Case Reports. Case reports should be arranged as follows: Title Page, Abstract (nonstructured, not exceeding 150 words), Introduction, Case Report, Discussion, Conclusions, References, and Legends. The length should not exceed 700 words.

Brief Communications. Original research papers can also be published in a brief format. Submitted papers that are of interest but are not acceptable as a full-length original

contribution are offered by the editor to be published in this section. Also, the authors can primarily submit their papers for consideration of publication in this section. An unstructured abstract not longer than 150 words is required for this section. The body of the manuscript should not exceed 1500 words, and no heading or subheading should be used. Tables and/or Figures should be limited to 2 ones and references to 15 in maximum.

Editorial. Editorials are concise scholarly articles that provide expert commentary, perspective, or insight on topics of current interest in nephrology, especially critical care nephrology, including recently published articles in the journal. Editorials are usually invited by the Editor-in-Chief or Editorial Board. Editorials should be focused, balanced, and evidence-based, not exceed 1,200 words, include a limited number of references (up to 15). It must not contain original unpublished data.

Commentary. A Commentary provides expert analysis, critique, or perspective on a published article, emerging clinical topic, or issue in critical care and nephrology. It is not original research but should be scholarly, evidence-based, and concise. Commentaries are usually invited by the Editor-in-Chief or Editorial Board. Commentaries should be focused, balanced, and evidence-based, not exceed 1,200 words, include a limited number of references (up to 20) and 1 to 2 Figures. It must not contain original unpublished data.

Letters to the Editors. Correspondence will be considered for publication if it contains constructive criticism on previously published articles in *the RJCCN*, the authors of which will have the right of reply. Also, reports of limited research or clinical experiences can be submitted in the form of a letter. The length should not exceed 700 words.

Fillers. Fillers are materials, including text and image, to be published in the blank spaces of the journal. The subject is not restricted, but those related directly or indirectly to medicine are preferred. Quotations, interesting pictures, historical notes, and notice on events are some examples. Please contact the editorial office via e-mail (info@rjccn.org) to send fillers.

References. Our reference style requirements are in accordance with Vancouver style as defined by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors (ICMJE updated October 2008, available from: http://www.icmje.org/). Number references in the order in which they appear in the text; do not alphabetize. In text, tables, and legends, identify references with superscript Arabic numerals in parentheses.
Note: List all authors when there are 6 or fewer; when there are 7 or more, list the first 6, followed by “et al”
Samples:
Articles in journals

Raaijmakers R, Schroder C, Monnens L, Cornelissen E, Warris A. Fungal peritonitis in children on peritoneal dialysis. Pediatr Nephrol. 2007;22:288-93.

More than 6 authors

Piraino B, Bailie GR, Bernardini J, Boeschoten E, Gupta A, Holmes C, et al. Peritoneal dialysis-related infections recommendations. Perit Dial Int. 2005;25:107-31.

Books and other monographs

Brady HR, Clarkson MR, Lieberthal W. Acute renal failure. In: Brenner BM, Livine SA, editors. Benner & Rector’s the kidney. 7th ed. Philadelphia: WB Saunders; 2004. p. 1215-75.

For samples of reference citation formats, authors should consult National Library of Medicine web site:
http://www.nlm.nih.gov/bsd/uniform_requirements.html

Keywords. Between 3 and 10 key words for indexing should be typed at the bottom of the title page for each manuscript. These words should be identical to the medical subject headings (MeSH) that appear in the Index Medicus of the National Library of Medicine.

Figures and Tables. Figures and tables should be kept to a necessary minimum and their information should not be duplicated in the text. Figures must be supplied either as JPEG or TIFF. Do not embed the figures in the manuscript file. Tables should be typed on separate sheets of the manuscript file, be numbered (with Arabic numbers), and have a title. Include double-spaced legends (maximum length, 60 words) on separate pages. Computer-generated images and photographs must have acceptable quality (at 300 dpi or higher).

Covering Letter. All manuscripts must be accompanied by a covering letter signed by all authors. The name, address, telephone number, fax number, and E-mail address of the corresponding author must be provided. Previous publications or presentations of the manuscript or its parts, conflict of interests, and financial supports, if any, should be addressed in the covering letter.

Ethical Requirements and Authors’ Responsibility

Author(s) should certify that neither this manuscript nor one with substantially similar content under their authorship has been published or being considered for publication elsewhere in any language, except as described in the covering letter. The Rjccn follows the latest definition for authorship provided by the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*. All authors should have a substantial contribution to the manuscript and take public responsibility for its contents. All persons designated as authors are assumed to qualify for authorship and all those who qualify are listed. The corresponding author takes responsibility for the integrity of the work as a whole, from inception to published article. In the event that an author is added or removed from the list of authors, written acceptance, signed by all authors, must be submitted to the editorial office.
Any financial interests, direct or indirect, in connection with the author(s) manuscript must be disclosed in the covering letter. Furthermore, sources of financial support of the project are named in the covering letter as well as the Acknowledgements.
If the work involves experimentation on living animals,

the author(s) must provide evidence that the study was performed in accordance with local ethical guidelines. If the study involves human beings, the author(s) must include a statement that the study was approved by the local ethical committee and that informed consent was obtained from the study participants. For those investigators who do not have formal ethics review committees, the principles outlined in the Declaration of Helsinki should be followed.

All relevant permissions to cite the unpublished observations of others must be obtained by the manuscript author(s). The names and initials of these persons must be cited in the text, and permission from the original author(s) must be obtained. Permission also must be obtained to reproduce or adapt any figures or tables that have been published previously.

Copyright

All authors must read, complete, sign, and submit the Authors' Agreement Form together with their manuscript as part of the submission process.

**Note: For a complete version of the instructions, see the RJCCN's web site.*

RJCCN
Research Journal of Critical Care Nephrology

AUTHORS' AGREEMENT FORM

Updated June 2026

Date: _____

Manuscript Title: _____

Author(s) of the abovementioned manuscript have read the following statements and agree with them by signing this form. If the manuscript is not published in either print or electronic versions of *the Research Journal of Critical Care Nephrology (RJCCN)* within 12 months of acceptance (or as otherwise agreed), this agreement shall automatically terminate.

Statement of Authorship

This statement acknowledges that each undersigned author has made a substantial contribution to the manuscript and is willing to take public responsibility for its contents. Author(s) attest that all persons designated as authors qualify for authorship and all those who qualify are listed. The corresponding author takes responsibility for the integrity of the work as a whole, from inception to published article. *The RJCCN* follows the latest definition provided by the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* (http://www.icmje.org): "Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3."
All others who contributed to the work but are not authors (if any) are named in the *Acknowledgements* of the manuscript.

Ethical Requirements

Author(s) herein attest that all human and/or animal studies undertaken as part of research from which this manuscript is derived, are in compliance with the regulations of their institution(s) and generally accepted guidelines governing such work. Author(s) warrant that this manuscript contains no violation of any existing copyright or other third party right or any material of an obscene, indecent, libellous, or otherwise unlawful nature and that to the best of their knowledge the manuscript does not infringe the rights of others.

Copyright

Conflict of Interest and Financial Supports

Author(s) warrant that any financial interests, direct or indirect, that exist or may be perceived to exist for individual contributors in connection with this manuscript have been disclosed in the covering letter. Furthermore, sources of financial support of the project are named in the covering letter as well as the *Acknowledgements*.

Previous Publications

Author(s) certify that neither this manuscript nor one with substantially similar content under their authorship has been published or being considered for publication elsewhere in any language, except as described in the covering letter. They also certify that any previous presentations of this paper in meetings are mentioned in the covering letter.

Names of all authors in order in which they appear in the Article:

Author's Name and Signature	Author's Name and Signature
1 _____	7 _____
2 _____	8 _____
3 _____	9 _____
4 _____	10 _____
5 _____	11 _____
6 _____	12 _____

Beyond Kidney Support: The New Frontiers of Critical Care Nephrology

RJCCN 2026; 2(3):161-3
www.rjccn.org
DOI: 10.66224/rjccn.2.3.62

The practice of critical care nephrology has undergone a remarkable transformation over the past several decades. What began as a discipline largely centered on the management of acute kidney injury, electrolyte disturbances, acid-base disorders, and renal replacement therapies has evolved into a sophisticated and multidisciplinary field that extends far beyond traditional concepts of kidney support. Today, critical care nephrologists are increasingly challenged to integrate advances in imaging, molecular biology, immunology, nutrition, rehabilitation, and personalized medicine into the care of some of the most vulnerable patients in modern healthcare.

As we present the fourth issue of the *Research Journal of Critical Care Nephrology (RJCCN)*, we are reminded that the future of our specialty will not be defined solely by our ability to replace kidney function during critical illness. Rather, it will be shaped by our capacity to understand complex biological systems, identify patients at risk before irreversible injury occurs, personalize therapeutic interventions, and promote meaningful recovery long after the acute phase of illness has passed.

The articles featured in this issue reflect several of the most exciting directions currently emerging within critical care nephrology. Collectively, they highlight a field that is increasingly focused on precision, prediction, and recovery.

One of the most important developments in contemporary nephrology is the growing recognition that the kidney cannot be viewed as an isolated organ. Instead, it participates in a dynamic network of bidirectional interactions involving the cardiovascular system, immune system, gastrointestinal tract, skeletal muscle, and other organs. This concept of organ crosstalk is transforming our understanding of disease pathogenesis and therapeutic opportunities.

The emerging Gut-Kidney-GBM Axis discussed in this issue exemplifies this paradigm shift. The growing body of evidence linking microbial metabolites to alterations in glomerular structure and function challenges conventional views of kidney disease and suggests that future interventions may extend beyond traditional pharmacologic approaches to include manipulation of the intestinal microbiome and its metabolic products. Such investigations underscore the importance of expanding our scientific horizons and embracing novel mechanistic pathways that may ultimately redefine kidney protection.

Equally important is the movement toward individualized and biomarker-guided medicine. The study evaluating the efficacy of prednisone combined with leflunomide in lupus nephritis, alongside the prognostic significance of TL1A and serum cystatin C, reflects the broader trend toward precision nephrology. As our understanding of immune-mediated kidney diseases continues to deepen, biomarkers are increasingly becoming essential tools for diagnosis, risk stratification, treatment selection, and outcome prediction. The future nephrologist must be equipped not only with clinical expertise but also with the ability to interpret and apply complex biological information in everyday practice.

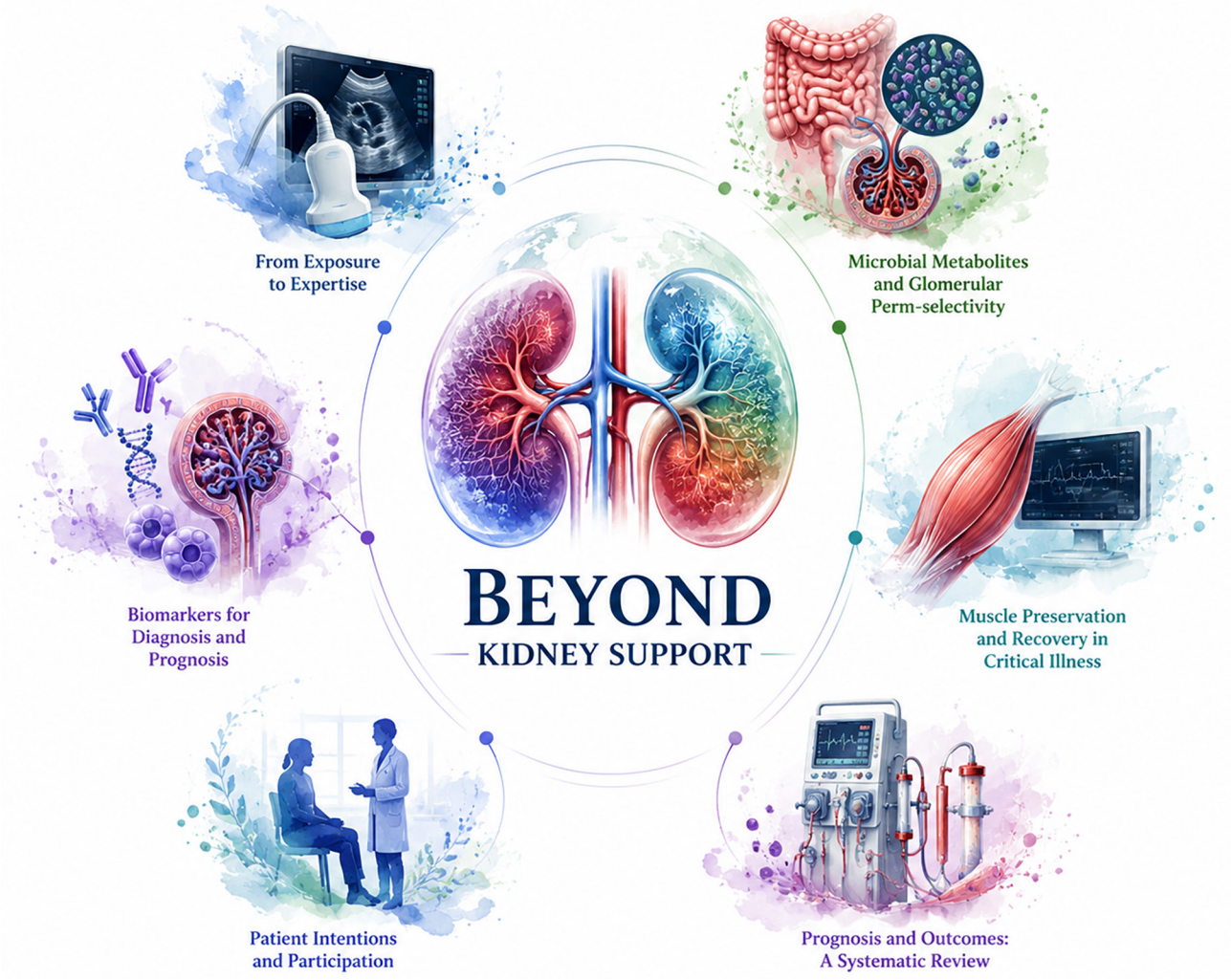
Another defining characteristic of modern critical care nephrology is the integration of bedside technologies that bring diagnostic capabilities directly to the patient. Point-of-care ultrasonography (POCUS) has emerged as one of

Please cite this article as: Nassiri AA. Beyond Kidney Support: The New Frontiers of Critical Care Nephrology. RJCCN. 2026;2(3):161-3.

the most transformative tools in acute and critical care medicine. Beyond simply acquiring images, the challenge now lies in developing robust frameworks for competency, education, and quality assurance. The discussion presented in this issue regarding POCUS competency in nephrocritical care highlights an important reality: mastery of bedside ultrasound is becoming a core component of contemporary nephrology practice. As technology continues to evolve, the nephrologist's role increasingly includes real-time physiological assessment and image-guided clinical decision-making.

Perhaps one of the most significant shifts occurring across critical care medicine is the recognition that survival alone is no longer an adequate measure of success. Advances in critical care have improved mortality outcomes, but many survivors face substantial physical, cognitive, and functional impairments that persist long after hospital discharge. Consequently, recovery has emerged as a central goal of patient care.

The qualitative study exploring exercise participation among maintenance hemodialysis patients reminds us that patient-centered outcomes remain fundamental to the practice of nephrology. Understanding the motivations, barriers, and perceptions that influence physical activity is essential for designing interventions that enhance quality of life and functional independence. Similarly, the systematic review examining β-hydroxy-β-methylbutyrate (HMB) supplementation and muscle outcomes in critically ill patients addresses an increasingly important aspect of critical illness recovery. Preservation of



The contributions in this issue illustrate a specialty that is continuously expanding its scientific and clinical boundaries. The future of critical care nephrology lies at the intersection of technology, biology, and patient-centered care.

muscle mass and physical function has become a major priority in intensive care medicine, where prolonged immobilization and catabolism contribute significantly to long-term disability.

The importance of prediction and prognostication is further highlighted by the systematic review examining outcomes in patients with severe acute kidney injury requiring renal replacement therapy. Despite substantial advances in critical care and extracorporeal support technologies, severe AKI remains associated with significant morbidity and mortality. Improving our ability to identify risk, predict recovery, and tailor therapeutic strategies represents one of the most pressing challenges facing the field. Such work not only informs clinical practice but also provides direction for future research efforts aimed at improving outcomes in critically ill patients.

Taken together, the contributions in this issue illustrate a specialty that is continuously expanding its scientific and clinical boundaries. The future of critical care nephrology lies at the intersection of technology, biology, and patient-centered care. It is a future in which bedside ultrasound complements clinical examination, biomarkers guide individualized therapies, microbiome science reveals previously unrecognized mechanisms of disease, and recovery is valued as highly as survival (Figure).

At the *Research Journal of Critical Care Nephrology*, our mission is to provide a platform for innovative scholarship that advances both the science and practice of nephrology in critically ill patients. We remain committed to promoting rigorous research, fostering international collaboration, and encouraging multidisciplinary dialogue among nephrologists, intensivists, researchers, nurses, pharmacists, and allied healthcare professionals. As the field continues to evolve, so too must our collective efforts to generate evidence, challenge assumptions, and translate discoveries into better patient outcomes.

We extend our sincere gratitude to the authors, reviewers, editorial board members, and readers whose dedication and expertise make this journal possible. Their contributions are helping to shape the future of critical care nephrology and strengthen a growing global community committed to excellence in patient care and scientific inquiry.

As we look ahead, one message becomes increasingly clear: the future of critical care nephrology extends beyond supporting failing kidneys. It encompasses understanding biological complexity, embracing innovation, fostering recovery, and ultimately improving the lives of the patients we serve. We hope that the articles presented in this issue will stimulate thoughtful discussion, inspire new research, and contribute meaningfully to the continued advancement of our specialty.

On Behalf of Editorial Board
Amir Ahmad Nassiri
Editor-in-Chief, RJCCN

Received July 2026

RJCCN COMMENTARY

From Exposure to Expertise: Rethinking POCUS Competency in Nephrocritical Care

Abhilash Koratala

Division of Nephrology, Medical College of Wisconsin, Milwaukee, USA

RJCCN 2026; 2(3):164-7
www.rjccn.org
DOI: 10.66224/rjccn.2.3.51

Keywords. POCUS, ultrasound, training, competency

Point-of-care ultrasound (POCUS) has rapidly transitioned from a niche skill to a widely discussed tool in nephrocritical care. What began as an aid for procedures has evolved into a comprehensive bedside framework for hemodynamic assessment, encompassing cardiac, pulmonary, and venous evaluation, among other applications.[1,2] This expansion reflects both clinical need and technological advances that have made ultrasound more portable and easier to deploy at the bedside. However, the pace of adoption is outpacing the development of structured pathways to ensure competency. Across institutions and countries, the meaning of being "POCUS-trained" varies considerably, ranging from limited procedural guidance to more advanced multiparametric assessment. This variability is not merely academic. In a field where clinical decisions are often nuanced and physiologically complex, inconsistency in training translates directly into variability in care. This gap is further compounded by a degree of "new toy" enthusiasm, whereby ease of access may promote use without a corresponding emphasis on training and competency development.

The appeal of POCUS is undeniable. It offers immediacy, integration, and a sense of autonomy that traditional consultative imaging pathways cannot match. A clinician can move from question to answer within minutes, often at the bedside. For example, in acute kidney injury, a good quality handheld device can function as a surrogate for multiple imaging modalities that would otherwise need to be ordered separately, including kidney ultrasound, chest radiography, echocardiography, and abdominal Doppler. Yet this accessibility creates a subtle but important misconception. Having an ultrasound device at the bedside does not, by itself, improve decision-making. Its value depends on the operator's ability to obtain reliable images, interpret them correctly, recognize both technical limitations of the equipment being used and patient-related constraints, and integrate the findings within the appropriate clinical context. Without this foundation, POCUS risks becoming another source of diagnostic uncertainty rather than a solution.

Short-format workshops have played an important role in introducing clinicians to POCUS. These sessions are often engaging and serve as effective entry points, allowing clinicians to develop initial familiarity with image acquisition and common findings. They build confidence and stimulate interest, both of which are necessary for adoption. However, "confidence" acquired in a short course should not be mistaken for "competence". The skills required for consistent image acquisition, nuanced interpretation, and clinical integration cannot be developed over a few hours or even a few days. Like other aspects of clinical examination, these abilities require longitudinal practice, expert

Please cite this article as: Koratala A. From Exposure to Expertise: Rethinking POCUS Competency in Nephrocritical Care. RJCCN. 2026;2(3):164-7.

feedback, and clinical experience. The notion that a brief training course can produce independent proficiency is not unique to POCUS, but the visual immediacy of ultrasound can make this misconception particularly convincing.

Attempts to define competency have often relied on numerical thresholds, with scan counts serving as a proxy for experience. While minimum numbers are important, they are not synonymous with expertise. Two clinicians may perform a similar number of scans yet demonstrate markedly different levels of skill depending on the quality of supervision, feedback, and their prior exposure to ultrasound during earlier stages of training. Repetition alone without expert supervision can reinforce errors rather than resolve them. Competency in POCUS extends beyond the act of image acquisition. It includes the ability to recognize limitations, identify technical pitfalls, and avoid overinterpretation. For example, a dilated inferior vena cava does not automatically suggest the need for fluid removal, nor does a small collapsible IVC necessarily indicate a need for intravenous fluids.[3] Acting on such findings without a broader understanding can lead to inappropriate management decisions.

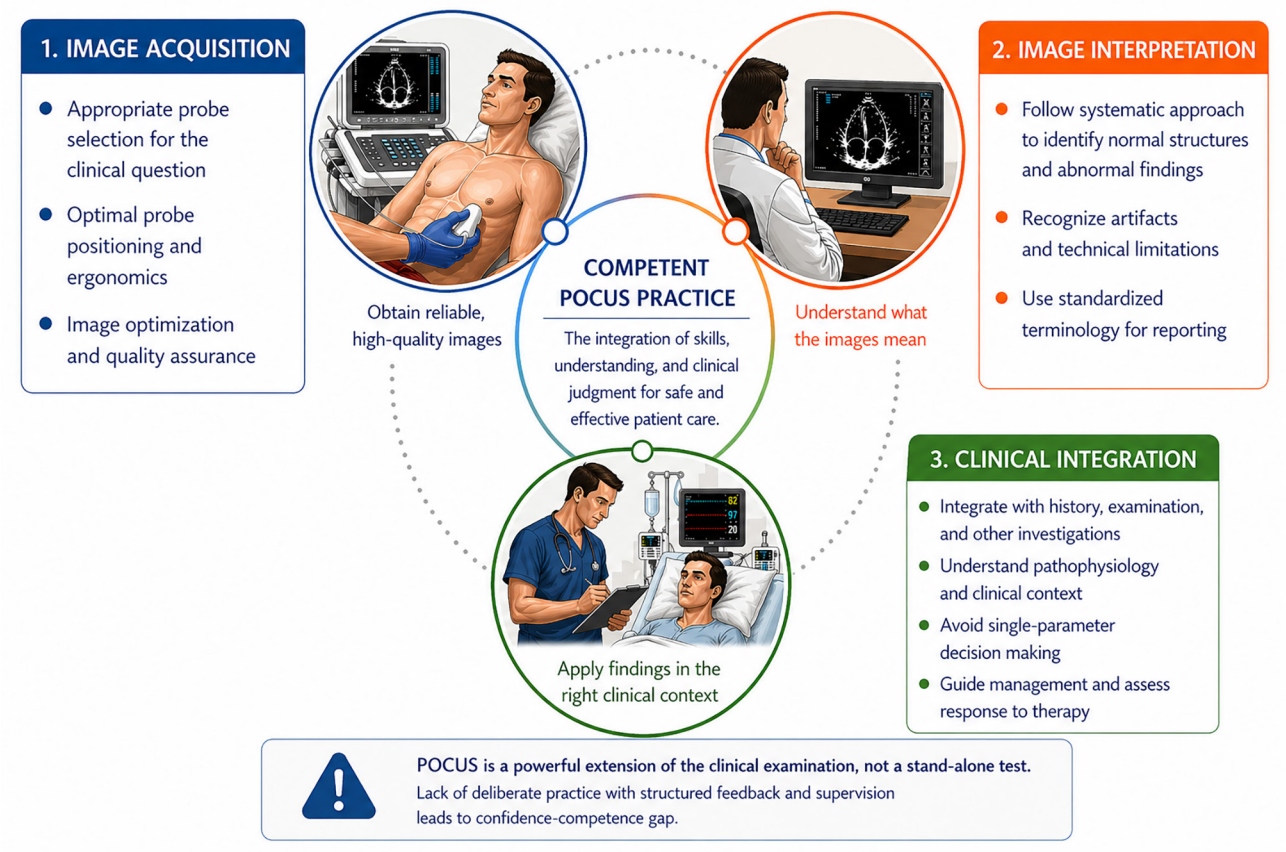
As clinicians gain exposure to POCUS, the questions they ask naturally evolve. Early on, especially in emergency settings, the focus is often on simple yes-or-no assessments, but nephrocritical care rarely presents such clear-cut scenarios. Questions surrounding fluid tolerance, venous congestion, and forward flow require integration of multiple parameters across organ systems. This progression from basic to integrative use is both expected and desirable. However, problems arise when this transition is assumed rather than achieved. For example, clinicians may begin to explore advanced Doppler applications without a sufficient grasp of waveform acquisition, machine settings, or interpretation. In such cases, the information obtained may appear sophisticated while remaining fundamentally incomplete or misleading.

This disconnect reflects a broader gap between confidence and competence that is well recognized in medical education.[4-6] Early learners often overestimate their abilities, particularly when feedback is limited. In the context of POCUS, where images provide immediate visual reinforcement, this effect can be amplified. Frameworks of skill acquisition suggest that most clinicians who complete an introductory course function at an early stage of development, relying on rules and pattern recognition rather than deeper contextual understanding. Treating this stage as equivalent to independent competence carries clinical risk, particularly in nephrocritical care where management decisions frequently involve balancing competing physiological priorities.

The implications extend beyond clinical care into research. POCUS has emerged as an attractive area for scholarly activity, particularly for early-career clinicians. While this interest is encouraging, the quality of research depends heavily on the competency of those conducting it. Studies designed without adequate understanding of POCUS principles and limitations may generate findings that are difficult to reproduce or apply in practice. Early publications in a developing field have an outsized influence, shaping both clinical perception and future research directions. When methodological rigor is lacking, misconceptions may persist and become embedded in clinical reasoning.

A global perspective further highlights both the opportunity and the responsibility associated with POCUS. In many regions, access to formal imaging is limited, and POCUS offers a means to bridge that gap. Its potential to improve diagnostic capacity and patient care in such settings is substantial.[7] At the same time, the absence of structured training programs and quality assurance systems may increase the risk of misapplication. Promoting POCUS adoption without parallel investment in education and competency assessment risks undermining its benefits.

Moving forward is not about tempering enthusiasm but channeling it into scalable and accountable training models. Competency in POCUS should be operationalized with clear expectations across three domains: acquisition, interpretation, and clinical integration (Figure). This requires moving beyond isolated workshops toward longitudinal training pathways that incorporate real-world clinical exposure and ongoing supervision. Hybrid models can help bridge this gap. Remote mentorship



Components of Competent POCUS Practice

using cloud-based image archiving, asynchronous feedback, and tele-supervision allows learners in resource-limited or geographically distant settings to access expertise that would otherwise be unavailable.[8,9] Complementing these approaches with interinstitutional POCUS case conferences and expert-led grand rounds can further enrich learning by exposing clinicians to diverse interpretations and real-world decision-making. At a broader level, nephrology and critical care professional societies, particularly those with an international reach, are well positioned to provide leadership by developing standardized, accessible online curricula, facilitating cross-institutional collaborations, and supporting short-term observerships or fellowships to promote equitable skill development across settings.

At the same time, emerging tools such as artificial intelligence offer opportunities but should be integrated cautiously.[10] AI-assisted guidance can support probe positioning and basic interpretation, lowering the barrier to entry, but current systems remain limited in handling complex hemodynamic scenarios, multimodal integration, and clinical nuance. Overreliance risks reinforcing superficial pattern recognition without true understanding. Therefore, AI should be framed as an adjunct to training rather than a substitute for competency.

POCUS has the potential to transform nephrocritical care, but its impact depends on how it is used. The goal is not simply to expand its use, but to ensure that its application reflects true understanding. In this regard, the probe itself is only a tool; its value lies in the judgment of the clinician who uses it.

REFERENCES

1. Kashani K, Omer T, Shaw AD. The Intensivist's Perspective of Shock, Volume Management, and Hemodynamic Monitoring. Clin J Am Soc Nephrol. 2022;17(5):706-16.
2. Koratala A, Argaiz ER, Romero-González G, Reisinger N, Anwar S, Beaubien-Souligny W, et al. Point-of-care ultrasound training in nephrology: a position statement by the International Alliance for POCUS in Nephrology. Clin Kidney J. 2024;17(11):sfae245.
3. Koratala A. Point-of-Care Ultrasound and Volume

Status: Embracing Physiology Over Proxies. RJCCN. 2026;2(2):72-5.

4. Stewart J, O'Halloran C, Barton JR, Singleton SJ, Harrigan P, Spencer J. Clarifying the concepts of confidence and competence to produce appropriate self-evaluation measurement scales. Med Educ. 2000 Nov;34(11):903-9.
5. Batalden P, Leach D, Swing S, Dreyfus H, Dreyfus S. General competencies and accreditation in graduate medical education. Health Aff (Millwood). 2002;21(5):103-11.
6. Ericsson KA. Deliberate practice and acquisition of expert performance: a general overview. Acad Emerg Med. 2008;15(11):988-94.
7. Beam M, Abdull Wahab SF, Ramos M. Point-of-Care Ultrasound in Resource-Limited Settings. Med Clin North Am. 2025;109(1):313-24.
8. Britton N, Miller MA, Safadi S, Siegel A, Levine AR, McCurdy MT. Tele-Ultrasound in Resource-Limited Settings: A Systematic Review. Front Public Health. 2019;7:244.
9. Stewart E, Tran TT, Tanabe K, Hunt A, Watson G, Kaizer A, et al. Remote guidance and focused point-of-care ultrasound (POCUS) training for cardiopulmonary instability assessment by novice sonographers. Resusc Plus. 2025;27:101184.
10. Kim S, Fischetti C, Guy M, Hsu E, Fox J, Young SD. Artificial Intelligence (AI) Applications for Point of Care Ultrasound (POCUS) in Low-Resource Settings: A Scoping Review. Diagnostics (Basel). 2024;14(15):1669.

Correspondence to:
Abhilash Koratala, MD, FASN
8701 W Watertown Plank Rd, HUB 7th floor, Room A7333,
Milwaukee, WI 53226, USA
ORCID ID: 0000-0001-5801-3574
E-mail: akoratala@mcw.edu

Received April 2026

RJCCN REVIEW
KIDNEY DISEASE

Giggle Incontinence in an Adolescent Girl: A Case-based Review

Banafshe Dormanesh,[1] Bahareh Marghoob[2]

[1]Department of Pediatric, AJA University of Medical Sciences, Tehran, Iran
[2]Department of Nephrology, Hasheminejad Kidney Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

Keywords. giggle incontinence, daytime urinary incontinence, urotherapy, biofeedback, methylphenidate

Giggle incontinence is a form of urinary incontinence triggered by giggling or laughter, with two distinct pathophysiological theories proposed for its etiology. Both neurologic receptor imbalance and urologic dysfunction have been suggested as potential underlying mechanisms.

We present a case-based review of a 12-year-old girl with refractory giggle incontinence who underwent comprehensive evaluation including physical examination, ultrasonography, bladder diary, uroflowmetry, and urodynamic studies. She was treated with a combined approach consisting of urotherapy and pelvic floor biofeedback. To enhance and accelerate therapeutic response, low-dose methylphenidate was added. Pharmacologic treatment was administered and tapered over four months, while non-pharmacologic interventions were continued for one year. Follow-up at 18 months demonstrated complete resolution of symptoms.

A comprehensive literature review on giggle incontinence was conducted using PubMed, Scopus, and Google Scholar databases for studies published since 2000. Based on current evidence, treatment should be individualized according to the presumed underlying mechanism, and successful management requires strong cooperation between the patient, her parents, and the healthcare team.

Based on our literature review, treatment depends on the causes, and success requires the patient's and her parents' trust and cooperation in carrying out the instructions.

RJCCN 2026; 2(3):168-73
www.rjccn.org
DOI: 10.66224/rjccn.2.3.51

INTRODUCTION

Giggle incontinence is characterized by involuntary, complete bladder emptying triggered exclusively by laughter or giggling. It is more prevalent in females and typically involves large-volume voiding due to detrusor contraction accompanied by coordinated sphincter relaxation, resulting in complete bladder emptying.[1] The pathogenesis remains poorly understood. One of the most widely accepted theories suggests a central nervous system–mediated mechanism.[2]

There is no universally accepted standard treatment. Some experts advocate anticholinergic agents such as oxybutynin, while others support the use of methylphenidate as an effective preventive therapy. In addition to pharmacotherapy, behavioral

Please cite this article as: Dormanesh B, Marghoob B. Giggle Incontinence in an Adolescent Girl: A Case-based Review. RJCCN. 2026;2(3):168-73.

interventions such as timed voiding and pelvic floor biofeedback therapy have been recommended.[3] Due to the significant social embarrassment associated with this condition, patient and parental cooperation is essential for successful treatment.[4,5]

Herein, we present a refractory pediatric case successfully managed with combined therapy and provide a review of current evidence regarding diagnostic evaluation and treatment strategies for giggle incontinence.

CASE REPORT

A 12-year-old girl presented with lifelong giggle incontinence triggered exclusively by laughter. She was described as cheerful and socially active; however, according to her parents, she had recently begun avoiding social gatherings and volleyball practice due to fear of embarrassment. She was an only child, born to non-consanguineous parents, with no family history of similar symptoms.

She achieved daytime urinary continence at 36 months of age and had no history of nocturnal enuresis. Previous treatment with oxybutynin for eight months had been ineffective.

She reported voiding approximately five times per day, with a maximum voided volume of 300 mL. Bowel movements occurred regularly (1 to 2 times daily), with a Bristol Stool Scale score of 3 to 4.[6] Physical examination was unremarkable. There was no abdominal or costovertebral tenderness. No signs of puberty were present, and genital examination revealed no erythema, inflammation, or discharge.

A 48-hour bladder diary demonstrated an average urine output of approximately 2 mL/kg/h, with consistent daily fluid intake.

Urinalysis and urine culture were normal. Blood urea nitrogen and serum creatinine levels were within normal limits.

Ultrasonography (Figure 1) showed normal renal size and echogenicity, normal parenchymal thickness, and no hydronephrosis or pelvic dilation. Bladder wall thickness was normal, and post-void residual volume was insignificant.

Uroflowmetry (Figure 2) demonstrated a relatively normal urinary flow pattern without evidence of obstruction but with delayed initiation of voiding, suggestive of pelvic floor over activity or anxiety-related voiding delay.[7]

Video urodynamic study (Figure 3) was unremarkable except for delayed voiding initiation without evidence of anatomical or functional obstruction.

A one-hour educational and counseling session was conducted with the patient to explain the nature of her condition and the proposed treatment plan. A combined therapeutic strategy was initiated, including Urotherapy, pelvic floor biofeedback therapy (PFBT), Kegel exercises, and low-dose methylphenidate (Table 1).

Symptoms improved significantly within four

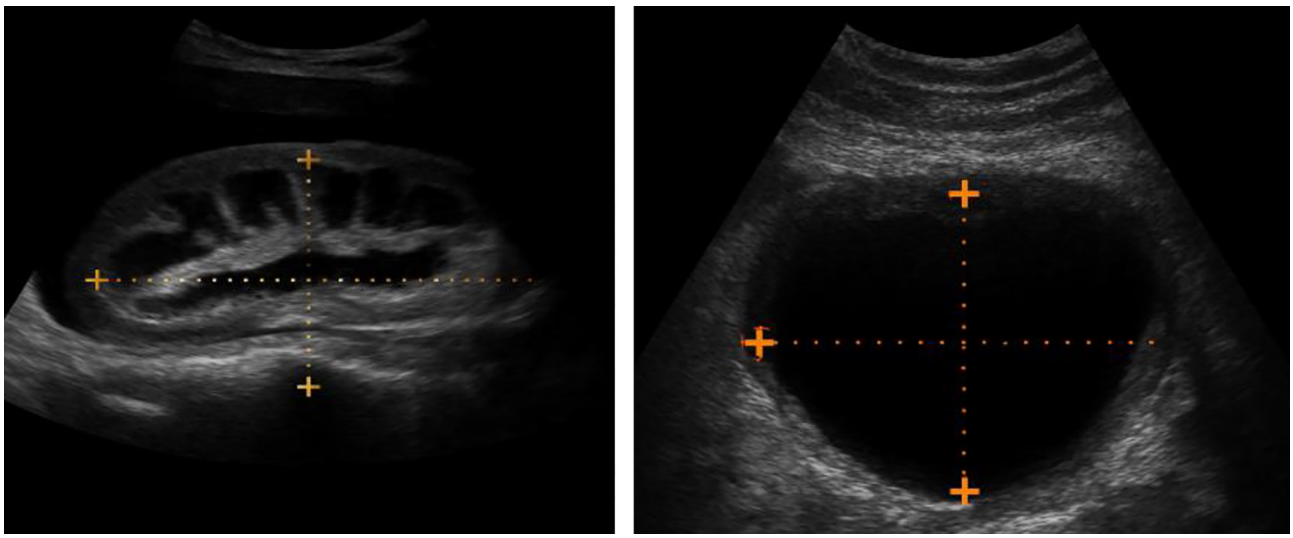


Figure 1. Abdominal and Pelvic Ultrasonography

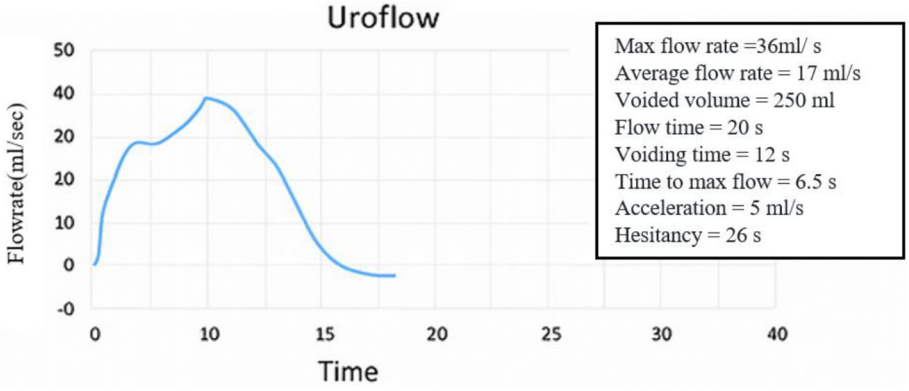


Figure 2. Flowmeter Results

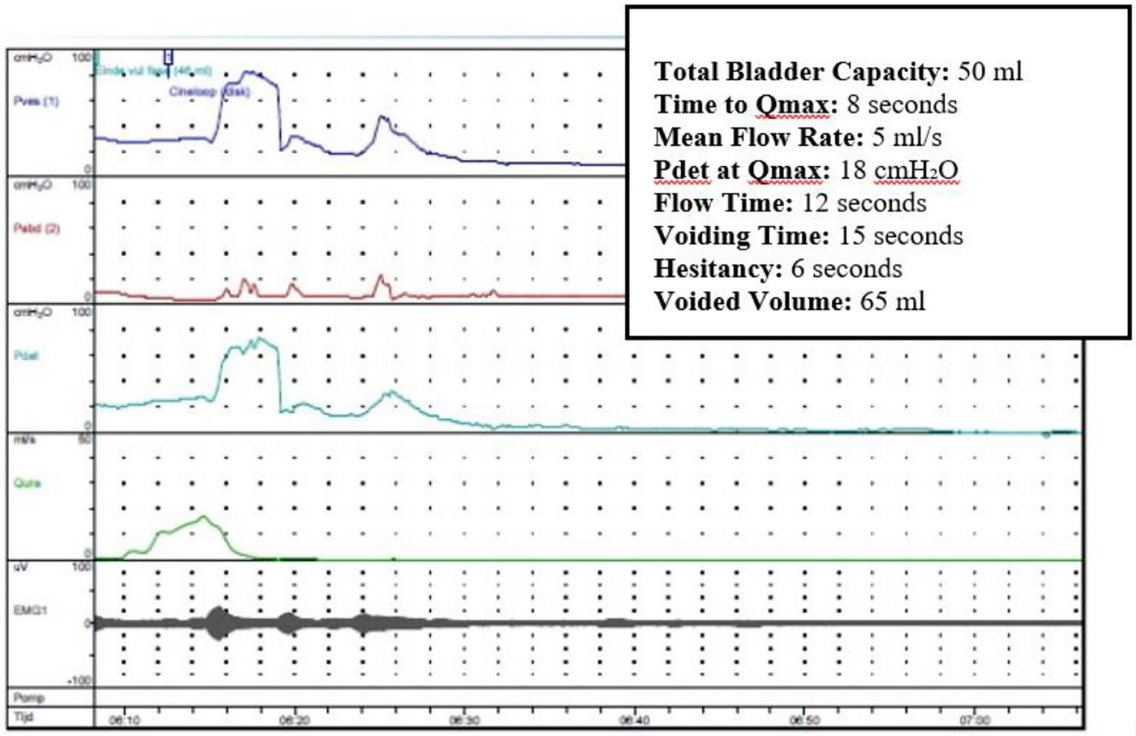


Figure 3. Video Urodynamic Investigation

months, and complete remission was maintained during 18 months of follow-up.

LITERATURE REVIEW

We reviewed published case reports and case series on giggle incontinence identified through PubMed, Scopus, and Google Scholar using the following keywords: giggle incontinence, daytime urinary incontinence, urotherapy, biofeedback, methylphenidate. Studies published since 2000 in English or Persian were included.

The search yielded 18 case reports and 34 review articles in the pediatric population.

Giggle incontinence is considered a rare but distinct subtype of childhood daytime urinary incontinence, characterized by sudden, complete bladder emptying exclusively during laughter. It predominantly affects school-aged children and adolescents, particularly females.[1,8,21]

Two principal pathophysiological theories have been proposed. The first suggests a neurologic origin resembling cataplexy or other central nervous system disorders. This theory emphasizes neural pathway modulation and supports the use

Table 1. Combined Treatment Strategy Which Was Done for Our Patient

Education (advise)	should not be punished for wetting void regularly during the day (about seven times each day) restrict fluid at each intake to 100-150 cc restrict specific fluid intake (caffeine such as cola or tea or bubbles, citrus juices & sports drinks) Consume a variety of fresh fruits and vegetables in the day Consume whole grains bread in the diet to prevent constipation Reduce the consumption of high-fat meat Keep their lower limbs warm Void before starting an activity, which can help avoid leaks avoid lifting heavy objects wear absorbent urinary pads or underwear in activities
Urotherapy	improve bladder emptying quality by urinating in a relaxed way, and to achieve this purpose: ● Sit up straight, keep both feet on the ground ● Keep your tummy relaxed, and breath out gently ● Stay calm, and don't force yourself to urinate. Let your urine flow out on its own. Just listen to make sure your urine flow is in a steady stream trying and going for urinate at regular times (about seven times each day) don't delay your regular urination schedule for any reason way at regular Be sure to urinate during breaks at school, even if the toilets are dirty, which you can do in a standing position, or you can skip washing yourself and change your underwear after you get back from school
Pelvic floor biofeedback therapy (PFBT)	Conducting physiotherapy sessions twice a week for a total of 12 sessions to strengthen the pelvic floor muscles Performing Kegel exercises to increase awareness, and control of pelvic floor muscles contraction, which initially practices in both lying and sitting position, and under ultrasound and digital palpation controls in office, then continue your practice by gymnastics balance exercises, and walking and about one hour a day Re-emphasizing the need to be calm while urinating and ensuring complete emptying of your bladder
Pharmacotherapy	Low dose chewable Methylphenidate 5mg twice daily and preferably taken 30-45 minutes before meals, and the last dose should be taken before 6 p.m., so it doesn't cause problems such as constipation or insomnia

of methylphenidate.[9,10]

The second theory proposes a primary urologic dysfunction, supporting the use of Urotherapy and pelvic floor biofeedback.[10,11]

In 2023, von Gontard *et al.* developed a clinical guideline for diagnosis and treatment based on literature review, surveys, and consensus conferences, although universal acceptance has not yet been achieved.[12]

DISCUSSION

The primary limitation of this report is its single-case design, which precludes determining the individual contribution of each treatment modality.

As summarized in Table 2, most studies rely on clinical history, physical examination, and bladder diaries for diagnosis. Some include Uroflowmetry or electromyography. Treatment strategies vary and include pharmacotherapy, pelvic floor biofeedback therapy, intravesical botulinum toxin injection, and transcutaneous electrical nerve stimulation.

Across studies, no single treatment strategy has demonstrated clear superiority. Complete resolution has rarely been reported, and most interventions achieve approximately 55 to 65% clinical improvement.

Our patient achieved complete remission with a combined multimodal approach, suggesting that individualized therapy addressing both neurologic and urologic mechanisms may improve outcomes.

CONCLUSIONS

Giggle incontinence is a rare but socially distressing disorder in children and adolescents. Accurate diagnosis and exclusion of other causes of urinary incontinence are essential.

Current evidence supports an individualized, multimodal therapeutic approach, particularly combining Urotherapy, pelvic floor rehabilitation, and selective pharmacologic treatment.

Our case highlights the importance of detailed patient education and reassurance. Ensuring diagnostic accuracy and carefully explaining even seemingly minor treatment details can significantly enhance adherence and clinical outcomes.

ACKNOWLEDGEMENTS

None.

Table 2. Summary of Reported Cases of Patients with Giggle Incontinence

	Patient (age, sex)	Diagnostic Evaluation	Diagnostic findings	Treatment strategy
Chandra M. et al. 2002[15]	109 patients 5 -15 y.	Clinical History & Physical exam	detrusor instability	Pharmacotherapy (anti cholinergic)
Telli O. et al. 2016[16]	48 patients median age 8.4 y. (5-16)	Uroflowmetry -EMG & post-void residual volume evaluation	detrusor instability	Pharmacotherapy (alpha-adrenergic blockers)
Taylor AS et al. 2019[14]	229 patients (64 F.) median age 10.1y. (6.2-17.0)	Bladder Bowel Dysfunction (BBD) questionnaires & EMG during voiding	High post-void residual (PVR)	Pelvic floor Biofeedback Therapy (PFBT)
Nieuwhof-Leppink AJ. et al. 2021[9]	52 patients 8 -17 y.	Clinical History & Physical exam Urinary chart	Just based on history	pelvic floor biofeedback therapy & anal balloon expulsion (BABE) Urotherapy
Mohan Kunnath S. et al. 2021[12]	seven patients (6 F., 1 M.) median age13.5 y. (10.4-15.7)	Video-urodynamic	Detrusor over activity (in 6) sudden pelvic floor relaxation (in 3)	Pharmacotherapy
San ST et al. 2021[3]	227 patients median age 9.5 y. (5-14)	Bladder Bowel Dysfunction (BBD) questionnaires & real-time Uroflowmetry	Detrusor over activity	Pharmacotherapy & Education (regular bladder empting)
Hacıislamoğlu A. et al. 2021[17]	38 patients median age 7.5 y. (5-11)	Clinical History & Physical exam	Just based on history	Pharmacotherapy & pelvic floor strengthening exercises at home
Wefer B. et al. 2007[18]	A 20 y. female	Refractory GI despite anti-muscarinic therapy	Just based on history	Intra-vesical Botox injection
Szwarcberg E. et al. 2026[19]	17 patients median age 11 y. (6-17)	Clinical History & Physical exam	Just based on history	Intra-vesical Botox injection
Tugtepe H. et al. 2015[20]	27 patients median age 7.2 y.	Uroflowmetry -EMG parameters & bladder capacity	Decrease bladder capacity & increase Qmax, Qave and flow time	transcutaneous electrical nerve stimulation

FUNDING

None.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Consent was obtained to participate.

CONSENT FOR PUBLICATION

Consent was obtained for publication.

AVAILABILITY OF DATA

All data generated or analyzed during this study are included in this published article

REFERENCES

1. González-Maldonado AA, García-Mérida M. Giggle incontinence: a scoping review. Pediatr Res 2024;95:1720.
2. Abdelmonem II, Khan MK, Abdulrahman Al Muhammadi O, Rozan A, Merdad MJ, et al. Giggle incontinence: A rare condition with a successful management. Urol Case Rep. 2022; 42:102033.
3. San ST, Barnes EH, Caldwell PHY. Urinary incontinence during laughter in children: Is it giggle incontinence? J Paediatr Child Health. 2021;57(12):1971-5.
4. Rakowska-Silska M, Jobs K, Paturej A, Kalicki B. Voiding Disorders in Pediatrician's Practice. Clin Med Insights Pediatr. 2020;14:1179556520975035.
5. Richardson I, Palmer LS. Successful treatment for giggle incontinence with biofeedback. J Urol 2009;182:2062.
6. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32(9):9204.
7. Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn. 2010;29(1):420.
8. Logan BL, Blais S. Giggle incontinence: Evolution of concept and treatment. J Pediatr Urol. 2017;13(5):430-5.
9. Nieuwhof-Leppink AJ, Hussong J, Chase J, Larsson J, Renson C, Hoebeke P, et al. Definitions, indications

and practice of urotherapy in children and adolescents: - A standardization document of the International Children's Continence Society (ICCS). J Pediatr Urol. 2021;17(2):172-81.

10. Malykhina AP, Brodie KE, Wilcox DT. Genitourinary and gastrointestinal co-morbidities in children: The role of neural circuits in regulation of visceral function. J Pediatr Urol. 2017;13(2):177-82.
11. Taylor AS, Cabo JJ, Lauderdale C, Maskan N, Thomas JC, Tanaka ST, et al. Pelvic floor biofeedback therapy in children: Assessment of symptom scores in responders and non-responders. Neurourol Urodyn. 2019;38(1):254-60.
12. von Gontard A, Kuwertz-Bröking E. Enuresis und nicht-organische (funktionelle) Harninkontinenz bei Kindern und Jugendlichen – klinische Leitlinie zur Diagnostik und Therapie [Functional (Nonorganic) Enuresis and Daytime Urinary Incontinence in Children and Adolescents: Clinical Guideline for Assessment and Treatment]. Z Kinder Jugendpsychiatr Psychother. 2023;51(5):375-400.
13. Mohan Kunnath S, Clothier J, Solomon E, Wright AJ, Taghizadeh A. Urodynamic characterization of giggle incontinence in children. Neurourol Urodyn. 2021;40(6):1600-8.
14. Taylor AS, Cabo JJ, Lauderdale C, Maskan N, Thomas JC, Tanaka ST, et al. Pelvic floor biofeedback therapy in children: Assessment of symptom scores in responders and non-responders. Neurourol Urodyn. 2019;38(1):254-60.
15. Chandra M, Saharia R, Shi Q, Hill V. Giggle incontinence in children: a manifestation of detrusor instability. J Urol. 2002;168(5):2184-7; discussion 2187.
16. Telli O, Hamidi N, Kayis A, Suer E, Soygur T, Burgu B. Can the success of structured therapy for giggle incontinence be predicted? Int Braz J Urol. 2016;42(2):334-8.
17. Hacıislamoğlu A, Ekşi M, Özlü DN, Yavuzsan AH, Evren İ, Karadağ S, et al. Evaluation of the efficacies of methylphenidate and biofeedback treatments in giggle incontinence: One-year follow-up study. J Pediatr Urol. 2021;17(5):646.e1-646.e5.
18. Wefer B, Seif C, van der Horst C, Jünemann KP, Braun PM. Botulinumtoxin-A-Injektion bei therapierefraktärer Giggle-Inkontinenz [Botulinum toxin A injection for treatment-refractory giggle incontinence]. Urologe A. 2007;46(7):773-5. German.
19. Szwarcberg E, Kimber C, Taghavi K. Intravesical botox as an effective therapy for giggle incontinence in children. Pediatr Surg Int. 2026;42(1):103.
20. Tugtepe H, Thomas DT, Ergun R, Kalyoncu A, Kaynak A, Kastarli C, et al. The effectiveness of transcutaneous electrical neural stimulation therapy in patients with urinary incontinence resistant to initial medical treatment or biofeedback. J Pediatr Urol. 2015;11(3):137.e1-5.
21. Nevéus T, von Gontard A, Hoebeke P, Hjälmås K, Bauer S, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the ICCS. J Urol. 2006;176(1):31424.

Correspondence to:
Bahareh Marghoob, MD
Assistant Professor of Nephrology. Nephrology Section, Department of Medicine, Hasheminejad Kidney Center, School of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran
ORCID ID: 0000-0002-1895-2785
E-mail: baharehmarghoob@yahoo.com

Received April 2026
Revised June 2026
Accepted July 2026

RJCCN ORIGINAL PAPER
KIDNEY DISEASE

The Gut-Kidney-GBM Axis: Emerging Evidence That Microbial Metabolites May Modify Glomerular Basement Membrane Perm-selectivity: A Systematic Review

Maryam Ghaffari Rahbar,[1] Ali Zarei,[2] Saeed Changizi-Ashtiyani,[3] Farshid Haghverdi[4]

[1]Department of Internal Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[2]Department of Physiology, Estahban School of Paramedical Sciences, School of Nursing Hazrat Zahra (P.B.U.H) Abadeh, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Department of Physiology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[4]Department of Internal Medicine, School of Medicine, Arak University of Medical Sciences, Arak, Iran

Keywords. glomerular basement membrane, gut microbiota, indoxyl sulfate, chronic kidney disease, glomerular disease, nephrotic syndrome, steroid-resistant nephrosis, mendelian randomization

Introduction. The glomerular basement membrane (GBM) is the final filtration barrier in the kidney, and its dysfunction is central to nephrotic syndrome. Emerging evidence suggests that gut microbiota-derived metabolites directly modify GBM perm-selectivity, yet this axis remains underexplored.
Methods. We conducted a systematic review following PRISMA guidelines, searching PubMed, Scopus, Web of Science, Embase, and Cochrane Library from January 2000 to April 2026. Studies examining relationships between gut microbiota or microbial metabolites (indoxyl sulfate, TMAO, p-cresyl sulfate, SCFAs) and GBM structure/function were included.
Results. Mendelian randomization studies provide causal evidence linking Alistipes putredinis, Veillonellaceae, and RuminococcaceaeUCG002 to CKD risk. Indoxyl sulfate upregulates heparanase, degrading GBM heparan sulfate and disrupting charge selectivity. TMAO and p-cresyl sulfate activate AhR signaling, inducing aberrant sulfation patterns. Conversely, short-chain fatty acids (particularly butyrate) protect GBM via HDAC inhibition and Treg modulation. A novel gut-lymphatic-renal feedback loop involving Th17 cells explains treatment resistance in chronic nephrosis. Clinical studies suggest that AST-120 and probiotic supplementation may reduce proteinuria and improve eGFR, although heterogeneity across studies limits definitive conclusions.
Conclusions. The gut-kidney-GBM axis represents a bona fide pathophysiological pathway in nephrotic syndrome. Microbiome-targeted interventions represent promising but still investigational adjunctive strategies that require confirmatory human trials for preserving GBM integrity. Screening for gut dysbiosis and uremic toxins should guide personalized therapy in steroid-resistant nephrosis.

RJCCN 2026; 2(3):174-82
www.rjccn.org
DOI: 10.66224/rjccn.2.3.54

INTRODUCTION

Chronic kidney disease (CKD) affects over 850 million individuals globally, and its prevalence continues to rise at an alarming rate.[1] Among the earliest and most consistent manifestations of glomerular injury is proteinuria—a cardinal sign of nephrotic syndrome and a powerful, independent predictor of progressive renal function decline

Please cite this article as: Ghaffari Rahbar M, Zarei A, Changizi-Ashtiyani S, Haghverdi F. The Gut-Kidney-GBM Axis: Emerging Evidence That Microbial Metabolites May Modify Glomerular Basement Membrane Perm-selectivity. RJCCN. 2026;2(3):174-82.

and cardiovascular morbidity.[2] The glomerular basement membrane (GBM), a highly specialized 240 to 370 nm thick extracellular matrix situated between fenestrated endothelial cells and podocyte foot processes, serves as the final and most selective barrier to protein filtration. Its unique composition, predominantly laminin-521 (α5β2γ1), collagen IV (α3α4α5), nidogen, and the heparan sulfate proteoglycan agrin, creates a charge- and size-selective sieve essential for maintaining the composition of plasma.[3] Traditionally, dysfunction in nephrotic syndrome has been attributed to primary podocyte injury or immune-mediated damage to this matrix. However, a growing body of evidence compels us to expand our pathophysiological framework beyond the glomerulus itself.[4]

Over the past decade, the concept of a bidirectional "gut-kidney axis" has emerged as a critical paradigm in renal medicine. Initially described in the context of uremic toxicity in advanced CKD, it is now evident that this inter-organ communication network begins much earlier, playing a significant role in the initiation and perpetuation of proteinuria and GBM dysfunction.[5] The crux of this axis lies in the gut microbiota—a vast and complex ecosystem of trillions of microorganisms that act as a metabolic "endocrine organ," profoundly influencing host physiology.[6] In a state of health, a symbiotic relationship exists, characterized by a predominance of beneficial commensals, particularly short-chain fatty acid (SCFA)-producing bacteria such as Faecalibacterium, Lachnospiraceae, and Clostridiales. These microbes ferment dietary fiber to produce SCFAs (acetate, propionate, and butyrate), which are crucial for maintaining intestinal epithelial barrier integrity, modulating systemic inflammation, and exerting direct renoprotective effects.[7] Notably, butyrate, the preferred energy source for colonocytes, has been shown to inhibit histone deacetylases (HDAC) and reduce albuminuria in experimental models.[8]

However, a fundamental shift occurs in the setting of renal disease. The "uremic milieu" drives a characteristic dysbiosis, marked by a depletion of these beneficial SCFA-producing commensals and a concurrent overgrowth of proteolytic, urease-expressing pathogenic taxa, including Enterobacteriaceae and certain Clostridium species.[9] This compositional shift has profound functional consequences. The dysbiotic microbiota generates a surplus of potentially toxic metabolites, including trimethylamine (TMA), indole, and p-cresol. These precursors are absorbed into the portal circulation and subsequently delivered to the liver, where host enzymes—specifically flavin-containing monooxygenase 3 (FMO3) for TMA and sulfotransferase 1A1 (SULT1A1) for p-cresol—convert them into their nephrotoxic end-products: trimethylamine N-oxide (TMAO), indoxyl sulfate (IS), and p-cresyl sulfate (PCS), respectively.[10,11]

The clinical relevance of this pathway is underscored by robust correlative data. In patients with CKD, elevated plasma concentrations of IS and PCS are strongly associated with faster progression to end-stage renal disease, increased systemic inflammation, and heightened cardiovascular risk.[12] Furthermore, clinical trials have demonstrated that interventions aimed at modulating the gut microbiota, such as the traditional Chinese medicine Yi-Shen-Hua-Shi (YSHS), can significantly reduce proteinuria, and this effect directly correlates with favorable changes in the abundance of beneficial genera like Lachnospiraceae.[13]

Despite these compelling associations, a critical gap remains in our mechanistic understanding: How do these gut-derived metabolites specifically target and modify the glomerular basement membrane? Current literature largely focuses on their effects on tubular injury, interstitial fibrosis, or systemic inflammation.[14] The specific molecular interactions between circulating uremic toxins and the unique extracellular matrix proteins of the GBM are just beginning to be elucidated. For instance, IS has been shown to upregulate plasminogen activator inhibitor-1 (PAI-1) and increase ROS via activation of NF-κB and NOX4 signaling in renal cells.[15,16] However, the direct impact on GBM components—such as the heparan sulfate side chains of agrin (critical for charge selectivity) or the structural integrity of the collagen IV network—remains poorly defined.

Terminological clarification

This review uses the following definitions consistent with KDIGO 2025. Chronic kidney disease (CKD) is defined as abnormalities of

kidney structure or function present for > 3 months, irrespective of diagnosis. Glomerular diseases (e.g., IgA nephropathy, membranous nephropathy, minimal change disease) are a subset of CKD with primary or secondary injury to the glomerulus. Nephrotic syndrome is a clinical phenotype (heavy proteinuria > 3.5 g/d, hypoalbuminemia, edema, hyperlipidemia) that can occur in multiple glomerular diseases. Steroid-resistant nephrosis refers specifically to nephrotic syndrome that fails to achieve remission after 4 to 8 weeks of high-dose glucocorticoids. The gut-kidney-GBM axis has been studied across these entities, but most mechanistic data derive from CKD and experimental glomerulopathies, not specifically steroid-resistant nephrosis. Extrapolation to steroid-resistant nephrosis requires caution.[17]

This review aims to synthesize current evidence on the Gut-Kidney-GBM Axis, with a specific focus on the novel and under-explored hypothesis that circulating microbial metabolites directly modify GBM perm-selectivity. We will: 1) detail the current understanding of gut dysbiosis in CKD and its systemic consequences, 2) critically evaluate the evidence for direct effects of key metabolites (TMAO, IS, PCS, and SCFAs) on GBM structure and function, 3) explore the mechanistic pathways linking microbial metabolism to podocyte injury and proteinuria, and 4) discuss emerging therapeutic opportunities, including prebiotics, probiotics, postbiotics, and novel microbiome-targeted interventions that may preserve GBM integrity. By bridging the fields of microbiome science and glomerular biology, this review seeks to establish a new conceptual framework for understanding and treating proteinuric kidney diseases—one that extends from the colonic lumen to the glomerular filtration barrier.

MATERIALS AND METHODS

Search Strategy and Study Selection

This systematic review was conducted following PRISMA guidelines. A comprehensive literature search was performed in PubMed, Scopus, Web of Science, Embase, and Cochrane Library from January 2000 to April 2026 using MeSH terms and keywords including "gut microbiome," "dysbiosis," "TMAO," "indoxyl sulfate," "p-cresyl sulfate," "short-chain fatty acids," "glomerular basement membrane," "proteinuria," "nephrotic syndrome," and "podocyte." Two independent reviewers screened titles, abstracts, and full texts. Inclusion criteria comprised original human or animal studies, randomized controlled trials, and systematic reviews evaluating the relationship between gut-derived metabolites and GBM structure/function (proteinuria, GBM thickness, heparan sulfate content, or foot process effacement). Exclusion criteria were non-English articles, editorials, conference abstracts, in-vitro-only studies, and investigations of acute kidney injury without nephrotic-range proteinuria or those with low methodological quality (Newcastle-Ottawa Scale < 6 or SYRCLE high risk of bias). The PRISMA 2020 flow diagram summarizes the number of records identified, screened, excluded, and finally included in this systematic review (see PRISMA Flow Diagram).

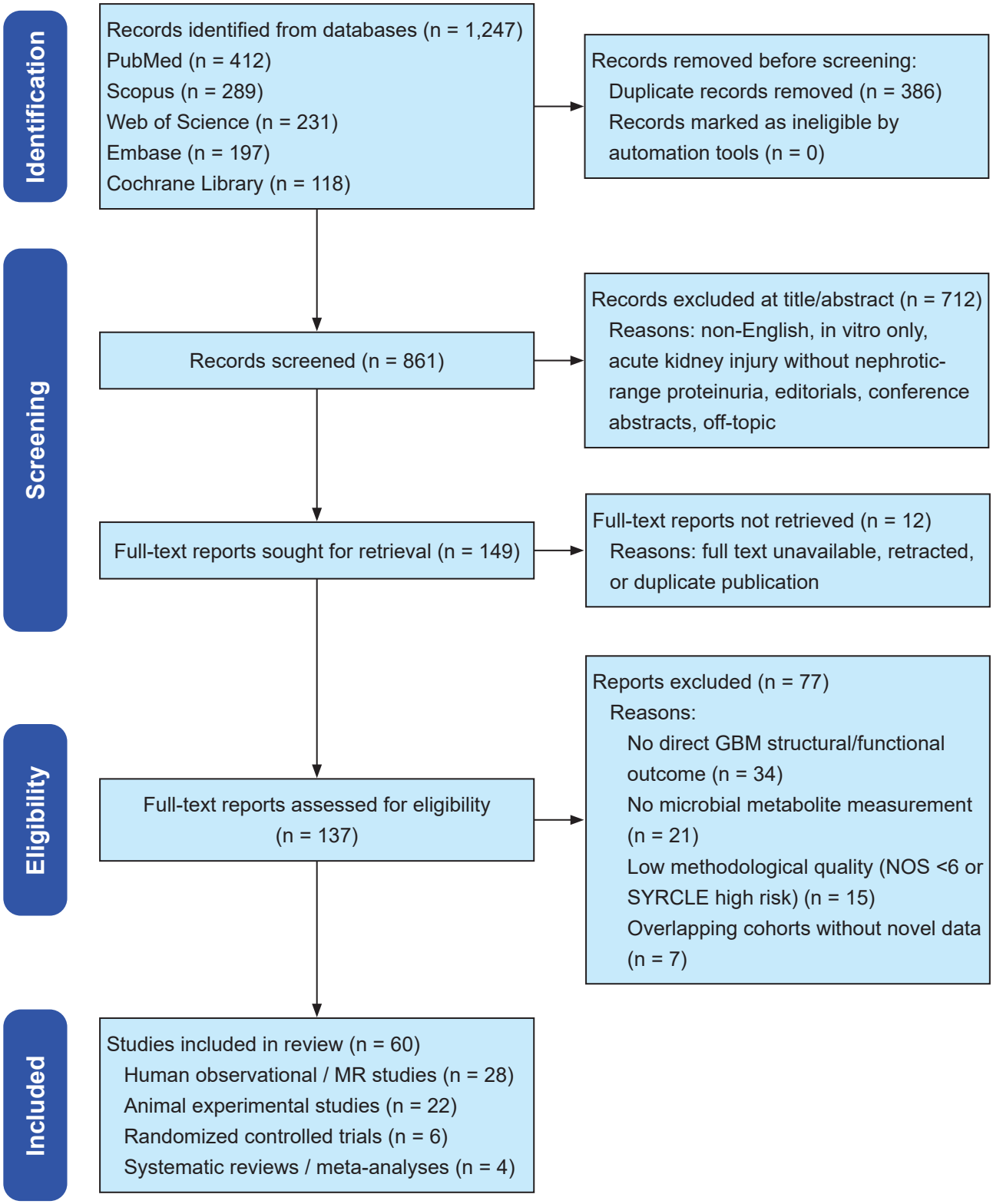
Quality Assessment, Ethics, and Summary

Quality of included studies was appraised using the Newcastle-Ottawa Scale for human cohorts, SYRCLE's tool for animal studies, and Cochrane RoB 2.0 for trials. As this is a secondary analysis of previously published literature, no ethical approval or informed consent was required, in accordance with the Declaration of Helsinki. The protocol has been registered with the Open Science Framework (OSF). In summary, this review systematically synthesizes evidence from approximately 60 original articles to elucidate how microbial metabolites modify GBM perm-selectivity, providing a mechanistic framework for the gut-kidney-GBM axis in nephrotic syndrome.

RESULTS

Gut Dysbiosis in Glomerular Disease: From Correlation to Causation

Comprehensive analysis of the retrieved literature reveals that patients with primary glomerular diseases, including IgA nephropathy (IgAN) and membranous nephropathy (MN), exhibit significant reductions in gut microbial α-diversity.[9,18] A consistent finding across multiple studies is the marked depletion of short-chain fatty acid (SCFA)-producing bacteria, particularly Lachnospiraceae and Ruminococcaceae species.[7,19] Importantly, the pattern of dysbiosis appears shared across



A total of 1,247 records were identified from five databases. After removal of 386 duplicates, 861 records were screened by title/abstract. Of these, 712 were excluded, primarily for being non English, in vitro only, or unrelated to GBM perm-selectivity. A total of 149 full text articles were sought, of which 12 could not be retrieved. The remaining 137 full text articles were assessed in detail; 77 were excluded for lack of direct GBM outcomes, no metabolite measurement, low methodological quality (Newcastle Ottawa Scale < 6 or SYRCLE high risk of bias), or overlapping data. Ultimately, 60 studies met inclusion criteria and were synthesized in this review.

different glomerulopathies, suggesting a common pathophysiological signature rather than disease-specific alterations.

However, the critical question remains whether this dysbiosis is merely an epiphenomenon or truly causal in disease pathogenesis. Mendelian randomization (MR) studies have now provided compelling evidence for causality. A landmark two-sample MR analysis utilizing GWAS data from the MiBioGen consortium (18,340 participants) and CKDGen consortium demonstrated causal relationships between 8 gut microbiota taxa and CKD risk(20). Specifically, Alistipes putredinis (β = 0.131, 95% CI: 0.014 to 0.248, *P* = .029), RuminococcaceaeUCG002 (β = 0.112, 95% CI: 0.025 to 0.200, *P* = .012), and family Veillonellaceae (β = 0.080, 95% CI: 0.020 to 0.140, *P* = .009) showed significant positive associations with CKD.[18] Conversely, LachnospiraceaeUCG010 (β = -0.118, 95% CI: -0.214 to -0.022, *P* = .016) emerged as a protective factor.[21]

These findings are reinforced by additional MR studies. A Chinese population-based MR analysis identified 18 gut microbiome features associated with CKD onset, with genus Alistipes demonstrating consistent causality across independent cohorts.[22] Furthermore, mediation MR analysis revealed that 26.7% of the effect of Alistipes on CKD risk was mediated through serum protein FBLN1, providing a mechanistic link between gut microbiota and kidney injury.[22] Other independent MR studies have confirmed causal relationships for Porphyromonadaceae (OR = 1.351, *P* = 0.002) and Ruminococcus torques group (OR = 1.290, *P* = 0.024) as risk factors, while Prevotellaceae (OR = 0.814, *P* = 0.001) demonstrated protection.[23]

Critical Appraisal. While MR provides robust evidence for causality, effect sizes are modest (β values ranging from 0.04 to 0.13), indicating that the gut microbiome is one among multiple factors in the complex pathogenesis of nephrosis. Additionally, reverse MR analysis identified that CKD itself can alter three microbial taxa, suggesting a bidirectional relationship.[22,24]

Microbial Metabolites and GBM Injury: Molecular Mechanisms

Indoxyl Sulfate (IS). A Dual-Action Toxin. Indoxyl sulfate, a tryptophan metabolite generated by gut bacterial proteolysis, has emerged as a central mediator of GBM dysfunction. Niwa and colleagues first demonstrated that IS administration accelerates renal damage in subtotal nephrectomized rats.[25,26] Mechanistically, IS enters renal cells via organic anion transporters (OAT1/3) and activates NADPH oxidase (Nox4), generating reactive oxygen species.[27] More critically for GBM integrity, IS upregulates heparanase (HPSE) expression through NF-κB activation, leading to degradation of heparan sulfate (HS) side chains—the primary determinants of GBM charge selectivity.[28]

Interestingly, a paradox emerges from the literature: genetic knockout of both agrin and perlecan HS in murine models does not produce significant proteinuria[29] yet IS-mediated partial HS loss in nephrosis is associated with severe protein leakage. The resolution likely lies in altered sulfation patterns rather than absolute HS content. IS induces aberrant 4S rather than 2S/6S sulfation, disrupting growth factor binding (VEGF, TGF-β) and integrin signaling.[30,31]

Trimethylamine N-Oxide (TMAO) and p-Cresyl Sulfate (PCS). Both TMAO (derived from dietary choline/carnitine) and PCS (from tyrosine/phenylalanine) accumulate as GFR declines and are poorly dialyzable due to protein binding.[10,32] These uremic toxins activate the aryl hydrocarbon receptor (AhR) upon cellular entry, triggering pro-inflammatory and pro-fibrotic transcriptional programs.[30] In renal tubular cells, IS and related toxins dysregulate over 2,000 genes, with approximately 1,500 remaining dysregulated despite standard hemodialysis, explaining the persistent inflammatory state in dialysis patients.[33]

Short-Chain Fatty Acids (SCFAs): The Protective Counterpart. In striking contrast to the above toxins, SCFAs (acetate, propionate, and butyrate) derived from dietary fiber fermentation by beneficial commensals exert potent renoprotective effects. In an experimental anti-GBM disease model, treatment with sodium butyrate significantly reduced urinary protein, serum creatinine, and blood urea nitrogen, while decreasing crescent formation and IgG deposition along the GBM.[8] Butyrate also enhanced Treg differentiation and reduced Th17 responses, highlighting the

immunomodulatory role of SCFAs.[34,35]

The Immune Cell Mediation Pathway

A crucial finding from recent MR studies is that circulating immune cells, rather than cytokines, mediate the effects of gut microbiota on CKD. Specifically, Alistipes indistinctus and Alistipes putredinis affect CKD via CD28+CD45RA+CD8+ T cells, with the mediation effect showing that immune cells—not cytokines—are the primary mediators.[20] This challenges the conventional paradigm that inflammation acts solely through soluble mediators and suggests that cell-based therapies or targeted immunomodulation may be more effective than generalized anti-inflammatory approaches.

A Novel Gut-Lymphatic-Renal Feedback Loop. Recent evidence has identified a gut-lymphatic-renal circuit that may explain treatment resistance in chronic nephrosis. Proteinuric kidney injury induces intestinal lymphangiogenesis, which facilitates the trafficking of Th17 cells from the gut to the kidney, thereby perpetuating renal inflammation.[36] This feedback loop creates a self-sustaining cycle of injury that may be unresponsive to conventional immunosuppression alone. Targeting this circuit with lymphatic-specific interventions or Th17 blockade represents a novel therapeutic frontier.[37,38]

DISCUSSION

Clinical Implications and Therapeutic Targets

The accumulated evidence supports several actionable strategies for preserving GBM integrity (Table 1). AST-120 (spherical carbon adsorbent) reduces the absorption of indole and other uremic precursors from the gut, and Phase IV trials have demonstrated significant reductions in proteinuria and improvements in eGFR.[39] Probiotic supplementation aimed at restoring SCFA-producing bacteria has shown positive results in reducing the urinary albumin-to-creatinine ratio (UACR) in CKD patients.[40] SCFA (particularly butyrate) administration exerts protective effects via HDAC inhibition and GPR41/43 activation, though data remain largely preclinical.[8,34] Finally, OAT inhibition with probenecid has been shown to block IS cellular entry experimentally, representing a potential adjunctive therapy.[41]

Importantly, no current clinical practice guideline (KDIGO 2025, ERA 2024) recommends microbiome-targeted therapy for nephrotic syndrome. The evidence base remains predominantly preclinical (rodent models of toxin administration) or associative (human MR studies), and direct demonstration of metabolite-induced GBM structural change in human kidney tissue is absent.[17,47]

This review establishes the gut-kidney-GBM axis as a bona fide pathophysiological pathway in nephrotic syndrome with the following key conclusions:

1. Causal Evidence: Mendelian randomization studies have definitively established causal relationships between specific gut microbiota taxa (Alistipes, RuminococcaceaeUCG002, Veillonellaceae) and CKD, moving beyond mere association.
2. Molecular Mechanisms: Indoxyl sulfate, TMAO, and p-cresyl sulfate disrupt GBM integrity through multiple parallel pathways—enzymatic HS degradation, aberrant sulfation patterns, and AhR-mediated inflammation—while SCFAs (particularly butyrate) exert protective effects via HDAC inhibition and Treg modulation.
3. Immune Mediation: Immune cells (CD28+CD45RA+CD8+ T cells), not cytokines, serve as the primary mediators linking gut dysbiosis to CKD progression, redirecting therapeutic strategies toward cellular immunomodulation.
4. Gut-Lymphatic-Renal Axis: A novel feedback

Therapeutic Strategies Targeting the Gut-Kidney-GBM Axis

Therapeutic Strategy	Target	Evidence Level
AST-120 (oral adsorbent)	Indole/IS absorption	Clinical studies; reduces proteinuria[42,43]
Probiotic supplementation	Restore SCFA-producing bacteria	Positive results in UACR reduction[44,45]
SCFA (butyrate)	HDAC inhibition, GPR41/43 activation	Preclinical (anti-GBM model)[8,34]
OAT inhibition (probenecid)	Block IS cellular entry	Experimental[46]

loop involving intestinal lymphangiogenesis and Th17 cell trafficking contributes to treatment resistance and represents an underexplored therapeutic target.

5. Therapeutic Translation: Targeting the gut-kidney-GBM axis through AST-120, probiotics, or SCFA supplementation represents a hypothesis-generating adjunctive strategy that should be tested alongside conventional RAS blockade and SGLT2 inhibition.
6. Future Directions: Direct evidence of microbial metabolite effects on isolated human GBM sulfation patterns remains lacking and should be prioritized. Additionally, the role of the gut-lymphatic-renal circuit in nephrosis requires further mechanistic elucidation in human studies.

CONCLUSIONS

Final Clinical Message

In patients with steroid-resistant nephrotic syndrome, screening for gut dysbiosis and elevated uremic toxins (IS, TMAO, PCS) should guide personalized microbiome-targeted interventions. Modulation of the gut microbiota cannot yet be recommended as guideline-based therapy; however, it is a mechanistically justified adjunctive strategy warranting further clinical evaluation for preserving glomerular basement membrane integrity and slowing disease progression.

CONFLICT OF INTEREST

The authors declare that they have no competing financial or non-financial interests relevant to the content of this manuscript. However, it is noted that two of the authors (Saeed Changizi-Ashtiyani and Farshid Haghverdi) are members of the editorial board of the journal to which this manuscript is submitted. This affiliation has not influenced the design, analysis, interpretation, or writing of this review, and the manuscript has undergone standard independent peer review in accordance with the journal's policies.

ABBREVIATIONS

Abbreviation	Definition
AhR	Aryl hydrocarbon receptor
CKD	Chronic kidney disease
GBM	Glomerular basement membrane
GFR	Glomerular filtration rate
GWAS	Genome-wide association study
HDAC	Histone deacetylase
HPSE	Heparanase
HS	Heparan sulfate
IS	Indoxyl sulfate
MR	Mendelian randomization
OAT	Organic anion transporter
PCS	p-cresyl sulfate
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
ROS	Reactive oxygen species
SCFA	Short-chain fatty acid
TMA	Trimethylamine
TMAO	Trimethylamine N-oxide
UACR	Urinary albumin-to-creatinine ratio

REFERENCES

1. Bikbov B, Purcell CA, Levey AS, Smith M, Abdoli A, Abebe M, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The lancet. 2020;395(10225):709–33.
2. Heerspink HJ, Grams ME, Sang Y, Ballew SH, Coresh J, Surapaneni A, et al. Proteinuria or Albuminuria as Markers of Kidney and Cardiovascular Disease Risk: An Individual Patient–Level Meta-analysis. Annals of internal medicine. 2026;179(1):32–41.
3. Miner JH. The glomerular basement membrane. Experimental cell research. 2012;318(9):973–8.
4. Hall AM. Protein handling in kidney tubules. Nature Reviews Nephrology. 2025;21(4):241–52.
5. Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. Journal of the American Society of Nephrology. 2014;25(4):657–70.
6. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nature Reviews Microbiology. 2021;19(1):55–71.
7. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell. 2016;165(6):1332–45.
8. Liu J, Gu Q-h, Cui Z, Zhao M-h, Jia X-y. Short-chain fatty acids ameliorate experimental anti-glomerular basement membrane disease. Clinical Immunology. 2024;259:109903.
9. Vaziri ND, Wong J, Pahl M, Piceno YM, Yuan J, DeSantis TZ, et al. Chronic kidney disease alters intestinal microbial flora. Kidney international. 2013;83(2):308–15.
10. Tang WHW, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. New England Journal of Medicine. 2013;368(17):1575–84.

11. Gryp T, Huys GRB, Joossens M, Van Biesen W, Glorieux G, Vaneechoutte M. Isolation and quantification of uremic toxin precursor-generating gut bacteria in chronic kidney disease patients. International journal of molecular sciences. 2020;21(6):1986.
12. Lin C-J, Wu V, Wu P-C, Wu C-J. Meta-analysis of the associations of p-cresyl sulfate (PCS) and indoxyl sulfate (IS) with cardiovascular events and all-cause mortality in patients with chronic renal failure. PloS one. 2015;10(7):e0132589.
13. Dong X, Zhang J, Li W, Li Y, Jia L, Liu Z, et al. Yi-Shen-Hua-Shi regulates intestinal microbiota dysbiosis and protects against proteinuria in patients with chronic kidney disease: a randomized controlled study. Pharmaceutical Biology. 2024;62(1):356–66.
14. Evenepoel P, Poesen R, Meijers B. The gut–kidney axis. Pediatric nephrology. 2017;32(11):2005–14.
15. Sun C-Y, Young G-H, Hsieh Y-T, Chen Y-H, Wu M-S, Wu V-C, et al. Protein-bound uremic toxins induce tissue remodeling by targeting the EGF receptor. Journal of the American Society of Nephrology. 2015;26(2):281–90.
16. Motojima M, Hosokawa A, Yamato H, Muraki T, Yoshioka T. Uremic toxins of organic anions up-regulate PAI-1 expression by induction of NF-κB and free radical in proximal tubular cells. Kidney international. 2003;63(5):1671–80.
17. Disease K, In IGOKNS, Floege J, Gibson KL, Vivarelli M, Liew A, et al. KDIGO 2025 clinical practice guideline for the management of nephrotic syndrome in children. Kidney International. 2025;107(5):S241–S89.
18. Zhang L, Hu L, Tan L, Zhang Z, Chen M, Gan W, et al. The dysbiosis of gut microbiota and dysregulation of metabolites in IgA nephropathy and membranous nephropathy. Frontiers in Medicine. 2025;12:1618947.
19. De Angelis M, Montemurno E, Piccolo M, Vannini L, Lauriero G, Maranzano V, et al. Microbiota and metabolome associated with immunoglobulin A nephropathy (IgAN). PloS one. 2014;9(6):e99006.
20. Tan J, Xiong Z, Yu S, Lu W, Yu L. Mendelian randomization study revealed a gut microbiota-immune system-kidney junction axis in chronic kidney disease. Scientific Reports. 2025;15(1):21685.
21. Hu X, Wang L, Lin C, Zhu Z, Yang S, Wang S, et al. Mendelian randomization analysis of gut microbiota and chronic kidney disease: Implications for herbal interventions. Medicine. 2025;104(45):e45730.
22. Lin W, Liang Z, Fang J, Liu Y, Lei L, Lin J, et al. Association Between Gut Microbiota and Chronic Kidney Disease: A Two-Sample Mendelian Randomization Study in a Chinese Population. Biomedicines. 2025;13(6):1397.
23. Zhang WW, Huo JL, Di Xiao M, Xu YJ, Zhou J. Exploring the potential link between gut microbiota and chronic kidney disease in causality: a 2-sample Mendelian randomization study. Medicine. 2024;103(43):e40236.
24. Yang W. The causal links between gut microbiota and both acute and chronic renal failure: A two-sample mendelian randomization study. Medicine. 2025;104(50):e46336.
25. Niwa T. Uremic toxicity of indoxyl sulfate. Nagoya journal of medical science. 2010;72(1-2):1.
26. Niwa T. Indoxyl sulfate is a nephro-vascular toxin. Journal of Renal Nutrition. 2010;20(5):S2–S6.
27. Watanabe H, Miyamoto Y, Honda D, Tanaka H, Wu Q, Endo M, et al. p-Cresyl sulfate causes renal tubular cell damage by inducing oxidative stress by activation of NADPH oxidase. Kidney international. 2013;83(4):582–92.
28. Shimizu H, Yisireyili M, Higashiyama Y, Nishijima F, Niwa T. Indoxyl sulfate upregulates renal expression of ICAM-1 via production of ROS and activation of NF-κB and p53 in proximal tubular cells. Life sciences. 2013;92(2):143–8.
29. Goldberg S, Harvey SJ, Cunningham J, Tryggvason K, Miner JH. Glomerular filtration is normal in the absence of both agrin and perlecan–heparan sulfate from the glomerular basement membrane. Nephrology Dialysis Transplantation. 2009;24(7):2044–51.
30. Bishop JR, Schuksz M, Esko JD. Heparan sulphate proteoglycans fine-tune mammalian physiology. Nature. 2007;446(7139):1030–7.
31. Meijers B, Jouret F, Evenepoel P. Linking gut microbiota to cardiovascular disease and hypertension: Lessons from chronic kidney disease. Pharmacological Research. 2018;133:101–7.
32. Vanholder R, Schepers E, Pletinck A, Nagler EV, Glorieux G. The uremic toxicity of indoxyl sulfate and p-cresyl sulfate: a systematic review. Journal of the American Society of Nephrology. 2014;25(9):1897–907.
33. Jhawar S, Singh P, Torres D, Ramirez-Valle F, Kassem H, Banerjee T, et al. Functional genomic analysis identifies indoxyl sulfate as a major, poorly dialyzable uremic toxin in end-stage renal disease. PloS one. 2015;10(3):e0118703.
34. Arpaia N, Campbell C, Fan X, Dikiy S, Van Der Veeken J, Deroos P, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. 2013;504(7480):451–5.
35. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly-y M, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013;341(6145):569–73.
36. Zheng S, Wen H, Yin W, Chen D, Zhong X. Inflammatory bowel disease and renal disorders: from clinical associations to shared mechanisms and management strategies. Frontiers in Immunology. 2026;17:1812348.
37. Krebs CF, Paust H-J, Krohn S, Koyro T, Brix SR, Riedel J-H, et al. Autoimmune renal disease is exacerbated by S1P-receptor-1-dependent intestinal Th17 cell migration to the kidney. Immunity. 2016;45(5):1078–92.
38. Li T, Ma X, Wang T, Tian W, Liu J, Shen W, et al. Clostridium butyricum inhibits the inflammation in children with primary nephrotic syndrome by regulating Th17/Tregs balance via gut-kidney axis. BMC microbiology. 2024;24(1):97.
39. Okada K, Matsumoto K, Takahashi S. Oral adsorbent prevents reduction of anionic sites of the glomerular basement membrane in diabetic nephropathy. Nephron Experimental Nephrology. 2005;99(2):e56–e62.
40. Xie R, Yuen SK, Tsang Z, Tai WC, Yap DY. The relationship between probiotics and prebiotics, kidney dysfunction and mortality–Results from a longitudinal cohort study and Mendelian randomization. Clinical Nutrition ESPEN. 2025;65:272–81.

41. Favretto G, Souza LM, Gregório PC, Cunha RS, Maciel RA, Sassaki GL, et al. Role of organic anion transporters in the uptake of protein-bound uremic toxins by human endothelial cells and monocyte chemoattractant protein-1 expression. Journal of Vascular Research. 2017;54(3):170–9.
42. Asai M, Kumakura S, Kikuchi M. Review of the efficacy of AST-120 (KREMEZIN®) on renal function in chronic kidney disease patients. Ren Fail. 2019;41(1):47-56.
43. Yamaguchi J, Tanaka T, Inagi R. Effect of AST-120 in Chronic Kidney Disease Treatment: Still a Controversy? Nephron. 2017;135(3):201-6.
44. Huang HW, Chen MJ. Exploring the Preventive and Therapeutic Mechanisms of Probiotics in Chronic Kidney Disease through the Gut-Kidney Axis. J Agric Food Chem. 2024;72(15):8347-64.
45. Liu C, Yang L, Wei W, Fu P. Efficacy of probiotics/synbiotics supplementation in patients with chronic kidney disease: a systematic review and meta-analysis of randomized controlled trials. Front Nutr. 2024;11:1434613.
46. Enomoto A, Takeda M, Taki K, Takayama F, Noshiro R, Niwa T, Endou H. Interactions of human organic anion as well as cation transporters with indoxyl sulfate. Eur J Pharmacol. 2003;466(1-2):13-20.
47. Floege J, Barratt J, Cook HT, Noronha IL, Reich HN, Suzuki Y, et al. Executive summary of the KDIGO 2025 clinical practice guideline for the management of immunoglobulin A nephropathy (IgAN) and immunoglobulin A vasculitis (IgAV). Kidney International. 2025;108(4):548–54.

Correspondence to:
Farshid Haghverdi, MD
Assistant Professor, Department of Internal Medicine, School of Medicine, Arak University of Medical Sciences, Arak, Iran
ORCID ID: 0000-0003-0699-7887
E-mail: farshid_430@yahoo.com

Received March 2026
Revised April 2026
Accepted June 2026

ORIGINAL PAPER KIDNEY DISEASE RJCCN

Efficacy of Prednisone Combined with Leflunomide in Lupus Nephritis and the Prognostic Value of TL1A and Serum Cystatin C

Qing Li, Lixia Chen, Ming Gao

Department of Rheumatoid and Clinical Immunology, Affiliated Hospital of Qingdao University, 266000, China

Keywords. TL1A, cystatin C, prednisone, leflunomide, lupus nephritis, efficacy, prognostic prediction

Introduction. To evaluate the therapeutic efficacy of prednisone combined with leflunomide in patients with lupus nephritis (LN) and investigate the prognostic value of serum tumor necrosis factor-like ligand 1A (TL1A) and cystatin C.

Methods. This study included 64 patients with LN treated with prednisone and leflunomide between June 2020 and March 2022 and 64 healthy controls. Serum TL1A and cystatin C levels were measured before and after treatment. Clinical and laboratory parameters were compared, and the predictive values of TL1A and cystatin C for treatment response and prognosis were assessed using ROC analysis. Independent prognostic factors were identified by multivariate analysis.

Results. Before treatment, serum TL1A and cystatin C levels were significantly higher in patients with LN than in healthy controls ($P < .05$). Both biomarkers decreased significantly after treatment but remained above control levels ($P < .05$). Treatment also significantly reduced 24-hour urinary protein, serum creatinine, and BUN, while increasing serum albumin and complement C3 ($P < .05$). Baseline TL1A and cystatin C levels were significantly lower in patients with an effective treatment response than in those with ineffective treatment ($P < .05$). ROC analysis showed good predictive performance for treatment response and prognosis. Multivariate analysis identified elevated 24-hour proteinuria, serum cystatin C, TL1A, and higher renal pathological grade as independent predictors of poor prognosis.

Conclusions. Serum cystatin C and TL1A are promising biomarkers for predicting treatment response and prognosis in LN patients receiving prednisone plus leflunomide. Elevated levels of both biomarkers are independently associated with poor clinical outcomes.

RJCCN 2026; 2(3):183-90
www.rjccn.org
DOI: 10.66224/rjccn.2.3.57

INTRODUCTION

Lupus nephritis (LN), as a secondary immune complex nephritis, is mainly due to kidney injury caused by kidney invasion by systemic lupus erythematosus as an autoimmune disease.[1] LN is mainly characterized by abnormal renal function, and glomerulonephritis caused by LN has a more complicated pathogenesis. It's more difficult to treat

Please cite this article as: Li Q, Chen L, Gao M. Efficacy of Prednisone Combined with Leflunomide in Lupus Nephritis and the Prognostic Value of TL1A and Serum Cystatin C. RJCCN. 2026;2(3):183-90.

it clinically, and its course of disease is longer, with poor prognosis and high possibility of relapse.[2,3] Therefore, it is of great clinical significance for LN patients to effectively treat LN and predict its efficacy. At present, the clinical treatment of LN mainly adopts the combination of glucocorticoid and immunosuppressant. Although it has good efficacy for most patients, there are still some patients whose efficacy is not ideal. If the treatment scheme cannot be adjusted in time, the prognosis of them will be adversely affected.[4,5]

Prednisone, as a glucocorticoid, has anti-inflammatory and anti-allergic effects. It can effectively stabilize lysosomal membrane and reduce fibrin deposition, thus decreasing proteinuria and achieving efficacy by reducing capillary permeability. At present, prednisone is also widely used in clinical practice.[6] Leflunomide, as a low toxicity immunosuppressant, not only can inhibit cell proliferation and excessive immune response, but also can improve renal interstitial fibrosis with fewer adverse reactions.[7] Although prednisone and leflunomide are both widely used clinically, there is still some controversy about the efficacy of their combined application. At present, clinical evaluation of the efficacy of LN is mostly carried out by creatinine or urea nitrogen, but the changes of these indexes are not obvious for patients with minor renal injury, and cannot reflect the condition or efficacy of patients very well.[8] serum cystatin C is a protein constantly produced by nucleated cells in the body. Because it can only be filtered through glomerulus, it can be used as an important marker for evaluating renal function and efficacy of drugs.[9] Tumor necrosis factor-like ligand 1A (TL1A), as a member of tumor necrosis factor superfamily, was thought to form TL1A-DR3 complexes by binding with 3 (death receptor 3, DR3) of its receptor superfamily members, thus stimulating T cell activation and further promoting inflammatory response.[10] Previous studies[11] have shown that TL1A plays an important role in various autoimmune diseases, but few studies have analyzed its expression and clinical significance in LN.

In order to find a new effective scheme for the treatment of LN, we investigated the efficacy of prednisone combined with leflunomide on LN and effect on the expression levels of serum cystatin C and urine N-acetyl-**β**-D-glucosidase.

MATERIALS AND METHODS

General Information

Sixty-four LN patients treated in our hospital from June 2020 to March 2022 were selected as the research group, including 34 male patients and 30 female patients; the average age of all patients was (37.21 ± 6.33) years old, and they were treated with prednisone combined with leflunomide. Sixty-four healthy people who underwent physical examination in our hospital during the same period were selected as the control group. Inclusion and exclusion criteria were as follows: patients diagnosed as LN by pathological diagnosis. Exclusion criteria: patients with primary nephritis; patients who had taken hormone or immunosuppressant orally in the past 2 months; patients with severe cardiopulmonary insufficiency; patients with communication or cognitive impairment; patients who did not cooperate with this study. All patients and their families agreed to participate in the experiment and sign an informed consent. The experiment was approved by the Hospital Ethics Committee.

Treatment Methods

All patients in the research group took prednisone tablets, with an initial dose of 10mg/kg/d. After the condition of patients improved, the dosage was reduced to a maintenance dose of 10mg/d according to their specific conditions. Then 40 mg/d leflunomide on the basis of prednisone was taken orally, and it was reduced to 20 mg/d after 3 days, with a treatment period of 6 months. After efficacy evaluation, prednisone combined with cyclophosphamide was used for the treatment of patients with ineffective treatment.

Index Detection

Altogether 5ml of venous blood was taken from patients in the research group on an empty stomach in the early morning of the next day after admission and 6 months after treatment, centrifuged at 3000 r/min for 10min. Serum cystatin C was detected by immunoturbidimetry, the expression of serum TL1A was detected by ELISA, and the detection was carried out in strict accordance with the operation instructions of the kit. In addition, 24-hour urine protein quantitation, plasma albumin,

serum creatinine (Scr), serum urea nitrogen (BUN) and serum complement C3 were detected before and after treatment.

Statistical Methods

In this study, SPSS 20.0 was used for statistical analysis of experimental data. Chi-square test was used for the counting data, and mean ± standard deviation was used for the measurement data. T test was used for comparison between the two groups, paired T test was used for comparison before and after treatment, and GraphPad Prism 6 software was used for drawing the experimental pictures. A P value lower than .05 was considered to indicate a statistical difference.

RESULTS

General Information

There was no significant difference in gender, age and BMI between the two groups ($P > .05$), and there was no significant difference in gender, age, 24-hour urine protein quantitation, plasma albumin, complement C3, Scr, BUP, and SLEDAI score before treatment ($P > .05$), which was comparable. More details were shown in Table 1.

Expression of Serum Cystatin C and TL1A

The expression levels of serum cystatin C and TL1A in the research group before treatment were significantly higher than those in the control group ($P < .05$), the expression levels of serum cystatin C and TL1A in the research group after treatment were significantly lower than those before treatment, but still higher than those in normal people ($P < .05$), as shown in Figure 1.

Detection and Evaluation of Other Indexes Before and After Treatment

After treatment, 24-hour urine protein quantitation, Scr, and BUN of the patients in the research group were significantly lower than those before treatment, and plasma albumin and C3 were significantly higher than those before treatment ($P < .05$). After treatment, Scr, BUN, plasma albumin, and C3 of the patients in the research group had no significant difference with the control group ($P > .05$), but 24-hour urine protein quantitation was still higher than the control group ($P < .05$), as shown in Figure 2.

Predictive Value of Serum Cystatin C and TL1A for Efficacy

We divided the patients into effective group and ineffective group according to their different efficacy, of which 49 patients were effective and 15 patients were ineffective. It was found that the expression levels of cystatin C and TL1A in serum of the patients in the effective group were

Table 1. General Data

Factor	Research group (n = 64)	Control group (n = 64)	t/χ^2	*P*
Gender				
Male	34 (53.13)	32 (50.00)	0.125	.724
Female	30 (46.87)	32 (50.00)		
Age, y	36.26 ± 7.19	36.53 ± 7.15	0.211	.833
BMI, kg/m^2	21.73 ± 2.06	21.68 ± 2.11	0.135	.893
History of smoking				
Yes	38 (59.38)	39 (60.94)	0.027	.869
No	36 (56.25)	35 (54.69)		
Systolic pressure, mmHg	127.25 ± 11.34	125.14 ± 9.25	1.153	.251
Diastolic pressure, mmHg	81.75 ± 8.02	79.59 ± 7.05	1.618	.108
White blood cells, ×10^9/L	6.11 ± 1.32	5.96 ± 1.25	0.660	.510
Platelets, ×10^9/L	239.45 ± 62.18	243.65 ± 59.37	0.391	.697
SLEDAI (score)	19.52 ± 0.11	-	-	-
Renal pathological grading				
III	21 (32.81)	-	-	-
IV	16 (25.00)	-		
III-V	17 (26.56)	-		
IV-V	10 (15.63)	-		

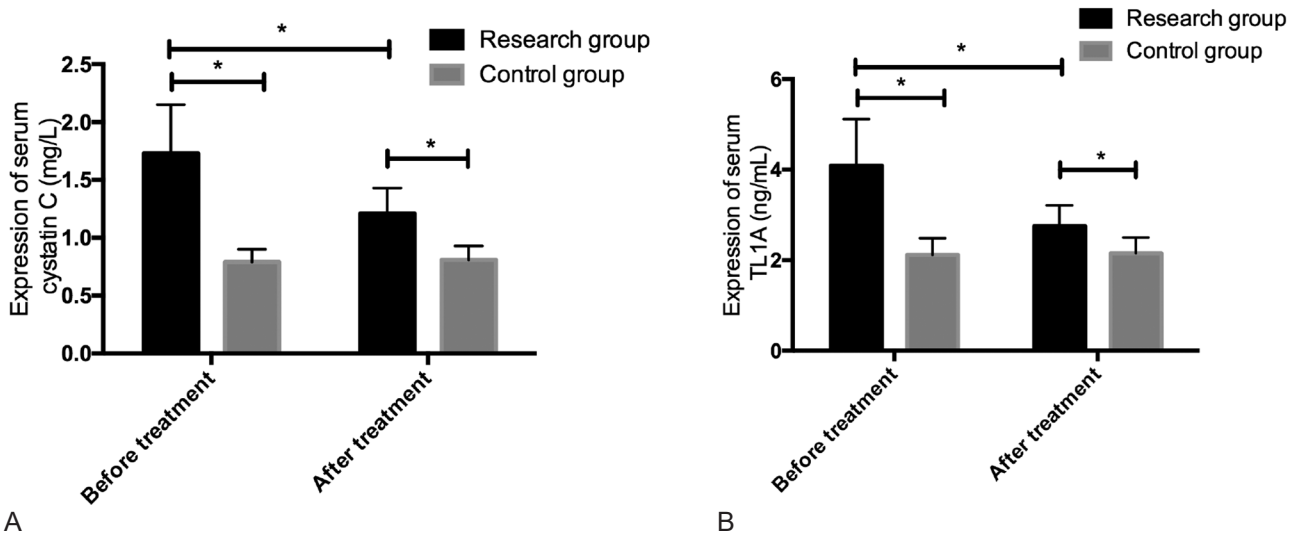


Figure 1. Expression of Serum Cystatin C and TL1A. (A) expression of serum cystatin C before and after treatment; (B) expression of TL1A before and after treatment) (*indicated $P < .05$).

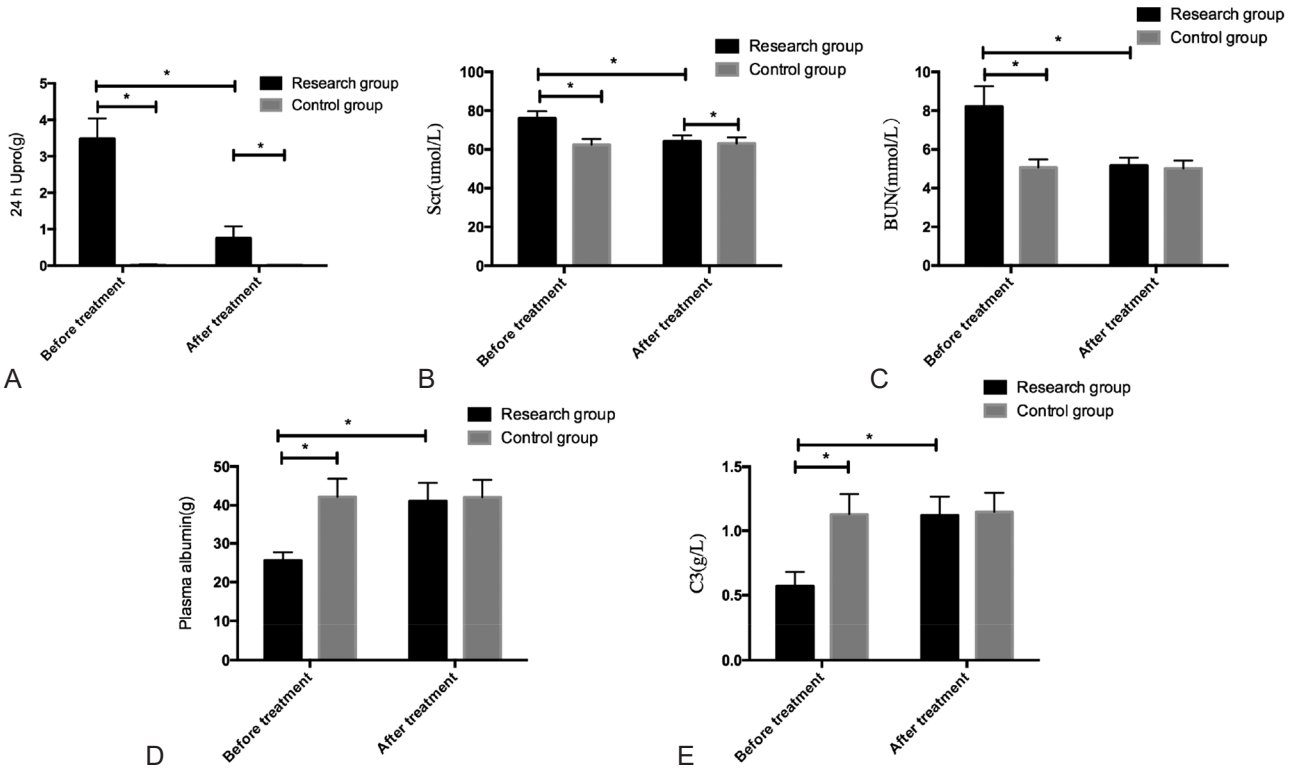


Figure 2. Detection and Evaluation of Other Indexes Before and After Treatment. (A) 24-hour urine protein quantification before and after treatment; (B) Scr before and after treatment; (C) BUN before and after treatment; (D) serum albumin before and after treatment; and (E) complement C3 before and after treatment (*indicated $P < .05$).

significantly lower than those in the ineffective group before treatment, and the difference was statistically significant ($P < .05$). ROC analysis showed that the predicted AUC of serum cystatin C for ineffective treatment was 0.917, and the predicted AUC of TL1A for ineffective treatment was 0.860, both of which had high predictive value, as shown in Figure 3.

Predictive Value of Serum Cystatin C and TL1A for Poor Prognosis

We followed up the patients for 3 years.

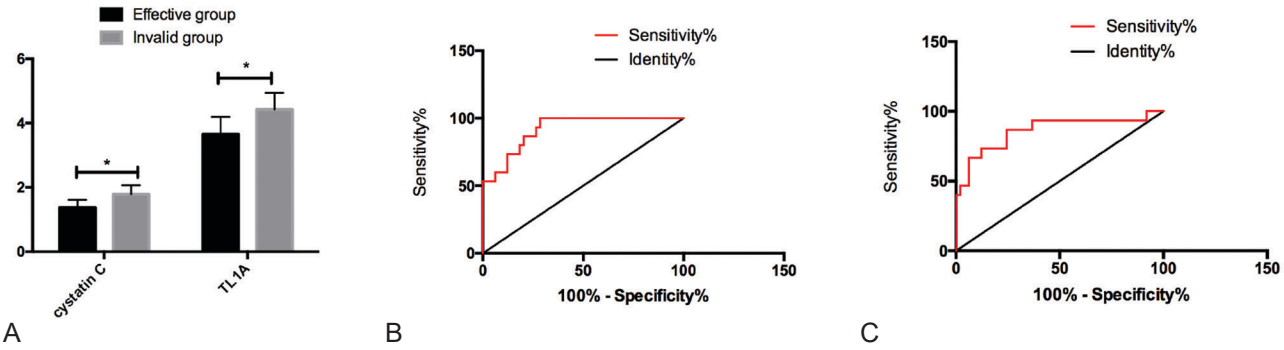


Figure 3. Predictive Value of Serum Cystatin C and TL1A for Efficacy. (A) expression levels of serum cystatin C and TL1A in serum of patients with different efficacy; (B) predictive value of serum cystatin C for efficacy; and (C) predictive value of TL1A for efficacy) (*indicated $P < .05$).

According to whether LN patients entered the end stage of renal disease (uremia), they were divided into good prognosis group (40 cases) and poor prognosis group (24 cases). After detecting the expression levels of cystatin C and TL1A in serum of patients in the two groups after treatment, it was found that the expression levels of cystatin C and TL1A in serum of the patients with good prognosis were significantly lower than those with poor prognosis ($P < .05$). After drawing ROC curve, predicted AUC of cystatin C for LN patients with poor prognosis was 0.855, and predicted AUC of TL1A for LN patients with poor prognosis was 0.850, all of which had high predictive value, as shown in Figure 4.

Univariate Analysis of Poor Prognosis in LN Patients

According to univariate analysis of patients with good prognosis and those with poor prognosis, we found that there were no significant differences in gender, age, Scr, BUN, C3, ESR, and other aspects between the two groups ($P > .05$). There were significant differences in renal pathological grading, 24-hour urine protein quantification, serum cystatin C and TL1A ($P < .05$). More details were shown in Table 2.

Multivariate Analysis of Poor Prognosis in LN Patients

We included renal pathological grading, 24-hour urine protein quantitation, serum cystatin C and TL1A into analysis, and listed them as dependent variables for assignment (Table 3). Logistic regression model was used for multivariate analysis, and the results showed that renal pathological grading, 24-hour urine protein quantitation, serum miR-1231 and miR-192 were independent risk factors for patients with poor prognosis (Table 4).

DISCUSSION

LN is the basis of systemic lupus erythematosus comorbid with kidney injury. Its pathogenesis is closely related to the formation of immune

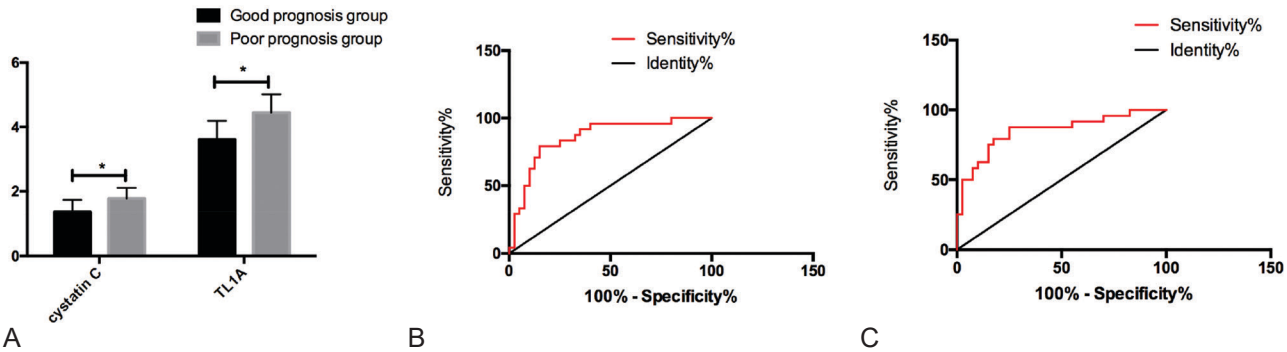


Figure 4. Predictive Value of Serum Cystatinc C and TL1A for Poor Prognosis. (A) expression of cystatin C and TL1A in serum of patients with different prognosis; (B) predictive value of cystatin C for poor prognosis; (C) predictive value of TL1A for poor prognosis) (*indicated $P < .05$).

Table 2. Univariate Analysis of Poor Prognosis in LN Patients

Factor	Good prognosis group (n = 40)	Poor prognosis group n = 24	t/χ^2	*P*
Gender (n, (%))				
Male	21 (52.50)	13 (54.17)	0.017	.897
Female	19 (47.50)	11 (45.83)		
Age, y	36.17 ± 7.05	36.28 ± 7.09	0.060	.952
Renal pathological grading				
III	18 (45.00)	3 (12.50)	13.42	.004
IV	12 (30.00)	4 (16.67)		
III-V	6 (15.00)	11 (45.83)		
IV-V	4 (10.00)	6 (25.00)		
24-hour urine protein, g	0.42 ± 0.18	0.89 ± 0.15	10.74	< .001
Scr, umol/L	65.72 ± 3.42	64.95 ± 3.52	0.863	.392
BUN, mmol/L	5.12 ± 0.39	5.15 ± 0.41	0.292	.771
Plasma albumin, g	42.31 ± 4.59	42.65 ± 4.71	0.284	.777
C3, g/L	1.13 ± 0.12	1.09 ± 0.11	1.331	.188
Serum cystatin C, mL/L	1.36 ± 0.37	1.78 ± 0.33	4.573	< .001
TL1A, ng/mL	3.61 ± 0.58	4.45 ± 0.57	5.645	< .001

Table 3. Assignment Table

Factor	Assignment
Renal pathological grading	III, IV = 1; III-V, IV-V = 2
24-hour urinary protein quantification	Data belong to continuous variables and are analyzed with original data.
Serum cystatin C	Data belong to continuous variables and are analyzed with original data.
TL1A	Data belong to continuous variables and are analyzed with original data.

Table 4. Multivariate Analysis of Poor Prognosis in LN Patients

Factor	β	S.E	Wald	OR	95% CI	*P*
Renal pathological grading	1.155	0.518	4.785	3.204	1.115 to 9.147	< .05
24-hour urine protein quantitation	1.015	0.338	9.411	2.742	1.435 to 5.204	< .05
Serum cystatin C	0.018	0.065	3.674	1.395	1.033 to 1.702	< .05
TL1A	0.193	0.425	7.164	1.233	1.165 to 4.405	< .05

complexes and various immune abnormalities in the body.[12] At present, the primary treatment for LN is drug therapy. Prednisone, as a commonly used hormone clinically, can regulate the immune state of the body. Although hormone drugs have good efficacy, they also have many side effects. Therefore, a small amount of hormone drugs are often used together with immunosuppressants in clinical practice.[13,14] Because LN patients have a long course of disease and treatment time, once the efficacy is not good, it is necessary to find a more appropriate treatment plan, so the prediction of drug efficacy and prognosis has important clinical significance for selecting treatment plan.[15]

In our study, prednisone combined with leflunomide was selected to treat LN patients. Leflunomide, as a new immunosuppressive agent, can reduce the formation of B cells and antibodies in the body through the activity of light lactate dehydrogenase. It can also inhibit the signal transmission of cells by inhibiting the activity of tyrosine kinases, thus inhibiting the generation of fibroblasts in renal interstitium and finally relieving the fibrosis process of kidney.[16,17] Previous studies[18] also found that leflunomide not only had better efficacy on LN, but also had fewer adverse reactions and higher safety when analyzing the efficacy of leflunomide in LN. However, for LN patients, there are still some differences in the efficacy of drugs. Therefore, it is necessary to predict the efficacy and prognosis of patients from the detection of other indexes, so as to timely change the therapeutic scheme and improve the prognosis. Serum cystatin C is widely

present in nucleated cells and body fluids, and it is only filtered through glomerulus, so once kidney function is damaged, the expression of serum cystatin C will rise sharply, and its expression in the body is relatively stable in general. However, when kidney function changes, its change occurs earlier than Scr, so it can have higher sensitivity to changes in kidney function.[19,20] As a member of tumor superfamily, TL1A has been shown to promote the occurrence of autoimmune diseases in many studies in the past, such as rheumatoid arthritis.[21] Since the occurrence of LN is also related to autoimmune, there has been no discussion on the role of TL1A in LN in the past.

Besides, we found that the expression levels of cystatin C and TL1A in serum of LN patients were significantly higher than those of normal people, but their expression significantly decreased after treatment, which indicated that serum cystatin C and TL1A could reflect the efficacy of LN. Then we divided the patients into the effective group and the ineffective group according to their efficacy. After comparing the serum cystatin C and TL1A of patients in the two groups before treatment, we found that the serum cystatin C and TL1A of the patients in the effective group before treatment were significantly lower than those of without treatment. After ROC analysis, we found that the serum cystatin C and TL1A had higher predictive value for the efficacy of LN. This suggested that serum cystatin C and TL1A might be used as predictors of the efficacy of prednisone combined with leflunomide in the treatment of LN patients, but no studies had confirmed them. Then we analyzed the predictive value of serum cystatinc C and TL1A for poor prognosis of LN patients, and the results showed that serum cystatinc C and TL1A had high predictive value for their poor prognosis and were also independent risk factors for poor prognosis of them. Serum cystatin C, as a newly emerging indicator of renal function in recent years, when its expression increases, it often means that glomerular filtration rate decreases, and the decrease of glomerular filtration rate often indicates poor prognosis of patients.[22] Previous studies[23] revealed that TL1A was less expressed under normal conditions of monocytes and dendritic cells, and its expression would increase significantly after it was stimulated by inflammation or Toll-like receptor, so the increase of TL1A expression often indicates the intensification of immune response in vivo. However, there is relatively little research on TL1A in LN at present, and its specific mechanism is not clear for the time being, which needs further research.

CONCLUSIONS

To sum up, serum cystatin C and TL1A have high predictive value for the efficacy and prognosis of prednisone combined with leflunomide in the treatment of lupus nephritis, and the increase of serum cystatin C and TL1A are independent predictive factors for poor prognosis of LN patients, which may provide a certain reference direction for the treatment and prognosis of them. However, there are still some limitations in this study. For example, firstly, our conclusion is different from some other studies due to the small sample size. Therefore, our conclusion may need further verification. Secondly, we have not elaborated in detail on the mechanism of serum cystatin C and TL1A in LN, which also needs to be supplemented by further basic experiments.

REFERENCES

1. Solé C, Moliné T, Vidal M, Ordi-Ros J, Cortés-Hernández J. An Exosomal Urinary miRNA Signature for Early Diagnosis of Renal Fibrosis in Lupus Nephritis. Cells. 2019;25;8(8):773.
2. Rashad Nearmeen M, El-Shabrawy Reham M, Said Dina, et al. Serum Levels of Transforming Growth Factor Beta -1 (TGF-β1) as An Early No Invasive Marker for Diagnosis of Lupus Nephritis in Systemic Lupus Erythematosus Patients. Egypt J Immunol. 2019;26:31-42.
3. Deng Weijuan, Xu Minwen, Meng Qiaoyun, et al. CD8+CD103+ iTregs inhibit the progression of lupus nephritis by attenuating glomerular endothelial cell injury. Rheumatology (Oxford). 2019;undefined: undefined.
4. Jung Ui Hong, Kwak Sang Gyu, Choe Jung Yoon, et al. The Effect of Mycophenolate Mofetil on Non-Renal Manifestations in Systemic Lupus Erythematosus: Results from Korean Lupus Network Registry. J. Korean Med. Sci. 2019;34:e185.
5. Olsen Nancy. Should Generalized Immunosuppression or Targeted Organ Treatment be the Best Principle for Overall Management of Systemic Lupus Erythematosus? Rheum. Dis. Clin. North Am. 2019;45:369-77.
6. Ugarte Amaia, Danza Alvaro, Ruiz-Irastorza Guillermo. Glucocorticoids and antimalarials in systemic lupus erythematosus: an update and future directions. Curr Opin Rheumatol. 2018;30:482-9.

7. An Yuan, Zhou Yunshan, Bi Liqi, et al. Combined immunosuppressive treatment (CIST) in lupus nephritis: a multicenter, randomized controlled study. Clin. Rheumatol. 2019;38:1047-54.
8. Qin Ling, Stanley Samantha, Ding Huihua, et al. Urinary pro-thrombotic, anti-thrombotic, and fibrinolytic molecules as biomarkers of lupus nephritis. Arthritis Res. Ther. 2019;21:176.
9. Al-Naimi MS, Rasheed HA, Hussien NR, Al-Kuraishy HM, Al-Gareeb AI. Nephrotoxicity: Role and significance of renal biomarkers in the early detection of acute renal injury. J Adv Pharm Technol Res. 2019;10:95-9.
10. Prehn JL, Thomas LS, Landers CJ, Yu QT, Michelsen KS, Targan SR. The T cell costimulator TL1A is induced by FcgammaR signaling in human monocytes and dendritic cells. J Immunol. 2007;178(7):4033-8.
11. Takedatsu H, Michelsen KS, Wei B, Landers CJ, Thomas LS, Dhall D, et al. TL1A (TNFSF15) regulates the development of chronic colitis by modulating both T-helper 1 and T-helper 17 activation. Gastroenterology. 2008;135(2):552-67.e2.
12. Li X, Luo F, Li J, Luo C. MiR-183 delivery attenuates murine lupus nephritis-related injuries via targeting mTOR. Scand J Immunol. 2019;90(5):e12810.
13. Wang D, Chen X, Fu M, Li Z. Transcriptomics analysis of sirolimus treatment in lupus nephritis. Mol Med Rep. 2019;20: 245-51.
14. Liu B, Ou Q, Tang Y, Fu S, Liang P, Yu Y, et al. Corticosteroids combined with doublet or single-agent immunosuppressive therapy for active proliferative lupus nephritis. Clin Rheumatol. 2019;38(9):2519-28.
15. Yang M, Akbar U, Mohan C. Curcumin in Autoimmune and Rheumatic Diseases. Nutrients. 2019;11(5):1004.
16. Wu MY, Chen YW, Hung LY, Lee CH, Chen HA, Hsu YH, et al. Successful Treatment for BK Virus Nephropathy by Leflunomide in a Kidney Transplant Patient: A Case Report. Transplant Proc. 2019;51(5):1472-4.
17. Liao XY, Deng QQ, Han L, Wu ZT, Peng ZL, Xie Y, et al. Leflunomide increased the renal exposure of acyclovir by inhibiting OAT1/3 and MRP2. Acta Pharmacol Sin. 2020;41(1):129-37.
18. Cao H, Rao Y, Liu L, Lin J, Yang H, Zhang X, et al. The Efficacy and Safety of Leflunomide for the Treatment of Lupus Nephritis in Chinese Patients: Systematic Review and Meta-Analysis. PLoS ONE. 2015;10:e0144548.
19. Ding Y, Wu T, Zhang W, Zhang S, Wang W. Pretransplant renal function evaluated by serum cystatin C was associated with mortality after liver transplantation: a single-center experience. Ann Transl Med. 2019;7:243.
20. Miyaoka D, Inaba M, Imanishi Y, Hayashi N, Ohara M, Nagata Y, et al. Denosumab improves glomerular filtration rate in osteoporotic patients with normal kidney function by lowering serum phosphorus. J Bone Miner Res. 2019;34(11):2028-35.
21. Zhang J, Wang X, Fahmi H. Role of TL1A in the pathogenesis of rheumatoid arthritis. J Immunol. 2009;183(8):5350-7.
22. Grubb A. Cystatin C is Indispensable for Evaluation of Kidney Disease. Ejifcc. 2017;28(4):268-76.
23. Migone TS, Zhang J, Luo X, Zhuang L, Chen C, Hu B, et al. TL1A is a TNF-like ligand for DR3 and TR6/DcR3 and functions as a T cell costimulator. Immunity. 2002;16(3):479-92.

Correspondence to:
Ming Gao, MD
Department of Rheumatoid and Clinical Immunology, Affiliated Hospital of Qingdao University, 266000, China
ORCID ID: 0009-0003-8763-1250
E-mail: gaoming1769@outlook.com

Received April 2026
Revised May 2026
Accepted June 2026

A Qualitative Study of Exercise Participation Intentions Among Patients Undergoing Maintenance Hemodialysis

Qianqian Wei,[1] Fei Chen,[2] Lixia Yin,[3] Yanan Ban,[1] Hailin Zhang[1]

[1]Department of Hemopurification Center, Lianyungang Clinical College of Nanjing Medical University, Lianyungang City, Jiangsu Province, 222000, China
[2]Department of Hemopurification Center, The Affiliated Lianyungang Hospital of Xuzhou Medical University, Lianyungang City, Jiangsu Province, 222000, China
[3]Department of Hemopurification Center, The First People's Hospital of Lianyungang, Lianyungang City, Jiangsu Province, 222000, China

Keywords. maintenance hemodialysis, exercise intention, COM-B model, influence factor, qualitative study

Introduction. Exercise improves physical function and quality of life in patients undergoing maintenance hemodialysis (MHD). However, exercise participation remains suboptimal in this population. This study explored factors influencing exercise participation intentions among patients undergoing MHD to provide evidence for developing targeted interventions.

Methods. A qualitative study was conducted using purposive sampling to recruit 16 patients undergoing MHD. Data were collected through semi-structured interviews and analyzed using Colaizzi's phenomenological method. Themes were identified based on the Capability, Opportunity, Motivation–Behavior (COM-B) model.

Results. Three major themes and 12 subthemes were identified. Capability included insufficient exercise-related knowledge, limited self-management skills, and poor perceived physical condition. Opportunity comprised the need for individualized exercise prescriptions and professional guidance, limited opportunities for exercise, positive social support, and social isolation. Motivation encompassed fear of exercise, recognition of the value of exercise, previous exercise habits and experiences, expectations of exercise benefits, and strengthened role identity. These factors collectively influenced patients' willingness to participate in exercise.

Conclusions. Exercise participation intentions among patients undergoing MHD are shaped by multiple capability-, opportunity-, and motivation-related factors. Healthcare professionals should strengthen exercise education, provide individualized exercise prescriptions and professional guidance, enhance social support, offer timely feedback on exercise outcomes, and implement multidimensional strategies to improve patients' self-efficacy and motivation, thereby promoting greater participation in regular exercise.

RJCCN 2026; 2(3):191-200
www.rjccn.org
DOI: 10.66224/rjccn.2.3.58

INTRODUCTION

The common complications observed in patients undergoing maintenance hemodialysis (MHD), including gastrointestinal dysfunction, depression, malnutrition, sarcopenia, and cognitive impairment, have significantly compromised their physical and mental health as well as their overall quality of life.[1-3] A substantial body of research indicates that

Please cite this article as: Wei Q, Chen F, Yin L, Ban Y, Zhang H. A Qualitative Study of Exercise Participation Intentions Among Patients Undergoing Maintenance Hemodialysis. RJCCN. 2026;2(3):191-200.

exercise not only enhances the physiological function and quality of life in patients undergoing MHD, but also improves their dialysis adequacy.[4,5] Both domestic and international expert consensus and guidelines also recommend and encourage exercise for MHD patients without contraindications.[6,7] However, only 42.57% of patients were willing to participate in exercise.[8] Although some studies showed that the overall willingness to exercise was high, only 40% of the patients could actually exercise regularly, and their willingness to exercise did not match their exercise behavior.[9] It can be seen that the overall exercise situation of MHD patients is still not optimistic.[8-11] At present, most studies related to exercise in MHD patients focus on exercise prescription and exercise experience, and pay relatively little attention to exercise willingness. The willingness to exercise is complex and diverse, focusing on the participant's perspective and experience, and can predict the future exercise behavior. More autonomous and voluntary exercise will make patients better participate in and persist in exercise.[12] Understanding and enhancing the exercise willingness of MHD patients, promoting the change of their exercise behavior and improving exercise compliance are important prerequisites to maximize the benefits of exercise. The core of the trans-theoretical model (TTM) posits that behavior change has five stages: precontemplation, contemplation, preparation, action, and maintenance,[13] which can be used to reflect an individual's willingness to engage in physical activity.[14] Michie *et al*.[15] introduced the Capacity, Opportunity, Motivation-behavior (COM-B) model in 2011 to elucidate the relationship between individual intentions and behaviors. This model serves as a valuable tool for identifying both individual and contextual factors that influence behavioral change. Therefore, this study investigated patients' willingness to exercise based on TTM, guided by the COM-B model, and adopted qualitative research methods to understand the factors affecting patients' willingness to exercise, so as to provide a basis for formulating intervention programs to promote MHD patients' exercise behavior.

MATERIALS AND METHODS

Research Objects

Patients who underwent maintenance hemodialysis at the blood purification center of a Grade III hospital between April and June 2024 were included in this study. Inclusion criteria: 1) MHD treatment ≥ 3 months, 2) age ≥ 18 years, 3) be conscious and able to communicate normally, 4) Voluntarily participate in the study and agree to the interview and recording. Exclusion criteria: Contraindications to exercise, including conditions such as angina pectoris, atrial fibrillation, tachycardia, and other significant arrhythmias; frequent hypotension during dialysis; and other relevant factors. The purposive sampling method was employed to account for aspects such as gender, age, culture, and duration of dialysis among the interviewees. This approach aimed to enhance the representativeness of the sample participants. The sample size was determined based on the principle of information saturation, ensuring that no new themes emerged during data analysis. Additionally, three extra subjects were interviewed. Finally, a total of 13 patients were included in the study, identified as P1 through P13. Their ages ranged from 25 to 70 years, with dialysis durations spanning from 2 to 13 years. Among these participants, 62% were female. Educational attainment varied, with seven individuals holding a high school diploma or higher. Employment status showed diversity: seven participants were unemployed, two worked as freelancers, two were employed in regular positions, and two were retirees. The willingness to engage in exercise was categorized into five distinct groups corresponding to the pre-intention stage, intention stage, preparation stage, action stage, and retention stage, with a distribution of 5, 2, 3, 1, and 2 cases respectively. The general data are shown in Table 1. This study was reviewed and approved by the Ethics Committee of Lianyungang First People's Hospital (KY-20240409001-02).

Study Methods

Prepare an interview outline. The data collection was conducted utilizing a semi-structured interview outline. Based on a thorough literature review and discussions with the research team regarding the objectives of the study, we developed an initial interview guide. Prior to the formal interviews, adjustments were made based on pre-interviews conducted with two patients to refine

Basic Characteristics of Interviewees

ID	Age (year)	Gender	Dialysis Duration (years)	Education level	Marriage	Occupation	Comorbidity	Willingness to exercise
P1	40	male	3	High school	Married	Freelance	hypertension	Preintention stage
P2	60	male	3	Junior high school	Married	Unemployed	High blood pressure, type 2 diabetes	Intention stage
P3	52	female	5	Junior high	Married	Unemployed	hypertension	Preintention stage
P4	42	female	5	Junior college	Married	Unemployed	High blood pressure, type 2 diabetes	Action phase
P5	39	female	3	Junior college	unmarried	Unemployed	High blood pressure, post-parathyroidectomy	Preintention stage
P6	36	female	4	Undergrad	Divorced	Designers	High blood pressure, liver cysts, secondary hyperparathyroidism	Preparation stage
P7	66	male	13	Junior high	Married	unemployed	Grade 3 hypertension, chronic left heart dysfunction	Stage of intention
P8	50	female	3	Elementary school	Married	Unemployed	Diabetes, high blood pressure, heart dysfunction	Maintenance phase
P9	25	male	2	High school	unmarried	Unemployed	hypertension	Preintention stage
P10	28	female	3	Undergraduate course	unmarried	Public servants	High blood pressure, hypertensive retinopathy	Preparation stage
P11	70	female	4	Elementary school	Married	Retired	Nothing	Preintention stage
P12	31	male	9	Undergrad	Married	Freelance	Nothing	Holding stage
P13	57	female	5	Junior high	Married	Retired	hypertension	Holding stage

Note. Pre-contemplation Stage: The patient exhibits no intention to engage in physical activity within the next six months; Contemplation Stage: The patient is considering a change but has not yet committed to it; Preparation Stage: The patient intends to take action within the next 30 days and has initiated some preparatory steps; Action Stage: The patient has commenced physical activity, although this engagement has lasted less than six months and lacks stability; and Maintenance Stage: The patient's physical activity behavior has been sustained for at least six months.

and finalize the interview outline.

1) Are you familiar with the concept of sports rehabilitation? Additionally, do you know which types of exercise are appropriate for patients undergoing dialysis?
2) Do you believe that your current physical condition is conducive to engaging in exercise? Are you aware of the numerous benefits that regular exercise can provide for your overall well-being?
3) Do you engage in regular physical exercise? If so, what factors motivate you to maintain this habit? Conversely, if you do not exercise regularly, what barriers prevent you from doing so?
4) What kind of exercise do you usually do? Do your family, friends or medical staff support your exercise? How do they support you?
5) Do you know what is exercise in dialysis? What are the ways?
6) Would you be willing to participate in a sports rehabilitation program if our dialysis center offers one in the future?
7) What are the main obstacles that you do not want to participate in? Under what circumstances would you be willing to participate?

Data Collection Methods. The interview was conducted collaboratively by two researchers. Prior to the interview, the researchers explained the purpose of the study to the participant and obtained written informed consent. Following an established interview outline, targeted questions were posed, with certain inquiries explored in greater depth based on specific circumstances. Concurrently, non-verbal behaviors and emotional responses of the participants were observed and documented, along with detailed records of the interviews. Each session lasted between 20 to 30 minutes, and all interviews were audio-recorded with the participants' consent.

Data Analysis Methods. According to the sequence of interviews, the participants were designated as P1 through P13. The data were analyzed by two researchers utilizing Colaizzi's

seven-step method,[17] which includes: 1) becoming thoroughly acquainted with the interview data; 2) identifying significant statements that hold meaning; 3) constructing units of meaning; 4) organizing these into themes and categories; 5) defining and describing each theme; 6) forming a foundational structure; and 7) providing feedback on the results to respondents for verification of authenticity.

RESULTS

Based on the COM-B model, themes were identified and synthesized to establish the analytical framework. A total of three primary themes and twelve sub-themes were delineated.

Ability factors: This category encompasses three sub-themes: a lack of sports-related knowledge, insufficient self-management skills, and poor physical awareness.

Opportunity factors: This category includes personalized exercise prescriptions and guidance, limited access to exercise facilities, strong social support, and the impact of social distancing—comprising four sub-themes.

Motivation factors: This category consists of five sub-themes: fear of sports participation, identification with the value of sports, established sports habits and experiences, anticipated benefits from engaging in sports activities, and reinforcement of role cognition.

Ability Factors

Lack of sports-related knowledge. The lack of knowledge regarding exercise and the understanding of its importance significantly influence patients' willingness to engage in physical activity. During interviews, it was revealed that most patients were unaware of suitable modes, types, and intensities of exercise. Additionally, they had limited knowledge about the benefits associated with long-term regular physical activity. Many believed that exercise offered little advantage for their current health status and felt there was no necessity to engage in it. P1: "I don't know what kind of exercise is appropriate for us; I think my body isn't suited for it, so I don't exercise myself. I can't see any benefit—it doesn't manifest itself in me anyway." P2: "Playing sports certainly isn't suitable because there's a fistula on my arm; I'm afraid to move too vigorously. As for what might be appropriate, I'm not clear on that—so walking will have to suffice." P10: "I don't pay attention to which sports are suitable; I assume as long as I move a bit it's fine. I usually take occasional walks—small amounts of exercise don't seem very beneficial and aren't worth overthinking." P6: "It's definitely beneficial for cardiopulmonary function. Patients in our group who have been on dialysis for an extended period have shared this information with me, so I'm eager to give it a try." P12: "I understand that exercising is good for me—I can find all the information online.I wouldn't persist with exercising."

Lack of self-management skills. Some patients who express a willingness to engage in physical activity but have not yet adopted regular exercise habits report that they are uncertain about how to exercise. They find it challenging to select an appropriate form of exercise and often forget to participate in physical activities for various reasons. P2: "When you wish to engage in exercise, it is advisable to do so twice. At times, there may be an overwhelming number of thoughts that hinder your ability to exercise." P6: "We have fistulas in our arms, which complicates our ability to select various sports activities, such as kettlebell swings. Is this permissible? If there are clear guidelines available, I would have no concerns." Patients who possess good habits and self-management skills tend to remain more active. P12: "My typical forms of exercise include jogging and climbing. I generally opt for physical activity after waking up in the morning and approximately half an hour after dinner. Additionally, I consistently wear a fitness tracker to monitor my condition and review my exercise records to ensure that I meet my daily workout goals."

Perceiving poor physical condition. Fatigue and weakness are prevalent co-occurring symptoms among patients undergoing MHD, with their effects being most pronounced on dialysis days. In the interview, the majority of patients expressed that they were inclined to engage in exercise only when they felt rested and perceived their dialysis condition as favorable. Otherwise, they did not consider participating in physical activity. P1: "Engaging in even a small amount of strenuous

exercise can lead to panting. When you experience panting and fatigue, how likely are you to consider exercising?" P2: "On dialysis days, I refrain from walking if I'm feeling tired or unwell. I prefer to rest at home and focus on recovering my strength." P6: "Currently, I've noticed an increase in body fat. While I can manage half an hour of aerobics, after just five minutes of jumping, I find myself fatigued and slightly out of breath; this discourages me from continuing as my physical stamina seems insufficient." P9: "I used to exercise regularly before falling ill. However, after becoming sick, prolonged exercise now leaves me feeling dizzy and bloated, with elevated blood pressure that makes me reluctant to move." P13: "I undergo dialysis on Tuesdays, Thursdays, and Saturdays. If I'm feeling overly fatigued or have not recovered well the following day, I will abstain from exercising; I only engage in physical activity when I'm in good condition."

Chance Factors

Personalized exercise prescription and instruction. Simple, safe and effective exercise prescription and scientific guidance of medical staff can mobilize the enthusiasm of patients to exercise, on the contrary, patients will be discouraged and lose interest. P1: "I don't like too complicated sports, the brain is not as good as before, we are already very busy, who is willing to bother to remember complex actions"; P2: "the movement is not so simple as the mouth says, it should consider physical strength and time, but also consider safety, it must vary from person to person, and if I do not do the action in place, there is no effect, it is better not to move"; P4: "I hope the medical staff can give some simple guidance, one can learn, do not trouble you the kind, I may be more active."

Limited exercise conditions. Good condition support is the promoting factor to enhance patients' willingness to exercise. In this study, the majority of patients indicated that they had no condition to exercise. P1: "My own time is limited, I don't want to spare some time to exercise"; P3: "Take up time to go home"; P10: "I come to dialysis three times a week, plus work, the day of the week only weekend is my own, I must first want to lie at home and rest, do not want to exercise"; P2: "At home, I can go to the small park to use the exercise equipment, but you can see that the bed I lie on during dialysis does not have any exercise conditions, and I cannot insist on stretching my arms and legs by myself." Inconvenient transportation and inclement weather can also affect patients' willingness to exercise. P4: "I do not exercise when it is raining, windy or cold, and I am afraid of catching a cold. Moreover, I live in a mountain, and it is difficult to climb hills, so I have no place to move when I want to exercise. But now that it's getting warmer, I'm sure I'll walk more than before."

Good social support. The importance medical staff attaches to exercise affects patients' enthusiasm for exercise. P8: "The medical staff did not require me to exercise, so I did not pay attention to it. But they were strict with me in terms of diet and water control, so I paid more attention to diet and water control." P5: "There will be doctors and nurses to do some exercise appropriately, but it is like a mantra to 'exercise more', I did not say how to do it, I did not take it seriously"; P10: "The nurse sister said that my poor emotional state was due to lack of exercise, and I often joked that it was better for me to 'go to the field to do farm work', so I did not reject exercise". The support, encouragement and companionship from family and friends improved the patient's exercise compliance and became an important factor affecting the patient's willingness to exercise. P2: "My family members will accompany me to go out more when they are free, and going out for exercise can help me communicate with others and kill the boring time"; P8: "If the family is free from pressure and happy in body and mind, then we are definitely willing to go dancing or something"; P10: "We have a group of patients who share sports knowledge, introduce some experiences, and encourage us to do more sports. My family members will drag me to do sports together." However, it was found in the interview that excessive family support became a stumbling block that hindered the patients from doing exercise. P5: "My two children are very filial, and they all rush to do their work at home. My husband also does housework and doesn't let me do anything. Every day, I just lie down or sit at home and have nothing to do"; P11: "When I am

old, my children are afraid of falling and no one will take care of them, so I am asked to take more rest at home. Every time I come for dialysis, I am sent to the door, so I really have little chance to exercise". Some patients also expressed their concern about the extra cost of exercise rehabilitation. P8: "We spend a lot of money, if there is any extra cost for this exercise rehabilitation, I am definitely not willing to participate in it."

Social distancing. Social alienation refers to the patient's perception of negative treatment from the outside world when participating in social interaction, resulting in natural alienation[19] from social relations, reduced social activities of the patient, and withdrawal behavior, resulting in decreased physical activity and low motivation for sports. In this interview, it was found that some patients had a low sense of social participation, resulting in a sense of social alienation. P8: "My reaction is a little slow now, I can't see people greeting me all the time, which is very embarrassing. After a long time, people will ignore me, thinking that I don't care about people, and I don't want to say hello to others, so I don't want to go out and walk around for fear of meeting acquaintances"; P11: "Since I got sick, I don't sociate with others. I come for dialysis three days a week and have no time, so I don't want to go out. I can only talk with my old man and son at home every day, mixing it up day by day."

Motivation Factors

Fear of sports. Patients have doubts about the safety of exercise and worry about new symptoms or aggravating the progression of the disease and bringing unnecessary injuries to themselves. P1: "I heard that creatinine is produced during exercise, like our own creatinine is high, isn't exercise even higher? Is it safe "; P8: "I have a fistulous hand, the doctor asked me not to use too much strength, cannot lift things, in addition to walking, other hand sports I certainly cannot do it, if the fistula is broken, then I do not have more than the loss." The patient's fear of exercise is widespread, which hinders the patient's willingness to exercise to a certain extent. P3: "I dare not think, I will be tired after dialysis, and exercise will definitely aggravate my symptoms, I am not willing to take risks"; P4: "Especially after dialysis, I feel so tired that I can hardly walk home without falling down. I am not even able to walk steadily, let alone do sports. I am afraid that sports will bring more fatigue"; P6: "Because I easily lose blood pressure, so I do not dare to try, I am afraid that the blood pressure will drop faster if I toss again, so I dare not"; P7: "Walking too fast will make the heart a little vague and uncomfortable, if you do strenuous exercise, you can only take a walk." Some patients said that under the premise of safety and security, they may be willing to try to exercise. P10: "If you can guarantee my safety, supervise me and monitor my vital signs, I will dare to exercise."

Recognition of the value of exercise. Patients' disidentification of sports value leads to their rejection of sports. P1: "Why do you have to force yourself to do some exercise, cannot achieve any effect, exercise cannot take medicine, no injections, no dialysis? Do not want to fix these bells and whistles". And the recognition of the value of exercise is the basis for cultivating the awareness of exercise and promoting the change of patients' behavior. P2: "Exercise is good for health and makes people feel happy, so I am definitely willing to take part in it." P8: "I am not in good health, but exercise is definitely good for me, and I must do something good for my health."

Exercise habits and experience. Inherent exercise habits can bring comfortable inner experience to patients. In this study, it was found that patients with exercise habits have a strong willingness to exercise, otherwise, they have a psychological rejection of exercise. P5: "I didn't like sports before I got sick. Without that habit, I was busy making a living, so I didn't have the leisure to take special exercise"; P7: "I still like sports very much, have the habit of walking, although not regular, but as long as I have time I still love to go out for a walk"; P12: "I like sports. In the past, I played ball games, then I climbed mountains and ran. I am not used to doing sports, so sports are not difficult for me. And positive exercise feedback can stimulate patients' willingness to participate in sports. P2: "I feel that after exercise, blood pressure can be lowered, blood sugar is good, and blood circulation can be increased"; P4: "I used to walk stably, but I feel lighter than before

after slow exercise." And my appetite is much better than before; Many indicators are better than before, and the number of falls is less." P8: "I feel good after exercise, and I can sweat more, which is metabolized from the skin, so that less water can be removed during dialysis"; P12: "Because of regular exercise, so I feel my physical strength is better than other friends; I sweat through exercise, so I can drink a little more water."

Expected Benefits of exercise. Having a positive expectation of the outcome of exercise is an important promoter of willingness to exercise, and some patients indicated that they would be willing to try exercise if they knew the expected benefit of exercise. P1: "If exercise is helpful to the condition, safe and effective, and the effect is foreseeable, it can be considered"; P3: "If exercise can help me not take medicine, reduce my inflammation index, and improve my dialysis adequacy, then I will be willing to get up and move; If all the work is useless, then I would rather rest." P6: "If it helps me lose weight, I should be able to keep going"; P10: "I am a little anxious, and if exercise can improve this state, I am willing to exercise more actively."

Enhancement of role cognition. Patients' different cognition of their roles affected their willingness to exercise. In the interview, it was found that the negative role cognition hindered the patients' willingness to exercise. P1: "I have been in this state. I used to exercise before I got sick, but now I don't move much and I don't have expectations"; P6: "After a day's work, all the energy has been used up, and I am physically and mentally exhausted at home. I am already a patient, so I feel at ease that I will not think about exercising anymore"; P11: "I am so old, why do I exercise?" When young people move, it makes sense, so I don't need to do it anymore." However, positive role cognition can promote the patients' willingness to exercise. P9: "After all, I am a young person, and I am the only child in the family. I can't lie down like a disabled person all the time, but I still want to be active." P12: "I have to take my wife to exercise, she wants to lose weight, in order to motivate her, I also have to move; And if I can get other patients to start exercising, I'm happy to do that too."

DISCUSSION

Improve the Patient's Motor Ability and Build Motor Belief

This study shows that most patients do not know enough about exercise, do not have a comprehensive understanding of the benefits of exercise, and think that their physical state is not suitable for exercise. However, the symptoms of fatigue and weakness often associated with MHD patients aggravate their negative disease perception and lead to their low willingness to exercise, which is consistent[20,21] with the results of previous studies, and is manifested as a lack of awareness and confidence to participate in sports. Although some patients have the willingness to exercise, they are often unable to change from the intention stage to the action stage due to the lack of certain motor skills and self-management ability. This suggests that medical staff should use a variety of information channels to show patients the positive outcome related to exercise, the choice of exercise mode, intensity judgment, the use of auxiliary equipment and other guidance, strengthen patients' recognition of the value of exercise, help patients establish the belief in exercise, help stimulate their exercise motivation.[22]

Provide Environmental Resources and Social Support to Enhance Self-efficacy

From the results of this study, it can be seen that the lack of personalized exercise guidance and appropriate exercise conditions will make patients afraid of difficulty. There are also patients who think that medical staff pay more attention to their diet and water control, and pay less attention to exercise, which affects their attention to exercise. The interview found that patients with a strong willingness to exercise were usually encouraged and supported by family members and medical staff, while patients with excessive[21] protection from family members gradually became dependent and formed a sedentary habit due to the inclusion of daily household activities, and their willingness to exercise was generally low. In the interview, it was also found that some patients had a sense of social alienation, resulting in the reduction of their social activities and negative emotions, and their willingness to exercise was not optimistic.

The behavioral attitude of medical staff and family members is the main external motivation that affects patients' willingness to participate in sports. Therefore,[11,23] medical staff should encourage and urge patients to participate in sports, provide them with personalized exercise programs, help patients solve their perceived movement disorders, and help patients gradually adapt to exercise intensity and build self-confidence. Similarly, the support of the patient's family can enhance the patient's willingness to exercise, and ensure the safety of the patient, strengthen social support, so that the patient has the intention[24,25] to participate in sports rehabilitation. Dialysis units should actively carry out exercise in dialysis if conditions permit, which can not only improve the dialysis adequacy of patients, but also enable patients to obtain higher exercise self-efficacy through more communication, fully mobilize patients' subjective initiative,[26] strengthen exercise willingness, and promote the establishment of regular[27] exercise behavior.

Overcome the Fear of Exercise and Promote the Participation in Exercise

Sports fear refers to an excessive, irrational fear of exercise due to the fear[28] of injury or re-injury. The interview results showed that some patients questioned the safety of exercise, and worried that exercise would aggravate their existing symptoms and bring unnecessary trouble to their families and themselves, which became the most important factor affecting their willingness to exercise. The elderly patients in this interview also showed the fear of falling, which is consistent with other research results, and this psychology is one of the factors that reduce their physical activity.[29] Tao Ying *et al*.[30] found that 67.97% of 256 MHD patients had exercise fear. The reduction of exercise led to the decline of motor function, and the decline of motor function further increased the fear of exercise, forming a vicious circle. Therefore, in the future, professional exercise therapists and psychological counselors should be included in the exercise management team of MHD patients, and multi-disciplinary cooperation should be carried out to reasonably assess the exercise risk of patients, increase the concern about the level of exercise fear and the fear of falling, actively find out the causes, help them overcome the fear of exercise, eliminate the safety concerns of patients, and prevent and improve the current situation of patients' falls. On the premise of ensuring the safety of exercise, improve the quality of exercise and promote the active participation of the patients.

Multi-dimensional Effective Incentives to Guide the Formation of Exercise Habits

Studies have shown that habits can bring comfortable experience and internal satisfaction[23] to patients, and the positive experience actually perceived after exercise may be an important factor[31] for patients to adhere to long-term exercise. This study found that patients with exercise habits and positive experience of exercise had stronger exercise willingness and higher compliance. Similarly, patients who did not start regular exercise but had high expectations for the benefits of future exercise were more likely to shift their exercise willingness to the intention stage or the action stage. Encouraging patients to use low-cost wearable devices (such as pedometers and accelerometers) or smartphone apps to record and track actual steps can improve their exercise levels.[32] Therefore, medical staff can take multi-dimensional measures such as wechat group reminder, exercise punch, and exercise during dialysis to help patients establish exercise habits, and set goals step by step according to patients' exercise ability, increase exercise prescriptions consistent with patients' exercise habits as much as possible, pay attention to patients' feedback during exercise, timely detect patients' adverse emotions and assist in adjustment. Actively guide patients to perceive the benefits of exercise. At the same time, patients who perceive the benefits can be encouraged to show the positive results related to exercise to their patients, such as the improvement of physical function, the adjustment of psychological state, the reduction of disease symptoms, etc., stimulate the interest of patients, mobilize the enthusiasm for sports participation, help patients have the willingness to exercise independently, and further promote the generation and maintenance of patients' exercise behavior.

CONCLUSIONS

Through a descriptive study, this research

investigated the factors that influence the willingness of patients undergoing MHD to engage in exercise. It identified three primary themes—ability, opportunity, and motivation—and delineated twelve sub-themes based on the COM-B model. The findings led to specific recommendations aimed at informing intervention strategies designed to enhance exercise behavior among MHD patients, ultimately improving their adherence to physical activity. As a single central qualitative study, this research does not allow for definitive conclusions regarding the overall characteristics of exercise willingness among MHD patients. Furthermore, it did not examine the extent to which various factors—including ability, opportunity, and motivation—influence patients' willingness to exercise nor did it explore the dynamic process by which their willingness may change over time. To address these limitations, future studies should consider expanding the sample size and conducting hybrid research that integrates longitudinal qualitative methods with quantitative approaches for a more comprehensive analysis.

FUNDING

2023 Lianyungang Health Science and Technology Project (202303)

REFERENCES

1. Lin YL, Liou HH, Wang CH, Lai YH, Kuo CH, Chen SY, et al. Impact of sarcopenia and its diagnostic criteria on hospitalization and mortality in chronic hemodialysis patients: A 3-year longitudinal study. J Formos Med Assoc. 2020;119(7):1219-29.
2. Mosleh H, Alenezi M, Al-Johani S, Alsani A, Fairaq G, Bedaiwi R. Prevalence and Factors of Anxiety and Depression in Chronic Kidney Disease Patients Undergoing Hemodialysis: A Cross-sectional Single-Center Study in Saudi Arabia. Cureus. 2020;12(1):e6668.
3. Hu H, Chau PH, Choi EPH. Physical activity, exercise habits and health-related quality of life in maintenance hemodialysis patients: a multicenter cross-sectional study. J Nephrol. 2024;37(7):1881-91.
4. Valenzuela PL, Castillo-García A, Saco-Ledo G, Santos-Lozano A, Lucia A. Physical exercise: a polypill against chronic kidney disease. Nephrol Dial Transplant. 2024;39(9):1384-91.
5. Kanbay M, Copur S, Yildiz AB, Tanriover C, Mallamaci F, Zoccali C. Physical exercise in kidney disease: A commonly undervalued treatment modality. Eur J Clin Invest. 2024;54(2):e14105.
6. Baker LA, March DS, Wilkinson TJ, Billany RE, Bishop NC, Castle EM, et al. Clinical practice guideline exercise and lifestyle in chronic kidney disease. BMC Nephrol. 2022;23(1):75.
7. Renal Rehabilitation Professional Committee, Chinese Medical Doctor Association Rehabilitation Physician Branch. Expert consensus on exercise rehabilitation of adult patients with chronic kidney disease in China. Chinese Journal of Nephrology. 2019;(07):537-43.
8. Di Q. Current Situation of Exercise Rehabilitation in Maintenance Hemodialysis Patients. Advances in Clinical Medicine. 2020;10(02):129-133.
9. Xu J, Ji XJ, Chen R. Investigation on exercise status and influencing factors of maintenance hemodialysis patients. Evidence-based Nursing. 2022;8(08):1107-12.
10. Bulighin F, Aucella F, Bellizzi V, Cupisti A, Faga T, Gambaro G, et al. Physical activity and exercise programs for kidney patients: an Italian survey of nephrology centres. J Nephrol. 2024;37(3):695-705.
11. Zhang F, Liao J, Zhang W, Huang L. Association Between Exercise Self-Efficacy and Health-Related Quality of Life Among Dialysis Patients: A Cross-Sectional Study. Front Psychol. 2022;13:875803.
12. Kang S, Lee K, Kwon S. Basic psychological needs, exercise intention and sport commitment as predictors of recreational sport participants' exercise adherence. Psychol Health. 2020;35(8):916-32.
13. Nie L T, Xu Q, Yin X M. Construction of theoretical model of patient participation in patient safety behavior. China Hospital Management. 2020;40(10):64-7.
14. Hu Y, Tang Y, Chen P, Zhu Z, Cao Z, Zhang J, et al. [Article title in Chinese]. China Sport Science and Technology. 2019;55(2):35–45. (In Chinese)
15. Michie S, Van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci. 2011;6:42.
16. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. Am J Health Promot. 1997;12(1):38-48.
17. Liu M. Application of Colaizzi Seven Steps in data analysis of phenomenological research. Journal of Nursing. 2019;34(11):90-2.
18. Xing Z, Wenqin Z, Fan Z. Research progress of exercise compliance in maintenance hemodialysis patients. Nursing Research. 2021;35(15):2742-5.
19. Zhu B, Lv S, Wu H, Xu Y, Liu Y. Experience of social alienation in maintenance hemodialysis patients: a qualitative study. Nursing Research. 2024;38(09):1578-84.
20. Li T, Lv A, Xu N, Huang M, Su Y, Zhang B, et al. Barriers and facilitators to exercise in haemodialysis patients: A systematic review of qualitative studies. J Adv Nurs. 2021;77(12): 4679-92.
21. Cao T, Chen H, Qin JX. Sedentary behavior and its influencing factors in elderly patients undergoing maintenance hemodialysis. Journal of Nursing Science (护理学杂志). 2023;38(9):35–9. (In Chinese with English abstract) 22. Boonstra MD, Reijneveld SA, Foitzik EM, Westerhuis R, Navis G, de Winter AF. How to tackle health literacy problems in chronic kidney disease patients? A

systematic review to identify promising intervention targets and strategies. Nephrol Dial Transplant. 2020;36(7):1207-21.

22. Gao M, Sun G, Wang Q. A qualitative study on influencing factors of exercise rehabilitation behavior in patients with chronic heart failure. Journal of Nursing. 2021;36(20):88-92.
23. Clyne N, Anding-Rost K. Exercise training in chronic kidney disease-effects, expectations and adherence. Clin Kidney J. 2021;14(Suppl 2):ii3-ii14.
24. Fang F, Liu SX, Meng BL, Gao YB. The mediating effect of exercise self-efficacy on perceived exercise benefits and barriers and exercise intention in patients with end-stage kidney disease. Journal of Nursing Science (护理学杂志). 2023;38(1):26–30. (In Chinese)
25. Fang HY, Burrows BT, King AC, Kenneth RW. A Comparison of Intradialytic versus Out-of-Clinic Exercise Training Programs for Hemodialysis Patients. Blood Purif. 2020;49(1-2):151-7.
26. Selzler AM, Rodgers WM, Berry TR, McFadden K, Husband C, Hall C. Reciprocal relationships between self-efficacy, outcome satisfaction, and attendance at an exercise programme. Br J Health Psychol. 2019;24(1):123-40.
27. Vlaeyen JW, Kole-Snijders AM, Rotteveel AM, Ruesink R, Heuts PH. The role of fear of movement/(re)injury in pain disability. J Occup Rehabil. 1995;5(4): 235-52.
28. Shirai N, Inoue T, Ogawa M, Okamura M, Morishita S, Suguru Y, et al. Relationship between Nutrition-Related Problems and Falls in Hemodialysis Patients: A Narrative Review. Nutrients. 2022;14(15).
29. Ying T, Xiaojing J, Xintao Y. Study on exercise fear and its influencing factors in maintenance hemodialysis patients. Journal of Nursing Administration. 2024;24(01):50-4.
30. Warehime S, Dinkel D, Alonso W, Pozehl B. Long-term exercise adherence in patients with heart failure: A qualitative study. Heart Lung. 2020;49(6): 696-701.
31. Zhang H, Wang H, Huang L, Bai Y, Zhang F. Interventions to increase physical activity level in patients with whole spectrum chronic kidney disease: a systematic review and meta-analysis. Ren Fail. 2023;45(2):2255677.

Correspondence to:
Hailin Zhang, MD
Department of Hemopurification Center, Lianyungang Clinical College of Nanjing Medical University, Lianyungang City, Jiangsu Province, 222000, China
ORCID ID: 0000-0002-7663-0418
E-mail: luckihailin@163.com, luckywei_yyds@163.com

Received March 2026
Revised May 2026
Accepted June 2026

Effect of β-Hydroxy-β-methyl butyrate (HMB) Supplementation on Muscle Changes and Clinical Outcomes with Sonography Assessment in ICU: A Systematic Review

Sahar Kavand,[1] Parisa Delkash,[2] Afsaneh Safarian,[3] Arezoo Ranjbar Arani,[3] Minoo Heidari Almasi,[4] Hoda Zahedi,[5,6] Mohammad-Reza Jowshan,[7] Fatemeh Mofidi[1]

[1]Clinical Research Development Unit, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Adult Rheumatology, School of Medicine, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Department of Internal Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Clinical Research Development Unit, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5]Department of Clinical Nutrition and Dietetics, National Nutrition and Food Technology Research Institute, School of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[6]Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[7]Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

Keywords. β-hydroxy-β-methyl butyrate (HMB), critical illness, muscle atrophy, nutritional supplementation, muscle strength

Introduction. To evaluate the effects of β-Hydroxy-β-methyl butyrate (HMB) supplementation on muscle changes in critically ill patients, focusing on muscle mass, strength, and functional recovery.

Methods. A literature search was conducted -across multiple electronic databases, including PubMed, Scopus, and Web of Science, from database inception to December 2023. Data extraction was performed using a standardized form, and quality assessment was -assessed using the Newcastle-Ottawa Scale (NOS).

Results. Six randomized controlled trials (RCTs), comprising 398 participants, were included in the analysis. The studies enrolled intensive care unit (ICU) patients with trauma, liver cirrhosis, or those requiring mechanical ventilation. The HMB dose was 3 g/d, and the duration of supplementation ranged from 10 to 84 days. Regarding muscle mass changes, no significant differences in diaphragm or quadriceps muscle thickness were found in one study ($P = .87$). However, a subgroup analysis of patients with lower SOFA scores showed that HMB supplementation significantly preserved muscle volume ($P = .047$). In another trial, HMB supplementation significantly improved quadriceps thickness ($P < .05$) compared with placebo. Additionally, significant improvements in muscle function were observed in the HMB group, including better performance in the chair-stand and six-minute walk tests ($P < .05$). HMB supplementation also reduced net protein breakdown and increased amino acid production in muscle, although these metabolic improvements did not consistently translate into measurable preservation of muscle mass.

Conclusions. HMB supplementation in critically ill patients may offer modest benefits in preserving muscle mass and improving functional recovery, particularly in patients with less severe illness.

RJCCN 2026; 2(3):201-10
www.rjccn.org
DOI: 10.66224/rjccn.2.3.52

Please cite this article as: Kavand S, Delkash P, Safarian A, Ranjbar Arani A, Heidari Almasi M, Zahedi H, Jowshan MR, Mofidi F. Effect of β-Hydroxy-β-methyl butyrate (HMB) Supplementation on Muscle Changes and Clinical Outcomes with Sonography Assessment in ICU: A Systematic Review. RJCCN. 2026;2(3):201-10.

INTRODUCTION

Admission to the intensive care unit (ICU) is frequently associated with severe physiological stress, prolonged immobilization, systemic inflammation, and inadequate nutritional intake, all of which contribute to rapid skeletal muscle wasting and ICU-acquired weakness.[1] ICU-acquired muscle wasting affects approximately 40 to 50% of critically ill patients and may develop within the first week of ICU admission, with muscle mass declining by up to 15 to 20% during the initial 7 to 10 days in patients requiring prolonged mechanical ventilation.[2] Muscle wasting is particularly common in patients with sepsis, trauma, burns, or other severe systemic illnesses and is characterized by a substantial loss of muscle mass and strength.[1,2] In addition to its clinical consequences, ICU-acquired weakness imposes a considerable economic burden by increasing ICU and hospital length of stay, rehabilitation requirements, healthcare costs, and long-term disability.[3] Furthermore, muscle wasting is independently associated with prolonged mechanical ventilation, higher rates of hospital-acquired infections, poorer functional recovery, increased mortality, and greater healthcare resource utilization.[4] Therefore, preventing or attenuating muscle loss has become a major therapeutic goal in the management of critically ill patients.

Various non-pharmacological strategies have been employed to mitigate muscle loss in the critically ill, ranging from early mobilization to nutritional support. Among the latter, specific amino acids and supplements have garnered attention for their potential to enhance muscle protein synthesis and minimize muscle breakdown during acute illness.[5] HMB is primarily known for its role in supporting muscle protein turnover. As a metabolite of leucine, one of the essential branched-chain amino acids (BCAAs), HMB plays a vital role in stimulating muscle protein synthesis while simultaneously inhibiting protein degradation. These dual effects make it a particularly attractive supplement for critically ill patients who are at high risk for muscle loss due to the catabolic nature of critical illness.[6] Various studies have shown that HMB supplementation helps reduce muscle loss, promotes muscle regeneration, and improves strength, which may contribute to faster recovery and better functional outcomes.[7-9]

In clinical settings, the impact of HMB supplementation has been examined in a variety of studies, including those involving patients with chronic obstructive pulmonary disease (COPD),[13] cancer,[14] and, more recently, critically ill individuals.[11] These studies have consistently demonstrated that HMB supplementation can reduce the extent of muscle loss, improve muscle strength, and enhance functional recovery. In critically ill patients, particularly those in the intensive care unit (ICU), maintaining muscle mass is crucial for improving physical recovery and reducing the likelihood of developing long-term complications, such as post-intensive care syndrome (PICS), which includes both physical and psychological impairments.[11]

While HMB has shown promise in muscle preservation, its role in the broader context of critical illness management, including its interaction with other therapeutic interventions such as nutrition and exercise, is still not fully understood. Therefore, this review aims to explore the effect of HMB supplementation on muscle changes in critically ill patients. Understanding the role of HMB in muscle preservation could provide valuable insights into improving the outcomes of critically ill patients, reducing complications, and facilitating quicker recovery, both during hospitalization and in the long-term rehabilitation process.

MATERIALS AND METHODS

The present study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[16]

Search Strategy

A comprehensive literature search was conducted in multiple electronic databases, including PubMed, Scopus, and Web of Science, to identify studies investigating the Effect of β-HMB supplementation on muscle changes in critically ill patients. The following keywords were used: "β-Hydroxy-β-methyl butyrate (HMB)", "critical illness", "muscle atrophy", "nutritional supplementation", "muscle strength", "lean body mass", "muscle regeneration", "ICU patients", " clinical outcomes", "muscle wasting", and "muscle loss". The search was limited

to these electronic databases; hand searching of reference lists and grey literature sources was not performed. We also included relevant studies published in languages other than English through translation.

Study Selection

After removing duplicate records, the titles and abstracts of the remaining studies were screened for eligibility.

Exclusion criteria. Studies were excluded if they involved patients not admitted to the intensive care unit (ICU), including those in general wards or outpatient settings; patients with non-critical conditions such as elective surgery or stable chronic diseases; interventions not involving β-Hydroxy-β-methylbutyrate (HMB) supplementation; studies that did not assess muscle-related outcomes (e.g., muscle mass, strength, or function); studies including populations with conditions that could confound muscle assessment (e.g., neuromuscular disorders or severe malnutrition unrelated to critical illness); studies without appropriate control groups, such as case reports or expert opinions; and studies with HMB supplementation duration of less than 7 days or without sufficient follow-up.

Inclusion criteria. Eligible studies included patients admitted to the ICU due to conditions such as sepsis, trauma, burns, or respiratory failure; studies involving HMB supplementation alone or in combination with other nutritional interventions in the ICU setting; studies assessing muscle mass, strength, or function (e.g., grip strength, muscle cross-sectional area) as primary or secondary outcomes; and randomized controlled trials (RCTs) or observational studies with appropriate control groups.

A meta-analysis was not performed due to substantial heterogeneity in study populations, interventions, and outcome measures across the included studies. Therefore, the findings were synthesized narratively.

Data Extraction and Quality Assessment

Data were extracted from the selected studies using a standardized form by two independent reviewers. The extracted information included authors' names, study location, publication date, sample size, patient demographics (age, gender, HMB Dose (g/d), body composition, strength and functionality of muscle, muscle thickness, and femoral muscle volume loss (%) in control and HMB groups, were also recorded.

Other authors independently reviewed the extracted data for potential biases, and final confirmation was obtained through consensus. To assess the methodology and quality of the studies, the Newcastle-Ottawa Scale (NOS) was used.[17] This scale evaluates studies based on selection, comparability, and outcome. Studies with NOS scores of 0 to 3 were classified as low quality, those with scores of 4 to 6 were classified as medium quality, and studies with scores of 7 to 9 were considered high quality. Studies with NOS scores less than 4 were excluded from further analysis (Table 1).

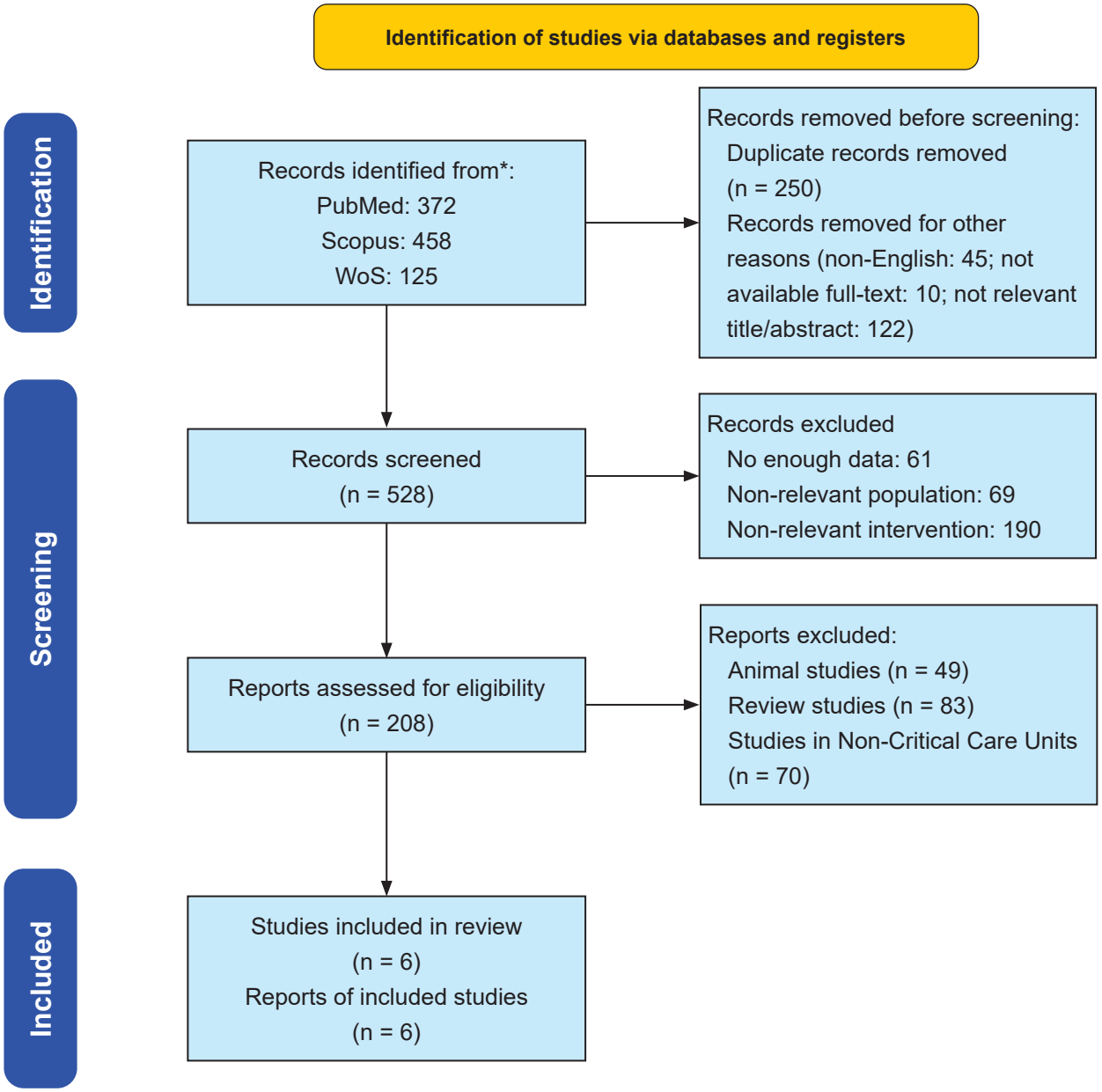
RESULTS

Patient Demographics and the Selection of Studies

Database searches yielded a total of 955 records: 372 from PubMed, 458 from Scopus, and 125 from Web of Science. After removing 250 duplicate records and 177 for various reasons (non-English language, 45; lack of full text, 10; irrelevant titles/abstracts, 122), 528 records remained for screening. During the screening process, 320 studies were excluded due to insufficient data (61), non-relevant populations (69), and non-relevant interventions (190). Of the 208 reports assessed for eligibility, an

Table 1. Quality Assessment of the Included Studies

Study ID	Selection	Comparability	Outcome	Total
Supinski et al. (2021)[18]	4	2	3	9
Lattanzi et al. (2021)[19]	4	2	3	9
Nakamura et al. (2020)[20]	4	1	3	8
Viana et al. (2021)[21]	4	1	3	8
Kuhls et al. (2007)[22]	4	2	3	9
Witthol et al. (2023)[23]	4	1	2	7



PRISMA Flow Diagram Illustrating the Selection of Articles

additional 202 studies were excluded, including animal studies (49), review articles (83), and studies conducted in non-critical care units (70). Ultimately, 6 studies were included in the final review and analysis (Figure).

In total, 6 RCTs investigated how HMB supplementation affected protein metabolism, muscle mass, and functional outcomes. In total, 398 participants from a range of clinical demographics, including critically ill patients, those with liver cirrhosis, and trauma patients, were involved in the research.

Three studies enrolled patients in intensive care units (ICUs) who were on mechanical ventilation, with a mean age ranging from 50.3 ± 7.2 to 65 ± 6.9 years.[18,20,21] These studies were conducted in France, Germany, and Brazil (as reported in Table 2). In addition, the Simplified Acute Physiology Score II (SAPS II) was measured, ranging between 45 and 52. The population recruited by19 included 24 patients, of whom 10 received placebo and 14 received HMB supplementation. All participants

Table 2. Characteristics of Included Studies

Study ID	Country	Mean Age	Control Group	Case Sample Size	Control Sample Size	HMB Dose (g/day)	Duration (days)	Body Composition	Strength	Functionality	Muscle Thickness	Femoral Muscle Volume Loss (%)	
												Control	HMB group
Supinski et al. (2021)[18]	USA	55.5 years	Placebo	18	20	3 g/day	10 days				Quadriceps thickness (cm): Control: 2.8 (2.4,3.3); HMB: 3.1 (2.6,3.6); Diaphragm thickness (cm): Control: 0.26 (0,23-0.29); HMB: 0.26 (0,23-0.30)		
Lattanzi et al. (2021)[19]	Italy	Placebo: 56 ± 4.6 years, HMB: 59.2 ± 8.4 years	Placebo group (sorbitol powder, 3 g/day)	14	10	3 g/day	84 days (12 weeks)	Lean mass (kg/h^2): Placebo: No change (11.3 ± 2.1 to 11.4 ± 2); HMB: No change (11.1 ± 1.6 to 11.2 ± 1.6). Fat mass (kg/h^2): Placebo: No change (10.7 ± 3.4 to 10.3 ± 3.9); HMB: No change (9.3 ± 5.2 to 9.4 ± 4.9). BMI (kg/m^2): Placebo: No change (29.9 ± 4.4 to 29.6 ± 4.6); HMB: No change (29.6 ± 6.8 to 29.2 ± 6.7).	Handgrip (kg): Placebo: No change (32.4 ± 12.6 to 33.4 ± 13.5); HMB: Improved (26 ± 11.3 to 29.1 ± 13.4). Chair Stand Test (s): Placebo: No change (12.2 ± 5.1 to 11.7 ± 4); HMB: Improved (14.2 ± 5 to 11.7 ± 2.3). 6MWT (m): Placebo: No change (387 ± 96 to 396 ± 63); HMB: Improved (361.8 ± 68 to 407.3 ± 73).	Frailty: Liver Frailty Index (LFI) reduced in HMB group (4.1 ± 0.4 to 3.6 ± 0.6, $P < 0.05$); no change in placebo group.			
Nakamura et al. (2020)[20]	Japan	Control: 76.6 ± 12.3 years, HMB: 71.8 ± 12.4 years	Standard ICU nutrition without HMB	26	24	3 g/day (1.5 g twice daily)	10 days	Femoral muscle volume: Control: -14.4 ± 7.1%; HMB: -11.4 ± 8.1%. HMB group showed significant preservation in SOFA < 10 subgroup ($P = 0.04$).	Barthel Index at discharge: Control: 49.7 ± 29.4, HMB: 54.7 ± 36.2 ($P = 0.65$). No significant differences in physical function between groups.	Mechanical ventilation days: Control: 6.8 ± 4.8, HMB: 7.1 ± 5.6 ($P = 0.87$). Hospital stay: Control: 19.8 ± 12.5 days, HMB: 20.4 ± 10.7 days ($P = 0.85$).		14.4 ± 7.1	11.4 ± 8.1

Table 2. Continued

Study ID	Country	Mean Age	Control Group	Case Sample Size	Control Sample Size	HMB Dose (g/day)	Duration (days)	Body Composition	Strength	Functionality	Muscle Thickness	Femoral Muscle Volume Loss (%)	
												Control	HMB group
Viana et al. (2021)[21]	Switzerland	65 [59, 71] years	Placebo with maltodextrin (1.5 g twice daily)	15	15	3 g/day	10 days	Fat-Free Mass (kg): HMB: 62.01 → 58.15 Control: 62.01 → 58.15 Significance: Not significant Fat Mass (kg): HMB: 18.88 → 23.50 Control: 18.88 → 27.62 Significance: $P = 0.0256$ Intracellular Water (L): HMB: 28.69 → 25.89 Control: 28.69 → 25.89 Significance: Not significant Extracellular Water (L): HMB: 20.13 → 17.71 Control: 20.13 → 17.71 Significance: Not significant Phase Angle: HMB: 3.77 → 3.88 Control: 3.77 → 3.21 Significance: $P = 0.0247$	No significant differences in handgrip strength between groups.	QoL: SF-12 Global Health: HMB group improved by +27.39 [1.59, 53.19] points ($P = 0.04$).		Skeletal muscle area (SMA) of of the quadriceps femoris: Placebo Group: SMA reduced from 114.0 cm^2 (day 4) to 100.4 cm^2 (day 15).	Skeletal muscle area (SMA) of of the quadriceps femoris: HMB Group: SMA reduced from 110.5 cm^2 (day 4) to 99.32 cm^2 (day 15).
Kuhls et al. (2007)[22]	USA	Control: 37 ± 3.3 years, HMB: 41 ± 3.2 years	Placebo (isonitrogenous, isocaloric control)	28	22	3 g/day	14 days	Nitrogen balance: Control: -9.0 ± 1.3 g/day, HMB: -6.50 ± 1.2 g/day. Muscle proteolysis (3-MH): No significant differences.	No significant difference in muscle strength observed.	SIRS Score: Control group had higher incidence of SIRS scores: Control: 2.4 +0.2; HMB: 2.3+0.2			
Witthol et al. (2023)[23]	Australia	Control: 49.5 [33.0–58.0], HMB: 52.0 [36.0–56.0]	Placebo (water/orange juice, isocaloric)	26	24	3 g/day	28 days	Weekly muscle ultrasound Control: 4.0 (2.5–5.0) HMB: 3.5 (3.0–5.0)	Weekly handgrip strength Control: 1.0 (0.5–2.0) HMB: 0.0 (0.0–1.0	Physical Function in ICU Test Score (PFIT-s): Control: 10.5 ± 2.1, HMB: 12.7 ± 2.3.			

were below 70 years of age, with a mean age of 59.8 ± 8.3 years. The baseline Liver Failure Index (LFI) was higher in the HMB group (4.1 ± 0.4) compared with the placebo group (3.4 ± 0.6) ($P < .01$). Two trials involved patients with severe injuries, defined as a mean Injury Severity Score (ISS) > 25.[22,23] The participants were mostly male (> 70% in both studies), and their mean ages ranged from 35.6 ± 9.8 to 41.2 ± 12.5 years (Table 2).

Muscle Mass Changes

The effects of HMB supplementation on muscle mass were heterogeneous across the included studies. Supinski *et al.* (2021)[18] reported no significant differences in quadriceps thickness (HMB = 3.1 cm [IQR: 2.6 to 3.6] vs. control = 2.8 cm [IQR: 2.4 to 3.3]) or diaphragm thickness (HMB = 0.26 cm [IQR: 0.23 to 0.30] vs. control = 0.26 cm [IQR: 0.23 to 0.29]) after 10 days of supplementation ($P > .05$). Similarly, Nakamura *et al.* (2020)[20] observed a reduction in femoral muscle volume of 11.4% in the HMB group compared with 14.4% in the control group, although this difference was not statistically significant ($P = .18$). However, subgroup analysis demonstrated that patients with lower SOFA scores in the HMB group experienced significantly less muscle loss compared with controls ($P = .047$), suggesting a potential protective effect in less severely ill patients.

In contrast, Lattanzi *et al.* (2021)[19] reported a significant increase in quadriceps muscle thickness after 12 weeks of HMB supplementation compared with placebo ($P < .05$), indicating a potential benefit with longer intervention duration. Viana *et al.* (2021)[21] found no significant reduction in muscle atrophy after 10 days of supplementation; however, changes in body composition were observed, including a reduction in fat mass and an improvement in phase angle, reflecting improved cellular integrity. Wittholz *et al.* (2023)[23] also reported only a marginal reduction in quadriceps muscle loss in the HMB group compared with placebo, without statistical significance ($P > .05$), suggesting that the effects of HMB on muscle mass may depend on patient population and intervention duration.

Protein Metabolism

Regarding protein metabolism, Viana *et al.* (2021)[21] found that the HMB group significantly reduced net protein breakdown and increased amino acid production. This aligns with the known catabolic effects of critical illness and suggests that HMB may help in reducing protein degradation, even if it does not directly prevent muscle loss. Furthermore, the reduction in liver fragility index in the HMB group provides evidence of its potential benefits in improving overall nutritional status and muscle function in patients with liver cirrhosis.

Kuhls *et al.* (2007)[22] reported that HMB supplementation improved nitrogen balance, indicating a more anabolic state in the body. In contrast, the study found no significant differences in muscle strength or muscle proteolysis markers such as urinary 3-methylhistidine, the improved nitrogen balance suggests that HMB might support muscle protein synthesis, a key factor in mitigating muscle loss in critically ill patients.

Functional and Other Outcomes

The effects of HMB on functional outcomes were also varied. Supinski *et al.* (2021)[3] did not observe any improvement in respiratory muscle strength or time to wean from mechanical ventilation, suggesting that HMB may not significantly affect respiratory function in critically ill patients, at least in the short term. Similarly, Viana *et al.* (2021)[21] found no differences in physical function between the HMB and placebo groups. However, they did report an improvement in net protein anabolism and phase angle, which may indicate better overall health and recovery potential.

Lattanzi *et al.* (2021)[19] observed significant improvements in physical performance, including reduced chair-stand test time and increased six-minute walk test distance. These findings suggest that long-term HMB supplementation may enhance functional recovery, particularly in patients with liver cirrhosis, a population known to suffer from muscle wasting and functional decline. This highlights the potential for HMB supplementation to improve quality of life and physical independence in certain clinical populations.

Kuhls *et al.* (2007)[22] found no significant differences in muscle strength, but they did report that the HMB group had improved nitrogen balance, which could contribute to better functional

outcomes in the long run. Meanwhile, Wittholz *et al.* (2023)[23] demonstrated improvements in physical function as measured by the Physical Function in ICU Test (PFIT-s), with HMB patients showing better recovery than those on placebo, despite only marginal differences in muscle loss.

DISCUSSION

This systematic review included six studies evaluating the effects of HMB supplementation on muscle outcomes in ICU patients. Overall, the findings were heterogeneous. Most studies did not demonstrate statistically significant differences in muscle mass preservation with short-term HMB supplementation; however, some evidence suggested marginal or subgroup-specific benefits, particularly in patients with lower illness severity or in studies with longer intervention durations. Improvements in muscle function were reported in a limited number of trials, including better performance in functional assessments. Overall, while HMB showed potential anabolic and anti-catabolic effects, the evidence for consistent muscle mass preservation in ICU patients remains inconclusive.

Three studies (Supinski *et al.*,[18] Nakamura *et al.*,[20] Viana *et al.*[21]) focused on ICU patients, including those receiving mechanical ventilation, a condition strongly associated with muscle wasting and catabolic stress. The mean age of participants in these studies ranged from 50.3 to 65 years, indicating a population at high risk of muscle loss and functional decline during critical illness. In addition, disease severity, assessed using the Simplified Acute Physiology Score II (SAPS II), ranged between 45 and 52, further highlighting the severity of illness in the recruited populations.

Lattanzi *et al.*'s (2021)[19] study involved patients with liver cirrhosis, a condition often linked with frailty and muscle loss due to altered protein metabolism. The baseline LFI was significantly higher in the HMB group than in the placebo group, suggesting an initial degree of frailty that could benefit from muscle-preserving interventions like HMB. Meanwhile, two trials (Kuhls *et al.*,[22] Wittholz *et al.*[23]) targeted trauma patients and those with significant injuries, such as an Injury Severity Score greater than 25. The trauma patients were mostly male (over 70% in both studies), and their mean ages ranged from 35.6 to 41.2 years, an age group generally characterized by higher resilience but still potentially vulnerable to muscle wasting after severe trauma.

The role of HMB supplementation in critically ill patients has been investigated primarily in relation to its potential to attenuate muscle wasting and improve muscle function. Mechanistically, HMB is a metabolite of leucine that enhances muscle protein synthesis through activation of the mTOR signaling pathway, while simultaneously inhibiting proteolysis by downregulating the ubiquitin–proteasome system and reducing activation of the NF-κB-mediated inflammatory cascade. These combined anabolic and anti-catabolic effects provide a biological rationale for its potential to preserve muscle strength in catabolic conditions such as critical illness.

However, the clinical trials included in this review showed inconsistent functional outcomes. For example, Supinski *et al.* (2021)[18] did not demonstrate significant improvements in muscle thickness or function, which may be explained by the presence of severe systemic inflammation and multi-organ dysfunction in mechanically ventilated ICU patients, conditions that can blunt anabolic signaling pathways such as mTOR and reduce muscle responsiveness to nutritional interventions. Similarly, Viana *et al.* (2021)[21] reported no significant effect on muscle preservation despite observed changes in body composition, suggesting that metabolic alterations (e.g., improved phase angle) may occur independently of measurable gains in muscle strength or mass. In contrast, studies reporting functional improvements were generally conducted in populations with lower disease severity or more stable metabolic conditions, indicating that the efficacy of HMB may be strongly influenced by the underlying inflammatory and catabolic state rather than methodological factors alone.

Consistent with our findings, Phillips *et al.*'s review study (2022) suggests limited and inconsistent evidence supporting the use of HMB as an ingredient in oral nutritional supplements or as a standalone supplement (or in combination with other amino acids) to increase or promote

the retention of lean soft tissue mass (LSTM) and improve strength. However, no evidence indicates that HMB enhances physical function in older adults or clinical populations.[25]

Several studies have investigated the effects of HMB on muscles in various populations. A meta-analysis by Rowlands *et al.* (2009), which examined the impact of HMB supplementation on muscle strength, body composition, and muscle damage in young men, found no effect on body composition.[26] This contrasts with our findings, which indicate a positive effect of HMB on muscle mass in older adults. These differences suggest that the response to HMB and HMB-containing supplements may vary across different populations.

Limitations

This systematic review has several limitations. First, the search strategy was limited to three electronic databases (PubMed, Scopus, and Web of Science), and neither hand searching of reference lists nor grey literature sources were included, which may have led to the omission of relevant studies. Second, the number of included randomized controlled trials was relatively small, which may limit the generalizability of the findings. Third, there was heterogeneity among studies in terms of patient populations, clinical conditions, intervention duration, and outcome measures, which may have influenced the comparability of results. Finally, most included studies had relatively short follow-up periods, limiting conclusions regarding long-term effects of HMB supplementation in critically ill patients.

CONCLUSIONS

HMB supplementation in critically ill patients may offer modest benefits in preserving muscle mass and improving functional recovery, particularly in patients with less severe illness. However, the overall impact on muscle preservation remains inconclusive, and further studies are needed to clarify its long-term effects and to identify patient subgroups that might benefit most from HMB supplementation. The data also suggest that HMB may improve metabolic outcomes and functional parameters, contributing to a more favorable clinical recovery trajectory.

REFERENCES

1. Batt J, Dos Santos CC, Cameron JI, Herridge MS. Intensive care unit–acquired weakness: clinical phenotypes and molecular mechanisms. American journal of respiratory and critical care medicine. 2013;187(3):238-46.
2. Latronico N, Rasulo FA, Eikermann M, Piva S. Critical illness weakness, polyneuropathy and myopathy: diagnosis, treatment, and long-term outcomes. Critical Care. 2023;27(1):439.
3. Henning PC. Leucine metabolite, beta-hydroxy beta-methylbutyrate (HMB) as an intervention to maintain lean body mass and performance during sustained military operations. 2010: The Florida State University.
4. Schefold JC, Wollersheim T, Grunow JJ, Luedi MM, Z'Graggen WJ, Weber-Carstens S. Muscular weakness and muscle wasting in the critically ill. Journal of cachexia, sarcopenia and muscle. 2020;11(6):1399-412.
5. Nor MBM. Optimal nutritional therapy in critically ill patients: a narrative review. Malaysian Journal of Anaesthesiology. 2024;3(1):42-54.
6. Cavallucci V, Pani G. The leucine catabolite and dietary supplement β-Hydroxy-β-Methyl butyrate (HMB) as an epigenetic regulator in muscle progenitor cells. Metabolites. 2021;11(8):512.
7. Slater GJ, Jenkins D. β-hydroxy-β-methylbutyrate (HMB) supplementation and the promotion of muscle growth and strength. Sports Medicine. 2000;30:105-16.
8. Holeček M. Beta-hydroxy-beta-methylbutyrate supplementation and skeletal muscle in healthy and muscle-wasting conditions. Journal of cachexia, sarcopenia and muscle. 2017;8(4):529-41.
9. Portal S, Eliakim A, Nemet D, Halevy O, Zadik Z. Effect of HMB supplementation on body composition, fitness, hormonal profile and muscle damage indices. Journal of Pediatric Endocrinology & Metabolism. 2010;23(7):641-50.
10. Liu S, Zhang L, Li S. Advances in nutritional supplementation for sarcopenia management. Frontiers in Nutrition. 2023;10:1189522.
11. Rahman A, Wilund K, Fitschen PJ, Jeejeebhoy K, Agarwala R, Drover JW, et al. Elderly persons with ICU-acquired weakness: the potential role for β-hydroxy-β-methylbutyrate (HMB) supplementation?. Journal of parenteral and enteral nutrition. 2014 Jul;38(5):567-75.
12. Pimentel GD, Rosa JC, Lira FS, Zanchi NE, Ropelle ER, Oyama LM, et al. β-Hydroxy-β-methylbutyrate (HMβ) supplementation stimulates skeletal muscle hypertrophy in rats via the mTOR pathway. Nutrition & metabolism. 2011;8(1):11.
13. Hsieh L, Chien S, Huang M, Tseng H, Chang C. Anti-inflammatory and anticatabolic effects of short-term beta-hydroxy-beta-methylbutyrate supplementation on chronic obstructive pulmonary disease patients in intensive care unit. Asia Pacific journal of clinical nutrition. 2006;15(4):544.
14. Prado CM, Orsso CE, Pereira SL, Atherton PJ, Deutz NE. Effects of β-hydroxy β-methylbutyrate (HMB) supplementation on muscle mass, function, and other outcomes in patients with cancer: a systematic

review. Journal of cachexia, sarcopenia and muscle. 2022;13(3):1623-41.

15. Gala K, Desai V, Liu N, Omer EM, McClave SA. How to increase muscle mass in critically ill patients: lessons learned from athletes and bodybuilders. Current nutrition reports. 2020;9(4):369-80.
16. Vrabel M. Preferred reporting items for systematic reviews and meta-analyses. 2015;42(5):552-4.
17. Lo CK-L, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. BMC medical research methodology. 2014;14:1-5.
18. Supinski GS, Netzel PF, Westgate PM, Schroder EA, Wang L, Callahan LA. A randomized controlled trial to determine whether beta-hydroxy-beta-methylbutyrate and/or eicosapentaenoic acid improves diaphragm and quadriceps strength in critically Ill mechanically ventilated patients. Critical Care. 2021;25(1):308.
19. Lattanzi B, Bruni A, Di Cola S, Molfino A, De Santis A, Muscaritoli M, et al. The effects of 12-week beta-hydroxy-beta-methylbutyrate supplementation in patients with liver cirrhosis: Results from a randomized controlled single-blind pilot study. Nutrients. 2021;13(7):2296.
20. Nakamura K, Kihata A, Naraba H, Kanda N, Takahashi Y, Sonoo T, et al. β-Hydroxy-β-methylbutyrate, arginine, and glutamine complex on muscle volume loss in critically ill patients: a randomized control trial. Journal of Parenteral and Enteral Nutrition. 2020;44(2):205-12.
21. Viana MV, Becce F, Pantet O, Schmidt S, Bagnoud G, Thaden JJ, et al. Impact of β− hydroxy-β− methylbutyrate (HMB) on muscle loss and protein metabolism in critically ill patients: A RCT. Clinical Nutrition. 2021;40(8):4878-87.
22. Kuhls DA, Rathmacher JA, Musngi MD, Frisch DA, Nielson J, Barber A, et al. β-Hydroxy-β-methylbutyrate supplementation in critically ill trauma patients. Journal of Trauma and Acute Care Surgery. 2007;62(1):125-32.
23. Wittholz K, Fetterplace K, Karahalios A, Ali Abdelhamid Y, Beach L, Read D, et.al. Beta-hydroxy-beta-methylbutyrate supplementation and functional outcomes in multitrauma patients: a pilot randomized controlled trial. Journal of Parenteral and Enteral Nutrition. 2023;47(8):983-92.
24. Lin Z, Zhao A, He J. Effect of β-hydroxy-β-methylbutyrate (HMB) on the Muscle Strength in the Elderly Population: A Meta-Analysis. Frontiers in Nutrition. 2022;9:914866.
25. Phillips SM, Lau KJ, D'Souza AC, Nunes EA. An umbrella review of systematic reviews of β-hydroxy-β-methyl butyrate supplementation in ageing and clinical practice. Journal of cachexia, sarcopenia and muscle. 2022;13(5):2265-75.
26. Rowlands DS, Thomson JS. Effects of β-hydroxy-β-methylbutyrate supplementation during resistance training on strength, body composition, and muscle damage in trained and untrained young men: A meta-analysis. The Journal of Strength & Conditioning Research. 2009;23(3):836-46.

Correspondence to:
Fatemeh Mofidi, MD
Clinical Research Development Unit, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
ORCID ID: 0009-0005-5435-3500
Fax: 0098 224 7000
Tel: 0098 913 178 1968
E-mail: dr.fatemehmofidi@gmail.com

Received March 2026
Revised May 2026
Accepted June 2026

Prognosis of Severe Acute Kidney Injury Requiring Renal Replacement Therapy: A Systematic Review

Meysam Ghanbari Saray,[1] Mohammad Mahdi Heidari[2]

[1]Scientific Research Center of Azerbaijan Medical University, Baku, Azerbaijan
[2]Department of Pediatrics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

Keywords. prognosis, acute kidney injury, renal replacement therapy, systematic review

Introduction. Acute kidney injury (AKI) requiring renal replacement therapy (RRT) represents the most severe spectrum of AKI in critically ill patients and is associated with high mortality and long-term morbidity. To systematically review short- and long-term outcomes and prognostic factors in adult patients with severe AKI requiring RRT in intensive care settings.

Methods. A systematic search of PubMed, Embase, and the Cochrane Library was conducted from January 2000 to June 2024 in accordance with PRISMA 2020 guidelines. Adult studies reporting mortality and/or renal outcomes in AKI requiring RRT were included. Data were synthesized narratively.

Results. Thirty-two studies involving over 80,000 patients were included. Short-term mortality ranged from 40% to 70%, with hospital mortality frequently exceeding 50%. Long-term mortality remained high, approaching 70 to 80% at 5 to 10 years. Renal recovery occurred in approximately 30 to 40% of survivors, while 10 to 20% remained dialysis-dependent at discharge. Prognosis was predominantly influenced by sepsis, multi-organ failure, illness severity scores, advanced age, and fluid overload.

Conclusions. Severe AKI requiring RRT is associated with poor short- and long-term outcomes. Prognosis is driven primarily by the severity of critical illness rather than dialysis-related factors, highlighting the need for early risk stratification and structured post-ICU follow-up.

RJCCN 2026; 2(3):211-5
www.rjccn.org
DOI: 10.66224/rjccn.2.3.59

INTRODUCTION

Acute kidney injury (AKI) is a common complication of critical illness, affecting up to 50% of patients admitted to the intensive care unit (ICU) and contributing substantially to morbidity, mortality, and healthcare costs.[1,2] While many episodes of AKI are mild and reversible, a significant subset progresses to severe AKI requiring renal replacement therapy (RRT), representing the most advanced stage of renal dysfunction in critically ill patients.[3]

The requirement for RRT in AKI reflects profound systemic derangement and is frequently accompanied by sepsis, hemodynamic instability, and multi-organ failure.[4] Epidemiological studies have consistently demonstrated that AKI requiring RRT is associated with markedly higher mortality compared with AKI not requiring dialysis and

Please cite this article as: Ghanbari Saray M, Heidari MM. Prognosis of Severe Acute Kidney Injury Requiring Renal Replacement Therapy: A Systematic Review. RJCCN. 2026;2(3):211-5.

with critically ill patients without AKI.[5] Despite advances in critical care management and dialysis technology, mortality rates among patients with AKI requiring RRT have remained persistently high over the past two decades.[6]

Beyond short-term outcomes, AKI requiring RRT has emerged as a strong predictor of long-term adverse events. Survivors are at increased risk of chronic kidney disease (CKD), end-stage kidney disease (ESKD), cardiovascular events, and late mortality.[7,8] Importantly, renal recovery following AKI requiring RRT is often incomplete, and dialysis dependence at hospital discharge or during follow-up is associated with poor long-term survival.[9]

Accurate prognostication in this population remains challenging. Traditional severity-of-illness scoring systems, such as APACHE II and SOFA, incompletely capture the risk associated with severe AKI and RRT initiation.[10] Furthermore, uncertainty persists regarding the prognostic significance of dialysis-related factors, including modality and timing of RRT initiation, compared with patient-related and illness-related determinants.[11]

Given the clinical, ethical, and prognostic implications of initiating RRT in critically ill patients, a comprehensive synthesis of available evidence on outcomes and prognostic factors is essential. This systematic review aims to evaluate short- and long-term mortality, renal recovery, and determinants of prognosis in adult patients with severe AKI requiring RRT.

MATERIALS AND METHODS

Study Design and Reporting

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Search Strategy

A comprehensive search of PubMed/MEDLINE, Embase, and the Cochrane Library was performed for studies published between January 2000 and June 2024. Search terms included combinations of acute kidney injury, renal replacement therapy, dialysis, critical illness, intensive care, mortality, outcome, and prognosis.

Eligibility Criteria

Inclusion criteria.

- Adult patients (≥ 18 years)
- AKI requiring RRT in ICU or critical care settings
- Reported mortality and/or renal recovery outcomes
- Observational studies or randomized controlled trials

Exclusion criteria.

- Pediatric studies
- Chronic dialysis or ESKD populations
- Case reports, editorials, conference abstracts
- Studies without extractable outcome data

Data Extraction and Quality Assessment

Two reviewers independently screened studies and extracted data. Risk of bias was assessed using the Newcastle–Ottawa Scale for observational studies and the Cochrane Risk of Bias Tool for randomized trials.

RESULTS

Study Selection and Characteristics

A total of 4,126 records were identified, and 32 studies were included in the final qualitative synthesis. Most were retrospective cohort studies conducted in mixed ICUs. Continuous renal replacement therapy (CRRT) was the predominant modality (Figure).

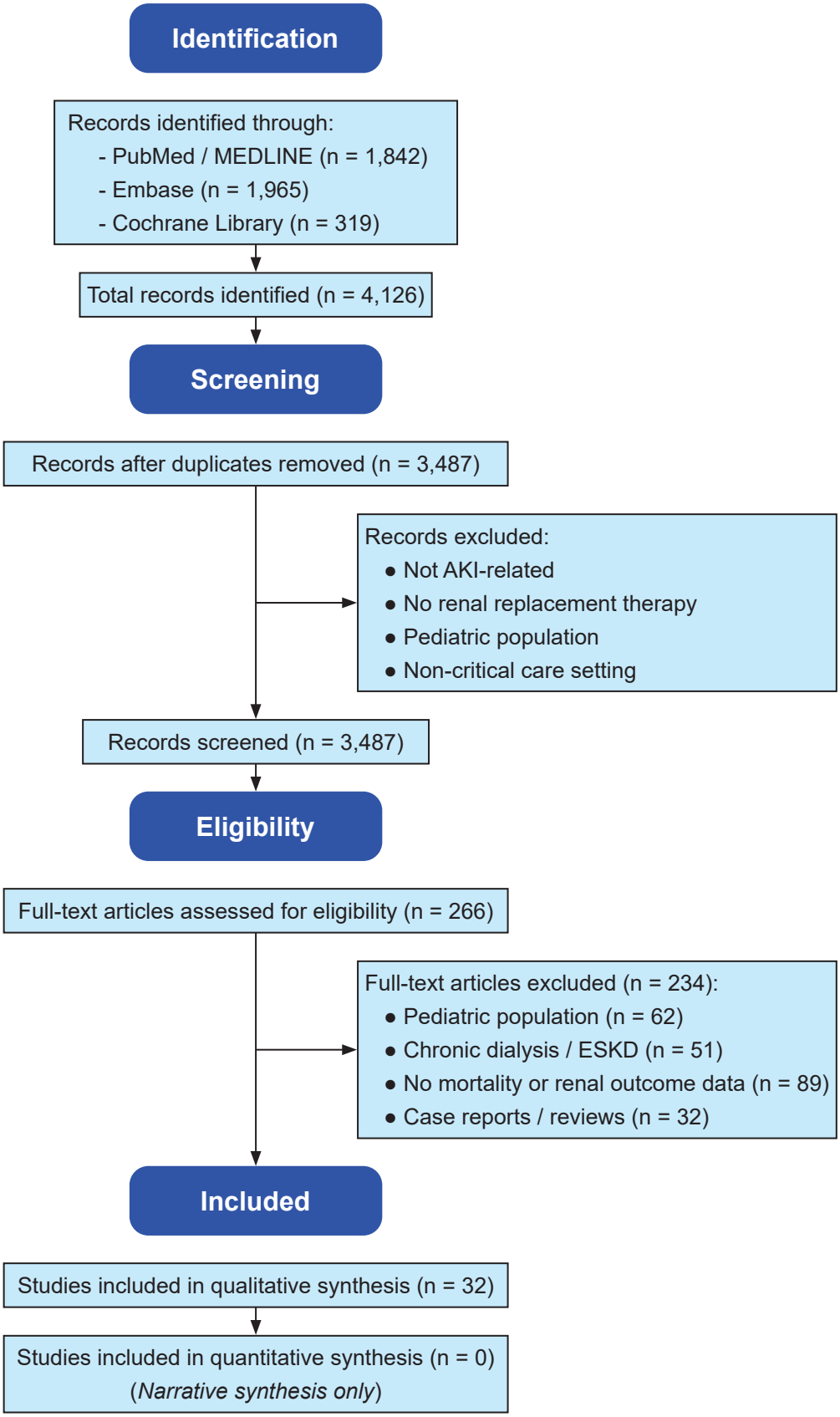
Short-Term Mortality

Short-term mortality was consistently high across studies. In a large cohort of 573 critically ill patients with AKI requiring RRT, in-hospital mortality was 52%, with early deaths occurring predominantly within the first week of RRT initiation.[12] Similarly, a UK ICU cohort of 821 patients reported ICU mortality of 55% and hospital mortality of 66%.[13]

A single-center study reported 30-day survival of 54.4% and 90-day survival of 47.2%, highlighting substantial early attrition.[14] Mortality was strongly associated with the presence of multi-organ failure and septic shock.

Long-Term Mortality

Long-term outcomes remained poor even among



PRISMA Flowchart. A total of 4,126 records were identified, and 32 studies were included in the final qualitative synthesis.

hospital survivors. A prospective cohort with five-year follow-up demonstrated that only 25% of patients were alive at five years following AKI requiring RRT.[15] Other long-term studies reported progressively increasing mortality over time, with AKI requiring RRT emerging as an independent predictor of late death.[7,8]

Renal Recovery

Renal recovery was incomplete in a substantial proportion of survivors. In one cohort, only 32.5% recovered sufficient kidney function to discontinue RRT before discharge, while 15.9% remained dialysis-dependent.[12] At one year, approximately 25 to 30% of patients were RRT-independent, although many had persistent CKD.[14,16] Late recovery after hospital discharge was uncommon.

Prognostic Factors

Consistent predictors of poor prognosis included:

- Sepsis and septic shock[12,14]
- High SOFA and APACHE II scores[10,12]
- Advanced age[13,16]
- Oliguria and fluid overload[12,17]
- Mechanical ventilation and vasopressor requirement[13]

Dialysis modality and timing of RRT initiation were not consistently associated with improved survival, suggesting that prognosis is driven primarily by systemic illness severity rather than dialysis-specific variables.[11,18]

DISCUSSION

This systematic review demonstrates that severe AKI requiring RRT remains a condition with devastating short- and long-term outcomes. Across diverse ICU populations, hospital mortality exceeds 50%, and long-term mortality approaches 70 to 80% in extended follow-up studies.[12-5] These findings confirm that the need for RRT represents a marker of advanced critical illness rather than isolated renal failure.

Renal recovery occurs in only a minority of patients and is frequently incomplete. Survivors with persistent renal dysfunction face an increased risk of CKD progression, cardiovascular disease, and late mortality.[7,9] Importantly, renal recovery typically occurs early, emphasizing the prognostic importance of kidney function status at hospital discharge.

Prognosis is consistently determined by non-renal factors, particularly sepsis, multi-organ failure, and overall illness severity.[4,12,14] The lack of consistent survival benefit associated with RRT modality or timing supports the concept that dialysis serves as supportive therapy rather than a disease-modifying intervention.[11]

These findings have important implications for clinical practice. Early recognition of patients with a poor prognostic profile may facilitate shared decision-making, realistic goal setting, and timely integration of palliative care. Furthermore, survivors of AKI requiring RRT should be considered a high-risk population requiring structured post-ICU nephrology follow-up.

CONCLUSIONS

Severe AKI requiring RRT in critically ill adults is associated with high mortality and frequent incomplete renal recovery. Prognosis is driven predominantly by the severity of systemic illness rather than dialysis-related factors. Improved prognostic tools, early risk stratification, and long-term survivorship care are essential to improve outcomes in this vulnerable population.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

AI USAGE STATEMENT

The authors used artificial intelligence (AI)-assisted tools for language editing and grammar improvement during the preparation of this manuscript. All scientific content, interpretations, and conclusions were reviewed and approved by the authors.

REFERENCES

1. Hoste EAJ, Kellum JA. Acute kidney injury: epidemiology and diagnostic criteria. Curr Opin Crit Care. 2021;27:548–55.
2. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients. JAMA. 2005;294:813–8.
3. Kellum JA, Lameire N. KDIGO AKI Guideline Work Group. Kidney Int Suppl. 2012;2:1–138.

4. Bagshaw SM, George C, Bellomo R. Sepsis-associated acute kidney injury. Crit Care. 2008;12:R47.
5. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay. J Am Soc Nephrol. 2005;16:3365–70.
6. Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM, et al. Chronic dialysis and death after AKI requiring dialysis. JAMA. 2009;302:1179–85.
7. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term mortality and CKD after AKI. Kidney Int. 2009;76:893–9.
8. Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, et al. AKI and risk of ESRD. Clin J Am Soc Nephrol. 2009;4:175–83.
9. Schiffl H, Lang SM. Long-term outcomes of ICU AKI requiring dialysis. Am J Kidney Dis. 2008;51:447–55.
10. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294(7):813-8.
11. STARRT-AKI Investigators. Timing of RRT initiation. N Engl J Med. 2020;383:240–51.
12. Wang IK, Wang ST, Lin CL, Chen TC, Chang HY, Kuo HL, et al. Early prognostic factors in patients with acute renal failure requiring dialysis. Renal Failure. 2006;28(1):43–9.
13. Schiffl H, Lang SM, Fischer R. Long-term outcomes of survivors of ICU acute kidney injury requiring renal replacement therapy: a 10-year prospective cohort study. Clinical Kidney Journal. 2012;5(4):297–302.
14. Schiffl H, Fischer R. Short- and long-term outcomes in AKI-RRT. QJM. 2011;104:739–46.
15. Schiffl H, Lang SM. Five-year outcomes after AKI-RRT. Am J Kidney Dis. 2008;51:447–55.
16. Schneider AG, Bellomo R, Bagshaw SM, Glassford NJ, Lo S, Jun M, et al. Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Medicine. 2013;39(6):987–97.
17. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, et al. Fluid overload and mortality in AKI. Kidney Int. 2009;76:422–7.
18. AKIKI Study Group. Early vs delayed RRT. N Engl J Med. 2016;375:122–33.

Correspondence to:
Meysam Ghanbari Saray
Scientific Research Center of Azerbaijan Medical University, Baku, Azerbaijan
ORCID ID: 0009-0003-4568-117X
E-mail: meysamghanbari2202@gmail.com

Received April 2026
Revised June 2026
Accepted July 2026

RJCCN Case Report
KIDNEY DISEASE

Urinary Ammonium: A Renewed Compass for Renal and Extra-Renal Disorders, a Case Series

Lara Mary Titherington,[1] Stefano Romagnoli,[1] Pietro Caironi,[2,3]

[1]Department of Anesthesia and Intensive Care, Azienda Ospedaliero-Universitaria Careggi, Department of Health Science, University of Florence, Florence, Italy
[2]Department of Oncology, University of Turin, Turin, Italy
[3]Department of Acute Brain and Cardiovascular Injury, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy

Keywords. urinary electrolytes, ammonium, KING, renal transplant, chronic renal failure

Introduction. Assessment of urinary ammonium (uNH_4^+) describes one of the kidney's most important physiological functions, yet direct measurement is not routinely available. Historically, urine anion gap has been used as a surrogate for uNH_4^+, although this approach is unreliable, particularly in patients with chronic kidney disease. The ability to directly measure uNH_4^+ may therefore provide clinically relevant diagnostic and therapeutic information.
Case Series. In this case series, we present three clinical cases illustrating the utility of uNH_4^+ measurement, now available as a bedside point-of-care measurement (KING, Kures®). These include comparison between a dysfunctional native kidney and a recovering transplanted graft, and the differential diagnosis of a-lactic metabolic acidosis in two distinct clinical settings. Across cases, uNH_4^+ provided timely physiological insight into tubular function, supporting diagnosis and recovery assessment beyond traditional markers.
Conclusions. These observations underscore the importance of distinguishing tubular from glomerular function and complement traditional markers in renal assessment.

RJCCN 2026; 2(3):216-21
www.rjccn.org
DOI: 10.66224/rjccn.2.3.39

INTRODUCTION

In December 2021, 174 American nephrologists signed a petition addressed to Directors of Clinical Laboratories, requesting that urinary ammonium (uNH_4^+) be made a readily available test nationwide. The petition was reported in *Kidney News*, [1] and was first disseminated via Twitter.

The nephrologists who signed the petition argued that estimating uNH_4^+ using the urine anion gap (UAG) is less accurate than direct uNH_4^+ measurement. They consider uNH_4^+ valuable *"not only in the diagnosis of renal tubular acidosis but also in managing acidosis in progressive [chronic kidney disease] CKD and in evaluating and treating patients with kidney stones, where it will give us clues about the acid load the patients consume."*

The ability to measure uNH_4^+ in routine care and to have this information readily available may provide clinically relevant diagnostic and therapeutic information across several specialties, particularly for assessing acid-base disorders and managing CKD. NH_4^+ (Figure 1) plays a fundamental role in renal tubule handling of acid-base regulation. Ammonium is primary produced in the proximal tubule through the catabolism of glutamine catabolism, where glutamine is metabolized via glutaminase and glutamate dehydrogenase. This process produces two molecules of NH_4^+ and

Please cite this article as: Titherington LM, Romagnoli S, Caironi P. Urinary Ammonium: A Renewed Compass for Renal and Extra-Renal Disorders, a Case Series. RJCCN. 2026;2(3):216-21.

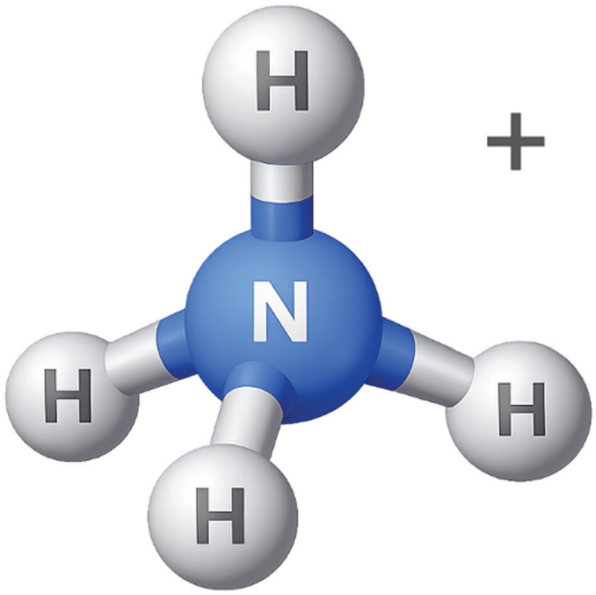


Figure 1. Ammonium molecule represented in graphic form.

alpha-ketoglutarate. The alpha-ketoglutarate is then further metabolised into two molecules HCO_3^- which are absorbed into the blood while the NH_4^+ is secreted into the lumen. This process is enhanced in metabolic acidosis.

From a diagnostic standpoint, direct measurement of uNH_4^+ allows differentiation between metabolic acidosis of either renal or extrarenal origin (See Table 1 for reference ranges). In metabolic acidosis, low uNH_4^+ excretion indicates impaired renal urine acidification, whereas high excretion reflects an appropriate renal response to an extrarenal acid load.[2,3] From a therapeutic perspective, measuring uNH_4^+ enables early identification of patients with CKD at risk of progression, even in the absence of overt acidosis, allowing consideration of alkalizing therapies before clinical acidosis develops.[4,5]

The use of UAG to estimate uNH_4^+ has proven unreliable, particularly in patients with CKD[2,5,6] (Figures 2 and 3). In hospitalized patients, multiple pathological and iatrogenic factors, including underlying disease, diuretics, fluid therapy and other treatments, may independently influence urinary electrolyte excretion and UAG, regardless of acid-base status. Additionally, alterations of unmeasured ions may further limit the reliability of UAG-based uNH_4 estimation.[7]

In response to the nephrologists' petition, an Italian company, Kures® (Milan, Italy) developed the KING® system (Kidney Instant monitoring), which enables direct measurement of uNH_4^+, either from a single random urine sample or through quasi-continuous monitoring at minimum interval of 10 minutes[8]. Access to point-of-care uNH_4^+ measurement could transform the way we assess renal function assessment by enabling us to differentiate between the glomerular and tubular components.[9]

In this article, we present three case reports illustrating a series of clinically applicable uses of this instrument. These examples highlight the clinical utility of uNH_4^+ and its use in evaluating tubular function.

CASE SERIES

Case 1: Comparing a Dysfunctional Kidney with a Successfully Transplanted Kidney, The Basics

The first case describes a 69-year-old female patient who underwent renal transplant for end-stage CKD of unknown origin. On post-operative day 5, there was an abrupt reduction of urine output, which was accompanied by a decrease in uNH_4^+, coinciding with the development of graft hydronephrosis. A nephrostomy was placed, and uNH_4^+ concentration measured from

uNH_4^+ Reference Range and Clinical Interpretation[2, 5,12]

Spot uNH4+	uNH4+excretion	Interpretation	Clinical Implications
< 5, mEq/L	< 20, mEq/d	Low	Alkaline diet, respiratory and metabolic alkalosis, impaired renal acidification (may indicate renal tubular acidosis or CKD).
5 to 30, mEq/L	20 to 40, mEq/d	Normal	Normal renal acid excretion in healthy adults.
> 30, mEq/L	> 40, mEq/d	High	Increased plasma acid load and urine excretion, chronic diarrhoea, high protein intake, or infection with urease-producing bacteria.

Note. Please note that spot urinary ammonium concentrations should be strictly interpreted in the context of the patient's overall clinical and biochemical profile. Serial measurements and longitudinal trends provide greater clinical insight than isolated values. Moreover, the measured "concentration" strictly depends on urine volume, which may physiologically range from 500 mL up to 10 to 15 L/d, depending on water balance regulation. Single spot uNH_4^+ values should therefore be interpreted with caution, whereas longitudinal assessment may better capture changes in NH_4^+ excretion over time.

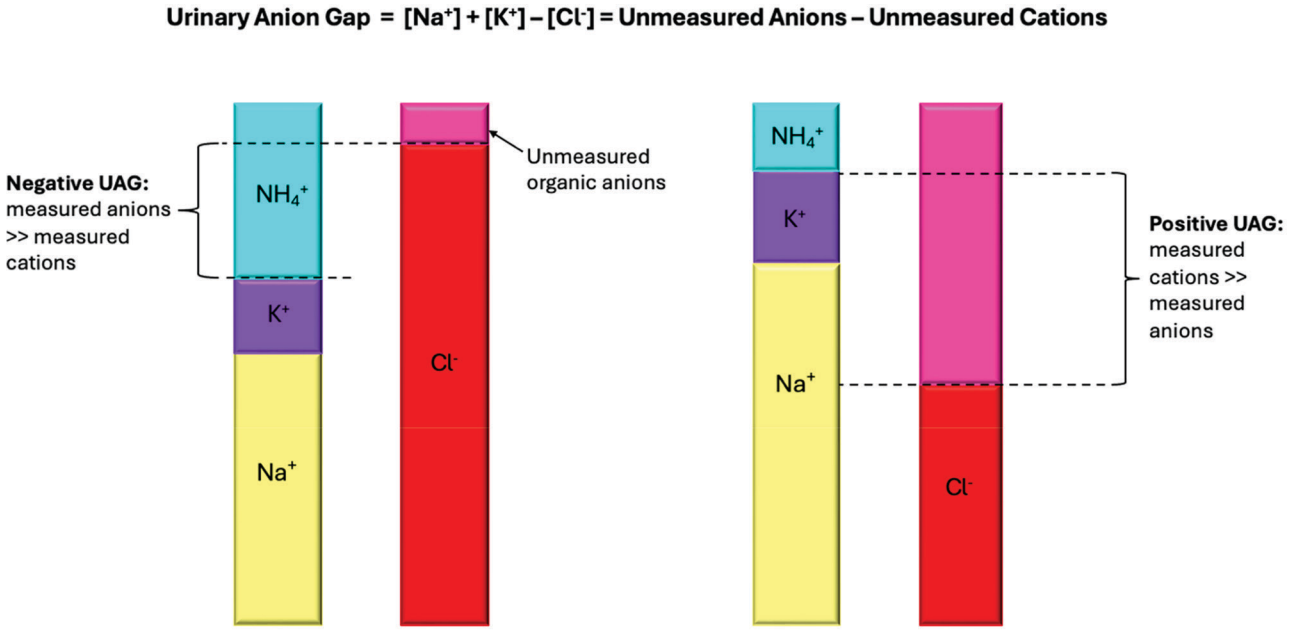


Figure 2. Limitations of the Urine Anion Gap (UAG) as a Surrogate for Urinary NH_4+ Excretion
(Since most urinary NH_4^+ is excreted as NH_4Cl, increased urinary Cl^- generally reflects enhanced NH_4^+ excretion, whereas low urinary Cl^- suggests reduced NH_4^+ elimination. However, several important limitations must be considered. The presence of excess unmeasured anions may lead to over- or underestimation of NH_4^+. The UAG does not account for NH_4^+ excretion with non-chloride anions (e.g., ketoacids or other organic anions). Polyuria and urine pH > 6.5 may alter the relationship between NH_4^+ and Cl^-. Dietary factors, including potassium or sodium salts containing non-chloride anions, can further confound interpretation[6]. In chronic kidney disease, the correlation between UAG and directly measured urinary NH_4^+ becomes unreliable.[2,7])

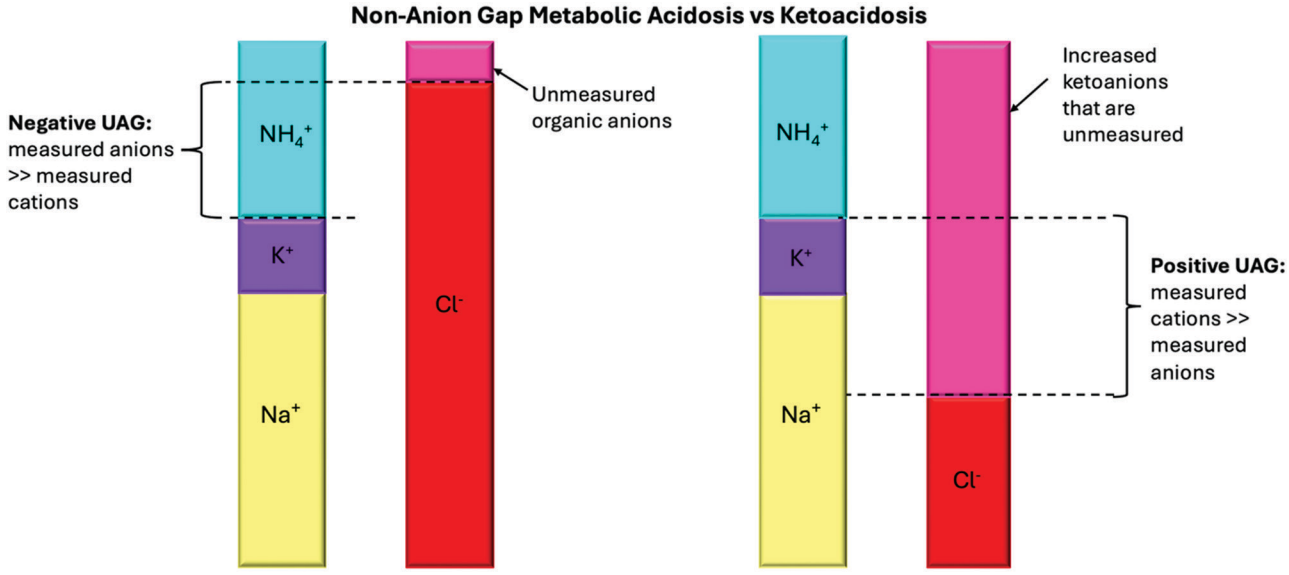


Figure 3. Reduced Reliability of the Urine Anion Gap in Metabolic Ketoacidosis
(In metabolic ketoacidosis, if renal function is preserved, urinary NH_4^+ excretion appropriately increases; however, the accompanying anion differs from chloride. Rather than being excreted as NH_4Cl, NH_4^+ is primarily excreted with β-hydroxybutyrate$^-$ and acetoacetate$^-$. In this setting, urinary Na^+ and K^+ remain relatively unchanged, NH_4^+ increases but is not included in the UAG calculation, Cl^- remains normal or may decrease, and ketoanions rise but are likewise unmeasured. Consequently, when applying the formula $[Na^+] + [K^+] - [Cl^-]$, the UAG may appear positive or only minimally negative, substantially underestimating true urinary NH_4^+ excretion.[2,7])

the nephrostomy urine (originating from the transplanted kidney) was substantially higher than that measured from the urinary catheter (originating from the native kidneys) on post-operative day 10 (25.0 vs. 4.7 mEq/L), supporting recovery of tubular function in the graft (Figure 4).

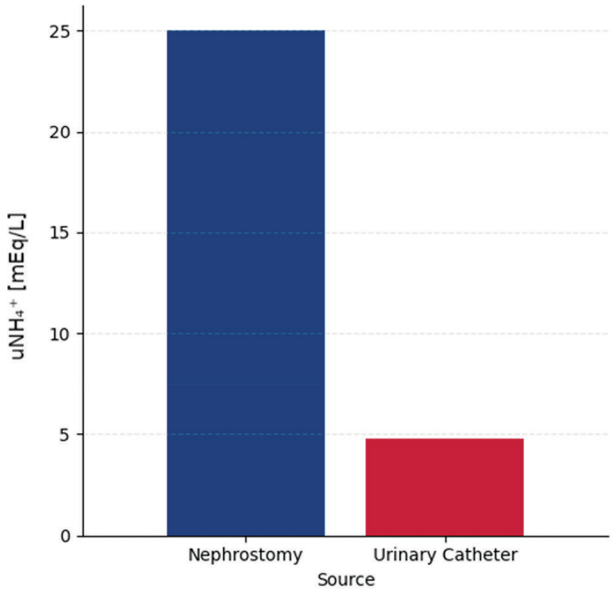


Figure 4. Comparison of Urinary Ammonium (uNH$_4^+$) Concentrations From Nephrostomy and Urinary Catheter in a Renal Transplant Recipient
(On post-operative day 10, uNH$_4^+$ measured from the nephrostomy (reflecting the transplanted kidney) was markedly higher than that from the urinary catheter (reflecting native kidneys) (25.0 vs. 4.7 mEq/L), indicating preserved tubular ammonium excretion and functional recovery of the graft.)

The differing concentrations of uNH$_4^+$ from the transplanted and native kidney demonstrates the physiology of renal compensation when there is adequate tubular function. Notably, despite the acute functional impairment, serum creatinine continued to decline and failed to reflect this deterioration (Figure 5), underscoring its limitation as a predominantly glomerular marker. In contrast, serial uNH$_4^+$ measurements promptly tracked both injury and recovery, suggesting a potential role for daily uNH$_4^+$ monitoring in the assessment of renal tubular function following transplantation.

Case 2: Differential Diagnosis of a-Lactic Metabolic Acidosis in a Critically Ill Patient

The second case describes a 56-year-old female admitted to the ICU with abdominal sepsis secondary to colonic perforation. The patient presented with a-lactic metabolic acidosis with elevated anion gap (pH = 7.27, $PaCO_2$ = 46 mmHg, lactate = 0.9 mmol/L, SBE = -5.5 mmol/L, AG = 18 mmol/L). The absence of lactic acid and the high AG level strongly suggested renal dysfunction as the likely cause, also considering the clinical presentation of sepsis. In the event of renal dysfunction, the kidneys are unable to reabsorb HCO_3^- and experience a reduced ability to produce and excrete NH_4^+. A urine sample was collected, and the uNH$_4^+$ levels were found to be 43.5 mEq/L, which suggests that ammoniagenesis was preserved. Further laboratory tests revealed the presence of ketoacids (20 mg/dL as urine concentration), prompting a different treatment approach. After appropriate therapy, acid-base balance normalized (pH = 7.43, $PaCO_2$ = 36 mmHg, BE = -0.8 mmol/L, AG = 7.5

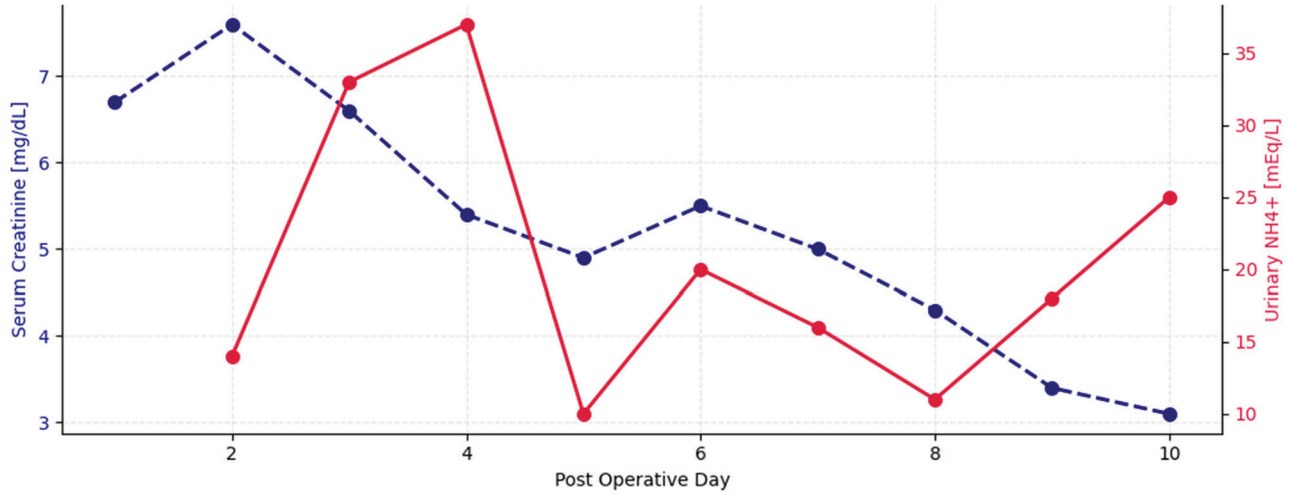


Figure 5. Temporal Evolution of Serum Creatinine and Urinary Ammonium (uNH$_4^+$) Following Renal Transplantation
(Serial measurements over the first 10 post-operative days demonstrate a progressive decline in serum creatinine, indicating improving glomerular function, while uNH$_4^+$ showed an early reduction corresponding with graft hydronephrosis followed by recovery after nephrostomy placement. The divergent trajectories highlight the sensitivity of uNH$_4^+$ to dynamic changes in tubular function that were not immediately reflected by serum creatinine.)

mmol/L). In cases of metabolic acidosis, ruling out a renal cause through a simple measurement of uNH_4^+ can provide valuable and importantly timely information on the underlying aetiology, thereby guiding appropriate treatment. At the same time, early AKI may may not immediately impair ammoniagenesis, making evaluation of trends over time particularly important.

Case 3: Differential Diagnosis of a-Lactic Metabolic Acidosis in a Surgical Patient with Reduced Baseline Renal Reserve

The third case describes a 73-year-old male with a medical history of non-insulin-dependent diabetes mellitus, as well as prior left nephrectomy and right kidney tumour enucleation. The patient underwent a second enucleation of his right kidney. Prior to the surgical procedure, a CT scan with contrast media was performed, resulting in an increase in his serum creatinine from 1.33 to 1.44 mg/dL.

The day of surgery an arterial blood gas analysis was performed and revealed a metabolic acidosis (pH = 7.25, $PaCO_2$ = 44 mmHg, lactate = 0.3 mmol/L, SBE = -8.1 mmol/L, AG = 14 mmol/L). The physicians hypothesised that he had contrast-induced AKI superimposed on CKD. Due to the high risk of exacerbation of CKD, the patient underwent surgical enucleation without renal artery clamping to avoid the potential for ischemia-reperfusion injury. Post-surgery the patient's urine analysis revealed a uNH_4^+ of 29.34 mEq/L, indicating that the residual kidney was attempting to compensate for the metabolic acidosis, likely of non-renal origin. Following the surgical procedure, the patient was transferred to the ICU, where ketone levels were measured and found to be 10 mg/dL. Consequently, a diagnosis of ketoacidosis was established.

DISCUSSION

This descriptive case series provides physiological observations that highlight the potential importance of measuring uNH_4^+ directly. This instrument may assist differential diagnoses and facilitates real-time monitoring of renal tubular function, distinguishing it from glomerular filtration function, which is measured with latency using serum creatinine. Moreover, the assessment of longitudinal trends in uNH_4^+ may also yield valuable information regarding the recovery of AKI, even in conditions of oliguria.

Previous studies have investigated the potential of urine physicochemical profiling to characterize the development of AKI independently of traditional parameters, such as urine output and serum creatinine. For instance, a seminal study by Maciel *et al.* delineated a distinctive urinary physicochemical profile of AKI that was independent of urine output[11]. In this study, AKI was associated with an increase in urinary Strong Ion Difference (uSID) – a different terminology for UAG –, which represents an inverse surrogate of uNH_4^+ excretion. An elevated uSID reflects impaired renal acid excretion, consistent with reduced uNH_4^+ and chloride excretion. Notably, recovery of kidney function was associated with a progressive decrease in uSID, often normalizing earlier than serum creatinine levels. Taken together, these findings once again suggest that uNH_4^+ may serve as a dynamic marker of tubular functional integrity during AKI recovery.

The potential for this concept's application may extend to other domains of critical care, including the assessment of tubular function in patients undergoing renal replacement therapy (RRT). There are currently no large-scale trials investigating the use of uNH_4^+ as a predictor of initiation or weaning from RRT. Nevertheless, in patients with CKD, reduced uNH_4^+ has been independently associated with increased risk of progression to end-stage renal disease requiring chronic dialysis[4]. Based on these observations, we may therefore reason that uNH_4^+ may represent a physiologically relevant marker of tubular functional reserve, with potential utility in future studies aimed at refining assessment of renal recovery and RRT dependency. In addition, a similar line of reasoning may be applied to other, albeit similarly relevant, clinical conditions, such as monitoring renal tubular function in patients with severe ARDS undergoing permissive hypercapnia or in patients with COPD exacerbations, in whom uNH_4^+ assessment may reveal the renal functional reserve to compensate for respiratory acidosis.

Although the potential clinical applications of uNH_4^+ are broad, caution should be exercised when interpreting single measurements. Early or partial acute kidney injury may preserve ammoniagenesis

despite reductions in glomerular filtration rate, and systemic conditions such as sepsis can affect tubular function independently. Therefore, uNH_4^+ values should be considered alongside longitudinal trends in the context of the patient's overall clinical picture.

CONCLUSIONS

Renal function is a multifaceted process involving numerous physiological roles in addition to glomerular filtration. Conceptually, the separation of renal function into glomerular and tubular components may facilitate a more comprehensive assessment of kidney health. Integrating uNH_4^+ with serum creatinine and urine output could offer a simple and clinically feasible approach to assess tubular function, thereby enabling a more global evaluation of renal function.

CONFLICT OF INTEREST AND FUNDING

The authors declare that they have no financial relationships, intellectual property interests, or personal affiliations that could be perceived as influencing the work reported in this manuscript. The device used for urinary ammonium measurement was employed solely for clinical and observational purposes, and no external funding or industry sponsorship was received for this study.

REFERENCES

1. Nephrologists campaign to replace urine anion gap with urine ammonium test. Kidney News. 2021;13(12).
2. Uribarri J, Goldfarb DS, Raphael KL, Rein JL, Asplin JR. Beyond the urine anion gap: in support of the direct measurement of urinary ammonium. Am J Kidney Dis. 2022;80(5):667-76.
3. Ha LY, Chiu WW, Davidson JS. Direct urine ammonium measurement: time to discard urine anion and osmolar gaps. Ann Clin Biochem. 2012;49(6):606-8.
4. Vallet M, Metzger M, Haymann JP, Flamant M, Gauci C, Thervet E, et al. Urinary ammonia and long-term outcomes in chronic kidney disease. Kidney Int. 2015;88(1):137-145.
5. Raphael KL, Carroll DJ, Murray J, Greene T, Beddhu S. Urine ammonium predicts clinical outcomes in hypertensive kidney disease. J Am Soc Nephrol. 2017;28(8):2483-90.
6. Uribarri J, Oh MS. The urine anion gap: common misconceptions. J Am Soc Nephrol. 2021;32(5):1025-8.
7. Batlle D, Ismail A, Mohammed B, Rosa R. The concept, usefulness, and limitations of the urine anion gap. Clin J Am Soc Nephrol. 2025;20(12):1810-3.
8. Caironi P, Langer T, Taccone P, Bruzzone P, De Chiara S, Vagginelli F, et al. Kidney instant monitoring (K.IN.G.): a new analyzer to monitor kidney function. Minerva Anestesiol. 2010;76(5):316-24.
9. Traynor J, Mactier R, Geddes CC, Fox JG. How to measure renal function in clinical practice. BMJ. 2006;333(7571):733-7.
10. Elkinton JR, Huth EJ, Webster GD, McCance RA. The renal excretion of hydrogen ion in renal tubular acidosis. I. Quantitative assessment of the response to ammonium chloride as an acid load. Am J Med. 1960;29(4):554-75.
11. Maciel AT, Park M, Macedo E. Physicochemical analysis of blood and urine in the course of acute kidney injury in critically ill patients: a prospective observational study. BMC Anesthesiol. 2013;13(1):31.
12. Asplin JR. Neglected analytes in the 24-h urine: ammonium and sulfate. Curr Opin Nephrol Hypertens. 2022 Mar;31(2):168–74.

Correspondence to:
Lara Mary Titherington, MD
Department of Anaesthesia and Intensive Care, Azienda Ospedaliero-Universitaria Careggi
Largo Brambilla 3, 50134 Florence, Italy
ORCID ID: 0009-0009-5470-6352
Phone: 0039 3336989150
E-mail: laramary.titherington@unifi.it

Received April 2026
Revised May 2026
Accepted June 2026

Erratum to: Efficacy of Hemoadsorption Therapy in Patients With Sepsis-associated Acute Kidney Injury: A Systematic Review and Meta-analysis

RJCCN 2026; 2(3):222
www.rjccn.org
DOI: 10.66224/rjccn.2.3.60

Citation of original article: Saeedian B, Babajani N, Hakemi M, Jodeiri F, Aslani MA, Alavi Darazam I, Kasaeian A, Schneider A, Nassiri AA. Efficacy of Hemoadsorption Therapy in Patients With Sepsis-associated Acute Kidney Injury: A Systematic Review and Meta-analysis. RJCCN. 2026;2(2):115-32. DOI: 10.66224/rjccn.2.2.46

Following publication of the above article, an error was identified in the authors' affiliations. The affiliations were published incorrectly due to a production error. The correct affiliations are provided below.

Correct Authors' Affiliations

Behrad Saeedian,[1] Nastaran Babajani,[2] Monir Sadat Hakemi,[3] Fatemeh Jodeiri,[4,5] Mohammad Amin Aslani,[6,7] Ilad Alavi Darazam,[8] Amir Kasaeian,[9,10] Antoine Schneider,[11,12] Amir Ahmad Nassiri[13]

[1]Liver and Pancreatobiliary Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[2]Digestive Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Nephrology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
[4]Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[5]School of Medicine, Islamic Azad University, Tehran Medical Branch, Tehran, Iran
[6]School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[7]Vascular Disease and Thrombosis Research Center, Rajaie Cardiovascular Institute, Tehran, Iran
[8]Department of Infectious Diseases and Tropical Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[9]Research Center for Chronic Inflammatory Diseases, Tehran University of Medical Sciences, Tehran, Iran
[10]Digestive Oncology Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[11]Service de médecine intensive adulte, Centre Hospitalier Universitaire Vaudois (CHUV), Rue du Bugnon 46, Lausanne, 1011, Switzerland
[12]Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland
[13]Department of Nephrology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

The authors' affiliations have been corrected in the online version of the article.
The Publisher apologizes to the authors and readers for this error.

Merolic®
Mycophenolic Acid

Rolima®
Everolimus

Suprotac®
Tacrolimus

Orchid Pharmed
Sky's the Limit

FINERENAL®
Finerenone

CinnaPoietin®
Erythropoietin beta

RJCCN

Research Journal of Critical Care Nephrology

Volume 2, Number 3, July 2026