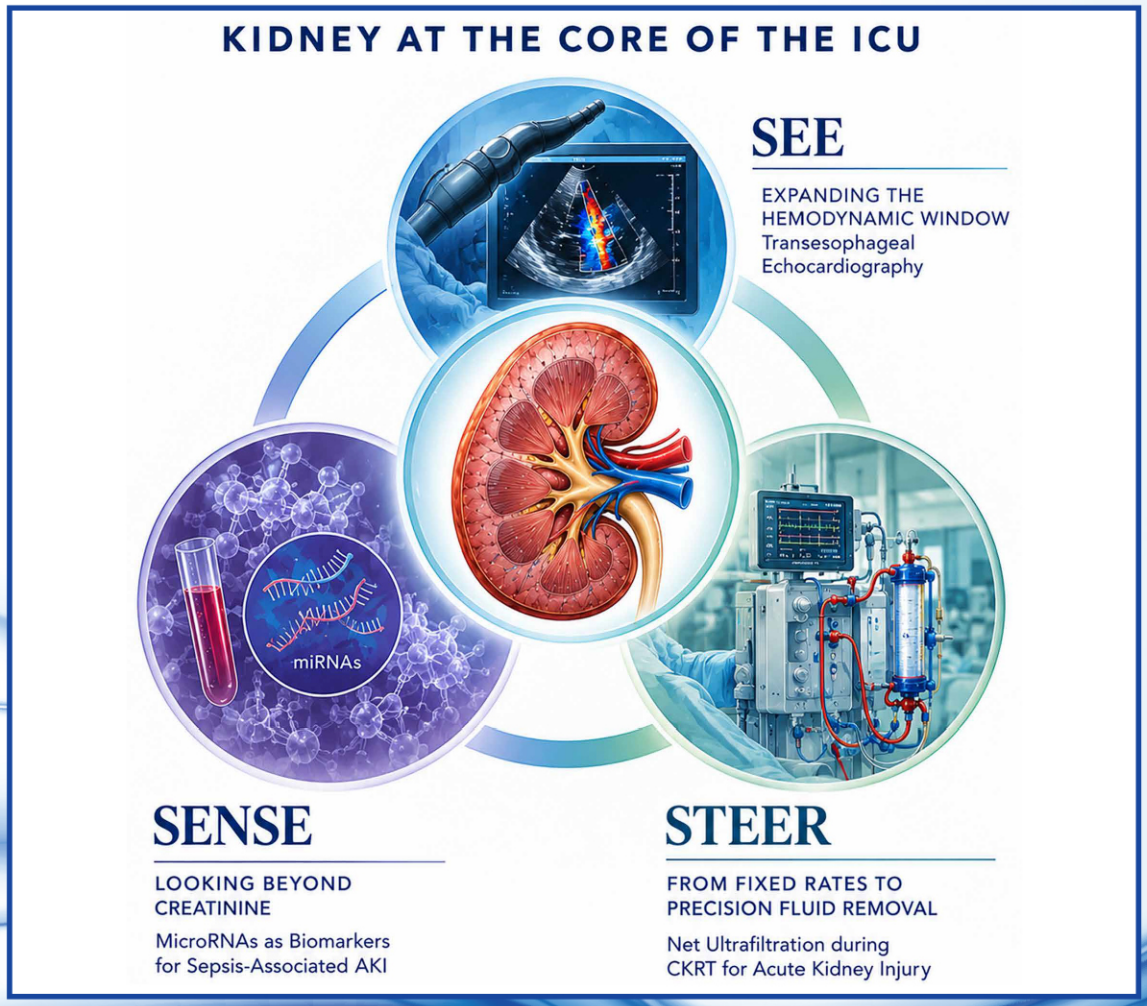
RJCCN

Research Journal of Critical Care Nephrology

Volume 2, Number 4, October 2026



RESEARCH JOURNAL OF CRITICAL CARE NEPHROLOGY

eISSN 3115-8463

Research Journal of Critical Care Nephrology Volume 2 Number 4 October 2026

RJCCN

Research Journal of Critical Care Nephrology

Chairperson:
Dr. Amir Ahmad Nassiri (Iran)
Publisher:
It is a self-publish journal that is located in Iran.
Editor-in-Chief:
Dr. Amir Ahmad Nassiri (Iran)
Editorial Manager:
Dr. Atefeh Amouzegar (Iran)
Associate Editor (POCUS Section):
Dr. Abhilash Koratala (USA)
Associate Editor (Nephrology Section):
Dr. Monir-Sadat Hakemi (Iran)
Associate Editor (Sepsis Section):
Dr. Ilad Alavi-Darazam (Iran)
Assistant Editor:
Dr. Kiana Entezarmahdi (Iran)
Dr. Behrang Alipour (Iran)
Assistant Editor in Nursing Field:
Ms. Azam Rahimzadeh-Kalaleh (Iran)
Editorial Board Members (in alphabetical order):
Dr. Pedram Ahmadpoor (France)
Dr. Moayed Alavian (Iran)
Dr. Ilad Alavi-Darazam (Iran)
Dr. Atefeh Amouzegar (Iran)
Dr. Seyed-Hossein Ardehali (Iran)
Dr. Hassan Argani (Iran)
Dr. Varshasb Broumand (USA)
Dr. Mojtaba Chahardoli (Iran)
Dr. Saeed Changizi-Ashtyani (Iran)
Dr. Alireza Esteghamati (Iran)
Dr. Shahrokh Ezzatzadegan-Jahromi (Iran)
Dr. Farzad Fatehi (Iran)
Dr. Farshid Haghverdi (Iran)
Dr. Monir-Sadat Hakemi (Iran)
Dr. Seyed-Mohammadreza Hashemian (Iran)
Dr. Hossein Imani (Iran)
Dr. Kianoush Kashani (USA)
Dr. Arda Kiani (Iran)
Dr. Abhilash Koratala (USA)
Dr. Mirmohammad Miri (Iran)
Dr. Mohammadreza Mohajeri (Iran)
Dr. Masoumeh Mohkam (Iran)
Dr. Majid Mokhtari (Iran)
Dr. Nasim Naderi (Iran)
Dr. Mohsen Nafar (Iran)
Dr. Shervin Najafizadeh (Iran)
Dr. Amir-Hassan Nassiri (France)
Dr. Marlies Ostermann (UK)
Dr. Maryam Pourkar-Jadid (Iran)
Dr. Farin Rashid-Farokhi (Iran)
Dr. Sajad Razavi (Iran)
Dr. Thomas Rimmele (France)
Dr. Saeid Safari (Australia)
Dr. Farhad Samiei (Iran)
Dr. Antoine Schneider (Switzerland)
Dr. Babak Sharif-Kashani (Iran)
Dr. Mohammad Sistanizad (Iran)
Dr. Payam Tabarsi (Iran)
Dr. Ali Tabibi (Iran)
Executive Manager:
Dr. Behrang Alipour (Iran)

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

Copyright. © [Year] Author(s). Authors retain the copyright of their published work without restriction. All articles published by *RJCCN* are licensed under the Creative Commons Attribution 4.0 International (CC BY 4.0) license.

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: Kidney at the Core of the ICU. See page 223

www.rjccn.org

RJCCN

Research Journal of Critical Care Nephrology

Volume 2, Number 4, October 2026

Table of Contents

FROM THE EDITORS

- Seeing, Steering, and Sensing the Injured Kidney
  Nassiri AA 223

COMMENTARY

- Critical Care Transesophageal Echocardiography: Expanding the Hemodynamic Window
  Koratala A 227

REVIEW

AKI

- Net Ultrafiltration During Continuous Kidney Replacement Therapy for Acute Kidney Injury: From Fixed Rates to Precision Fluid Removal
  Kashani KB, Murugan R 231

Kidney Disease

- Multi-Omics Integration for Enhanced Insights into Chronic Kidney Disease: Unraveling Biological Networks and Therapeutic Targets, A Mini Review
  Kianfar T, Zakikhani A, Taherkhani S 248

ORIGINAL PAPER

Sepsis

- Diagnostic Value of MicroRNAs as Biomarkers for Sepsis-associated Acute Kidney Injury: A Systematic Review and Meta-Analysis
  Javandoust Gharehbagh F, Lotfollahi L, Gerami D, Alavi Darazam I 255

Kidney Disease

- Epidemiological Characteristics of Children with Nephrotic Syndrome Referred to Amir-Kabir Hospital in Arak, Iran: A Cross-Sectional Study
  Yousefichaijan P, Rafiei F, Rezagholizamenjany M 272

Dialysis

- Association of Dialysis Adequacy and Estimated Kidney Function with Mineral Metabolism Parameters in Patients Undergoing Peritoneal Dialysis
  Mortazavi M, Rahimifar R, Seirafian S, Miralaei P 279

Transplantation

- Clinical Profile, Immunosuppressive Management and Outcome in Adult Renal Allograft Recipients with COVID-19 Infection
  Mahjabin S, Islam N, Rahman R, Haque E, Ebne Mobin M 289

CASE REPORT

Dialysis

- Diagnostic Challenges of ESA-Resistant Anemia with MDS-Like Marrow Abnormalities: The Importance of Excluding Reversible Causes
  Ikegishi Y 301

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

© [Year] Author(s). Authors retain the copyright of their published work without restriction.

All articles published in *RJCCN* are made available under the CC BY 4.0 license.

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

© [Year] Author(s). Authors retain the copyright of their published work without restriction.
All articles published by *RJCCN* are licensed under the Creative Commons Attribution 4.0 International (CC BY 4.0) license. This license permits anyone to copy, distribute, reproduce, adapt, and build upon the work, including for commercial purposes, provided that appropriate credit is given to the original author(s), a link to the license is provided, and any changes made are indicated.

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 _____

Seeing, Steering, and Sensing the Injured Kidney

RJCCN 2026; 2: 223-6
www.rjccn.org
DOI: 10.61882/rjccn.2.4.81

© 2026 Author(s). This article is licensed under the CC By 4.0 International License.

The next frontier of critical care nephrology may not be another kidney replacement therapy. It may be our ability to see, understand, and anticipate kidney injury before it becomes irreversible.

Critical illness rarely respects the boundaries of individual organs.

The kidney may be where acute injury becomes most visible, but the forces that produce that injury are rarely confined to the kidney itself. Hemodynamic instability, venous congestion, inflammation, endothelial dysfunction, sepsis, fluid accumulation, and the therapies required to support other failing organs all converge on renal function.

This is one of the reasons critical care nephrology has evolved so rapidly.

We are no longer simply asking whether the kidney has failed. Increasingly, we are asking *why it is failing, how its trajectory can be modified, and whether we can recognize injury before conventional markers declare it.*

The fifth issue of the *Research Journal of Critical Care Nephrology* brings together three contributions that, although apparently different, converge on this very idea.

They can be summarized in three words: SEE, STEER, SENSE (Figure).

SEE; EXPANDING THE HEMODYNAMIC WINDOW

The first article, "Critical Care Transesophageal Echocardiography: Expanding the Hemodynamic Window," addresses the first requirement of precision medicine in the ICU: seeing the physiology that lies beneath the numbers.[1]

For the critically ill patient with AKI, a low blood pressure does not provide a sufficient explanation. Is renal perfusion compromised because of inadequate forward flow? Is the right ventricle failing? Is venous congestion limiting renal function? Is there impaired preload, altered ventricular interaction, or another cardiovascular process that is invisible when we look only at conventional vital signs?

For the nephrologist, these are not merely cardiology questions.

They are kidney questions.

The kidney exists within a circulation. Renal perfusion cannot be separated from cardiac function, venous pressure, vascular tone, intravascular volume, and the complex interaction between the heart, lungs, and venous system.

TEE therefore represents more than another imaging technique. It expands the hemodynamic window through which the nephrologist can interpret AKI.

The future of critical care nephrology will require us to become increasingly comfortable with this physiological language.

Not because every nephrologist must become an echocardiographer—but because understanding the kidney increasingly requires understanding the circulation around it.

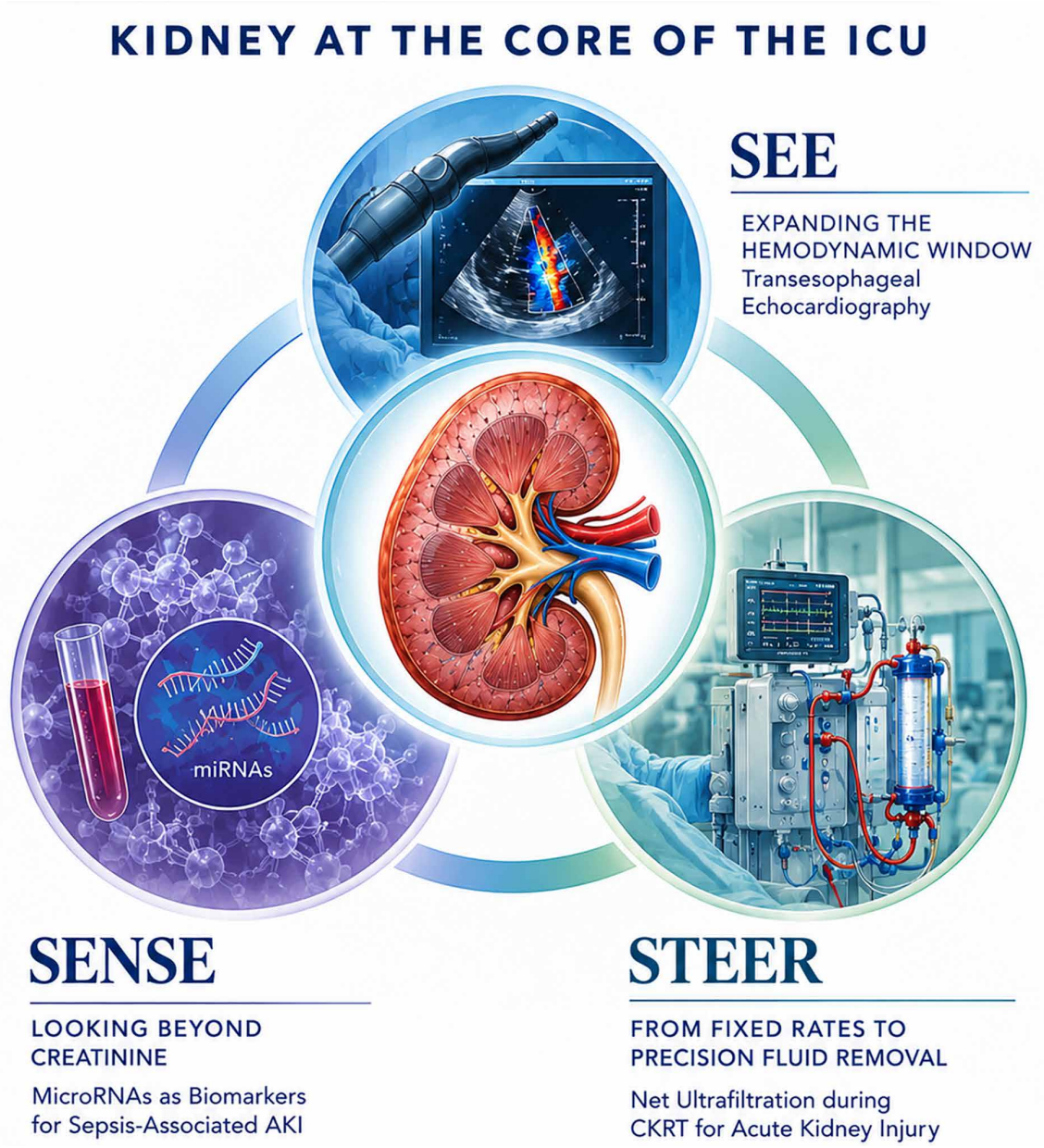
STEER; FROM FLUID REMOVAL TO PRECISION FLUID REMOVAL

The second article, "Net Ultrafiltration During Continuous Kidney Replacement Therapy for Acute Kidney Injury: From Fixed Rates to Precision Fluid Removal," brings us to one of the most difficult therapeutic decisions in contemporary critical care nephrology: how much fluid should we remove, and how fast?[2]

For decades, ultrafiltration could be approached primarily as a prescription.

Today, that approach is becoming increasingly

Please cite this article as: Nassiri AA. Seeing, Steering, and Sensing the Injured Kidney. RJCCN. 2026;2(4):223-6.



difficult to defend.

Fluid overload is associated with important adverse consequences, yet fluid removal itself is not physiologically neutral. Net ultrafiltration represents a cardiovascular stress. When the rate of intravascular fluid removal exceeds the patient's capacity for vascular refilling, circulating volume may fall, potentially compromising cardiac output and organ perfusion.

The important question, therefore, is no longer simply: What is the ultrafiltration rate?

It is: "What ultrafiltration rate is appropriate for this patient, at this moment, given this patient's physiology and trajectory?"

This is the essence of precision fluid removal.

The concept moves us away from a universal prescription and toward an individualized strategy that considers body weight, fluid accumulation, ongoing inputs, urine output, hemodynamics, vascular refilling, organ congestion, and tolerance to fluid removal. Contemporary observational evidence suggests that the relationship between net ultrafiltration intensity and outcome is complex, and importantly, causality remains uncertain.

This uncertainty should not weaken the concept of precision.

It should strengthen the need to study it rigorously.

Fluid removal should not simply be prescribed. It should be titrated.

SENSE; LOOKING BEYOND CREATININE

The third article, "Diagnostic Value of MicroRNAs as Biomarkers for Sepsis-Associated Acute Kidney Injury: A Systematic Review and Meta-Analysis," takes us to another frontier: the possibility of detecting kidney injury at the level of biology before its functional consequences become fully apparent.[3]

Serum creatinine remains an essential clinical marker, but it is not a direct real-time measurement of kidney injury. Its concentration reflects multiple physiological variables and may lag behind the biological events that initiate AKI.

MicroRNAs offer a fundamentally different perspective.

Rather than simply measuring the consequence of impaired filtration, they may provide information about the molecular processes accompanying kidney injury.

This is an exciting field—but excitement should not be confused with readiness for clinical implementation.

The challenge is now to determine whether molecular signals can be sufficiently reproducible, standardized, specific, temporally informative, and clinically actionable to change bedside decisions.

The important question is therefore not merely: "Can microRNAs predict AKI?"

It is: "Can molecular information change what we do for the patient?"

That distinction marks the difference between an interesting biomarker and a clinically useful biomarker.

FROM REPLACEMENT THERAPY TO PRECISION PHYSIOLOGY

Taken together, these three articles illustrate a broader transformation occurring within critical care nephrology.

TEE helps us SEE the physiology.

Precision ultrafiltration helps us STEER the trajectory.

Molecular biomarkers may allow us to SENSE injury earlier.

This progression—from observation, to intervention, to anticipation—is perhaps one of the most important directions for our field.

Critical care nephrology is moving beyond the traditional paradigm in which the nephrologist becomes involved primarily when kidney replacement therapy is required.

The emerging nephrologist is instead becoming a physiologist at the bedside: someone who integrates hemodynamics, fluid balance, congestion, renal function, extracorporeal therapies, inflammation, biomarkers, and the trajectory of multiorgan dysfunction.

This is particularly important because AKI is not simply an isolated renal event.

It is often the kidney's expression of a much larger systemic disturbance.

The kidney is simultaneously a victim, a sensor, a regulator, and a participant in critical illness.

And perhaps this is where the future of our specialty lies.

Not in choosing between technology and physiology, but in bringing them together.

Not in asking whether a patient "needs dialysis," but in asking what physiological problem we are trying to solve.

Not in reacting to kidney injury once it is established, but in recognizing its trajectory earlier.

And not in treating the kidney as an isolated organ, but in understanding the kidney within the patient.

THE NEXT FRONTIER

The fifth issue of the *Research Journal of Critical Care Nephrology* is therefore more than a collection of articles on echocardiography, ultrafiltration, and biomarkers.

It reflects a common direction: better visualization of physiology, more precise intervention, and earlier recognition of biological injury.

The technologies will continue to evolve.

TEE will continue to expand our ability to interrogate the circulation. CKRT will increasingly become a platform for individualized fluid and solute management. Molecular biomarkers may

eventually complement—or redefine—the way we recognize AKI.

But technology alone will not define the future of critical care nephrology.

Physiological thinking will.

Our challenge is to connect the signal to the physiology, the physiology to the intervention, and the intervention to the patient's trajectory.

That is the promise of precision critical care nephrology: See the physiology, Steer the trajectory, and Sense the injury.

And ultimately; treat the patient, not the kidney in isolation.

REFERENCES

1. Koratala A. Critical Care Transesophageal Echocardiography: Expanding the Hemodynamic Window. RJCCN. 2026;2(4):227-30.
2. Kashani KB, Murugan R. Net Ultrafiltration During Continuous Kidney Replacement Therapy for Acute Kidney Injury: From Fixed Rates to Precision Fluid Removal. RJCCN. 2026;2(4):231-47.
3. Javandoust Gharehbagh F, Lotfollahi L, Gerami D, Alavi Darazam I. Diagnostic Value of MicroRNAs as Biomarkers for Sepsis associated Acute Kidney Injury: A Systematic Review and Meta-Analysis. RJCCN. 2026;2(4):255-71.

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

Received October 2026

Critical Care Transesophageal Echocardiography: Expanding the Hemodynamic Window

Abhilash Koratala

Division of Nephrology and Division of Surgical Critical Care, Medical College of Wisconsin, Milwaukee, USA

RJCCN 2026; 2: 227-30
www.rjccn.org
DOI: 10.61882/rjccn.2.4.74

Keywords. POCUS, ultrasound, transesophageal, resuscitation

© 2026 Author(s). This article is licensed under the CC By 4.0 International License.

Focused cardiac and lung ultrasound have become integral to bedside hemodynamic assessment in critically ill patients, allowing rapid characterization of ventricular function, pulmonary congestion, and fluid tolerance. Transthoracic imaging remains the natural first-line approach and is sufficient to answer urgent questions in many patients. Yet the ICU is not always an ultrasound-friendly environment. Obesity, mechanical ventilation, pulmonary disease, edema, surgical dressings, trauma, and difficulty with patient positioning frequently limit transthoracic echocardiography (TTE); indeed, the image quality has been reported to be limited in more than 30% of ICU studies.[1]

Critical care transesophageal echocardiography (ccTEE) extends bedside echocardiography when transthoracic imaging is inadequate or impractical. Its scope is scalable, from a few goal-directed views during initial evaluation of shock or cardiac arrest to more detailed assessment of biventricular function, stroke volume, filling physiology, and response to therapy.

One of its most compelling applications is undifferentiated circulatory shock. A limited ccTEE examination can rapidly reveal ventricular dysfunction, pericardial effusion, stigmata of pulmonary embolism, dynamic left ventricular outflow tract (LVOT) obstruction, profound underfilling, or major valvular pathology. The value lies not merely in obtaining better images, but in converting the nonspecific diagnosis of "shock" into a physiologic phenotype that can guide treatment. Across the studies summarized by Prager and colleagues, ccTEE changed diagnosis in 52 to 78% of patients and management in 32 to 79%, although these data remain largely observational.[2]

Cardiac arrest represents an even more distinctive use case. During cardiopulmonary resuscitation (CPR), transthoracic imaging must compete with chest compressions, defibrillator pads, and the need to minimize interruptions, often leaving only a limited subcostal window. In this context, once an advanced airway is secured, the TEE transducer can remain in position and provide continuous visualization without interfering with chest compressions. Beyond identifying reversible causes such as tamponade, massive pulmonary embolism, severe hypovolemia, or aortic dissection, it can reveal cardiac activity despite an apparent non-shockable electrical rhythm on surface electrocardiography and shorten interruptions in compressions. TEE may also provide information about the quality of CPR itself. Several studies have shown that external compressions may occur over the LVOT or aortic root rather than directly over the left ventricle, potentially impairing forward flow. TEE allows real-time visualization of the area of maximal compression and guides repositioning

Please cite this article as: Koratala A. Critical Care Transesophageal Echocardiography: Expanding the Hemodynamic Window. RJCCN. 2026;2(4):227-30.

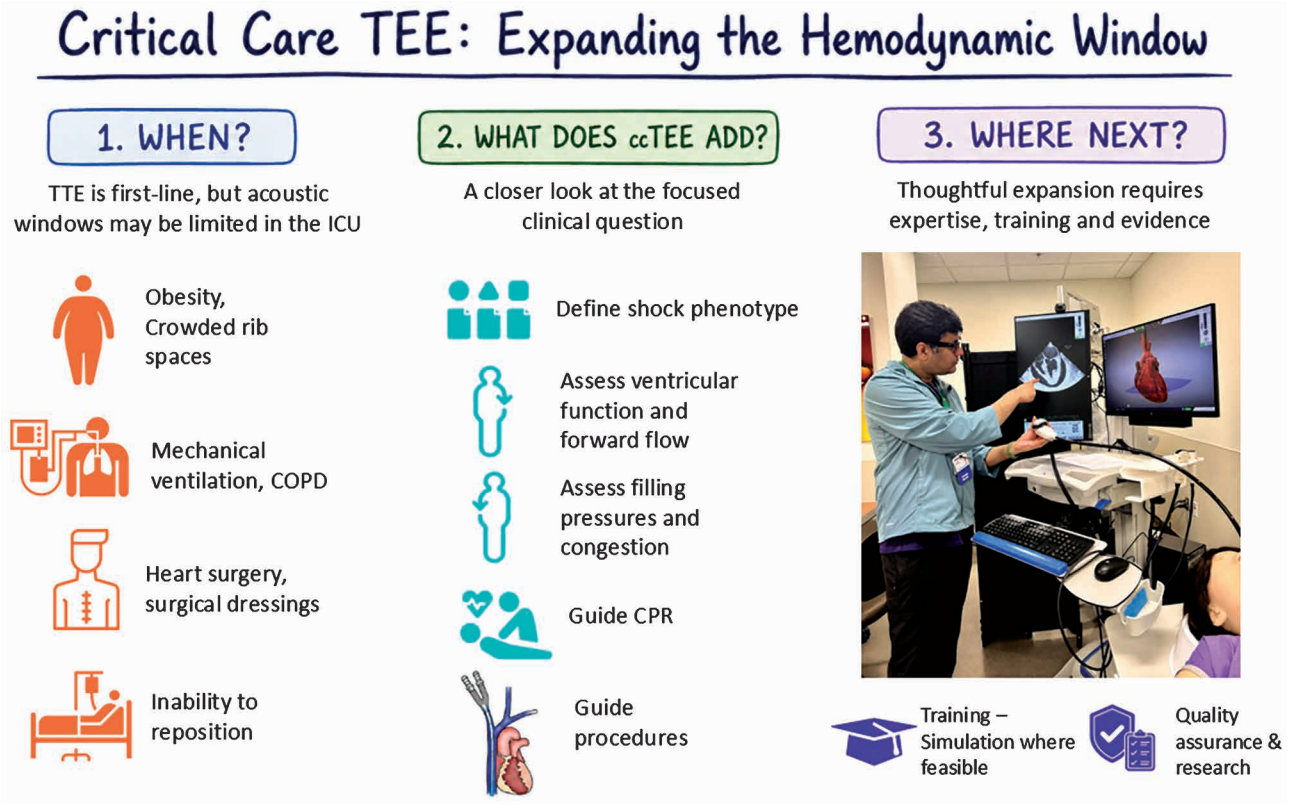
of the hands when necessary; compression closer to the left ventricle has been associated with greater generated stroke volume.[3,4] This ability to interrogate not only the cause of arrest but also the mechanics of the resuscitation is difficult to reproduce with intermittent transthoracic imaging.

The usefulness of ccTEE does not necessarily end once the initial diagnosis has been established. Hemodynamics in critically ill patients evolve rapidly, making serial assessment of biventricular function, right ventricular size, tricuspid regurgitation, LVOT velocity-time integral, and cardiac output useful for evaluating response to therapy. Beyond the heart, the feasibility of extending the TEE examination to assess venous congestion using hepatic, portal, and renal parenchymal Doppler, the components of VExUS, has also been demonstrated.[5] Together, these assessments can help address evolving clinical questions: Is forward flow improving with inotropic therapy? Is right ventricular dilation and/or venous congestion improving with diuresis or ultrafiltration? If hypotension persists, is the circulation still preload responsive, or has the physiology shifted toward ventricular dysfunction or congestion? SVC respiratory variation may provide additional information regarding fluid responsiveness, although it should not be interpreted in isolation.[6] Thus, the strength of ccTEE lies not in any single parameter, but in integrating gross cardiac function, flow, loading conditions, and their evolution in response to therapy.

The esophageal vantage point can also address questions that may be difficult to resolve transthoracically. TEE provides excellent visualization of posterior cardiac structures, including the left atrium and left atrial appendage, as well as favorable alignment of the atrioventricular valves.[7] These views can facilitate assessment of significant valvular pathology and intracardiac thrombi, including potential embolic sources in cryptogenic stroke or before cardioversion for refractory tachyarrhythmias. In patients with unexplained hypoxemia, the mid-esophageal bicaval view provides optimal anatomic alignment of the interatrial septum for evaluating right-to-left shunting.[8] TEE can also guide bedside procedures such as Extracorporeal membrane oxygenation (ECMO) cannulation and cannula repositioning, as well as transvenous pacemaker placement, where real-time visualization of guidewires and intracardiac devices is particularly valuable.

These advantages must be balanced against the fact that TEE is invasive. Esophageal pathology such as strictures, active gastrointestinal bleeding, prior gastrointestinal surgery, coagulopathy, thrombocytopenia, and varices require careful consideration.[8] Esophageal varices are generally regarded as a relative rather than absolute contraindication.[9] In higher-risk patients for variceal bleeding, the examination should be tailored to the clinical question; if adequate information can be obtained from mid-esophageal views, advancement into transgastric views may reasonably be avoided. The published safety profile is reassuring but should not be overstated. In a scoping review of 108 studies involving 6,739 patients, only two significant gastrointestinal bleeding events requiring intervention were reported, with no reported deaths or esophageal perforations attributable to ccTEE.[2] Minor complications were uncommon, although retrospective reporting likely underestimates their true incidence. Accordingly, patient selection, operator training, and institutional quality assurance remain essential. Simulation should play an important role in this training, particularly given the invasive nature of TEE. It provides a safe environment to develop probe manipulation skills, become familiar with cardiac anatomy from an esophageal perspective, and encounter a range of simulated pathologies before performing examinations in patients (Figure).

Where the field goes next is likely to depend less on demonstrating that ccTEE can produce excellent images and more on defining when those images meaningfully improve care. The current literature establishes feasibility, diagnostic yield, and influence on management, but high-quality evidence for patient-centered outcomes remains limited. Not every diagnostic or monitoring intervention should be expected to improve mortality; however, measurable benefits such as more timely diagnosis, faster resolution of hemodynamic instability, fewer additional diagnostic studies, or improved procedural efficiency will be important to justify



Critical Care Transesophageal Echocardiography (ccTEE) complements TTE when transthoracic windows are limited, enabling focused hemodynamic assessment, resuscitation, and procedural guidance. Safe expansion requires appropriate training, quality assurance, and continued research. The photograph in the right panel illustrates TEE training using a high-fidelity simulator, demonstrating simulated pathology (pericardial effusion) alongside a 3D anatomical representation of the corresponding imaging plane.

the resources required to establish and sustain ccTEE programs. In a randomized trial, continual indwelling TEE monitoring was associated with earlier resolution of hemodynamic instability during the 72-hour period of active monitoring, although this difference was no longer significant when the primary outcome was assessed over 6 days and did not translate into differences in mortality or length of stay.[10]

The future of ccTEE therefore should not be one of indiscriminate expansion. Its value will lie in selective use: when transthoracic imaging is inadequate, when uninterrupted visualization matters, when serial physiology can guide therapy, or when an anatomic or procedural question is better approached from the esophagus. As critical care POCUS matures, the relevant question may increasingly be not whether TTE or TEE is the "better" modality, but which acoustic window can most reliably answer the physiologic question, and whether that answer will change what we do next.

REFERENCES

1. Main ML, Hibberd MG, Ryan A, Lowe TJ, Miller P, Bhat G. Acute mortality in critically ill patients undergoing echocardiography with or without an ultrasound contrast agent. JACC Cardiovasc Imaging. 2014;7(1):40-8.
2. Prager R, Bowdridge J, Pratte M, Cheng J, McInnes MDF, Arntfield R. Indications, clinical impact, and complications of critical care transesophageal echocardiography: a scoping review. J Intensive Care Med. 2023;38(3):245-72.
3. Teran F, Prats MI, Nelson BP, Kessler R, Blaivas M, Peberdy MA, et al. Focused transesophageal echocardiography during cardiac arrest resuscitation: JACC review topic of the week. J Am Coll Cardiol. 2020;76(6):745-54.
4. Chen CC, Chen TY, Lin LC, Wu CY, Wu MC, Hsu SH, et al. Hemodynamic effects of TEE-guided adjustment of the area of the maximal compressions during cardiopulmonary resuscitation. Resuscitation. 2026;111097.
5. Waldron NH, Pandompatam G, Sareyyupoglu B, Kalagara H. Transesophageal echocardiographic acquisition of the venous excess ultrasound exam—a case series and technical description. Can J Anaesth. 2024;71(3):422-30.
6. Vignon P, Repessé X, Bégot E, Léger J, Jacob C, Bouferrache K, et al. Comparison of echocardiographic indices used to predict fluid responsiveness in ventilated

patients. Am J Respir Crit Care Med. 2017;195(8):1022-32.

7. Pathan F, Hecht H, Narula J, Marwick TH. Roles of transesophageal echocardiography and cardiac computed tomography for evaluation of left atrial thrombus and associated pathology: a review and critical analysis. JACC Cardiovasc Imaging. 2018;11(4):616-27.
8. Hahn RT, Abraham T, Adams MS, Bruce CJ, Glas KE, Lang RM, et al. Guidelines for performing a comprehensive transesophageal echocardiographic examination: recommendations from the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. Anesth Analg. 2014;118(1):21-68.
9. Odewole M, Sen A, Okoruwa E, Lieber SR, Cotter TG, Nguyen AD, et al. Systematic review with meta-analysis: incidence of variceal hemorrhage in patients with cirrhosis undergoing transesophageal echocardiography. Aliment Pharmacol Ther. 2022;55(9):1088-98.
10. Merz TM, Cioccari L, Frey PM, Bloch A, Berger D, Zante B, et al. Continual hemodynamic monitoring with a single-use transesophageal echocardiography probe in critically ill patients with shock: a randomized controlled clinical trial. Intensive Care Med. 2019;45(8):1093-102.

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 August 2026

Net Ultrafiltration During Continuous Kidney Replacement Therapy for Acute Kidney Injury: From Fixed Rates to Precision Fluid Removal

Kianoush B. Kashani[1,2], Raghavan Murugan[3,4,5]

[1]Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN 55905, USA
[2]Division of Pulmonary, Critical Care, Allergy & Sleep Medicine, Department of Medicine, Mayo Clinic, Rochester, MN 55905, USA
[3]The Program for Critical Care Nephrology, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
[4]The Center for Research, Investigation, and Systems Modeling of Acute Illness (CRISMA), Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
[5]Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Keywords. acute kidney injury, continuous kidney replacement therapy, continuous renal replacement therapy, net ultrafiltration, fluid overload, fluid balance, de-resuscitation, hemodynamic instability

© 2026 Author(s). This article is licensed under the CC By 4.0 International License.

Fluid overload is common among critically ill patients with acute kidney injury (AKI), particularly those requiring continuous kidney replacement therapy (CKRT), and is consistently associated with adverse clinical outcomes. Net ultrafiltration (UFNET), defined as the extracorporeal removal of fluid from the patient to reduce extracellular volume, is therefore a fundamental component of CKRT. However, unlike solute clearance, UFNET has historically been prescribed without well-established dosing principles. Insufficient fluid removal may prolong exposure to pulmonary, systemic, and organ edema, whereas overly rapid fluid removal may exceed vascular refill, reduce effective circulating volume, provoke hemodynamic instability, and potentially impair organ perfusion and kidney recovery. Observational studies have suggested a J- or U-shaped relationship between UFNET rate and mortality, with intermediate rates potentially indicating a favorable outcome with lower mortality.

More recent evidence challenges the interpretation of these observational thresholds as causal treatment targets. A recent multicenter analysis using hourly CKRT and fluid-balance found that the association between UFNET and mortality was substantially mediated by achieved fluid balance. Furthermore, the RELIEVE-AKI feasibility randomized trial demonstrated that maintaining targeted restrictive and liberal UFNET was challenging, as clinicians repeatedly adjusted the prescribed regimen. These findings suggest that UFNET should not be conceptualized as a fixed dose analogous to small-solute clearance. Rather, UFNET is a dynamic intervention whose appropriate intensity depends on the competing objectives of relieving congestion and preserving circulatory and organ perfusion.

This review examines the terminology, physiology, observational and interventional evidence, challenges in causal inference, bedside assessment, clinical phenotypes, kidney recovery, and future research priorities related to UFNET during CKRT. We propose a conceptual framework in which fluid-removal need and fluid-removal tolerance could determine individualized UFNET prescription, with repeated reassessment based on achieved fluid balance and physiologic response.

RJCCN 2026; 2: 231-47
www.rjccn.org
DOI: 10.61882/rjccn.2.4.75

Please cite this article as: B. Kashani K, Murugan R. Net Ultrafiltration During Continuous Kidney Replacement Therapy for Acute Kidney Injury: From Fixed Rates to Precision Fluid Removal. RJCCN. 2026;2(4):231-47.

INTRODUCTION

Acute kidney injury is among the most frequent forms of organ dysfunction encountered in the ICU.[1,2] In the most severely ill patients, kidney replacement therapy is required to control metabolic abnormalities and volume status. CKRT is particularly useful in patients with hemodynamic instability because it enables continuous removal of solutes and fluids over prolonged periods.[3] Despite advances in CKRT technology and substantial investigation into modality, solute-clearance dose, anticoagulation, and timing of treatment initiation, mortality among patients with severe AKI requiring kidney replacement therapy remains high.[3] Tehranian and colleagues noted mortality of approximately 50% in this population, illustrating that optimization of conventional CKRT solute dosing alone has not resolved the substantial residual risk associated with critical illness and severe AKI.[4]

Fluid accumulation is particularly relevant to this risk.[5-7] Approximately two-thirds of critically ill patients with AKI requiring kidney replacement therapy develop clinically relevant fluid overload, as fluid accumulation is associated with mortality, impaired kidney recovery, prolonged mechanical ventilation, and other organ dysfunction. More recent literature has adopted the broader concept of fluid accumulation syndrome, commonly characterized by cumulative positive fluid balance exceeding approximately 5 to 10% of the admission body weight.[8] This syndrome has been highlighted as an important determinant of prolonged ventilation, ICU resource use, and mortality.[8-10]

Once diuretic therapy and fluid restriction are insufficient, extracorporeal fluid removal becomes an important therapeutic function of CKRT.[11-3] The objective, however, is not simply to remove as much fluid as technically possible. Inadequate removal may perpetuate interstitial and organ edema, whereas removal faster than the circulatory tolerance may reduce intravascular volume, compromise cardiac output, and impair tissue perfusion.[11,14] The UFNET prescription, therefore, represents a balance between two competing hazards.[11]

Despite its clinical importance, UFNET remains less standardized than almost every other component of CKRT prescription. A European survey of 485 practitioners across 31 countries demonstrated marked variation in practice. The median initial UFNET prescription in hemodynamically stable patients was 149 mL/h, the maximum prescription was 300 mL/h, and the typical rate in hemodynamically unstable patients was 98 mL/h, with substantial between-country variation.[15]

Over the past decade, UFNET has increasingly been viewed as a potentially modifiable CKRT exposure. Initial observational studies suggested that greater fluid removal could improve survival among markedly fluid-overloaded patients.[4,16] Subsequent analyses, however, associated high weight-normalized UFNET rates with increased mortality, prompting the hypothesis that both extremes might be harmful.[11,17,18] More recent analyses have further complicated this paradigm by suggesting that achieved fluid balance, not UFNET rate itself, may be the more clinically meaningful exposure.[9]

The objectives of this review are therefore to define UFNET terminology, examine the physiologic rationale for fluid removal and potential mechanisms of harm, critically evaluate the observational and interventional evidence, examine causal inference challenges, describe an individualized bedside approach, and identify priorities for future research. The central premise is that UFNET should be considered a dynamic, titratable treatment embedded within overall fluid management, rather than an isolated machine setting with a universally applicable target rate.[9,14,19]

TERMINOLOGY AND CONCEPTUAL FRAMEWORK

Ultrafiltration Versus Net Ultrafiltration

Terminological inconsistency has complicated the interpretation of the UFNET literature. "Ultrafiltration" may refer technically to water movement across the hemofilter membrane, total machine effluent, or clinically intended fluid removal from the patient. These quantities are not interchangeable.[11] For CKRT fluid-management research, net ultrafiltration (UFNET or NUF) is the most clinically relevant concept. The most common definition of UFNET is the "net extracellular

volume of fluid removed from the patient using an extracorporeal device with the intention of reducing fluid overload".[11,19] This definition focuses appropriately on the patient-level therapeutic exposure rather than total extracorporeal effluent.

In continuous venovenous hemodiafiltration, for example, net ultrafiltration can be expressed as total effluent volume minus dialysate and replacement fluid volumes. The RENAL-derived heterogeneity analysis used this formulation and subsequently calculated weight-normalized UFNET rate as cumulative UFNET volume divided by body weight and actual treatment duration.[17]

Machine Fluid Removal Versus Patient Fluid Balance

A crucial distinction exists between extracorporeal fluid removal and whole-patient net fluid balance. A patient receiving UFNET of 150 mL/h while simultaneously receiving 200 mL/h of intravenous medications, nutrition, blood products, and other fluids remains in positive fluid balance despite active ultrafiltration. Conversely, an identical UFNET rate in a patient receiving minimal fluid intake may result in a substantial negative balance.[9]

Thus, patient fluid balance is equivalent to all fluid inputs minus all fluid outputs, where outputs include urine, gastrointestinal losses, drains, blood loss, and extracorporeal net fluid removal. Identical UFNET rates can produce substantially different net fluid balances depending on concurrent fluid administration, and the apparent mortality association of UFNET is largely mediated through its effect on fluid balance.[9]

Prescribed Versus Delivered UFNET

Another important distinction is between the ultrafiltration rate clinicians intend to deliver and the rate actually delivered. Delivered UFNET may diverge from the prescription due to hemodynamic instability, circuit downtime or clotting, procedures and transport, interruptions for diagnostic testing, changes in fluid intake, clinician or nursing adjustments, rescue fluid administration, changes in urine output and deliberate physician override.[19,20] In the RELIEVE-AKI trial, substantial separation existed between intended treatment strategies, yet the delivered rates converged because liberal UFNET was frequently reduced, and restrictive UFNET was frequently required to escalate or rescue.[19,21]

Absolute Versus Weight-normalized UFNET

UFNET can be expressed as an absolute rate, usually mL/h, or normalized to body weight as mL/kg/h or mL/kg/d.[11] Absolute rates are intuitive at the bedside but yield markedly different physiologic exposures across patients of different sizes. Weight normalization potentially improves comparability, but the appropriate denominator is unresolved. Published studies have variously used admission weight, weight at CKRT initiation, enrollment weight, or predicted body weight.[4,16,17,19] Fluid accumulation itself alters measured body weight, making it possible that the denominator is partly determined by the exposure being treated.[16,17] For example, in the RENAL trial analyses, investigators used weight at enrollment. The investigators acknowledged that this weight could already have been affected by fluid overload, introducing uncertainty into the normalized exposure.[17] RELIEVE-AKI instead used predicted body weight within its automated dosing strategy.[19,22]

Cumulative Fluid Balance and Percentage Fluid Overload

Fluid accumulation is commonly quantified using cumulative balance or percentage fluid overload. Percentage fluid overload is roughly estimated as cumulative fluid balance divided by the reference body weight multiplied by 100. Thresholds of 5 and 10% have frequently been used to identify clinically important fluid accumulation.[5-7] Importantly, these cutoffs describe accumulated volume burden rather than the rate at which fluid is subsequently removed.

UFNET Intensity, Cumulative Removal, and Duration

The literature has sometimes used the term "UFNET intensity" to refer to a time-averaged rate.[16] These measures should be separated conceptually as: 1) UFNET rate: fluid removed per unit time, often mL/kg/h; 2) Cumulative UFNET: total extracorporeal volume removed; 3) UFNET

exposure duration: duration over which active removal occurs; 4) UFNET trajectory: how the rate changes over time; and 5) Achieved fluid balance: overall result after accounting for all inputs and outputs. Two patients can therefore have the same average UFNET rate but substantially different peak rates, cumulative removal, treatment duration, fluid inputs, and resulting fluid balance.[9,17]

Proposed Terminology

For clarity, the terminology for this review is outlined in Table 1. This terminology reinforces an essential distinction that UFNET is an intervention and fluid balance is an outcome of that intervention, combined with all other fluid inputs and outputs.[9]

WHY REMOVE FLUID DURING CKRT?

Fluid accumulation during critical illness results from both disease biology and treatment. Sepsis, systemic inflammation, surgery, shock, and ischemia increase endothelial permeability and promote the movement of fluid from the vascular to the interstitial compartment.[8] At the same time, patients commonly receive substantial quantities of resuscitation fluids, maintenance solutions, medication carriers, nutrition, and blood products. When AKI reduces urine output, the ability to excrete this volume is impaired.[10,13] Fluid accumulation is therefore not merely an increase in total body water. It represents the redistribution of sodium and water across vascular and interstitial compartments in a patient whose endothelial permeability, vascular tone, cardiac function, and renal function may all be abnormal.[8,14]

Pulmonary Consequences

Pulmonary interstitial and alveolar edema impair lung compliance and gas exchange, increase ventilatory requirements, and may prolong the need for mechanical ventilation.[23] Consistent with this biological rationale, fluid accumulation syndrome is associated with prolonged mechanical ventilation and longer ICU stays.[7,24]

Renal Congestion

The kidney is particularly vulnerable to venous congestion. Increased central and renal venous pressure raises renal interstitial pressure, potentially reducing the effective transrenal perfusion gradient.[23,25] Intra-abdominal hypertension may amplify this process. Tehranian and colleagues summarized evidence linking cumulative fluid balance, intra-abdominal hypertension, venous congestion, and AKI, suggesting that fluid accumulation can be both a consequence and a potential contributor to persistent renal dysfunction.[23,25]

Cardiac and Systemic Consequences

Interstitial edema may adversely influence myocardial function, hepatic congestion, gastrointestinal wall integrity and absorption, tissue oxygen diffusion, and wound healing.[13] Congestion is particularly important in cardiorenal syndrome, where elevated venous pressure, sodium retention, neurohormonal activation, and reduced cardiac performance form a reinforcing cycle.[23,25] The cardiorenal review in the uploaded literature describes systemic congestion and "nephrosarca" as clinically relevant manifestations of this interaction.

FLUID ACCUMULATION AS MARKER OF MEDIATOR

Fluid accumulation is also strongly confounded by illness severity. Patients with profound shock receive more fluid, develop more severe AKI, require more vasopressors, and are simultaneously more likely to die. A positive balance can therefore be a marker of disease severity.[10,26] Nevertheless, the consistency of associations between persistent

Table 1. Terminology

Concept	Definition
UFNET rate	delivered net extracorporeal fluid removal normalized to weight and time
UFNET volume	cumulative net extracorporeal fluid removal
Fluid balance	whole-patient inputs minus outputs
Fluid accumulation/fluid overload	accumulated positive balance relative to a reference body weight
UFNET prescription	intended rate or range
Delivered UFNET	fluid-removal exposure actually received

positive balance and adverse outcomes, the biologic mechanisms underlying organ edema and venous congestion, and the improvement associated with successful decongestion support the possibility that fluid accumulation is also a mediator of injury.[5,6,10]

This distinction has major implications for UFNET research. If fluid accumulation is purely a marker, increasing extracorporeal removal would not necessarily improve the outcome. If it is partly mediated, timely decongestion may represent an important modifiable treatment target.[9,16]

PHYSIOLOGY OF NET ULTRAFILTRATION

The physiologic effect of UFNET is determined not by extracorporeal removal alone but by the interaction between fluid removal and redistribution of fluid among extracellular compartments.[14]

Plasma Volume and Interstitial Fluid

UFNET directly removes plasma volume from the vascular compartment. Maintenance of effective circulating volume, therefore, depends on the movement of fluid from the interstitial space into the intravascular compartment, commonly referred to as plasma refill.[14] When vascular refill approximately matches extracorporeal removal, substantial total-body decongestion may occur without major circulatory compromise. When UFNET exceeds refill, intravascular volume falls.[11,14]

Plasma refill depends on hydrostatic and oncotic gradients, vascular permeability, venous pressures, interstitial fluid availability, cardiac function, and the underlying inflammatory state. In critical illness, these determinants may change over hours in the course of critical illness.[14] A patient with severe peripheral edema may appear to have abundant removable fluid but simultaneously have limited effective intravascular reserve. Conversely, patients with venous congestion and relatively preserved vascular refill may tolerate substantial removal. Patients with severe illness, vasopressor requirements, and ongoing capillary leak, refill may be too limited to compensate for high UFNET rates.[27]

Venous Capacitance, Preload, and Cardiac Output

The circulation contains both stressed and unstressed blood volume. A reduction in stressed volume can reduce mean systemic filling pressure and thus venous return. Whether this translates into lower cardiac output depends on ventricular function and preload responsiveness.[14] Consequently, the same absolute volume removal can produce very different hemodynamic consequences. A preload-independent patient with venous congestion may tolerate removal well. A preload-responsive patient with distributive shock may experience a fall in stroke volume.[14]

Neurohormonal and Microcirculatory Effects

Rapid intravascular volume contraction can stimulate sympathetic and neurohormonal responses and may impair microvascular perfusion despite apparently acceptable systemic blood pressure. Evidence from maintenance hemodialysis demonstrates an association between rapid ultrafiltration and myocardial hypoperfusion or stunning. This is while chronic hemodialysis differs substantially from CKRT-treated critical illness, these observations provide biologic plausibility for cardiovascular injury when fluid removal exceeds circulatory tolerance.[11,28-30]

The implication is fundamental, which is that UFNET cannot be interpreted as a dose with a uniform biological effect. A rate of 1.5 mL/kg/h may be well tolerated in one patient and excessive in another.[11,14]

FLUID TOLERANCE

Fluid management is often framed in terms of fluid responsiveness, meaning cardiac output increases after fluid administration. Fluid responsiveness, however, does not determine whether additional fluid is desirable.[14] A patient may be fluid responsive while simultaneously experiencing pulmonary or venous congestion. This distinction motivates the complementary concept of fluid tolerance. Fluid tolerance is the patient's ability to receive or retain additional fluid without clinically significant organ consequences.[14]

The corresponding concept during de-resuscitation is fluid-removal tolerance. This is the ability to remove fluid without compromising effective circulation, tissue perfusion, or organ function.[14] Fluid-removal tolerance depends on

the degree and distribution of congestion, vascular refill, cardiac reserve, vasoplegia, vasopressor dependence, capillary permeability, mechanical ventilation, right ventricular function, ongoing fluid inputs, and trajectory of kidney recovery.[14]

This framework helps reconcile seemingly contradictory observations. A patient may have a strong need for fluid removal because of pulmonary or systemic congestion, but poor tolerance because of severe vasoplegia or right ventricular preload dependence.[14] Thus, the clinically meaningful question is not the optimal UFNET rate, but it is about the rate and trajectory of fluid removal that will achieve the desired fluid-balance goal while remaining within each patient's current physiologic tolerance. This leads to the conceptual framework that fluid-removal need and fluid-removal tolerance could determine individualized UFNET prescription. Notably, both of these variables change over time.[9,14]

FLUID STEWARDSHIP, ROSE, AND TIMING OF UFNET

Fluid therapy in critical illness can be conceptualized using the ROSE framework, i.e., resuscitation, optimization, stabilization, and evacuation.[8] During resuscitation, the immediate priority is restoration of perfusion. Active net fluid removal may be inappropriate when uncontrolled shock and true intravascular depletion dominate.[8] During optimization, clinicians repeatedly assess whether additional fluid, vasopressors, inotropes, or other therapies can improve circulation while avoiding unnecessary accumulation.[8] During stabilization, ongoing fluid input should be minimized, and cumulative fluid balance should be reassessed. The presence of persistent oliguria or fluid accumulation may become increasingly important.[8] Finally, during evacuation or de-resuscitation, accumulated fluid becomes an active therapeutic target. Diuretics are generally preferred when effective, but CKRT-based UFNET becomes important when kidney failure, oliguria, diuretic resistance, or other CKRT indications coexist.[8,13]

The transition between these phases is rarely discrete. Fluid removal may begin while low-dose vasopressors are still required, particularly when pulmonary edema or severe venous congestion is itself contributing to organ dysfunction.[8,14] The European practice survey illustrates this variability. Persistent oliguria or anuria was the most frequently reported criterion for UF initiation, followed by pulmonary edema.[15]

Active fluid removal should generally be reconsidered when evidence emerges that UFNET is exceeding physiologic tolerance. However, hypotension alone should not automatically trigger complete cessation. CKRT-associated hypotension may arise from vasoplegia, impaired myocardial performance, or other processes unrelated to fluid removal.[14,15] The survey authors specifically cautioned that reducing or stopping UFNET may not always be appropriate in a persistently congested patient.[15] The endpoint of de-resuscitation is also dynamic. As congestion resolves, urine output returns, or effective circulating volume becomes increasingly limiting, the treatment objective should shift from negative balance toward neutrality and, eventually, CKRT liberation.[14]

PRESCRIBED AND DELIVERED UFNET DURING CKRT

UFNET prescription requires translation of a clinical fluid-balance goal into an extracorporeal fluid-removal rate. One simple approach is to define the desired 24-hour net balance and estimate expected inputs and non-CKRT outputs. The resulting extracorporeal requirement can then be distributed across treatment hours.[11,19] Yet this apparently straightforward calculation becomes complex because ICU fluid inputs and outputs change continuously.[9] Relevant inputs include maintenance and resuscitation fluids, vasopressor and sedative carriers, antibiotics, nutrition, blood products, and other medication infusions.[31] Outputs include urine, gastrointestinal losses, drains, blood loss, insensible loss, and UFNET.[9]

Daily fluid-balance goals provide clinical direction, but hourly titration allows adaptation to physiologic changes. Both levels are necessary.[9,12] An hourly rate without a daily goal risk treating the machine rather than the patient. Conversely, a daily goal without frequent reassessment risks continuing at an inappropriate rate.[9]

Real-world practice frequently diverges from prescription. In the European survey, only

about one-quarter of practitioners reported hourly monitoring of net fluid balance, and substantial discrepancies between prescribed and delivered balance were recognized.[12,15] Frequent UFNET assessment and management is unusual among ICU therapies because bedside nurses may need to make frequent adjustments while simultaneously managing numerous competing clinical demands.[20,22]

RELIEVE-AKI provides valuable implementation data. In a survey of 90 nurses, 59% believed weight-based UFNET reduced severe fluid overload, and 50% believed it reduced intradialytic hypotension; however, increased workload, time requirements, and reduced perceived flexibility were common concerns.[22] These observations emphasize that a theoretically optimal UFNET protocol will fail if it cannot be reliably implemented within the bedside workflow.[20,22]

RELIEVE-AKI used a web-based calculator incorporating predicted body weight, treatment assignment, and concurrent intravenous fluid infusion to generate an hourly UFNET range.[19,22] Automated decision support could eventually integrate fluid inputs, urine output, CKRT interruptions, vasopressor trajectory, blood pressure, congestion measures, current UFNET exposure, and cumulative fluid balance. However, nursing feedback emphasized that automation should augment rather than replace bedside clinical judgment.[22]

UFNET RATE AND OUTCOMES

The central challenge in the UFNET literature is that observational studies have produced apparently discordant associations. Chronologically, however, these studies describe an evolving understanding rather than necessarily contradictory biology. Murugan and colleagues studied 1,075 critically ill patients with at least 5% fluid overload before kidney replacement therapy. UFNET intensity was classified as ≤ 20, > 20 to 25, or > 25 mL/kg/d. One-year mortality was 69.7, 60.2, and 59.4%; respectively. After multivariable adjustment, UFNET > 25 mL/kg/d was associated with lower mortality than UFNET ≤ 20 mL/kg/d (adjusted odds ratio = 0.61; 95% CI: 0.41 to 0.93). Propensity-matched analyses produced similar findings.[16] The study therefore suggested that insufficient extracorporeal removal in substantially fluid-overloaded patients might be harmful. However, the authors appropriately questioned whether the capacity to tolerate higher UFNET represented a treatment effect or simply a marker of recovery.[16]

A separate retrospective Mayo Clinic cohort included 1,398 patients with AKI receiving CRRT. UFNET was classified as < 35 versus ≥ 35 mL/kg/d. Thirty-day mortality was 60% in the lower-intensity group and 48% in the higher-intensity group. After adjustment, ≥ 35 mL/kg/d was associated with lower 30-day mortality (adjusted OR = 0.47, 95% CI: 0.37 to 0.59).[4] Again, the data appeared to favor more aggressive net removal, but the retrospective design prevented the determination of causality.[4]

The above-drawn picture was updated by the secondary analysis of the RENAL trial.[11,17] Among 1,434 patients receiving continuous venovenous hemodiafiltration, Murugan and colleagues categorized UFNET as: 1) low < 1.01, 2) middle: 1.01 to 1.75, and high > 1.75 mL/kg/h. Median rates were 0.52, 1.38, and 2.21 mL/kg/h; respectively.[17] When adjusted for risk factors, including fluid balance, the high-rate group demonstrated lower survival than the low-rate group after the first week of treatment, with adjusted hazard ratios of 1.51 from days 7 to 12, 1.52 from days 13 to 26, and 1.66 from days 27 to 90.[17] Importantly, high UFNET was also associated with longer mechanical ventilation, ICU, and hospital stays.[17,27] Dialysis dependence at day 28 was 21.9% among survivors in the high-rate group, compared with 11.7 and 6.6% in the middle- and low-rate groups, although the difference was no longer significant at day 90.[17] These findings raised concern that excessive removal might impair organ recovery even while achieving a more negative fluid balance.[17]

Naorungroj and colleagues then focused specifically on the first 48 hours of CKRT, using actual hourly fluid data in a contemporary single-center cohort of 347 patients.[18] The same categories as post-hoc RENAL trial analysis were used, i.e., < 1.01, 1.01 to 1.75, and 1.75 mL/kg/h. In comparison of different UFNET rates during the earlier phases of CKRT, 1.75 mL/kg/h was associated with increased 28-day mortality across

multiple time periods, with adjusted hazard ratios rising from 1.27 (days 0 to 5) to 4.18 (days 27 to 28).[18] This analysis strengthened concerns about high UFNET because the investigators used directly recorded early-hour data rather than averaging exposure over the duration of treatment.[18] The putative effect on mortality was direct and not mediated by a causal pathway that included fluid balance, low blood pressure, vasopressor use, hypokalemia, or hypophosphatemia. However, the investigators themselves recognized the difficulty of time-varying confounding and competing mortality in UFNET studies.[32]

Serpa Neto and colleagues subsequently reanalyzed the RENAL data to determine whether the effect of UFNET differed across clinical phenotypes.[27,33] Two broad clusters emerged. The first contained patients with greater acute illness severity, more sepsis, edema, and vasopressor use. In these patients, high UFNET was particularly associated with harm, and an increase in the cardiovascular SOFA score amplified this relationship.[27,33] Consistent with this, in the primary RENAL secondary analysis, a UFNET > 1.75 mL/kg/h was associated with mortality among patients with cardiovascular SOFA scores of 3 or greater (adjusted HR = 1.89; 95% CI: 1.27 to 2.81).[17] The presence of edema complicated the picture. Among congested patients (cluster 1 and those with baseline edema), both high and low rates, relative to the middle rate, increased mortality risk, whereas the intermediate group consistently showed more favorable associations. This analysis provides one of the strongest arguments against a universal threshold: a rate associated with benefit in one phenotype may be poorly tolerated in another.

In summary, the earlier studies supported a biologically plausible nonlinear relationship that a low UFNET could lead to persistent fluid overload and organ edema, while an intermediate UFNET could result in effective decongestion with acceptable hemodynamic tolerance, and a high UFNET causes circulatory stress, hypoperfusion, and organ injury.[9,17,27] This is better conceptualized as a hypothesis than an established therapeutic curve. The boundaries of < 1.01 and > 1.75 mL/kg/h were largely data-derived categories rather than prospectively validated safety thresholds.[9,17]

Recently, Monai and colleagues provided a major challenge to a simple UFNET-rate paradigm.[9] The study included 973 critically ill adults and 6,914 CKRT treatment-days from two European ICUs. UFNET was classified as none, < 1.01, 1.01 to 1.75, or > 1.75 mL/kg/h, while the daily fluid-balance change was classified separately.[9] When the UFNET was modeled without accounting for fluid balance, it was associated with mortality. Once fluid balance was incorporated, however, the independent association with UFNET was substantially attenuated. Causal mediation analysis suggested that the apparent effect of higher UFNET was largely mediated by achieving a more negative balance. Positive fluid balance remained consistently associated with adverse outcomes.[9] This observation changes the interpretation of the prior literature. Therefore, the relevant therapeutic exposure may not be the amount of (mL/kg/h) fluid removed, but rather the fluid-balance trajectory and its related physiologic cost.[9] Table 2 summarizes the major studies in this field.

CAUSAL INFERENCE

The observational UFNET literature is exceptionally vulnerable to causal inference problems, including: 1) Confounding by indication: Clinicians do not assign UFNET randomly. A hemodynamically unstable patient may receive low or zero UFNET because clinicians believe the patient cannot tolerate removal. Such patients already have a high mortality risk. Therefore, even a low UFNET could be associated with death. This may actually represent the fact that in severe shock, fluid removal is challenging, and it is associated with high mortality rates. This phenomenon likely contributes to the high mortality observed among patients receiving no UFNET in the Monai cohort.[9] The authors specifically noted that a zero UFNET may identify patients with hemodynamic instability and persistent fluid overload who are clinically unable to tolerate removal.[9,34] Conversely, high UFNET may be prescribed because fluid accumulation is severe. Thus, a high UFNET could be associated with high mortality, which may partly reflect that severe fluid overload would require a higher UFNET and is associated with a higher risk of death;[9,16] 2) Tolerance bias:

Table 2. Summary of Major Studies

Study	Population	UFNET exposure	Principal finding	Key interpretation
Murugan 2018[16]	1,075 critically ill patients with ≥ 5% fluid overload receiving RRT	≤ 20, > 20 to 25, > 25 mL/kg/d	> 25 mL/kg/d associated with lower 1-year mortality	Low removal may prolong harmful fluid overload
Tehranian 2019[4]	1,398 AKI patients receiving CRRT	< 35 vs. ≥ 35 mL/kg/d	≥ 35 mL/kg/d associated with lower 30-day mortality	Higher cumulative removal associated with survival
Murugan 2019, RENAL[17]	1,434 patients receiving CVVHDF	< 1.01, 1.01 to 1.75, > 1.75 mL/kg/h	> 1.75 associated with lower 90-day survival	High rates may be harmful
Naorungroj 2021[18,32]	347 CRRT patients	first-48-h rate using the same categories	> 1.75 associated with greater 28-day mortality	Early high-rate exposure may matter
Serpa Neto 2021[33]	RENAL secondary phenotype analysis	same tertiles	Harm from extremes varied by severity, edema, and cardiovascular SOFA	The UFNET effect is heterogeneous
Monai 2026[9]	973 patients, 6,914 CRRT days	none, < 1.01, 1.01 to 1.75, > 1.75	UFNET was not independently associated after accounting for fluid balance	Achieved fluid balance may be more important than rate
RELIEVE-AKI 2026[19]	97 patients in 10 ICUs	restrictive 0.5 to 1.5 vs. liberal 2 to 5 mL/kg/h	Poor separation of delivered exposure	Dynamic physiology limits fixed-rate strategies

The ability to sustain high UFNET may itself be a prognostic marker. Patients recovering from shock can tolerate greater removal.[16] Therefore, an association between higher delivered UFNET and improved outcome does not prove that increasing UFNET caused the improvement. The 2018 study by Murugan *et al.*, using the University of Pittsburgh Medical Center ICU cohort, explicitly acknowledged this problem;[16] 3) Time-varying confounding: UFNET, vasopressors, fluid intake, urine output, cardiac function, and illness severity all change over time.[27,32,33] A patient may receive low UFNET during shock, higher UFNET after stabilization, and low UFNET again as euvolemia approaches. Averaging these rates over several days obscures the clinical trajectory. At the same time, prior UFNET affects subsequent fluid balance and hemodynamics, which themselves influence future UFNET prescription. Conventional regression cannot fully resolve this feedback loop;[9,27,33] 4) Survivor bias: Patients must survive long enough to accumulate substantial UFNET exposure. Conversely, early death truncates treatment exposure. Monai and colleagues therefore performed landmark analyses at 48 and 72 hours and showed that early UFNET remained a poor predictor of subsequent mortality after accounting for fluid balance, whereas positive early fluid balance remained associated with worse outcomes;[9] 5) Selection bias: Clinical trials and observational cohorts exclude different types of patients. RELIEVE-AKI, for example, excluded patients requiring emergent fluid removal for pulmonary edema because clinical equipoise between restrictive and liberal strategies did not exist.[19,21] Thus, trial populations may not represent patients in whom the clinical consequences of fluid removal are greatest; and finally 6) measurement error: Exposure classification depends on the weight denominator, actual treatment time, accurate documentation of replacement and dialysate fluids, machine data, interruptions, distinction between prescription and delivery, and concurrent fluid intake. These factors differ across studies.[17,19] The central implication is that observational categories should not be converted into therapeutic thresholds without randomized evidence.[14,17]

HARMS OF EXCESSIVELY RAPID UFNET

The principal concern with aggressive UFNET is that extracorporeal removal may exceed vascular refill (Figure 1).[14,34] The immediate consequence is contraction of the effective circulating volume. Depending on cardiovascular reserve, this may produce hypotension, increased vasopressor requirement, reduction in venous return, decreased stroke volume and cardiac output, arrhythmia, myocardial ischemia, tissue hypoperfusion, and organ dysfunction.[14,34]

Rapid fluid removal during maintenance hemodialysis has been associated with coronary hypoperfusion and myocardial stunning, providing a mechanistic precedent for cardiovascular injury

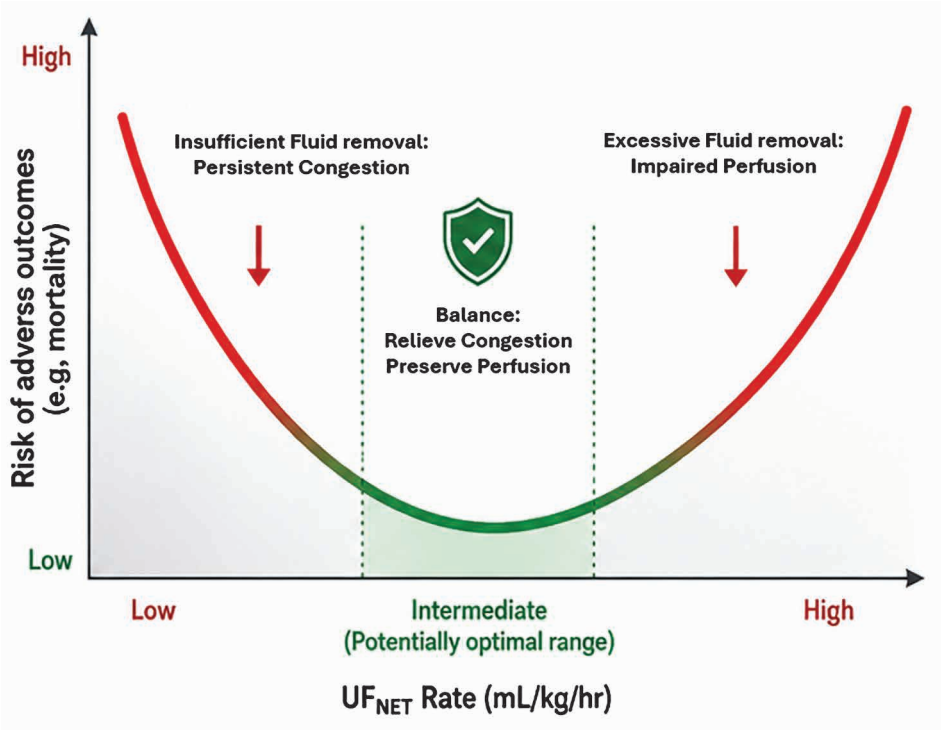


Figure 1.

from excessive ultrafiltration.[29,30,35] In critically ill patients, the vulnerability may be greater because vasoplegia, mechanical ventilation, myocardial dysfunction, and impaired vascular refill frequently coexist.[14,34] Renal recovery may also be vulnerable. High UFNET was associated with greater dialysis dependence on day 28 in the RENAL analysis, although the difference disappeared by day 90.[17] This association cannot establish direct ischemic renal injury, but it raises an important mechanistic concern.[17] Critically, a numerical rate does not become "excessive" solely because it crosses a universal threshold. Excess is better defined physiologically as fluid removal exceeding the patient's refill and circulatory tolerance.[14]

HARMS OF INADEQUATE UFNET

At the opposite extreme, insufficient fluid removal prolongs exposure to positive fluid balance (Figure 1).[9,16] Consequences may include persistent pulmonary edema, impaired oxygenation, prolonged mechanical ventilation, systemic tissue edema, venous congestion, renal interstitial congestion, delayed mobilization, impaired wound healing, and persistent organ dysfunction.[9]

The 2018 Murugan cohort provides the clearest observational signal supporting this concern that patients with fluid overload receiving ≤ 20 mL/kg/d had substantially higher mortality than those receiving > 25 mL/kg/d.[16] Importantly, low UFNET may also fail simply because ongoing fluid administration exceeds extracorporeal removal. Thus, the response to a persistent positive balance should not always be to increase UFNET; reducing unnecessary fluid intake may achieve the same balance objective with less circulatory stress.[9] This reinforces a broader principle that fluid stewardship requires management of both sides of the balance equation.[9]

HEMODYNAMIC INSTABILITY RELATED TO CKRT

Hemodynamic instability during CKRT is common but difficult to attribute specifically to UFNET.[34] The European survey defined new hemodynamic instability as new or worsening tachycardia, hypotension, or need to initiate or increase vasopressors. Practitioners estimated that it occurred in approximately 20% of patients. When instability developed, 70.1% reduced fluid removal

and 51.3% initiated or increased vasopressors. Not all hypotension during CKRT is caused by fluid removal. Potential contributors include progressive septic vasoplegia, myocardial dysfunction, arrhythmia, bleeding, sedation, positive-pressure ventilation, changes in temperature, extracorporeal circuit effects, and worsening underlying illness.[34]

Consequently, reflexively setting UFNET to zero may be inappropriate in a patient with severe pulmonary or systemic congestion.[34] The appropriate response requires determining whether removal is contributing to the reduction in effective circulation. Relevant questions include whether blood pressure fell shortly after increasing UFNET; whether vasopressor requirement changed; whether there is evidence of reduced stroke volume; whether passive leg raising suggests preload responsiveness; whether congestion is still substantial; whether lactate is increasing; whether urine output has changed; and whether another cause of shock is emerging.[14,34] A temporary reduction, rather than complete cessation, may maintain decongestion while improving tolerance.[34]

DETERMINING THE APPROPRIATE UFNET RATE AT THE BEDSIDE

Because no validated universal UFNET target exists, the prescription should begin with two parallel assessments, i.e., how urgently the patient needs fluid removal, and how much fluid removal the patient can currently tolerate (Figure 2).[14]

Assessing Fluid-removal Need

Assessment should integrate cumulative balance, percentage fluid overload, weight trajectory, pulmonary edema, peripheral edema, oxygenation, mechanical ventilation, intra-abdominal pressure when clinically relevant, central and systemic venous congestion, urine output, and ongoing fluid input.[14] Physical examination remains useful, but should not be considered definitive.[14]

Hemodynamics

Blood pressure alone is insufficient. Trends in mean arterial pressure, vasopressor and inotrope dose, heart rate, capillary refill, lactate, mental status, skin temperature, urine output, and other markers of tissue perfusion provide a more complete assessment.[14,34]

Echocardiography and Point-of-Care Ultrasound

Cardiac ultrasound may identify left ventricular systolic dysfunction, right ventricular failure, major preload dependence, pericardial pathology, and changes in filling patterns. Lung ultrasound can quantify pulmonary congestion using B-lines and pleural findings. Venous Doppler approaches, including the Venous Excess Ultrasound grading system (VexUS)-type assessment,[36] may help characterize systemic venous congestion.[14] The cardiorenal review specifically identifies lung and cardiac ultrasound, VExUS, natriuretic peptides, hemoconcentration markers, and related measures as potential tools for monitoring decongestion. Their role in specifically titrating CKRT UFNET, however, remains insufficiently validated.[14]

Initiation and Titration

A conservative strategy is to begin at a relatively low rate and progressively titrate according to congestion and tolerance rather than immediately pursuing a maximal negative balance.[14] RELIEVE-AKI used this principle operationally, when both study groups began at 0.5 mL/kg/h and increased in increments of 0.5 mL/kg/h as tolerated.[19,21] This should not be interpreted as validation of 0.5 mL/kg/h as a universal starting dose; rather, it illustrates a clinically adaptable titration strategy.[19,21]

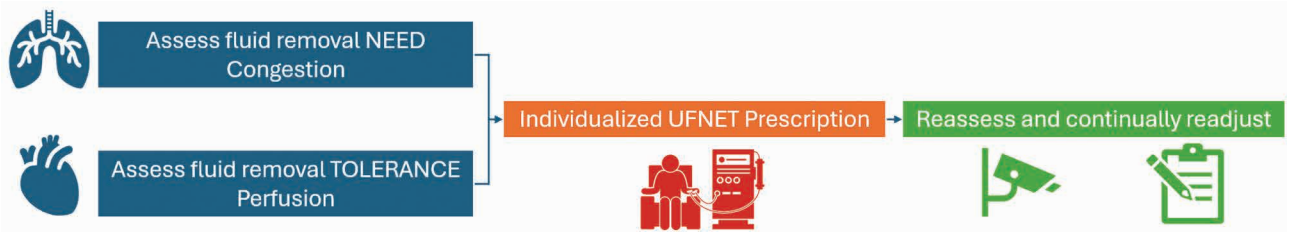


Figure 2.

To define the goal of fluid balance before ordering UFNET, a useful sequence is to define the desired fluid-balance trajectory, estimate fluid input and other outputs, prescribe UFNET, reassess actual balance and physiologic response, and then adjust.[9,14] This is preferable to selecting a rate first and observing where the patient ends up.

UFNET should be reassessed with new or worsening hypotension temporally related to removal, rapidly escalating vasopressors, evidence of reduced cardiac output, increasing lactate or impaired peripheral perfusion, new arrhythmia, evidence of myocardial ischemia, resolution of congestion, spontaneous diuresis, or signs suggesting intravascular depletion.[14,34] The goal should be the lowest rate sufficient to achieve the desired fluid-balance trajectory without exceeding physiologic tolerance, rather than maximal fluid removal.[14]

UFNET IN SPECIFIC CLINICAL PHENOTYPES

A phenotype-based framework is more defensible than a single numerical rate.[14] Among patients with septic/distributive shock, when a combination of capillary leak, vasodilation, and variable myocardial dysfunction is present, severe edema may coexist with limited effective circulating volume. High vasopressor requirements and ongoing capillary leak may reduce tolerance for rapid removal. The RENAL heterogeneity analysis raised particular concern about high UFNET among patients with greater illness severity and cardiovascular dysfunction.[27] Fluid removal may still be needed, but titration should be especially responsive to perfusion and vasopressor trajectory.[14,37] This is because among patients with cardiogenic shock and acute heart failure, venous congestion may derive substantial physiologic benefit from decongestion, particularly when elevated venous pressure contributes to renal dysfunction. However, severe biventricular failure may also make cardiac output highly preload dependent. Ultrasound and hemodynamic assessment are therefore particularly valuable.[14] For example, right ventricular failure is a paradigmatic example of why "volume overloaded" does not necessarily mean "tolerates rapid removal." Reduction in venous congestion may improve organ function, but excessive reduction in preload can reduce right ventricular output and consequently left ventricular filling.[14]

Among patients with acute respiratory distress syndrome (ARDS), persistent positive balance contributes to pulmonary edema and may prolong mechanical ventilation. Fluid removal is therefore an important objective once resuscitation is complete, but removal must remain compatible with systemic perfusion.[14,23]

During the postoperative time, rapidly changing fluid inputs, bleeding, vasoplegia, and ventricular dysfunction complicate prescription. The practical experience from RELIEVE-AKI demonstrated specific protocol challenges in cardiovascular surgical ICUs due to complex CKRT plans and procedures, as well as rapidly changing clinical requirements.[19,20] Patients with liver failure have a marked third spacing that can coexist with reduced effective circulating volume and profound vasodilation. Edema alone, therefore, cannot determine the appropriate UFNET rate.[14] During treatment with extracorporeal membrane oxygenation (ECMO), additional extracorporeal circuitry, an increased inflammatory burden, and complex volume targets make volume management very challenging. Evidence specifically defining UFNET rates for this phenotype remains limited in the uploaded source set.[14]

When patients are experiencing severe capillary leak, interstitial accumulation is accompanied by poor vascular refill and ongoing vasoplegia. Aggressive removal may cause hypotension before substantial tissue decongestion occurs.[14] This is while among parents with a recovery phenotype, as spontaneous urine output increases, the extracorporeal UFNET requirements should generally decrease. Failure to account for the recovery of kidney output can lead to an excessive net negative balance.[9]

UFNET AND KIDNEY RECOVERY

The relationship between decongestion and kidney recovery is bidirectional.[14,23] Persistent venous congestion can impair renal perfusion gradients and contribute to interstitial edema. Therefore, relieving congestion may improve renal function. Conversely, excessive intravascular contraction may reduce renal blood flow and

potentially delay recovery.[14,23,34] Observational evidence reflects both possibilities. Fluid overload has been associated with reduced kidney recovery; therefore, patients with > 10% fluid accumulation were less likely to recover renal function.[5,7] In the RENAL UFNET analysis, high rates were associated with greater dialysis dependence among survivors at day 28,[17] and, in a separate analysis after accounting for the competing risk of death, high UFnet was independently associated with longer time to renal recovery.[38] RELIEVE-AKI similarly showed no significant difference in dependence on kidney replacement therapy at discharge, but the study was designed for feasibility and was not powered to assess clinical outcomes.[17]

During kidney recovery, clinicians should incorporate spontaneous urine output into the total fluid-removal equation. A CKRT setting that was appropriate during anuria may rapidly become excessive once native diuresis begins.[9] Kidney recovery should trigger active reevaluation of UFNET rather than continuation of an established machine rate.

PRECISION AND DYNAMIC UFNET

The concept of a single optimal UFNET rate is increasingly difficult to reconcile with available evidence.[9,14,19] The traditional model treats UFNET as a static exposure, in which a specific rate can be delivered consistently. A precision model instead treats it as a continuously updated intervention. In this model, frequent assessment is needed to provide an appropriate prescription. This also needs to be followed by observing responses and updating the prescription continuously.[14]

The relevant variables to be monitored include congestion phenotype, hemodynamic phenotype, cumulative fluid burden, rate of ongoing fluid input, vasopressor trajectory, kidney function and urine output, mechanical ventilation, cardiac function, plasma refill capacity, and prior response to fluid removal.

Future research should move beyond the mean rate. Potentially important features include starting rate, rate of escalation, peak rate, duration at high rates, cumulative dose, variability, time spent with no UFNET, time spent outside a target range, and the relation between rate and concurrent fluid balance.[9] Monai and colleagues examined upper-quartile exposure, early exposure, and first-48-hour measures, illustrating how different rate summaries can capture different treatment dimensions.[9]

Automated systems could continuously integrate EHR and CKRT machine data, estimate projected fluid balance, and suggest adjustments. The practical literature from RELIEVE-AKI proposes automation and even AI-assisted approaches to reduce the burden of manual calculations and nursing documentation.[20] Any such system should support, not replace, clinician assessment because the most important variables, including bleeding, changing shock states, procedures, and emerging organ dysfunction, cannot be reduced reliably to a single rate calculation.[20]

CLINICAL TRIALS AND INTERVENTIONAL EVIDENCE

For many years, almost all UFNET evidence was observational. The RELIEVE-AKI trial represents an important transition toward prospective testing.[19] This trial was a stepped-wedge cluster-randomized feasibility study conducted in 10 ICUs across two US healthcare systems, assigning patients to restrictive UFNET (0.5 to 1.5 mL/kg/h) or liberal UFNET (2.0 to 5.0 mL/kg/h).[19,21] Ninety-seven patients (55 liberal, 42 restrictive) were enrolled. Despite substantial intended separation in UFNET dosage, mean delivered rates were 2.05 versus 1.81 mL/kg/h and did not differ significantly in the primary analysis. Meanwhile, the investigators reported that the rescue UFNET was substantially more frequent in the restrictive group (66.7 vs. 14.5%).[21]

The result is important not because it attempted to establish an optimal rate, but because it demonstrates that fixed UFNET strategies are difficult to sustain amid changing physiology. The UFNET in liberal arm was frequently reduced due to hemodynamic instability or physician override, whereas restrictive patients frequently required rescue removal.[19,21] Clinical outcomes, including mechanical ventilation duration, ICU stay, hospital mortality, dependence on kidney replacement therapy, intradialytic hypotension, and arrhythmia, did not differ significantly, but the trial was not powered to assess these endpoints.

A definitive UFNET trial faces several challenges, including: 1) treatment contamination as clinicians alter rates for safety; 2) poor exposure separation as patient physiology drives convergence; 3) dynamic fluid inputs, so the same UFNET does not produce the same balance; 4) changing disease state, so an appropriate rate today may be inappropriate tomorrow; 5) marked heterogeneity in congestion and tolerance; 6) nursing burden from frequent calculations and titration; and 7) outcome selection, since mortality may be too distal to fluid-management biology.[19-21] The investigators' experience suggests that future interventions should be adaptive rather than rigid.[20]

A recent proof-of-concept trial has already shown that a hemodynamically guided UFNET strategy can safely achieve markedly more negative fluid balance than usual care in patients receiving vasopressors, supporting the feasibility of physiology-driven titration.[37] In future trials, candidate endpoints could include fluid-balance trajectory, organ failure-free days, ventilator-free days, duration of vasopressor support, kidney recovery, CKRT-free days, MAKE, ICU length of stay, and patient-centered functional outcomes.[14,21]

PRACTICAL APPROACH TO UFNET PRESCRIPTION

A practical bedside strategy can be organized around a repeated decision cycle, to include assessing congestion and tolerance, defining fluid-balance goal, initiating UFNET, reassessing response, continued titration, and transition toward euvolemic status and recovery.[9,14] In this regard, the following phenotypes (Table 3) could be recognized: 1) Phenotype 1: congested and hemodynamically stable (pulmonary / systemic edema, stable or decreasing vasopressor requirements, adequate perfusion, no strong evidence of preload dependence). Active fluid removal is appropriate; initiate or continue UFNET and titrate toward the desired negative balance while monitoring tolerance;[14] 2) Phenotype 2: congested and hemodynamically unstable (congestion remains important while vasopressors are required). Do not assume UFNET must be zero; determine whether hypotension is driven by fluid removal or the underlying shock state, and consider slower removal, treatment of the underlying circulatory disorder, and frequent reassessment;[34,37] 3) Phenotype 3: uncertain congestion (physical findings and cumulative balance conflict). Avoid aggressive empiric removal; use multimodal assessment, including fluid history, ultrasound when available, oxygenation, venous congestion, hemodynamic response, and fluid-balance trajectory;[14] 4) Phenotype 4: approaching euvolemia (congestion improved, rationale for persistent negative balance weakening). Reduce UFNET toward a neutral balance and avoid overshooting the decongestion target;[9,14] and 5) phenotype 5: suspected intravascular depletion (worsening perfusion temporally associated with removal, escalating vasopressors, preload responsiveness, or spontaneous large-volume diuresis). Reduce or discontinue UFNET and reassess the overall fluid strategy.[14,34] These categories intentionally indicate direction, not a universal numerical dose.[14]

KNOWLEDGE GAPS AND RESEARCH PRIORITIES

Several fundamental questions remain unresolved:[14] 1) There is no standardized definition of UFNET. Studies should clearly report machine-derived net extracorporeal removal and distinguish it from whole-patient fluid balance;[9] 2) Optimal exposure metrics are uncertain. The biologically relevant exposure may be hourly UFNET, time-weighted mean, peak rate, cumulative volume, duration above a threshold, trajectory, rate of escalation, or the interaction between UFNET and

Table 3. Volume Status Phenotypes

Clinical state	Fluid-removal need	Fluid-removal tolerance	General UFNET direction
Congested, stable[14]	High	High	Increase or maintain
Congested, unstable[14,34,37]	High	Low / uncertain	Individualize; slower titration, frequent reassessment
Congestion uncertain[14]	Uncertain	Variable	Avoid aggressive escalation until clarified
Near euvolemia9,[14]	Low	Maybe adequate	De-escalate toward neutral
Intravascular depletion[14,34]	Low	Low	Reduce or stop

achieved fluid balance, possibilities that require prospective evaluation.[9] These possibilities require prospective evaluation; 3) Appropriate weight denominator is unclear. Admission weight, pre-illness weight, CKRT-start weight, and predicted body weight produce different normalized rates. Fluid accumulation can distort the measured weight;[17] 4) Integration of fluid balance in UFNET prescription is infrequently done. Future studies should not examine UFNET without measuring concurrent fluid input and achieved balance. The Monai analysis demonstrates why doing so can fundamentally alter interpretation;[9] 5) Definition of UFNET-related organ injury needs to be established. The potential intermediate endpoints should include cardiac injury, cerebral perfusion, hepatic and splanchnic perfusion, microcirculatory dysfunction, kidney recovery, and vasopressor requirement;[14] 6) We need to develop and validate biomarkers of removal tolerance. No validated biomarker or physiologic test currently defines the maximum safe rate of fluid removal in critically ill patients; 7) Ultrasound-guided decongestion needs to be further studied and implemented in clinical practice. Lung ultrasound, echocardiography, and "venous Doppler / VE x US" are biologically attractive tools, but prospective trials must establish whether ultrasound-guided UFNET improves outcomes rather than merely improving measurement; 8) Phenotype-specific strategies need to be validated and implemented. Septic shock, right ventricular failure, cardiorenal syndrome, ARDS, postoperative vasoplegia, liver failure, and severe capillary leak almost certainly differ in both need and tolerance; 9) The safety and effectiveness of UFNET during vasopressor therapy should be tested. Vasopressor use is frequently treated as synonymous with inability to remove fluid, yet congested patients may benefit from continued decongestion despite low-dose support. Prospective studies are needed to determine the appropriate interaction between the vasopressor trajectory and UFNET; 10) Kidney recovery should be considered an important clinical outcome of safe UFNET prescription. Trials should incorporate the duration of kidney replacement therapy, CKRT-free days, dialysis dependence, and MAKE, rather than mortality alone;[17] 11) Dynamic adaptive trials to accommodate the dynamic nature of patients should be conducted. RELIEVE-AKI suggests that rigid target separation may be unrealistic. Future trials should test algorithms that permit physiologically defined adaptations rather than fixed rates; and 12) Automated, AI-enabled fluid management needs further development and validation. Continuous integration of machine, EHR, ultrasound, and hemodynamic data could permit personalized decision support. However, algorithms must be interpretable, clinically validated, and designed around workflow rather than adding documentation burden.

CONCLUSIONS

Net ultrafiltration is one of the most consequential yet least standardized components of CKRT for severe AKI. Fluid accumulation is associated with mortality, prolonged ventilation, organ edema, and impaired kidney recovery, providing a strong rationale for active decongestion when spontaneous or diuretic-mediated fluid removal is inadequate. At the same time, extracorporeal removal can reduce effective circulating volume when UFNET exceeds vascular refill and cardiovascular tolerance. Observational studies have produced conflicting results. The controversies arise from nonrandomized exposures that are strongly influenced by illness severity, clinician selection, fluid burden, treatment duration, and hemodynamic tolerance.

RELIEVE-AKI demonstrated that maintaining fixed restrictive and liberal UFNET strategies was challenging because changing patient physiology repeatedly compelled clinicians to deviate from protocolized targets. Therefore, there is a need to transition to a dynamic, tightly regulated model for fluid removal during CKRT. The clinical objective should not be to identify and universally apply a single "optimal UFNET rate." Instead, UFNET should be viewed as a dynamic therapeutic lever used to achieve an individualized fluid-balance goal. The prescription should then be continuously revised according to congestion, fluid input, hemodynamics, organ perfusion, urine output, kidney recovery, and the achieved fluid-balance trajectory.

Accordingly, the future of UFNET research should move from static rate thresholds toward precision decongestion by identifying which patients require

fluid removal, determining how rapidly they can safely tolerate it, defining measurable physiologic responses, and developing adaptive strategies that can change as rapidly as the critically ill patients in whom they are applied.

DISCLOSURE

R.M. received research funding from the National Institute of Diabetes and Digestive and Kidney Diseases, Novartis Inc., Spectral Medical Inc., Vantive Healthcare Inc., and consulting fees from Vantive Healthcare Inc., Fresenius Medical Care Inc., unrelated to this study.

REFERENCES

1. Cerda J, Kashani K, Ostermann M, Basu RK, Bell S, Cantaluppi V, et al. The global epidemiology of acute kidney injury: challenges and opportunities. Nat Rev Nephrol. 2026;22(3):179-98.
2. Kashani K, Shao M, Li G, Williams AW, Rule AD, Kremers WK, et al. No increase in the incidence of acute kidney injury in a population-based annual temporal trends epidemiology study. Kidney Int. 2017;92(3):721-8.
3. Gaudry S, Palevsky PM, Dreyfuss D. Extracorporeal kidney-replacement therapy for acute kidney injury. N Engl J Med. 2022;386(10):964-75.
4. Tehranian S, Shawwa K, Kashani KB. Net ultrafiltration rate and its impact on mortality in patients with acute kidney injury receiving continuous renal replacement therapy. Clin Kidney J. 2021;14(2):564-9.
5. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, et al. Program to Improve Care in Acute Renal Disease (PICARD) Study Group. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int. 2009;76(4):422-7.
6. Messmer AS, Zingg C, Müller M, Gerber JL, Schefold JC, Pfortmueller CA. Fluid overload and mortality in adult critical care patients—a systematic review and meta-analysis of observational studies. Crit Care Med. 2020;48(12):1862-70.
7. Woodward CW, Lambert J, Ortiz-Soriano V, Li Y, Ruiz-Conejo M, Bissell BD, et al. Fluid overload associates with major adverse kidney events in critically ill patients with acute kidney injury requiring continuous renal replacement therapy. Crit Care Med. 2019;47(9):e753-e60.
8. Pfortmueller CA, Dabrowski W, Wise R, van Regenmortel N, Malbrain MLNG. Fluid accumulation syndrome in sepsis and septic shock: pathophysiology, relevance and treatment—a comprehensive review. Ann Intensive Care. 2024;14(1):115.
9. Monai NC, Pfortmueller CA, Schefold JC, Cioccari L, Faltys M. Net ultrafiltration rate and mortality in critically ill patients: a multicenter cohort study with analysis of fluid balance changes. Crit Care Med. 2026.
10. Garzotto F, Ostermann M, Martín-Langerwerf D, Sánchez-Sánchez M, Teng J, Robert R, et al. The Dose Response Multicentre Investigation on Fluid Assessment (DoReMIFA) in critically ill patients. Crit Care. 2016;20(1):196.
11. Murugan R, Bellomo R, Palevsky PM, Kellum JA. Ultrafiltration in critically ill patients treated with kidney replacement therapy. Nat Rev Nephrol. 2021;17(4):262-76.
12. Murugan R, Ostermann M, Peng Z, Kitamura K, Fujitani S, Romagnoli S, et al. Net ultrafiltration prescription and practice among critically ill patients receiving renal replacement therapy: a multinational survey of critical care practitioners. Crit Care Med. 2020;48(2):e87-e97.
13. Claure-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. BMC Nephrol. 2016;17(1):109.
14. Melo P, Ramírez-Guerrero G, Castro R, Wong A, Argaiz ER, Ostermann M, et al. Ultrafiltration in the critically ill patient: a framework for personalized care. Crit Care. 2026;30(1):87.
15. Lumlertgul N, Murugan R, Seylanova N, McCready P, Ostermann M. Net ultrafiltration prescription survey in Europe. BMC Nephrol. 2020;21(1):522.
16. Murugan R, Balakumar V, Kerti SJ, Priyanka P, Chang CCH, Clermont G, et al. Net ultrafiltration intensity and mortality in critically ill patients with fluid overload. Crit Care. 2018;22(1):223.
17. Murugan R, Kerti SJ, Chang CH, Gallagher M, Clermont G, Palevsky PM, et al. Association of net ultrafiltration rate with mortality among critically ill adults with acute kidney injury receiving continuous venovenous hemodiafiltration: a secondary analysis of the Randomized Evaluation of Normal vs Augmented Level (RENAL) of Renal Replacement Therapy Trial. JAMA Netw Open. 2019;2(6):e195418.
18. Naorungroj T, Serpa Neto A, Zwakman-Hessels L, Yanase F, Eastwood G, Murugan R, et al. Early net ultrafiltration rate and mortality in critically ill patients receiving continuous renal replacement therapy. Nephrol Dial Transplant. 2021;36(6):1112-9.
19. Murugan R, Talisa V, Chang CCH, Nikravangolsefid N, Singh W, Butcher BW, et al. Alternative net ultrafiltration rate strategies in acute kidney injury: a feasibility randomized clinical trial. Crit Care. 2026;30(1):228.
20. Nikravangolsefid N, Suppadungsuk S, Singh W, Palevsky PM, Murugan R, Kashani KB. Behind the scenes: Key lessons learned from the RELIEVE-AKI clinical trial. J Crit Care. 2024;83:154845.
21. Murugan R, Chang CH, Raza M, Nikravangolsefid N, Huang DT, Palevsky PM, et al. Restrictive versus Liberal Rate of Extracorporeal Volume Removal Evaluation in Acute Kidney Injury (RELIEVE-AKI): a pilot clinical trial protocol. BMJ Open. 2023;13(7):e075960.
22. Singh W, Nikravangolsefid N, Palevsky PM, Kashani KB, Murugan R. Feasibility and acceptability of weight-based net fluid removal during continuous kidney replacement therapy: a nursing survey. Appl Nurs Res. 2026;88:152066.
23. Legrand M, Rossignol P. Cardiovascular consequences of acute kidney injury. N Engl J Med. 2020;382(23):2238-47.

24. Hayashi Y, Shimazui T, Tomita K, Shimada T, Miura RE, Nakada TA. Associations between fluid overload and outcomes in critically ill patients with acute kidney injury: a retrospective observational study. Sci Rep. 2023;13(1):17410.

25. Rangaswami J, Bhalla V, Blair JEA, Chang TI, Costa S, Lentine KL, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. Circulation. 2019;139(16):e840-e78.

26. Balakumar V, Murugan R, Sileanu FE, Palevsky P, Clermont G, Kellum JA. Both positive and negative fluid balance may be associated with reduced long-term survival in the critically ill. Crit Care Med. 2017;45(8):e749-e57.

27. Prowle J, Mehta R. Fluid balance management during continuous renal replacement therapy. Semin Dial. 2021;34(6):440-8.

28. National Kidney Foundation. KDOQI Clinical Practice Guideline for Hemodialysis Adequacy: 2015 update. Am J Kidney Dis. 2015;66(5):884-930.

29. Ahmadmehrabi S, Tang WHW. Hemodialysis-induced cardiovascular disease. Semin Dial. 2018;31(3):258-67.

30. Chao CT, Huang JW, Yen CJ. Intradialytic hypotension and cardiac remodeling: a vicious cycle. Biomed Res Int. 2015;2015:724147.

31. Van Regenmortel N, Verbrugghe W, Roelant E, Van den Wyngaert T, Jorens PG. Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population. Intensive Care Med. 2018;44(4):409-17.

32. Naorungroj T, Neto AS, Zwakman-Hessels L, Yanase F, Eastwood G, Murugan R, et al. Mediators of the impact of hourly net ultrafiltration rate on mortality in critically ill patients receiving continuous renal replacement therapy. Crit Care Med. 2020;48(10):e934-e42.

33. Serpa Neto A, Naorungroj T, Murugan R, Kellum JA, Gallagher M, Bellomo R. Heterogeneity of effect of net ultrafiltration rate among critically ill adults receiving continuous renal replacement therapy. Blood Purif. 2021;50(3):336-46.

34. Douvris A, Zeid K, Hiremath S, Bagshaw SM, Wald R, Beaubien-Souligny W, et al. Mechanisms for hemodynamic instability related to renal replacement therapy: a narrative review. Intensive Care Med. 2019;45(10):1333-46.

35. Lai AC, Bienstock SW, Sharma R, Skorecki K, Beerkens F, Samtani R, et al. A personalized approach to chronic kidney disease and cardiovascular disease: JACC review topic of the week. J Am Coll Cardiol. 2021;77(11):1470-9.

36. Beaubien-Souligny W, Rola P, Haycock K, Bouchard J, Lamarche Y, Spiegel R, et al. Quantifying systemic congestion with Point-Of-Care ultrasound: development of the venous excess ultrasound grading system. Ultrasound J. 2020;12(1):16.

37. Bitker L, Dupuis C, Pradat P, Deniel G, Klouche K, Mezidi M, et al. Fluid balance neutralization secured by hemodynamic monitoring versus protocolized standard of care in patients with acute circulatory failure requiring continuous renal replacement therapy: results of the GO NEUTRAL randomized controlled trial. Intensive Care Med. 2024;50(12):2061-72.

38. Murugan R, Kerti SJ, Chang CH, Gallagher M, Neto AS, Clermont G, et al. Association between net ultrafiltration rate and renal recovery among critically ill adults with acute kidney injury receiving continuous renal replacement therapy: an observational cohort study. Blood Purif. 2022;51(5):397-409.

Correspondence to:
Kianoush B Kashani, MD, MS
Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA
ORCID ID: 0000-0003-2184-3683
Phone: 001 507 266 7960
Fax: 001 507 266 7891
E-mail: kashani.kianoush@mayo.edu

Received August 2026
Revised August 2026
Accepted September 2026

RJCCN Review
KIDNEY DISEASE

Multi-Omics Integration for Enhanced Insights into Chronic Kidney Disease: Unraveling Biological Networks and Therapeutic Targets, A Mini Review

Tina Kianfar,[1] Atrin Zakikhani,[2] Soroush Taherkhani[1,3]

[1]Department of Physiology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[2]School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[3]Student Research Committee, Iran University of Medical Sciences, Tehran, Iran

Keywords. chronic kidney disease, multi-omics, transcriptomics, precision medicine, genomics, metabolomics, proteomics, epigenomics

© 2026 Author(s). This article is licensed under the CC By 4.0 International License.

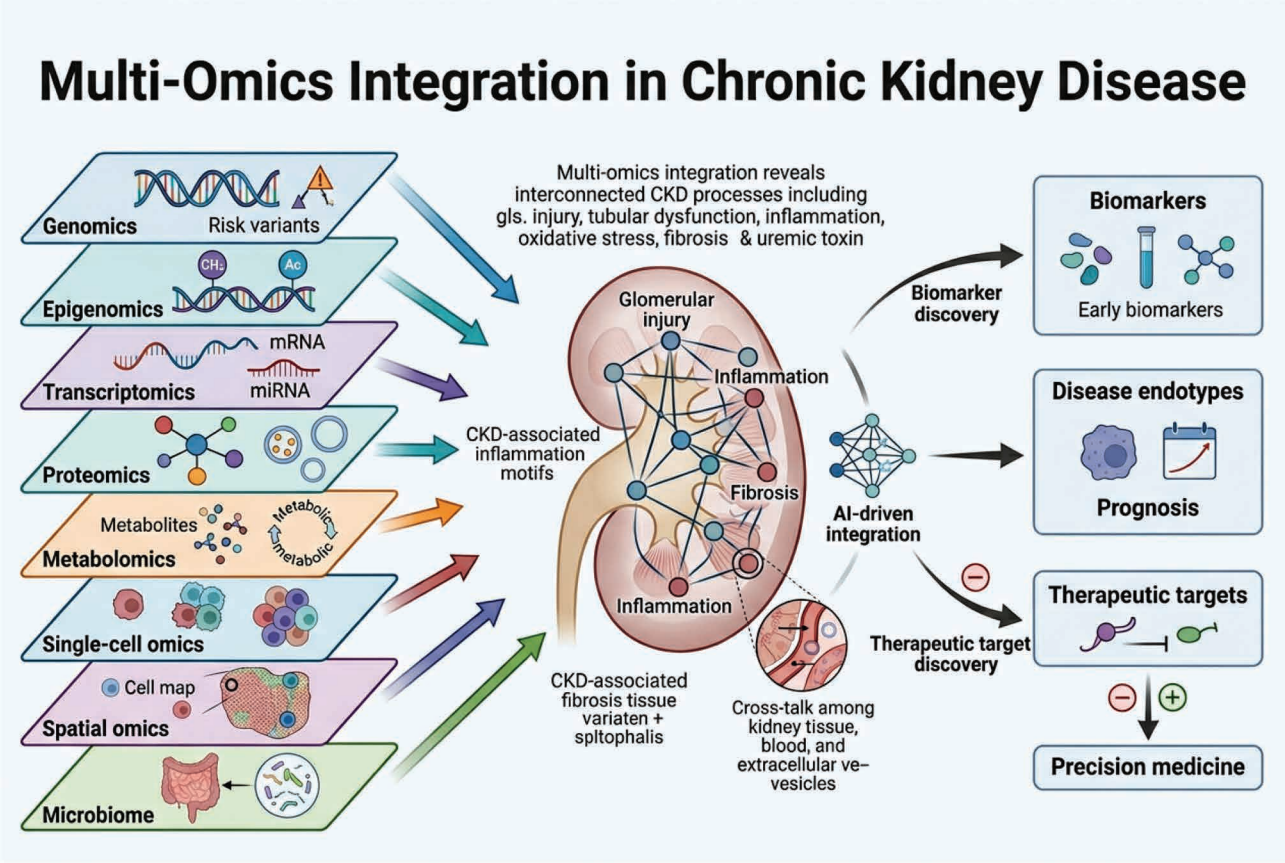
Chronic Kidney Disease (CKD) is a major worldwide health concern associated with a gradual decline in kidney function, cardiovascular complications, and considerable variability in clinical progression among affected individuals. Although estimated glomerular filtration rate (eGFR) and albuminuria remain central to the clinical assessment of CKD, these conventional measures provide only a limited representation of the complex molecular processes underlying the disease. In this mini review, we explore the potential integrated multi-omics approaches to improve the understanding and clinical management of CKD. Combining information from genomics, epigenetics, transcriptomics, proteomics, and metabolomics analyses can provide a more comprehensive picture of the biological mechanisms involved in disease development and progression. By providing a high-resolution, systems-level view of renal pathophysiology, multi-omics enables the discovery of novel early biomarkers, reveals distinct molecular endotypes within the CKD spectrum. We synthesize current evidence supporting the application of multi-omics in CKD, from risk prediction and early detection to precise subtyping and the guidance of personalized therapeutic strategies. We further discuss the computational and translational challenges, including data integration, validation, clinical implementation, and ethical considerations, that must be addressed to realize the promise of precision nephrology. The integration of multi-omics data into clinical workflows stands to revolutionize CKD care, shifting it from reactive management to proactive, personalized medicine. Finally, this review posits that the future of CKD therapeutics lies in targeting hubs within these identified networks, rather than single molecules, and provides a forward-looking roadmap for translating integrated network insights into clinically actionable biomarkers and rationally designed combination therapies.

RJCCN 2026; 2: 248-54
www.rjccn.org
DOI: 10.61882/rjccn.2.4.55

INTRODUCTION

With a global burden exceeding 850 million cases, chronic kidney disease (CKD) represents a substantial contributor to illness, premature mortality, and the growing costs of healthcare.[1] Defined by abnormalities in structure or function

Please cite this article as: Kianfar T, Zakikhani A, Taherkhani S. Multi-Omics Integration for Enhanced Insights into Chronic Kidney Disease: Unraveling Biological Networks and Therapeutic Targets, A Mini Review. RJCCN. 2026;2(4):248-54.



Graphical Abstract. Integrated multiomics layers, genomics, transcriptomics, epigenomics, metabolomics, proteomics, singlecell and spatial profiling, and microbiome, are fused by AIdriven analytics to reconstruct CKD biological networks (glomerular injury, inflammation, fibrosis). Extracellularvesicle crosstalk links kidney and circulation. The pipeline enables early biomarker discovery, disease endotyping/prognosis, and therapeutic target nomination toward precision nephrology.

of kidney persisting for more than three months, CKD encompasses a vast etiological spectrum, from diabetes and hypertension to glomerulonephritides and rare genetic disorders. Current clinical paradigms are heavily reliant on functional (eGFR) and structural (albuminuria) parameters. While useful, these markers are often late indicators of damage, exhibit poor correlation with underlying molecular mechanisms, and fail to predict disease progression or treatment response accurately.[2] Consequently, patients are diagnosed late, stratified crudely, and managed with broadly applied guidelines, leading to suboptimal outcomes.

The emergence of high-throughput "omics" technologies offers an unprecedented opportunity to deconstruct CKD's biological complexity. Genomics identifies hereditary predispositions; transcriptomics reveal changes in gene expression over time; proteomic analysis profiles protein levels and post-translational changes; metabolomics characterize downstream metabolic phenotypes; and epigenomics maps regulatory alterations that affect gene expression. Individually, each omics layer provides valuable but fragmented insights. However, their integrative analysis, multi-omics, facilitates the construction of comprehensive molecular networks that underlie disease pathogenesis.[3]

This mini-review argues for integrative multi-omics profiling as the cornerstone of a new CKD paradigm. We detail its application in: 1) Early Diagnosis: Identifying sensitive biomarkers long before eGFR decline; 2) Molecular Stratification: Moving beyond etiology to define disease endotypes based on shared biological pathways; and 3) Personalized Management: Informing targeted therapies, monitoring treatment response, and predicting complications. Finally, we outline the roadmap and hurdles for translating this research vision into clinical practice.

THE MULTI-OMICS TOOLKIT: APPLICATIONS IN CKD PATHOBIOLOGY

Genomics and Epigenomics: Unraveling Predisposition and Regulation

Genome-wide association studies (GWAS) analyses have uncovered numerous genetic variants linked to both CKD susceptibility and variation in eGFR (Figure 1), implicating pathways in podocyte function, renal development, and metabolism.[4] For example, variants in APOL1 confer high risk for CKD in individuals of African ancestry, illustrating a genetic basis for health disparities.[5] Beyond common variants, whole-exome sequencing uncovers rare, penetrant mutations in diseases like atypical hemolytic uremic syndrome, directly guiding therapy with eculizumab. Epigenomics, including DNA methylation, histone modification, and non-coding RNA expression (e.g., miRNAs), mediates the interaction between genes and environment. Hypermethylation of RASAL1, a suppressor of renal fibrosis, has been linked to sustained fibrotic responses in CKD.[6] Circulating miRNAs (e.g., miR-21, miR-29) show promise as stable biomarkers reflecting renal fibrosis and inflammation.[7]

Transcriptomics and Proteomics: Capturing Active Disease States

Single-cell and bulk RNA-sequencing of kidney biopsies have revolutionized our understanding of intra-renal cellular heterogeneity and disease-specific gene signatures (Table 1). In diabetic kidney disease (DKD), transcriptomics has identified activation of inflammatory (NF-κB) and fibrotic (TGF-β) pathways, and revealed distinct prognostic signatures beyond histology.[8] Proteomics, particularly using mass spectrometry, analyzes the functional effector molecules. Urinary

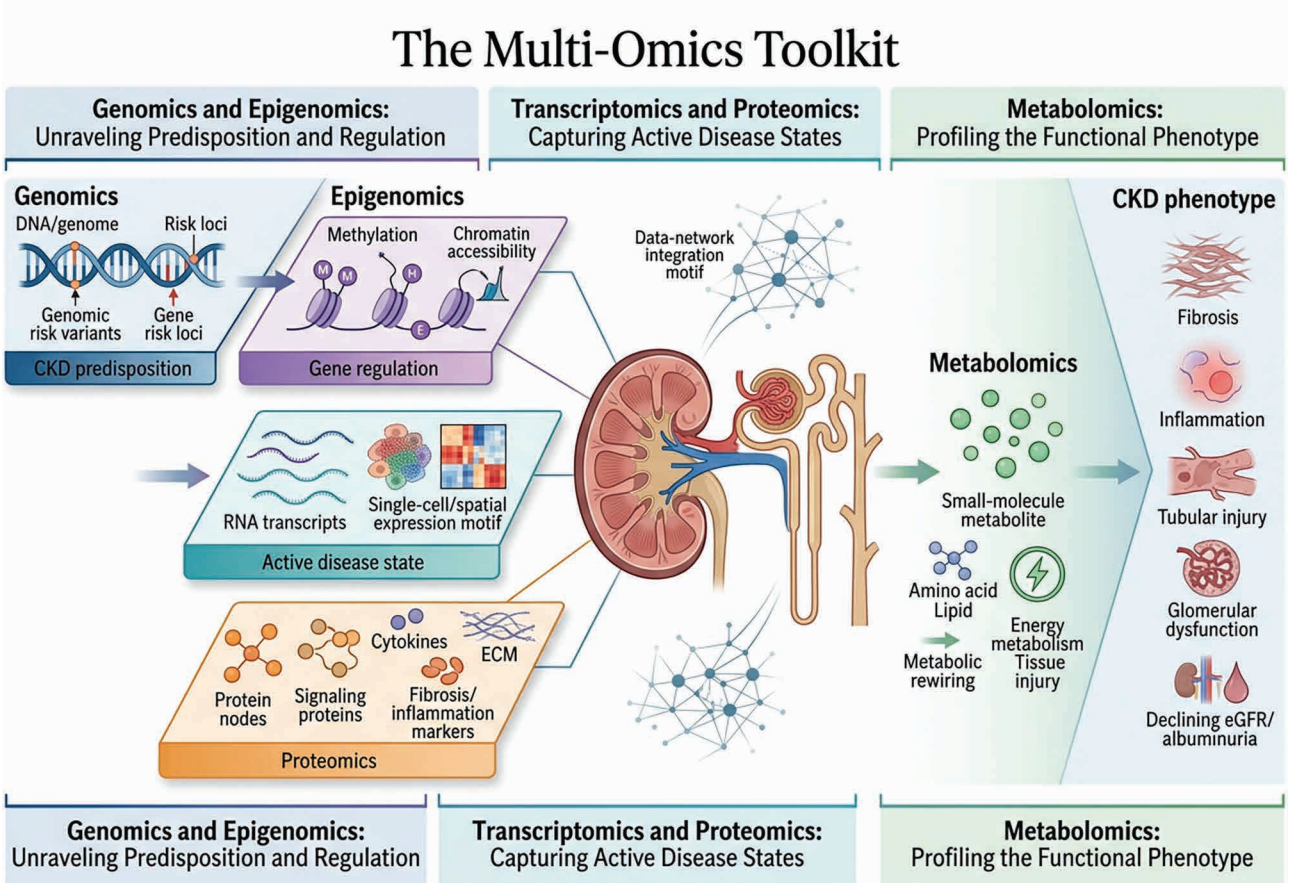


Figure 1. The MultiOmics Toolkit for CKD Pathobiology [Genomic and epigenomic features define predisposition and regulatory context; transcriptomic and proteomic layers capture cellstate and effector pathways; metabolomics profiles functional phenotype. Integrated network analytics across kidney compartments link molecular signals to CKD phenotypes including fibrosis, inflammation, tubular and glomerular injury, and declining renal function (eGFR / albuminuria).]

A Multi-Omics Framework for Target Discovery in CKD

Omic Layer (The Toolkit)	Biological Question Addressed (The Lens)	Key Technological Platforms	Application in CKD Pathobiology (The Target Discovery)	Specific Insights into Therapeutic Targets
Genomics (The Blueprint)	What is the inherited risk or fixed genetic predisposition to CKD onset and progression?	- GWAS (Genome-Wide Association Studies) - WES/WGS (Whole Exome/ Genome Sequencing) - Polygenic Risk Scores (PRS)	Identifying risk alleles for CKD (e.g., APOL1 in African Americans, UMOD mutations). Discovering monogenic causes of kidney disease (e.g., collagenopathies, podocytopathies).	- Target Validation: Confirming a causal role for a gene (e.g., APOL1) provides a high level of confidence for drug development. - Patient Stratification: PRS can identify "high-risk" populations for early intervention or clinical trial enrichment.
Epigenomics (The Environmental Regulator)	How do environmental factors (diabetes, hypertension, toxins) and aging modify gene activity without changing the DNA sequence?	- ChIP-seq (Histone modifications) - ATAC-seq (Chromatin accessibility) - Bisulfite sequencing (DNA methylation)	Mapping aberrant DNA methylation patterns in kidney fibrosis. Identifying changes in chromatin accessibility in renal proximal tubular epithelial cells under metabolic stress.	- Epigenetic Therapies: Targeting "writers" and "erasers" (e.g., HDAC inhibitors, DNMT inhibitors) to reverse maladaptive transcriptional programs. - Reprogramming Potential: Identifying accessible chromatin regions that could be targeted to induce regenerative cell states.
Transcriptomics (The Dynamic Script)	What are the actively expressed genes and RNA networks driving the disease phenotype in specific kidney cells?	- Bulk RNA-seq - Single-cell RNA-seq (scRNA-seq) - Spatial Transcriptomics	Deconvoluting the cellular landscape of the fibrotic kidney (e.g., identification of novel pro-fibrotic fibroblast subtypes, inflammatory macrophage signatures). Mapping the "zonation" of injury along the nephron.	- Cellular Precision: scRNA-seq pinpoints the exact cell type expressing a drug target (e.g., a cell-surface receptor on an activated myofibroblast). - Biomarker Discovery: Identifying cell-type-specific secreted factors as non-invasive biomarkers of disease activity.
Proteomics (The Functional Machinery)	What are the functional proteins and signaling networks that constitute the disease's machinery, including post-translational modifications?	- Mass Spectrometry (MS) - Proximity Extension Assay (PEA) - Antibody arrays	Profiling the urinary proteome to discover early indicators of tubular damage (e.g., KIM-1, NGAL) or the glomerular proteome to identify podocyte injury pathways. Quantifying thousands of circulating proteins associated with kidney function decline.	- Direct Druggable Entities: Proteins are the most common drug targets. Proteomics directly measures their abundance and activation state (e.g., phosphorylation). - Pathway Mapping: Identifying dysregulated signaling cascades (e.g., TGF-β, JAK-STAT) that are amenable to intervention with biologics or small molecules.
Metabolomics (The Physiological Readout)	What are the downstream metabolic consequences of kidney dysfunction, and how do metabolic derangements (uremic toxins) drive further injury?	- Nuclear Magnetic Resonance (NMR) - Liquid/Gas Chromatography-Mass Spectrometry (LC/GC-MS)	Identifying and quantifying the accumulation of uremic toxins (e.g., indoxyl sulfate, p-cresyl sulfate, TMAO). Mapping shifts in energy metabolism (e.g., fatty acid oxidation) in the diseased kidney.	- Therapeutic Intervention: Developing adsorbents to remove uremic toxins or inhibitors to block their production by the gut microbiota (e.g., targeting microbial TMA lyase to reduce TMAO). - Metabolic Reprogramming: Identifying nodes in metabolic pathways (e.g., in glycolysis or fatty acid oxidation) that, if targeted, could restore cellular energetics and slow degeneration.

proteomics has yielded classifiers (e.g., CKD273, a 273-peptide signature) that can detect early CKD and predict progression with high accuracy, even in normoalbuminuric diabetic patients.[9] Plasma proteomic panels are also being developed to assess cardiovascular risk specifically in CKD populations.

Metabolomics: Profiling the Functional Phenotype

Metabolomics provides a snapshot of systemic and local biochemical processes. CKD is characterized by a profound disruption of metabolism, including the accumulation of uremic toxins (indoxyl sulfate, p-cresyl sulfate), alterations in the tricarboxylic acid (TCA) cycle, and dysregulation of amino acid and lipid metabolism.[10] Specific metabolite panels can distinguish CKD etiologies and correlate more strongly with residual renal function than traditional markers.

INTEGRATIVE MULTI-OMICS: FORGING A NEW PARADIGM

The true power lies in data integration, where complementary omics layers are combined to construct causal networks.

Early Diagnosis: Beyond Creatinine

Integrative models outperform single-omics approaches. For instance, combining a genomic risk score with a urinary proteomic classifier and a panel of serum metabolites can significantly enhance the prediction of incident CKD in at-risk populations (e.g., hypertensive or diabetic patients). Such models can identify "silent" disease during the molecular injury phase, enabling preventative strategies.

Molecular Stratification: Defining Endotypes

CKD is not one disease. Multi-omics clustering can stratify patients into endotypes with shared molecular drivers, irrespective of clinical diagnosis. A seminal study in DKD identified distinct endotypes: an "inflammatory," a "fibrotic," and a "metabolic" cluster, each with different progression rates and potential therapeutic vulnerabilities.[11] Similarly, in IgA nephropathy, integrative analyses have defined subgroups with varying activity of the complement system, guiding the use of complement inhibitors.

Personalized Management: Guiding Targeted Therapy

Multi-omics can match patients to optimal treatments. A patient with a lupus nephritis transcriptomic signature dominated by interferon pathways may be a prime candidate for anifrolumab (an interferon receptor antagonist). Proteomic monitoring can reveal early response (or resistance) to therapies like SGLT2 inhibitors, allowing for timely adjustment. Furthermore, metabolomic profiling can personalize dietary recommendations and manage uremic toxin accumulation.

This table presents a layered, systems biology approach to understanding CKD pathobiology. Each "omic" layer serves as a distinct investigative tool that addresses a unique biological question, providing a multi-dimensional view of the disease. By integrating insights across these layers, from fixed genetic risk (Genomics) to dynamic environmental responses (Epigenomics), active cellular programs (Transcriptomics), functional protein networks (Proteomics), and ultimate metabolic consequences (Metabolomics), researchers can identify and validate novel therapeutic targets with greater precision. This integrated strategy moves beyond single biomarkers to uncover the complex, interconnected networks that drive CKD progression, facilitating the development of targeted, rational therapies.

CHALLENGES AND FUTURE DIRECTIONS

Despite its promise, several hurdles remain: i) Technical & Computational: Integrating heterogeneous, high-dimensional datasets requires advanced bioinformatics (AI, machine learning) and robust statistical frameworks to avoid overfitting. A major computational challenge in multi-omics studies is the risk of overfitting, particularly when high-dimensional molecular datasets are analyzed in relatively small clinical cohorts. Models may capture noise or cohort-specific patterns rather than robust biological signals, resulting in poor generalizability to new patients. Therefore, rigorous feature selection, appropriate regularization, cross-validation, and, importantly, testing in independent external validation cohorts are essential to establish model robustness and clinical utility.[12,15,17] In addition, batch effects arising from differences in sample processing, analytical platforms, laboratory procedures, or study sites can introduce systematic variation across multi-omics datasets. Careful experimental design, standardized protocols, and appropriate computational batch-correction strategies are consequently required to distinguish true biological signals from technical variation; ii) Validation and Standardization: Discoveries must be validated in large, diverse, prospective cohorts. Assay standardization and quality control are critical for clinical adoption; iii) Clinical Implementation and Ethics: Integrating multi-omics into electronic health records, demonstrating cost-effectiveness, and training clinicians are major tasks. Ethical issues surrounding data privacy, incidental findings, and equitable access must be proactively addressed;[15-8] iv) Economic Feasibility: The high cost of comprehensive multi-omics profiling remains an important barrier

to routine clinical implementation. Future research should therefore evaluate the cost-effectiveness of multi-omics-guided care and focus on translating broad multi-omics discoveries into targeted, clinically validated panels containing a smaller number of informative biomarkers. Such lower-cost approaches may provide a more scalable and practical strategy for incorporating molecular profiling into routine CKD management, particularly in resource-limited settings; v) Biological Sample Access: While urine and blood are accessible, kidney tissue provides the most direct insight. Biopsy biobanking and non-invasive methods to assess tissue status are vital. Although kidney tissue provides direct information about intrarenal molecular changes, repeated biopsy is invasive and may not be feasible for longitudinal monitoring. Liquid biopsy approaches, including circulating cell-free DNA and urinary extracellular vesicles, may offer a minimally invasive means of capturing molecular signals associated with ongoing renal injury. Serial assessment of these biomarkers could complement tissue-based analyses by enabling repeated monitoring of disease progression and treatment response. However, their clinical utility still requires rigorous validation, standardization, and correlation with tissue-level molecular findings[12-20].

CONCLUSIONS

The integrative multi-omics approach represents a paradigm shift in nephrology, moving from a phenotype-based to a mechanism-based understanding of CKD. By defining the molecular features that drive CKD heterogeneity, multi-omics may not only support earlier disease detection and mechanistic patient stratification but also help predict how individual patients will respond to established therapies, including SGLT2 inhibitors and mineralocorticoid receptor antagonists, thereby enabling more informed and personalized treatment decisions. While significant translational challenges exist, coordinated efforts across research, clinical, and computational domains are paving the way for a future where CKD management is proactive, predictive, and precisely tailored to the individual patient's molecular profile. The era of precision nephrology, grounded in multi-omics, is on the horizon.

DECLARATIONS

Conflict of Interest

The author declares that there are no competing interests that could have influenced the preparation or content of this manuscript.

Generative AI Statement

The authors declare that generative artificial intelligence (GenAI) tools and large language models (LLMs) were used during the preparation of this manuscript. Tools including Instatext, Wordvice, and DeepL were used to assist with language refinement, structural editing, and improvement of the clarity and overall quality of the written text. The authors remain fully responsible for the content, interpretation, and conclusions presented in the manuscript.

Acknowledgments

Not applicable.

Author Contribution

I confirm that the submitted author list is complete and that the authors are presented in the correct order. I acknowledge that any subsequent modification to the authorship, including adding or removing authors or changing their order, must be formally submitted to the editor and approved in writing by all authors.

Tina Kianfar, conceptualization, writing - Original Draft; **Atrin Zakikhani,** conceptualization, writing - Original Draft; **Soroush Taherkhani;** conceptualization, writing - Original Draft, supervision, project administration.

Funding

No funding was received.

Data Availability

This study did not involve the generation or analysis of any new data.

REFERENCES

1. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication—worldwide more than 850 million individuals have kidney diseases. Nephrology Dialysis Transplantation. 2019;34(11):1803-5.
2. Cisek K, Krochmal M, Klein J, Mischak H. The application

of multi-omics and systems biology to identify therapeutic targets in chronic kidney disease. Nephrology Dialysis Transplantation. 2016;31(12):2003-11.

3. Chen C, Wang J, Pan D, Wang X, Xu Y, Yan J, et al. Applications of multi-omics analysis in human diseases. MedComm. 2023;4(4):e315.
4. Wuttke M, Li Y, Li M, Sieber KB, Feitosa MF, Gorski M, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. Nature genetics. 2019;51(6):957-72.
5. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. 2010;329(5993):841-5.
6. Bechtel W, McGoohan S, Zeisberg EM, Müller GA, Kalbacher H, Salant DJ, et al. Methylation determines fibroblast activation and fibrogenesis in the kidney. Nature medicine. 2010;16(5):544-50.
7. Glowacki F, Savary G, Gnemmi V, Buob D, Van der Hauwaert C, Lo-Guidice JM, et al. Increased circulating miR-21 levels are associated with kidney fibrosis. PloS one. 2013;8(2):e58014.
8. Ju W, Nair V, Smith S, Zhu L, Shedden K, Song PX, et al. Tissue transcriptome-driven identification of epidermal growth factor as a chronic kidney disease biomarker. Science translational medicine. 2015;7(316):316ra193.
9. Good DM, Zürbig P, Argiles A, Bauer HW, Behrens G, Coon JJ, et al. Naturally occurring human urinary peptides for use in diagnosis of chronic kidney disease. Molecular & cellular proteomics. 2010;9(11):2424-37.
10. Hocher B, Adamski J. Metabolomics for clinical use and research in chronic kidney disease. Nature Reviews Nephrology. 2017;13(5):269-84.
11. Reznichenko A, Nair V, Eddy S, Fermin D, Tomilo M, Slidel T, et al. Unbiased kidney-centric molecular categorization of chronic kidney disease as a step towards precision medicine. Kidney International. 2024;105(6):1263-78.
12. Seo CW, Lee EY, Oh JS, Choi D. Urinary extracellular vesicle proteins for biomarker discovery in chronic kidney disease. Kidney Research and Clinical Practice. 2025;45(1):36.
13. Morrison E, Bailey MA, Dear JW. Renal extracellular vesicles: from physiology to clinical application. The Journal of physiology. 2016;594(20):5735-48.
14. Seo CW, Lee EY, Oh JS, Choi D. Urinary extracellular vesicle proteins for biomarker discovery in chronic kidney disease. Kidney Research and Clinical Practice. 2025;45(1):36.
15. Alobaidi S. Emerging biomarkers and advanced diagnostics in chronic kidney disease: early detection through multi-omics and AI. Diagnostics. 2025;15(10):1225.
16. Si S, Liu H, Xu L, Zhan S. Identification of novel therapeutic targets for chronic kidney disease and kidney function by integrating multi-omics proteome with transcriptome. Genome medicine. 2024;16(1):84.
17. Kianfar T, Kadkhodaee M, Seifi B, Abdi A, Adelipour M, Pishkenari BH, et al. The effect of tannic acid on renal renin-angiotensin signaling pathway in a model of unilateral ureteral obstruction in male Wistar rats. Naunyn-Schmiedeberg's Archives of Pharmacology. 2023;396(12):3569-79.
18. Si S, Liu H, Xu L, Zhan S. Identification of novel therapeutic targets for chronic kidney disease and kidney function by integrating multi-omics proteome with transcriptome. Genome medicine. 2024;16(1):84.
19. Givechian N, Ashabi G, Kadkhodaee M, Seifi B, Abdi A, Kianian F, Kianfar T. Prevention of glycerol-induced acute kidney injury by isoflurane inhalation in male rats. Physiology and Pharmacology. 2024;28(2):91–8.
20. Rutka B, Danieluk A, Wiewiórska-Krata N, Mucha K. Multi-Modal, Machine Learning-Driven Framework Integrating Multi-Omics for Personalized Chronic Kidney Disease Management. Journal of Clinical Medicine. 2026;15(13):5213.

Correspondence to:
Soroush Taherkhani,
Department of Physiology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
ORCID ID: 0000-0002-0655-1060
E-mails: soroushtaherkhani95@gmail.com, taherkhani.s@iums.ac.ir

Received July 2026
Revised August 2026
Accepted September 2026

Diagnostic Value of MicroRNAs as Biomarkers for Sepsis-associated Acute Kidney Injury: A Systematic Review and Meta-Analysis

Farid Javandoust Gharehbagh,[1,2] Legha Lotfollahi,[3] Darya Gerami,[1,4] Ilad Alavi Darazam[2,5]

[1]Iranian Social Security Organization, Imam Reza Hospital, Urmia, Iran
[2]Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Department of Nephrology, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Biochemistry Department, Urmia University of medical sciences, Urmia, Iran
[5]Department of Infectious Diseases and Tropical Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Keywords. sepsis-associated acute kidney injury, microRNA; circular RNA, biomarker, diagnostic accuracy, meta-analysis

© 2026 Author(s). This article is licensed under the CC By 4.0 International License.

Introduction. Sepsis-associated acute kidney injury (SA-AKI) is a common and serious complication in critically ill patients, associated with high morbidity and mortality. Early diagnosis remains challenging due to the limitations of traditional biomarkers such as serum creatinine and urine output. MicroRNAs (miRNAs) and circular RNAs (circRNAs) have emerged as promising non-invasive biomarkers for early SA-AKI detection. To systematically evaluate the diagnostic accuracy of individual non-coding RNA biomarkers for predicting SA-AKI in sepsis patients.

Methods. We systematically searched PubMed from inception to August 2026 and manually screened reference lists of relevant systematic reviews. Studies were included if they evaluated non-coding RNAs for SA-AKI diagnosis in sepsis patients, compared sepsis patients with AKI to sepsis patients without AKI.

Results. Fourteen studies comprising 1,840 patients (908 with SA-AKI and 932 controls) were included. The pooled sensitivity was 83.5% and pooled specificity was 81.5%. The pooled DOR was 22.29, and the area under the HSROC curve was 0.885, indicating excellent diagnostic accuracy. The most promising individual biomarkers identified were miR-210 (AUC = 0.913), miR-155 (AUC = 0.910), miR-132-3p (AUC = 0.910), and miR-769-5p (AUC = 0.928). Heterogeneity was low to moderate (I^2: 30.4 to 35.9% for sensitivity, 0.8 to 0.9% for specificity).

Conclusions. Individual non-coding RNA biomarkers demonstrate good to excellent diagnostic accuracy for SA-AKI, with performance comparable to or exceeding that of established protein biomarkers. Their biological plausibility, stability in body fluids, and potential for early detection make them attractive candidates for clinical translation.

RJCCN 2026; 2: 255-71
www.rjccn.org
DOI: 10.61882/rjccn.2.4.77

INTRODUCTION

Sepsis is one of the greatest critical care challenges and is estimated to cause 11 million deaths globally every year, consuming a significant amount of intensive care resources. Despite improvements in early recognition and treatment, mortality in septic patients has been reported as between 20 and 50%, depending on the severity of the disease.[1,2]

Please cite this article as: Javandoust Gharehbagh F, Lotfollahi L, Gerami D, Alavi Darazam I. Diagnostic Value of MicroRNAs as Biomarkers for Sepsis-associated Acute Kidney Injury: A Systematic Review and Meta-Analysis. RJCCN. 2026;2(4):255-71.

Sepsis can have a multitude of complications, and acute kidney injury (AKI) is one of the most frequent, occurring in 20 to 50% of septic patients and representing a distinct and independent poor prognostic factor.[3-5] This systemic inflammatory process, combined with microvascular dysfunction, oxidative stress, mitochondrial injury, and tubular epithelial cell damage, is a multifactorial phenomenon and not merely a reflection of poor renal perfusion; it constitutes sepsis-associated AKI (SA-AKI).[6]

Early diagnosis of SA-AKI remains challenging. The current clinical standard, serum creatinine, only increases after significant nephron loss and is influenced by non-renal factors including muscle mass, hydration status, and medication use.[7,8] Protein-based biomarkers that have attempted to fill this void have yielded only moderate and inconsistent diagnostic value in studies, with AUCs of 0.65 to 0.87 reported in most studies.[9-12]

MicroRNAs (miRNAs) are emerging as potential biomarkers for SA-AKI. These small non-coding RNAs are released into circulation and urine in tissue- and injury-specific patterns, and their release into plasma is linked to key pathophysiological pathways involved in sepsis-induced renal injury, such as hypoxic signaling and inflammatory cascades.[13-18] Importantly, miRNAs are highly resistant to RNase degradation, withstand repeated freeze-thaw cycles, and are clinically stable in body fluids, making them promising candidates for clinical assays.[19] In addition to miRNAs, circular RNAs (circRNAs) have recently emerged as potential biomarkers. These covalently closed non-coding RNAs are remarkably stable due to their resistance to exonuclease degradation and have been shown to function as miRNA sponges, making them attractive diagnostic targets.[20-22] Several studies have focused on particular miRNAs, multi-marker miRNA panels, or circRNAs as diagnostic markers for SA-AKI. However, these studies have generally been small and heterogeneous. Previous reviews in this field have been narrative or have not quantitatively synthesized diagnostic accuracy data comparing individual non-coding RNA biomarkers.[23-26]

The aim of this systematic review and meta-analysis was to quantify the diagnostic accuracy of individual non-coding RNA biomarkers for the diagnosis of SA-AKI, and to evaluate their potential clinical utility compared to established protein-based biomarkers.

MATERIALS AND METHODS

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[27]

Search Strategy

We systematically searched the PubMed database from inception to August 2026. Additionally, we manually screened the reference lists of four relevant systematic reviews[23-26] to identify additional studies. The search strategy combined terms for microRNAs, sepsis, acute kidney injury, and diagnostic accuracy.

The following search strings were applied:

1. *("miR-210" OR "microRNA-210") AND ("sepsis" OR "septic") AND ("acute kidney injury" OR "AKI") AND ("diagnostic" OR "biomarker")*
2. *("miR-582-5p" OR "microRNA-582-5p" OR "miR-23a-3p" OR "microRNA-23a-3p" OR "miR-320-3p" OR "microRNA-320-3p" OR "miR-22-3p" OR "microRNA-22-3p" OR "miR-15a-5p" OR "microRNA-15a-5p") AND ("sepsis" OR "septic") AND ("acute kidney injury" OR "AKI") AND ("diagnostic" OR "biomarker" OR "ROC" OR "AUC")*
3. *("microRNAs"[MeSH Terms] OR "microRNA"[Title/Abstract] OR "miRNA"[Title/Abstract] OR "miR-"[Title/Abstract]) AND ("acute kidney injury"[MeSH Terms] OR "acute kidney injury"[Title/Abstract] OR "AKI"[Title/Abstract] OR "acute renal injury"[Title/Abstract]) AND ("sepsis"[MeSH Terms] OR "sepsis"[Title/Abstract] OR "septic"[Title/Abstract]) AND ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "Meta-Analysis"[Title/Abstract] OR "Systematic Review"[Title/Abstract])*

Eligibility Criteria

Studies were included if they: 1) evaluated miRNAs, circRNAs, or other non-coding RNAs as diagnostic biomarkers for sepsis-associated acute

kidney injury (SA-AKI) in human populations; 2) reported diagnostic accuracy data including AUC, sensitivity, and specificity, or provided sufficient information to construct a 2 × 2 contingency table; 3) used validated AKI definitions based on KDIGO, AKIN, or RIFLE criteria; 4) compared sepsis patients with AKI to sepsis patients without AKI; and 5) were published in English.

We excluded: 1) preclinical or animal studies; 2) in vitro investigations without clinical validation; 3) review articles, editorials, conference abstracts, and case reports; 4) studies not specifically focused on sepsis-associated AKI; 5) studies comparing AKI patients to healthy controls without a sepsis-non-AKI group; 6) studies evaluating AKI of mixed etiologies not exclusively sepsis-related; 7) articles with incomplete diagnostic data; 8) retracted publications; and 9) studies with unavailable full text.

For Chinese-language studies identified during the search, we utilized DeepSeek (深度求索), an artificial intelligence language model, to translate the full texts into English and assist with data extraction. The translated content was independently verified by two reviewers to ensure accuracy and consistency of the extracted variables.

Study Selection and Data Extraction

Two reviewers independently screened titles and abstracts (FJG and DG), followed by full-text assessment of potentially eligible articles. Disagreements were resolved through discussion or consultation with a third reviewer (L.L or IAD).

Data extraction was performed using a standardized form that captured:

- Study characteristics: author, year, country, and design
- Sample characteristics: sample type (serum, plasma, urine, or whole blood)
- AKI definition: KDIGO, AKIN, RIFLE, or other criteria
- Biomarker information: biomarker(s) evaluated, category (single miRNA, best-performing miRNA from multi-miRNA panel, or circRNA)
- Diagnostic accuracy metrics: AUC with 95% CI, sensitivity, specificity
- 2 × 2 contingency table data: true positives, false positives, false negatives, and true negatives
- Sampling timing: early (within 24 hours of admission), at diagnosis (at the time of clinical diagnosis), or late (at renal replacement therapy initiation)
- Assay methodology: RNA extraction kit, normalization method, detection chemistry, PCR platform

For Chinese-language publications, data extraction was performed with the assistance of DeepSeek AI translation, followed by manual verification by the review team.

Quality Assessment

Methodological quality was evaluated using the QUADAS-2 tool, which assesses risk of bias across four domains: patient selection, index test, reference standard, and flow and timing.[28] Each domain was rated as low, high, or unclear risk of bias, and applicability concerns were also assessed for each domain.

Statistical Analysis

All meta-analyses were conducted using R software (version 4.5.2) with the metafor, meta, and mada packages.

The primary outcomes were pooled sensitivity, specificity, and diagnostic odds ratio (DOR). A bivariate random-effects model[29] was applied to account for between-study heterogeneity and the correlation between sensitivity and specificity. The hierarchical summary receiver operating characteristic (HSROC) model was used to generate the summary ROC curve and estimate the area under the curve (AUC).[30] To handle zero cells in 2 × 2 tables, a continuity correction of 0.5 was added to all cells.[31] For one study (Fan *et al*.[32]), the reported AUC was 1.91 (95% CI: 1.61 to 2.19), which is mathematically impossible. We inferred that this represented a reporting error and used the value 0.910, which is consistent with the reported sensitivity (91.12%) and specificity (84.52%).

Between-study heterogeneity was quantified using the I^2 statistic and Cochran's Q test. I^2 values below 25% indicated low heterogeneity, 25 to 50% moderate heterogeneity, and above 50% high heterogeneity.[33] For the bivariate model, I^2 was

calculated using Holling's approach (sample size unadjusted for sensitivity, sample size adjusted for specificity) and the Zhou and Dendukuri approach. Subgroup analyses were performed to explore potential sources of heterogeneity based on clinically relevant variables, including sampling time, sample type, and detection chemistry.[33]

Publication bias was evaluated using Egger's regression test with sample size as the predictor,[34] Begg's rank correlation test,[35] visual inspection of funnel plots, and trim-and-fill analysis.[35] Egger's regression test was implemented using the regtest function in the metafor package with predictor = "ni" to model the relationship between study precision (sample size) and effect size on the logit scale. Trim-and-fill analysis was performed using the L0 estimator for sensitivity and the R0 estimator for specificity, following the default recommendations of the metafor package. All tests were two-sided with a significance level of $P < .05$. The complete, reproducible R script used for all analyses (data entry, bivariate random-effects modeling, subgroup analyses, miR-210 cross-study comparison, publication bias assessment, and funnel plot generation) is provided as Supplementary Code S1.

Study Selection

The systematic literature search identified 46 records from database searches and 280 additional records from the reference lists of four systematic reviews. After removing 4 duplicates, 322 records were screened by title and abstract, of which 270 were excluded. The remaining 52 full-text articles were assessed for eligibility. Of these, 14 studies (26.9%) provided complete diagnostic accuracy data (2 × 2 contingency tables, AUC, sensitivity, and specificity) comparing sepsis patients with AKI to sepsis patients without AKI and were included in the quantitative meta-analysis: 11 single miRNA marker studies, 1 study reporting an individual miRNA from a multi-miRNA panel (from which the best-performing miRNA was extracted), and 2 circRNA studies (Table 1).

Thirty-eight studies (73.1%) were excluded for the following reasons: incomplete diagnostic data (lack of sensitivity/specificity reporting or absence of 2 × 2 contingency tables); different study populations (e.g., neonatal sepsis, non-sepsis AKI); comparison

Table 1. Characteristics and Diagnostic Performance of Included Biomarkers for Sepsis-associated AKI

#	Study	Year	Country	Biomarker	Sample	Timing	AKI Definition	Total (AKI/Control)	AUC (95% CI)	Sens (%)	Spec (%)
1	Zhang et al.[39]	2026	China	miR-210	Serum	Early	KDIGO	81 (41/40)	0.913	92.21	91.37
2	Liu et al.[40]	2020	China	miR-452	Urine	At Dx	KDIGO	97 (47/50)	0.899	87.23	78.00
3	Susianti et al.[41]	2024	Indonesia	miR-210[a]	Serum	At Dx	KDIGO	52 (26/26)	0.777	84.60	63.90
4	Fan et al.[32]	2024	China	miR-155	Serum	Early	RIFLE	150 (79/71)	0.910b	91.12	84.52
5	Chen et al.[42]	2026	China	miR-4772-3p	Serum	At Dx	KDIGO	192 (93/99)	0.864	85.10	84.00
6	Peng et al.[43]	2025	China	miR-769-5p	Serum	Early	Not specified	162 (82/80)	0.928	87.80	83.80
7	Wang et al.[44]	2026	China	miR-379-5p	Serum	Early	KDIGO	159 (74/85)	0.820	75.70	72.90
8	Tian et al.[45]	2026	China	miR-151a-3p	Serum	Early	KDIGO	208 (110/98)	0.883	84.60	77.60
9	Gong et al.[46]	2024	China	miR-625-5p	Serum	Early	KDIGO	120 (62/58)	0.844	79.03	74.60
10	Wu S-Y et al.[47]	2020	China	miR-21-3p	Serum	Early	KDIGO	142 (49/93)	0.863	87.50	81.60
11	Lan et al.[48]	2026	China	miR-132-3p	Plasma	At Dx	KDIGO	208 (108/100)	0.910	82.40	91.00
12	Xu et al.[49]	2025	China	miR-577[b]	Urine	Early	KDIGO	135 (70/65)	0.888	80.0	86.15
13	Pu et al.[22]	2026	China	hsa_circ_0056869	Plasma	Early	KDIGO	68 (34/34)	0.818	79.41	82.35
14	Peng et al.[21]	2024	China	hsa_circ_0072463	Plasma	Early	KDIGO	66 (33/33)	0.866	78.8	87.9
Total								N = 1,840z			

Abbreviations: Dx, diagnosis; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss, End-stage kidney disease; AUC, area under the receiver operating characteristic curve; CI, confidence interval; Sens, sensitivity; Spec, specificity.

[a] Susianti et al. specifically measured the miR-210-3p strand; both miR-210 and miR-210-3p are grouped as miR-210 for pooling.

[b] AUC corrected from the reported value of 1.91, which is mathematically impossible; 0.910 is consistent with the reported sensitivity and specificity.

groups other than sepsis-non-AKI (e.g., healthy controls, ATN vs. HRS); or reporting multi-marker panels without individual biomarker data. The PRISMA flow diagram is presented in Figure 1.

Study Characteristics

A total of 14 studies were included in the meta-analysis. The studies were published between 2020 and 2026, with the majority (n = 13, 92.9%) published in 2020 or later, reflecting the growing interest in non-coding RNA biomarkers for SA-AKI. The included studies originated from 2 countries: China (n = 13, 92.9%) and Indonesia (n = 1, 7.1%). Of the 14 studies, 11 (78.6%) evaluated single

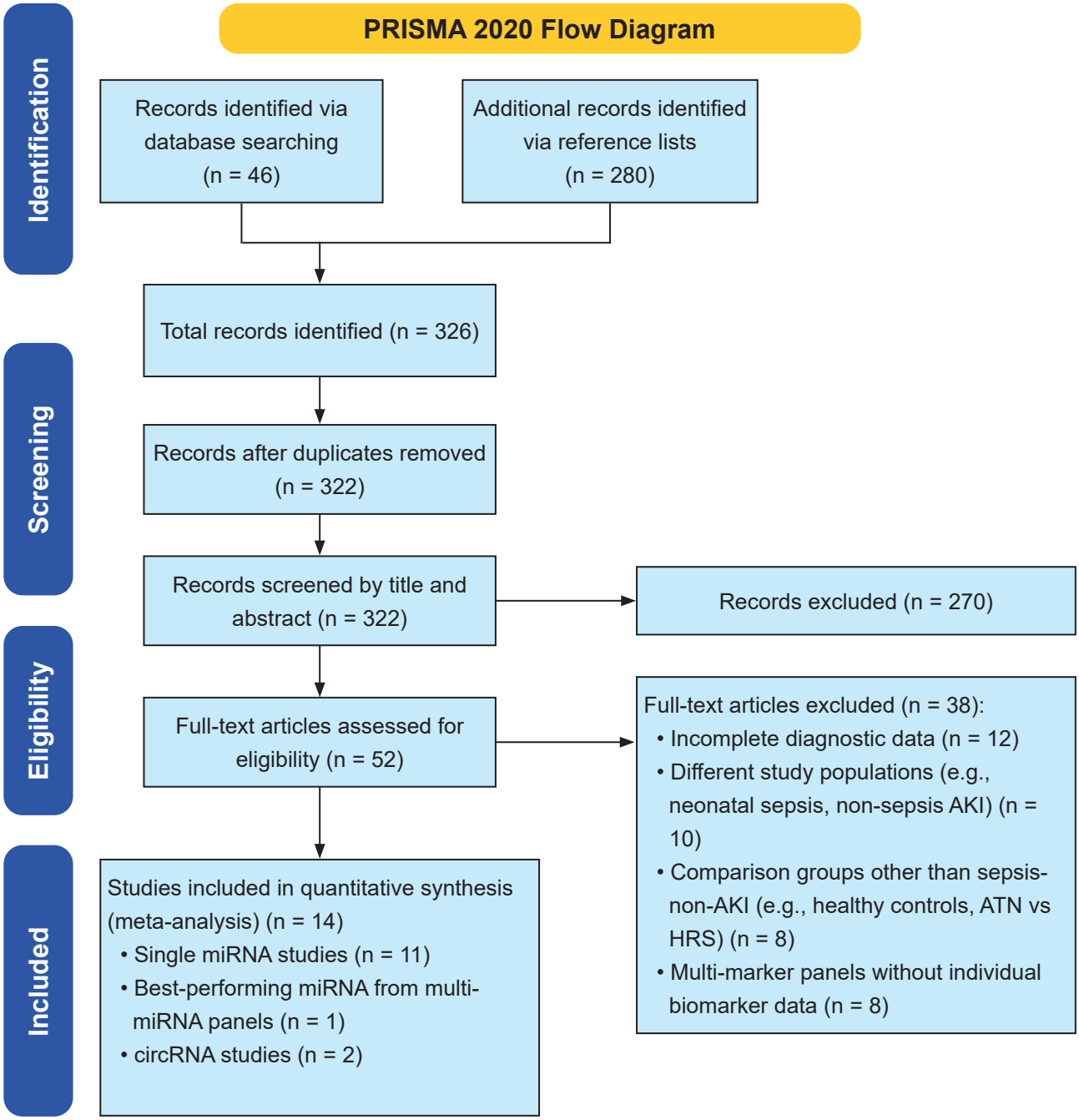


Figure 1. PRISMA Flow Diagram of Study Selection
Flow diagram showing the identification, screening, eligibility, and inclusion of studies for the systematic review and meta-analysis. A total of 322 records were screened, of which 52 full-text articles were assessed for eligibility, resulting in 14 studies included in the quantitative synthesis.

miRNA markers, 1 (7.1%) reported an individual miRNA from a multi-miRNA panel (from which the best-performing miRNA was extracted), and 2 (14.3%) evaluated circRNA biomarkers. Sample types included serum (n = 9, 64.3%), plasma (n = 3, 21.4%), and urine (n = 2, 14.3%). AKI was defined using KDIGO criteria (n = 12, 85.7%) or RIFLE criteria (n = 1, 7.1%); one study (7.1%) did not explicitly report the AKI diagnostic criteria used. The most commonly investigated biomarkers were miR-210 (n = 2, 14.3%), with all other biomarkers evaluated in single studies. The 2 × 2 contingency table data for all studies are presented in Table 2, and the detailed assay methods are summarized in Table 3. Regarding sepsis diagnostic criteria, 12 studies (85.7%) employed the Sepsis-3 definitions, while one study (Gong *et al.*) used the 2001 SCCM/ESICM/ACCP/ATS/SIS criteria, and one pediatric study (Wu *et al.*) used the Chinese Pediatric Sepsis Shock Expert Consensus (2015 version). Notably, Wu *et al.* was the only study including a pediatric population, with all other 13 studies conducted in adult populations

The 14 included studies comprised 1,840 patients (908 with SA-AKI and 932 controls), with 11 single miRNA studies (n = 1,571 patients), 1 study with a best-performing miRNA from a panel (n = 135 patients), and 2 circRNA studies (n = 134 patients). The characteristics of all included studies are summarized in Table 1.

The methodological quality of the 14 included studies was assessed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool, which evaluates four domains: patient selection, index test, reference standard, and flow and timing. A summary of the quality assessment is presented in Figure 2.

Patient Selection: The majority of studies (n = 10, 71.4%) were at low risk of bias, as they included consecutive or random patient samples and avoided inappropriate exclusions. Four studies (28.6%) were at unclear risk due to insufficient reporting of sampling methods. No studies were at high risk of bias in this domain.

Index Test: All 14 studies (100%) were at low risk of bias for the index test domain, as they prespecified the miRNA / circRNA cut-off values or used standardized methods (RT-qPCR) for RNA quantification.

Reference Standard: Thirteen studies (92.9%) used validated AKI definitions (KDIGO or RIFLE criteria) and were at low risk of bias. One study (7.1%) did not explicitly report the AKI diagnostic criteria used and was classified as unclear risk of bias. No studies were at high risk of bias in this domain

Flow and Timing: The majority of studies (n = 11, 78.6%) were at low risk of bias, as they

Table 2. Two-by-Two Contingency Tables Derived from Reported Diagnostic Accuracy

#	Study	Biomarker	Total (n)	TP	FP	FN	TN
1	Zhang et al. 2026	miR-210	81	38	4	3	36
2	Liu et al. 2020	miR-452	97	41	11	6	39
3	Susianti et al. 2024	miR-210[a]	52	22	9	4	17
4	Fan et al. 2024	miR-155	150	72	11	7	60
5	Chen et al. 2026	miR-4772-3p	192	79	16	14	83
6	Peng et al. 2025	miR-769-5p	162	72	13	10	67
7	Wang et al. 2026	miR-379-5p	159	56	23	18	62
8	Tian et al. 2026	miR-151a-3p	208	93	22	17	76
9	Gong et al. 2024	miR-625-5p	120	49	15	13	43
10	Wu S-Y et al. 2020	miR-21-3p	142	43	17	6	76
11	Lan et al. 2026	miR-132-3p	208	89	9	19	91
12	Xu et al. 2025	miR-577	135	56	9	14	56
13	Pu et al. 2026	hsa_circ_0056869	68	27	6	7	28
14	Peng et al. 2024	hsa_circ_0072463	66	26	4	7	29
Total			1,840	763	169	145	763

Note. Cell counts (true positive [TP], false positive [FP], false negative [FN], true negative [TN]) were back-calculated from the reported total sample size and diagnostic accuracy metrics (sensitivity and specificity) for use in meta-analytic pooling. Non-integer values reflect rounding during back-calculation from reported sensitivity and specificity.

[a]Susianti et al. specifically measured the miR-210-3p strand; Zhang et al. did not specify the strand. Both are referred to as miR-210 for pooling purposes.

Table 3. Sample Handling and Assay Methodology of Included Studies

#	Study	Sample Type	RNA Extraction Kit	Normalization Method	Detection Chemistry	PCR Platform	Assay Kit / Reagents
1	Zhang et al. 2026	Serum	miRNA test kit (Invitrogen)	Endogenous (U6 snRNA)	SYBR Green	Not specified	Reverse transcription kit (Fermentas)
2	Liu et al. 2020	Urine/Serum	mirVana; miRNeasy (Qiagen)	Exogenous (cel-miR-39); Endogenous (sno202)	TaqMan	Not specified	TaqMan MicroRNA RT Kit; TaqMan assay kit (Applied Biosystems)
3	Susianti et al. 2024	Serum	microRNA isolation kit (Tiangen)	Endogenous (hsa-U6)	SYBR Green	Not specified	qRT-PCR kit (Tiangen Biotech)
4	Fan et al. 2024	Serum	Not specified	Endogenous (U6)	SYBR Green	9700 gene amplification instrument	Primers synthesized by Invitrogen
5	Chen et al. 2026	Serum/Cells	TRIzol reagent (Invitrogen)	Endogenous (U6 for miRNA; GAPDH for mRNA)	SYBR Green	LightCycler 480 (Roche)	Reverse transcription kit (Takara)
6	Peng et al. 2025	Serum/Cells	TRIzol reagent (Invitrogen)	Endogenous (U6 for miRNA; GAPDH for mRNA)	SYBR Green	Not specified	miScript II RT Kit (Qiagen); SuperScript IV RT Kit (Invitrogen)
7	Wang et al. 2026	Serum/Cells	TRIzol reagent (Invitrogen)	Endogenous (U6 for miRNA; GAPDH for mRNA)	SYBR Green	CFX real-time PCR (Bio-Rad)	PrimeScript RT kit (Takara); Mir-X miRNA synthesis kit (Takara)
8	Tian et al. 2026	Serum/Cells	TRIzol (Invitrogen); miRNeasy (Qiagen)	Endogenous (U6 for miRNA; GAPDH for mRNA)	SYBR Green	QuantStudio 5 (Applied Biosystems)	miRcURY LNA RT Kit (Qiagen); PrimeScript RT Kit (Takara)
9	Gong et al. 2024	Serum/Cells	TRIzol reagent (Invitrogen)	Endogenous (U6)	SYBR Green	7500 Real-Time PCR (Applied Biosystems)	RT kit (Takara); iQ SYBR Green Supermix (Bio-Rad)
10	Wu S-Y et al. 2020	Serum	Rapid RNA Extraction Kit	Endogenous (U6)	TaqMan	ABI7500 Real-Time PCR (Applied Biosystems)	TaqMan MicroRNA Assay; TaqMan 2× Universal PCR Master Mix
11	Lan et al. 2026	Plasma/Cells	TRIzol (Invitrogen)	Not specified (GAPDH primers listed but not confirmed as internal control) [a]	—	—	—
12	Xu et al. 2025	Urine	Trizol kit (Dakwi Biotechnology)	Endogenous (U6)	SYBR Green	Not specified	Reverse transcription kit (Wanbo Biomedical)
13	Pu et al. 2026	Plasma/Cells	TRIzol reagent (Thermo Fisher)	Endogenous (U6 for miRNA; β-tubulin for mRNA)	SYBR Green	LightCycler 480 (Roche)	PrimeScript RT kit with gDNA Eraser (Takara); AG SYBR Green Pro Taq HS Premix
14	Peng et al. 2024	Plasma/Cells	TRIzol reagent (Invitrogen)	Endogenous (U6 for miRNA; β-tubulin for mRNA)	SYBR Green	LightCycler 480 (Roche)	PrimeScript RT Kit with gDNA Eraser (Takara); AG SYBR Green Pro Taq HS Premix

Abbreviations. RT, reverse transcription; PCR, polymerase chain reaction; —, not applicable/not reported.
[a]The paper lists GAPDH primers in Table 1 but does not explicitly state which gene was used as the internal reference for normalization.

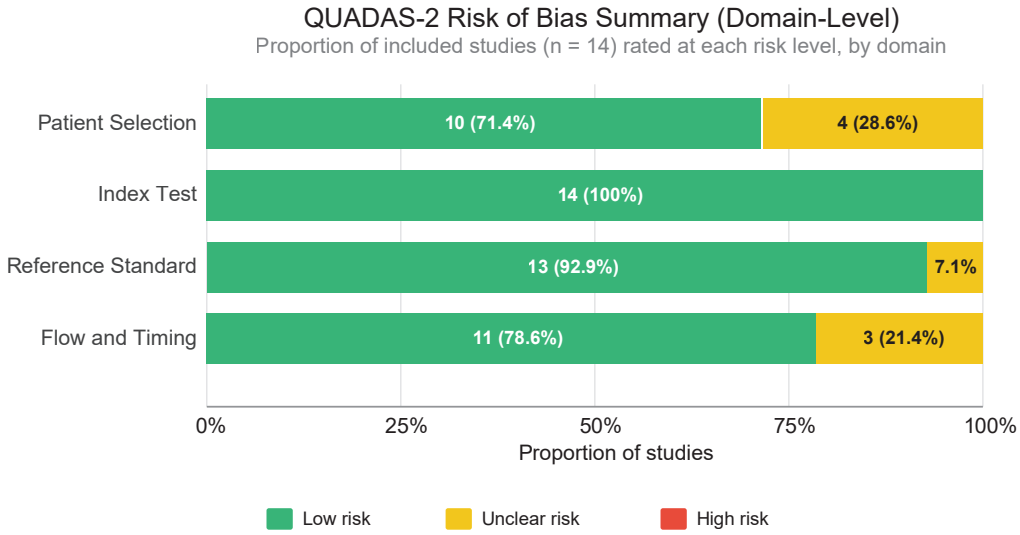


Figure 2. QUADAS-2 Quality Assessment Summary of Included Studies
Risk of bias assessment across four domains: patient selection, index test, reference standard, and flow and timing. Green indicates low risk of bias, yellow indicates unclear risk, and red indicates high risk of bias. In the patient selection domain, 10 studies (71.4%) were at low risk and 4 studies (28.6%) at unclear risk. In the index test domain, all 14 studies (100%) were at low risk. In the reference standard domain, 13 studies (92.9%) were at low risk and 1 study (7.1%) at unclear risk; no studies were at high risk. In the flow and timing domain, 11 studies (78.6%) were at low risk and 3 studies (21.4%) at unclear risk. Overall, 11 studies (78.6%) were rated as low risk and 3 studies (21.4%) as moderate risk of bias.

reported appropriate intervals between index test and reference standard, and all patients received the same reference standard. Three studies (21.4%) were at unclear risk due to incomplete reporting of time intervals or patient exclusions. No studies were at high risk of bias in this domain.

The overall methodological quality of the included studies was good, with 11 studies (78.6%) rated as low risk and 3 studies (21.4%) at moderate risk of bias.

Diagnostic Accuracy of Individual Biomarkers

A total of 14 studies evaluating individual biomarkers for SA-AKI diagnosis were included in the quantitative meta-analysis. These comprised 11 single miRNA marker studies, 1 study reporting the best-performing miRNA from a multi-miRNA panel, and 2 circRNA studies, encompassing 1,840 patients (908 with SA-AKI and 932 controls). The characteristics of all included studies are summarized in Table 1.

Pooled Estimates

The bivariate random-effects meta-analysis of 14 studies yielded a pooled sensitivity of 83.5% (95% CI: 80.7 to 86.0%) and a pooled specificity of 81.5% (95% CI: 77.9 to 84.6%). Forest plots of pooled sensitivity and specificity are presented in Figure 3. The pooled false positive rate was 18.5% (95% CI: 15.4 to 22.1%). The pooled diagnostic odds ratio (DOR) was 22.29 (95% CI: 16.60 to 29.92). The hierarchical summary receiver operating characteristic (HSROC) model yielded a mean area under the curve (AUC) of 0.885, indicating excellent overall diagnostic accuracy. The SROC curve is presented in Figure 4.

Heterogeneity was low to moderate across studies. For sensitivity, the I^2 was 30.4 to 35.9% (Holling sample size unadjusted approaches), and for specificity, the I^2 was 0.8 to 0.9% (Holling sample size adjusted approaches). The Zhou and Dendukuri approach yielded an I^2 of 0% for both sensitivity and specificity, suggesting that the included studies were relatively consistent in their diagnostic performance.

Publication Bias

Publication bias was assessed using funnel plots, Egger's regression test with sample size as the predictor, Begg's rank correlation test, and trim-and-fill analysis. Visual inspection of the funnel plots (Figure 5A & 5B) revealed approximate symmetry for both sensitivity and specificity, suggesting no substantial publication bias. Egger's test was not

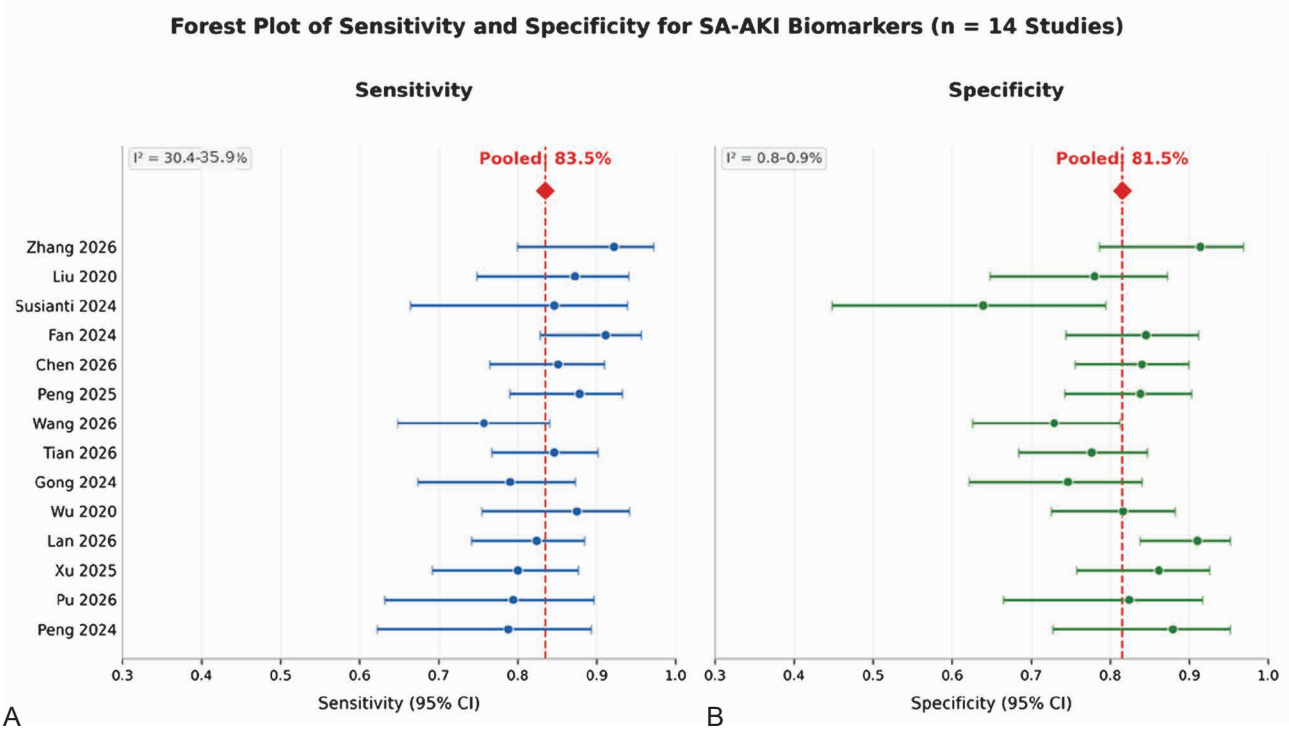


Figure 3. Forest Plots of Pooled Sensitivity and Specificity for Non-coding RNA Biomarkers in Diagnosing SA-AKI
(A) Forest plot showing individual study sensitivities with 95% confidence intervals and the pooled sensitivity estimate (diamond). Heterogeneity was low to moderate (I^2: 30.4 to 35.9%); (B) Forest plot showing individual study specificities with 95% confidence intervals and the pooled specificity estimate (diamond). Heterogeneity was very low (I^2: 0.8 to 0.9%). The pooled estimates were derived from a bivariate random-effects model of 14 studies (1,840 patients) (AUC = 0.885).

statistically significant for sensitivity (P = .848) or specificity (P = .495), supporting the absence of small-study effects. Begg's rank correlation test yielded, P = .157 for sensitivity; and P = .079 for specificity, likewise indicating no significant funnel-plot asymmetry. Trim-and-fill analysis (L0 estimator) identified 2 potentially missing studies for sensitivity, with the adjusted pooled sensitivity (82.6%) remaining close to the original estimate (83.5%). Using the R0 estimator, no missing studies were identified for specificity, and the adjusted pooled specificity (81.5%) was unchanged. These findings suggest that publication bias is unlikely to have substantially influenced the pooled estimates.

Subgroup Analysis

To explore potential sources of heterogeneity and to evaluate the diagnostic performance of biomarkers across different clinical and methodological contexts, we performed subgroup analyses based on sampling time (Early vs. at Diagnosis), sample type (Serum vs. Plasma vs. Urine vs. Serum / Cells), and detection method (SYBR Green vs. TaqMan). The results of the subgroup analyses are summarized in Table 4.

Subgroup Analysis by Sampling Time

Subgroup analysis based on sampling time revealed that biomarkers measured early (within 24 hours of ICU admission or prior to clinical AKI diagnosis) demonstrated a pooled sensitivity of 83.8% (95% CI: 79.7 to 87.3%) and a pooled specificity of 81.0% (95% CI: 77.0 to 84.5%).

Biomarkers measured at diagnosis (concurrent with clinical AKI diagnosis based on KDIGO criteria) demonstrated a pooled sensitivity of 84.8% (95% CI: 79.8 to 88.8%) and a pooled specificity of 81.6% (95% CI: 69.7 to 89.5%).

Notably, biomarkers measured at diagnosis showed slightly higher sensitivity (84.8 vs. 83.8%) compared to early sampling. However, the confidence intervals for both subgroups overlapped substantially, indicating no statistically significant difference between the two-timing groups. The subgroup analysis by sampling time is presented in Table 4 and Figure 6A.

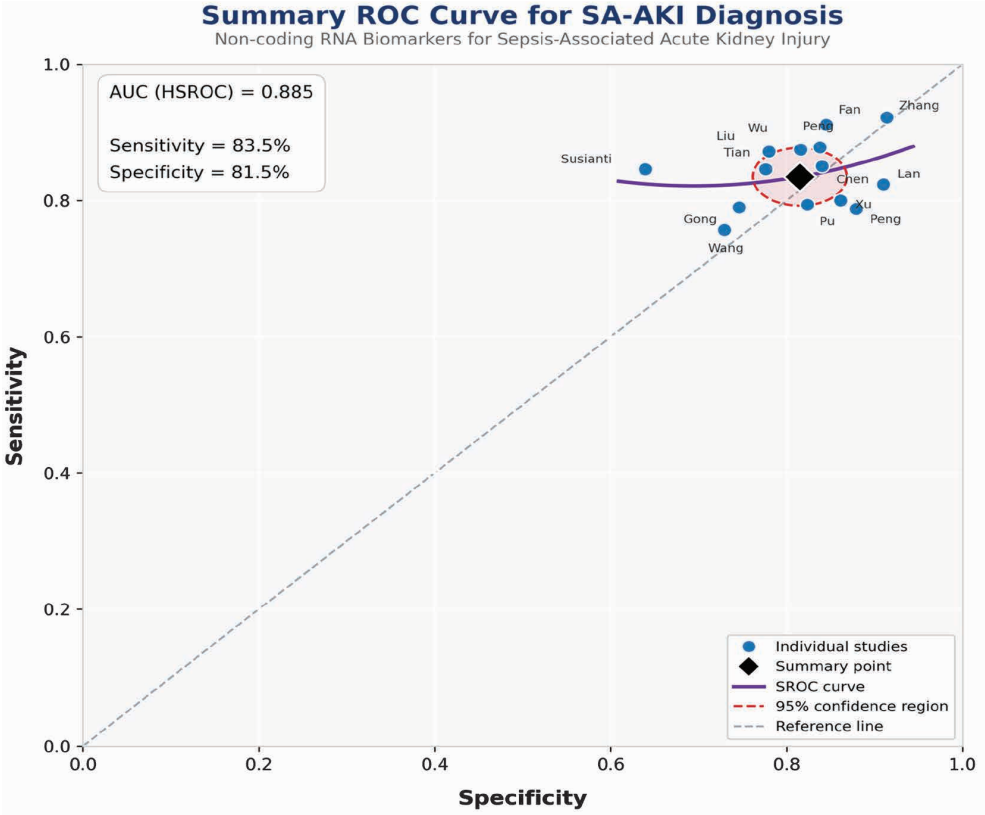


Figure 4. Summary Receiver Operating Characteristic (SROC) Curve for Non-coding RNA Biomarkers in Diagnosing SA-AKI
Blue circles represent individual study estimates. The red diamond represents the summary estimate (sensitivity = 83.5%, specificity = 81.5%). The red dashed ellipse indicates the 95% confidence region. The purple line represents the SROC curve. The area under the curve (AUC) was 0.885, indicating excellent diagnostic accuracy. Analysis included 14 studies with 1,840 patients.

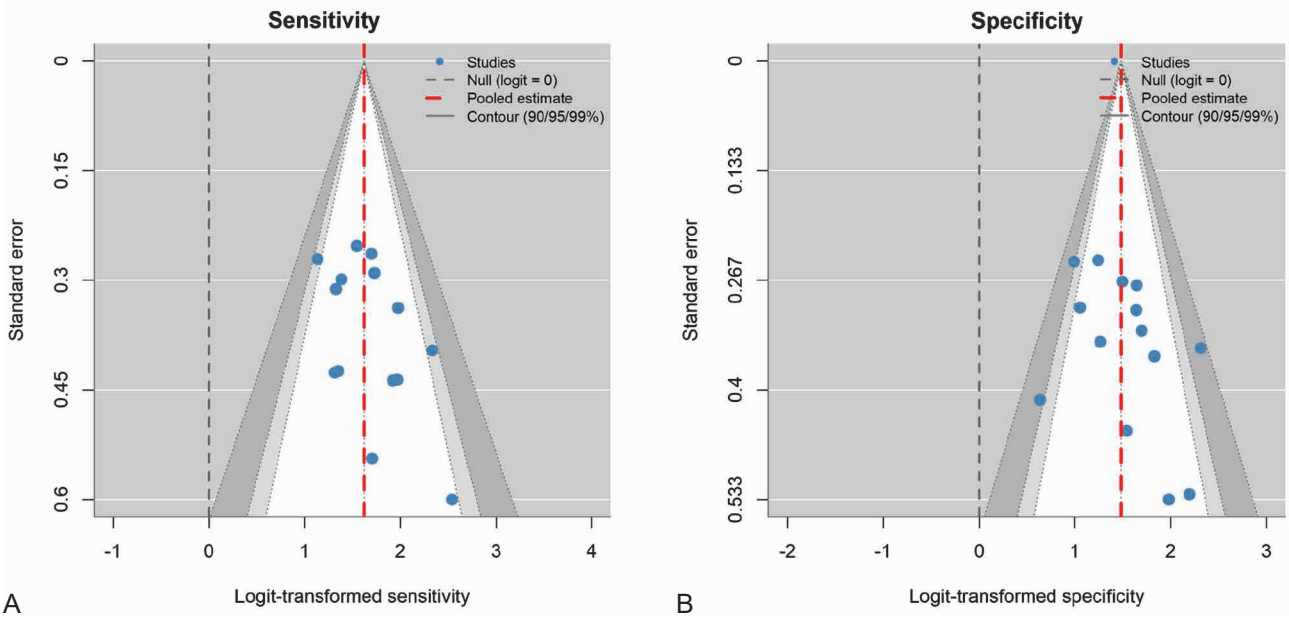


Figure 5. Funnel Plots for Publication Bias Assessment
(A) Funnel plot for logit-transformed sensitivity; (B) Funnel plot for logit-transformed specificity. Blue circles represent individual studies. The grey dashed vertical line marks the null value (logit = 0); the red dashed vertical line marks the pooled estimate. The shaded regions represent the pseudo-90, 95, and 99% confidence contours. Visual inspection of both panels suggests approximate symmetry, consistent with the non-significant Egger's regression test (sensitivity, $P = .848$; specificity, $P = .495$) and Begg's rank correlation test (sensitivity, $P = .157$; specificity, $P = .079$).

Table 4. Subgroup Analysis of Individual Biomarkers

Subgroup	Studies	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	AUC
Sampling Time				
Early	10	83.8 (79.7–87.3)	81.0 (77.0–84.5)	0.889
At Diagnosis	4	84.8 (79.8–88.8)	81.6 (69.7–89.5)	0.869
Sample Type				
Serum	9	85.1 (80.6–88.6)	79.9 (75.3–83.9)	0.891
Urine	2	83.4 (72.7–90.4)	82.4 (71.1–89.8)	0.895
Plasma	3	81.0 (74.3–86.2)	88.1 (81.4–92.6)	0.868
Detection Method				
SYBR Green	11	83.5 (79.7–86.6)	80.6 (76.5–84.2)	0.888
TaqMan	2	87.5 (79.3–92.8)	80.4 (73.0–86.1)	0.897
Same miRNA (Cross-Study Comparison)				
miR-210 (pooled)	2	89.2 (73.6–96.1)	80.0 (45.9–95.0)	0.918

Abbreviations. CI, confidence interval; AUC, area under the curve.
Note. Values are pooled estimates (%) with 95% CI.

Subgroup Analysis by Sample Type

Subgroup analysis by sample type revealed that serum samples (n = 9 studies) demonstrated the highest sensitivity (85.1%, 95% CI: 80.6 to 88.6%) and the highest mean AUC (0. 0.891), with a specificity of 79.9% (95% CI: 75.3 to 83.9%). Plasma samples (n = 3 studies) showed the highest specificity (88.1%, 95% CI: 81.4 to 92.6%) but lower sensitivity (81.0%, 95% CI: 74.3 to 86.2%), with a mean AUC of 0.868. Urine samples (n = 2 studies) demonstrated balanced diagnostic performance with a sensitivity of 83.4% (95% CI: 72.7 to 90.4%), specificity of 82.4% (95% CI: 71.1 to 89.8%), and mean AUC of 0.895 (Figure 6B).

Subgroup Analysis by Detection Method

Subgroup analysis based on detection method revealed that studies using SYBR Green (n = 11 studies) demonstrated a pooled sensitivity of 83.5% (95% CI: 79.7 to 86.6%) and a pooled specificity of 80.6% (95% CI: 76.5 to 84.2%). Studies using TaqMan (n = 2 studies) demonstrated a pooled sensitivity of 87.5% (95% CI: 79.3 to 92.8%) and a pooled specificity of 80.4% (95% CI: 73.0 to 86.1%). SYBR Green-based assays showed comparable diagnostic performance to TaqMan assays, with overlapping confidence intervals for both sensitivity and specificity. The subgroup analysis by detection method is presented in Table 4 and Figure 6C.

Same miRNA Cross-Study Comparison (miR-210)

To assess the consistency of diagnostic performance across independent cohorts, we performed a cross-study comparison of studies evaluating the same miRNA biomarker. Two studies evaluated miR-210 (Zhang *et al.* 2026 and Susianti *et al.* 2024). The pooled sensitivity for miR-210 was 89.2% (95% CI: 73.6 to 96.1%), and the pooled specificity was 80.0% (95% CI: 45.9 to 95.0%). Despite the wide confidence intervals due to the limited number of studies, miR-210 consistently demonstrated good diagnostic performance across both cohorts, supporting its potential as a reliable biomarker for SA-AKI. The cross-study comparison of miR-210 is presented in Table 4.

DISCUSSION

This systematic review and meta-analysis of 14 studies encompassing 1,840 patients demonstrates that circulating microRNAs (miRNAs) and circular RNAs (circRNAs) possess good-to-excellent diagnostic accuracy for sepsis-associated acute kidney injury (SA-AKI), diagnosed according to Sepsis-3[36] and KDIGO[37] criteria. The pooled sensitivity was 83.5% and specificity was 81.5%, with an HSROC-derived AUC of 0.885. The pooled diagnostic odds ratio of 22.29 indicates that patients with SA-AKI were, on average, more than 20 times more likely to have an elevated biomarker than sepsis patients without AKI — a magnitude comparable to, and in several respects exceeding, that reported for established renal injury biomarkers in critically ill populations.[9-11] These findings extend a growing body of evidence that non-coding RNAs represent a mechanistically distinct class of injury-responsive biomarkers that

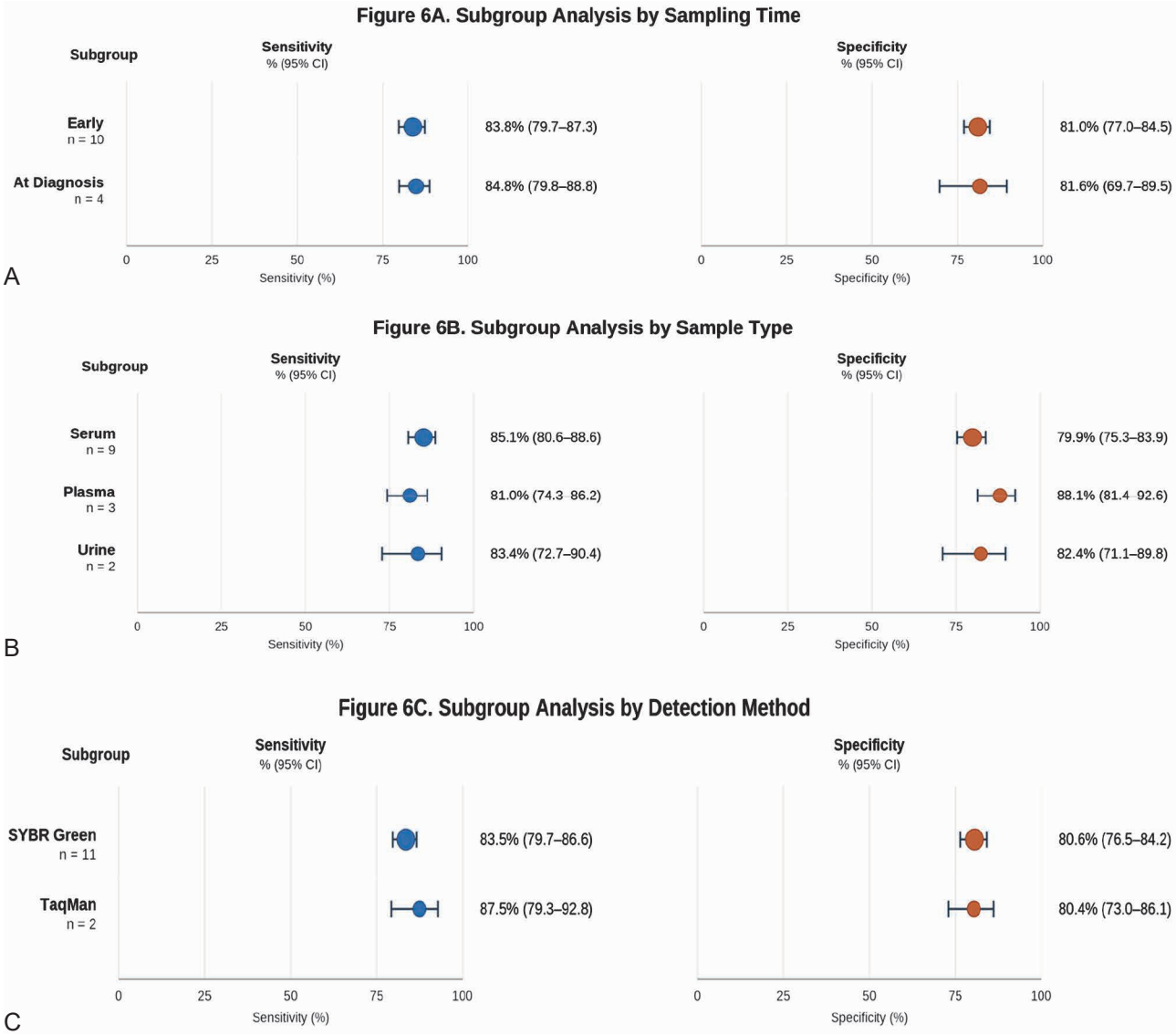


Figure 6. Forest Plots of Subgroup Analyses
(A) Forest plot showing pooled sensitivity and specificity by sampling time (early vs. at diagnosis); (B) Forest plot showing pooled sensitivity and specificity by sample type (serum, plasma, and urine); (C) Forest plot showing pooled sensitivity and specificity by detection method (SYBR Green vs. TaqMan). Error bars represent 95% CI. Subgroup analysis showed comparable performance across sampling times and detection methods, with serum samples demonstrating the highest sensitivity (85.1%) and plasma samples demonstrating the highest specificity (88.1%).

may complement, and in some contexts outperform, conventional markers of kidney function.

SA-AKI remains a major driver of morbidity and mortality in critically ill patients and substantially increases the risk of progression to chronic kidney disease and death.[1-6] Serum creatinine and urine output, the criteria on which the KDIGO definition of AKI is built, are insensitive to early tubular injury and are confounded by fluid balance, muscle mass, and the physiological trajectory of sepsis itself.[7,8] This diagnostic lag has motivated a search for biomarkers capable of detecting injury before functional decline becomes apparent. Protein-based candidates such as NGAL, KIM-1, and the cell-cycle arrest markers TIMP-2•IGFBP7 have been the most extensively studied to date,[9-11] and a recent our meta-analysis of serum and urinary NGAL specifically in SA-AKI reported pooled accuracy in a broadly similar range to these findings,[12] suggesting that non-coding RNA biomarkers can perform competitively with the most mature protein biomarkers in this field rather than representing a

categorically inferior alternative. Compared with earlier, broader systematic reviews of miRNAs spanning all AKI etiologies,[23,24] which pooled heterogeneous populations including cardiac surgery; contrast-induced, and sepsis-related AKI together and reported wider, less consistent accuracy estimates, our sepsis-restricted analysis benefits from a more homogeneous clinical context, likely explaining the comparatively narrow confidence intervals around our pooled estimates despite the modest number of included studies. A recent narrative review focused specifically on microRNAs in septic AKI[25] similarly concluded that miRNAs are mechanistically well-suited biomarker candidates for this condition, though it did not provide pooled diagnostic accuracy estimates which is a gap the present meta-analysis address directly.

The diagnostic performance observed here is consistent with the underlying biology of the candidate markers. miR-210, the most frequently evaluated biomarker in our dataset and the only one assessed in more than one study, is a well-characterized "hypoxamir" induced by hypoxia-inducible factor-1α under low-oxygen conditions,[13,14] a state relevant to both septic microcirculatory dysfunction and tubular hypoxic injury. Its release into the circulation has previously been linked to survival in critically ill patients with AKI,[16] and its consistent performance across the two independent cohorts in our cross-study comparison (pooled sensitivity 89.2%, specificity 80.0%) despite differing countries, sample types, and assay platforms supports genuine biological relevance rather than a single-cohort artifact. miR-21, another prominently studied sepsis-related miRNA, modulates innate immune signaling via TLR4/PDCD4 and has demonstrated organ-protective effects in preclinical models of ischemic preconditioning against sepsis,[15,17,18] providing mechanistic grounding for its diagnostic signal. circRNAs, meanwhile, are increasingly recognized as stable, protease- and RNase-resistant molecules that act as competing endogenous RNAs; ciRs-126 has previously been shown to predict survival in critically ill AKI patients,[20] and the two SA-AKI-specific circRNAs included here (hsa_circ_0072463 and hsa_circ_0056869) have documented regulatory roles in tubular injury pathways in mechanistic follow-up of the same cohorts.[21,22] The convergence of plausible mechanism and empirical diagnostic performance strengthens confidence that these associations are unlikely to reflect chance alone.

Between-study heterogeneity was low to moderate depending on the estimation approach, and was negligible under methods designed for the correlated sensitivity–specificity structure of diagnostic accuracy data.[31,33,38] This consistency was corroborated by our subgroup analyses: neither sampling time (early vs. at diagnosis) nor detection chemistry (SYBR Green vs. TaqMan) significantly altered pooled accuracy, and confidence intervals overlapped substantially across all comparisons. This is clinically reassuring, as it suggests the diagnostic signal is not an artifact of a particular assay platform or a narrow sampling window, and that biomarker measurement obtained either at ICU admission or at the time of clinical AKI diagnosis may be similarly informative. Sample type showed a more interpretable pattern: serum yielded the highest sensitivity and mean AUC, while plasma yielded the highest specificity — a trade-off that may reflect differences in pre-analytical RNA stability and clotting-related contamination between matrices[19] rather than a true difference in underlying biomarker performance, and one that warrants direct head-to-head comparison in future prospective cohorts using matched serum and plasma from the same patients.

The QUADAS-2 assessment indicated generally good methodological quality, with the majority of studies at low risk of bias across all four domains.[28] The one domain of concern was the reference standard, where one study was judged unclear risk for not explicitly reporting the AKI diagnostic criteria used; because diagnostic thresholds directly determine case ascertainment, this is the most consequential potential source of bias in the dataset and should be weighted accordingly when interpreting the pooled estimates. Reassuringly, formal assessment of small-study effects did not suggest meaningful publication bias: funnel plots were visually symmetric; Egger's regression test with sample size as the predictor was non-significant for both sensitivity (P = .848) and specificity (P = .495),[34] Begg's rank correlation test

was likewise non-significant (sensitivity, $P = .157$; specificity, $P = .079$) ; and trim-and-fill analysis identified only 2 potentially missing studies for sensitivity, with the adjusted pooled estimate (82.6%) remaining close to the original (83.5%) and no missing studies for specificity. Together, these findings indicate that the overall conclusions are unlikely to be driven by selective reporting of positive results.

Several limitations should temper the interpretation of these findings. First, the evidence base remains small: only 14 studies met inclusion criteria, and 12 of 14 individual biomarkers were evaluated in only a single study, precluding meaningful biomarker-specific pooling for any candidate other than miR-210. Second, 13 of the 14 studies (92.9%) originated from China, raising concerns about generalizability to populations with different sepsis epidemiology, genetic backgrounds, and clinical practice patterns; external validation in geographically and ethnically diverse cohorts is a priority for future work. Third, 2×2 contingency data for several studies were back-calculated from reported sensitivity, specificity, and sample size rather than extracted directly from source publications, introducing a small degree of rounding-related imprecision, though this is a common and generally well-tolerated limitation in diagnostic meta-analyses of this type. Additionally, one included study (Fan *et al.*) reported an impossible AUC value of 1.91; we corrected this to 0.910 based on the reported sensitivity and specificity, but this approximation introduces some imprecision. Fourth, considerable methodological heterogeneity existed in RNA extraction kits, normalization strategies (endogenous references ranging from U6 to GAPDH), and detection platforms across studies; despite the reassuring subgroup analysis by detection chemistry, the two-study TaqMan arm is underpowered to rule out unmeasured technical variability. None of the included studies reported head-to-head comparisons against established protein biomarkers such as NGAL or KIM-1 within the same patient cohort, precluding a direct within-study assessment of whether non-coding RNA biomarkers add incremental diagnostic value over, or in combination with, currently available tests. Finally, we did not systematically extract or report whether included studies enrolled patients with septic shock, excluded them, or included them alongside non-shock sepsis patients. Only 2 of the 14 included studies reported any cohort-level hemodynamic data: Fan *et al.* recorded norepinephrine dosage, and Tian *et al.* reported vasopressor requirement (38.2% in SA-AKI vs. 30.6% in non-AKI). The remaining studies either did not report this information or mentioned septic shock only in the introduction as background. Septic shock is a distinct clinical phenotype within sepsis — defined by Sepsis-3 as sepsis requiring vasopressors plus elevated lactate despite adequate fluid resuscitation — and it carries substantially higher mortality and distinct AKI pathophysiology. Because biomarkers may perform differently in shock versus non-shock sepsis, the generalizability of our pooled estimates to shock-specific or non-shock-specific populations remains uncertain

Future studies should prioritize external validation of miR-210 and other leading candidates in multi-center, multi-ethnic cohorts using prespecified sampling protocols and standardized normalization strategies to reduce assay-related heterogeneity. Head-to-head or combined-panel studies pairing non-coding RNA biomarkers with NGAL, KIM-1, or established clinical risk scores would clarify whether they offer incremental value as an adjunct rather than a replacement for existing tools. Future diagnostic accuracy studies should also systematically report the proportion of patients with septic shock, vasopressor use, and lactate levels at enrollment, and stratify diagnostic performance by shock status to clarify whether non-coding RNA biomarkers retain their accuracy across the full spectrum of sepsis severity. Given the mechanistic diversity captured here including hypoxia signaling (miR-210), innate immune regulation (miR-21), and circRNA-mediated competing endogenous RNA networks, combination biomarker panels integrating markers from distinct pathophysiological pathways may ultimately outperform any single non-coding RNA, an approach supported by the modestly superior performance of multi-marker panel strategies reported in the broader AKI biomarker literature.

CONCLUSIONS

This metaanalysis demonstrates that circulating

noncoding RNAs, particularly miR210, miR155, miR1323p, and miR7695p, have good to excellent diagnostic accuracy for SAAKI (sensitivity = 83.5%, specificity = 81.5%, AUC = 0.885). Their biological plausibility, stability, and potential for early detection make them promising biomarkers, though the predominance of Chinese studies and lack of headtohead comparisons with established markers warrant caution. Prospective multicenter validation studies are needed before clinical implementation.

DECLARATIONS

Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary materials and are available from the corresponding author upon reasonable request.

Acknowledgements

The authors did not receive external technical or editorial assistance for this work. Artificial intelligence–based tools were used only for language editing and to improve clarity and flow of the manuscript. All study design, data extraction, statistical analyses, interpretation of results, and final manuscript content were performed and verified by the authors. The authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their help and support in conducting this study.

Conflict of Interest

Ilad Alavi Darazam serves as members of the RJCCN editorial team. The author had no involvement in the peerreview or editorial decisionmaking processes for this manuscript.

Funding

This study received no specific funding from public, commercial, or notforprofit funding agencies.

Author Contributions

F.J.G. conceived the study, designed the protocol, performed data extraction, statistical analysis, and drafted the manuscript. L.L. independently screened studies, verified extracted data, and contributed to interpretation of results. DG performed data extraction, statistical analysis. I.A.D. Conceptualization, Supervision, Manuscript review & editing and Correspondence with journal. All authors have participated in drafting or editing the manuscript.

REFERENCES

1. Fleischmann-Struzek C, Mellhammar L, Rose N, Cassini A, Rudd KE, Schlattmann P, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. Intensive Care Med. 2020;46(8):1552-62.
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395(10219):200-11.
3. Bagshaw SM, George C, Bellomo R; ANZICS Database Management Committee. Early acute kidney injury and sepsis: a multicentre evaluation. Crit Care. 2008;12(2):R47.
4. Hoste EAJ, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411-23.
5. Poston JT, Koyner JL. Sepsis associated acute kidney injury. BMJ. 2019;364:k4891.
6. Zarbock A, Nadim MK, Pickkers P, Gomez H, Bell S, Joannidis M, et al. Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup. Nat Rev Nephrol. 2023;19(6):401-17.
7. Endre ZH, Pickering JW, Walker RJ. Clearance and beyond: the complementary roles of GFR measurement and injury biomarkers in acute kidney injury (AKI). Am J Physiol Renal Physiol. 2011;301(4):F697-F707.
8. Ostermann M, Bellomo R, Burdmann EA, Doi K, Endre ZH, Goldstein SL, et al. Controversies in acute kidney injury: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. Kidney Int. 2020;98(2):294-309.
9. Bihorac A, Chawla LS, Shaw AD, Al-Khafaji A, Davison DL, DeMuth GE, et al. Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. Am J Respir Crit Care Med. 2014;189(8):932-9.
10. Devarajan P. Neutrophil gelatinase-associated lipocalin (NGAL): a new marker of kidney disease. Scand J Clin Lab Invest Suppl. 2008;241:89-94.
11. Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney injury molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int. 2002;62(1):237-44.
12. Javandoust Gharehbagh F, Lotfollahi L, Nassiri AA, Alavi Darazam I. Diagnostic accuracy of serum and urinary neutrophil gelatinase-associated lipocalin for predicting sepsis-associated acute kidney injury: a systematic review and meta-analysis. Res J Crit Care Nephrol.

2026;2(2):133-48.

13. Chan YC, Banerjee J, Choi SY, Sen CK. miR-210: the master hypoxamir. Microcirculation. 2012;19(3):215-23.
14. Fasanaro P, D'Alessandra Y, Di Stefano V, Melchionna R, Romani S, Pompilio G, et al. MicroRNA-210 modulates endothelial cell response to hypoxia and inhibits the receptor tyrosine kinase ligand Ephrin-A3. J Biol Chem. 2008;283(23):15878-83.
15. Jia P, Wu X, Dai Y, Teng J, Fang Y, Hu J, et al. MicroRNA-21 is required for local and remote ischemic preconditioning in multiple organ protection against sepsis. Crit Care Med. 2017;45(7):e703-e10.
16. Lorenzen JM, Kielstein JT, Hafer C, Gupta SK, Kümpers P, Faulhaber-Walter R, et al. Circulating miR-210 predicts survival in critically ill patients with acute kidney injury. Clin J Am Soc Nephrol. 2011 Jul;6(7):1540-6.
17. Sheedy FJ, Palsson-McDermott E, Hennessy EJ, Martin C, O'Leary JJ, Ruan Q, et al. Negative regulation of TLR4 via targeting of the proinflammatory tumor suppressor PDCD4 by the microRNA miR-21. Nat Immunol. 2010 Feb;11(2):141-7.
18. Tahamtan A, Teymoori-Rad M, Nakstad B, Salimi V. Anti-inflammatory microRNAs and their potential for inflammatory diseases treatment. Front Immunol. 2018;9:1377.
19. Weber JA, Baxter DH, Zhang S, Huang DY, Huang KH, Lee MJ, et al. The microRNA spectrum in 12 body fluids. Clin Chem. 2010 Nov;56(11):1733-41.
20. Kölling M, Seeger H, Haddad G, Kistler AD, Nowak A, Faulhaber-Walter R, et al. The circular RNA ciRs-126 predicts survival in critically ill patients with acute kidney injury. Kidney Int Rep. 2018 Sep;3(5):1144-52.
21. Peng X, Li H, Zhang W, Zhang D. Discovery and verification of mmu_Circ_26986/hsa_Circ_0072463 as a potential biomarker and intervention target for sepsis-associated acute kidney injury. Cell Mol Life Sci. 2024;81(1):154.
22. Pu Y, Tang X, Wu C, Li H, Feng Y, Wu L, et al. Mmu_Circ_0001022/hsa_Circ_0056869-miRNA-92a-2-5p/SKI axis suppressed the progression of sepsis-associated acute kidney injury. Int Immunopharmacol. 2026;170:116045.
23. Brown N, Roman M, Miller D, Murphy G, Woźniak MJ. A systematic review and meta-analysis of microRNA as predictive biomarkers of acute kidney injury. Biomedicines. 2024;12(8):1695.
24. Douvris A, Viñas JL, Akbari S, Tailor K, Lalu MM, Burger D, et al. Systematic review of microRNAs in human acute kidney injury. Ren Fail. 2024;46(2):2419960.
25. Nikolov G, Nikolov D, Naydenov M, Stefanov C. Micro RNAs in septic acute kidney injury: pathophysiology, biomarkers and therapeutic targets. Folia Med (Plovdiv). 2026;68(2):e166581.
26. Zankar S, Rodriguez RA, Vinas JL, Burns KD. The therapeutic effects of microRNAs in preclinical studies of acute kidney injury: a systematic review protocol. Syst Rev. 2019;8(1):235.
27. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg. 2021;88:105906.
28. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.
29. Reitsma JB, Glas AS, Rutjes AWS, Scholten RJPM, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol. 2005 Oct;58(10):982-90.
30. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med. 2001 Oct 15;20(19):2865-84.
31. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004;23(9):1351-75.
32. Fan H, Sun M, Zhu JH. Clinical role of serum microRNA-155 in early diagnosis and prognosis of septic patients with acute kidney injury. Int Urol Nephrol. 2024;56(5):1687-94.
33. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
34. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
35. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088-101.
36. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.
37. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013;17(1):204.
38. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.
39. Zhang Z, Zhang Z, Liu J, Qiao L, Fan X. Diagnostic value and prognostic significance of microRNA-210, serum creatinine, neutrophil gelatinase-associated lipocalin, blood urea nitrogen, cystatin C, and sequential organ failure assessment scores in patients with sepsis-associated acute kidney injury. Front Med (Lausanne). 2026;12:1671599.
40. Liu Z, Yang D, Gao J, Xiang X, Hu X, Li S, et al. Discovery and validation of miR-452 as an effective biomarker for acute kidney injury in sepsis. Theranostics. 2020;10(26):11963-75.
41. Susianti H, Sutrisnani CS, Santosa IPA, Febrianto W, Kusdjianto AY, Kuwoyo KP, et al. Evaluation of microRNA-10a and microRNA-210 as biomarkers in sepsis patients with acute kidney injury. Int J Nephrol. 2024;2024:1555811.
42. Chen Q, Zhu G. miR-4772-3p serves as a potential diagnostic and prognostic biomarker in septic acute kidney injury by targeting CISD2. Ren Fail. 2026;48(1):2665541.

43. Peng Y, Sun X, Ma Y, Yang X, Zhao Y, Jia Y, et al. miR-769-5p has diagnostic value in acute kidney injury in intensive care unit patients and mediates disease development by targeting SIRT6. BMC Nephrol. 2025;26(1):337.

44. Wang X, Li H, Yu X, Li M. miR-379-5p serves as a biomarker and regulates sepsis-associated acute kidney injury via targeting EDN1. BMC Immunol. 2026;27(1):76.

45. Tian Y, Zhu H, Wang J, Wang L, Liu L, Gui X. Predictive value of miR-151a-3p for the onset of sepsis-induced acute kidney injury and its functional role during disease development. BMC Immunol. 2026;27(1):82.

46. Gong B, Chen J, Yu H, Li S. Clinical significance of miR-625-5p in patients with sepsis-induced acute kidney injury based on bioinformatics analysis. Int Urol Nephrol. 2025;57(2):603-11.

47. Wu SY, Zhang H, Wu W, Wu YY. Value of serum miR-21-3p in predicting acute kidney injury in children with sepsis. Zhongguo Dang Dai Er Ke Za Zhi. 2020;22(3):269-73.

48. Lan C, Shen M, Liao J, Yuan H, Liu N. Predictive value of miR-132-3p for the onset of sepsis-induced acute kidney injury and its functional role during disease development. Per Med. 2026;23(3):179-89.

49. Xu L, Li J, Li L, Zhang Q, Feng Q, Bai L. Exploring miR-577 and miR-494-3p as emerging biomarkers in sepsis-associated acute kidney injury: diagnostic and prognostic perspectives. Microbiol Immunol. 2025;69(5):297-306.

Correspondence to:
Ilad Alavi Darazam, MD
Attending Physician (Infectious Diseases), Clinical Fellowship in Immunodeficiency and Transplantation Infectious Diseases (Infectious Diseases and Tropical Medicine)
Address: Department of Infectious Diseases, Loghman Hakim Hospital, Makhsoos St, South Kargar Ave, Tehran, Iran
ORCID ID: 0000-0002-4440-335X
E-mail: Ilad13@yahoo.com, Ilad.alavi@sbmu.ac.ir

Received July 2026
Revised August 2026
Accepted September 2026

RJCCN ORIGINAL PAPER
KIDNEY DISEASE

Epidemiological Characteristics of Children with Nephrotic Syndrome Referred to Amir-Kabir Hospital in Arak, Iran: A Cross-Sectional Study

Parsa Yousefichaijan,[1] Fatemeh Rafiei,[2] Masoud Rezagholizamenjany[3]

[1]Clinical Research Development Center of Amir-Kabir Hospital, Arak University of Medical, Arak, Iran
[2]Department of Epidemiology and Biostatistics, Tehran University of Medical Science, Tehran, Iran
[3]Department of Pediatrics, Arak University of Medical Sciences, Arak, Iran

Keywords. nephrotic syndrome, children, epidemiology, hypoalbuminemia, hypercholesterolemia, Iran

© 2026 Author(s). This article is licensed under the CC By 4.0 International License.

Introduction. Nephrotic syndrome is one of the most common glomerular diseases in childhood and is associated with significant morbidity and healthcare burden. Understanding its epidemiological and clinical characteristics is essential for improving patient management and outcomes. To investigate the epidemiological, clinical, and laboratory characteristics of children diagnosed with nephrotic syndrome referred to Amir-Kabir Hospital, Arak, Iran.

Methods. This cross-sectional study was conducted on 100 children diagnosed with nephrotic syndrome. Participants were enrolled using a census sampling method. Demographic, socioeconomic, perinatal, clinical, and laboratory data were collected from medical records and structured interviews. Data were analyzed using SPSS version 21 and presented as mean ± standard deviation, frequency, and percentage.

Results. Among the 100 patients, 51% were male and 49% were female. The mean age was 7.87 ± 3.12 years. Preterm birth was reported in 53% of patients. Hypoalbuminemia (< 2.5 g/dL) was observed in all patients, while hypercholesterolemia (> 350 mg/dL) was present in 69%. Prerenal azotemia, microscopic hematuria, urinary tract infection, allergy, and hyponatremia were observed in 56, 54, 38, 42, and 55% of patients; respectively. Periorbital edema was the most common clinical presentation (43%). Maternal risk factors included preeclampsia (38%), diabetes (52%), and hypertension (45%).

Conclusions. Children with nephrotic syndrome demonstrated a high prevalence of metabolic abnormalities, edema, and maternal prenatal risk factors. Early recognition of these characteristics may improve disease management and prognosis.

RJCCN 2026; 2: 272-8
www.rjccn.org
DOI: 10.61882/rjccn.2.4.71

INTRODUCTION

Nephrotic syndrome (NS) is one of the most common glomerular disorders in childhood and is characterized by massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia. Despite advances in diagnosis and treatment, NS remains an important cause of morbidity in children because of its relapsing course, risk of complications, and impact on quality of life.[1] The incidence of childhood nephrotic syndrome varies

Please cite this article as: Yousefichaijan P, Rafiei F, Rezagholizamenjany M. Epidemiological Characteristics of Children with Nephrotic Syndrome Referred to Amir-Kabir Hospital in Arak, Iran: A Cross-Sectional Study. RJCCN. 2026;2(4):272-8.

worldwide, with reported rates ranging from 2 to 7 cases per 100,000 children annually. Although most cases are classified as idiopathic nephrotic syndrome and respond well to corticosteroid therapy, many patients experience frequent relapses or develop treatment-related complications. In addition to renal manifestations, children with NS are at increased risk of infections, thromboembolic events, electrolyte disturbances, and acute kidney injury.[2]

Several demographics, environmental, and perinatal factors have been suggested to influence the occurrence and clinical presentation of nephrotic syndrome. Previous studies have reported associations between NS and factors such as sex, family history, consanguinity, preterm birth, maternal hypertension, diabetes, and other prenatal conditions.[3] However, the reported findings have varied across populations, indicating the importance of regional epidemiological investigations.[4]

In developing countries, comprehensive data regarding the epidemiological and clinical characteristics of childhood nephrotic syndrome remain limited. In Iran, most published studies have focused on treatment outcomes or pathological findings, while fewer studies have evaluated demographic, socioeconomic, maternal, clinical, and laboratory characteristics simultaneously.[5]

A better understanding of the epidemiological profile of children with nephrotic syndrome may facilitate early diagnosis, improve patient management, and identify potential risk factors associated with disease development and progression. Therefore, the present study aimed to investigate the demographic, perinatal, clinical, and laboratory characteristics of children diagnosed with nephrotic syndrome who were referred to Amir-Kabir Hospital in Arak, Iran.

MATERIALS AND METHODS

Study Design and Setting

This cross-sectional study was conducted at Amir-Kabir Hospital, a tertiary pediatric referral center in Arak, Iran.

Participants

The study population consisted of all children diagnosed with nephrotic syndrome who attended the pediatric nephrology clinic during the study period. A total of 100 patients were included using a census sampling method.

Inclusion Criteria

- Confirmed diagnosis of nephrotic syndrome.
- Age < 18 years.

Exclusion Criteria

- Presence of chronic hematological disorders.
- Presence of other chronic systemic diseases.
- Use of medications or supplements for unrelated chronic illnesses.
- Incomplete clinical records.

Data Collection

Data were obtained from medical records and face-to-face interviews with parents or guardians using a structured questionnaire.

Collected variables included:

- Demographic characteristics
- Socioeconomic status
- Parental educational level
- Birth history
- Maternal medical conditions
- Family history
- Clinical manifestations
- Laboratory findings
- Treatment-related variables

Statistical Analysis

Data were analyzed using SPSS software version 21. Quantitative variables were presented as mean ± SD, while categorical variables were expressed as frequencies and percentages.

Ethical Considerations

The study was approved by the Ethics Committee of Arak University of Medical Sciences (IR.ARAKMU.REC.1395.277). Written informed consent was obtained from parents or legal guardians before participation.

RESULTS

Baseline Characteristics of Study Population

A total of patients with nephrotic syndrome were categorized into four clinical response groups: steroid-responsive (SR), steroid-dependent (SD),

steroid-resistant (SRNS), and frequently relapsing nephrotic syndrome (FRNS). Baseline demographic and clinical characteristics were compared among the four groups.

Sex Distribution Among Nephrotic Syndrome Subgroups

A significant difference was observed in sex distribution among the studied groups (P = .004). Female patients represented the majority of the steroid-responsive group (76%), whereas male predominance was observed in steroid-dependent (76%), steroid-resistant (52%), and frequently relapsing groups (52%) (Table 1).

Clinical Manifestations at Diagnosis

Urinary Tract Infection and Microscopic Hematuria. The prevalence of urinary tract infection did not significantly differ among the four groups (P = .133). However, microscopic hematuria showed a significant association with clinical subgroup (P = .001). The frequency of microscopic hematuria was markedly higher among steroid-resistant (76%), steroid-dependent (68%), and frequently relapsing patients (64%) compared with steroid-responsive patients (8%) (Table 2).

Inflammatory Marker and Electrolyte Abnormalities. Positive CRP levels were significantly more frequent in patients with steroid-dependent, steroid-resistant, and frequently relapsing disease compared with steroid-responsive patients (60, 56, and 64% vs. 16%; respectively, P = .001). Serum sodium abnormalities also differed significantly among groups (P = .001). Hyponatremia was more prevalent in steroid-resistant (80%) and frequently relapsing patients (64%), whereas normal sodium levels were predominant in steroid-responsive patients (84%) (Table 2).

Edema Characteristics at Initial Presentation. The distribution of edema location at diagnosis significantly differed among clinical groups (P = .001). Periorbital/facial edema was the most common presentation in steroid-responsive patients (64%). In contrast, anasarca was predominantly observed among steroid-resistant patients (60%), while ascites was more frequent in steroid-dependent patients (44%) (Table 3).

Perinatal and Maternal Factors Associated with Disease Subgroups

Mode of Delivery. A significant association was observed between mode of delivery and

Table 1. Demographic and Baseline Characteristics of Children with Nephrotic Syndrome According to Clinical Subgroup

Variable	Category	Steroid-responsive (n = 25)	Steroid-dependent (n = 25)	Steroid-resistant (n = 25)	Frequently relapsing (n = 25)	*P*
Sex	Male	6 (24%)	19 (76%)	13 (52%)	13 (52%)	.004
	Female	19 (76%)	6 (24%)	12 (48%)	12 (48%)	
BMI at diagnosis	Obesity	1 (4%)	5 (20%)	13 (52%)	4 (20%)	.001
	Overweight	5 (20%)	7 (28%)	5 (20%)	11 (44%)	
	Normal	14 (56%)	10 (40%)	6 (24%)	2 (8%)	
	Underweight	5 (20%)	3 (12%)	1 (4%)	8 (32%)	
Delivery mode	Vaginal	16 (64%)	19 (76%)	13 (52%)	18 (72%)	.001
	Cesarean	9 (36%)	6 (24%)	12 (48%)	7 (28%)	

Table 2. Clinical and Laboratory Characteristics at Diagnosis According to Nephrotic Syndrome subgroup

Variable	Category	Steroid-responsive	Steroid-dependent	Steroid-resistant	Frequently relapsing	*P*
UTI	Present	6 (24%)	9 (36%)	9 (36%)	14 (56%)	.133
	Absent	19 (76%)	16 (64%)	16 (64%)	11 (44%)	
Microscopic hematuria	Present	2 (8%)	17 (68%)	19 (76%)	16 (64%)	.001
	Absent	23 (92%)	8 (32%)	6 (24%)	9 (36%)	
CRP	Positive	4 (16%)	15 (60%)	14 (56%)	16 (64%)	.001
	Negative	21 (84%)	9 (36%)	11 (44%)	9 (36%)	
Serum Na	Normal	21 (84%)	9 (36%)	5 (20%)	9 (36%)	.001
	High	0	1 (4%)	0	0	
	Low	4 (16%)	15 (60%)	20 (80%)	16 (64%)	

Table 3. Clinical Presentation and Maternal Factors Associated with Nephrotic Syndrome Phenotype

Variable	Category	Steroid-responsive	Steroid-dependent	Steroid-resistant	Frequently relapsing	*P*
Edema location at diagnosis	Face / eyes	16 (64%)	11 (44%)	9 (36%)	7 (28%)	.001
	Ascites	0	11 (44%)	0	1 (4%)	
	Hands / feet	0	2 (8%)	0	2 (8%)	
	Anasarca	2 (8%)	0	15 (60%)	5 (20%)	
	Face / eyes + ascites	6 (24%)	1 (4%)	1 (4%)	7 (28%)	
Maternal preeclampsia	Present	1 (4%)	11 (44%)	13 (52%)	13 (52%)	.004
	Absent	24 (96%)	14 (56%)	12 (48%)	12 (48%)	
Maternal eclampsia	Present	3 (12%)	0	1 (4%)	1 (4%)	.432
	Absent	22 (88%)	25 (100%)	24 (96%)	24 (96%)	
Maternal diabetes	Pregestational DM	2 (8%)	6 (24%)	10 (40%)	5 (20%)	.118
	Gestational DM	6 (24%)	6 (24%)	9 (36%)	8 (32%)	
	No DM	17 (68%)	13 (52%)	6 (24%)	12 (48%)	

nephrotic syndrome subgroup (P = .001). Vaginal delivery was the predominant mode in all groups; however, cesarean delivery was relatively more frequent among steroid-resistant patients (48%) compared with other groups (Table 1).

Maternal Pregnancy Complications. A history of maternal preeclampsia was significantly associated with nephrotic syndrome phenotype (P = .004). The frequency of preeclampsia increased from 4% in steroid-responsive patients to 44%, 52%, and 52% in steroid-dependent, steroid-resistant, and frequently relapsing groups, respectively.

No significant difference was observed regarding maternal eclampsia history among the groups (P = .432) (Table 3).

Anthropometric Characteristics at Diagnosis. BMI classification differed significantly among the studied groups (P = .001). Obesity was most prevalent among steroid-resistant patients (52%), whereas normal BMI was more common in steroid-responsive patients (56%). The frequently relapsing group showed a higher proportion of overweight (44%) and underweight (32%) patients compared with other groups (Table 1).

Corticosteroid Initiation Timing and Disease Phenotype

The interval between edema onset and corticosteroid initiation was significantly associated with clinical phenotype (P = 0.001). Early initiation of corticosteroid therapy within one week was most common among steroid-responsive patients (76%). Conversely, delayed initiation was observed more frequently among steroid-resistant patients (68% after two weeks) and frequently relapsing patients (64% after three weeks) (Table 4).

Maternal Diabetes Status. Maternal diabetes status was not significantly associated with nephrotic syndrome subgroup classification (P = .118). However, pregestational diabetes was more frequent among steroid-resistant patients (40%), while absence of maternal diabetes was more common among steroid-responsive patients (68%) (Table 3).

DISCUSSION

Childhood nephrotic syndrome is a heterogeneous glomerular disorder characterized by significant proteinuria, hypoalbuminemia, and edema, with a highly variable response to corticosteroid therapy. Although the majority of children achieve remission with glucocorticoids, a considerable proportion experience steroid dependency, frequent relapses, or steroid resistance, which are associated with prolonged immunosuppressive treatment and increased risk of chronic kidney

Table 4. Relationship Between Corticosteroid Initiation Timing and Nephrotic Syndrome Subgroup

Time from edema onset to corticosteroid initiation	Steroid-responsive	Steroid-dependent	Steroid-resistant	Frequently relapsing	*P*
≤ 1 week	19 (76%)	13 (52%)	3 (12%)	2 (8%)	.001
2 weeks	4 (16%)	6 (24%)	17 (68%)	7 (28%)	
3 weeks	2 (8%)	6 (24%)	5 (20%)	16 (64%)	

disease. Identification of clinical and laboratory factors associated with unfavorable phenotypes may improve early risk stratification and allow more individualized therapeutic approaches.[2,6]

In the present study, several demographic, clinical, laboratory, and maternal factors were associated with different clinical phenotypes of nephrotic syndrome. Sex distribution differed significantly among the groups, with a higher proportion of females in the steroid-responsive group and a predominance of males among steroid-dependent, steroid-resistant, and frequently relapsing patients. Childhood nephrotic syndrome has consistently been reported to have a male predominance, particularly in younger children; however, the association between sex and steroid response remains inconsistent across studies. Previous investigations suggest that sex alone is unlikely to determine treatment response, and differences may instead reflect variations in genetic susceptibility, immune regulation, or underlying histopathological patterns.[7]

Microscopic hematuria was significantly more frequent among steroid-dependent, steroid-resistant, and frequently relapsing patients compared with steroid-responsive patients in our cohort. Hematuria is considered an atypical finding in classic minimal change disease, which accounts for the majority of steroid-sensitive nephrotic syndrome cases. In contrast, persistent hematuria may suggest more extensive glomerular injury and has been associated with pathological lesions such as focal segmental glomerulosclerosis (FSGS), which is more commonly associated with steroid resistance and poorer renal outcomes.[5,8] Therefore, the presence of microscopic hematuria at presentation may serve as a useful clinical marker for identifying patients who require closer monitoring and further evaluation.

We also observed a significant association between inflammatory status and nephrotic syndrome phenotype. Elevated CRP levels were considerably more common among steroid-dependent, steroid-resistant, and frequently relapsing groups compared with steroid-responsive patients. Although nephrotic syndrome is primarily driven by immune dysregulation and podocyte injury rather than systemic inflammation, increasing evidence indicates that inflammatory pathways, cytokine abnormalities, and immune cell activation contribute to alterations in glomerular permeability and disease progression.[9] The higher frequency of CRP positivity among patients with unfavorable responses may therefore reflect greater inflammatory activity or more severe disease expression.

Serum sodium abnormalities, particularly hyponatremia, were significantly associated with disease subgroup in our study. Hyponatremia was more prevalent among steroid-resistant and frequently relapsing patients, whereas normal sodium levels were more common among steroid-responsive children. Electrolyte disturbances in nephrotic syndrome may occur as a consequence of severe proteinuria, reduced effective circulating volume, activation of neurohormonal pathways, and increased secretion of antidiuretic hormone despite total body fluid excess.[10] The association between hyponatremia and unfavorable disease characteristics may indicate a greater degree of physiological disturbance at disease onset.

The pattern of edema at diagnosis showed significant differences among clinical groups. Periorbital edema was the most common initial manifestation in steroid-responsive patients, whereas generalized edema (anasarca) was more frequent among steroid-resistant children. The severity of edema reflects the extent of urinary protein loss, hypoalbuminemia, and disturbances in fluid distribution. Although edema pattern is not currently included among formal predictors of steroid response, extensive edema at presentation may represent a marker of higher disease burden and more severe clinical presentation.[2]

An important finding of the present study was the association between BMI category and nephrotic syndrome phenotype. Obesity was markedly more frequent among steroid-resistant patients, whereas normal BMI was more common among steroid-responsive children. Obesity has emerged as an important modifier of kidney disease through mechanisms involving chronic inflammation, oxidative stress, insulin resistance, altered adipokine production, and podocyte injury. Previous studies have demonstrated that increased body weight may be associated with increased proteinuria and

accelerated progression of renal disease; however, whether obesity directly contributes to steroid resistance or reflects underlying disease severity remains uncertain.[11,12]

Maternal preeclampsia was significantly associated with unfavorable nephrotic syndrome phenotypes in our study. Children born to mothers with a history of preeclampsia showed higher frequencies of steroid dependency, steroid resistance, and frequent relapse compared with steroid-responsive patients. Preeclampsia is characterized by placental dysfunction, endothelial injury, and impaired fetal development, and accumulating evidence suggests that adverse intrauterine environments may influence lifelong renal susceptibility through altered nephron development and renal programming.[13] Although this association is biologically plausible, further prospective studies are required to confirm whether maternal vascular disorders contribute directly to childhood glomerular disease susceptibility.

In contrast, maternal eclampsia and diabetes status were not significantly associated with nephrotic syndrome phenotype. The absence of significant associations may be related to the relatively small number of affected mothers, limiting statistical power. Additionally, the relationship between maternal metabolic disorders and childhood kidney disease is complex and may involve multiple genetic, environmental, and developmental factors.

The timing of corticosteroid initiation was strongly associated with clinical phenotype. Steroid-responsive patients were more likely to receive corticosteroid therapy within one week of edema onset, whereas delayed initiation was more common among steroid-resistant and frequently relapsing patients. Early diagnosis and prompt initiation of standard corticosteroid therapy remain central components of childhood nephrotic syndrome management.[2] However, delayed treatment may represent a consequence of more severe or atypical disease rather than an independent cause of poor response. Therefore, this finding should be interpreted cautiously and requires confirmation in prospective studies.

Taken together, our findings indicate that childhood nephrotic syndrome phenotypes are associated with a combination of clinical, laboratory, anthropometric, and maternal characteristics. The presence of microscopic hematuria, elevated CRP, hyponatremia, severe edema, obesity, maternal preeclampsia history, and delayed corticosteroid initiation may help identify patients at increased risk of steroid resistance or frequent relapse. Incorporating these factors into early clinical assessment may improve prediction of treatment response and support individualized management strategies.

The present study has several limitations. The observational design limits the ability to establish causal relationships between associated factors and disease outcomes. In addition, kidney biopsy findings, genetic testing, and long-term renal outcomes were not available for all patients, which may have provided further insight into mechanisms underlying steroid resistance. Future multicenter prospective studies integrating clinical, pathological, and molecular data are warranted.

CONCLUSIONS

The present study identifies several factors associated with unfavorable nephrotic syndrome phenotypes, including microscopic hematuria, elevated CRP, hyponatremia, severe edema, obesity, maternal preeclampsia, and delayed corticosteroid initiation. Recognition of these characteristics may improve early risk stratification and facilitate personalized management of children with nephrotic syndrome.

REFERENCES

1. Vivarelli M, Gibson K, Sinha A, Boyer O. Childhood nephrotic syndrome. The Lancet. 2023;402(10404):809-24.
2. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. The Lancet. 2018;392(10141):61-74.
3. Hahn D, Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. Cochrane database of systematic reviews. 2015(3).
4. Park SJ, Shin JI. Complications of nephrotic syndrome. Korean journal of pediatrics. 2011;54(8):322.
5. Gipson DS, Massengill SF, Yao L, Nagaraj S, Smoyer WE, Mahan JD, et al. Management of childhood onset nephrotic syndrome. Pediatrics. 2009;124(2):747-57.
6. Wang C-s, Gbadegesin R. KDOQI US Commentary on the KDIGO 2025 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children.

American Journal of Kidney Diseases. 2026;87(2):141-52.

7. Vivarelli M, Massella L, Ruggiero B, Emma F. Minimal change disease. Clinical Journal of the American Society of Nephrology. 2017;12(2):332-45.
8. Trautmann A, Vivarelli M, Samuel S, Gipson D, Sinha A, Schaefer F, et al. IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome. Pediatric Nephrology. 2020;35(8):1529-61.
9. Shalhoub R. Pathogenesis of lipoid nephrosis: a disorder of T-cell function. The Lancet. 1974;304(7880):556-60.
10. Eddy AA, Symons JM. Nephrotic syndrome in childhood. The lancet. 2003;362(9384):629-39.
11. Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD. Obesity-related glomerulopathy: an emerging epidemic. Kidney international. 2001;59(4):1498-509.
12. Chagnac A, Weinstein T, Korzets A, Ramadan E, Hirsch J, Gafter U. Glomerular hemodynamics in severe obesity. American Journal of Physiology-Renal Physiology. 2000;278(5):F817-F22.
13. Luyckx VA, Brenner BM. Low birth weight, nephron number, and kidney disease. Kidney International. 2005;68:S68-S77.

Correspondence to:
Masoud Rezagholizamenjany, MD
Department of Pediatrics, Arak University of Medical Sciences, Arak, Iran
ORCID ID: 0000-0002-5824-2366
E-mail: masoudrezagholi074@gmail.com

Received July 2026
Revised August 2026
Accepted September 2026

ORIGINAL PAPER DIALYSIS RJCCN

Association of Dialysis Adequacy and Estimated Kidney Function with Mineral Metabolism Parameters in Patients Undergoing Peritoneal Dialysis

Mojgan Mortazavi,[1] Romina Rahimifar,[2] Shiva Seirafian,[3] Pantea Miralaei[1]

[1]Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[3]Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran

Keywords. peritoneal dialysis, chronic kidney disease, mineral metabolism, eGFR, KT/V

© 2026 Author(s). This article is licensed under the CC By 4.0 International License.

Introduction. In terminal CKD, imbalance of calcium and phosphate can lead to complications such as skeletal and cardiovascular involvements. Disturbances in mineral metabolism are common among patients with advanced CKD and may be influenced by dialysis adequacy and estimated kidney function. We aimed to evaluate selected serum mineral metabolism parameters and their associations with dialysis adequacy and estimated kidney function in patients undergoing PD.

Methods. This cross-sectional study included 85 adult patients undergoing PD. eGFR was calculated using the CKD-EPI equation, and urea Kt/V was used as a measure of dialysis adequacy. An independent-samples t-test was used to compare calcium and phosphate levels between patients with Kt/V < 1.7 and those with Kt/V ≥ 1.7.

Results. The mean age was 55.91 ± 16.45 years, and 52.9% were male. The mean serum calcium level differed significantly according to the number of daily PD exchanges (P = .034). Tukey's post-hoc analysis showed a significant difference between patients receiving two and three exchanges per day (P = .048), with a higher mean calcium concentration in patients receiving two exchanges per day. Serum calcium showed a modest positive correlation with eGFR, while serum phosphate showed significant inverse correlations with urea Kt/V and eGFR. No significant differences in serum calcium or phosphate were observed between patients with Kt/V < 1.7 and those with Kt/V ≥ 1.7.

Conclusions. These findings suggest an association between dialysis adequacy, estimated kidney function, and selected biochemical parameters of mineral metabolism. However, the cross-sectional design does not permit causal inference.

RJCCN 2026; 2: 279-88
www.rjccn.org
DOI: 10.61882/rjccn.2.4.63

INTRODUCTION

Chronic kidney disease (CKD) involves a variety of pathophysiological processes with abnormal renal function and progressive decline in glomerular filtration rate.[1,2] Disturbances in mineral metabolism are particularly common in advanced CKD and include abnormalities in serum phosphate, calcium, PTH, vitamin D metabolism, and bone turnover.

Please cite this article as: Mortazavi M, Rahimifar R, Seirafian S, Miralaei P. Association of Dialysis Adequacy and Estimated Kidney Function with Mineral Metabolism Parameters in Patients Undergoing Peritoneal Dialysis. RJCCN. 2026;2(4):279-88.

These abnormalities are important components of CKD-mineral and bone disorder (CKD-MBD) and have been associated with cardiovascular complications and adverse outcomes. Studies over the last 20 years have shown the impact of biochemical changes on the survival and quality of life of patients with CKD-MBD.[3,4] Prevention and correction of hyperphosphatemia is a major goal of the treatment of CKD–MBD, so special attention must be given to phosphate balance.[5] In terminal chronic kidney disease most patients have hyperphosphatemia, elevated parathyroid hormone (PTH) levels, elevated levels of Fibroblast Growth Factor 23 (FGF23), and low vitamin D levels because the calcium (Ca) and phosphate (Ph) control mechanisms are disrupted and inadequate. Previous studies have shown this imbalance disturbs the regulation of calcium and phosphorus levels in the blood which can lead to complications such as skeletal, cardiovascular, and sometimes, severe extracellular soft tissue involvement.[3,6,7] High serum phosphate is the most important risk factor for cardiovascular disease. Therefore, control of serum phosphate levels should be considered one of the most important therapeutic goals in patients with CKD.[5,8] A retrospective study conducted by Liu CT *et al.* indicated that serum calcium level of ≥ 9.5 mg/dL, serum phosphate levels of either ≥ 6.5 mg/dL or < 3.5 mg/dL and alkaline phosphatase (ALP) level of ≥ 100 IU/L were correlated with increased mortality, but higher serum levels of PTH did not have any association with increased mortality.[9]

Renal replacement therapy in patients with CKD consists of dialysis which has two forms: hemodialysis (HD) and peritoneal dialysis (PD). Xianglei Kong *et al.* documented that serum Ca and Ph levels were statistically higher ($P < .05$) in the HD patients in comparison with those of PD patients, but serum PTH level was statistically higher in the PD patients in comparison with those of HD patients ($P = .03$).[10]

PD may influence mineral metabolism through several mechanisms, including dialysis adequacy, residual kidney function, and the composition of the dialysis solution. In particular, the calcium concentration of the dialysate may influence calcium balance and PTH regulation. Glucose concentration affects ultrafiltration and volume management, while icodextrin-containing solutions may provide sustained ultrafiltration during long dwell periods. These factors may indirectly influence the management of mineral metabolism abnormalities in PD patients.[11,12]

Given the above, most studies of mineral metabolism disorders have been performed in patients undergoing hemodialysis, and fewer studies have been conducted in patients undergoing PD.

Furthermore, the relationship between dialysis adequacy and serum phosphate is clinically relevant because phosphate removal may occur through both peritoneal and residual renal clearance. Previous studies have suggested an association between phosphate clearance and measures of urea clearance in PD patients.[13]

The present study therefore aimed to evaluate selected serum mineral metabolism parameters, including calcium, phosphate, PTH, ALP, and vitamin D, and to determine their associations with dialysis adequacy and estimated kidney function in patients undergoing PD.

MATERIALS AND METHODS

This cross-sectional study has been verified by Isfahan University of Medical Sciences with ethical code "IR.MUI.MED.REC.1398.618" and was conducted in April 2020.

The study was conducted at Alzahra Hospital, affiliated with Isfahan University of Medical Sciences, Iran.

The study population consists of both male and female peritoneal dialysis patients from Alzahra Hospital who were chosen based on inclusion and exclusion criteria. Eighty-five patients who verified the inclusion criteria were selected.

Inclusion criteria include patients over the age of 18 who have been on peritoneal dialysis for at least 3 months and patients who have complete file information and tests.

Exclusion criteria include the patients who recorded any febrile infections in their medical records in the previous month, a history of metabolic disorders related to calcium and phosphate imbalances, and the patients who needed an acute change in the peritoneal dialysis solution in the

past month.

The data collected included variables of age, gender, underlying disease leading to renal failure, the type of peritoneal dialysis solutions, daily dialysis frequency, the serum levels of calcium, phosphate, parathyroid hormone, alkaline phosphatase, vitamin D, urea KT/V (which is considered a valid adequacy parameter concerning small solute clearance), and estimated Glomerular Filtration Rate (eGFR).[14]

The underlying causes of kidney disease were classified according to the diagnoses documented in the patients' medical records and included hypertension, diabetes mellitus, vesicoureteral reflux, polycystic kidney disease, nephrolithiasis, neurogenic bladder, glomerulonephritis, congenital kidney disease, trauma, and unknown/unspecified causes.[15]

All variables were extracted from the patient's medical record and laboratory tests.

Estimated GFR was calculated using the CKD-EPI equation and was considered an estimate of kidney function. In this study, eGFR was not considered equivalent to directly measured residual kidney function in patients receiving PD. Daily peritoneal dialysis exchanges included 2 to 6 times. Also, the type of peritoneal dialysis solutions included types 1.5, 2.5, and 4.25% glucose solutions and Extraneal solutions.

The last measured values of Serum levels of Ca, Ph, PTH, ALP, and Vitamin D were considered in the study. Furthermore, a 24-hour urinalysis test was used to calculate the patient's KT/V. Direct measurements of residual renal clearance and daily urine output were not systematically available for all participants and therefore could not be incorporated into the present analysis.

Statistical Analysis

Descriptive information for variables is expressed as mean and standard deviation for quantitative variables and frequency and percentage for qualitative variables.

One-way analysis of variance was used to compare the mean of calcium, phosphate, PTH, ALP, and Vit D in patients according to the type of peritoneal dialysis solution and the number of peritoneal dialysis exchanges per day.

In cases in which analysis of variance was significant, Tukey's post-test was used to identify the subgroups whose means were significantly different as well. Pearson correlation coefficient was also used to investigate the relationship between variables and dialysis adequacy and renal function. The Independent t-test was used to compare the mean serum levels of calcium and phosphate depending on the total KT/V < 1.7 and ≥ 1.7. All statistical operations were performed using SPSS software at an error level of $P < .05$.

RESULTS

The average age of participants was (55.91 ± 16.45) years. In this study, about 53% of subjects were male, and hypertension was the most common cause of chronic kidney disease. The present study also showed that 42.4% (36) patients were with total KT/V < 1.7 and 57.6% (49) subjects ≥ 1.7 (Table 1).

One-way analysis of variance resulted in the mean serum levels of calcium, phosphate, PTH, ALP, and vitamin D were not different significantly depending on the type of peritoneal dialysis solution ($P \geq .05$) (Table 2).

These findings indicate that, within this study population, the recorded type of PD solution was not significantly associated with the evaluated mineral metabolism parameters. However, the relatively small number of patients in some solution categories limits the interpretation of these comparisons.

Also, the one-way analysis of variance resulted in the mean serum level of calcium being different

Table 1. Descriptive Results of Variables

Variables	Categories	n (%)
Age (Mean)	-	55.91 (16.45)
Sex	Male	45 (52.9)
	Female	40 (47.1)
Causes	Congenital	2 (2.4)
	DM	19 (22.4)
	GN	3 (3.5)
	HTN	41 (48.23)
	Nephrolithiasis	1 (1.2)
	Neurogenic bladder	1 (1.2)
	PCKD	2 (2.4)
	Trauma	2 (2.4)
	Unknown	9 (10.6)
	VUR	5 (5.9)
KT/V	< 1.7	36 (42.4)
	≥ 1.7	49 (57.6)

Table 2. Comparison of Bone Mineral Metabolism Indexes by the Type of Peritoneal Dialysis Solution

Variables	PD solutions	Mean	SE	*P*
Ca	1.5% glucose	9.1944	.28588	
	1.5 and 2.5% glucose	9.1083	.22001	
	1.5 and 2.5% glucose & Extraneal	9.0857	.16421	
	1.5% glucose & Extraneal	8.9000	.13744	.626
	2.5% glucose	9.6000	0	
	2.5% glucose & Extraneal	9.0357	.11749	
	Extraneal	10.4000	.	
Ph	1.5% glucose	4.4294	.23837	
	1.5 and 2.5% glucose	4.6667	.35018	
	1.5 and 2.5% glucose & Extraneal	4.7819	.35517	
	1.5% glucose & Extraneal	5.0278	.24466	.179
	2.5% glucose	4.5000	0	
	2.5% glucose & Extraneal	5.7000	.30777	
	Extraneal	5.1000	0	
PTH	1.5% glucose	458.1222	106.15942	
	1.5 and 2.5% glucose	488.6017	120.28541	
	1.5 and 2.5% glucose & Extraneal	398.8414	125.82693	
	1.5% glucose & Extraneal	334.0072	63.07728	.961
	2.5% glucose	355.0000	0	
	2.5% glucose & Extraneal	412.2571	107.46337	
	Extraneal	167.0000	0	
ALP	1.5% glucose	275.9444	27.23961	
	1.5 and 2.5% glucose	291.5833	28.28948	
	1.5 and 2.5% glucose & Extraneal	313.2381	28.43170	
	1.5% glucose & Extraneal	303.1667	47.13850	.582
	2.5% glucose	529.0000	0	
	2.5% glucose & Extraneal	385.0714	79.61048	
	Extraneal	288.0000	0	
Vit D	1.5% glucose	26.3833	3.53330	
	1.5 and 2.5% glucose	32.4558	9.38076	
	1.5 and 2.5% glucose & Extraneal	31.7714	6.39555	
	1.5% glucose & Extraneal	27.4617	5.06375	.869
	2.5% glucose	18.3000	0	
	2.5% glucose & Extraneal	21.6286	2.93743	
	Extraneal	18.9000	0	

significantly depending on the number of daily peritoneal dialysis exchanges ($P = .034$) (Table 3), and the mean of phosphate, PTH, ALP, and vitamin D were not showed different significantly ($P \geq .05$) (Table 3). Tukey's post-test results indicated that the calcium-mean-difference between patients who were on dialysis twice a day and those with 3 times a day, was significant ($P = .048$), which was higher in patients who were on dialysis twice a day (Figure).

Pearson correlation coefficient was done to evaluate the relationship between variables of serum levels of calcium, phosphate, PTH, ALP, and Vit D and the dialysis adequacy (KT/V) and eGFR. The relationship between calcium and eGFR was significantly a direct relationship ($r = 0.22$, $P = .039$) (Table 4).

Serum phosphate showed significant inverse correlations with urea Kt/V ($r = -0.242$, $P = .026$) and eGFR ($r = -0.586$, $P < .001$) (Table 5).

The Independent t-test was done to compare the mean serum levels of calcium and phosphate depending on the total KT/V < 1.7 and ≥ 1.7 ($P = .458$). Similarly, the difference in mean serum phosphate between the two Kt/V groups did not reach statistical significance ($P = .062$) (Table 5).

Although serum phosphate was inversely correlated with Kt/V when Kt/V was analyzed as a continuous variable, categorization of Kt/V into < 1.7 and ≥ 1.7 did not demonstrate a statistically

Table 3. Comparison of Bone Mineral Metabolism Indexes by the Number of Peritoneal Dialysis Exchanges per Day

Variables	PD exchanges	Mean	SE	*P*
Ca	2	10.0333	.59255	
	3	9.0333	.13978	
	4	8.9731	.10342	.034
	5	9.2000	.14720	
	6	9.5000	.10000	
Ph	2	4.5717	.40481	
	3	4.7057	.21691	
	4	4.9808	.19765	.854
	5	5.0250	.61424	
	6	5.3500	.85000	
PTH	2	329.2000	89.91744	
	3	351.4976	51.01384	
	4	434.9071	68.92623	.841
	5	563.7500	341.05483	
	6	282.0000	73.00000	
ALP	2	367.3333	30.13267	
	3	260.3714	38.30322	
	4	313.3308	19.34578	.172
	5	466.0000	258.84390	
	6	440.0000	89.00000	
Vit D	2	23.1667	5.61199	
	3	22.5952	2.84599	
	4	30.4169	3.74717	.719
	5	30.4500	7.07124	
	6	24.4500	6.15000	

Table 4. The Relationship Between Bone Mineral Metabolism Indexes with Dialysis Adequacy and Residual Renal Function

Variables	eGFR	KT/V
Ca		
Pearson correlation	.224*	-.145
P	.039	.184
Ph		
Pearson correlation	-.586*	-.242*
P	.000	.026
PTH		
Pearson correlation	-.097	.125
P	.376	.255
ALP		
Pearson correlation	.126	-.154
P	.251	.160
Vit D		
Pearson correlation	-.140	-.016
P	.202	.885

significant difference in mean phosphate levels.

DISCUSSION

The present study evaluated selected biochemical parameters of mineral metabolism in patients undergoing PD and examined their associations with dialysis adequacy and estimated kidney function. The main findings were that serum calcium differed

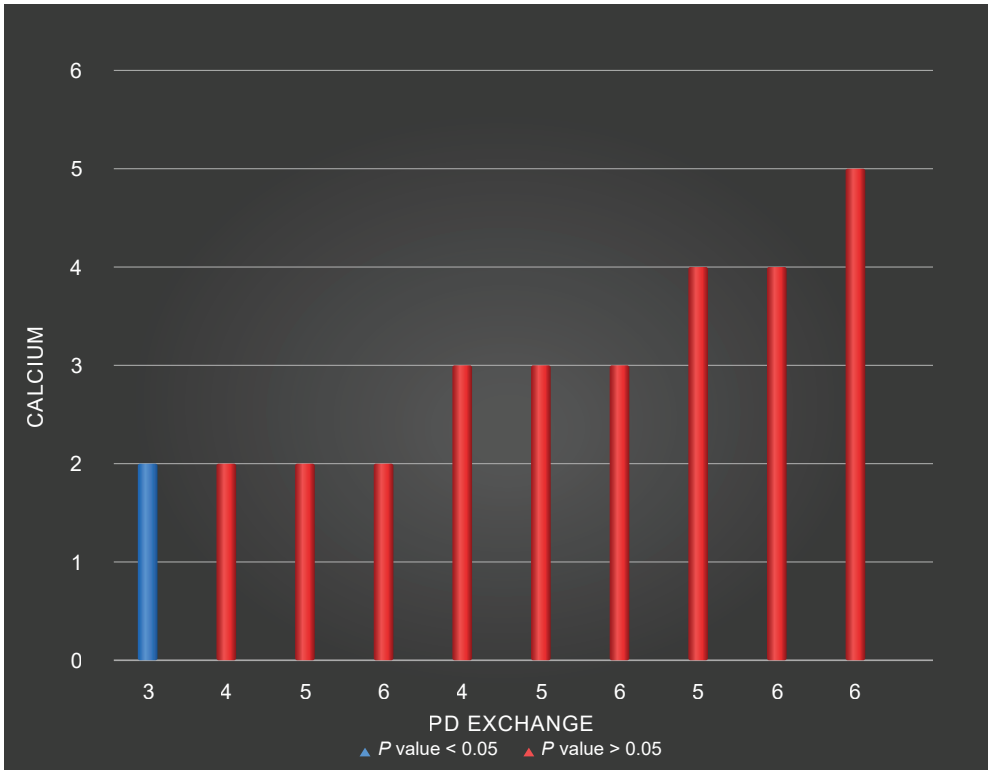


Figure 1.

Table 5. The Comparison of the Mean Serum Levels of Calcium and Phosphate, Depending on the Total KT/V < 1.7 and ≥ 1.7

KT/V	Mean	STD	*P* (independent t-test)
Ca			
< 1.7	9.1639	.88387	.458
≥ 1.7	9.0286	.73824	
Ph			
< 1.7	5.1953	1.42292	.062
≥ 1.7	4.6739	1.11793	

according to the number of daily PD exchanges, serum calcium was positively correlated with eGFR, and serum phosphate was inversely correlated with both eGFR and urea Kt/V. The results revealed that the mean of serum Ca level was different depend on the number of dialysis sessions.

However, this finding should be interpreted cautiously. Although the overall ANOVA was statistically significant, the only significant pairwise comparison was between the groups receiving two and three exchanges per day. PD prescriptions are individualized according to several clinical factors, including volume status, solute clearance, residual kidney function, and patient characteristics. Therefore, confounding by treatment indication cannot be excluded.

Although it is not clear whether low levels of Ca are detrimental, high levels are known to be associated with a poor prognosis.[16,17] Vascular calcification due to a high level of Ca is an important pathological condition that affects survival prognosis. Also, the prevalence of aortic and cardiac valve calcification is much higher in patients with higher serum adjusted-calcium levels.[18] In the present study, however, clinical outcomes such as vascular calcification, bone density, fractures, or cardiovascular events were not directly evaluated. Therefore, our findings should be interpreted as associations involving biochemical mineral metabolism parameters rather than a comprehensive assessment of CKD-MBD.

Chen Z *et al.* have come to this conclusion that the combination of low serum PTH and high serum ALP levels was independently associated with higher cardiovascular mortality in peritoneal dialysis patients.[19] Doi *et al.* documented that a serum calcium level > 8.5 mg/dL at hemodialysis initiation was associated with poor outcomes one year after dialysis initiation,[20] but only a few other reports have described similar findings. Thus, managing of Ca level is more important in the dialysis process.

The finding of the present cross-sectional study suggests a direct relationship between eGFR and serum Ca in men and women selected from a population sample, but this relationship does not indicate a cause-and-effect one. Because this study was cross-sectional, the observed association does not establish a causal relationship. It cannot be determined whether lower calcium levels contribute to declining kidney function or whether reduced kidney function contributes to alterations in calcium metabolism.

Therefore, it not simply means that lower serum Ca levels impair kidney function, or, conversely, that lower serum Ca levels are a consequence of a rapid decrease in GFR. A 1-year follow-up study of a general non-CKD Japanese population, documented that lower serum Ca levels, even when they were within a normal physiological range, were a significant risk factor for a rapid decrease in GFR, independent of metabolic risk factors for kidney dysfunction such as blood pressure, diabetes and dyslipidemia. In the above-mentioned study, multivariable correlation analysis revealed serum Ca levels as the best correlated with GFR variation after adjustment with multiple factors ($\beta = 0.184$, $P < .001$). It means that serum Ca level is related to several factors such as serum level of Vit D and PTH; lower serum Ca level appears not to be simply a reflection of existing or current kidney dysfunction but is a reflection of a steady or rapid decrease in GFR.[21] Also, we found an inverse relationship between serum Ph and eGFR and peritoneal dialysis adequacy, KT/V.

The inverse association between serum phosphate and eGFR is biologically plausible because declining kidney function reduces renal phosphate excretion and may lead to phosphate retention.[22] The inverse association between serum phosphate and Kt/V may reflect the contribution of adequate dialysis to phosphate removal. Previous studies have reported associations between phosphate clearance and urea clearance in patients undergoing PD.[23] However, Kt/V is primarily a measure of small-solute clearance and does not directly quantify phosphate

clearance. Serum phosphate is also influenced by dietary phosphate intake, phosphate binder therapy, residual kidney function, bone turnover, and other factors.[22] Therefore, the observed association should not be interpreted as evidence of a causal effect of increasing Kt/V on serum phosphate. Serum phosphate is used to monitor Ph retention that is a consequence of low glomerular filtration rate and a determinant of severe metabolic bone disease and the cardiovascular system of patients with kidney failure.[24] In agree with our findings, John GB *et al.* in a prospective cohort analysis including 1492 patients indicated when the glomerular filtration rate decreases, serum phosphate level increases, and becomes especially significant in CKD stage G4.[25] Selamet U *et al.* showed in patients with GFR of less than 30 mL/min/ 1.73 m^2 serum phosphate concentration increased because renal function decreased.[26] An inverse relationship between kidney function and serum Ph could be explained by changes in the level of parathyroid hormone.[27,28] Phosphatonins[29] and active vitamin D[30,31] secondary to GFR reduction.

To investigate whether dialysate calcium concentrations were significantly associated with cardiac function, in a study conducted by Wang Z *et al.*, a total of 60 PD patients were registered, with a calcium content of the PD solution of 1.25 mmol/L in 30 patients (low-calcium group) and 1.75 mmol/L in 30 patients (standard-calcium group). They showed that no significant difference in calcium, phosphorus, parathyroid hormone (PTH), blood pressure, etc., have been found between the two groups after 12-month follow-up. The same study also showed that residual renal function, which is associated with left ventricular diastolic function, was significantly decreased in the standard-calcium group in comparison with the low-calcium group (5.64 ± 3.23 vs. 9.38 ± 3.17; $P = .001$). The data collected by the above-mentioned researchers suggested that low calcium dialysate treatment is significantly associated with better left ventricular diastolic function.[32]

Hence, the limited information on dietary factors should have played a minor role, if any. Another possible limitation was the collection of data on a single ethnic group residing in one town. An inverse relationship between KT/V and serum Ph level in this study could be explained by the higher phosphate clearance that was associated with lower serum phosphorus. Joana Santos *et al.* evaluated if peritoneal phosphate clearance correlates to urea clearance in patients with peritoneal dialysis, and regression analysis in this study showed that phosphate clearance was associated with creatinine clearance ($r = 0.87$, $P < 0.001$) and with urea KT/V ($r = 0.74$, $P < .001$), also a negative correlation between peritoneal phosphate clearance and serum phosphate ($r = -5.19$, $P < .001$) but no correlation was found to PTH.[33] Also similar to the present study, Malgorzata Debowska *et al.* found that in automated peritoneal dialysis patients, the peritoneal and total phosphate clearances correlated positively with peritoneal and total urea KT/V, respectively. Also higher phosphate clearance was associated with lower serum phosphorus,[34] but in another study no correlations were found between KT/V and biochemical outcomes such as hemoglobin ($P = .4922$), calcium ($P = .650$), phosphate ($P = .508$), and phosphatase ($P = .091$) in hemodialysis patients.[35]

These findings are consistent with our observation that phosphate was inversely correlated with Kt/V. Nevertheless, differences in study populations, dialysis prescriptions, residual kidney function, dietary intake, and medication use should be considered when comparing these findings.

An important point is that the continuous correlation between phosphate and Kt/V should be distinguished from the categorical comparison according to Kt/V < 1.7 versus ≥ 1.7. In our study, the continuous correlation was statistically significant ($r = -0.242$, $P = .026$), whereas the difference in mean phosphate between the two Kt/V categories was not statistically significant ($P = .062$). Categorization of a continuous variable can reduce statistical information and statistical power and may therefore result in different findings.

Regarding PD solution type, dialysate composition may influence mineral metabolism. Dialysate calcium concentration can affect calcium balance and PTH regulation, whereas glucose concentration influences ultrafiltration and volume management. Icodextrin-containing solutions may provide sustained ultrafiltration during long dwell periods.[11]

In our study, no significant differences in calcium, phosphate, PTH, ALP, or vitamin D were observed according to PD solution type.

This finding should be interpreted cautiously because some solution categories contained relatively few patients. In addition, the selection of PD solution is individualized and may depend on clinical factors such as fluid status and dialysis requirements. Therefore, confounding by indication cannot be excluded.

The underlying cause of kidney disease may also influence mineral metabolism through differences in disease duration, comorbidities, nutritional status, inflammation, residual kidney function, and treatment patterns. Although the underlying kidney disease was recorded in our study, the relatively small sample size and the small number of patients in several individual disease categories prevented reliable subgroup analyses. Therefore, we cannot determine whether the underlying cause of CKD independently influenced mineral metabolism parameters.

Limitations

This study has several limitations. First, its cross-sectional design prevents assessment of temporal relationships and causal inference. Therefore, the observed associations between mineral metabolism parameters, eGFR, and Kt/V should not be interpreted as causal relationships.

Second, the study was conducted at a single center and included a relatively small number of patients. This limits the generalizability of the findings and reduced the ability to perform reliable subgroup analyses according to underlying kidney disease or specific PD prescriptions.

Third, detailed information regarding medications that may affect mineral metabolism, including vitamin D analogues, calcium supplements, phosphate binders, and calcimimetics, was not systematically available in the dataset. Consequently, treatment-related confounding could not be assessed or adjusted for.

forth, detailed information regarding dietary phosphate intake, nutritional status, inflammatory markers, and other factors that may affect serum phosphate and calcium was not comprehensively available.

Finally, some categories of PD solution type and exchange frequency included relatively few patients, which may have limited statistical power and increased uncertainty in subgroup comparisons.

CONCLUSION

Among patients undergoing peritoneal dialysis, serum phosphate was inversely associated with both urea Kt/V and eGFR, while serum calcium showed a modest positive association with eGFR. Serum calcium also differed according to the number of daily PD exchanges.

However, categorization of patients according to Kt/V < 1.7 versus ≥ 1.7 did not demonstrate significant differences in serum calcium or phosphate.

These findings suggest that dialysis adequacy and estimated kidney function may be associated with selected biochemical parameters of mineral metabolism in patients undergoing PD. However, the cross-sectional design, limited sample size, and lack of detailed information on medications and directly measured residual kidney function limit causal interpretation. Further prospective studies incorporating residual renal clearance, daily urine output, medication use, dietary factors, and longitudinal mineral metabolism measurements are warrant.

DECLARATIONS

Disclosure

Nothing to disclose.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Acknowledgements

we thank Hooman Hadian M.D for his useful suggestions.

Funding

we did not have any funding for this research.

Author's Contributions

Mojgan Mortazavi carried out the presented idea and supervised the findings of this work. Romina Rahimifar helped for data collection and analytic

calculation. Shiva Seirafian helped supervise the project and analytic calculation. Pantea Miralaei wrote the manuscript with support from other authors. All authors discussed the results and contributed to the final manuscript.

Conflict of Interest Statement

there is no conflict of interest in our study.

REFERENCES

1. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. The lancet. 2021;398(10302):786-802.
2. Egamberdieva G. PATHOPHYSIOLOGICAL BASIS OF CHRONIC DISEASE PROGRESSION: FROM CELLULAR STRESS TO ORGAN DYSFUNCTION. Journal of Clinical and Biomedical Research. 2026;1(1):41-5.
3. Cannata-Andía JB, Martín-Carro B, Martín-Vírgala J, Rodríguez-Carrio J, Bande-Fernández JJ, Alonso-Montes C, et al. Chronic kidney disease—mineral and bone disorders: pathogenesis and management. Calcified tissue international. 2021;108:410-22.
4. Jiang H, Wang J, Fan M, Xu Y, Xia J, Yin L. Association of routine laboratory parameters with chronic kidney disease-mineral and bone disorder in patients on maintenance hemodialysis: A retrospective study. Science Progress. 2026;109(3):00368504261481408.
5. Waziri B, Duarte R, Naicker S. Chronic kidney disease–mineral and bone disorder (CKD-MBD): current perspectives. International journal of nephrology and renovascular disease. 2019:263-76.
6. Haarhaus M, Monier-Faugere M-C, Magnusson P, Malluche HH. Bone alkaline phosphatase isoforms in hemodialysis patients with low versus non-low bone turnover: a diagnostic test study. American Journal of Kidney Diseases. 2015;66(1):99-105.
7. Sardiwal S, Magnusson P, Goldsmith DJ, Lamb EJ. Bone alkaline phosphatase in CKD–mineral bone disorder. American journal of kidney diseases. 2013;62(4):810-22.
8. Streja E, Wang H-Y, Lau WL, Molnar MZ, Kovesdy CP, Kalantar-Zadeh K, et al. Mortality of combined serum phosphorus and parathyroid hormone concentrations and their changes over time in hemodialysis patients. Bone. 2014;61:201-7.
9. Liu C-T, Lin Y-C, Lin Y-C, Kao C-C, Chen H-H, Hsu C-C, et al. Roles of serum calcium, phosphorus, PTH and ALP on mortality in peritoneal dialysis patients: a nationwide, population-based longitudinal study using TWRDS 2005–2012. Scientific reports. 2017;7(1):33.
10. Kong X, Zhang L, Zhang L, Chen N, Gu Y, Yu X, et al. Mineral and bone disorder in Chinese dialysis patients: a multicenter study. BMC nephrology. 2012;13:1-7.
11. Supparitsch S, Vychytil A, Zeitlinger M, Nussbaumer-Pröll A. Efficacy of ceftazidime/avibactam against 10 clinical isolates of Pseudomonas aeruginosa in icodextrin-based peritoneal dialysis solution and patient-derived dialysate. Journal of Antimicrobial Chemotherapy. 2026;81(6):dkag185.
12. Dai Z, Zhou F, Xu L, Lin H, Li M, Luo Q. Comparison and analysis of low-calcium and standard-calcium dialysates in patients undergoing continuous ambulatory peritoneal dialysis and their effects on calcium–phosphorus metabolism indicators. Therapeutic Apheresis and Dialysis. 2025;29(4):646-52.
13. Miller B. Dialysis Adequacy. Applied Home Hemodialysis: A Clinical Guide. 2025:33-43.
14. Garzotto F, Lorenzin A, Zaccaria M, Clark WR. Solute and water transport in hemodialysis: Dialyzers, flow distribution, and cross-filtration. Critical Care Nephrology: Elsevier; 2019. p. 909-18. e1.
15. Deng L, Guo S, Liu Y, Zhou Y, Liu Y, Zheng X, et al. Global, regional, and national burden of chronic kidney disease and its underlying etiologies from 1990 to 2021: a systematic analysis for the Global Burden of Disease Study 2021. BMC public health. 2025;25(1):636.
16. Stevens LA, Djurdjev O, Cardew S, Cameron E, Levin A. Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: evidence for the complexity of the association between mineral metabolism and outcomes. Journal of the American Society of Nephrology. 2004;15(3):770-9.
17. Taniguchi M, Fukagawa M, Fujii N, Hamano T, Shoji T, Yokoyama K, et al. Serum phosphate and calcium should be primarily and consistently controlled in prevalent hemodialysis patients. Therapeutic Apheresis and Dialysis. 2013;17(2):221-8.
18. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJL, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. The Lancet. 2013;382(9889):339-52.
19. Chen Z, Zhang X, Han F, Xie X, Hua Z, Huang X, et al. High alkaline phosphatase and low intact parathyroid hormone associate with worse clinical outcome in peritoneal dialysis patients. Peritoneal Dialysis International. 2021;41(2):236-43.
20. Doi T, Yamamoto S, Morinaga T, Sada K-e, Kurita N, Onishi Y. Risk score to predict 1-year mortality after haemodialysis initiation in patients with stage 5 chronic kidney disease under predialysis nephrology care. PloS one. 2015;10(6):e0129180.
21. Mizushiri S, Daimon M, Murakami H, Kamba A, Osonoi S, Yamaichi M, et al. Lower serum calcium levels are a risk factor for a decrease in eGFR in a general non-chronic kidney disease population. Scientific Reports. 2018;8(1):14213.
22. Raju S, Saxena R. Hyperphosphatemia in kidney failure: pathophysiology, challenges, and critical role of phosphorus management. Nutrients. 2025;17(9):1587.
23. Ji J, Lu M, Guo S, Xiang B, Wu W, Li Y, et al. Five-year time profiles of clearances of different uremic solutes in incident peritoneal dialysis patients. American journal of nephrology. 2025;56(4):433-44.
24. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero J-J, Chan W, et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. American Journal of Kidney Diseases. 2020;76(3):S1-S107.

25. John GB, Cheng C-Y, Kuro-o M. Role of Klotho in aging, phosphate metabolism, and CKD. American journal of kidney diseases. 2011;58(1):127-34.
26. Selamet U, Tighiouart H, Sarnak MJ, Beck G, Levey AS, Block G, et al. Relationship of dietary phosphate intake with risk of end-stage renal disease and mortality in chronic kidney disease stages 3–5: The Modification of Diet in Renal Disease Study. Kidney international. 2016;89(1):176-84.
27. Hill Gallant KM, Spiegel DM. Calcium balance in chronic kidney disease. Current osteoporosis reports. 2017;15:214-21.
28. Rubio-Aliaga I, Krapf R. Phosphate intake, hyperphosphatemia, and kidney function. Pflügers Archiv-European Journal of Physiology. 2022;474(8):935-47.
29. Silver J, Naveh-Many T. FGF-23 and secondary hyperparathyroidism in chronic kidney disease. Nature Reviews Nephrology. 2013;9(11):641-9.
30. Huish SA, Jenkinson C, Dunn JA, Meredith DJ, Bland R, Hewison M. Low serum 1, 25 (OH) 2D3 in end-stage renal disease: is reduced 1α-hydroxylase the only problem? Endocrine Connections. 2021;10(10):1291-8.
31. Bover J, Massó E, Gifre L, Alfieri C, Soler-Majoral J, Fusaro M, et al. Vitamin D and Chronic Kidney Disease Association with Mineral and Bone Disorder: An Appraisal of Tangled Guidelines. Nutrients. 2023;15(7):1576.
32. Wang Z, Wen Y, Liang J, Liang X, Shi W. The influence of low calcium dialysate on left ventricular diastolic function in peritoneal dialysis patients. Renal Failure. 2016;38(10):1665-71.
33. Santos J, Silva R, Fiel D, Vicente R, Santos I, Malvar B, et al. SP517 PHOSPHATE BALANCE IN PERITONEAL DIALYSIS AND ITS RELATION WITH CREATININE CLEARANCE AND KT/V UREA. Nephrology Dialysis Transplantation. 2019;34(Supplement_1):gfz103. SP517.
34. Debowska M, Gomez R, Pinto J, Waniewski J, Lindholm B. Phosphate clearance in peritoneal dialysis. Scientific reports. 2020;10(1):17504.
35. Azar AT, Wahba K, Mohamed AS, Massoud WA. Association between dialysis dose improvement and nutritional status among hemodialysis patients. American Journal of Nephrology. 2007;27(2):113-9.

Correspondence to:
Pantea Miralaei, MD
General Practitioner, Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
ORCID ID: 0000-0002-5231-3370.
E-mail: Miralaip@gmail.com.

Received July 2026
Revised August 2026
Accepted September 2026

ORIGINAL PAPER
TRANSPLANTATION
RJCCN

Clinical Profile, Immunosuppressive Management and Outcome in Adult Renal Allograft Recipients with COVID-19 Infection

Sonia Mahjabin,[1] Nurul Islam,[2] Rezwanur Rahman,[1]
Elena Haque,[2] Muntasir Ebne Mobin[3]

[1]Department of Nephrology, Bangladesh Medical College, Dhaka, Bangladesh
[2]Department of Nephrology, Continental Hospital PLC (previous United Hospital Limited) Dhaka, Bangladesh
[3]Department of Medicine, Dhaka Medical College Hospital, Dhaka, Bangladesh

Keywords. COVID-19 infection, renal allograft recipient, immunosuppressive management, acute kidney injury, calcineurin inhibitors

© 2026 Author(s). This article is licensed under the CC By 4.0 International License.

Introduction. Coronavirus disease 2019 (COVID-19) has placed considerable strain on healthcare systems worldwide with renal allograft recipients (RARs) representing a particularly vulnerable group. Lifelong immunosuppression increases susceptibility to severe infection and complicates clinical management. Data on COVID-19 in RARs from South Asia and other resource-limited settings are limited. This study describes the clinical features, immunosuppressive adjustments, and outcomes of renal allograft recipients with COVID-19.

Methods. We analyzed data from 26 adult RARs with moderate-to-severe COVID-19, confirmed by RT-PCR, who were admitted to the Department of Nephrology, Continental Hospital PLC (previous United Hospital Limited) Dhaka, Bangladesh, between December 2020 and June 2025.

Results. The mean age was 59.6 years (range: 34 to 75 years), and 73.1% of patients were male. DM (46.2%), glomerulonephritis (23.1%), and hypertensive nephrosclerosis (19.2%) were the most common primary renal diseases. The most frequent symptoms were cough (96.2%) and fever (88.5%). Immunosuppressive therapy was modified in all patients: antimetabolites were discontinued, corticosteroids were switched to dexamethasone or IV methylprednisolone, and CNIs were withheld in 34.6% or halved in 26.9%. Laboratory results showed elevated inflammatory markers (CRP 96.4 mg/L, ferritin 854.3 ng/mL, D-dimer 2016.3 ng/mL). Chest CT revealed ground-glass opacities in 76.9% (most commonly bilateral peripheral, 35%) and consolidation in 61.5%, with a mean total severity score of 9.6 ± 4.9. Acute kidney injury occurred in 26.9%, among them 23.1%required dialysis and 7.7% remained dialysis-dependent. Mechanical ventilation was needed in 23.1%. Overall mortality was 26.9%, while 65.4% of patients recovered and were discharged.

Conclusion. COVID-19 is associated with significant morbidity and mortality in RARs. Despite most patients recovering, mortality remained significant, highlighting the need for careful immunosuppressive adjustment, aggressive infection control, and close monitoring in this high-risk population.

RJCCN 2026; 2: 289-300
www.rjccn.org
DOI: 10.61882/rjccn.2.4.53

Please cite this article as: Mahjabin S, Islam N, Rahman R, Haque E, Ebne Mobin M. Clinical Profile, Immunosuppressive Management and Outcome in Adult Renal Allograft Recipients with COVID-19 Infection. RJCCN. 2026;2(4):289-300.

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has rapidly spread across the world, leading the World Health Organization (WHO) to declare a global pandemic in March 2020.[1] Kidney transplant recipients (KTRs) are among the most vulnerable to this pandemic, facing a dual threat: chronic immunosuppression necessary to prevent allograft rejection markedly increases susceptibility to severe infection, while the inflammatory cascade triggered by SARS-CoV-2 significantly affects both native and transplant kidney function.[2,3]

Kidney transplant recipients experience substantially worse outcomes following COVID-19 infection than the general population. Systematic reviews and meta-analyses have consistently demonstrated that hospitalized kidney transplant recipients with COVID-19 face a mortality rate of 21 to 23%,[4,5] which is markedly higher than the 1 to 5% typically reported in the general population.[6] The risk of critical illness is equally concerning, with ICU admission reported in 24% and mechanical ventilation required in 18% of cases.[4] Acute kidney injury occurs in up to 48 to 50% of infected transplant recipients, with 12 to 23% requiring renal replacement therapy.[3-5] Several factors drive this vulnerability: older age, a heavy load of comorbidities such as diabetes and hypertension, and immunosuppressive medications that suppress the body's natural defenses against viruses.[4,7]

The optimal management of immunosuppressive therapy in kidney transplant recipients with COVID-19 remains an area of considerable uncertainty and ongoing debate. While some evidence supports the reduction or discontinuation of antimetabolites (mycophenolate mofetil or azathioprine) to facilitate viral clearance, findings across different cohorts have been inconsistent.[2] Current expert recommendations suggest discontinuing mycophenolic acid or mTOR inhibitors in patients with moderate to severe disease, reducing calcineurin inhibitor (CNI) doses by approximately 30 to 50%, and maintaining or increasing corticosteroid therapy.[2] However, these strategies must be carefully balanced against the risk of graft rejection, particularly in highly sensitized patients or those with recent transplantation.[2]

The clinical presentation of COVID-19 in kidney transplant recipients closely resembles that of the general population, with fever, cough, and dyspnea representing the most common symptoms.[6] However, the progression to severe disease appears to be accelerated in this immunocompromised group, with acute respiratory distress syndrome developing in over half of hospitalized patients in pooled analyses.[6] Radiological findings frequently reveal bilateral ground glass opacities (GGO) and consolidation, with disease severity correlating strongly with adverse outcomes. Laboratory abnormalities, including elevated inflammatory markers (CRP, ferritin, D-dimer), lymphopenia, and worsening renal function, serve as important prognostic indicators.[7]

The morbidity and mortality burden of COVID-19 in RARs extends beyond acute infection: 27 to 30% of hospitalized patients require ICU admission, and approximately 22% die, mainly from sepsis, ARDS, and multiorgan failure.[3] Advanced age, diabetes mellitus, dyspnea at presentation, pneumonia, and AKI have been identified as independent predictors of mortality.[7,8] Furthermore, survivors often experience persistent graft dysfunction, with a subset progressing to permanent dialysis dependence.[3] The substantial case fatality ratio, coupled with the high rates of critical illness and renal complications, highlights the urgent need for optimized management strategies in this high-risk population.

Despite the growing body of evidence from high-income countries, data on COVID-19 in kidney transplant recipients from South Asia and other resource-limited settings remain scarce. Differences in healthcare infrastructure, immunosuppressive protocols, and patient demographics could shape outcomes in ways that studies from wealthier settings simply do not capture. This study describes the clinical features, immunosuppressive adjustments, and outcomes of adult renal allograft recipients with RT-PCR-confirmed COVID-19 admitted with moderate to severe disease at a tertiary care center in Dhaka, Bangladesh. By characterizing this vulnerable population in a resource-limited South Asian setting, we aim to inform clinical

management strategies and contribute to the global understanding of COVID-19 in kidney transplant recipients.

MATERIALS AND METHODS

We conducted this retrospective study at the Department of Nephrology, Continental Hospital PLC,(Previous United Hospital Limited), Dhaka, Bangladesh, between December 2020 and June 2025, including 26 adult RARs with COVID-19 infection. Patients were selected based on the following criteria:

Inclusion Criteria

- Adults (≥ 18 years) with a functioning renal allograft
- RT-PCR confirmed COVID-19
- Hospitalized with moderate to severe disease
- Complete clinical, laboratory, radiological, and outcome data available in medical records

Exclusion Criteria

- Age < 18 years
- Mild / asymptomatic cases managed as outpatients
- COVID-19 diagnosed without RT-PCR confirmation
- History of dialysis after transplantation (graft failure)
- History of acute graft rejection
- Incomplete medical record

Ethical Issue

This study was conducted using routinely collected clinical data without any interventional procedures. Ethical approval was obtained from the department head and ethics committee prior to data analysis. This study posed no additional risk to patients and did not interfere with routine patient management. All patient data were anonymized before analysis in accordance with the Declaration of Helsinki. Informed consent for treatment and the use of anonymized clinical data for research purposes was obtained from the patients or their families.

Data Collection Procedure

This retrospective study included 26 adult renal transplant recipients with RT-PCR confirmed COVID-19 at a single tertiary center in Bangladesh. Demographic, clinical, laboratory, radiological, treatment, and outcome data were collected. Clinical data included symptoms, vital signs, oxygen requirements, and the need for renal replacement therapy. Laboratory and radiological evaluations assessed organ function and inflammatory status, including chest CT findings and Total Severity Scores (TSS).

Data Analysis

All collected data were entered into Microsoft Excel and analyzed using SPSS version 25. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were summarized using frequencies and percentages.

RESULTS

In this study of 26 Renal Allograft Recipients (RARs) with COVID-19, demographic characteristics, initial oxygen saturation, immunosuppressive modifications, and overall outcomes are summarized in Table 1.

The baseline characteristics of the 26 kidney transplant recipients are summarized in Table 2. The mean age was 59.6 years (range: 34 to 75), with a male predominance (73%). The median time since transplantation was 85.7 months. Diabetes mellitus (46%), glomerulonephritis (23%), and hypertensive nephrosclerosis (19%) were the most common primary renal diseases. Common presenting symptoms included cough (96%), fever (88%), and dyspnea (46%).

Common presenting symptoms included cough (96%), fever (88%), and dyspnea (46%).

Immunosuppression was modified in all patients: antimetabolites were discontinued, steroids were switched to low-dose dexamethasone (73%) or IV methylprednisolone (27%), and calcineurin inhibitors were stopped (35%), reduced by half (27%), or continued at the same dose (38%). All patients received LMWH, 88% received remdesivir and additional therapies included antibiotics, favipiravir (12%), rivaroxaban (42%), and tocilizumab (8%).

Biochemical parameters, and radiological features

Table 1. All Patients Baseline Data (n = 26)

No	Age/Sex (year / Male or Female)	Duration Of Transplant (months)	Primary Disease	Comorbidities	O_2 Saturation During Admission (%)	Immunosuppression Modification	Management Of COVID-19 Pneumonia	Overall Outcome
1	52 / F	76	ADPKD	HTN, DM	97	Complete Cessation of MMF, Steroid switched to low-dose dexamethasone, Continued CNI	LMWH, Antibiotics Remdesivir, Rivaroxaban	Discharged
2	34 / M	118	IgA Nephropathy	NODAT, CAN HTN	96	Complete Cessation of MMF, Steroid switched to Low-Dose dexamethasone, 50% Dose Reduction of CNI	LMWH, Antibiotics Remdesivir Rivaroxaban	Discharged
3	54 / M	48	DM	HTN Post PCI State CAN	89	Complete Cessation of MMF, Steroid switched to Low-Dose Dexamethasone, Complete Cessation of CNI (Tacrolimus)	LMWH, Antibiotics Remdesivir	Death due to Sepsis, MOF & NSTEMI
4	55 / M	76	DM	HTN IHD	84	Complete Cessation of MMF, Steroid switched to IV Methylprednisolone 50% Dose Reduction of CNI	LMWH, Antibiotics Remdesivir Rivaroxaban	Discharged
5	62 / F	62	Chronic Pyelonephritis	HTN, DM, CAN	90	Complete Cessation of MMF, Steroid switched to Low-Dose Dexamethasone Complete Cessation CNI (Tac)	LMWH Antibiotics Remdesivir	Death due to Sepsis & MOF
6	70 / M	82	Hypertensive nephrosclerosis	DM, IHD COPD	85	Complete Cessation of MMF, Steroid switched to Steroid switched to IV Methylprednisolone , Complete Cessation of CNI (Tacrolimus)	LMWH Antibiotics Remdesivir	Death due to Sepsis, MOF & ARDS
7	43 / F	122	Presumed GN	HTN, NODAT Bronchial Asthma CAN	95	Complete Cessation of MMF, Steroid switched to low-dose dexamethasone, Complete Cessation of CNI (Tacrolimus)	LMWH Antibiotics Remdesivir Rivaroxaban	Discharged
8	55 / M	75	DM	HTN	85	Complete Cessation of MMF, Steroid switched to low-dose dexamethasone, Continued CNI (Tac)	LMWH Remdesivir Tocilizumab	Discharged
9	75 / M	129	DM	HTN ICM, COPD	89	Complete Cessation of MMF, Steroid switched to Low-Dose Dexamethasone, 50% Dose Reduction of CNI	LMWH Antibiotics Remdesivir Apixaban	Discharged
10	55 / M	38	Presumed GN	HTN, DM	96	Complete Cessation of MMF, Steroid switched to low-dose dexamethasone, Continued CNI (Tac)	LMWH Antibiotics Favipiravir	Discharged

Table 1. Continued

No	Age/Sex (year / Male or Female)	Duration Of Transplant (months)	Primary Disease	Comorbidities	O_2 Saturation During Admission (%)	Immunosuppression Modification	Management Of COVID-19 Pneumonia	Overall Outcome
11	48 / F	119	FSGS	HTN, NODAT CAN	90	Complete Cessation of MMF, Steroid switched to low-dose dexamethasone, Complete Cessation of CNI (Tacrolimus)	LMWH Antibiotics Remdesivir	Death due to Sepsis & MOF
12	75 / M	87	Presumed Gn	HTN, Morbid Obesity, Post PCTA State, Post-Transplant FSGS	83	Complete Cessation of MMF, Steroid switched to low-dose dexamethasone, Continued CNI (Tac)	Antibiotics LMWH Remdesivir Tocilizumab Rivaroxaban	Discharged
13	63 / M	52	DM	HTN, Post PCTA State	90	Complete Cessation of MMF, Steroid switched to low-dose dexamethasone, Continued CNI (Tac)	LMWH Antibiotics Remdesivir Rivaroxaban	Discharged
14	60 / M	134	DM	HTN,	95	Complete Cessation of MMF, Steroid switched to low-dose dexamethasone, Continued CNI (Tac)	LMWH Antibiotics Remdesivir Rivaroxaban	Discharged
15	66 / F	114	Hypertensive nephrosclerosis	NODAT Bronchial Asthma	98	Complete Cessation of MMF, Steroid switched to low-dose dexamethasone, Continued CNI (Tac)	LMWH Antibiotics Favipiravir	Discharged
16	55 / M	79	DM	HTN, CABG	88	Complete Cessation of MMF, Steroid switched to Steroid switched to IV Methylprednisolone, Complete Cessation of CNI	LMWH Antibiotics Remdesivir	Death due to Sepsis, ARDS, Secondary Bacterial Infection
17	51 / M	23	Hypertensive Nephrosclerosis	DM Bronchial Asthma	98	Complete Cessation of Azathioprine, Steroid switched to low-dose dexamethasone, Continued CNI (Tac)	LMWH Antibiotics Favipiravir	Discharged
18	71 / M	115	Obstructive Nephropathy	HTN,DM	97	Complete Cessation of MMF, Steroid switched to low-dose dexamethasone, 50% Dose Reduction of CNI	LMWH Antibiotics Remdesivir	Death due to Cardiogenic Shock
19	70 / M	95	DM	HTN, Permanent Pacemaker	98	Complete Cessation of MMF, Steroid switched to low-dose dexamethasone, Complete Cessation of CNI (Tacrolimus)	LMWH Antibiotics Remdesivir Rivaroxaban	Discharged
20	61 / M	118	DM	HTN, CABG, COPD	90	Complete Cessation of MMF, Steroid switched to low-dose dexamethasone, Continued CNI (Tac)	LMWH Antibiotics Remdesivir	Discharged

Table 1. Continued

No	Age/Sex (year / Male or Female)	Duration Of Transplant (months)	Primary Disease	Comorbidities	O_2 Saturation During Admission (%)	Immunosuppression Modification	Management Of COVID-19 Pneumonia	Overall Outcome
21	69 / M	84	Hypertensive Nephrosclerosis	NODAT	88	Complete Cessation of MMF, Steroid switched to Steroid switched to IV Methylprednisolone low-dose dexamethasone, Complete Cessation of CNI (Tacrolimus)	LMWH Antibiotics Remdesivir Rivaroxaban	Discharged
22	57 / F	29	DM	DM	92	Complete Cessation of MMF, Steroid switched to low-dose dexamethasone, 50% Dose Reduction of CNI	LMWH Remdesivir Rivaroxaban	Discharged
23	74 / M	104	DM	HTN, COPD	85	Complete Cessation of MMF, Steroid switched to Steroid switched to IV Methylprednisolone low-dose dexamethasone 50% Dose Reduction of CNI	LMWH Antibiotics Remdesivir	Death due to Neutropenic Sepsis, Type 2 Respiratory failure, ARDS
24	53 / M	106	Hypertensive Nephrosclerosis	NODAT, Bronchial Asthma	89	Complete Cessation of MMF, Steroid switched to Steroid switched to IV Methylprednisolone, 50% Dose Reduction of CNI	LMWH Antibiotics Remdesivir	Discharged
25	71 / M	89	DM	HTN,	78	Complete Cessation Of MMF, Steroid switched to Steroid switched to IV Methylprednisolone , Complete Cessation of CNI (Tacrolimus)	LMWH Antibiotics Remdesivir	Discharged
26	51 / F	27	Lupus Nephritis	HTN, NODAT	91	Complete Cessation of MMF, Steroid switched to low-dose dexamethasone, Continued CNI (Tac)	LMWH Antibiotics Remdesivir Rivaroxaban	Discharged

shown in Table 3. Inflammatory markers were elevated (CR*P* = 96.4 mg/L, procalcitonin = 3.1 ng/mL, ferritin = 854 ng/mL, D-dimer = 2016 ng/mL). Chest CT most commonly showed ground-glass opacities (77%), with bilateral peripheral distribution (35%) and consolidation (62%), often with pleural effusion (38%). Six patients (23%) had normal CT findings. The mean total severity score was 9.6 ± 4.9.

Respiratory profile shown in Table 4. The mean oxygen saturation was 92%, with respiratory support ranging from room air (27%) to low-flow nasal cannula (23%), high-flow nasal cannula (19%), Bi-PAP (8%), and mechanical ventilation (23%). Preexisting renal disease included chronic allograft nephropathy (CAN) (19%) and recurrent UTIs (12%), with a mean serum creatinine of 1.64 mg/dL.

AKI occurred in 27% of patients, 23% of patients required renal replacement therapy, and 8% remained dialysis-dependent. Overall mortality

Table 2. Baseline Characteristics of Renal Allograft Recipients

Baseline characteristics	(n = 26)	(%)
Mean age, y	59.62 ± 10.48 (34 to 75)	
Gender		
Male	19	73.08
Female	7	26.92
Mean time interval between kidney transplantation (mo)	85.69 ± 40.12 (23 to 134)	
Primary Disease	-	-
DM	12	46.15
Glomerulonephritis	6	23.07
IgA nephropathy	1	3.85
FSGS	1	3.85
Lupus nephritis	1	3.85
Presumed Glomerulonephritis (GN)	3	11.54
Hypertensive Nephrosclerosis	5	19.23
ADPKD	1	3.85
Obstructive Nephropathy	1	3.85
Chronic pyelonephritis	1	3.85
Renal abnormality	-	-
Chronic allograft Nephropathy (CAN)	5	19.23
Post Transplant FSGS	1	3.85
Clinical Features	-	-
Cough	25	96.15
Fever	23	88.46
Myalgia	15	57.69
Dyspnea	12	46.15
Sore throat	15	57.69
Diarrhea	3	11.54
Immunosuppression modification	-	-
Complete cessation of MMF	25	96.15
Complete cessation of Azathioprine	1	3.85
Steroid switched to low-dose Dexamethasone	19	73.07
Steroid switched to IV Methylprednisolone	7	26.9
Complete cessation of CNI (Tacrolimus)	9	34.62
Continued CNI (Tacrolimus)	10	38.49
50% dose reduction of CNI (Tac)	7	26.9
Management of COVID-19 pneumonia	-	-
LMWH	26	100.00
Antibiotics	21	80.77
Remdesivir	23	88.46
Rivaroxaban	11	42.31
Apixaban	1	3.85
Tocilizumab	2	7.69
Favipiravir	3	11.54

Abbreviations: CAN, chronic allograft nephropathy, NODAT; new-onset diabetes after transplantation; COPD, chronic obstructive pulmonary disease, CABG; coronary artery bypass grafting, LMWH; low molecular weight heparin, MMF; mycophenolate mofetil, CNI; calcineurin inhibitors

Table 3. Laboratory, X-ray, and CT Findings of Study Patients at Baseline (n = 26)

Laboratory Findings	Mean ± SD	
Hemoglobin, g/dL	11.92 ± 1.56	
Total count of WBCs, /μL	14307.69 ± 7195.37	
Neutrophil (%)	77.58 ± 18.00	
CRP, mg/L	96.38 ± 86.66	
Procalcitonin, ng/mL	3.10 ± 2.47	
Serum Ferritin, ng/mL	854.31 ± 357.07	
Serum Creatinine, mg/dL	1.66 ± 0.68	
Serum D-Dimer, ng/mL	2016.25 ± 1286.86	
X-ray findings		
Normal	7	26.92
Consolidation (unilateral/bilateral)	11	42.31
Consolidation and pleural effusion	4	15.38
Bilateral patchy opacity	4	15.38
CT findings		
Ground Glass Opacity (GGO)	20	76.92
Bilateral peripheral	7	35.0
Bilateral peripheral + subpleural GGO	3	15.0
Diffuse bilateral GGO	5	25.0
Unilateral GGO (left / right)	3	15.0
Central GGO	2	10.0
Reverse halo sign	2	10.0
Intralobular septal thickening	3	11.54
Consolidation	16	61.54
Bilateral consolidation	3	18.8
Unilateral consolidation (left/right)	3	18.8
Bilateral basal consolidation	3	18.8
Consolidation with pleural effusion	6	37.5
Subpleural bands	3	18.8
Normal CT scan	6	23.08
Mean Total severity score	9.56 ± 4.88	

was 27%, primarily due to sepsis with ARDS, multi-organ failure, cardiogenic shock, or type 2 respiratory failure.

DISCUSSION

The COVID-19 pandemic has imposed a heavy burden on RARs, who face a higher risk of severe infection, AKI, and death due to their impaired immune systems and common comorbidities like DM, HTN, and ischemic heart disease.[4,5,7] This study evaluated the clinical features, management, renal outcomes, and mortality of RARs hospitalized with COVID-19 pneumonia.

Demographics

Our study showed a relatively older age with a male predominance, a demographic pattern consistent with international reports of COVID-19

Table 4. Respiratory Parameters and Renal Outcome Variables in Renal Allograft Recipients (n = 26)

Respiratory Parameters	n	P (%)
Mean Oxygen saturation level (%)	92.12 ± 5.32	
Respiratory support required		
Room air	7	26.92
Low-flow nasal cannula	6	23.08
High flow nasal cannula	5	19.23
BiPAP (Bilevel Positive Airway Pressure)	2	7.69
Mechanical ventilation	6	23.08
Renal outcome parameters		
Urine routine examination		
NAD	15	57.69
Protein trace	4	15.39
Protein +	3	11.54
Protein ++	3	11.54
Leucocyte ++	1	3.85
UTI	4	15.39
Preexisting renal abnormality		
Nothing significant	19	73.08
CAN	5	19.23
Recurrent UTI	3	11.54
Serum creatinine at admission, mg/dL	1.66 ± 0.68	
Serum creatinine after 7 days, mg/dL	3.35 ± 2.64	
Renal outcome		
Acute Kidney Injury (AKI)	7	26.92
AKI requiring renal replacement therapy	6	23.08
Dialysis dependent	2	7.69
Remain same	17	65.38
Urinary Tract Infection (UTI)	3	11.54
Overall outcome		
Discharged (recovered)	17	65.38
Discharged on maintenance hemodialysis (MHD) 3/week	2	7.69
Death	7	26.92
Death due to sepsis with multiorgan failure (MOF)	1	14.29
Death due to septic shock	1	14.29
Death due to sepsis with ARDS	3	42.86
Death due to cardiogenic shock	1	14.29
Death due to type 2 respiratory failure with ARDS and pneumonia	1	14.29

in KTRs. Crespo *et al.* described an older Spanish cohort with a mean age of 73.6 years and 75% male predominance, while Akalin *et al.* and Alberici *et al.* reported younger cohorts with male predominance ranging from 65 to 80%.[9-11] Importantly, Nowak *et al.* demonstrated that advanced age and male remain independent predictors of severe disease and mortality among KTRs with COVID-19, even in the post-vaccination era, supporting our findings.[12] A large multinational study by the Asian Society of Transplantation Registry (ASTREGO) reported outcomes of 87 kidney transplant recipients (KTRs) with COVID-19 across seven Asian countries. The relatively young cohort (median age = 43 years) mostly had mild-to-moderate disease, yet overall mortality was 23%, with higher deaths among those needing intensive care. Disease severity at presentation independently predicted mortality, highlighting persistently high COVID-19 mortality in Asian KTRs, especially when healthcare resources are limited.[13]

The interval between transplantation and COVID-19 diagnosis in our cohort was longer than that reported by Crespo *et al.* (49 months) and Santeusanio *et al.* (69.6 months), but comparable to the Asian cohorts reported by Kee *et al.* and the ASTREGO registry, suggesting that COVID-19 risk persists well beyond the early post-transplant period.[9,13,14] Geethanjali *et al.*, similarly reported that severe COVID-19 can occur at any stage posttransplant, highlighting the ongoing vulnerability of long term KTRs in the region.[15]

Primary Renal Disease and Comorbidities

DM, glomerulonephritis, and hypertensive nephrosclerosis were the most common primary renal diseases, while hypertension, DM, and IHD were the most common comorbidities. These findings are consistent with prior reports indicating that metabolic and cardiovascular comorbidities substantially increase the risk of severe COVID-19 and mortality in KTRs.[7,13,15] Specifically, DM and HTN have been consistently associated with higher rates of hospitalization, ICU admission, and death among KTRs with COVID-19. Recent multicenter analyses further confirmed that diabetes and cardiovascular disease are independent risk factors for adverse outcomes in this population.[4,7]

Clinical Features

Fever and cough were the most frequent presenting symptoms among our patients, followed by dyspnea, while gastrointestinal symptoms were relatively uncommon. This clinical profile closely consistent with the findings reported by Akalin *et al.*, Jasuja *et al.*, and Jha *et al.*, indicating that the initial presentation of COVID-19 in KTRs is similar to that of the general population, although progression to severe disease is more frequent.[10,16,17]

Radiological Features and Respiratory Severity

The Chest radiography and CT findings in our cohort were dominated by consolidation and ground- glass opacities (GGO), predominantly with bilateral peripheral distribution, indicating moderate pulmonary involvement. A meaningful proportion of patients required mechanical ventilation, while others required high-flow nasal cannula or noninvasive ventilation. Similar associations between extensive radiological involvement, ventilatory support requirements, and mortality have been reported by Demir *et al.*, and Nowak *et al.*, highlighting the prognostic significance of respiratory severity in KTRs.[12,18.]

Immunosuppressive Modification and COVID-19 Treatment

All patients underwent modifications of immunosuppressive therapy, including discontinuation of antimetabolites. Maintenance corticosteroids were adjusted to alternative regimens according to the disease severity. Patients with mild-to-moderate oxygen requirements received low-dose dexamethasone, consistent with the RECOVERY trial demonstrating a mortality benefit in hospitalized patients requiring oxygen support.[19] In patients with progressive COVID-19 pneumonia or worsening inflammatory markers, IV methylprednisolone was administered to suppress the hyperinflammatory response. This approach is supported by transplant cohort experiences, suggesting that short-course IV methylprednisolone may improve respiratory outcomes without significantly increasing the risk of acute rejection when accompanied by appropriate immunosuppressive adjustments.[9,10]

Calcineurin inhibitors (CNIs) were continued, dose reduced, or temporarily withheld depending on illness severity and drug–drug interaction concerns. This management strategy aligns with international experience and expert recommendations. Studies by Akalin *et al.*, Crespo *et al.*, and Demir *et al.* emphasized early withdrawal of antimetabolites and individualized CNI modification as central to COVID-19 management in kidney transplant recipients.[9,10,18] Importantly, Nowak *et al.* reported that temporary reduction of immunosuppression during acute infection was not associated with an increased risk of acute rejection.[12]

Supportive therapy included universal anticoagulation with low molecular weight heparin, and the most patients received remdesivir. Remdesivir was well tolerated, with no nephrotoxicity observed. Consistent with multicenter data, its use in KTRs has not been associated with an increased risk of AKI and may reduce ICU mortality when administered early.[20] Although experience with oral antivirals such as nirmatrelvir / ritonavir in transplant recipients remains limited, emerging evidence supports their feasibility with careful management of drug–drug interactions, particularly involving CNIs.[21]

A small number of patients with progressive hypoxemia and worsening inflammatory markers despite corticosteroids received tocilizumab, an IL-6 receptor antagonist, to attenuate the COVID-19 associated cytokine storm.[22] This is supported by the RECOVERY trial, which showed that tocilizumab improved 28-day survival in hospitalized COVID-19 patients with hypoxia and systemic inflammation when added to standard care.[23] Data specific to KTRs are limited but reassuring on safety: a multicenter cohort of 80 KTRs treated with tocilizumab reported no drug-related safety issues, though mortality remained high given the severity of illness in this subgroup.[22] Given this mixed evidence, tocilizumab was reserved for select patients with severe, progressive disease unresponsive to corticosteroids alone.

Incidence of Acute Kidney Injury and Need for Dialysis

A notable proportion of our cohort developed AKI, of whom a majority required renal replacement therapy, and a smaller subset remained dialysis-dependent at last follow-up, indicating significant graft injury within a portion of the recipients. Chronic allograft dysfunction was present in a subset of patients, several of whom subsequently developed AKI during the course of the illness. This finding suggests that pre-existing graft dysfunction may predispose RARs to worsening graft function during acute viral illness.

AKI is more common and severe in RARs than in the general population. While AKI occurs in 10 to 15% of hospitalized COVID-19 patients in the general population, its incidence in RARs

is markedly higher, ranging from 30 to 57% in individual studies, with pooled analyses around 40 to 44%.[5,24,25]

Our observed AKI rate was lower than that reported by Geethanjali *et al.* who documented a markedly higher incidence of AKI among KTRs with COVID-19. Their study emphasized the influence of disease severity and modifications in immunosuppressive therapy on graft outcomes. The discrepancy between their findings and ours may be attributed to differences in patient characteristics, severity of infection, sample size, and management protocols.[15]

Overall, our results reinforce the existing evidence that COVID-19 carries a significant threat to graft function, particularly in recipients with underlying CAN. Close monitoring of renal and inflammatory parameters and individualized adjustment of immunosuppressive therapy are essential to minimize the risk of irreversible graft dysfunction.

Mortality

The overall mortality rate in our study, with most deaths attributable to sepsis complicated by ARDS, multi-organ failure, and cardiogenic shock, was consistent with previously reported mortality rates of 20 to 30% among hospitalized KTRs.[10,18,20] Moreover, recent systematic reviews and meta-analyses have confirmed that transplant recipients experience significantly higher mortality rates than the general hospitalized population.[4,5] The increased vulnerability reflects the combined effects of chronic immunosuppression, a high burden of comorbidities such as diabetes and cardiovascular disease, and impaired antiviral immune responses.

Data from the ERACODA (European Renal Association COVID-19 Database) collaboration demonstrated higher rates of ICU admission, mechanical ventilation, and secondary infections among transplant recipients with COVID-19.[20] In a large multicenter cohort study of 250 kidney transplant recipients from India, Kute and colleagues reported substantial mortality and identified AKI as an important predictor of poor outcome.[26] Similarly, Bajpai *et al.* observed high mortality rates in patients with severe disease, particularly among those requiring intensive care support.[27] Nowak *et al.* and Geethanjali *et al.* identified advanced age, DM, cardiovascular disease, severe lung involvement, and AKI as independent predictors of mortality, with AKI being particularly significant due to its association with systemic inflammation, hemodynamic instability and poor outcomes.[12,15]

Taken together, these findings reinforce that KTRs remain a high-risk population despite advances in supportive care and antiviral therapy, underscoring the importance of early risk stratification and individualized management strategies to improve survival.

Clinical Implications

This study highlights the persistent vulnerability of RARs to severe COVID-19. Early modification of immunosuppression, prompt anti-viral therapy, close monitoring of clinical, biochemical, respiratory, and renal parameters, and aggressive supportive care are essential to improving outcomes. High-risk patients particularly the elderly and those with DM, cardiovascular disease, or preexisting CAN require early hospitalization and a multidisciplinary approach involving nephrology, infectious disease, and critical care teams. Individualized treatment strategies that balance infection control with graft preservation remain fundamental to optimizing outcomes in this vulnerable population.

Strengths and Limitations

A Strength of this study is the detailed clinical and laboratory characterization of RARs during the pandemic in a tertiary center. However, the relatively small sample size and single-center design limit generalizability. The retrospective nature may also introduce bias in treatment uniformity and data completeness.

CONCLUSIONS

Renal transplant recipients are highly vulnerable to adverse outcomes following COVID-19 infection, with clinical severity ranging from mild symptoms to severe pneumonia and multi-organ failure. Prompt adjustment of immunosuppressive therapy, along with supportive care and antiviral therapy, is critical for preserving graft function

and improving outcomes. Despite a high rate of recovery, mortality remains significant, highlighting the need for intensive monitoring, individualized management. Further multicentric prospective studies are warranted to establish standardized treatment protocols for this high-risk population.

DECLARATION

Author Contributions

Sonia Mahjabin. Conceptualization, study design, data collection, supervision, and overall management of the study. Corresponding author responsible for manuscript preparation and submission.

Nurul Islam. Clinical supervision, data interpretation and critical review of the manuscript.

Rezwanur Rahman. Clinical supervision, data interpretation, presentation of results, and critical review of the manuscript.

Elena Haque. Data collection, clinical management of patients and review of the manuscript.

Muntasir Ebne Mobin. Results review, formal analysis and presentation of results.

Acknowledgments

The authors would like to thank the medical and nursing staff of the Department of Nephrology, Continental Hospital PLC (previous United Hospital Limited), Dhaka, Bangladesh, for their dedicated care of the patients in this study. A preliminary version of this work was presented as an abstract at the 2023 ISN World Congress of Nephrology (WCN). We also extend our gratitude to the patients and their families for their cooperation.

Funding Statement

This study received no specific funding.

Conflict of Interest

The authors declare no conflicts of interest.

REFERENCES

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed. 2020;91(1):157–60.
2. Angelico R, Blasi F, Manzia TM, Toti L, Tisone G, Cacciola R. The management of immunosuppression in kidney transplant recipients with COVID-19 disease: an update and systematic review of the literature. Medicina (Kaunas). 2021;57(5):435.
3. Marinaki S, Tsiakas S, Korogiannou M, Grigorakos K, Papalois V, Boletis I. A systematic review of COVID-19 infection in kidney transplant recipients: a universal effort to preserve patients' lives and allografts. J Clin Med. 2020;9(9):2986.
4. Duarsa MDVI, Kandarini Y, Yogiswara N, Kloping YP. Survival and clinical outcomes of kidney transplant recipients with coronavirus disease infection: an updated systematic review and meta-analysis. Turk J Urol. 2022;48(1):17–29.
5. Chen JJ, Kuo G, Lee TH, Yang HY, Wu HH, Tu KH, et al. Incidence of mortality, acute kidney injury and graft loss in adult kidney transplant recipients with coronavirus disease 2019: systematic review and meta-analysis. J Clin Med. 2021;10(21):5162.
6. Jayant K, Reccia I, Bachul PJ, Al-Salmay Y, Pyda JS, Podda M, et al. The impact of COVID-19 on kidney transplant recipients in pre-vaccination and Delta strain era: a systematic review and meta-analysis. J Clin Med. 2021;10(19):4533.
7. Udomkarnjananun S, Kerr SJ, Townamchai N, Susantitaphong P, Tulvatana W, Praditpornsilpa K, et al. Mortality risk factors of COVID-19 infection in kidney transplantation recipients: a systematic review and meta-analysis of cohorts and clinical registries. Sci Rep. 2021;11(1):20073.
8. Hasan I, Rashid T, Suliman S, Amer H, Chirila RM, Mai ML, et al. Predictors of disease severity and outcome of hospitalized renal transplant recipients with COVID-19 infection: a systematic review of a globally representative sample. Rom J Intern Med. 2021;59(1):10–42.
9. Crespo M, Pérez-Sáez MJ, Redondo-Pachón D, Llinàs-Mallol L, Montero MM, Villar-García J, et al. COVID-19 in elderly kidney transplant recipients. Am J Transplant. 2020;20(10):2883-9.
10. Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, et al. Covid-19 and kidney transplantation. N Engl J Med. 2020;382(25):2475-7.
11. Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, et al. Management of patients on dialysis and with kidney transplantation during the SARS-CoV-2 (COVID-19) pandemic in Brescia, Italy. Kidney Int Rep. 2020;5(5):580-5.
12. Nowak A, Caldinelli A, Segelmark M, Rydell H, Artborg A, Bellocco R, et al. COVID-19 among kidney transplant recipients: evaluating risk factors during the initial phase of the pandemic. Clin Kidney J. 2025;18(3):sfaf030.
13. Kee T, Jeong JC, Ur-Rashid H, Begum NAS, Arakama MH, Danguilan R, et al. Clinical characteristics, outcomes, and management of COVID-19 in kidney transplant recipients across Asia: an ASTREGO report. Korean J Transplant. 2021;35(4):218-29.
14. Santeusanio AD, Menon MC, Liu C, Bhansali A, Patel N, Mahir F, et al. Influence of patient characteristics and immunosuppressant management on mortality in kidney transplant recipients hospitalized with coronavirus disease 2019 (COVID-19). Clin Transplant. 2021;35(4):e14221.
15. Geethanjali G, Ramprasad E, Manikantan S, Jayakumar M. Impact of COVID-19 on renal transplant recipients. Immunopathol Persa. 2024;10(2):e39489.
16. Jasuja S, Sagar G, Bahl A, Verma S. COVID-19 infection

clinical profile, management, outcome, and antibody response in kidney transplant recipients: a single centre experience. Int J Nephrol. 2021;2021:3129411.

17. Jha PK, Shukla S, Bansal D, Bansal SB, Sethi S, Jain M, et al. COVID-19 in renal transplant recipients – a single center experience from India. Indian J Nephrol. 2022;32(5):416-22.
18. Demir E, Uyar M, Parmaksiz E, Sinangil A, Yelken B, Dirim AB, et al. COVID-19 in kidney transplant recipients: a multicenter experience in Istanbul. Transpl Infect Dis. 2020;22(5):e13371.
19. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693–704.
20. Hilbrands LB, Duivenvoorden R, Vart P, Franssen CFM, Hemmelder MH, Jager KJ, et al. COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. Nephrol Dial Transplant. 2020;35(11):1973-83.
21. Salerno DM, Jennings DL, Lange NW, Kovac DB, Shertel T, Chen JK, et al. Early clinical experience with nirmatrelvir/ritonavir for the treatment of COVID-19 in solid organ transplant recipients. Am J Transplant. 2022;22(8):2083-8.
22. Pérez-Sáez MJ, Blasco M, Redondo-Pachón D, Ventura-Aguiar P, Cacho J, Marion CH, et al. Use of tocilizumab in kidney transplant recipients with COVID-19. Am J Transplant. 2020;20(11):3182–90.
23. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637–45.
24. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97(5):829–38.
25. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020;98(1):209–18.
26. Kute VB, Bhalla AK, Guleria S, Ray DS, Bahadur MM, Shingare A, et al. Clinical profile and outcome of COVID-19 in 250 kidney transplant recipients: a multicenter cohort study from India. Transplantation. 2021;105(4):851–60.
27. Bajpai D, Deb S, Bose S, Gandhi CP, Modi T, Katyal A, et al. Clinical course and outcomes of COVID-19 in kidney transplant recipients. Indian J Nephrol. 2022;32(5):467-75.

Correspondence to:
Sonia Mahjabin, MD
Assistant Professor, Department of Nephrology, Bangladesh Medical College, Dhaka, Bangladesh
Cellphone: 01753336796
ORCID ID: 0009-0008-3935-2384
E-mail: soniabmc1985@gmail.com

Received July 2026
Revised August 2026
Accepted September 2026

CASE REPORT DIALYSIS RJCCN

Diagnostic Challenges of ESA-Resistant Anemia with MDS-Like Marrow Abnormalities: The Importance of Excluding Reversible Causes

Yukinobu Ikegishi

Fuefuki Central Hospital, Yamanashi, Japan

Keywords. hemodialysis, ESA hyporesponsiveness, marrow dysplasia

© 2026 Author(s). This article is licensed under the CC By 4.0 International License.

Introduction. Erythropoiesis-stimulating agent (ESA) hyporesponsiveness in elderly patients undergoing maintenance hemodialysis is frequently multifactorial and may be difficult to distinguish from anemia associated with primary bone marrow disorders.

Case Report. We report an 89-year-old man with ESA-resistant, transfusion-dependent anemia. Bone marrow examination demonstrated dysplastic megakaryocytic changes and isolated loss of the Y chromosome, raising concern for an underlying clonal marrow disorder. However, serum copper and ceruloplasmin levels showed no evidence of copper deficiency, and no zinc excess was identified. Hematologic improvement occurred during a period in which pneumonia and volume overload improved; however, luspatercept had previously been administered while ESA and intravenous iron therapy were continued, precluding attribution of the response to any single intervention.

Conclusions. This case highlights the importance of integrating MDS-like marrow findings with systematic and longitudinal assessment of potentially reversible contributors to ESA hyporesponsiveness, because marrow abnormalities and reversible causes of impaired erythropoiesis may coexist in elderly hemodialysis patients.

RJCCN 2026; 2: 301-6
www.rjccn.org
DOI: 10.61882/rjccn.2.4.61

INTRODUCTION

Erythropoiesis-stimulating agent (ESA) hyporesponsiveness in patients receiving maintenance hemodialysis may result from several coexisting conditions, including iron deficiency or impaired iron availability, infection and inflammation, inadequate dialysis, nutritional abnormalities, secondary hyperparathyroidism, occult blood loss, and trace-element deficiencies.[1,2] Accordingly, potentially reversible causes should be systematically assessed before anemia is attributed to a primary bone marrow disorder.

The diagnostic process becomes more complex in older patients because age-related clonal hematopoiesis and morphologic dysplasia may be detected in the bone marrow even in the absence of definite myelodysplastic syndrome (MDS).[3,8,9] In addition, acquired metabolic abnormalities, including copper deficiency, can produce cytopenias and marrow changes resembling MDS.[4,5] Thus,

Please cite this article as: Ikegishi Y. Diagnostic Challenges of ESA-Resistant Anemia with MDS-Like Marrow Abnormalities: The Importance of Excluding Reversible Causes. RJCCN. 2026;2(4):301-6.

the presence of marrow dysplasia or an isolated cytogenetic abnormality does not necessarily establish that a clonal myeloid disorder is the principal cause of ESA hypo-responsiveness.

We describe an elderly patient on maintenance hemodialysis who developed transfusion-dependent ESA-resistant anemia together with megakaryocytic dysplasia and isolated loss of the Y chromosome. Despite these MDS-like findings, the severity of anemia changed in parallel with inflammatory activity, iron availability, and volume status. This case illustrates the importance of integrating bone marrow findings with a systematic and longitudinal assessment of potentially reversible contributors to ESA hypo-responsiveness.

CASE REPORT

An 89-year-old Japanese man with end-stage renal disease secondary to hypertensive nephrosclerosis had undergone maintenance HD for approximately three years. Hemoglobin levels were initially maintained at 9–10 g/dL with darbepoetin alfa and intravenous iron.

Approximately 24 months after HD initiation, anemia progressively worsened despite escalation of ESA therapy. Laboratory testing demonstrated severe iron-restricted erythropoiesis with TSAT below 10% despite intravenous iron supplementation, and the patient became transfusion dependent.

Bone marrow aspiration performed because of persistent ESA-resistant anemia demonstrated normocellular marrow with dysplastic megakaryocytic changes involving 10–50% of cells, 0.6% blasts, no ring sideroblasts, and isolated loss of the Y chromosome in 4 of 20 metaphases. Serum copper and ceruloplasmin levels showed no evidence of overt copper deficiency, whereas serum zinc levels were below the reference range. Upper gastrointestinal endoscopy showed no evidence of gastrointestinal bleeding or malabsorption (Table).

Because the cause of persistent transfusion-dependent ESA hypo-responsiveness remained uncertain despite extensive evaluation and the bone marrow findings raised concern for an

Longitudinal Clinical and Laboratory Findings During the Course of ESA Hypo-responsiveness

	Reference Range	Month 28[a]	Month 32[b]	Month 34[c]	Month 36[d]	Month 37[e]
WBC, /μL	6,600 to 8,100	4,600	7,000	3500	5900	5900
Hemoglobin, g/dL	13.7 to 16.8	8.2	7.6	6.9	8.7	9.7
Hematocrit (%)	40.7 to 50.1	27.5	26.2	23.3	28.8	31.8
Platelet, $\times 10^3$/μL	158 to 348	196	90	135	181	180
CRP, mg/dL	0.00 to 0.14	0.2	7.2	4.1	0.42	0.11
Ferritin, ng/mL	21 to 274	60	59	68	43	112
TSAT (%)	> 20	6	9	7	12	22
Reticulocyte (%)	0.1 to 2.6	1.0	2.1	0.9	1.1	2.2
Albumin, g/dL	4.1 to 5.1	3.1	2.9	2.7	2.9	3.1
Zinc, μg/dL	80 to 130	54	66	44	49	48
Copper, μg/dL	66 to 130	97	132	114	101	96
Ceruloplasmin, mg/dL	21 to 37	25	35	33	28	25
hANP, pg/mL	0 to 43	129	292	446	158	76
Folate, ng/mL	3.6 to 12.9	-	4.1	-	-	-
Vitamin B12, pg/mL	233 to 914	-	297	-	-	-
AST / ALT, U/L	13 to 30 / 10 to 42	12 / 8	28 / 16	25/6	14/3	13/2
γ-GTP, U/L	13 to 64	33	36	62	60	42
Fibrinogen, mg/dL	150 to 400	-	248	-	-	-
PT (%) / aPTT, sec	70 to 130 / 24 to 34	-	71 / 24.8	-	-	-
Fecal occult blood	Negative	Negative	Negative	-	-	-
Ca/P, mg/dL	8.8 to 10.1/2.7 to 4.6	8.4/3.6	8.3/4.7	8.1/3.2	8.5/3.5	9.3/3.3
Intact PTH, pg/mL	10 to 65	110	160	93	34	93
Kt/V	≥ 1.2 (target ≥ 1.4)	1.27	1.45	1.52	1.55	1.64

Note: [a]At progression of transfusion-dependent anemia
[b]At admission for pneumonia
[c]During persistent inflammation after pneumonia
[d]During recovery from inflammation and volume overload
[e]After improvement of inflammatory activity and iron availability

underlying clonal myeloid disorder, luspatercept was introduced and administered four times between months 28 and 32. During follow-up, the patient developed pneumonia accompanied by pleural effusion, elevated C-reactive protein, thrombocytopenia, and marked elevation of human atrial natriuretic peptide, suggesting concomitant inflammation and volume overload. Treatment with ceftriaxone together with gradual reduction of dry weight improved inflammatory activity and fluid status (Figure 1).

Following resolution of pneumonia and optimization of volume status, hemoglobin increased to > 9 g/dL without additional transfusion. Platelet count recovered in parallel with improvement of inflammation. Because luspatercept had previously been administered four times between months 28 and 32 while ESA and intravenous iron therapy were continued, a delayed or contributory effect of luspatercept on the subsequent hematologic recovery could not be excluded. Therefore, the hematologic response could not be attributed to any single intervention (Figures 1 and 2).

DISCUSSION

This case demonstrates the difficulty of assigning a single cause to severe ESA hypo-responsiveness in an older patient receiving maintenance hemodialysis when abnormalities suggestive of a clonal marrow disorder are also present. ESA hypo-responsiveness in dialysis patients may arise from multiple and frequently overlapping conditions, including absolute or functional iron deficiency, infection and inflammation, blood loss, inadequate dialysis, malnutrition, secondary hyperparathyroidism, vitamin or trace-element deficiencies, and hematologic disorders.[1,2] Therefore, identification of a bone marrow abnormality does not eliminate the need to assess concurrent and potentially reversible contributors to anemia.

Bone marrow examination in our patient demonstrated megakaryocytic dysplasia involving 10–50% of cells and isolated loss of the Y chromosome (LOY) in 4 of 20 metaphases, with a

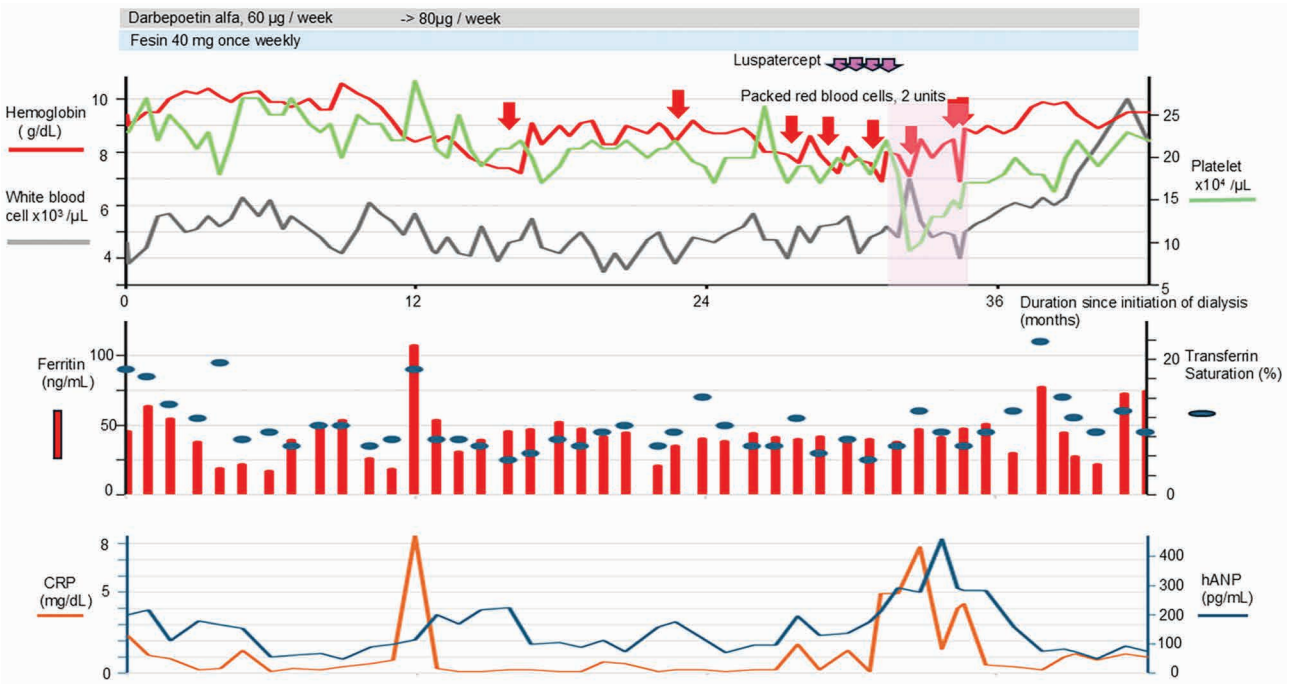


Figure 1. Overall Clinical Course Since Initiation of Dialysis
Top panel: Trends in hemoglobin (red line), platelet count (green line), and white blood cell count (gray line) are shown. Multiple transfusions of 2 units of packed red blood cells (red arrows) were administered due to worsening anemia. A shaded purple area indicates a period of inflammation associated with pneumonia, during which a transient drop in platelet count was observed. Luspatercept (purple arrows) was administered four times before the period of pneumonia-associated inflammation.
Middle panel: Serum ferritin levels (red bars) and transferrin saturation (TSAT; blue dots) throughout the course.
Bottom panel: Changes in C-reactive protein (CRP; orange line) and human atrial natriuretic peptide (hANP; blue line) are shown. Elevation of CRP and hANP was observed in parallel with the onset of pneumonia-related inflammation.

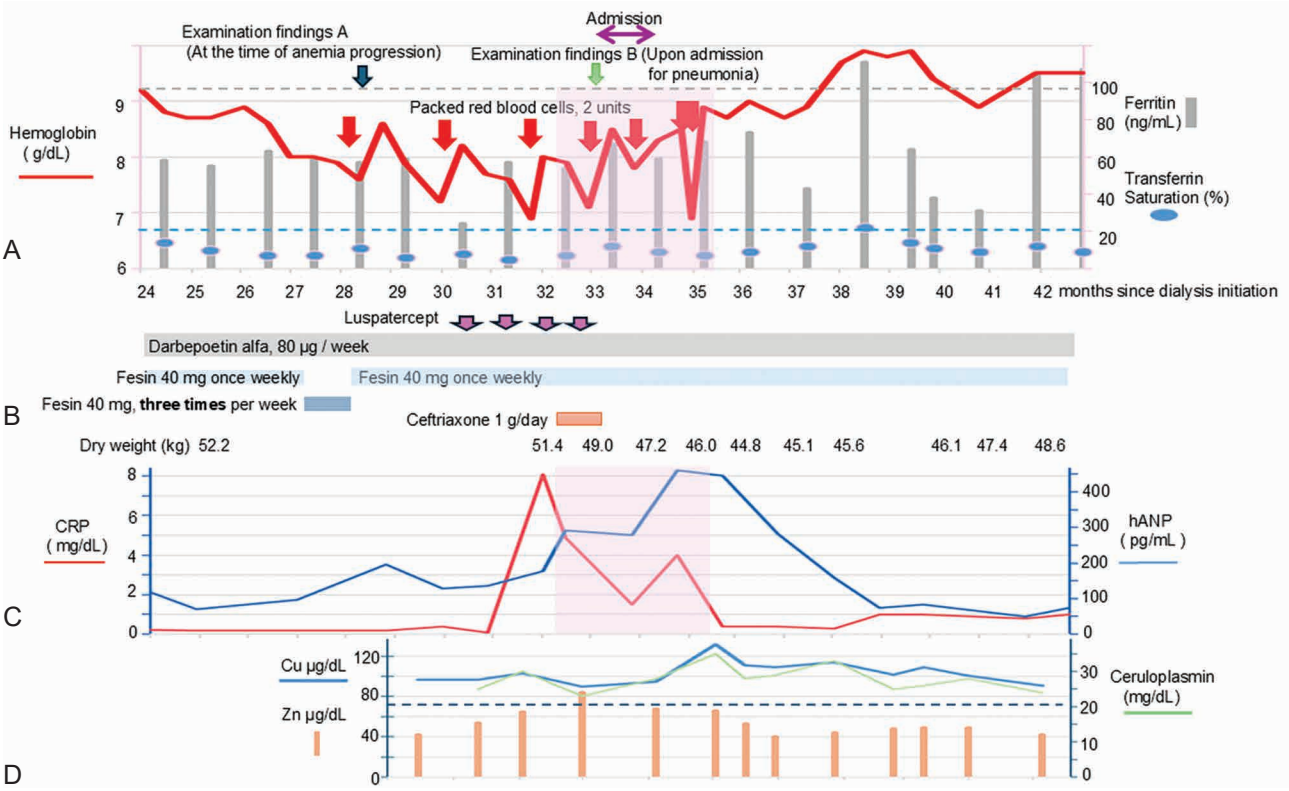


Figure 2. Clinical Course After 24 Months Since Initiation of Dialysis [A) Hemoglobin levels (red line), serum ferritin (gray bars), and transferrin saturation (TSAT, blue dots) are shown. Hemoglobin levels generally paralleled changes in TSAT values during the clinical course. The shaded area indicates the period of pneumonia-associated inflammation, during which anemia progression and thrombocytopenia were observed; B) Treatment course, including the administration of darbepoetin alfa (80 µg/week), Fesin (iron formulation) once or three times weekly, and four administrations of luspatercept between months 28 and 32 (purple arrows). Intravenous ceftriaxone (1 g/d) was administered during pneumonia; C) C-reactive protein (CRP, red line) and human atrial natriuretic peptide (hANP, blue line) levels. CRP elevation was followed by hospitalization due to pneumonia (shaded area); D) Serum levels of copper (Cu, blue line), ceruloplasmin (green line), and zinc (Zn, orange bars). Copper and ceruloplasmin levels showed no evidence of copper deficiency during the clinical course despite progressive anemia, whereas zinc levels gradually decreased]

low blast percentage (0.6%). These findings raised the possibility of an underlying clonal myeloid disorder. However, isolated LOY is increasingly recognized with advancing age, and its clinical significance depends partly on the proportion of affected metaphases and the accompanying morphologic and molecular findings.[3,8,9] In the present case, LOY was detected in only 20% of analyzed metaphases. Thus, the cytogenetic finding alone was insufficient to determine whether the patient's severe anemia was primarily attributable to MDS. Importantly, molecular testing for MDS-associated somatic mutations was not performed. An underlying clonal myeloid disorder therefore cannot be definitively excluded, and this represents an important limitation of the diagnostic evaluation.

The longitudinal clinical course provided additional information regarding the factors contributing to the severity of anemia. During pneumonia, the patient developed increased inflammatory activity, marked elevation of human atrial natriuretic peptide, worsening anemia, thrombocytopenia, and persistently low transferrin saturation. Following antibiotic treatment and adjustment of dry weight, inflammatory and volume-related abnormalities improved, accompanied by recovery of the platelet count and increases in hemoglobin and TSAT. Inflammation can impair iron availability and erythropoiesis and is a well-recognized contributor to ESA hyporesponsiveness in dialysis patients.[1,2] The parallel changes observed in this patient therefore support contributions from inflammation, functional iron restriction, and altered volume status to the severity of anemia. These observations do not exclude an underlying clonal marrow disorder; rather, they

indicate that the hematologic phenotype was likely multifactorial.

Copper deficiency was specifically considered because it can cause cytopenias and marrow dysplasia resembling MDS and has been reported as a reversible cause of severe ESA hypo-responsiveness in dialysis patients.[4–7] In our patient, however, serum copper and ceruloplasmin showed no evidence of overt copper deficiency during the period of progressive anemia, and hematologic improvement occurred without copper supplementation. Copper deficiency was therefore unlikely to be the principal explanation for the observed marrow abnormalities and ESA hypo-responsiveness. Our previous reports demonstrated that copper deficiency can represent one reversible contributor to severe ESA hypo-responsiveness and MDS-like hematologic abnormalities in dialysis patients.[6,7] In contrast, the present case suggests that a similar hematologic phenotype may emerge in the absence of copper deficiency through a different combination of physiological and clinical stressors. This distinction is important because MDS-like marrow findings in dialysis patients may occur in heterogeneous clinical settings and should be interpreted together with biochemical findings and the longitudinal clinical course.

More broadly, these observations may be viewed within a framework of hematologic vulnerability in older dialysis patients. Age-related or clonal marrow abnormalities may coexist with dynamic disturbances in erythropoiesis related to inflammation, impaired iron availability, nutritional status, volume overload, or trace-element abnormalities. Additional physiological stress may therefore accentuate anemia in a patient with limited hematopoietic reserve, without implying that any single factor fully accounts for the hematologic phenotype. In this context, clonal marrow abnormalities and potentially reversible contributors should not necessarily be regarded as mutually exclusive explanations for ESA hypo-responsiveness.

Interpretation of the hematologic recovery is complicated by the sequential and partially overlapping use of several interventions. Luspatercept was administered four times between months 28 and 32 while the patient continued to receive ESA and intravenous iron. Luspatercept, an activin receptor ligand trap that promotes late-stage erythroid maturation, has previously been considered as a potential therapeutic approach for anemia in CKD; however, its clinical development has primarily focused on indications other than CKD.[10] These doses were administered before the subsequent development of prominent inflammatory and volume-related abnormalities. Therefore, a delayed or contributory effect of luspatercept on the later increase in hemoglobin cannot be excluded.

During the subsequent clinical course, pneumonia was treated with antibiotics and volume status was managed by adjustment of dry weight, while changes in inflammatory activity, iron availability, ESA treatment, and intravenous iron administration also occurred. Because these factors changed within the same overall period, the hematologic recovery cannot be attributed to luspatercept, treatment of infection, volume optimization, ESA, or intravenous iron alone. Accordingly, we do not interpret the improvement as evidence against an underlying clonal marrow disorder or as evidence of a specific treatment effect. Rather, the parallel changes in inflammatory activity, volume-related parameters, iron availability, platelet count, and hemoglobin support a multifactorial interpretation of the hematologic course.

This case also underscores the importance of the sequence of diagnostic evaluation in ESA hypo-responsiveness. Common and treatable causes—including iron deficiency or impaired iron utilization, infection and inflammation, inadequate dialysis, blood loss, nutritional deficiencies, secondary hyperparathyroidism, and relevant trace-element abnormalities—should be systematically assessed before proceeding to invasive evaluation for a primary marrow disorder. When persistent unexplained cytopenia or other clinical findings warrant bone marrow examination, the resulting morphologic and cytogenetic abnormalities should subsequently be interpreted in the context of the entire clinical course rather than in isolation. In the present patient, the available findings did not permit definitive exclusion of MDS, but neither did they establish that a clonal marrow disorder was the predominant cause of the transfusion-dependent anemia.

The principal message of this case is therefore not that reversible causes of ESA hypo-responsiveness are newly recognized, but that their contribution may remain clinically important even after MDS-like marrow abnormalities have been identified. The distinctive aspect of this case is the coexistence of marrow abnormalities suggestive of a clonal disorder with dynamically changing and potentially reversible contributors to impaired erythropoiesis. In older dialysis patients, these processes may coexist and interact rather than represent mutually exclusive diagnoses. A longitudinal approach integrating marrow morphology, cytogenetic and, when available, molecular findings with dialysis adequacy, inflammation, iron availability, nutritional status, trace-element status, and volume status may help distinguish the presence of a marrow abnormality from its actual contribution to the severity of anemia.

This framework is hypothesis-generating rather than diagnostic and requires further investigation in larger populations.

DECLARATIONS

Funding

Not applicable.

Conflicts of Interest / Competing Interests

The authors declare no conflicts of interest.

Ethics Approval

Not applicable. This case report did not require institutional ethics approval according to local institutional policies.

Consent to Participate

Written informed consent to participate in this case study was obtained from the patient.

Written Consent for Publication

Written informed consent for publication of clinical details and accompanying images was obtained from the patient.

Availability of Data and Material

Not applicable.

Code Availability

Not applicable.

Acknowledgment

The authors would like to thank the dialysis unit staff at Fuefuki Central Hospital for their support and contributions to this submission.

REFERENCES

1. Wu HHL, Chinnadurai R. Erythropoietin-stimulating agent hyporesponsiveness in patients living with chronic kidney disease. Kidney Dis (Basel). 2022;8:103-14.
2. Kanbay M, Perazella MA, Kasapoglu B, Koroglu M, Covic A. Erythropoiesis stimulatory agent-resistant anemia in dialysis patients: review of causes and management. Blood Purif. 2010;29:1-12.
3. Vlasschaert C, Lanktree MB, Rauh MJ, Kelly TN, Natarajan P. Clonal haematopoiesis, ageing and kidney disease. Nature Reviews Nephrology. 2024;20(3):161–74.
4. Huff JD, Keung YK, Thakuri M, Beaty MW, Hurd DD, Owen J, et al. Copper deficiency causes reversible myelodysplasia. Am J Hematol. 2007;82:625-30.
5. Tahir N, Ashraf A, Waqar SHB, Rafae A, Kantamneni L, Sheikh T, et al. Copper deficiency, a rare but correctable cause of pancytopenia: a review of literature. Expert Rev Hematol. 2022;15:999-1008.
6. Ikegishi Y, Abe R, Maehata A, Takiyama Y. Diagnostic pitfalls of ESA-resistant anemia due to functional copper deficiency in a dialysis patient: a myelodysplastic syndrome mimic. CEN Case Rep. 2026;15:37.
7. Ikegishi Y, Abe R, Maehata A, Takiyama Y. Acute-onset copper deficiency following surgery in a dialysis patient: diagnostic challenges and risk factor interaction. Intern Med. 2026;65:1023-7.
8. Valent P, Orazi A, Steensma DP, Ebert BL, Haase D, Malcovati L, et al. Proposed minimal diagnostic criteria for myelodysplastic syndromes (MDS) and potential pre-MDS conditions. Oncotarget. 2017;8:73483-500.
9. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka HM, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140:1200-28.
10. Locatelli F, Del Vecchio L, Luise MC. Current and future chemical therapies for treating anaemia in chronic kidney disease. Expert Opin Pharmacother. 2017;18:781–8.

Correspondence to:
Yukinobu Ikegishi, MD, PhD
Fuefuki Central Hospital, 47-1 Yokkaichiba, Isawa-cho, Fuefuki-shi, Yamanashi 406-0032, Japan
Phone: 0081 55 262 2185
Fax. 0081 55 262 5985
ORCID ID: 0009-0006-7302-5761
E-mail: yikegishi@yahoo.co.jp

Received July 2026
Revised August 2026
Accepted September 2026

RJCCN

Research Journal of Critical Care Nephrology

Volume 2, Number 4, October 2026

FROM THE EDITORS

- Seeing, Steering, and Sensing the Injured Kidney
  Nassiri AA 223

COMMENTARY

- Critical Care Transesophageal Echocardiography: Expanding the Hemodynamic Window
  Koratala A 227

REVIEW

AKI

- Net Ultrafiltration During Continuous Kidney Replacement Therapy for Acute Kidney Injury: From Fixed Rates to Precision Fluid Removal
  Kashani KB, Murugan R 231

Kidney Disease

- Multi-Omics Integration for Enhanced Insights into Chronic Kidney Disease: Unraveling Biological Networks and Therapeutic Targets, A Mini Review
  Kianfar T, Zakikhani A, Taherkhani S 248

ORIGINAL PAPER

Sepsis

- Diagnostic Value of MicroRNAs as Biomarkers for Sepsis-associated Acute Kidney Injury: A Systematic Review and Meta-Analysis
  Javandoust Gharehbagh F, Lotfollahi L, Gerami D, Alavi Darazam I 255

Kidney Disease

- Epidemiological Characteristics of Children with Nephrotic Syndrome Referred to Amir-Kabir Hospital in Arak, Iran: A Cross-Sectional Study
  Yousefichaijan P, Rafiei F, Rezagholizamenjany M 272

Dialysis

- Association of Dialysis Adequacy and Estimated Kidney Function with Mineral Metabolism Parameters in Patients Undergoing Peritoneal Dialysis
  Mortazavi M, Rahimifar R, Seirafian S, Miralaei P 279

Transplantation

- Clinical Profile, Immunosuppressive Management and Outcome in Adult Renal Allograft Recipients with COVID-19 Infection
  Mahjabin S, Islam N, Rahman R, Haque E, Ebne Mobin M 289

CASE REPORT

Dialysis

- Diagnostic Challenges of ESA-Resistant Anemia with MDS-Like Marrow Abnormalities: The Importance of Excluding Reversible Causes
  Ikegishi Y 301

EUMEDICA
Pharmaceuticals
Ensuring Medical Care Continuity

Negaban® Temocillin

valean darou

In the Treatment of
Infections Caused by Susceptible Gram-negative micro-organisms

Stable to most β-lactamases, incl. ESBL and AmpC, and active against some KPC-producing isolates at urinary concentrations

Carbapenem-sparing Agent

REGISTERED INDICATIONS

- **Treatment of complicated urinary tract infections** (incl. pyelonephritis)
- **Treatment of bacteraemia** and **wound infections** when susceptible Gram-negative bacteria are confirmed or strongly suspected.

Less is more, when it's the right choice.

For more information, please contact Valean Darou
02188673760 Ext. 1070

For healthcare professionals only.