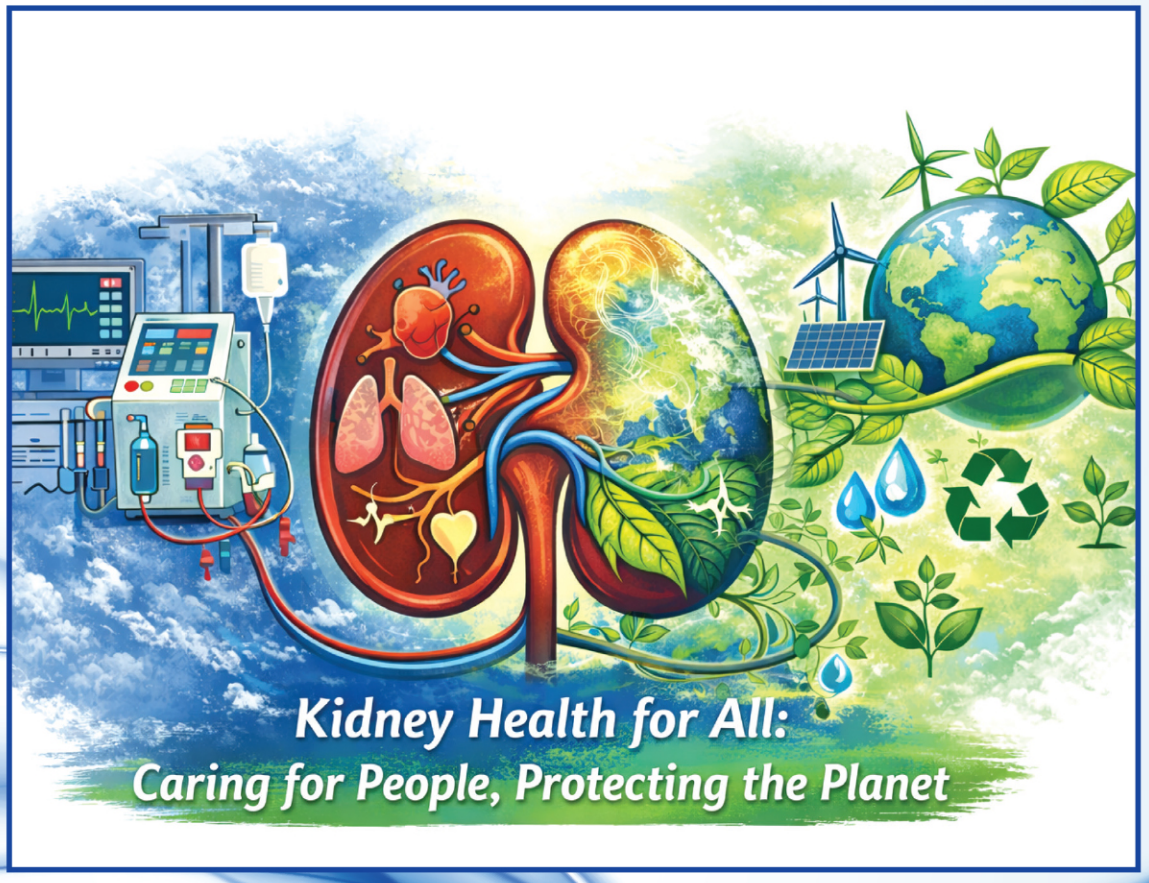
RJCCN

Research Journal of Critical Care Nephrology

Volume 2, Number 2, April 2026



RESEARCH JOURNAL OF
CRITICAL CARE
NEPHROLOGY

eISSN 3115-8463

Research Journal of Critical Care Nephrology Volume 2 Number 2 April 2026

RJCCN

Research Journal of Critical Care Nephrology

AIMS AND SCOPE

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

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eISSN. 3115-8463

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E-mail: info@rjccn.org, admin@rjccn.org, rjccn2024@gmail.com

Publisher. Self-published

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

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

Cover: Kidney Health for All: Caring for People, Protecting the Planet. See page 67

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INSTRUCTIONS TO AUTHORS

*Summarized Version**
April 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

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Identifiers

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

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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, Conclusion, 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 Conclusion) 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.

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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.

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

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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.

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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.

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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.

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All others who contributed to the work but are not authors (if any) are named in the *Acknowledgements* of the manuscript.

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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

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Critical Care Nephrology in the Era of Planetary Health: Aligning Intensive Kidney Care with the Vision of World Kidney Day

RJCCN 2026; 2: 67-9
www.rjccn.org
DOI: 10.66224/rjccn.2.2.48

Each year, International Society of Nephrology and International Federation of Kidney Foundations coordinate World Kidney Day to raise global awareness of kidney disease and promote strategies to improve kidney health worldwide. The theme for World Kidney Day 2026 *"Kidney Health for All: Caring for People, Protecting the Planet"* highlights an increasingly urgent reality: kidney health is inseparable from both human well-being and planetary sustainability.

Within this broader landscape, the field of critical care nephrology has emerged as one of the most dynamic and essential interfaces in modern medicine. At the intersection of nephrology, intensive care medicine, and extracorporeal therapies, critical care nephrology addresses some of the most complex and life-threatening conditions encountered in clinical practice, including acute kidney injury (AKI), multiple organ dysfunction, and the need for advanced renal replacement therapies in critically ill patients.

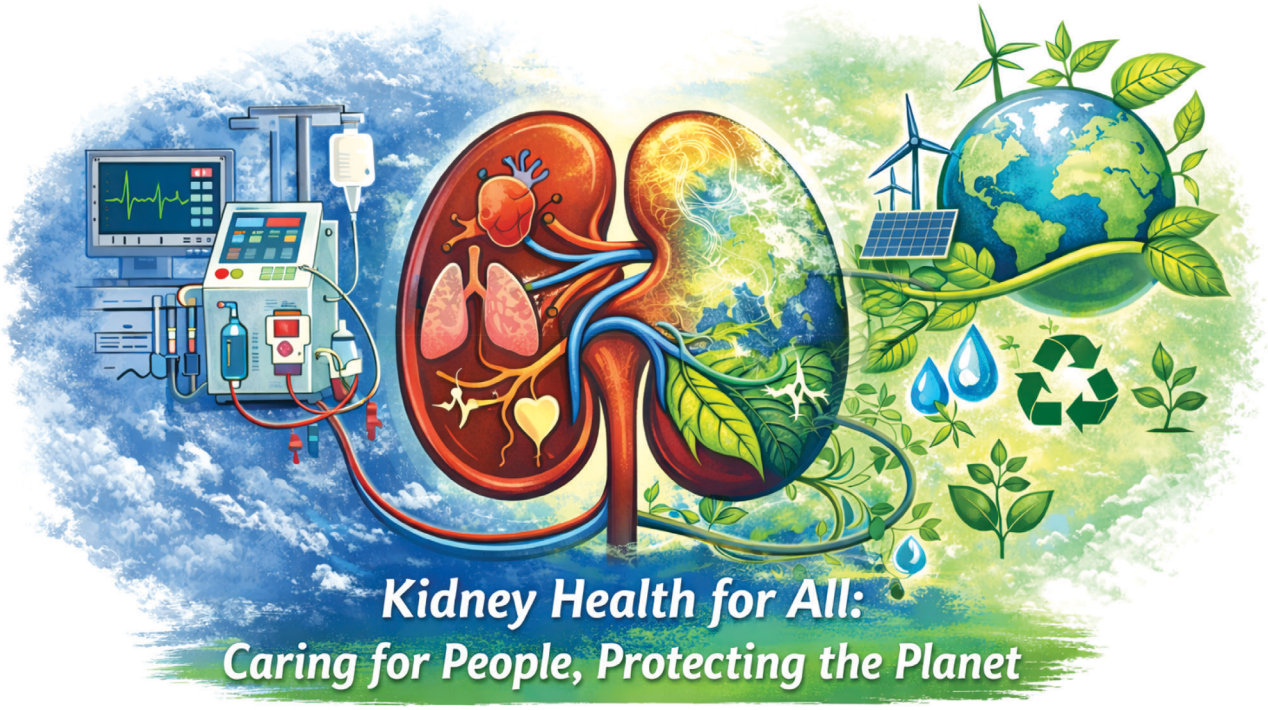
The global burden of kidney disease continues to rise. Kidney disease has never been confined to the kidney. It is a mirror of systemic vulnerability, a convergence point where inflammation, hemodynamic instability, environmental exposure, and social inequity silently intersect. Acute kidney injury affects millions of hospitalized patients each year and remains strongly associated with increased mortality, prolonged hospitalization, and long-term chronic kidney disease. In the modern intensive care unit, AKI is rarely an isolated event; rather, the renal expression of multiple organ failure, unfolding in real time. The management of such patients requires an integrated understanding of organ cross-talk—particularly the complex interactions between the kidney, heart, lung, and immune system.

Over the past two decades, critical care nephrology has evolved from a narrow technical domain focused primarily on dialysis delivery into a multidisciplinary field centered on comprehensive organ support. Innovations in continuous renal replacement therapy (CRRT), hemoadsorption and extracorporeal blood purification, fluid stewardship, and precision hemodynamic monitoring have transformed the role of nephrologists within the ICU. Increasingly, nephrologists participate not only in renal replacement therapy but also in broader decisions regarding fluid management, metabolic control, and extracorporeal organ support strategies.

The theme of *World Kidney Day—caring for people while protecting the planet—also invites reflection on the environmental impact of kidney care itself.* Dialysis therapies, particularly in the ICU setting, are resource-intensive and generate substantial volumes of plastic waste, water consumption, and energy use. As healthcare systems worldwide confront the challenge of climate change and environmental sustainability, nephrology—and critical care nephrology in particular—must assume a leadership role in developing greener models of care. Efforts toward sustainable dialysis technologies, optimized resource utilization, and environmentally responsible manufacturing of medical devices represent an emerging frontier for the specialty (Figure).

Equally important is the principle of equity in

Please cite this article as: Nassiri AA. Critical Care Nephrology in the Era of Planetary Health: Aligning Intensive Kidney Care with the Vision of World Kidney Day. RJCCN 2026; 2(2): 67-9.



access to life-saving therapies. Advanced renal replacement modalities such as continuous kidney replacement therapy and extracorporeal blood purification remain unavailable in many regions of the world, particularly in low- and middle-income countries. The vision of "Kidney Health for All" cannot be realized unless critical care nephrology expands beyond technologically advanced centers and reaches patients in resource-limited settings. Innovation in simplified technologies, telemedicine, training programs, and global collaborations will be essential to bridge these disparities.

Critical care nephrology also exemplifies the broader transformation of nephrology toward a more integrative and patient-centered discipline. As the boundaries between nephrology, cardiology, critical care, and metabolic medicine continue to blur, the modern nephrologist must be equipped with new competencies—ranging from ultrasonography and hemodynamic assessment to extracorporeal organ support and interdisciplinary collaboration.

This journal, *Research Journal in Critical Care Nephrology*, is dedicated to advancing scholarship at this crucial interface. By fostering research in acute kidney injury, extracorporeal therapies, organ cross-talk, and innovative models of kidney support in critically ill patients, the journal aims to contribute to a deeper understanding of how kidney care can improve outcomes in the most vulnerable populations.

On this occasion of World Kidney Day, we reaffirm the importance of critical care nephrology as a pillar of modern medicine. Protecting kidney health is not only a matter of chronic disease prevention but also of delivering timely, equitable, and sustainable care to patients facing life-threatening illness. As clinicians, scientists, and educators, we must continue to advance both the science and the stewardship of kidney care—caring for people while safeguarding the planet we share.

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

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Received March 2026

RJCCN EDITORIAL

The Integration of Palliative Care in the Critical Care Management of Patients with Advanced Renal Diseases:
A Necessity in Patient-centered Outcome

RJCCN 2026; 2: 70-1
www.rjccn.org
DOI: 10.66224/rjccn.2.2.40

End-stage kidney disease patients are frequently admitted to the ICU for critical and fatal conditions. These patients experience a high mortality rate, symptom burden, and difficult decisions about life-sustaining treatments such as renal replacement therapy. Previous studies have established that the current disease management approach in caring for ICU patients does not address the holistic needs of these patients.

Nephrology and critical care overlap to create a very intense field of practice and outcome. Most patients with end-stage renal disease have an increased incidence of requiring ICU care due to associated complications such as infections, cardiovascular complications, and metabolic derangements. Once in the ICU, the mortality rate for those patients requiring either invasive mechanical ventilation or inotropic/sympathomimetic therapy is greater than 50%. Not only do these patients face a high mortality rate, but they also face a high symptom burden due to associated pain, shortness of breath, fatigue, confusion, and itching. The use of technology in the ICU (such as dialysis) has often resulted in loss of focus on patient-centered goals and has been termed the 'Technological Imperative'. Ultimately, palliative care is a type of medical service for the purposes of helping improve the quality of life for an individual suffering from a serious or potentially life-threatening condition, and this is not the same as end-of-life care but is instead intended to occur at the same time as curative or life-prolonging treatment.

The World Health Organization has estimated that there are 40 million individuals annually who need palliative care, and 78% of these individuals live in low and middle-income areas.

Still, only a small percentage, less than 10%, of those people in low and middle-income areas are able to receive palliative care. Additionally, it has also been estimated that with the rate at which the population is increasing, the need for palliative care will only continue to grow in the coming years. For example, in the U.S., there are upwards of 90 million people suffering from different types of illnesses, with 80% of those people being in need of palliative care, yet only 50% of those hospitalized and in need of palliative care are able to receive it. The five basic principles on which palliative care is based are as follows, regardless of the differences among palliative care patients: the needs of the patient are the focus, the continuity of palliative care is important in the course of medical treatment, use palliative care at the time of diagnosis, use inter-professional teams, and the public should be able to access palliative care services in each community. These principles have been in place for a number of years in many countries. However, it appears there is no well-structured palliative care program in place for Iran. Instead, palliative care is viewed as a challenge to the Iranian health care system due to the lack of attention given to palliative care patients.

CHALLENGES FOUND IN THE NEPHROLOGY ICU

RRT Decision Making for Critically Patients

The concept of using, extending, or withholding dialysis from a patient who is critically ill can be difficult both ethically and practically in all

Please cite this article as: Rahimzadeh Kalaleh A. The Integration of Palliative Care in the Critical Care Management of Patients with Advanced Renal Diseases: A Necessity in Patient-Centered Outcome. RJCCN. 2026;2(2):70-1.

situations. "Time-limited trials of RRTs are a highly useful but largely underdeveloped tool."

The High Burden of Symptoms

The symptoms are often not recognized or treated adequately. The uremic symptoms also pose an additional burden to the already present critical illness, as well as the burden of dialysis itself, which may include leg cramping and fatigue.

Prognostic Uncertainty

It is common for both the healthcare providers and the families to have unrealistic expectations regarding the chances for survival as well as the chances for the restoration of function after the illness caused by ESRD for these patients.

Communication Breakdowns

The breakdown occurs regarding the discussion of prognosis, goals of care, long-term functional impairments.

Caregiver Distress

The families of these patients are already engaged with the duration of chronic dialysis treatments for the patients. When the family decides to consider the ICU admission for the patients, the caregiver expresses a high level of distress

Models for Integrating Palliative Care

Integration can be achieved through the primary or specialist models:

Primary Palliative Care. Palliative Care must have the ICU Team and Nephrologists with primary knowledge of assessing patient symptoms; both teams will require communication skills; at minimum should understand ethical issues. Develop core triggers that will enable the two teams to proactively start to work on developing an intervention with the service.

Trigger Criteria. Automatic referral to consult patients with ESRD after ICU admissions: ≥ 2 admissions within 30 days, metastatic cancer, end-stage dementia, prolonged mechanical ventilation (> 7 days), or significant pre-admission decline

Specialized Palliative Care Service. If the patient comes with severe symptoms that are complicated, there is a direct conflict between the family or patient, and there is a high degree of existential distress, then referral to a multidisciplinary palliative care service is likely. This type of referral is required for high psychosocial issues, complicated family sessions, or severe symptom management.

Azam Rahimzadeh Kalaleh

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Received February 2026

RJCCN COMMENTARY

Point-of-Care Ultrasound and Volume Status: Embracing Physiology Over Proxies

Abhilash Koratala

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

RJCCN 2026; 2: 72-5
www.rjccn.org
DOI: 10.66224/rjccn.2.2.41

Keywords. POCUS, ultrasound, right atrial pressure, hemodynamics, volume

INTRODUCTION

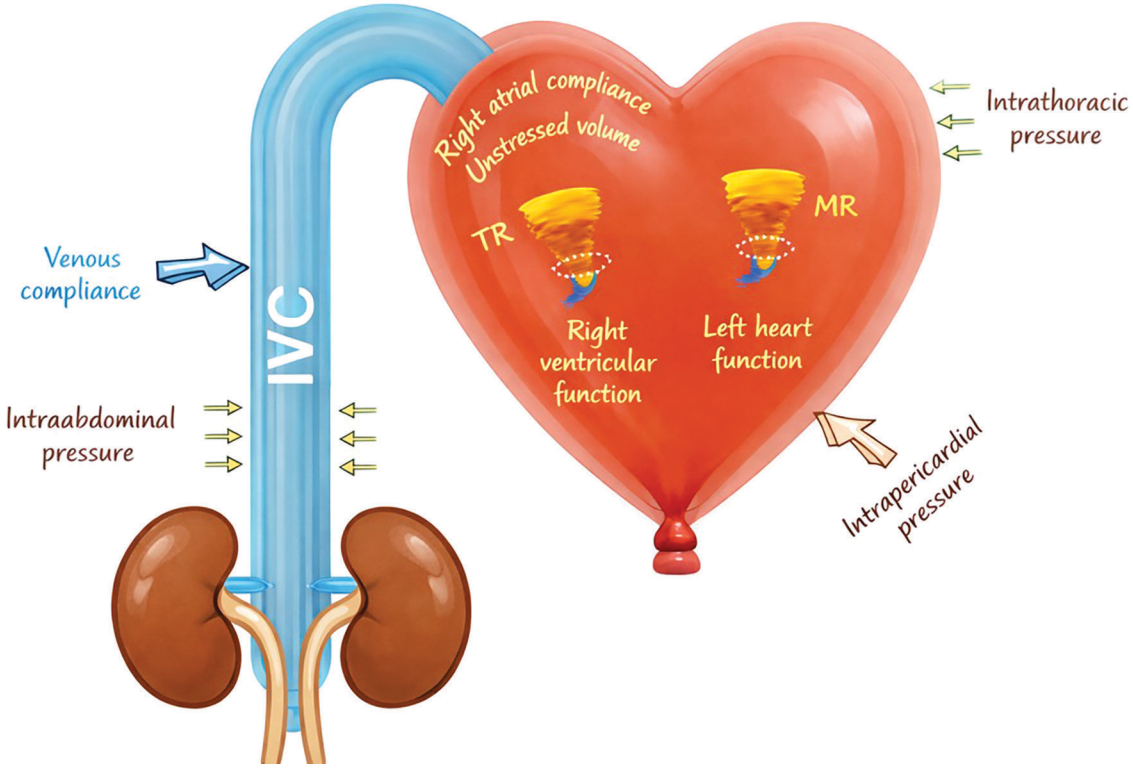
Few challenges in nephron-critical care generate as much debate and quiet uncertainty as the assessment of "volume status". Despite decades of clinical experience and an expanding array of bedside technologies, clinicians continue to wrestle with a deceptively simple question: is this patient volume overloaded, volume depleted, or neither? The persistence of this uncertainty reflects a deeper truth. Volume status is not a single physiologic variable, and any attempt to reduce it to one measurement will inevitably fall short.

Point of care ultrasound (POCUS) has increasingly entered this debate, often accompanied by the expectation that it can directly measure volume. In particular, inferior vena cava (IVC) ultrasound is frequently treated as a kind of magic wand for determining volume status. It is not. Importantly, neither are the invasive tools that have long been regarded as definitive. Even pulmonary artery catheterization does not measure volume; it reports pressures and derived indices that function as surrogates for complex hemodynamic states. Hemodynamic assessment, whether ultrasound based or invasive, is therefore inherently inferential.

Right atrial pressure (RAP) illustrates this limitation particularly well. It is frequently invoked as a proxy for intravascular volume, yet it reflects far more than volume alone. The dissociation between intravascular volume and RAP has been well documented.[1] Venous pressures are influenced by global cardiac performance, pericardial constraint, intrathoracic pressure, pulmonary vascular resistance, valvular pathology, venous compliance, and intraabdominal pressure. Any interpretation of IVC ultrasound as a surrogate for RAP must account for this physiologic complexity (**Figure**). Even then, its accuracy is limited, particularly in patients receiving mechanical ventilation. Parkin's assertion remains profoundly relevant: *RAP, and by extension IVC ultrasound, reflects true volume state only when the heart is not beating*.[2] The remark may come across as provocative, yet it distills a central physiologic truth. Pressure should not be mistaken for volume. The broader literature on IVC ultrasound further complicates matters. It often blurs the distinction between its intended role as a tool for estimating RAP and its controversial use in predicting fluid responsiveness. The latter concept is itself fraught with physiologic and methodological limitations, and the field is increasingly shifting toward the more clinically grounded construct of fluid tolerance as detailed in prior commentary.[3]

In practical terms, identical RA pressures can represent profoundly different physiologic states. One patient with an elevated pressure and a plethoric IVC may be truly hypervolemic and benefit from diuresis or ultrafiltration. Another may have elevated pressure driven by a large pericardial effusion, where indiscriminate fluid removal could precipitate hemodynamic collapse. In yet other cases, modulation of pulmonary

Please cite this article as: Koratala A. Point-of-Care Ultrasound and Volume Status: Embracing Physiology Over Proxies. RJCCN. 2026;2(2):72-5.



Conceptual framework illustrating physiologic determinants of inferior vena cava (IVC) dynamics during hemodynamic assessment, including right and left heart function, valvular regurgitation, venous compliance, intraabdominal and intrathoracic pressures, and pericardial constraint. TR denotes tricuspid regurgitation and MR denotes mitral regurgitation.

vascular resistance may be more appropriate than altering volume. Conversely, a small and collapsible inferior vena cava does not reliably distinguish hypovolemia from euvolemia or from vasodilatory states. As such, interpreting RAP in isolation risks conflating pressure with volume. That conceptual error can meaningfully distort clinical decision making and lead to inappropriate fluid administration or removal.

Lung POCUS findings are equally susceptible to oversimplification. B lines are sensitive indicators of increased extravascular lung water, yet they are not specific for cardiogenic pulmonary edema. Bilateral B lines may reflect a broad spectrum of conditions, including acute respiratory distress syndrome, diffuse interstitial pneumonia or pneumonitis, pulmonary fibrosis, and other chronic interstitial lung diseases. In contrast, localized or unilateral B lines more often point toward focal processes such as pneumonia, pulmonary contusion following trauma, or neoplastic involvement.[4] Interpretation therefore hinges on clinical context. Even with careful attention to structural and physiologic cues, overlap between cardiogenic and noncardiogenic causes of B lines is common and requires integration with cardiac structure and function. In some settings, lung POCUS is treated as a standalone measure of volume status, with enthusiasm that extends well beyond the evidence derived from hemodialysis cohorts. Accordingly, the absence of B lines may be misinterpreted as evidence of normal volume status, overlooking right sided congestion, or even construed as a risk factor for intradialytic hypotension. This reasoning can lead to suboptimal decongestion or fluid removal only in the presence of lung congestion. Such logic is no more defensible than arguing that a dialysis patient with a normal lung examination should not undergo ultrafiltration.[5]

These limitations underscore a central principle that is often underemphasized in discussions of volume status: the assessment must always include the heart. Whether through focused cardiac ultrasound or thoughtful interpretation of formal echocardiography, cardiac function provides the framework within which all other findings acquire

meaning. Left and right ventricular performance, diastolic function, chamber interactions, and valvular pathology directly shape filling pressures, venous congestion, and ultimately organ perfusion. POCUS is most informative when cardiac evaluation anchors the examination, allowing pulmonary and venous findings to be understood as downstream manifestations of upstream physiology. In its ideal form, POCUS based "hemodynamic status" assessment, a more accurate term than volume status assessment, encompasses the entire circulatory circuit, including forward flow, left sided filling pressures and their consequences such as mitral inflow patterns and lung ultrasound findings, as well as right sided pressures and their sequelae, including trans tricuspid gradients, IVC dynamics, and markers of venous congestion such as VExUS.[6]

Beyond ultrasound, clinicians rely on a range of complementary tools to estimate volume status, each with distinct strengths and important limitations. Physical examination remains universally accessible, and certain components, such as capillary refill time, have experienced renewed interest in recent years.[7] Capillary refill offers a rapid, inexpensive bedside estimate of peripheral perfusion; however, inconsistent measurement techniques and the absence of a uniform definition of normal have limited its clinical reliability and interpretability. More broadly, heavily relied-upon physical examination findings such as jugular venous pressure and pulmonary crackles have limited sensitivity and frequently fail to identify clinically significant congestion. Daily weights and intake-output records provide longitudinal trends but neither reflect compartmental fluid shifts nor escape the limitations of imperfect documentation. Bioimpedance techniques estimate total and extravascular body water but cannot reliably distinguish intravascular volume from interstitial or third spaced fluid, nor do they inform hemodynamic tolerance. Continuous hematocrit monitoring during renal replacement therapy reflects relative changes in intravascular volume but offers no insight into tissue congestion or cardiac reserve. Even invasive hemodynamic monitoring yields pressures and flows without clarifying where excess fluid resides or how well it is tolerated at the organ level. Advanced technologies aimed at assessing tissue perfusion, such as near infrared spectroscopy for direct measurement of tissue hemoglobin oxygen saturation and visualization of the sublingual microcirculation using polarized or darkfield microscopy, are not widely available and currently remain largely confined to research settings. More importantly, *each modality illuminates a different facet of volume physiology, but none resolves the problem in isolation.* The limitation is not primarily technological but conceptual. Volume status emerges from the dynamic interplay of cardiac function, vascular tone, venous compliance, and tissue characteristics. Any approach that compresses this complexity into a single metric will inevitably misclassify some patients.

In this context, POCUS is best understood not as a standalone solution but as a modality that helps reconcile discordant signals. Its value lies in bedside pattern recognition and physiologically grounded hypothesis testing, integrated with clinical history, laboratory data, and other available information. Ultimately, the assessment of volume status in nephrocritical care remains an art informed by science. Precision does not arise from pursuing a single metric, whether derived from ultrasound, invasive monitoring, or laboratory values. It emerges from synthesizing multiple strands of data within the unique clinical context of the individual patient. POCUS does not eliminate uncertainty; rather, when anchored in physiology and used alongside traditional assessment, it enables clinicians to navigate that uncertainty with greater clarity and humility.

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Received January 2026

RJCCN REVIEW
KIDNEY DISEASE

Psychological Interventions in Chronic Kidney Disease: A Comprehensive A Comprehensive Review of Evidence-based Approaches in Clinical Practice

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Keywords. chronic kidney disease, depression, anxiety, cognitive behavioral therapy, psychotherapy, dialysis, kidney transplantation

Chronic Kidney Disease (CKD) is a progressive condition associated with a high burden of psychological distress, including anxiety, depression, and diminished quality of life. These psychological comorbidities significantly impact clinical outcomes, treatment adherence, and overall survival. This integrative review synthesizes the current evidence regarding effective, evidence-based psychological interventions applicable in the clinical management of CKD patients across various stages of kidney replacement therapy (KRT). We examined the efficacy of cognitive behavioral therapy (CBT), mindfulness-based interventions (MBIs), problem-solving therapy (PST), and technologically delivered interventions (e.g., telehealth, mobile apps) in reducing psychological symptoms and improving self-management behaviors. The literature suggests that structured psychological interventions are effective adjuncts to standard medical care for managing distress in CKD populations. CBT and tailored behavioral therapies show robust evidence for reducing depressive symptoms.

Emerging technologies offer promising avenues for improving accessibility, particularly for patients receiving hemodialysis. Future research should focus on standardizing intervention protocols, exploring cost-effectiveness, and implementing stepped-care models within nephrology units. Integrating mental health screening and timely referral pathways is crucial for optimizing patient outcomes in CKD care.

RJCCN 2026; 2: 76-81
www.rjccn.org
DOI: 10.66224/rjccn.2.2.28

INTRODUCTION

Chronic Kidney Disease (CKD) affects millions globally and represents a major public health challenge, characterized by progressive decline in renal function that often necessitates complex medical management, including dialysis or kidney transplantation.[1] Beyond the profound physiological complications such as anemia, malnutrition, and cardiovascular disease, CKD imposes a significant psychological burden. The relentless nature of the disease, frequent medical appointments, invasive treatments, lifestyle restrictions, and the specter of end-stage renal disease (ESRD) contribute to high prevalence rates of psychological morbidity.[1]

Depression and anxiety are among the most frequently reported psychiatric comorbidities in

Please cite this article as: Adlkhah S. Psychological Interventions in Chronic Kidney Disease: A Comprehensive; Review of Evidence-Based Approaches in Clinical Practice. RJCCN. 2026;2(2):76-81.

CKD, with prevalence estimates often exceeding those found in the general population and other chronic illnesses.[2]

Untreated or undertreated mental health issues are associated with poorer adherence to complex medical regimens (e.g., fluid restriction, medication schedules), increased hospitalization rates, reduced quality of life (QoL), and higher mortality risk in both pre-dialysis and KRT populations.[3] Furthermore, psychological distress can exacerbate physical symptoms, creating a negative feedback loop that impairs patient functioning.

Given the demonstrated impact of mental health on clinical trajectories in nephrology, effective psychological interventions are imperative. Standard nephrology care often focuses predominantly on biomedical markers, frequently overlooking the psychological dimensions of chronic illness management. While pharmacotherapy may play a role, psychosocial interventions, which address coping mechanisms, illness perceptions, and behavioral strategies, are crucial components of holistic, patient-centered care.[4]

This integrative review aims to systematically survey the existing evidence base concerning psychological interventions implemented in CKD patients.

Specifically, we seek to synthesize findings on the efficacy, applicability, and practical implementation of evidence-based psychotherapeutic modalities (such as CBT, MBI, and PST) across the CKD continuum, including patients undergoing maintenance dialysis and those post-transplantation. The ultimate goal is to provide a concise summary to guide clinicians in integrating optimal psychological support into routine nephrology practice.

MATERIALS AND METHODS

Study Design and Search Strategy

This manuscript employs an integrative review methodology, as recommended for synthesizing evidence from varied study designs to establish a

comprehensive understanding of clinical topics lacking consistent meta-analytic data.[4] The primary objective was to identify, appraise, and synthesize evidence regarding the efficacy of structured psychological interventions in CKD patients.

A systematic literature search was conducted across major electronic databases, including PubMed/MEDLINE, PsycINFO, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL), from inception up to the preparation date. Key search terms included combinations of: ("Chronic Kidney Disease" OR CKD OR "End Stage Renal Disease" OR Dialysis OR Transplantation) AND ("Psychological Intervention" OR Psychotherapy OR CBT OR "Cognitive Behavioral Therapy" OR Mindfulness OR "Problem Solving Therapy" OR Counseling).

Inclusion and Exclusion Criteria

Inclusion Criteria. 1) Studies involving patients diagnosed with CKD (Stages 1 to 5, or KRT recipients). 2) Intervention focused on a structured, non-pharmacological psychological intervention (e.g., individual or group therapy). 3) Use of validated outcome measures assessing depression, anxiety, QoL, or coping. 4) Original research articles, including randomized controlled trials (RCTs), quasi-experimental studies, and high-quality observational studies. 5) Manuscripts published in English.

Exclusion Criteria. 1) Studies focusing solely on pharmacological interventions. 2) Case reports, editorials, or reviews. 3) Interventions primarily targeting caregivers or pediatric populations. 4) Studies where the psychological intervention was not the primary focus or where follow-up data were unavailable.

Data Extraction and Synthesis

Data extraction focused on the study design, patient population (CKD stage, KRT modality), intervention type, duration/format, control group comparator, primary outcomes (e.g., change in Δ in Beck Depression Inventory (BDI) scores), and key findings regarding efficacy.

The synthesis process involved thematic analysis of the extracted data, grouping interventions by their theoretical framework (e.g., cognitive-behavioral vs. supportive) and evaluating the consistency and strength of evidence supporting their use in specific CKD populations.

RESULTS

The literature review identified several distinct categories of psychological interventions utilized

in the CKD population. The evidence synthesis is structured based on the primary therapeutic modality examined (Table 1).

Cognitive Behavioral Therapy (CBT)

CBT, focusing on identifying and modifying maladaptive thoughts and behaviors related to illness, emerged as the most extensively studied intervention.

Efficacy in Depression and Anxiety. Multiple RCTs demonstrated that CBT, often adapted for chronic illness management (CBT-I), significantly reduces self-reported symptoms of depression and anxiety compared to usual care or waiting-list controls in both hemodialysis (HD) and pre-dialysis cohorts.[2,5] A meta-analysis comparing various psychosocial therapies noted that CBT consistently yielded moderate to large effect sizes ($g = 0.55$ to 0.72) in reducing depressive symptom severity among ESRD patients.[6]

Delivery Formats. CBT has been successfully delivered via individual sessions (typically 8 to 12 weeks), group formats, and increasingly, through digital platforms. Digital CBT (dCBT) has shown promise, offering flexibility crucial for patients with rigid treatment schedules like those on thrice-weekly HD. The effectiveness of dCBT appears comparable to face-to-face delivery, particularly for symptom management when structured support is provided.[6]

Impact on Self-Management. CBT components focusing on behavioral activation and problem-solving have been linked to improved adherence to fluid restrictions and dietary guidelines, although evidence linking psychological improvement directly to hard clinical endpoints (e.g., hospitalization) remains less consistent.[6]

Mindfulness-Based Interventions (MBIs)

Mindfulness-Based Stress Reduction (MBSR) and Mindfulness-Based Cognitive Therapy (MBCT) focus on non-judgmental awareness of present experience, aiming to decrease reactivity to distressing thoughts.[7]

Evidence Base. Evidence for MBIs in CKD is emerging but less mature than CBT. Studies involving CKD patients reported significant reductions in perceived stress and improvements in sleep quality following an 8-week MBSR program.[7] Furthermore, MBIs appeared particularly beneficial for improving psychological distress in kidney transplant recipients adjusting to immunosuppression and long-term surveillance, suggesting a role in managing uncertainty and health-related fear.[7]

Problem-Solving Therapy (PST)

PST is a structured, directive therapy focused on teaching patients concrete steps to manage specific stressors related to their disease (e.g., scheduling appointments, managing vascular access issues, dealing with fatigue).[8]

Clinical Utility. PST has shown high acceptability among patients who prefer concrete, solution-oriented approaches over purely introspective therapies. A small RCT in peritoneal dialysis patients found PST superior to supportive therapy in enhancing self-efficacy scores related to daily

Summary of Evidence for Key Psychological Interventions in CKD

Intervention Type	Primary Target Population	Typical Duration/Format	Key Efficacy Findings (Primary Outcomes)	Evidence Strength
CBT	Pre-dialysis, HD, Transplant	8 to 12 sessions (individual/group)	Significant reduction in depression/anxiety score, improved self-efficacy	High (multiple RCTs)
dCBT	HD, Pre-dialysis	Self-paced modules with therapist guidance	Comparable efficacy to face-t-face for mood symptoms	Moderate (emerging RCTs)
PST	Peritoneal dialysis, HD	4 to 6 structured sessions	Improved patient ratings of self-efficacy regarding daily management tasks	Moderate (Quasi-experimental/Small RCTs)
MBSR	CKD, Transplant	8 weeks (group format)	Decreased perceived stress and improved sleep quality	Low to moderate (Preliminary studies)
Brief Supporting Counseling	HD (bedside delivery)	Varies (short, unscheduled sessions)	Modest, acute reduction in immediate distress during treatment	Low (observational/pilot data)

management tasks.[8] Its brevity and focus on immediate, manageable problems make it highly practical for integration into standard clinic visits.[8]

Interventions in Specific Populations

HD Patients. HD patients face unique challenges, including treatment schedule rigidity and fatigue associated with the procedure. Interventions in this group often require modification. Brief supportive counseling integrated directly into the dialysis unit (bedside delivery) has shown modest but measurable reductions in acute distress during treatment sessions. Effectiveness is maximized when interventions are brief (under 30 minutes) and tailored to address immediate situational stressors.[9]

Kidney Transplantation. Psychological interventions post-transplant often target adherence to complex immunosuppressive regimens and managing post-transplant anxiety or depression, which can be triggered by medication side effects or fears of rejection. CBT targeting medication beliefs and adherence self-efficacy has demonstrated positive outcomes in reducing unintentional non-adherence rates.[9]

Technological Delivery Models (Telehealth and Mobile Applications)

The logistical challenges of accessing specialized mental health services are substantial for CKD patients. Telehealth delivery, including video conferencing for therapy sessions, has proven viable. Outcomes from tele-CBT mirror those of in-person delivery, significantly boosting attendance rates for geographically isolated or severely fatigued patients.[4]

Mobile Health (mHealth) apps are increasingly used for psychoeducation, symptom monitoring (e.g., mood tracking), and providing just-in-time coping strategies. While robust efficacy data for stand-alone mHealth apps are still accumulating, preliminary studies suggest they can enhance engagement and provide valuable data streams for clinicians regarding symptom fluctuations between appointments.[4]

DISCUSSION

The synthesis of current evidence firmly supports the integration of psychological interventions into the comprehensive management framework for CKD. The high prevalence of psychological distress mandates proactive screening and accessible treatment options, moving beyond the traditional focus solely on biochemical parameters.

Efficacy and Mechanism

CBT remains the cornerstone, demonstrating reliable efficacy in alleviating core symptoms of depression and anxiety across the CKD spectrum. Its effectiveness likely stems from directly addressing cognitive distortions common in chronic illness—such as catastrophizing or feelings of helplessness—and equipping patients with actionable coping skills. The successful adaptation of CBT into briefer, illness-specific modules highlights the potential for scalability in busy clinical settings.

The emerging role of MBIs suggests utility for patients struggling more with emotional regulation and chronic pain/fatigue rather than purely distorted cognition. PST serves as an excellent low-intensity intervention for patients who require practical tools for managing the day-to-day complexities of CKD management.[1]

Implementation Challenges and Future Directions

Despite strong evidence for efficacy, significant barriers impede the routine implementation of these interventions:

Integration and Access. Psychological services are often fragmented, requiring external referrals that CKD patients, especially those on dialysis, struggle to navigate due to transportation issues, scheduling conflicts, or lack of caregiver support.

Reimbursement and Training. Adequate reimbursement models for psychosocial services within nephrology settings are frequently lacking. Furthermore, many nephrology providers lack formal training in recognizing or initiating brief psychological interventions.

Measuring Clinical Impact. While reductions in validated psychological scales (e.g., BDI score reduction by 5 points) are significant, translating these psychological improvements into measurable improvements in mortality, hospitalization rates, or long-term adherence remains a necessary focus

for future, larger-scale RCTs.

Stepped-Care Models

The future likely lies in adopting stepped-care models.

This approach would involve universal screening followed by low-intensity interventions (e.g., psychoeducation, mHealth tools) for mild distress, escalating to high-intensity, specialized therapies (e.g., intensive CBT) for severe or refractory symptoms. Embedding mental health professionals (e.g., health psychologists) directly within multidisciplinary nephrology teams is the optimal model to facilitate rapid referral and integrated care delivery.

LIMITATIONS

This integrative review has inherent limitations. Firstly, heterogeneity across the included studies regarding intervention duration, patient population (e.g., HD vs. transplant), and primary outcome measures made direct comparison difficult.

Secondly, many studies utilized self-report measures for psychological outcomes, which may introduce response bias, though these remain the standard for initial screening. Thirdly, the evidence base for newer modalities, such as personalized digital therapeutics, requires longer-term follow-up studies to confirm sustained benefits compared to established therapies. Finally, economic evaluations assessing the cost-effectiveness of implementing these programs on a large scale are still underdeveloped.

CONCLUSION

Psychological interventions represent an essential, evidence-based component of optimal care for individuals living with CKD. Cognitive Behavioral Therapy demonstrates the strongest empirical support for reducing symptoms of depression and anxiety. The successful adaptation of these therapies via digital platforms and the utility of Problem-Solving Therapy highlight the feasibility of implementation even within the constraints of intensive renal replacement therapies. Nephrology practice must evolve to systematically screen for mental health needs and establish clear, accessible referral pathways, ensuring that psychological well-being is prioritized alongside physiological stability to improve the holistic trajectory of CKD patients.

ABBREVIATIONS

Abbreviation	Definition
BDI	Beck Depression Inventory
CBT	Cognitive Behavioral Therapy
CKD	Chronic Kidney Disease
dCBT	Digital Cognitive Behavioral Therapy
ESRD	End-Stage Renal Disease
HD	Hemodialysis
KRT	Kidney Replacement Therapy
MBCT	Mindfulness-Based Cognitive Therapy
MBSR	Mindfulness-Based Stress Reduction
mHealth	Mobile Health
PST	Problem-Solving Therapy
QoL	Quality of Life
RCT	Randomized Controlled Trial

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Received January 2026
Revised February 2026
Accepted March 2026

RJCCN ORIGINAL PAPER
KIDNEY DISEASE

Reno-protective Effects of *Coreopsis Tinctoria* Flavonoids in db/db Mice Models Through the AGE/RAGE Pathway

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Keywords. *Coreopsis Tinctoria,* flavonoids, diabetic nephropathy, advanced glycation end products, receptor for AGE

Introduction. The study investigates the renal protective effects of flavonoids derived from *Coreopsis tinctoria* Nutt in type 2 diabetes using *db/db* mice.

Methods. With the *db/m* mice born in the same litter as the non-diabetic normal group, 8-week-old *db/db* mice were divided into four groups: a diabetes model group, a low-dose (0.4 g/kg) flavonoids group, a high-dose (1.2 g/kg) flavonoids group, and a metformin positive control group. Mice were treated daily for 8 weeks.

Results. After 8 weeks of continuous gavage feeding, the high-dose group of flavonoids significantly improved fasting blood glucose levels in 16-week-old *db/db* mice, and both dosages of flavonoids reduced average daily water intake. The levels of serum creatinine (CRE) and BUN in *db/db* diabetic mice were significantly reduced by both high and low dosages of flavonoids, mitigating the loss of glomerular cells under hyperglycemic conditions, inhibiting glomerular hypertrophy and mesangial matrix hyperplasia, and demonstrating protective effects on renal function damage. The levels of AGEs in *db/db* mice kidneys were elevated compared to *db/m* mice, but significantly decreased with flavonoid treatment. Flavonoids also reduced RAGE protein expression and NF-κB activation. Additionally, both doses of flavonoids lowered MDA and IL-1β levels, and enhanced antioxidant enzyme activities.

Conclusions. The study concludes that flavonoids from *Coreopsis tinctoria* Nutt can inhibit the accumulation of AGEs and binding to RAGE in kidneys, improve oxidative stress and inflammation, and protect against renal damage induced by hyperglycemia. This suggests their potential of flavonoids from *Coreopsis tinctoria* Nutt as functional food and medicine for diabetic nephropathy.

RJCCN 2026; 2: 82-94
www.rjccn.org
DOI: 10.66224/rjccn.2.2.43

INTRODUCTION

DM is one of the major diseases that seriously endangers human health. The prevalence of diabetes and impaired glucose tolerance among adults worldwide has been increasing year by year. According to the International Diabetes Federation, it is estimated that 463 million adults aged 20 to 79 suffer from DM in the world in 2019. It is expected

Please cite this article as: Guo L, Meng Y, Zhang H, Li S, Zhang W. Reno-protective Effects of *Coreopsis Tinctoria* Flavonoids in db/db Mice Models Through the AGE/RAGE Pathway. RJCCN. 2026;2(2):82-94.

that the number of such individuals will reach 700 million by 2045. Diabetic nephropathy (DN) refers to chronic kidney disease that is caused by diabetes, making it one of the most common and severe microvascular complications associated with diabetes.[1] Its clinical features include persistent increase in urinary albumin excretion and/or progressive decrease in glomerular filtration rate, eventually leading to the development of ESRD. Its pathological features include thickening of the basement membrane, disappearance of foot processes, dilation of mesangial matrix, sclerosis of glomerular tuberosity, and fibrosis in the tubulointerstitial area.[2] Studies have found that DN is the primary cause of ESRD, and approximately 30 to 50% of ESRD cases worldwide are attributed to DN.[3] Furthermore, patients with DN have a mortality rate that is 50% higher than that of patients with type 2 diabetes alone.[4] Therefore, ameliorating nephropathy induced by diabetes is of significant importance as it not only preserves renal function and enhances the quality of life for diabetic patients but also reduces the escalating healthcare costs associated with ESRD.

The pathogenesis of DN is intricate and multifactorial, initiated and maintained by four causal factors that involve metabolic derangements, hemodynamic changes, growth factors, and inflammatory or profibrotic elements.[5] Numerous clinical studies have demonstrated that hyperglycemia is one of the primary causes of DN. The generation of advanced glycation end products (AGEs), which are closely associated with hyperglycemia, plays a pivotal role in the pathological mechanism of DN.[6] AGEs are large molecules formed through non-enzymatic glycation reactions between amino acids, proteins, and lipids with reducing sugars such as glucose.[7] Oxidative stress and inflammation are the primary damages caused by AGEs.[8] Recent evidence suggests that the expression of the receptor for AGE (RAGE) is increased in aging kidneys and DN, and this increased RAGE expression mediates the activation of oxidative stress and inflammation pathways such as the nuclear factor-κB (NF-κB) signaling pathway.[9,10] On the contrary, under diabetic conditions, AGEs-RAGE induces oxidative stress and inflammation, further promoting the formation of AGEs. The positive feedback mechanism between AGEs and downstream signaling pathways mediated by RAGE leads to a vicious cycle in DN.[11] Therefore, inhibiting the production of AGEs and preventing the activation of the AGE-RAGE axis are particularly important for the prevention and treatment of DN.

Flavonoid compounds (FCs) are an important class of plant secondary metabolites and serve as one of the primary active ingredients in traditional Chinese medicinal herbs. They possess anti-inflammatory properties, increase insulin sensitivity, and improve insulin resistance, which have been proven to be effective in the treatment of diabetes and its complications.[12] It was found that rutin alleviates insulin resistance in HepG2 cells induced by AGEs by inhibiting SOCS3/IRS1 and activating the PI3K/AKT signaling pathway.[13] Oleanolic acid can effectively inhibit the formation of AGEs.[14] The protective effects of apigenin and baicalein were associated with inhibiting the AGEs/RAGE/NF-κB pathway and improving oxidative damage.[15] The screening of natural plant FCs as inhibitors of AGEs, with their safety and minimal side effects, has become a prominent topic in current research.

Coreopsis tinctoria Nutt, commonly known as Golden Tickseed or Snow Chrysanthemum, originates from North America and has since spread worldwide. In China, it is mainly distributed in the Kunlun Mountains area of the northwest region at an altitude of about 3 km. Over 120 chemical constituents have been identified in *Coreopsis tinctoria* Nutt, with flavonoids being the predominant bioactive compounds, accounting for more than 20% of its dry weight, which indicates high nutritional and medicinal values.[16,17] Various solvent extracts of *Coreopsis tinctoria* Nutt have been shown to significantly improve kidney damage in multiple types of diabetic animals. Sprague-Dawley (SD) rats, treated with a high fructose and fat diet combined with a single intraperitoneal injection of 35 mg/kg streptozotocin (STZ), developed characteristics of DN. The inflammatory and fibrotic responses in the kidney were mitigated by a 4-week gavage of the ethyl acetate extract from *Coreopsis tinctoria* Nutt.[18] In the model of glomerular mesangial cell injury induced by high glucose and palmitic acid,

as well as in the *db/db* mice model, it was observed that the alcohol extract of *Coreopsis tinctoria* Nutt could protect against diabetic renal injury by inhibiting renal oxidation, inflammation, and fibrosis through the RhoA/ROCK and NF-κB/TGF-β/Smad signaling pathways.[19] The alcohol extract of *Coreopsis tinctoria* Nutt can also improve the degree of renal fibrosis in *db/db* mice through the miR-192/miR-200b and PTEN/AKT, as well as ZEB2/ECM pathways.[20] Currently, the research on the anti-DN mechanism of *Coreopsis tinctoria* Nutt is becoming increasingly profound. Furthermore, it remains to be demonstrated whether the total flavonoids of *Coreopsis tinctoria* Nutt (TFC) can effectively inhibit the formation and accumulation of AGEs in vivo, thus potentially playing a renal protective role.

In this study, eight-week-old *db/db* mice with type 2 diabetes mellitus were continuously administered gavage for 8 weeks. The control group consisted of *db/m* mice born in the same litters, and metformin was used as a positive drug. The sample groups were given low and high doses of TFC from *Coreopsis tinctoria* Nutt. Based on the basic metabolism, blood glucose levels, kidney pathological injury, oxidative stress, inflammatory factors, and the AGEs/RAGE/NF-κB signaling pathway in mice from each group were evaluated to investigate the efficacy and mechanism of TFC in improving DN injury. This study provides a theoretical basis and data support for the application and development of *Coreopsis tinctoria* Nutt in preventing complications associated with diabetes.

MATERIALS AND METHODS

Chemicals and Materials

Aminoguanidine (AG), bovine serum albumin (BSA), aqueous solutions of methylglyoxal (40%) and glucose were purchased from Sigma-Aldrich (St. Louis, MO, USA). High performance liquid chromatography (HPLC)-grade acetonitrile was purchased from Fisher (Fisher Scientific, Waltham, MA, USA). Metformin hydrochloride tablets (0.5 g/tablet) were purchased from Sino-American Shanghai Squibb Pharmaceuticals Ltd (Shanghai, China).

Preparation of the TFC

TFC were kindly supplied by the Department of Food Science at Rutgers University. The TFC powder was produced from dried flowers of *Coreopsis tinctoria* Nutt using the following extraction technology: soaking in ethanol, water extraction (using a tea-to-water ratio of 1:8 at 100 °C), filtering, concentrating, and freeze-drying. The powder was dissolved in DMSO to a concentration of 250 mg/mL and subjected to ultrasound for 30 min to accelerate dissolution. Subsequently, the solution was filtered using a 0.22 μm Millipore membrane filter (Millipore, Bedford, MA) and then diluted with sterilized PBS as required.

Fractionation of the TFC Using HPLC

The TFC were determined using an HPLC system 2695 (Waters Corp, Milford, MA, USA) equipped with a degasser, an autosampler, quaternary pump and coupled with a 2996 photodiode array detector (PDA), as well as a phenomenex luna C18 (150 mm × 4.6 mm, 3 μm) ID column. The extracted samples were injected at a flow rate of 1 mL min-1, with 10 μl being used. Separation was carried out at 35 °C, and the detection wavelength was set at 280 and 385 nm. The mobile phase consisted of A (0.1% trifluoroacetic acid solution) and B (CH3CN), using gradient elution conditions as follows: 0 to 10 min, 0 to 12% B; 12 to 20 min, 12 to 25% B; 20 to 25 min, 40% B; 25 to 30 min, 40-12% B. Samples were also filtered through 0.22 μm PTFE (polytetrafluoroethylene) membrane filters (Millipore, Madrid, Spain) before injection. For identification and quantification, the retention times of each peak were compared to external standards and stored.

Animals and Experimental Design

Six-week-old male C57BL/KsJ-Lepr$^{db/db}$ diabetic mice (db/db) and their non-diabetic lean heterozygous littermates (db/m) were purchased from the Model Animal Research Center (MARC) (Nanjing, Jiangsu, China). After a two-week acclimatization period, the mice were divided randomly into five groups (n = 8 /each group) as follows: *db/m* mice normal control group (db/m); *db/db* mice DN group (db/db); metformin group (*db/db* mice + metformin, 300 mg/kg/d) (Met); TFC low dose group (*db/db* mice + TFC, 40 mg/kg/d) (FL); TFC high dose group (*db/db* mice + TFC,

120 mg/kg/d) (FH). The *db/m* mice in the normal control group and the *db/db* mice in the DN group were administered sterile distilled water by gavage for 8 weeks. All drugs were dissolved in sterile distilled water and administered to *db/db* mice by gavage for 8 weeks. The animals were housed and provided with unrestricted access to food and water in the SPF barrier environment at 21 ± 2 °C, with humidity ranging from 40 to 50%, following a 12h light:12h dark cycle. Approval for animal studies was obtained from the Institutional Animal Care and Use Committee of Beijing Normal University.

Collection of Serum Samples and Assessment of Biochemical Parameters

During oral administration, body weight, food intake, and water intake were recorded consecutively every week. Blood was collected from the mice's tail vein once a week, and glucose readings were taken using a glucose meter. This included measurements of fasting and non-fasting blood glucose levels. Fasting blood glucose was measured approximately 8 hours after overnight fasting, while non-fasting blood glucose was measured at 21:00 on the same day. After 8 weeks of intervention, mice were anesthetized with pentobarbital sodium (30 mg/kg), and their blood samples were taken after a fasting period of 6 hours. The blood was centrifuged at a rotational speed of 3500 rpm for 15 minutes. The serum was carefully collected and subsequently frozen at -80 ℃ for future use. Biochemical parameters of serum creatinine (CRE) and BUN were measured using ELISA kits following the manufacturer's protocols.

Collection of Kidney Samples and Assessment of Biochemical Indices

After blood extraction, the right kidneys of mice were collected and frozen in a liquid nitrogen tank for protein extraction, while the left kidneys were fixed with 4% paraformaldehyde for pathological and immunohistochemical analyses.

The Expression Levels of RAGE and NFκB-p65 in the Kidney by Using Western Blot

Proteins extracted from kidneys were separated using 10% SDS-PAGE and then blotted with primary antibodies against RAGE (1:500, Santa Cruz), phospho-NF-κB P65, total NF-κB P65 (1:1000, Cell Signaling, Beverly, MA, USA), and β-actin (C4) (1:2000, Santa Cruz). β-actin was used as a loading control. The photo density analysis was quantified using a gel image analysis system (Odyssey, LI-COR, Lincoln, NE, USA).

The Levels of AGEs and IL-1β in the Kidney by Using An ELISA

The renal AGE levels were determined using commercially available ELISA kits purchased from Cell Biolabs (San Diego, CA, USA). IL-1β levels in the kidneys were measured using ELISA kits (R & D, Minneapolis, USA) according to the manufacturer's instructions. All of the results were normalized to total protein concentrations.

Detection of Oxidative Stress Related Indexes

A certain amount of mouse kidney tissue was cut on ice. A 10% homogenate of the kidney tissue was prepared by adding normal saline at a ratio of 1:9 (m/v). The mixture was then centrifuged at 4 °C and 2500 r/m for 20 minutes, and the resulting supernatant was collected. The total protein concentration was measured using a BCA kit, with a dilution ratio typically ranging from 80 to 100 times. The levels of MDA, SOD, CAT, and GSH-PX were determined strictly following the instructions provided in the kit.

Histopathological Examination

The left kidney tissues of mice were initially preserved in a 4% paraformaldehyde solution for 24h. After that, they underwent dehydration using alcohol and were then embedded in paraffin. Subsequently, sections of the tissue, each measuring 3 μm in thickness, were prepared using a microtome. These sections were later stained with H&E. Glomerular cell number and glomerular area were analyzed using Leica image analysis software (Leica, Buffalo Grove, IL, USA) through light microscopic examination. Renal morphometric changes were observed at a magnification of 400×, and 20 randomly selected glomeruli per mouse (n = 3 mice per group) were quantified.

Statistical Analysis

The results are expressed as the mean ± SEM.

Student's t-test and one-way ANOVA using SPSS 20 were performed to compare the experimental and control groups. A significance level of $P < .05$ was considered.

RESULTS

The Phytochemicals of TFC

HPLC was used to analyze the main chemical composition in FC. As shown in Figure 1 and Table 1, six compounds; including marein, flavanomarein, okalin, isokalin, 3,5-o-dicaffeoylquinic acid, and chlorogenic acid were identified. It can be observed that the TFC content is 50.06%, with Marein having the highest content of 343.2 mg/g, followed by flavanomarein at 107.5 mg/g, and isokalin at 10.8 mg/g.

Table 1. The Flavonoid Compounds and Their Content Changes in TFC

Items	TFC
Total flavonoids (%)	50.06
Marein, mg/g	343.2
Flavanomarein, mg/g	107.5
Okalin, mg/g	-
Isokalin, mg/g	10.8
3,5-o-dicaffeoylquinic acid, mg/g	21.6
Chlorogenic acid, mg/g	17.5

Effects of TFC on Body Weight, Daily Food Intake and Water Intake in *db/db* Mice

The effects of TFC on the basic signs of mice were evaluated by observing changes in appearance and body weight. The five groups of mice received intragastric administration once a day starting from 8 weeks old, and their weight was measured weekly. After 8 weeks of feeding, the mice's weight, food intake, and water intake were recorded in Table 2.

The results are shown in Table 2. The weight of mice in all groups increased with increasing age each week. At the age of 8 weeks, the weight of mice in the diabetes model group (db/db group) was significantly higher than that in the normal control group (db/m group), indicating early-onset obesity. By the 16th week, *db/db* mice weighed approximately 46 to 50 g, while *db/m* mice only weighed about 22 g. After continuous oral administration for 8 weeks, both TFC (FL and FH groups) and metformin (MET group) improved the hair color and appearance of *db/db* mice. However, despite drug intervention, the body weight of all *db/*

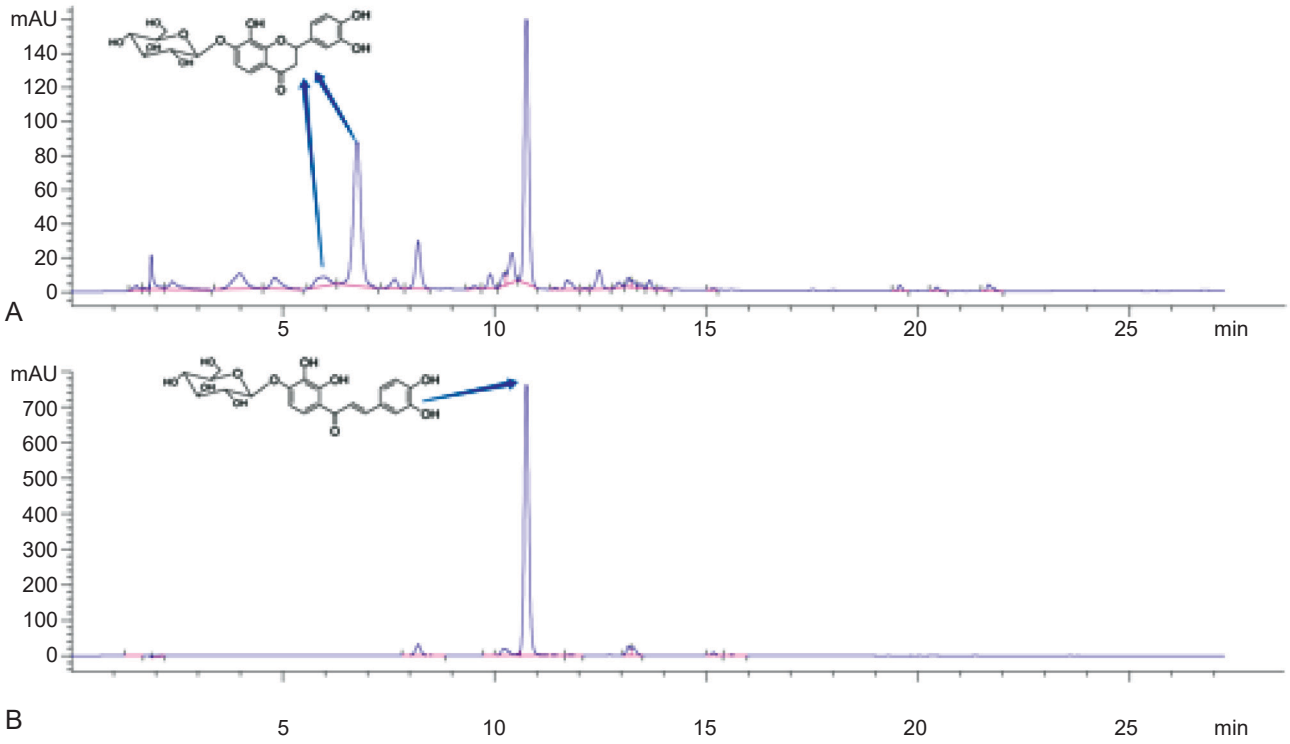

Figure 1. Analysis of TFC by HPLC

Table 2. Body Weight, Daily Average Food Intake and Water Intake in Each Group of Mice During Intragastric Administration

Parameters(g)	db/m	db/db	FL	FH	MET
Body weight (8 weeks)	19.39 ± 0.69	35.10 ± 0.75	35.04 ± 0.75	33.96 ± 0.79	35.03 ± 0.72
Body weight (12 weeks)	21.45 ± 0.69	44.95 ± 0.75	45.29 ± 0.75	42.10 ± 0.79	44.08 ± 0.72
Body weight (16 weeks)	22.78 ± 0.69	46.40 ± 0.75	50.70 ± 0.75	46.11 ± 0.79	48.60 ± 0.72
daily average food intake	3.21 ± 0.19	7.79 ± 0.81	7.35 ± 0.61	7.24 ± 0.39	7.71 ± 0.24
daily food intake/ body weight	0.192 ± 0.006	0.187 ± 0.009	0.173 ± 0.009	0.196 ± 0.011	0.176 ± 0.006
daily average water intake	4.07 ± 0.38	25.61 ± 1.89	19.86 ± 2.02	17.44 ± 1.56	15.24 ± 2.67
daily water intake/ body weight	0.179 ± 0.017**	0.553 ± 0.039	0.416 ± 0.049*	0.344 ± 0.033**	0.319 ± 0.065**

Note. The data are presented as the mean ± SD (*P < .05, **P < .01; respectively, compared to the *db/db* mice in the model group (n = 8)).

db mice remained relatively stable and consistent.

During the 8-week feeding period, there was no significant difference in the average daily food intake among all of the db/db group (n = 8, P > .05). However, after adjusting for body weight differences, there was a significant difference in average daily water intake. Compared to the model group's *db/db* mice, both the high dose group (FH) and positive control group (MET) showed a significant decrease in drinking water (P < .01), while the low dose group's *db/db* mice also exhibited a significant decrease in drinking water (P < .05).

Effects of TFC on Blood Glucose in *db/db* Mice

The changes in non-fasting blood glucose and fasting blood glucose were recorded at 0, 2, 4, 6, and 8 weeks after the intragastric administration of TFC. At the beginning of the 8-week administration period, there was a significant difference in non-fasting blood glucose levels between *db/db* mice in the model group and *db/m* mice in the negative control group (P < .05), as shown in Figures 2A and 2C. The fasting blood glucose level of *db/db* mice in the model group also exhibited a significant difference compared to that of *db/m* mice (P < .05, Figures 2B and 2D). After continuous intragastric intervention for 8 weeks, the fasting blood glucose level of *db/db* mice in the FH group significantly decreased compared to that in the model group (P < .05). Meanwhile, non-fasting blood glucose levels were consistent between the FH group and model group. These results indicate that TFC can improve to some extent the increase in fasting blood glucose levels of *db/db* diabetic mice. However, neither the low-dose nor high-dose groups receiving TFC via gavage over an 8-week period showed a significant inhibition of non-fasting blood glucose increase in *db/db* mice. Nevertheless, both the high-dose group (FH) and positive control group (MET) exhibited a significant improvement in fasting blood glucose levels of *db/db* mice (P < .05).

Effects of TFC on Renal Histology in *db/db* Mice

According to Table 2, the CRE content of *db/db* mice in the diabetic model group showed a significant increase, with an average value of 45.4625 ± 2.6938 μmol/L, which was 2.2 times higher than that of *db/m* mice in the normal control group (20.6625 ± 1.4469 μmol/L). After 8 weeks of continuous gavage, the CRE content of diabetic mice in the FL and FH groups decreased significantly to 35.7125 ± 2.6487 and 33.80 ± 1.6197 μmol/L, respectively (Table 3). In the positive control group (MET), the CRE content of *db/db* mice decreased to 29.7125 ± 2.2321 μmol/L after 8 weeks of continuous gavage with metformin, and the difference was extremely significant (P < .01).

BUN levels of *db/db* mice in the model group at 16 weeks old were significantly increased to 11.13 ± 0.46 mmol/L, which is 1.6 times higher compared to *db/m* mice (6.97 ± 0.72), respectively (Table 3). After continuous gavage intervention for 8 weeks, BUN levels of diabetic mice in the low and high dose groups (FL and FH) were significantly decreased (P < .01), measuring 8.88 ± 0.35 mmol/L and 7.52 ± 0.21 mmol/L, respectively. BUN content

Table 3. Serum Creatinine and Urine Nitrogen in Each Group of Mice

Group	CRE (μmol/L)	BUN (mmol/L)
db/m	20.6625 ± 1.4469**	6.97 ± 0.72**
db/db	45.4625 ± 2.6938	11.13 ± 0.46
FL	35.7125 ± 2.6487*	8.88 ± 0.35**
FH	33.8000 ± 1.6197**	7.52 ± 0.21**
MET	29.7125 ± 2.2321**	6.99 ± 0.30**

Note. The data are presented as the mean ± SD (*P < .05 and **P < .01, respectively; compared to the *db/db* mice in the model group (n = 8)).

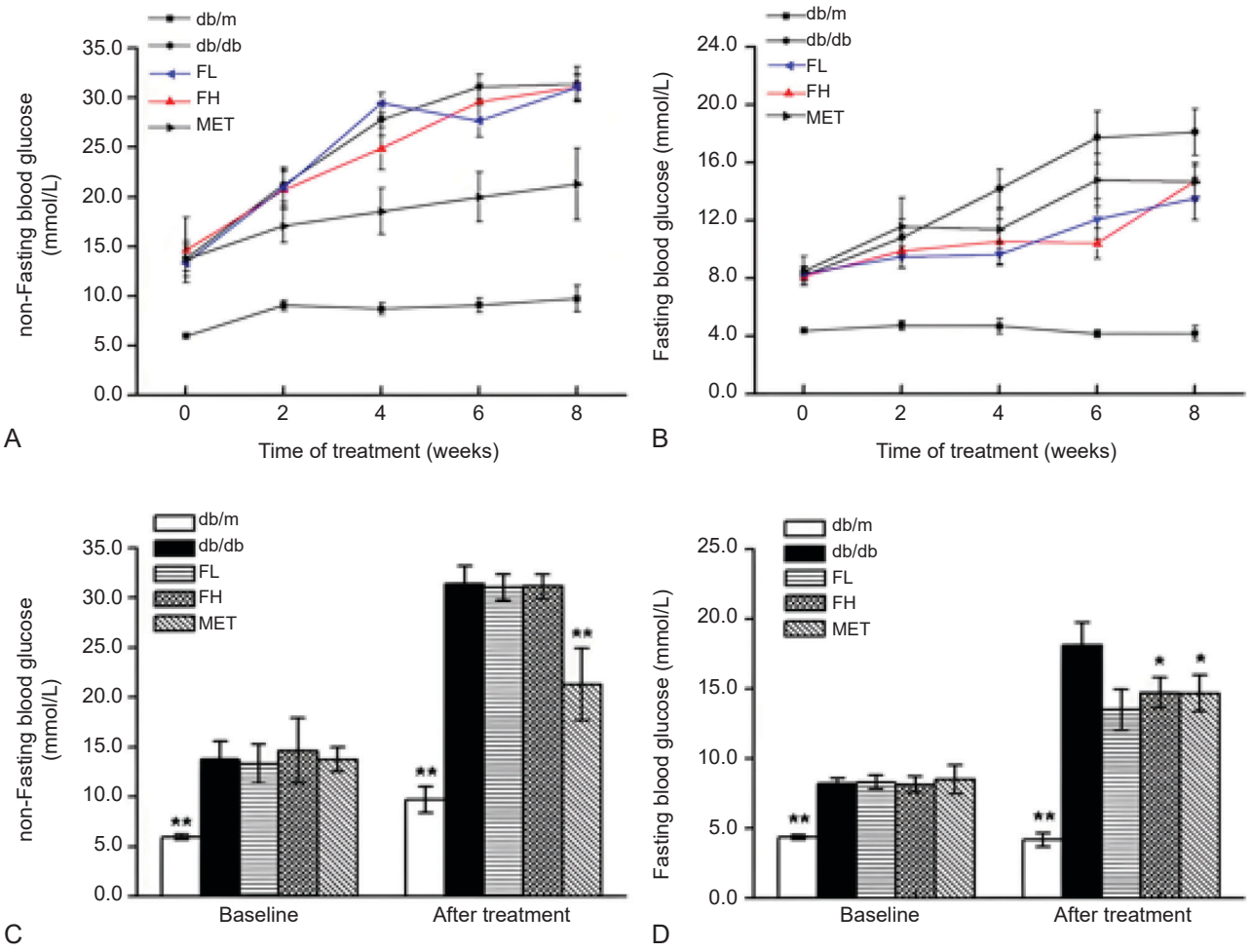

Figure 2. Changes in blood glucose levels during intragastric administration were observed in each group of mice. A) The trend of non-fasting blood glucose was measured every two weeks, B) The trend of fasting blood glucose was measured every two weeks, C) non-fasting blood glucose value of each group after the administration of TFC, and D) Fasting blood glucose value of each group after the administration of TFC. There were 8 mice in each group (The data are presented as the mean ± SD) (*P < .05 and **P < .01, respectively; compared to the *db/db* mice in the model group).

in the positive control group (MET) decreased to 6.99 ± 0.30 mmol/L (P < .01).

The results of histological examinations using H&E staining in Figure 3A reveal renal cell damage, which was found to be higher in the kidneys of *db/db* vehicle mice compared to those of *db/m* mice. In the control group, the structure of renal tissue appeared normal with no evident pathological changes. However, in the db/db model group, glomerular hypertrophy was noticeable and mild to moderate proliferation and glycogen accumulation were observed in some glomerular mesangial cells and matrix. Vacuolar degeneration occurred in renal tubular epithelial cells, along with individual thickening of the glomerular basement membrane. Nevertheless, after administering high and low doses of TFC (FH and FL groups) as well as metformin (MET group) for 8 weeks, there was a clear reduction in the degree of glomerular matrix hyperplasia and tubular vacuolar degeneration observed in *db/db* mice compared to that seen in the model group (db/db).

The results of H&E and PAS staining of mouse glomerular tissue sections were shown in Figure 3B, respectively. In the normal control group (db/m), the kidney tissue structure was normal, and no obvious lesions were observed. The model group consisting of *db/db* mice exhibited glomerular hypertrophy. For instance, there was mild to moderate hyperplasia in some mesangial cells and stroma, thickening of the glomerular basement membrane to a certain extent, as well as rare vacuolar degeneration and glycogen accumulation

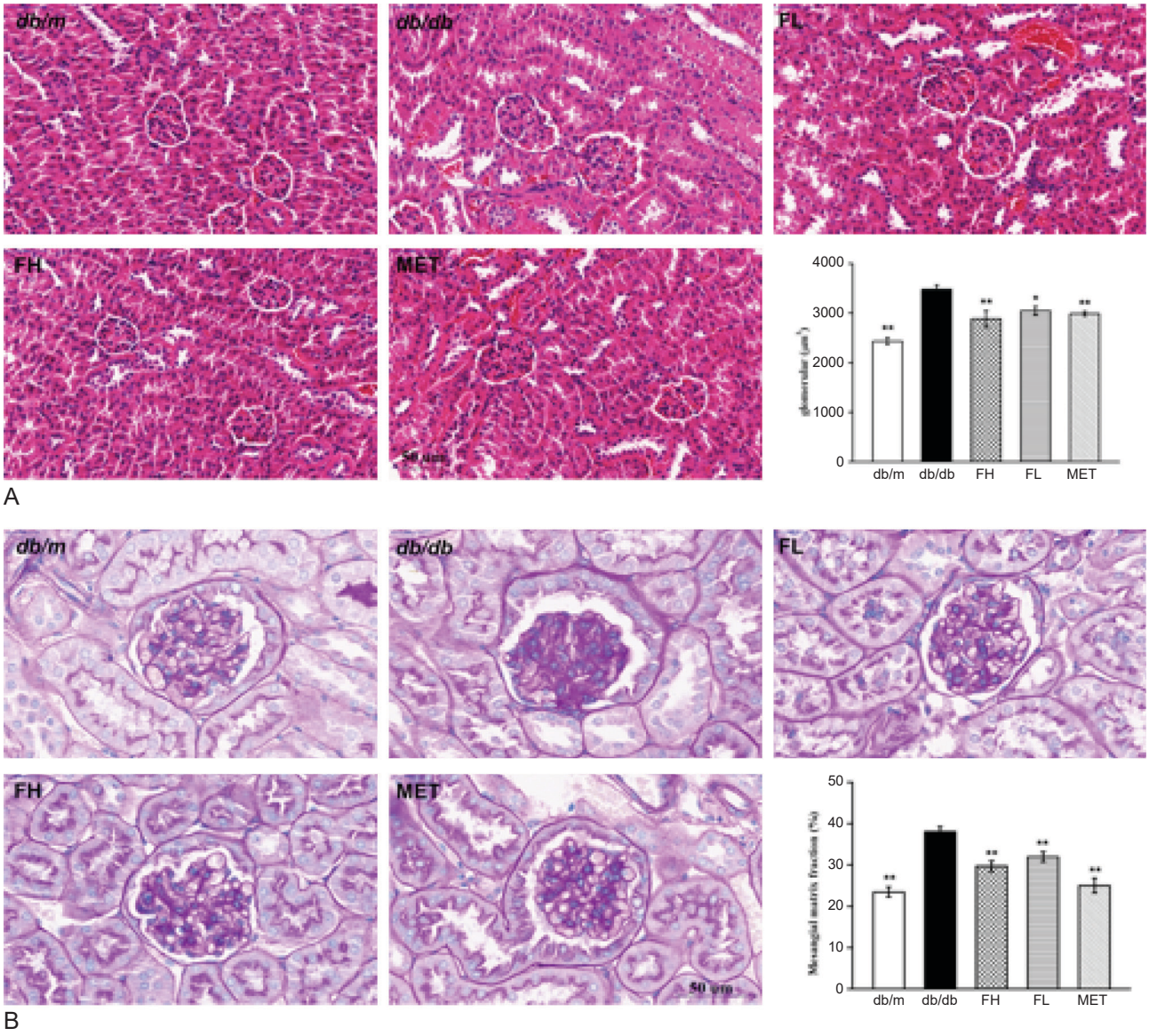

Figure 3. Effect of TFC on the Glomerular Area and the Expansion of Glomerular Extracellular Matrix in db/db Mice. A) Pathological features of renal tissue in db/m mice and db/db mice were observed using HE staining, B) Pathological features of renal tissue in *db/m* mice and *db/db* mice were observed using PAS staining. Three mice were randomly selected from each group, and 10 to 15 glomeruli were randomly chosen from each mouse for statistical quantification (original magnification, ×400))

in tubular epithelial cells. After an 8-week intervention with low-dose (FL) and high-dose (FH) TFC or metformin (MET), the proliferation degree of glomerular matrix decreased along with reduced renal tubule vacuolar degeneration, leading to relatively relieved mesangial matrix proliferation.

TFC Inhibits the Expression of AGE/RAGE in the Kidneys of *db/db* Mice

Compared with the normal control group (db/m), the levels of AGEs in the kidney tissues of diabetic mice in the 16-week-old diabetic model group (db/db) were significantly increased (4.39 ng/mg, $P < .01$, Figure 4). This increase was nearly 1.6 times that of the former (2.82 ng/mg). The level of AGEs in the kidney tissue effectively decreased in the treated group, with the high-dose group (FH) being only 75.3% of that in the model group (db/db), indicating an extremely significant difference ($P < .01$). A similar effect was observed in the positive control group (MET) with a decrease to 73.5%. The content of AGEs also decreased by 86.6% in the low dose

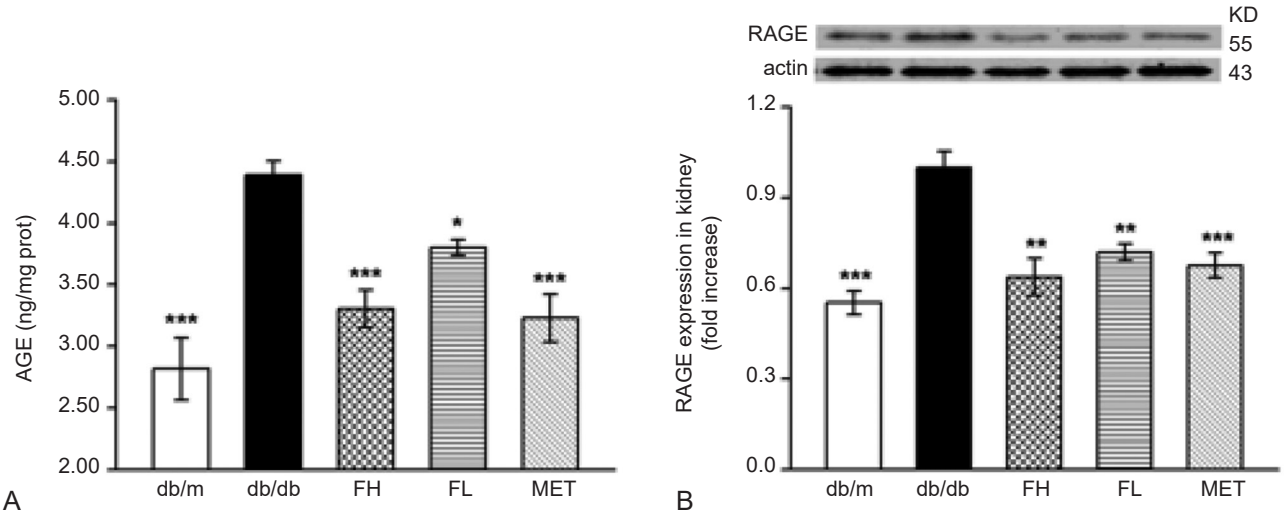

Figure 4. TFC inhibits the expression of AGE/RAGE in the kidneys of *db/db* mice. A) Protein expression and analysis of the AGE by ELISA assay, B) Protein expression and analysis of the RAGE by western blot, GAPDH was used as the internal control) (The data are presented as the mean ± SD (*$P < .05$ and **$P < .01$, respectively; compared to the *db/db* mice in the model group (n = 3)).

group (FL), and this difference was significant as well ($P < .05$). The protein expression of RAGE in kidney tissues of diabetic mice in the 16-week-old model group (db/db) was increased, approximately 1.8 times that of normal *db/m* mice, and this trend was consistent with the level of AGEs (as shown in Figure 4). After an 8-week intervention, RAGE expression decreased significantly by 28 and 36.2% in the low-dose and high-dose groups (FL and FH), respectively ($P < .01$), and these changes were consistent with the levels of AGEs.

TFC Suppresses AGE/RAGE to Prevent Renal Inflammation in *db/db* Mice

The *db/db* mice exhibited up-regulation of nuclear NF-κB p65 protein compared to *db/m* mice, but TFC treatment down-regulated these increased protein expressions in a concentration-dependent manner ($P < .05$). Additionally, IL-1β protein expressions in vehicle-treated *db/db* mice (db/db) were significantly higher than those in *db/m* mice. TFC-treated *db/db* mice at 120 mg·kg-1 (FH) showed significantly lower expressions of these proteins compared to vehicle-treated *db/db* mice (db/db), even lower than that of metformin-treated *db/db* mice (MET) ($P < .05$) (Figure 5).

TFC Suppresses AGE/RAGE to Prevent Renal Peroxidation in *db/db* Mice

As shown in Figure 6, kidney tissue MDA levels were found to be significantly higher in the db/db group when compared with the control db/m group ($P < .01$), while the values of SOD, CAT, and GSH-PX were significantly lower. On the other hand, TFC caused a significant decrease in the level of MDA in both treatment groups (FL and FH) compared to vehicle-treated *db/db* mice. Additionally, TFC was able to ameliorate the levels of SOD, CAT, and GSH-PX in both treatment groups (FL and FH) compared to the *db/db* model group.

DISCUSSION

In the state of hyperglycemia, osmotic diuresis leads to excessive water loss and intracellular dehydration in kidney tissue, resulting in stimulation of the thirst center and increased water intake. Therefore, there is a proportional relationship between increased urination and higher water consumption during hyperglycemia. This experiment investigated the appearance, body weight, food intake, water intake, and blood glucose levels of *db/db* mice. The results showed that compared to *db/m* mice in the control group, 16-week-old *db/db* mice (model group) had a significant difference in body weight, as well as significantly increased water intake and fasting blood glucose levels. These findings are consistent with previous literature reports.[21] After 8 weeks of consecutive TFC intervention, there were no significant changes observed in food intake or

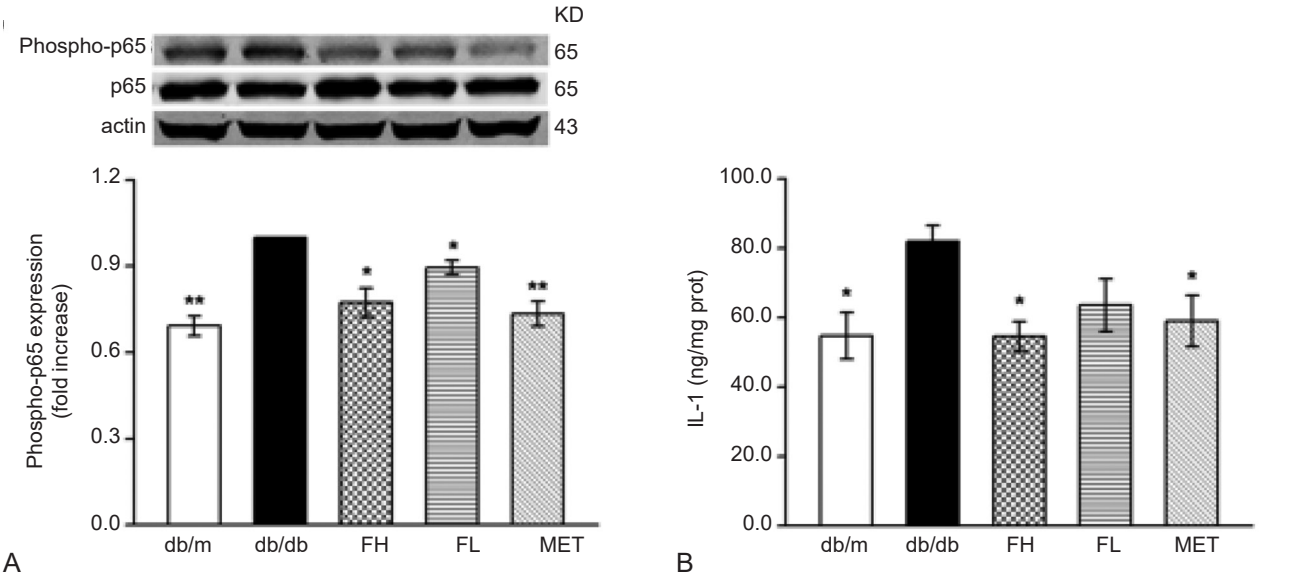

Figure 5. TFC inhibits the expression of NF-κB p65 and IL-1β in the kidneys of *db/db* mice. A) Protein expression and analysis of the NF-κB p65 by western blot, GAPDH was used as the internal control, B) Protein expression and analysis of the IL-1β by ELISA assay). The data are presented as the mean ± SD (**P* < .05 and ***P* < .01; respectively, compared to the *db/db* mice in the model group (n = 6).

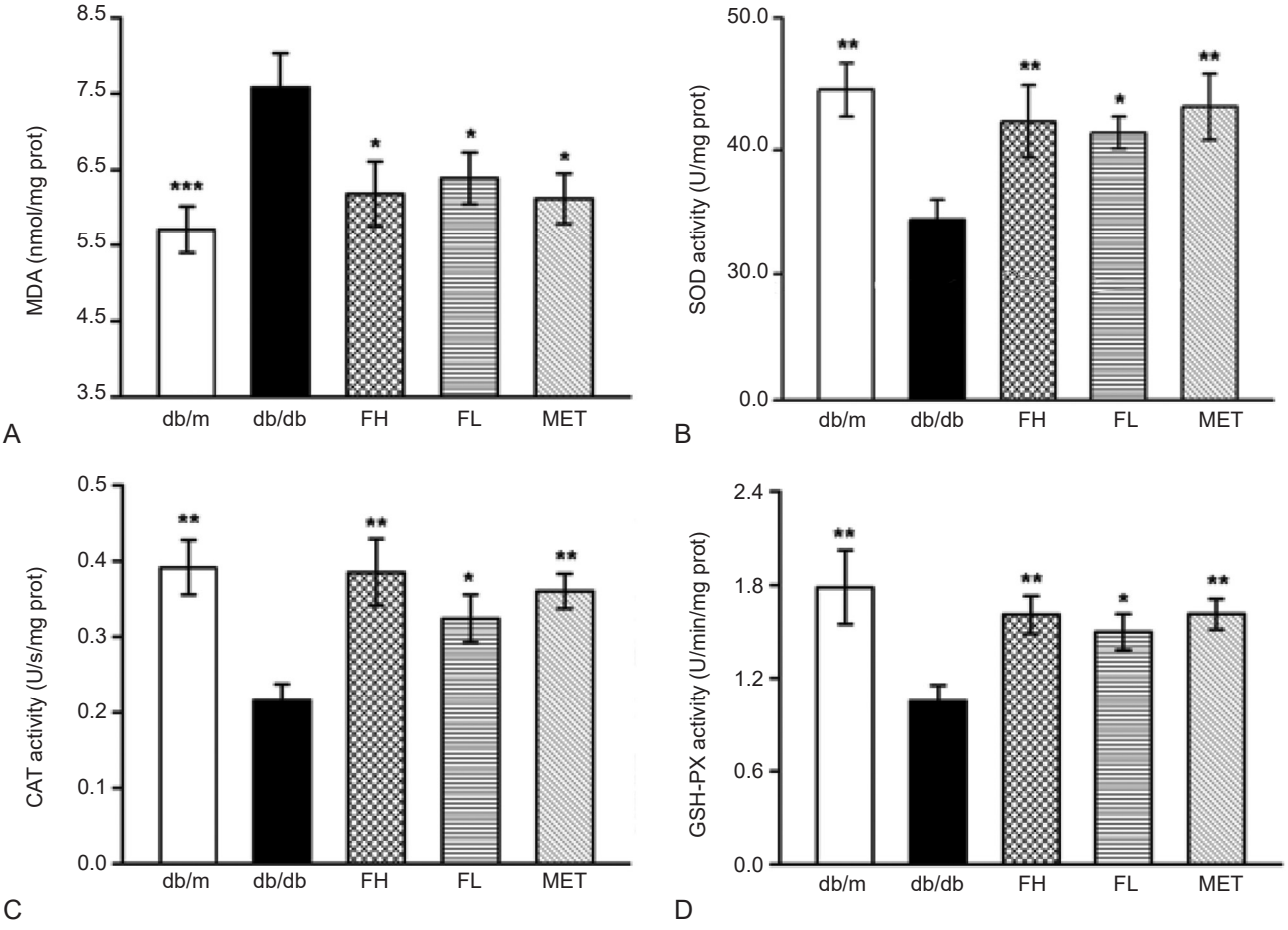

Figure 6. TFC inhibits the levels of MDA and improves the activities of SOD, CAT, and GSH-PX in the kidneys of *db/db* mice. A) The levels of MDA, B) The activity of SOD, C) The activity of CAT, and D) The activity of GSH-PX). The data are presented as the mean ± SD (**P* < .05 and ***P* < .01, respectively; compared to the *db/db* mice in the model group (n = 6)).

body weight of *db/db* mice (model group), but their water intake decreased significantly. The difference between low-dose and high-dose groups (FL and FH) of *db/db* mice reached a significant level, indicating an improvement in diabetes symptoms to some extent.

Glomerular hypertrophy, slight thickening of the basement membrane, and excessive deposition of the glomerular extracellular mesangial matrix are characteristic pathological changes in early DN. If not addressed, this condition progresses to glomerular sclerosis and renal interstitial fibrosis, which leads to a decrease in the glomerular filtration rate and ultimately results in renal failure.[22] *db/db* mice typically exhibit early symptoms of DN at around 2 months of age, making them an ideal model for studying the mechanisms underlying DN.[23] It has been reported that the flavonoids of cymbidium have a certain renal protective effect on diabetic animals, and its ethyl acetate extract (0.15 g/kg) can reduce the levels of blood glucose and lipids in diabetic SD rats, as well as effectively decrease serum CRE and uric acid levels.[24] In this study, 16-week-old *db/db* diabetic mice exhibited significant widening of the mesangial region, increased mesangial matrix, and glycogen deposition in renal tubules. Following TFC intervention, glomerular hypertrophy, mesangial matrix hyperplasia, and basement membrane thickening in kidney tissues were inhibited to a certain extent. Both low and high doses of TFC (FL and FH) effectively interfered with the increase of glomerular area and significantly decreased serum CRE and BUN levels for 8 weeks, which was consistent with the inhibitory effect observed in the MET group. These results indicate that TFC has an effect on improving renal lesions in DN.

Under pathological conditions, the combination of AGEs and RAGE can lead to increased oxidative stress in the kidney, resulting in inflammation and podocyte damage, thereby promoting the progression of kidney disease. Considering the specific mechanism of action of the AGE-RAGE axis, scholars are continuously searching for drugs that can reduce AGE levels in order to alleviate kidney damage caused by AGEs through blocking the signal transduction pathway of the AGE-RAGE axis. It has been found that pyridoxamine and aminoguanidine, as carbonyl scavengers, can inhibit the formation of AGEs, maintain the integrity of mesangium and renal tubules, and reduce oxidative stress in experiments.[25,26] In streptozotocin-induced diabetic mouse models, kidney damage was mitigated by neutralizing RAGE antibody therapy.[27] Additionally, gliclazide alleviates the damage to mesangial cells and tubular epithelial cells by inhibiting the RAGE-P22phox-NF-κB pathway.[28] Recently, it has been discovered that some proprietary Chinese medicine components also have therapeutic effects such as curcumin, ginger, cinnamon, and clove which can inhibit glycosylation in vitro. Their anti-glycosylation potential is related to their polyphenol content.[29] Luo Y *et al.* reported that natural tea polyphenols, especially catechins, regulate the expression of RAGE and subsequent MAPK and TGF-β pathways by blocking the formation of AGEs, significantly alleviating multiple diseases such as aging, DN, and retinopathy.[30] Feng Guo[19] found that continuous intragastric administration of TFC for 8 weeks interfered with and induced oxidative stress, inflammation, and fibrosis in the kidneys of *db/db* mice through the NF-κB/TGF-β/Smad signaling pathway. Marein may be the main component responsible for the anti-inflammatory and anti-renal fibrosis effects of TFC.[31]

In this study, protein glycation damage was observed in the kidney tissues of 16-week-old diabetic mice (db/db), accompanied by oxidative stress and inflammation. The levels of AGEs in the kidneys of the db/db group were significantly increased, along with activation of its cell membrane receptor RAGE and NFκB. Additionally, there was a decrease in antioxidant enzyme activity and an increase in lipid peroxidation product MDA levels, as well as up-regulation of IL-1β expression. After 8 weeks of intragastric administration, both dosage groups (0.4 and 1.2 g/kg) of TFC effectively reduced the levels of AGEs in the kidneys of diabetic *db/db* mice and down-regulated inflammatory signaling mediated by AGE-RAGE binding. Furthermore, NFκB activation was significantly inhibited while MDA levels decreased in the kidney. Partial restoration was observed in SOD, CAT, and GSH-PX activities. These results suggest a certain improvement on DN in *db/db* mice.

CONCLUSIONS

Following 8 weeks of continuous oral administration of TFC to diabetic mice, there was a notable reduction in CRE and BNU levels, indicating improved kidney function. While fasting blood glucose levels were positively impacted, postprandial blood glucose levels did not show a significant decrease. TFC treatment effectively reduced the loss of glomerular cells in diabetic mice, inhibited the enlargement of glomeruli and the proliferation of mesangial matrix, leading to a significant improvement in the pathological structure of the kidneys. Additionally, TFC treatment resulted in decreased expression of AGEs and RAGE in the kidneys, along with a reduction in downstream oxidative stress and inflammation. These findings suggest that TFC holds promise as a potential therapeutic agent for the prevention and treatment of DN. It can be inferred that TFC intervention may down-regulate renal inflammatory signaling mediated by the AGEs-RAGE pathway in response to hyperglycemia, thereby ameliorating kidney damage in *db/db* mice.

COMPLIANCE WITH ETHICS GUIDELINES

Limin Guo: Conceptualization, Formal analysis, Funding acquisition, Investigation, Resources, Validation, Visualization, Writing-original draft, Writing-review and editing.

Yina Meng: Investigation. Haijing Zhang: Investigation. Shiming Li: Conceptualization, Resources, Supervision.

Wensheng Zhang: Conceptualization, Resources, Writing-review and editing, Supervision, Project administration.

FUNDING

Xinjiang Academy of Agricultural Sciences Agricultural Science and technology innovation stability support special project [grant numbers xjnkywdzc-2023003-2]; the National Nature Science Fund of China [grant numbers 8206078]; and the Xinjiang Uygur Autonomous Region Outstanding Youth Science Fund project [grant numbers 2024D01E11]; and the Evaluation of Functional Property, Processing and Utilization of Xinjiang Characteristic Plant Resources [grant numbers G2023046003L].

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Received January 2026
Revised March 2026
Accepted March 2026

Quantification of Optimal Strength and Frequency of Grip Exercises in Patients After Autogenous Arteriovenous Endovascular Fistula

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Keywords. autogenous arteriovenous endovascular fistula, maturation, grip exercise strength, grip exercise frequency, color doppler ultrasound, hemodynamics

Introduction. To observe the hemodynamic changes of the upper limb cephalic veins in patients with ESRD who were pre-treated with hemodialysis and required an arteriovenous internal fistula after grip exercise at different grip strengths and frequencies, and to explore the optimal grip exercise strength and frequency to promote blood circulation in the upper limb cephalic veins.

Methods. 200 patients aged ≥ 18 years who had undergone internal fistula surgery were selected and divided into 2 groups, 100 patients in each group were divided into groups A and B. Group A determined the appropriate grip strength; group B used an electronic grip strength device to perform grip strength exercise at 4 frequencies of 15, 20, 25, and 30 times/min under the appropriate grip strength determined in group A. The changes in cephalic venous hemodynamics at different frequencies were observed. The hemodynamic changes of the cephalic vein at different frequencies were observed.

Results. When the grip strength was 70 to 100% of the maximum grip strength, the cephalic venous blood flow velocity and vascular pressure increased significantly compared to the resting state ($P < .01$).

Conclusions. Grip strength exercise can promote blood circulation in the cephalic veins of the upper limb, with 70 to 100% of the maximum grip strength and 25 exercises/min being the best method. This conclusion can provide a reference basis for clinical guidance on functional exercise of the upper limb and promotion of blood circulation in the cephalic veins of the upper limb and maturation of AVF in patients after AVF surgery.

RJCCN 2026; 2: 95-102
www.rjccn.org
DOI: 10.66224/rjccn.2.2.45

INTRODUCTION

In recent years, end stage renal disease (ESRD) has become a global public health problem that threatens human health. About 93% of ESRD patients choose hemodialysis (HD) as their treatment.[1] Vascular access is the "lifeline" for HD patients,[2] and the autogenous arteriovenous fistula (AVF) is internationally recognized as the

Please cite this article as: Lu W, Qiu Z, Kong Y, Lin Y, Zhou Q, LV Q. Quantification of Optimal Strength and Frequency of Grip Exercises in Patients After Autogenous Arteriovenous Endovascular Fistula. RJCCN. 2026;2(2):95-102.

most effective way of providing access to the arteries. The AVF is a surgical vascular access to the radial artery-cephalic vein in the upper limb of patients with ESRD for HD. The most common clinical approach is an anastomosis of the radial artery and cephalic vein end-to-end in the distal forearm. To facilitate the patient's daily life, the AVF is preferred to be established in the non-dominant hand.[3] The AVF needs to be used after maturation, which usually occurs 4 to 8 weeks after surgery.[4] After the AVF is established, the cephalic vein becomes the main channel for the patient's body surface puncture to drain blood during HD, called the draining vein (DV). It has been confirmed that the DV diameter and DV blood flow are the main markers for determining the maturity of the AVF at the wrist.[5-7] With the widespread use of AVF in clinical practice, the problem of AVF maturation has gradually emerged as a major challenge in clinical use,[8] and the literature generally reports that the immaturity rate of AVF can range from 30 to 60%,[5,9,10] with insufficient blood flow being at the core of its immaturity. Numerous studies[11-16] have pointed out that instructing patients to perform fist clenching exercises or ball clenching exercises after AVF can lead to thickening of the patient's cephalic veins, increased blood flow and improved AVF maturation rates. However, fewer studies have been reported on specific exercise methods, such as the amount of strength and frequency of exercise. In this study, the changes in cephalic venous blood flow velocity, vascular pressure, vascular diameter and blood flow in patients with pre-established AVF were observed by color-doppler ultrasound (CDU) before and after exercise with an electronic grip on the non-dominant limb at different strengths and frequencies to investigate and quantify the optimal grip exercise pattern to promote cephalic venous blood circulation in the upper limb. The results of the study are reported below. The results of the observational study are reported below.

MATERIALS AND METHODS

Study Population

A convenience sampling method was used to select patients with ESRD who were admitted to our department from November 2023 to July 2024, who were pre-treated with hemodialysis and required an arteriovenous internal fistula, and all patients were willing to accept the pilot study and could actively cooperate. The trial was planned and conducted in accordance with the requirements of the hospital ethics committee and was approved by the hospital ethics committee. A total of 200 patients were included and divided into 2 groups A and B. Inclusion criteria: diagnosed uremia; age ≥ 18 years; unimpeded operative cooperation; all patients with AVF established on the non-dominant upper limb; informed consent and voluntary participation. Exclusion criteria: history of neurological or psychiatric diseases; history of upper limb trauma and surgery, hand dysfunction; history of severe cardiovascular and cerebrovascular diseases, etc. There were 100 cases in Group A, 48 males and 52 females, aged 18 to 65 years, mean age (51.36 ± 9.79); 100 cases in Group B, 53 males and 47 females, aged 18 to 63 years, mean age (49.85 ± 11.22); the differences were not statistically significant when comparing the general data of age and gender between the 2 groups ($P > .05$).

Research Methods

Instrumentation and quality control

1) Instruments and equipment. VINNO Q5 portable ultrasound diagnostic instrument (model: VINNO Q5, equipped with 7L high frequency probe, manufactured by Feiyinuo Technology Co., Ltd.); CAMRY electronic grip strength device (model: EH101, Guangdong Xiangshan Weighing Instrument Group Co.)
2) Measuring personnel. The whole test was carried out by the same professional operator using the ultrasound diagnostic instrument.
3) Place, time and room temperature control. The whole study was conducted in the doctor's office of the hemodialysis center, and the uniform test time was from 14:00 to 18:00. The room temperature was air-conditioned and controlled, and the temperature was maintained at 25 ℃.

Measurement sites and methods.

1) Measurement site. All locations measured were cephalic veins, fixed in the distal 1/3 of the forearm of the upper limb.[17] The patient's

cephalic vein at this location was first located with the CDU and marked with a marker to facilitate measurement.

2) Measurement method. Using a VINNO Q5 portable ultrasound diagnostic instrument with a probe frequency of 7 L. The measurement method follows the recommendations of the guideline,[18] the patient is placed in a sitting position with the upper limb fully exposed and naturally extended, the probe is placed lightly on the skin and a cross-sectional view is made along the vascular path in B mode to measure and record the diameter of the vessel (select a vessel site that is flat, free of tumor-like dilatation, curvature and turbulence, and avoid branching). After the spectral curve has stabilized, freeze and take a screenshot of the spectral curve, measure and record the mean blood flow velocity (Vmean) and blood flow rate: Blood flow was calculated as Q = A(pr2) × V × 60s (Q represents blood flow in standard units of ml/min; A represents vessel area; V represents mean blood flow velocity in standard units of cm/s; s represents seconds),[19] and the amount of coupling agent was increased appropriately during the measurement, with the examiner holding the probe gently to avoid pressing on the vessel.

Grip strength exercise method. The study was divided into 2 processes, i.e. according to 2 groups A and B in sequence. Throughout the study, one researcher was fixed to explain the details of grip strength exercise essentials, grip strength and grip frequency in detail to ensure that the subjects understood them correctly and implemented them smoothly.

Group A) Determine the appropriate grip strength exercise. According to urn Changshui *et al*,[20] grip strength values measured in the seated position were greater and statistically significant, therefore the grip strength of the patients in this study was chosen to be measured in the seated position. According to the standard grip strength test posture,[21] the patient was placed in a seated position with both feet naturally on the ground, knees flexed at 90°, hips flexed, shoulders inward in a neutral position, elbows bent at 90° and forearms in a neutral position. The maximum grip strength (MGS) of the patient's non-dominant upper limb was first measured using an electronic grip strength device. The patient held the electronic grip strength device by its inner and outer grips with their maximum strength until the value on the display of the grip strength device did not jump, and the maximum value was determined by taking two consecutive tests with an interval of 60 seconds between tests.[22] During the measurement, the patient should not touch the body or clothing with the electronic grip and should not bend the arms, bend the waist or stir the feet. Calculate and record the values of 90, 80, 70, 60, 50, and 40% MGS based on the patient's MGS (during the conduct of the pre-experiment, it was found that the patient's grip strength was lower than the resting state in terms of cephalic venous vascular pressure and peak blood flow velocity at 10 to 30% MGS, in order to avoid excessive consumption of research time, manpower and material resources. (Therefore the 10 to 30% MGS strength experiment was removed). Patients were instructed to use an electronic grip strength device on the non-dominant upper limb at MGS; 90, 50, and 40% MGS; respectively, and to rest for at least 15 min after each grip,[23] to prevent interference with the hemodynamic measurements from two different grips before and after. Immediately after each grip, the patients were monitored by the measurement staff with a CDU for changes in cephalic vein vessel diameter, peak blood flow velocity and vessel pressure at the distal forearm marker of their upper limbs, and conclusions were drawn after statistical analysis.

Group B) Selection of grip exercise frequency under the appropriate grip strength determined by group A. Patients were first rested in a seated position for 15 min, and an electronic grip device was used to grip 15 times/min, 20 times/min, 25 times/min, and 30 times/min at the appropriate strength determined by group A. Each frequency was gripped for 1 min, and rested for at least 15 min after each operation,[23] and then the other frequencies were performed. For the accuracy of the operation, the researcher used the recorded audio "Grip, Loose, Grip" to repeat the instruction. Immediately after each frequency of operation, the patient's venous blood flow velocity, vessel diameter and blood flow were measured by a diagnostic ultrasound device. The data was

statistically processed and conclusions were drawn (if the blood flow rate continued to increase, the selection of the grip frequency was continued at an increasing rate of 5 times/min without causing discomfort to the subject until the maximum blood flow rate was achieved, which was achieved at the current frequency in this trial).

Data collection and recording. The cephalic venous blood flow velocity, vessel diameter, vessel pressure and blood flow detected by the ultrasound professional at different grip strengths and grip exercise frequencies were carefully recorded by the same investigator during the experiment; data were double-entered and checked for consistency using Epidata 3.1. If data inconsistencies were found, the original data were promptly consulted for confirmation.

Statistical Methods

IBM SPSS Statistics 25.0 was used for statistical analysis of the data. Data were expressed as`x ± s. Statistical tests were all performed using a two-sided test, and differences were considered statistically significant if $P < .05$. Data results for measures obeying normal distribution were expressed as mean ± standard deviation, while median or interquartile spacing was chosen for those not obeying normal distribution. Changes in vessel diameter, blood flow, peak velocity and vessel pressure were first analyzed by one-way ANOVA, and if the overall difference was statistically significant, further two-way comparisons between groups were made, and the least significant difference (LSD) method was used for two-way comparisons of means in ANOVA.

RESULTS

Changes in Cephalic Venous Blood Flow Velocity, Vascular Diameter and Vascular Pressure at Different Grip Strengths in Group A

Analysis of variance (ANOVA) showed that the changes in cephalic vein diameter with decreasing grip strength after maximum grip strength were not statistically significant ($P > .05$) compared to the resting state pair. In contrast, the changes in venous blood flow velocity and vascular pressure were statistically significant ($P < .01$), with a gradual decrease in cephalic venous blood flow velocity and vascular pressure with decreasing grip strength; a two-by-two comparison revealed that the differences in cephalic venous vascular pressure and blood flow velocity compared to the resting state when grip strengths of 70, 80, 90, and 100% MGS were used statistically significant ($P < .05$), as detailed in Table 1.

Changes in Venous Blood Flow Velocity, Vessel Internal Diameter and Blood Flow in Group B With Different Grip Exercise Frequencies

As shown by ANOVA, the effects of different frequencies on cephalic vein diameter, blood flow velocity and blood flow were statistically significant ($P < .01$) compared with the resting state, and the two comparisons showed that: with the increase of grip exercise frequency, the change of blood vessel diameter was not obvious; the cephalic vein blood flow velocity and blood flow continued to increase under different grip exercise frequencies, and when the grip exercise frequency was 25 times/min, the blood flow velocity When the frequency of grip exercise was 25 times/min, the blood flow velocity

Table 1. Changes in Cephalic Venous Hemodynamics at Different Grip Force Levels

Grip strength	Vessel diameter (cm)	Peak blood flow rate (cm/s)	Vascular pressure (mmHg)
Resting condition	0.23 ± 0.03	11.38 ± 1.86	0.06 ± 0.01
MGS	0.29 ± 0.03	16.90 ± 2.19[a]	0.12 ± 0.02[a]
90% MGS	0.31 ± 0.03	15.27 ± 1.67[a]	0.11 ± 0.02[a]
80% MGS	0.27 ± 0.03	14.31 ± 1.64[a]	0.10 ± 0.02[a]
70% MGS	0.31 ± 0.03	12.83 ± 1.80[a]	0.07 ± 0.01[a]
60% MGS	0.27 ± 0.00	11.76 ± 1.67	0.06 ± 0.01
50% MGS	0.26 ± 0.03	11.29 ± 1.73	0.05 ± 0.02
40% MGS	0.23 ± 0.03	9.94 ± 1.57	0.05 ± 0.02
F	0.382	182.976	260.431
P	.857	< .01	< .01

Note. A indicates statistically significant blood flow velocity and vascular pressure after grip compared to resting state ($P < .05$); the rest of the groups were not statistically significant in a two-by-two comparison ($P > .05$).

Table 2. Changes in Cephalic Venous Hemodynamics with Different Grip Exercise Frequencies

Frequency	Vessel diameter (cm)	Peak blood flow rate (cm/s)	Blood Flow (mL/min)
Resting condition	0.22 ± 0.03	9.91 ± 1.17	15.87 ± 8.06
15 times/min	0.23 ± 0.03[a]	11.41 ± 1.17[a]	24.30 ± 11.39[a]
20 times/min	0.25 ± 0.03[ab]	12.31 ± 1.12[ab]	29.75 ± 12.88[ab]
25 times/min	0.26 ± 0.03[abc]	13.21 ± 1.10[abc]	39.46 ± 14.92[abc]
30 times/min	0.25 ± 0.03[abd]	12.51 ± 1.15[abd]	27.80 ± 12.00[abd]
F	27.369	122.330	49.968
P	< .001	< .001	< .001

Note. A represents $P < .05$ compared to resting state, B represents $P < .05$ compared to 15 beats/min, C represents $P < .05$ compared to 20 beats/min; and D represents $P < .05$ compared to 25 beats/min.

reached the maximum (13.21 ± 1.10) cm/s and the blood flow reached the maximum (39.46 ± 14.92) mL/min, see Table 2 for details.

DISCUSSION

Functional upper limb exercise using 70 to 100% of maximum grip strength has the best effect on the cephalic vasculature.

In recent years, researchers at home and abroad have continued to explore methods to promote AVF maturation. Functional exercise, physiotherapy, pharmacological intervention, and surgical treatment have all produced good results; shortening the maturation time and extending the life of the AVF. Among them, functional exercise is the most commonly used method, which is safe, convenient and economical. The most commonly used exercise modality in functional exercise clinically is grip exercise.[24] It has been shown that grip exercise not only dilates and fills the AVF vessels, improves blood flow during dialysis and promotes the maturation of the internal fistula, but also reduces complications such as AVF stenosis and thrombosis, thus prolonging the life of the AVF.[25] The mechanism of grip exercise to promote AVF maturation is through rapid repetition of "grip-release" fist to squeeze muscle groups, stimulate musculoskeletal contraction, enhance muscle strength, promote venous and lymphatic return to the upper limb, and increase the internal diameter of AVF vessels and blood flow to improve AVF blood flow Kinetics. When a patient makes a fist, the muscles of the dorsal interosseous muscles of the palm, the short flexors of the little finger, the thumb retractors, the short flexors of the thumb and the deep flexors of the forearm, the long flexors of the thumb and the superficial flexors of the fingers contract sharply, generating pulsatile pressure on the veins and causing rapid flow of venous blood towards the heart, thus increasing the tangential and pulling forces on the endothelial cells of the blood vessels and causing a biochemical effect on the endothelial cells to release diastolic factors such as carbon monoxide and prostacyclin. The combined effect of these factors leads to vasodilation, which increases the internal diameter, cross-sectional area, mean blood flow velocity and blood flow, and promotes AVF maturation. Repeated grip strength exercise accelerates the rapid flow of venous blood to the heart, promotes blood and lymphatic circulation in the affected limb, helps to reduce blood viscosity, and reduces AVF thrombosis.[26,27] Therefore, grip strength exercises for patients are particularly important in promoting AVF.

In this study, we found that the differences in the degree of improvement in venous hemodynamics when patients performed 70% MGS to MGS grip strength were all significant when compared to the resting state. However, the majority of ESRD patients suffer from poor circulation, weakness and frailty, making it difficult for them to use their maximum strength for grip exercise, resulting in reduced compliance. From a humane point of view, it was considered "whether the patient could use the least amount of exercise to improve the quality of the AVF cephalic vessels and minimize the patient's burden". The patient can exercise with 70% MGS, which not only saves 30% of the grip force, but also improves the hemodynamic profile of the cephalic vessels in an equally effective way, resulting in improved AVF vascular quality, such as increased cephalic blood flow velocity, increased vascular pressure and better AVF maturation.

The functional upper limb exercise using 70 to 100% of maximum grip strength produced a significant boost to cephalic venous blood flow velocity and blood pressure.

A comparison with resting cephalic vein hemodynamics revealed that the use of various grip strengths did not have a statistically significant effect on the change in vein diameter ($P > .05$), and that there was a significant change in blood flow velocity and vascular pressure ($P < .05$). The results showed that when the strength of the grip exercise was reduced, there was a significant reduction in both cephalic venous blood flow velocity and vascular pressure. After statistical analysis, it was found that there was a statistically significant difference ($P < .05$) when grip strength was performed using 70% MGS to MGS compared to the resting state. The reasons for this were explored as follows: 1) Patients have the greatest effect of muscle compression on blood vessels at maximum grip strength. Therefore, the sudden pressure on the venous vessels can cause the blood in the veins to be pumped out rapidly, which results in a rapid increase in blood flow velocity and an increase in venous vascular pressure; 2) when the patients' grip strength gradually decreases, the squeezing effect of their muscles on the cephalic veins will gradually decrease, and the squeezing of the muscles cannot meet the pressure required for the vessels to empty the blood flow, thus, the blood flow velocity and intravascular pressure of the cephalic veins will decrease; and 3) The change in cephalic vein diameter at various sizes of grip force is not statistically significant, probably due to the thin and weak elasticity of the vein wall, which is easily compressed by the CDU probe during CDU examination and cannot measure the diameter of the venous vessels well and accurately. According to the results of this study: the use of 70 to 100% maximal grip exercise in ESRD patients had a positive promotion effect on the upper limb cephalic veins and did not cause any discomfort to the patients.

Grip strength exercises are most effective at a grip strength of 70% MGS to MGS and at a frequency of 25 times/min.

It has been demonstrated that regular continuous grip and release exercises of the hand have a greater effect on vasodilation and increased blood flow,[28] however excessive grip and release exercises of the hand can lead to fatigue of the arm muscles and trigger soreness. This soreness can be relieved by rhythmic grip and fist release and short rest periods between fist releases. Although grip exercises can improve blood flow in the upper limb by increasing circulation, there is no literature that specifies how hard and how often grip exercises can be performed to maximize hemodynamics in the upper limb while minimizing the strain on the patient when performing the exercise. It has been suggested that the force of sustained muscle contraction induced by grip force of a certain duration can exert a better effect on evacuating vascular blood over time than rhythmic contraction of the same force; however, rhythmic grip force has a longer duration and longer effect on muscle contraction than sustained grip force, and has a stronger effect on evacuating vascular blood over time than sustained grip force of the same force.[29] COOK M *et al*.[30] found in their experiments that the muscle contraction produced by grip force caused changes in vascular blood flow in the arm, with a very rapid blood flow response within 1 to 2 seconds of muscle contraction, peaking within 2 to 5 seconds of contraction. Furthermore, there is a clear correlation between the change in peak velocity of vascular blood flow in the arm caused by muscle contraction during handgrip and muscle contraction force, implying a direct stimulus-response relationship between grip force magnitude and vascular hemodynamics. It has been reported in the literature[31] that under steady-state conditions, the duration of sustained contraction of human skeletal muscle affects the associated skeletal muscle blood flow during exercise during grip strength exercise.

The results of the present study showed that at appropriate grip strength, blood flow velocity and blood flow were significantly increased ($P < .05$) after subjects performed grip exercise at different frequencies (15, 20, 25, and 30 times/min) compared to the resting state, indicating that grip exercise can have a good effect on cephalic venous blood circulation, which is consistent with the results of previous studies.[32] The results of this study showed that blood flow velocity and blood

flow in the upper limb veins was greatest at a grip exercise frequency of 25 beats/min ($P < .01$) and decreased at a grip exercise frequency of 30 beats/min compared to 25 beats/min. Therefore, this study suggests that patients should choose a frequency of 25 repetitions/min for grip exercise, which has the best effect on upper limb cephalic hemodynamics. In response to the study, cephalic venous blood flow velocity and blood flow did not increase consistently with increasing frequency of grip exercise. This may be due to the following factors: 1) If the frequency of grip exercise is too fast per unit time, the muscle contraction caused by grip force does not have enough time to compress the blood vessels so that the blood is completely pumped out of the upper limb veins, resulting in no significant increase in the velocity and flow of blood. 2) If the frequency of grip exercise is too slow, making the single grip and release time too long will cause the patient's hands to be easily fatigued during the exercise process, resulting in the strength of the grip exercise not achieving the effect of muscle contraction and not getting the desired exercise effect.

Therefore, this study recommends that the optimal grip strength to be used when clinically instructing patients to perform upper limb functional exercises after AVF is 70% of the patient's own maximum grip strength at a frequency of 25 times/min.

Limitations of the Study

By analyzing the effects of using different sizes of grip strength and frequency on the hemodynamics of the upper limb cephalic veins in patients with ESRD who have undergone pre-AVF surgery, this study remedies the current gap in the study of grip strength size and grip frequency of grip exercise in patients after AVF surgery, and achieves individualization of grip exercise in patients after AVF surgery. However, there are two limitations of this study: 1) This study used a before-and-after control method to quantify the optimal strength and frequency of grip exercise in patients who had undergone AVF surgery, and it has not yet been applied to clinical validation of the implementation of the quantified optimal strength and frequency of grip exercise, and it is recommended that a controlled trial be designed in subsequent studies to further analyze the effectiveness of this quantified grip exercise method in promoting AVF maturation. 2) This study took into account the effect on the maturation of the AVF.

CONCLUSION

In this study, considering that the quantification of strength and frequency in post-AVF patients may lead to bleeding from the surgical incision, the application of the quantification of optimal strength and frequency of grip exercise in patients who have undergone AVF surgery has certain shortcomings in the application of grip exercise in post-AVF patients, and may be considered in the future to find a suitable method for grip exercise in post-AVF patients when conditions permit. In the future, we may consider finding methods to quantify grip strength exercises in post-AVF patients, so that quantified grip strength exercises can better promote AVF maturation.

ACKNOWLEDGEMENTS

We thank Director Chen Jiejian, Dr. Zheng Peilan, Ms. Gao Dongfang, Ms. Lin Ling and Director Li Huizhong of the Ultrasound Department and all the nurses of the Nephrology Department of the 900th Hospital of the People's Liberation Army Joint Security Force for their guidance and assistance.

FUNDING

This work was supported by Fujian Medical University Qihang Fund Innovation Project (2021QH1330).

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Received January 2026
Revised February 2026
Accepted March 2026

Artificial Intelligence Models for Predicting Acute Kidney Injury in Adult Critical Care: A Systematic Review

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Keywords. acute kidney injury, critical care, intensive care unit, artificial intelligence, machine learning, prediction model, calibration, decision curve analysis, AUROC, clinical utility

Introduction. Acute kidney injury (AKI) is frequent in adult critical care and is associated with increased morbidity, mortality, and long-term kidney consequences. Artificial intelligence (AI) and machine-learning (ML) prediction models may enable earlier risk identification, but clinical adoption depends on robust reporting beyond discrimination, including calibration and clinical utility.
Methods. We performed a PubMed-based systematic review (English; last 5 years) of AI/ML models predicting AKI in adult critical care/ICU populations. Records were screened and full texts were assessed for eligibility. For synthesis within the journal page limit, we restricted the final evidence set to studies reporting a complete usability-oriented outcome set: AKI definition, model type(s), prediction horizon, validation approach, AUROC/AUC, calibration, and decision curve analysis (DCA)/net benefit.
Results. Of 357 records screened, 230 full texts were assessed, and 31 studies met complete-reporting criteria and were included. The most common model families included logistic regression baselines, random forest, gradient boosting/XGBoost, and deep learning. Reported AUROC/AUC values ranged from 0.64 to 1.00 (median 0.90), with the best-performing models typically reporting AUROC ≥ 0.95. External or temporal validation was reported in 74% (23/31). By design, 100% of included studies reported calibration (e.g., calibration plot and/or Brier score and/or Hosmer–Lemeshow) and 100% reported clinical utility using DCA/net benefit.
Conclusions. Among usability-focused studies, AI/ML models show generally strong discrimination for AKI prediction in adult critical care, but reporting and validation practices remain heterogeneous. Standardized AKI definitions, transparent validation, calibration reporting, and decision-analytic evaluation are essential to support safe implementation.

RJCCN 2026; 2: 103-14
www.rjccn.org
DOI: 10.66224/rjccn.2.2.42

INTRODUCTION

Background and Rationale

Acute kidney injury (AKI) is one of the most frequent and consequential complications in adult critical care, affecting more than half of intensive care unit (ICU) patients in large multinational data when complete consensus criteria are applied, and it is strongly associated with higher mortality

Please cite this article as: Tripathi S, Prasad Sunda J. Artificial Intelligence Models for Predicting Acute Kidney Injury in Adult Critical Care: A Systematic Review. RJCCN. 2026;2(2):103-14.

and worse kidney function at hospital discharge.[1] Beyond short-term outcomes, AKI is increasingly recognized as a "gateway" event that can accelerate progression to chronic kidney disease (CKD) and contribute to long-term morbidity and mortality even after apparent recovery.[2] Because AKI often develops dynamically during evolving critical illness, clinicians need tools that can support earlier recognition, risk stratification, and timely preventive actions (e.g., hemodynamic optimization, nephrotoxin stewardship, fluid strategy, and monitoring intensity).

Prediction models are therefore clinically important in the ICU. They can help identify high-risk patients earlier than traditional rule-based triggers and enable more targeted monitoring and interventions. Over the last decade, the increasing availability of electronic health records (EHRs), bedside monitoring streams, and high-dimensional laboratory/physiologic data has accelerated the development of artificial intelligence (AI) and machine learning (ML) approaches for clinical risk prediction.[3] In AKI prediction specifically, ML methods may flexibly model nonlinear relationships, complex interactions, and time-varying patterns that are difficult to capture with conventional approaches, potentially improving performance in heterogeneous ICU populations.

Nevertheless, discrimination is not the sole measure that can be used to evaluate the clinical utility of prediction models. Albeit the area under the receiver operating characteristic curve (AUROC) is commonly reported, it does not tell whether the risks under prediction are well calibrated (i.e. whether the predicted risks approximate the observed rates) or whether a model offers better clinical decision-making at plausible risk levels.[4] Decision-analytic approaches, including decision curve analysis (DCA) and net benefit, make a direct relationship between model predictions and downstream clinical actions and harms/benefits, and give a more practice-relevant utility estimate.[5,6] Transparent reporting standards are also required to make prediction model research interpretable and reproducible; the TRIPOD statement includes the core reporting items necessary to assess the validity and applicability,[7] whereas risk-of-bias instruments like PROBAST can be used to conduct a structured assessment of internal validity and clinical relevance.[8]

The AI/ML AKI prediction in adult critical care has a scattered evidence base. The definitions of AKI (e.g., KDIGO vs older consensus systems), prediction horizons, patients, and the time of predictors measured are usually different across settings, making prediction cross-setting comparisons difficult.[9–11] Another method of inconsistent reporting that further complicates the work with the interpretation of model readiness to bedside use is inconsistent reporting (especially of calibration and clinical utility).

Study Objectives

The main aim of the presented systematic review is to provide a summary of AI/ML models to predict AKI in adult critical care and outline the discrimination performance (AUROC) in included studies. Secondary goals include defining AKI and predicting horizons, reporting validation strategies (internal or external) and measuring reporting of calibration and clinical utility (with DCA/net benefit where possible). Lastly, we attempt to find common areas of reporting deficits and comment on what this means to clinical adoption and standards of future research in critical care nephrology.

MATERIALS AND METHODS

Protocol and Reporting Standard

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[12] A review protocol was not registered in PROSPERO prior to study initiation.

Eligibility Criteria

Population. We included studies involving adults (≥ 18 years) managed in critical care settings, including ICU or explicitly described critically ill adult cohorts. Studies that exclusively enrolled pediatric or neonatal populations were excluded. Studies conducted entirely outside critical care settings (e.g., general wards only, outpatient settings, and elective non-critical perioperative cohorts without ICU-level illness) were excluded.

Prediction Task. Eligible studies developed and/or validated prediction models to estimate the risk

of AKI. We considered both prognostic prediction (future AKI within a defined horizon) and early-detection/near-term prediction approaches, but studies focusing solely on AKI diagnosis after meeting criteria (without a predictive intent) were excluded.

Model Types and Scope. We included models described as artificial intelligence, machine learning, deep learning, or related algorithmic prediction approaches, as well as statistical prediction models reported alongside or as baselines within AI/ML studies. Models could be derived from structured EHR data, physiologic time-series, laboratory data, or combined sources. Studies that did not present a prediction model (e.g., biomarker-only association studies without a predictive model) were excluded.

Study Designs. We included original research studies such as retrospective or prospective cohorts, registry analyses, database studies, and clinical trials that reported AKI prediction models in adult critical care. We excluded narrative reviews, systematic reviews/meta-analyses, editorials, commentaries, letters without original model results, conference abstracts without full text, and case reports/case series without predictive model development or validation.

Outcomes and "Complete Reporting Set." To ensure clinical interpretability and bedside relevance within the journal page limit, the final qualitative synthesis was restricted to studies that reported a complete usability-oriented outcome set ("complete reporting set"), defined a priori as:

1. an explicit AKI outcome definition (e.g., KDIGO, RIFLE, AKIN, or clearly operationalized creatinine/urine output criteria)
2. model type(s)
3. prediction horizon (time window for AKI prediction)
4. validation approach (internal and/or external/temporal)
5. discrimination (AUROC/AUC) plus
6. calibration reporting (e.g., calibration plot, Brier score, calibration slope/intercept, or equivalent)
7. Clinical utility reporting using decision curve analysis (DCA), net benefit, or equivalent decision-analytic assessment

Studies lacking one or more of these elements were considered eligible at full-text stage but were excluded from the final synthesis due to incomplete reporting.

Overlapping Cohorts. When multiple publications analyzed overlapping cohorts with similar modeling objectives, the most complete and/or most recent report with the most comprehensive outcome reporting was retained, and the others were excluded to avoid double counting.

Information Sources

PubMed was searched as the primary information source. The search was performed with filters for English language and publication in the last five years (last search date: 23/12/2025). No additional databases were searched.

Search Strategy

The search combined three concept blocks: 1) acute kidney injury, 2) critical care/ICU populations, and 3) artificial intelligence/machine learning prediction models. The complete PubMed search string is provided in Appendix.

Study Selection Process

All records retrieved from PubMed were imported into Zotero for management and screening. Duplicate detection was performed within Zotero, and duplicates were removed if identified. Screening proceeded in three stages:

1. Title and abstract screening to identify potentially relevant studies and prioritize full-text retrieval
2. Full-text assessment for topic eligibility (adult critical care population and AKI prediction model study)
3. Application of the "complete reporting set" filter to restrict the final synthesis to studies reporting discrimination, calibration, and decision-analytic clinical utility in addition to core model descriptors

Screening was conducted by a single reviewer using a structured decision framework and standardized exclusion reasons; internal consistency checks were performed by re-reviewing uncertain cases and verifying eligibility against predefined criteria.

Data Extraction

A standardized extraction framework was used to collect: bibliographic information (first author, year), population and setting descriptors, AKI definition, model type(s), prediction horizon, validation approach, discrimination (AUROC/AUC), calibration reporting (and metrics where extractable), and clinical utility reporting (DCA/net benefit). When studies reported multiple models, the best-performing or primary model (as described by authors) was captured, and key ranges were noted where relevant.

Missing or non-extractable items were recorded as not reported (NR). When studies reported outcomes using different denominators (e.g., development vs validation cohorts), values were extracted using the denominators as reported by the original authors. Zotero and spreadsheet-based templates were used to manage citations and extraction.

Risk of Bias Assessment

Prediction model studies are best assessed using the Prediction model Risk Of Bias Assessment Tool (PROBAST), which evaluates risk of bias and applicability across participant selection, predictors, outcomes, and analysis domains[8]. In this review, we used a structured PROBAST-aligned heuristic assessment to summarize risk of bias across the included studies, focusing primarily on outcome definition clarity, avoidance of data leakage, handling of missing data, validation strategy, and transparency of model evaluation. Overall risk of bias was categorized as low, unclear, or high based on the balance of concerns across domains.

Synthesis Approach

We conducted a narrative synthesis supported by tabulation of study characteristics, performance reporting, and risk of bias. Meta-analysis was not performed due to heterogeneity in patient case-mix, AKI definitions, prediction horizons, modeling methods, validation strategies, and reporting of calibration and decision-analytic outcomes.

RESULTS

Study Selection

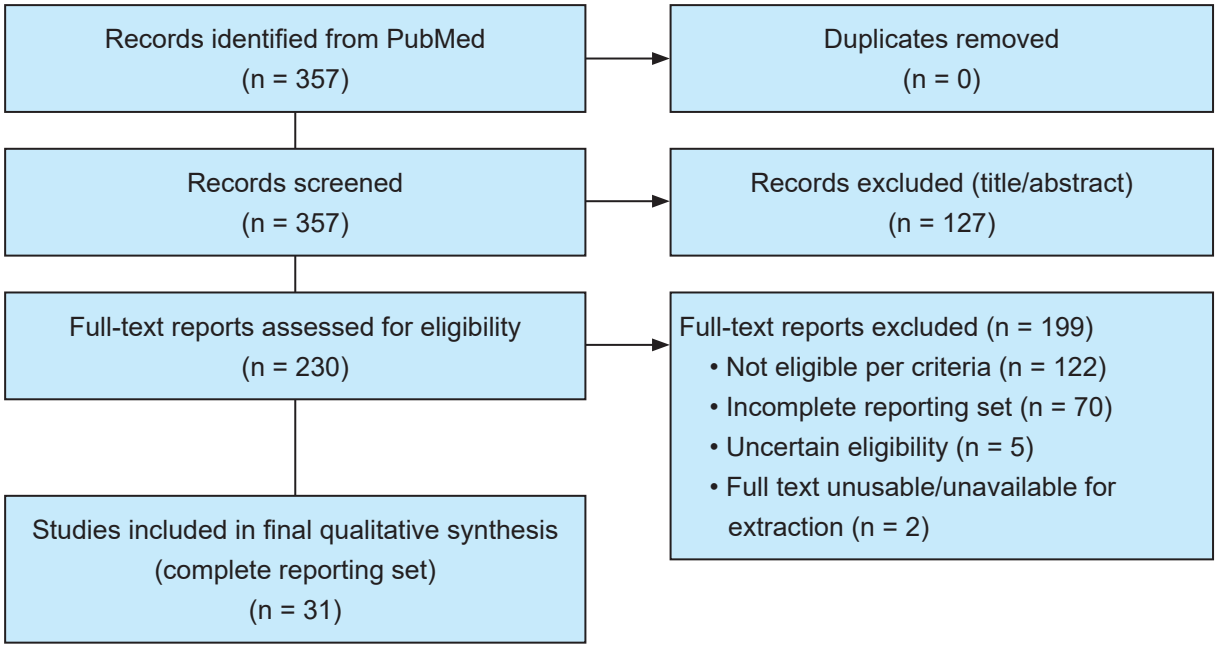
The PubMed search identified 357 records, all of which were screened at title/abstract (duplicates: 0). after title/abstract screening, 127 records were excluded, and 230 reports were sought and assessed in full text. Of these, 122 full-text reports were excluded for not meeting the review eligibility criteria, most commonly because they were not an AI/ML prediction model (n = 50), involved pediatric/neonatal populations (n = 25), were not original research (editorial/letter/protocol, n = 19), were not an AKI prediction model (n = 16), were reviews/meta-analyses (n = 7), were not ICU/critical care (n = 3), or did not use AKI as the outcome (n = 2). Five additional reports were classified as "maybe/uncertain" and set aside. This yielded 103 studies eligible at full-text decision, with 101 PDFs available for extraction.

To create a usability-focused synthesis within the journal page limit, we applied a predefined "complete reporting set" filter (core prediction descriptors plus calibration and decision-analytic utility). Seventy studies were excluded at this stage, most commonly because they lacked both calibration and clinical utility reporting (n = 41) or reported calibration without decision curve analysis/net benefit (n = 28); one study reported calibration and clinical utility but had non-extractable validation details (n = 1). Ultimately, 31 studies met the complete reporting set and were included in the final qualitative synthesis (Figure).

Characteristics of Included Studies

The final included set comprised 31 studies published between 2021 and 2025 (Table 1). Reporting of setting and cohort structure varied across studies; however, all were conducted in adult critical care/ICU populations and evaluated AI/ML prediction of AKI. AKI outcome definitions were most commonly KDIGO-based (27/31), while two studies used creatinine/urine output criteria without clearly naming a standard definition, and two studies referenced multiple/combined definitions (e.g., KDIGO with RIFLE/AKIN).

Prediction horizons were heterogeneous but most frequently short-term: 24-hour prediction windows were reported in 21/31 studies and 48-hour windows in 16/31; a smaller subset reported alternative horizons (e.g., 6 to 12 hours, 2 to 4 days, or longer windows such as 28 days). Validation



PRISMA Flow Diagram for Study Selection

approaches were mixed: external or temporal validation was reported in 23/31 (74%), while cross-validation/bootstrapping was reported in 25/31, and internal split/holdout validation in 16/31.

Model Performance and Reporting Quality

Across included studies, commonly represented model families included logistic regression baselines (30/31), random forests (28/31), gradient boosting/XGBoost variants (XGBoost: 26/31; boosting family: 24/31), and deep learning (21/31); several studies also evaluated SVM and decision-tree approaches.

Discrimination. All included studies reported AUROC/AUC by design (Table 2). The primary AUROC/AUC ranged from 0.64 to 1.00, with a median of 0.904 (interquartile range approximately 0.85 to 0.96). Reported discrimination commonly clustered in the high-0.8 to mid-0.9 range, with some studies reporting very high values (≥ 0.95) for selected models and horizons.

Validation. Although internal validation was common (cross-validation/bootstrapping and/or split-sample approaches), nearly three-quarters of included studies reported external or temporal validation (74%), supporting greater generalizability than development-only reports; nonetheless, the nature of external validation varied and was not always clearly described in extractable text.

Calibration. All included studies reported calibration in some form (a requirement of the complete reporting set). Among the included studies, Brier score reporting was detected in 11/31, and Hosmer–Lemeshow testing in 4/31; other calibration reporting was frequently described generically as "calibration" (e.g., calibration plots or narrative calibration statements).

Clinical Utility. By the complete reporting set definition, all 31 studies reported decision-analytic clinical utility (e.g., decision curve analysis and/or net benefit) to support evaluation of practical usefulness at clinically relevant thresholds.

Risk of Bias

Overall, risk-of-bias concerns were concentrated primarily in the analysis domain, while outcome definition concerns were comparatively lower within the included set (all studies reported AKI definitions sufficiently to satisfy the complete reporting filter) (Table 3). Common issues included the predominance of retrospective designs (risk of selection bias), incomplete clarity about the timing and availability of predictors relative to AKI onset

Table 1. Characteristics of Included Studies and Core Reporting Elements

First author	Year	Title	AKI definition	Prediction horizon	Model type(s)	Validation
Yue, Suru	2022	Machine learning for the prediction of acute kidney injury in patients with sepsis	KDIGO	24h/48h	DL, XGB, RF, GBM, SVM, LR, DT	CV/Boot
Wang, Yongbin	2024	Construction and evaluation of a mortality prediction model for patients with acute kidney injury undergoing continuous renal replacement therapy based on machine learning algorithms	KDIGO	24h/48h	DL, XGB, RF, GBM, LGBM, SVM, LR, DT	CV/Boot; Ext; Int
Li, Mingxia	2024	Machine Learning for Predicting Risk and Prognosis of Acute Kidney Disease in Critically Ill Elderly Patients During Hospitalization: Internet-Based and Interpretable Model Study	KDIGO	2d/48h/4d	XGB, RF, GBM, LGBM, LR	CV/Boot; Ext; Int
Yu, Shuangjiang	2025	A machine learning-based prediction model for sepsis-associated delirium in intensive care unit patients with sepsis-associated acute kidney injury	KDIGO	24h/3d	XGB, RF, GBM, SVM, LR, DT	CV/Boot; Ext; Int
Gottlieb, Eric R.	2022	Machine Learning for Acute Kidney Injury Prediction in the Intensive Care Unit	KDIGO	12h/24h/48h	DL, XGB, RF, GBM, SVM, LR, DT	Ext
Wang, Geng	2023	Machine learning-based models for predicting mortality and acute kidney injury in critical pulmonary embolism	KDIGO	24h/6h	XGB, RF, GBM, LR	CV/Boot; Ext; Int
Zuo, Fei	2025	Construction and validation of risk prediction models for renal replacement therapy in patients with acute pancreatitis	KDIGO	24h	DL, XGB, RF, GBM, SVM, LR	CV/Boot; Int
Li, Xunliang	2023	Machine learning algorithm to predict mortality in critically ill patients with sepsis-associated acute kidney injury	KDIGO	20h/24h/48h	DL, XGB, RF, GBM, SVM, LR, DT	Ext
Li, Xunliang	2024	Interpretable machine learning model for predicting acute kidney injury in critically ill patients	KDIGO	24h/48h/6h	DL, XGB, RF, GBM, SVM, LR, DT	Ext; Int
Jiang, Meng	2023	Explainable machine learning model for predicting furosemide responsiveness in patients with oliguric acute kidney injury	KDIGO	12h/18h/24h	DL, XGB, RF, SVM, LR, DT	CV/Boot; Int
Huang, Chun-Te	2023	Federated machine learning for predicting acute kidney injury in critically ill patients: a multicenter study in Taiwan	KDIGO; RIFLE	24h/3d/30h	DL, XGB, RF, GBM, LR	CV/Boot; Ext; Int; Temp
Xu, Yang	2025	Development and validation of a cardiac surgery-associated acute kidney injury prediction model using the MIMIC-IV database	KDIGO	0d/24h/48h	RF, LR	Int
Qin, Huayang	2025	Development of a machine learning-based prediction model for acute kidney injury associated with respiratory failure in the intensive care unit	KDIGO	28d/48h/6h	DL, XGB, RF, GBM, LGBM, SVM, LR	CV/Boot; Ext; Int
Zhong, Lei	2025	Construction and evaluation of prediction model for renal function recovery in acute kidney injury patients undergoing continuous renal replacement therapy based on machine learning algorithms	KDIGO	14d/24h/365d	DL, XGB, RF, GBM, LGBM, SVM, LR, DT	CV/Boot; Ext
Wang, Ruoran	2025	A machine learning predictive model for acute kidney injury among aneurysmal subarachnoid hemorrhage patients	KDIGO	2d/4d/48h	XGB, RF, GBM, SVM, LR	CV/Boot; Ext
Fan, Tingting	2023	Predicting the risk factors of diabetic ketoacidosis-associated acute kidney injury: A machine learning approach using XGBoost	KDIGO	24h	DL, XGB, GBM, SVM, LR	CV/Boot; Int

Table 1. Continued

First author	Year	Title	AKI definition	Prediction horizon	Model type(s)	Validation
Sun, Meina	2025	Predicting in-hospital mortality in patients with alcoholic cirrhosis complicated by severe acute kidney injury: development and validation of an explainable machine learning model	KDIGO	24h	DL, XGB, RF, GBM, LGBM, SVM, LR, DT	CV/Boot; Ext
Zhong, Lei	2024	Risk prediction models for successful discontinuation in acute kidney injury undergoing continuous renal replacement therapy	KDIGO	24h/365d/48h	DL, XGB, RF, GBM, LGBM, SVM, LR, DT	CV/Boot; Ext
Wang, Tsai-Jung	2024	Predictive approach for liberation from acute dialysis in ICU patients using interpretable machine learning	KDIGO	3d/30d/48h	DL, XGB, RF, GBM, LR	CV/Boot; Int
Li, Le	2024	Machine learning for the prediction of 1-year mortality in patients with sepsis-associated acute kidney injury	KDIGO	48h/4d/6h	XGB, RF, GBM, LGBM, CatB, LR, DT	Ext; Int
Zhang, Li	2025	Prediction of acute kidney injury in intensive care unit patients based on interpretable machine learning	KDIGO	24h	DL, XGB, GBM, LGBM, SVM, LR, DT	CV/Boot; Ext
Li, Mingxia	2022	Development and deployment of interpretable machine-learning model for predicting in-hospital mortality in elderly patients with acute kidney disease	KDIGO	48h/5d/5h	DL, XGB, RF, GBM, SVM, LR	CV/Boot; Ext
Dong, Lei	2024	Development and validation of a machine-learning model for predicting the risk of death in sepsis patients with acute kidney injury	KDIGO	24h/6h/72h	DL, XGB, RF, CatB, SVM, LR, DT	CV/Boot; Ext; Int
Liu, Xiaolong	2024	Machine learning-based model to predict severe acute kidney injury after total aortic arch replacement for acute type A aortic dissection	KDIGO; RIFLE; AKIN	2d/3d/48h	DL, RF, SVM, LR, DT	CV/Boot; Ext
Chang, Hsin-Hsiung	2022	Predicting Mortality Using Machine Learning Algorithms in Patients Who Require Renal Replacement Therapy in the Critical Care Unit	Creatinine/ UO criteria mentioned (unspecified)	1d/24h	DL, XGB, RF, LR, DT	CV/Boot; Ext
He, Jiawei	2021	Application of Machine Learning to Predict Acute Kidney Disease in Patients With Sepsis Associated Acute Kidney Injury	KDIGO	3d/48h/7d	DL, XGB, RF, GBM, LR, DT	CV/Boot; Ext
Cox, Eline G. M.	2023	External Validation of Mortality Prediction Models for Critical Illness Reveals Preserved Discrimination but Poor Calibration	Creatinine/ UO criteria mentioned (unspecified)	1h/2d/24h	RF, LR	Ext
Wang, Hongnian	2025	An effective multi-step feature selection framework for clinical outcome prediction using electronic medical records	KDIGO	1h/2h/6d	DL, XGB, RF, GBM, LGBM, CatB, SVM, LR, DT	CV/Boot
Ji, Wenwen	2025	A machine learning model for predicting 28-day mortality in ICU patients with community-acquired pneumonia and acute kidney injury	KDIGO	24h/28d/6h	RF, GBM, SVM, LR	CV/Boot; Ext; Int
Ma, Xia	2025	From glycemic variability to digital signal biomarker: a prognostic and precision medicine framework for sepsis-associated acute kidney injury	KDIGO	24h/28d/48h	RF	CV/Boot
Luo, Tiangui	2025	Clinical impact and safety of continuous renal replacement therapy in critically ill patients with solid tumors and acute kidney injury: a retrospective cohort analysis	KDIGO	0h/12h/18h	XGB, GBM, LR	CV/Boot; Ext; Int

Abbreviations: AKI, acute kidney injury; AUROC, area under the receiver operating characteristic curve; NR, not reported; DL, deep learning; XGB, XGBoost; RF, random forest; LR, logistic regression; Ext, external validation; Temp, temporal validation; CV/Boot, cross-validation/ bootstrapping; Int, internal split/holdout.

Table 2. Discrimination Performance of Included Models (AUROC/AUC) and Key Notes

First author	Year	AUROC/AUC (primary)	AUROC/AUC (range)	Calibration (reported)
Yue, Suru	2022	0.943	0.600 to 0.943	Calibration mentioned
Wang, Yongbin	2024	0.954	0.504 to 0.954	Brier score; Calibration mentioned
Li, Mingxia	2024	0.963	0.500 to 0.963	Calibration mentioned
Yu, Shuangjiang	2025	0.91	0.500 to 0.910	Calibration mentioned
Gottlieb, Eric R.	2022	0.89	0.660 to 0.890	Calibration mentioned
Wang, Geng	2023	0.904	0.586 to 0.904	Calibration mentioned
Zuo, Fei	2025	1.0	0.715 to 1.000	Brier score; Calibration mentioned
Li, Xunliang	2023	0.832	0.572 to 0.832	Calibration mentioned
Li, Xunliang	2024	0.824	0.630 to 0.824	Calibration mentioned
Jiang, Meng	2023	1.0	0.610 to 1.000	Brier score; Calibration mentioned
Huang, Chun-Te	2023	0.977	0.547 to 0.977	Calibration mentioned
Xu, Yang	2025	0.755	0.700 to 0.755	Calibration mentioned; Hosmer–Lemeshow
Qin, Huayang	2025	0.89	0.890 to 0.890	Brier score; Calibration mentioned
Zhong, Lei	2025	0.915	0.685 to 0.915	Brier score; Calibration mentioned
Wang, Ruoran	2025	1.0	0.500 to 1.000	Calibration mentioned
Fan, Tingting	2023	0.835	0.518 to 0.835	Calibration mentioned
Sun, Meina	2025	0.903	0.580 to 0.903	Brier score; Calibration mentioned
Zhong, Lei	2024	0.902	0.638 to 0.902	Brier score; Calibration mentioned
Wang, Tsai-Jung	2024	0.95	0.700 to 0.950	Brier score; Calibration mentioned
Li, Le	2024	0.964	0.565 to 0.964	Brier score; Calibration mentioned
Zhang, Li	2025	0.64	0.543 to 0.640	Calibration mentioned
Li, Mingxia	2022	0.921	0.527 to 0.921	Calibration mentioned
Dong, Lei	2024	0.941	0.511 to 0.941	Calibration mentioned
Liu, Xiaolong	2024	0.963	0.734 to 0.963	Calibration mentioned
Chang, Hsin-Hsiung	2022	0.854	0.514 to 0.854	Calibration mentioned; Hosmer–Lemeshow
He, Jiawei	2021	1.0	0.500 to 1.000	Calibration mentioned
Cox, Eline G. M.	2023	0.88	0.500 to 0.880	Brier score; Calibration mentioned
Wang, Hongnian	2025	0.821	0.553 to 0.821	Calibration mentioned; Hosmer–Lemeshow
Ji, Wenwen	2025	0.755	0.568 to 0.755	Calibration mentioned
Ma, Xia	2025	0.845	0.578 to 0.845	Brier score; Calibration mentioned
Luo, Tiangui	2025	0.86	0.600 to 0.860	Calibration mentioned; Hosmer–Lemeshow

Note. Evidence snippets are brief text fragments indicating where AUROC/AUC values were reported in the PDF.

(risk of "data leakage"), and inconsistent reporting of missing data handling and model calibration procedures beyond brief mentions. Although external validation was present in a substantial proportion of included studies, validation quality and transportability were variably described, and few studies provided enough detail to fully judge implementation readiness.

In the PROBAST-aligned heuristic summary, 24/31 studies were judged moderate/unclear overall and 7/31 were judged high risk of bias, largely driven by analysis-related limitations.

DISCUSSION

Principal Findings

In this systematic review of AI/ML prediction models for AKI in adult critical care, we deliberately focused the final synthesis on studies that reported a predefined "complete reporting set" that included not only discrimination (AUROC/AUC) but also calibration and decision-analytic clinical utility (DCA/net benefit). Within this higher-reporting subset, discrimination was generally favorable (AUROC/AUC range: 0.64 to 1.00), suggesting that many models can separate patients at higher versus lower risk of AKI under study conditions. However, our screening also highlighted an important reality: even within a rapidly growing literature, only a minority of full texts ultimately provided the combination of outcome definition, horizon anchoring, validation detail, calibration, and utility evaluation needed to judge bedside readiness. External or temporal validation was present in a substantial proportion of included

Table 3. Risk of Bias Assessment Summary (Prediction-Model Heuristic / PROBAST-aligned)

First author	Year	Analysis	Overall (heuristic)
Yue, Suru	2022	High	High
Wang, Yongbin	2024	Moderate	Moderate
Li, Mingxia	2024	Moderate	Moderate
Yu, Shuangjiang	2025	Moderate	Moderate
Gottlieb, Eric R.	2022	Moderate	Moderate
Wang, Geng	2023	Moderate	Moderate
Zuo, Fei	2025	High	High
Li, Xunliang	2023	Moderate	Moderate
Li, Xunliang	2024	Moderate	Moderate
Jiang, Meng	2023	High	High
Huang, Chun-Te	2023	Moderate	Moderate
Xu, Yang	2025	Unclear	Moderate
Qin, Huayang	2025	Moderate	Moderate
Zhong, Lei	2025	Moderate	Moderate
Wang, Ruoran	2025	Moderate	Moderate
Fan, Tingting	2023	High	High
Sun, Meina	2025	Moderate	Moderate
Zhong, Lei	2024	Moderate	Moderate
Wang, Tsai-Jung	2024	High	High
Li, Le	2024	Moderate	Moderate
Zhang, Li	2025	Moderate	Moderate
Li, Mingxia	2022	Moderate	Moderate
Dong, Lei	2024	Moderate	Moderate
Liu, Xiaolong	2024	Moderate	Moderate
Chang, Hsin-Hsiung	2022	Moderate	Moderate
He, Jiawei	2021	Moderate	Moderate
Cox, Eline G. M.	2023	Moderate	Moderate
Wang, Hongnian	2025	High	High
Ji, Wenwen	2025	Moderate	Moderate
Ma, Xia	2025	High	High
Luo, Tiangui	2025	Moderate	Moderate

Note. Judgments are PROBAST-aligned heuristics and can be finalized with full PROBAST item-level review if required.

studies, yet it remained inconsistent across the broader evidence base and often lacked enough detail to confidently infer transportability across ICUs and health systems. These findings align with long-standing concerns that prediction-model literature can overemphasize discrimination while underreporting calibration, clinical utility, and implementation-facing details.[7,8]

Interpretation and Clinical Meaning

Discrimination metrics such as AUROC are useful but incomplete. AUROC does not tell clinicians whether predicted probabilities are *numerically accurate* at clinically actionable thresholds, which is essential when model output is used to trigger interventions.[4] Calibration addresses this gap: a model with acceptable AUROC may still systematically overestimate or underestimate risk, leading to alarm fatigue, missed opportunities for prevention, or inappropriate escalation. For ICU deployment—where AKI risk evolves quickly—calibration should ideally be assessed with calibration plots and quantitative measures (e.g., Brier score, calibration slope and intercept), and recalibration should be reported when models are transported to new settings.[4]

Decision curve analysis and net benefit further advance the evaluation by connecting predictions to clinical consequences across a range of thresholds, which is more aligned with ICU decision-making than AUROC alone.[5,6] DCA can clarify whether a model is likely to improve decision-making compared with "treat all" or "treat none" strategies, especially when the downstream action (e.g., enhanced monitoring, nephrology consultation, hemodynamic optimization, avoidance of nephrotoxins) carries costs and potential harms. In practice, DCA reporting may also reveal that models with similar AUROC values can differ substantially in utility depending on calibration, event rates, and threshold selection.

Heterogeneity in AKI definitions and prediction horizons remains a major barrier to cross-study comparison and implementation. KDIGO provides standardized criteria and is the most widely used contemporary definition,[9] yet older systems (RIFLE, AKIN) and operational variants persist, and studies may differ in whether they use creatinine, urine output, or both.[10,11] Similarly, prediction horizons vary widely (e.g., 6 to 12 h, 24 to 48 h, several days), and horizon definitions are often poorly anchored to clinically meaningful time-zero events (ICU admission, initiation of vasopressors, onset of sepsis, etc.). These differences influence event prevalence and "difficulty" of prediction, which can inflate or depress AUROC and complicate benchmarking.

Finally, several mechanisms can explain why models may perform well during development yet degrade in deployment: dataset shift (differences in case-mix, measurement practices, lab ordering, and AKI ascertainment), temporal drift (changes in ICU protocols), missing-data patterns, and

unintentional leakage when predictors include information recorded after the true prediction time[8]. These issues are particularly relevant in ICU EHR-based modeling where timestamp alignment and predictor availability can be ambiguous.

Clinical Implications

The results of our study would be useful in guiding future studies of AKI prediction models in adult critical care. Originally, the investigators are expected to standardize AKI endpoints by KDIGO and report the presence or absence of creatinine and urine output criteria, including definitions of baseline creatinine and ascertainment windows.[9] Second, the prediction horizons are to be set with pre-defined and clearly anchored time-even predictors to a clinically interpretable time-zero, and clear statements made concerning the availability of the predictors at the prediction time. Third, Calibration reporting ought to be standard practice and it should contain calibration plots and quantitative measures (e.g., Brier score, slope/intercept) as well as recalibration strategies in cases where models are externally validated or transported.[4] Fourth, external or temporal validation is an aspect that should be held with a minimum expectation of any claims of generalizability, and validation cohorts must be described comprehensively enough to conclude about comparability and transportability.[7,8] Lastly, decision-analytic assessment (DCA/net benefit) is to be included to show that the model enhances decision-making within reasonable boundaries, rather than just that it predicts AKI.[5]

Clinically, critical care nephrology teams are able to view the existing AI/ML AKI models as potentially clinical risk stratification tools, although this should be approached with great caution. The models to be implemented should be based on externally-validated models, clearly calibrated, and tested on clinical utility in similar ICUs. Local piloting with observable performance drift and recalibration requirements are essential, since different centers differ both in terms of ICU population and practice.

Research Gaps and Future Directions

Key priorities include prospective impact studies that test whether model-guided interventions improve patient-centered outcomes (AKI severity, renal recovery, need for dialysis, ICU length of stay, mortality) rather than only predictive performance. Multicenter evaluations with transparent transportability analyses are needed to address heterogeneity across ICUs. Reporting adherence should be strengthened using emerging extensions and frameworks for prediction models (e.g., TRIPOD-AI and PROBAST-AI concepts), and investigators should more consistently report calibration, decision-analytic utility, and model updating/recalibration strategies.[7,8] Finally, fairness and subgroup performance assessment (by age, sex, comorbidity burden, and ethnicity where available) should be reported because AKI risk and care processes are not uniform across populations, and inequitable model performance could amplify disparities.

Strengths and Limitations

This review has several strengths. We used systematic methods, focused specifically on adult critical care, and applied a usability-oriented synthesis strategy to emphasize evidence that is closest to implementation needs. The compact evidence set supports a clearer narrative and tables suitable for journal page limits. Limitations include reliance on a single database (PubMed), which may miss some engineering- or conference-focused studies, and potential publication bias toward models with favorable performance. Our decision to apply a complete reporting filter improves interpretability but excludes many otherwise eligible studies; therefore, our synthesis should be interpreted as describing the best-reported and most implementation-relevant segment of the literature rather than the entire field. We did not perform meta-analysis due to heterogeneity in populations, horizons, and reporting. Finally, risk-of-bias assessment was summarized using a PROBAST-aligned heuristic approach rather than full PROBAST item-level adjudication, which should be considered when interpreting the certainty of evidence.

CONCLUSION

Artificial intelligence and machine-learning

prediction models for AKI in adult critical care demonstrate generally promising discrimination, but their readiness for bedside adoption depends on more than AUROC alone. Across the broader literature, incomplete reporting of prediction horizons, validation strategies, calibration, and clinical utility limits interpretability and slows translation into clinical workflows. In a usability-focused subset of studies that reported discrimination, calibration, and decision-analytic utility, model performance was often strong; however, heterogeneity in AKI definitions and outcome windows, variable external validation practices, and analysis-domain risks of bias remain important barriers to implementation. Future ICU AKI prediction research should standardize AKI endpoints (preferably KDIGO), clearly anchor prediction time and horizon, routinely report calibration with quantitative measures and recalibration strategies, and prioritize external/temporal validation alongside decision-analytic evaluation (DCA/net benefit). These steps—ideally paired with prospective impact studies—are essential for moving from promising algorithms to safe, clinically meaningful decision support in critical care nephrology.

ACKNOWLEDGEMENT

Full PubMed Search Strategy

Database: PubMed (National Library of Medicine)

Last search date: [23/12/2025]

Filters applied: in the last 5 years, English.

PubMed search string:

("Acute Kidney Injury"[Mesh] OR "acute kidney injury"[tiab] OR AKI[tiab]) AND

("Intensive Care Units"[Mesh] OR ICU[tiab] OR "critical care"[tiab] OR "critically ill"[tiab]) AND ("Artificial Intelligence"[Mesh] OR "Machine Learning"[Mesh]

OR "artificial intelligence"[tiab] OR "machine learning"[tiab] OR "deep learning"[tiab]

OR "neural network*"[tiab] OR "algorithm*"[tiab] OR "prediction model*"[tiab])

AI Tools

Artificial intelligence tools (ChatGPT) were used to support language refinement, organization of tables, and improvement of manuscript readability. No AI tool was used for data analysis, study selection, or interpretation of results. All scientific decisions and conclusions were made by the authors.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING

No external funding was received.

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Received January 2026
Revised March 2026
Accepted March 2026

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

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Keywords. hemoadsorption, sepsis, acute kidney injury, systematic review, meta-analysis

RJCCN 2026; 2: 115-32
www.rjccn.org
DOI: 10.66224/rjccn.2.2.46

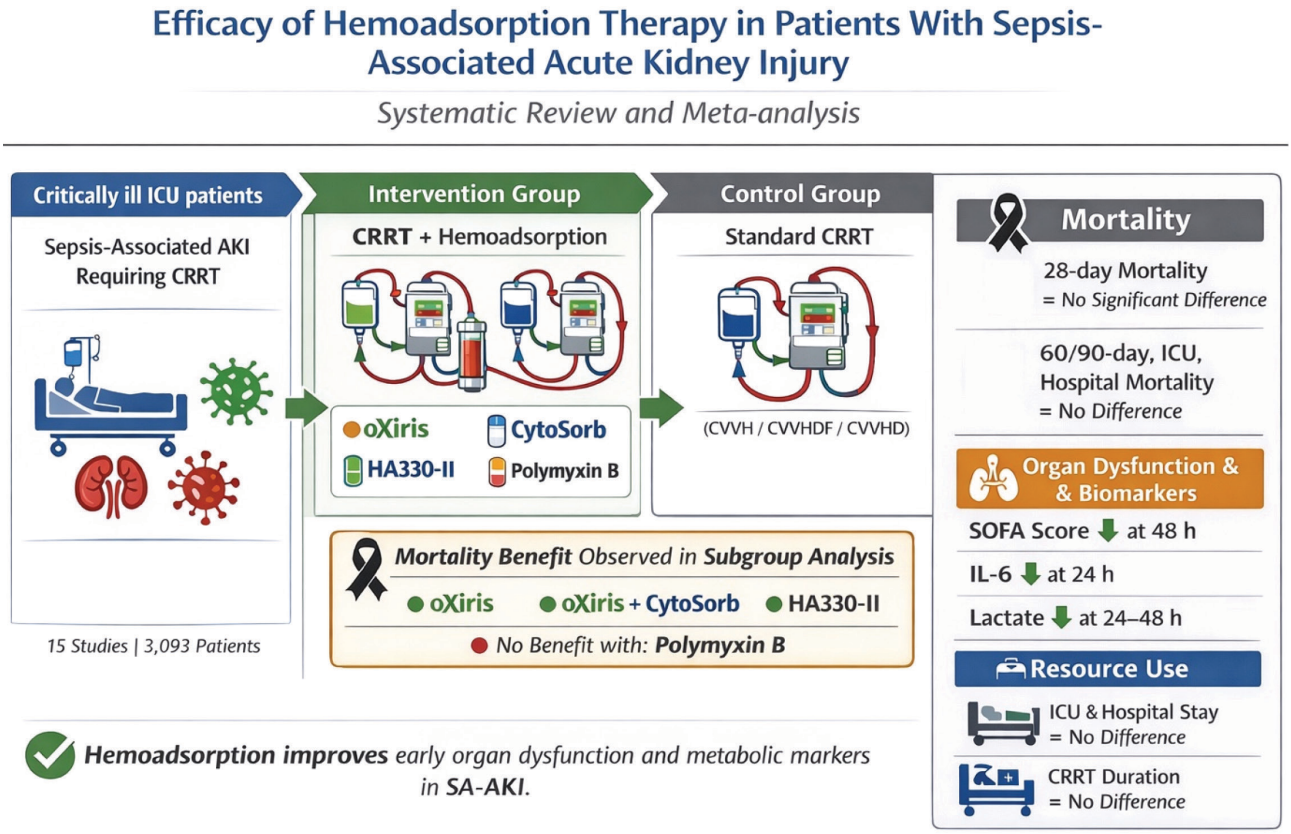
Introduction. Sepsis-associated acute kidney injury (SA-AKI) is a frequent and severe complication of sepsis with high mortality. Hemoadsorption has been increasingly used as an adjunct to continuous renal replacement therapy (CRRT) to remove inflammatory mediators, but its clinical efficacy in SA-AKI remains uncertain. We conducted a systematic review and meta-analysis to evaluate the effects of hemoadsorption added to CRRT in critically ill patients with SA-AKI.

Methods. Following PRISMA guidelines, we systematically searched PubMed, EMBASE, Web of Science, Scopus, Cochrane Library, ClinicalTrials.gov, and WHO ICTRP through December 1, 2025. Comparative studies evaluating hemoadsorption plus CRRT versus standard CRRT in septic patients with AKI were included. The primary outcome was mortality (28-, 60-, 90-day, ICU, and in-hospital). Secondary outcomes included ICU and hospital length of stay, CRRT duration, changes in SOFA score, vasopressor dose, lactate, IL-6, and procalcitonin. Random-effects meta-analyses were performed.

Results. Fifteen studies involving 3,093 patients (1,509 hemoadsorption plus CRRT; 1,584 CRRT alone) were included. Overall, hemoadsorption was not associated with a significant reduction in 28-day mortality (RR = 0.79, 95% CI: 0.61 to 1.02) or other mortality endpoints. However, hemoadsorption significantly reduced SOFA score at 48 hours (MD = −2.79, 95% CI: −4.00 to −1.58), IL-6 levels at 24 hours, and lactate levels at 24 and 48 hours compared with CRRT alone. It also did not affect ICU or hospital length of stay or CRRT duration. Subgroup analyses suggested a significant reduction in 28-day mortality with specific adsorption modalities (oXiris, oXiris plus CytoSorb, and HA330-II), but not with polymyxin B.

Conclusions. In critically ill patients with SA-AKI, adding hemoadsorption to CRRT improves short-term markers of organ dysfunction and metabolic derangement but does not confer a clear mortality benefit. Future large, multicenter trials with standardized protocols are needed to determine whether specific patient subgroups or adsorption modalities derive meaningful survival benefit.

Please cite this article as: Saeedian B, Babajani N, Hakemi MS, Jodeiri F, Aslani MA, Alavi Darazam I, Kasaeian A, Schneider A, Nassiri AA. Efficacy of Hemoadsorption Therapy in Patients With Sepsis-Associated Acute Kidney Injury: A Systematic Review and Meta-analysis. RJCCN. 2026;2(2):115-32.



Graphical Abstract

INTRODUCTION

Sepsis is a life-threatening condition caused by a dysregulated response to an infectious source in the body, which can lead to subsequent organ injury.[1] Sepsis-associated acute kidney injury (SA-AKI) is one of the serious complications of the mentioned organ injury. It is estimated that AKI occurs in 60% of patients admitted with sepsis, and it is a leading cause of mortality and morbidity in these patients.[2] A recent cohort study in France by Monard *et al.* reported that nearly 30% of patients with SA-AKI died during the disease course. They also found that compared to isolated sepsis patients, the occurrence of AKI increased the hospital length of stay (LOS) by about 33%, and the cost of treatment by 38%. Around 14.5% of SA-AKI patients required renal replacement therapy (RRT).[3]

The basic principles of SA-AKI rely on early recognition, administration of appropriate antibiotics for source control, fluids and vasopressors to maintain organ perfusion, and renal replacement therapy (RRT) to remove accumulated products.[4,5] Several RRT modalities are investigated to optimize clinical outcomes in SA-AKI, each with a distinct physiological mechanism.[6] Continuous renal replacement therapy (CRRT) modalities, including continuous Veno-venous hemofiltration (CVVH), continuous Veno-venous hemodialysis (CVVHD), and continuous Veno-venous hemodiafiltration (CVVHDF), work based on extracorporeal blood purification strategies in which uremic waste products and inflammatory mediators are removed simultaneously.[7] They can also be combined with other therapeutic measures. For example, CVVH can be used in combination with recombinant alkaline phosphatase (rALP), functioning as a dephosphorylating agent of lipopolysaccharide, which is the main pathogenic component of gram-negative bacterial endotoxins.[8]

Hemoadsorption has gained attention as RRT in SA-AKI management in recent years, which is an extracorporeal blood purification strategy designed for the removal of inflammatory mediators and pathogenic substances from the blood. Hemoadsorption can be beneficial for SA-AKI patients by regulating microcirculatory

oxygenation in the kidneys, protecting the kidneys from tubular cell injury, and facilitating rapid hemodynamic restoration, which leads to reduced vasopressor administration.[9,10] It has also been shown to be effective in critically ill COVID-19 patients.[11] CytoSorb is one of the most studied hemoadsorption devices, primarily used in conjunction with CRRT, which removes a wide range of inflammatory mediators non-specifically.[12] oXiris® Hemofilter is another unselective hemoadsorption modality in which both cytokines and endotoxins are removed simultaneously.[13] Seraph 100® is also an unselective device used for the direct removal of infectious pathogens like viruses or bacteria from the circulation.[14] Polymyxin B, a selective hemoadsorption modality mainly used for the removal of endotoxins, is highly useful in cases of endotoxemia.[15] Jafron® HA is a recent hemoadsorption modality with different models for different purposes (HA130, HA230, and HA330). HA130 is mainly used in combination with hemodialysis, while HA230 is usually used in drug, pesticide, or industrial poisoning.[16] HA330-II is used in the context of an acute hyperinflammatory state, such as SA-AKI, which removes a broad spectrum of inflammatory mediators and bacterial toxins from the bloodstream.[17]

Despite the increase in usage of hemoadsorption techniques in septic and SA-AKI patients in recent years, many uncertainties remain in this field. Moreover, direct comparison of hemoadsorption addition to CRRT with standard CRRT therapy in this population has not been made. This study aims to do a systematic review and meta-analysis in order to evaluate the efficacy of hemoadsorption in the SA-AKI clinical context.

MATERIALS AND METHODS

Eligibility Criteria

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[18] Studies reporting the use of hemoadsorption in septic patients with AKI were eligible for inclusion. Case reports, review articles, non-English manuscripts, protocols, non-comparative studies, and conference abstracts were dismissed. The protocol of our study was registered in PROSPERO (registration number = CRD420251270537).

Search Strategy

We systematically searched the following electronic databases: PubMed, EMBASE, Web of Science, Scopus, Cochrane Library, Clinicaltrials.gov, and WHO's International Clinical Trials Registry Platform (ICTRP) until December 1, 2025. No language restrictions or search filters were applied. Keywords and search terms were: "Hemoadsorption", "Hemoperfusion", "Blood Purification", "Sepsis", "Acute Kidney Injury", and "AKI". We also screened the reference list of eligible studies and relevant reviews on the topic.

Study Selection

The results of the systematic search were imported into EndNote software version 21.2 (Clarivate PLC, London, United Kingdom). Two independent authors (BS, NB) screened them using titles and abstracts of the studies. Disagreements were resolved by a third reviewer (AAN).

Data Collection

Full texts of selected studies were retrieved, and data were extracted according to a predesigned sheet. One of the reviewers (BS) did the data extraction, while a second reviewer (NB) cross-checked it. If any needed information was unavailable, we contacted the authors. From each trial, the following information was extracted: the first author's name, study year, country of origin, trial design, population and baseline characteristics, exclusion criteria, details on the CRRT protocol, sample size of each comparison group, and prespecified outcomes. Reported data only in the plots were extracted using the WebPlotDigitizer tool.[19] Our primary outcome was mortality (including 28-, 60-, 90-day, ICU, and hospital mortality). Secondary outcomes were: 1) ICU and hospital stay (days), 2) duration of CRRT (days), 3) Changes in lactate, IL-6, and PCT levels, and 4) Changes in SOFA score and norepinephrine dose.

Risk of Bias Assessment

The quality of the included randomized controlled trials (RCTs) was assessed using version 2.0 of the Cochrane Risk of Bias Assessment Tool

for Randomized Trials (RoB2).[20,21] Observational studies were rated using the Newcastle-Ottawa Scale (NOS) tool for cohort and case-control studies.[22] Lastly, the critical appraisal of case series studies was done using the JBI's critical appraisal tool.[23]

Data Synthesis and Statistical Analysis

We performed all statistical analyses using the R Programming language[24] and R Studio version 2025.09.1+401,[25] utilizing the "meta"[26] and "dmetar"[27] statistical packages. The random-effects model for the meta-analysis used the inverse-variance method (IV) for continuous outcomes and the Mantel-Haenszel method (MH) for dichotomous outcomes. Due to insufficient data, a survival meta-analysis of reported hazard ratios was not possible. Mean and standard deviation (SD) were used to calculate the mean difference (MD) with a 95% confidence interval (CI) for continuous variables or risk ratios (RR) with a 95% CI for dichotomous variables. For outcomes with different units (such as µg/h and µg/Kg/h for norepinephrine dose), standardized mean difference (SMD) with 95% CI was calculated. Median and interquartile range (IQR) were converted to mean and SD using the methods developed by Luo *et al*.[28] and Wan *et al*.[29] We calculated the change from baseline values from final and baseline measurements, assuming a correlation coefficient of 0.5. The restricted maximum likelihood (REML) model was used to estimate the between-study variance. Heterogeneity was evaluated using Higgin's I^2 test, with thresholds defined as ≤ 25% for low, 26 to 75% for moderate, and > 75% for high.[30] Meta-regression, subgroup, and leave-one-out sensitivity analyses were conducted to identify sources of heterogeneity. Publication Bias was evaluated using funnel plot visual assessments, and a trim-and-fill analysis was performed afterwards.[31] We utilized Egger's test[32] to check the significance of publication bias for continuous variables reported in more than ten studies. Due to the low number of studies in the analyses (< 10), performing a meta-regression using baseline SOFA or APACHE-II score was not feasible.

RESULTS

Study Characteristics

The selection process for the included studies is illustrated in the PRISMA flow diagram (Figure 1). Following the screening, 15 studies met the eligibility criteria and were included in the analysis.[13,36-49] Details of the included studies are presented in Table 1. Studies were published from 2002 to 2025, encompassing 1509 patients on hemoadsorption therapy and 1584 patients on standard CRRT therapy. All studies compared hemoadsorption plus CRTT with CRRT alone; four studies used polymyxin B, seven used oXiris, two used CytoSorb, one used a combination of oXiris and CytoSorb, and one used HA330-II. Seven studies performed CRRT using CVVHDF, six used CVVH, one used CVVHD, and in one study, the modality was not specified.[38] Further details of the CRRT protocols used in the included studies, including treatment duration and intervals, effluent flow rate, ultrafiltration, replacement flow rate, and blood flow rate, are presented in Table 2.

Risk of Bias in Studies

By using the RoB2 tool, of the four included RCTs, one was judged to have a low overall risk of bias, one had some concerns, and two were at a high risk. Cohort and case-control studies were evaluated using the NOS tool, and all received a low risk of bias except one.[41] One case series study with a historical control group was assessed using the case-series JBI tool and was deemed suitable for inclusion in the analysis.

Meta-analysis

Comparison of mortality rates between CRRT plus hemoadsorption and standard CRRT treatment. Compared to CRRT standard therapy, CRRT plus hemoadsoroption therapy was not associated with a significantly lower 28-day mortality rate (RR = 0.79, 95% CI: 0.61 to 1.02; I^2 = 65.6%, Figure 2). We performed subgroup analyses based on hemoadsorption type, CRRT modalities, and study design. oXiris, the combination of oXiris/CytoSorb, and HA330-II significantly reduced 28-day mortality, whereas PMX did not. Additionally, no significant differences were observed between studies using CVVH versus CVVHDF (P = .29) or between clinical trials and observational studies (P = .08). Sensitivity leave-one-out analysis revealed that excluding either the study by Suzuki *et al*.[36]

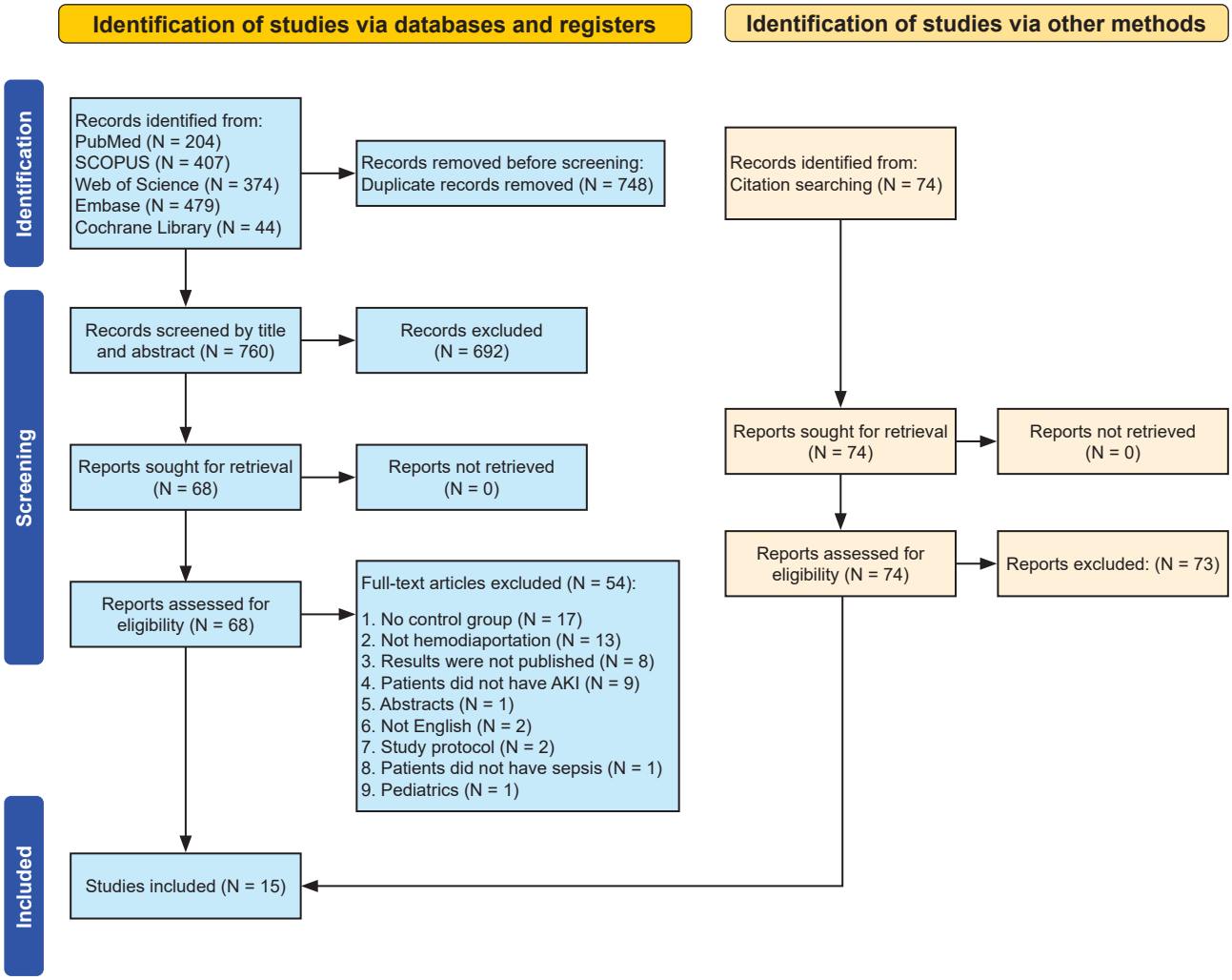


Figure 1. The PRISMA Flow Diagram of the Screening Process

or Lee *et al.*[42] would make the 28-day mortality reduction by hemoadsorption statistically significant (RR = 0.87, 95% CI: 0.81 to 0.94; RR = 0.85, 95% CI: 0.78 to 0.91; respectively). The visual assessment of the funnel plot did not indicate the presence of publication bias, and the Trim-and-Fill analysis did not alter the significance of the findings. Further analyses showed that adding hemoadsorption to CRRT did not significantly reduce 60-day, 90-day, ICU, or hospital mortality.

Comparison of secondary outcomes between CRRT plus hemoadsorption and standard CRRT treatment. Adding hemoadsorption to standard CRRT did not significantly affect ICU or hospital length of stay, nor CRRT duration (Figure 3). Sensitivity analyses, funnel plots, and Trim-and-Fill analyses confirmed the robustness of these results.

Compared to CRRT alone, the combination of CRRT and hemoadsoprtion demonstrated a significant reduction of the SOFA score 48 hours after CRRT (MD = -2.79, 95% CI: -4.00 to -1.58, I^2 = 0%), although no significant difference was found after 24 hours (Figure 4). Moreover, no significant differences in norepinephrine dose reduction 24 and 48 hours after CRRT were observed between the two groups (Figure 4).

Hemoadsorption significantly lowered IL-6 levels at 24 hours (MD = -593.59, 95% CI: -728.57 to -458.61, I^2 = 80.4%) and lactate levels at both 24 and 48 hours (MD = -0.88, 95% CI: -1.66 to -0.11, I^2 = 48.3%; MD = -0.72, 95% CI: -1.33 to -0.1, I^2 = 7.2%; respectively) compared with the control group (Figure 5). However, no significant difference was found in PCT reduction 24 hours

Table 1. Study Characteristics of the Included Studies

Author	Year	Country	Design	Population	Exclusion Criteria	Group 1, n	Group 2, n	SOFA1	SOFA2	APACHE1	APACHE2	Male%	Age	Main Findings
Suzuki et al.	2002	Japan	Randomized controlled double-blind	Patients with a clinical diagnosis of septic shock (ACCP-SCCM 1997) and ARF. Gram-negative sepsis was confirmed for most patients, while In a small number of patients, gram-negative infection was only suspected and no infection site was found despite an aggressive search.	Patients who were less than 18 years old, pregnant, and organ-transplant recipients, if informed consent from the patient's family was not granted, if they were experiencing acute organ transplant rejection, or if they were in a chronic vegetative state.	CVVHDF + PMX, 24	CVVHDF, 24			25 ± 2.1	25 ± 2.3	72.9	64.5 ± 2	At 28 days, survival was 25% with CHDF alone compared with 75% when CHDF was combined with PMX. The combination therapy led to a marked reduction in plasma endotoxin and interleukin-6, both relative to baseline and to CHDF alone.
Shum et al.	2013	China	Single-center Prospective case series with historical controls	Adult patients with sepsis-induced (ACCP-SCCM 2001) acute kidney injury due to gram-negative bacteria	Documented chronic kidney disease stage 5 (glomerular filtration rate <15 mL/min/1.73 m^2), End-stage renal failure on long-term dialysis, Those treated with renal replacement therapy prior to intensive care unit admission	CVVH + oXiris, 6	CVVH (FX80), 24	12 (9, 15)	13 (10, 15)	36 (28, 41)	34 (31, 37)	63.3	72.3 ± 12.7	The mean oXiris circuit lifespan was approximately 61 hours. At 48 hours, SOFA scores decreased by 37% in the oXiris-CVVH group, whereas a 3% increase was observed in controls. No significant adverse effects were reported, and mortality did not differ between groups.
Iwagami et al.	2016	Japan	Multicenter, retrospective cohort	Patients aged 18 or older satisfying all the following inclusion criteria were selected: 1) diagnosis of sepsis due to Haemophilus influenza, Gram-negative organisms, or unspecified; 2) started CRRT in ICU; and 3) required noradrenaline and/or dopamine on the day of CRRT initiation.	(i) ESRD at admission and/or the use of maintenance hemodialysis or peritoneal dialysis; (ii) records of cardiac intervention; (iii) started PMX before or after the day of CRRT initiation; (iv) diagnosis of viral, fungal, or Gram-positive bacterial infection; (v) received intermittent RRT (IRRT) before CRRT, and (vi) received plasma exchange before CRRT; (vii) acute pancreatitis and (viii) acute hepatic condition; (ix) interstitial pneumonia	CRRT + PMX, 978	CRRT, 978					59.1	70.5 ± 12.1	Logistic regression showed that PMX use was independently linked to lower 28-day mortality (adjusted OR 0.75; 95% CI 0.62–0.91).
Navas et al.	2018	Spain	Prospective case-control	Adult patients with acute septic shock and suspected gram-negative bacteria infection (an abdominal, biliary, or renal focus of infection), with acute kidney injury requiring CRRT and with elevated plasma endotoxin activity, defined as > 0.6 EU/ml on the Endotoxin Activity Assay		CVVH + PMX, 9	CVVH (AN69), 9	11 ± 2.4	11.6 ± 2.9	20.1 ± 4.3	21.2 ± 5.3	33.3	67.55 ± 9.6	Abdominal infections were the main source, with half of patients presenting with peritonitis. Compared with controls, the hemoperfusion group had longer durations of mechanical ventilation and CRRT. Both groups showed reductions in noradrenaline requirements and inflammatory markers. By day 5, endotoxin activity was significantly lower with hemoperfusion, but other biomarkers and ICU mortality were comparable. No hemoperfusion-related adverse events were reported.

Table 1. Continued

Author	Year	Country	Design	Population	Exclusion Criteria	Group 1, n	Group 2, n	SOFA1	SOFA2	APACHE1	APACHE2	Male%	Age	Main Findings
Broman et al.	2019	Sweden	Randomized crossover double-blind	Adult patients in ICU with septic shock, a blood culture positive for a Gram-negative bacteria or suspected to be caused by a Gram-negative agent, and associated KDIGO stage 3 acute renal failure. Patients with a plasma endotoxin level >0.03 EU/ml were enrolled.	Age <18 years and/or known human immunodeficiency virus (HIV) or hepatitis B/C infection.	CVVHDF + oXiris, 8	CVVHDF (ST150), 8					62.5	69.4 ± 11.16	During the treatment period, endotoxin levels fell in 78% of patients using the oXiris filter versus 17% with a standard filter (P = 0.02). Reductions in TNF-α, IL-6, IL-8, and IFN-γ were also greater with oXiris. Lactate decreased significantly with oXiris but not with the standard filter, and norepinephrine requirements declined only in the oXiris group.
Schittek et al.	2020	Germany	Prospective cohort with a historical control group	sepsis-associated acute kidney injury (KDIGO stage 3) in adult patients treated in ICU		CVVHDF + CytoSorb, 43	CVVHDF (M150), 33			39 (36, 42)	35 (33, 40)	21.1	62.4 ± 15.2	Patients receiving haemoadsorption had higher APACHE II scores, but risk-adjusted ICU mortality (O/E ratios) was similar between groups. Although haemoadsorption was associated with shorter ICU stay and reduced need for catecholamines and RRT, these differences were not confirmed after multivariate adjustment, where neither mortality nor LOS differed significantly between groups.
Lee et al.	2021	South Korea	Single-center retrospective cohort	Patients with septic shock and AKI	Patients with chronic dialysis, prior solid organ transplantation, and stage IV malignancy and patients aged younger than 18 years.	CVVHDF + PMX, 66	CVVHDF (ST-100), 66	13.7 ± 4.1	14.1 ± 2.6			58.4	60.9 ± 14.66	Both crude 28-day and 90-day mortality rates were higher in the PMX-HP plus CRRT group than with CRRT alone. After propensity score matching for illness severity and key clinical variables, 66 matched pairs confirmed significantly higher 28-day and 90-day mortality in the PMX-HP with CRRT group.
Guan et al.	2022	China	Single-center retrospective cohort	Patients who met the following criteria were eligible to participate: (I) CRRT ≥ 24 h; (II) septic shock (Sepsis-3); (III) AKI stage 2 or 3 (KDIGO 2012); (IV) cardiovascular SOFA score ≥ 3; (V) sepsis due to GNB infection (or suspected GNB infection).	AKI associated with chronic kidney disease; immunosuppressive treatment or steroids (prednisone > 0.5 mg/kg/day or equivalent); autoimmune disorder; coexisting illness with a high probability of death (<6 months); pregnancy; other modalities of blood purification were used; and inclusion in another ongoing study within the last 30 days.	CVVHDF + oXiris, 70	CVVHDF (ST150), 66	16.97 ± 3.56	14.98 ± 3.15			72.1	55.4 ± 13.97	Early mortality at 7 and 14 days was significantly lower with oXiris than with the ST150 filter (47.1% vs 74.2% and 58.5% vs 80.3%), though 90-day mortality did not differ. The oXiris group showed faster reductions in SOFA and VIS scores at 24–72 hours, as well as greater declines in procalcitonin. In multivariate Cox analysis, oXiris use was independently associated with improved prognosis (HR 0.50, 95% CI 0.28–0.89).

Table 1. Continued

Author	Year	Country	Design	Population	Exclusion Criteria	Group 1, n	Group 2, n	SOFA1	SOFA2	APACHE1	APACHE2	Male%	Age	Main Findings
Feng et al.	2022	China	Single-center randomized controlled trial	Surgical septic shock with AKI patients admitted in the ICU. The inclusion criteria consisted of (1) Diagnosis of Septic shock (Sepsis-3); (2) Any culture (such as blood, sputum, or drainage fluid) positive for bacteria or suspected to be caused by a Gram-negative agent; (3) Diagnosis of KDIGO Stage 3 AKI.	(1) Patient age <18 years old; (2) Weight ≤ 30 kg; (3) Patients with highly contagious infectious diseases such as open tuberculosis; (4) Previous renal replacement therapy; and (5) Patients that underwent cardio-pulmonary resuscitation (CPR)	CVVH + oXiris, 8	CVVH (AN69 ST), 8	9.9 ± 2.9	9 ± 1.5	19.9 ± 6.6	23.1 ± 4.2	68.8	65.75 ± 15.1	In the oXiris group, the first CRRT session significantly reduced PCT (p = 0.046) and IL-6 (p = 0.043) compared with pre-treatment levels. Lactate also decreased by 1.70 mmol/L (p = 0.028). Norepinephrine infusion rates were lower at 4, 6, and 8 hours post-treatment compared with the ST group.
Liu et al.	2022	China	Single-center retrospective cohort	Adult patients with septic shock (Sepsis-3) complicated with AKI (stage 2 or 3 KDIGO) admitted to the ICU	Pregnant or lactating women; survival time < 24 hours; those who had received CRRT before admission to ICU.	CVVH + oXiris, 15	CVVH (ST-100), 15	13.27 ± 2.28	12.00 ± 3.59	20.60 ± 3.83	19.27 ± 3.28	56.7	64 + 13.1	At 48 hours after CRRT, the oXiris group showed significant reductions in WBC count, hs-CRP, and PCT. Compared with controls, SOFA scores, lactate levels, and norepinephrine requirements were also lower. The duration of vasoactive support and CRRT was shorter with oXiris, while mechanical ventilation duration, ICU and hospital length of stay, and ICU or in-hospital mortality did not differ between groups.
Epstein et al.	2024	Israel	Single-center retrospective cohort	Adult patients admitted with severe septic shock or those who developed severe septic shock during their ICU stay and required CRRT (Sepsis-3).	Presence or suspicion of cardiogenic shock, haemorrhagic shock, obstructive shock, or anaphylactic shock; and initiation of blood purification or CRRT treatment more than 48 h after the diagnosis of septic shock.	CVVHDF + CytoSorb/ Oxiris, 47	CVVHDF (M150), 29	15 (13, 17)	13 (11, 14)			72.4	64.35 ± 14.7	Compared with CRRT alone, the haemoadsorption group showed greater 24-hour reductions in lactate and VDI. Mortality was lower with haemoadsorption in the ICU (34.0% vs 65.5%), and at 30 and 60 days. Adjusted analyses upheld its association with reduced ICU and 30-day mortality, but not 60-day mortality.
Zheng et al.	2024	China	Single-center retrospective cohort	(1) Age > 18, (2) Met the diagnostic criteria of Sepsis-3; (3) matched the diagnostic criteria for AKI from KDIGO 2012; (4) CRRT for at least 24 h.	(1) Other factors contributing to AKI, including prior use of nephrotoxic medications, contrast-induced nephropathy, and urinary blockages; (2) pre-existing CKD; (3) pregnancy; (4) treatment with immunosuppressive drugs; (5) active neoplasia; (6) insufficiency clinical data; (7)coexisting disease with a high probability of death (< 6 months).	CVVH + oXiris, 88	CVVH (M150), 155	10.02 ± 2.48	9.70 ± 2.55	27.35 ± 8.15	27.66 ± 8.42	65	68.1 ± 14.9	In the oXiris group, complete recovery, partial recovery, and dialysis dependence occurred in 60.3%, 13.6%, and 26.1% of patients, compared with 63.9%, 15.5%, and 20.6% in controls. Twenty-eight-day mortality did not differ. The oXiris group showed greater reductions in VIS scores at 24 and 48 hours, and lower lactate levels at 48 hours. Although baseline IL-6 levels were higher in the oXiris group, post-CRRT levels were comparable between groups. Multivariable Cox analysis indicated that oXiris use, along with SOFA score and inflammatory markers, was independently associated with reduced 28-day mortality (HR 0.466, 95% CI 0.233–0.934).

Table 1. Continued

Author	Year	Country	Design	Population	Exclusion Criteria	Group 1, n	Group 2, n	SOFA1	SOFA2	APACHE1	APACHE2	Male%	Age	Main Findings
Zhou et al.	2024	China	Randomized controlled single-blind	Adult patients with septic shock (Sepsis-3) complicated with AKI (KDIGO 2012)	Patients who died or abandoned treatment within 24 h, with underlying chronic kidney disease or malignant tumor, with immunodeficiency diseases, or taking immunosuppressants.	CVVHDF + HP (HA330-II machine), 10	CVVHDF, 10	12.10 ± 4.61	14.10 ± 1.91	17.00 ± 5.83	16.30 ± 6.22	65	67.4 ± 13.97	IL-6 and PCT levels were significantly lower in the treatment group, while decreases in IL-1β, TNFα, and CRP were not statistically significant. Lactate, SOFA scores, and norepinephrine requirements differed significantly between groups. Survival analysis demonstrated a significantly higher 28-day survival rate in the treatment group.
He et al.	2025	China	Single-center retrospective cohort	Adult SA-AKI patients (Sepsis-3, KDIGO stage 2 or 3)	Age < 18 years, pregnancy, end-stage renal disease (ESRD), and a history of renal transplantation	CVVH + oXiris, 126	CVVH (M150), 135	12 (8.5, 14)	12 (9, 15)	22.27 ± 7.11	20.89 ± 7.83	64.4	58.68 ± 16.34	After CRRT, the oXiris group demonstrated significant improvements compared with baseline, including increased MAP ($p < 0.001$) and decreased SI ($p < 0.001$), lactate ($p < 0.001$), and IL-6 ($p = 0.045$). No comparable changes were seen in the M150 group. The total norepinephrine dose was also lower in the oXiris group ($p = 0.020$). Mortality at 7, 14, 30, 60, and 90 days did not differ significantly between groups.
Mariano et al.	2024	Italy	Single-center retrospective cohort	Burn patients who developed AKI-associated septic shock (Sepsis-3) receiving CRRT for more than 72 h	All patients included in the study were without brain injury at Burn Center admission	CVVHD + CytoSorb, 11	CVVHD, 24	12 (11, 12)	12 (11, 13)			91.4	64.66 ± 25.36	7 of 11 patients initiated adsorption concurrently with CRRT. Compared with controls, the sorbent group showed a significant reduction in norepinephrine requirements and clinical improvement over the first four days, including a marked decrease in vasopressor use by day 4. In-hospital mortality was lower in the sorbent group (45.4% vs. 70.8%), with superior long-term survival on Kaplan–Meier analysis. All survivors in both groups recovered renal function at discharge, whereas nonsurvivors did not.

Table 2. Details of the CRRT Protocols Used in the Included Studies

Author	Year	Country	Design	Group 1	Group 2	n1	n2	CRRT protocol	Effluent flow rate	Ultrafilteration	replacement flow rate	blood flow rate
Suzuki et al.	2002	Japan	Randomized controlled double-blind	CVVHDF + PMX	CVVHDF	24	24	HP: 4h, CHDF was started after that for at least 24h		20 mL/kg/ h		100 to 150 mL/min
Shum et al.	2013	China	Single-center Prospective case series with historical controls	CVVH + oXiris	CVVH (FX80)	6	24			HP: 32.0 mL/kg/h (IQR, 29.3 to 38.1) contorl: 35.7 mL/ kg/h (IQR, 32.7 to 37.7)	2500 mL/h	150 mL/min
Iwagami et al.	2016	Japan	Multicenter, retrospective cohort	CRRT + PMX	CRRT	978	978	HP: 2h per session, the PMX sessions performed was 1 or 2 on consecutive days				80–120 mL/ min
Navas et al.	2018	Spain	Prospective case-control	CVVH + PMX	CVVH (AN69)	9	9	2h hemoperfusion on two consecutive days, starting within 24 h of ICU admission.	35 mL/kg/h			
Broman et al.	2019	Sweden	Randomized crossover double-blind	CVVHDF + oXiris	CVVHDF (ST150)	8	8	24h				
Schittek et al.	2020	Germany	Prospective cohort with a historical control group	CVVHDF + CytoSorb	CVVHDF (M150)	43	33					
Lee et al.	2021	South Korea	Single-center retrospective cohort	CVVHDF + PMX	CVVHDF (ST-100)	66	66	Two sessions of 2h hemoperfusion with an interval of 24 h			20 mL/kg/h	CRRT: 150 mL/min PMX-HP: 100 mL/min
Guan et al.	2022	China	Single-center retrospective cohort	CVVHDF + oXiris	CVVHDF (ST150)	70	66	oXiris was replaced with ST150 hemofilter when patients became stable.	30–35 mL/ kg/h			150-200 mL/ min
Feng et al.	2022	China	Single-center randomized controlled trial	CVVH + oXiris	CVVH (AN69 ST)	8	8				30–35 mL/ kg/h	150-200 mL/ min
Liu et al.	2022	China	Single-center retrospective cohort	CVVH + oXiris	CVVH (ST-100)	15	15	HP: 48h, then conventional hemofilter was replaced		35 mL/kg/h		150 mL/min
Epstein et al.	2024	Israel	Single-center retrospective cohort	CVVHDF + CytoSorb/ Oxiris	CVVHDF (M150)	47	29	72hr, after that CVVHDF as long as an indication for RRT existed.	30–35 mL/ kg/h			150-200 mL/ min
Zheng et al.	2024	China	Single-center retrospective cohort	CVVH + oXiris	CVVH (M150)	88	155	72hr, after that the M150 filter was replaced			35 mL/kg/h	150–180 ml/ min

Table 2. Continued

Author	Year	Country	Design	Group 1	Group 2	n1	n2	CRRT protocol	Effluent flow rate	Ultrafilteration	replacement flow rate	blood flow rate
Zhou et al.	2024	China	Randomized controlled single-blind	CVVHDF + HP (HA330-II HP machine)	CVVHDF	10	10	4hr, CVVHDF for the rest of the day. patients received 3–5 HP treatments.			3000–4000 mL/h	180–200 mL/min
He et al.	2025	China	Single-center retrospective cohort	CVVH + oXiris	CVVH (M150)	126	135	24h	20–30 mL/kg/h	20–35 mL/kg/h		150–200 mL/min
Mariano et al.	2024	Italy	Single-center retrospective cohort	CVVHD + CytoSorb	CVVHD	11	24	a minimum cycle of 2 sessions, and a maximum of 6 sessions. The indications for CytoSorb® were evaluated daily after 2 sessions	20–25 mL/kg/h			

and 48 hours after CRRT (Figure 5).

Qualitative Synthesis

Kidney Function and Prognosis. Utilizing multiple regression models, some studies found the use of oXiris hemoadsorption to be significantly and independently associated with reduction of ICU, 30-day, and 90-day mortality.[13,45] On the contrary, other studies found no association between the use of oXiris and 60- or 90-day mortality.[45,48] Moreover, He *et al.* found no interaction between the use of oXiris and age, AKI stage, or SOFA score in predicting 90-day mortality.[48] The use of PMX treatment was also found to have conflicting results regarding the association with 28-day mortality,[38,42] with no interaction found between PMX use and underlying malignancy, site of infection, previous surgery, ventilation support, or use of norepinephrine.[38] Regression models also showed CytoSorb not to have a significant association with ICU and hospital mortality.[41] Complete recovery of kidney function had no significant difference between CRRT standard therapy and using oXiris.[13,46] or CytoSorb.[49] This complete recovery was defined as a return of serum creatinine to baseline levels and a normal urine test[13,46] or recovery from CRRT need.[49] With hemoadsorption using oXiris, creatinine levels did not differ significantly between the two groups.[39,44] HA330-II decreased creatinine levels in the treatment group; still, the difference was not clinically significant.[47]

Hemodynamics. Two studies demonstrated that mean arterial pressure (MAP) values were identical in the oXiris and standard filter groups,[40,43] while another reported significant improvements in the oXiris group.[48] In a study by Epstein *et al.*, the vasopressor dependency index (VDI) showed a slight increase in the standard CRRT group, while patients receiving hemoadsorption (CytoSorb/Oxiris) experienced a significant reduction.[45] The reduction in vasoactive-inotropic score (VIS) was also found to be greater in the oXiris group than in the control group.[13,46] Patients receiving hemoadsorption via CytoSorb[41] or oXiris[44] were on a significantly shorter duration of catecholamine administration compared to standard filters. On the other hand, no significant differences in

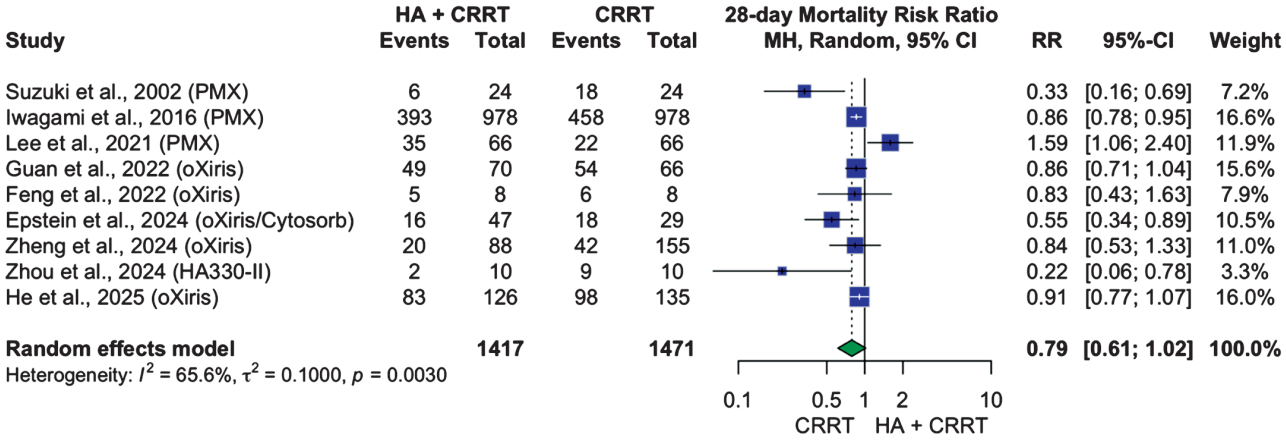
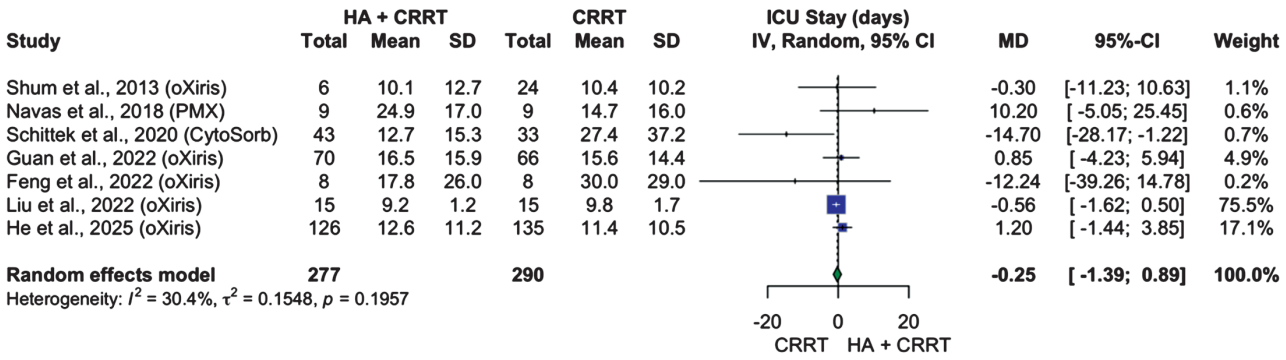
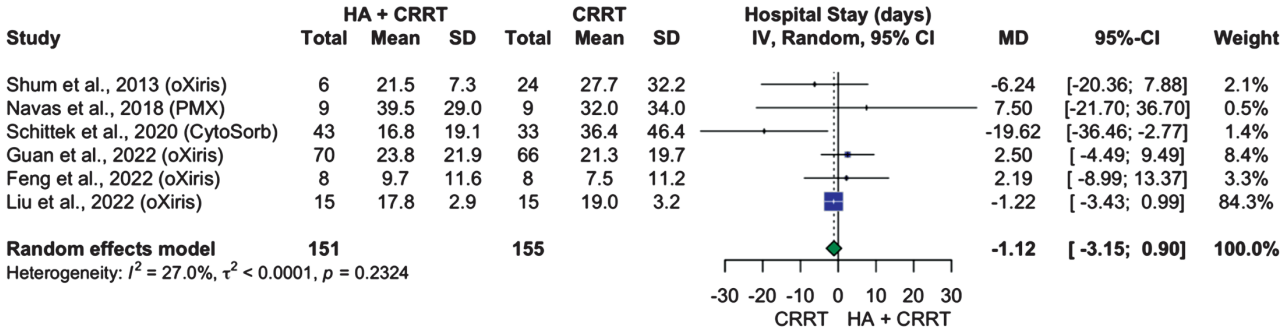


Figure 2. Forest Plot of the 28-day Mortality Risk Ratio Between hemoadsorption + CRRT and CRRT





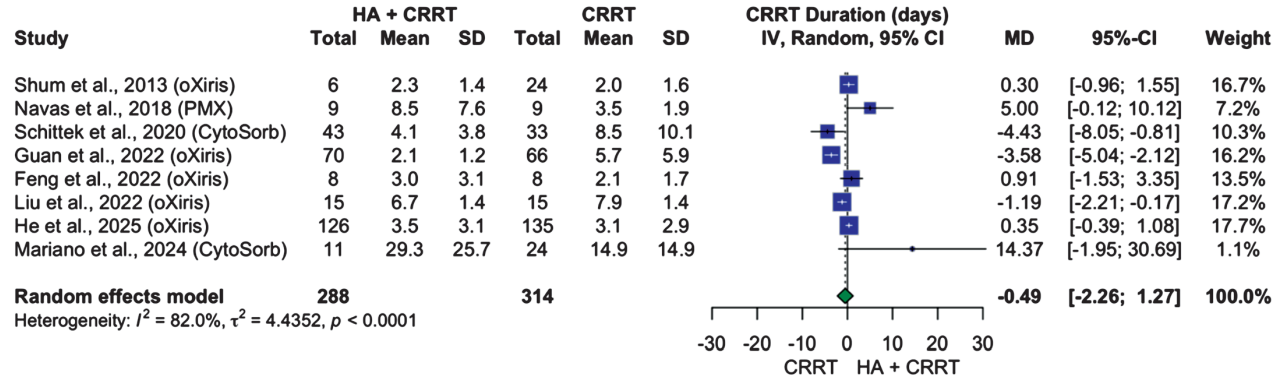


Figure 3. Forest Plot of ICU Stay, Hospital Stay, and CRRT Duration Mean Difference Between Hemoadsorption + CRRT and CRRT

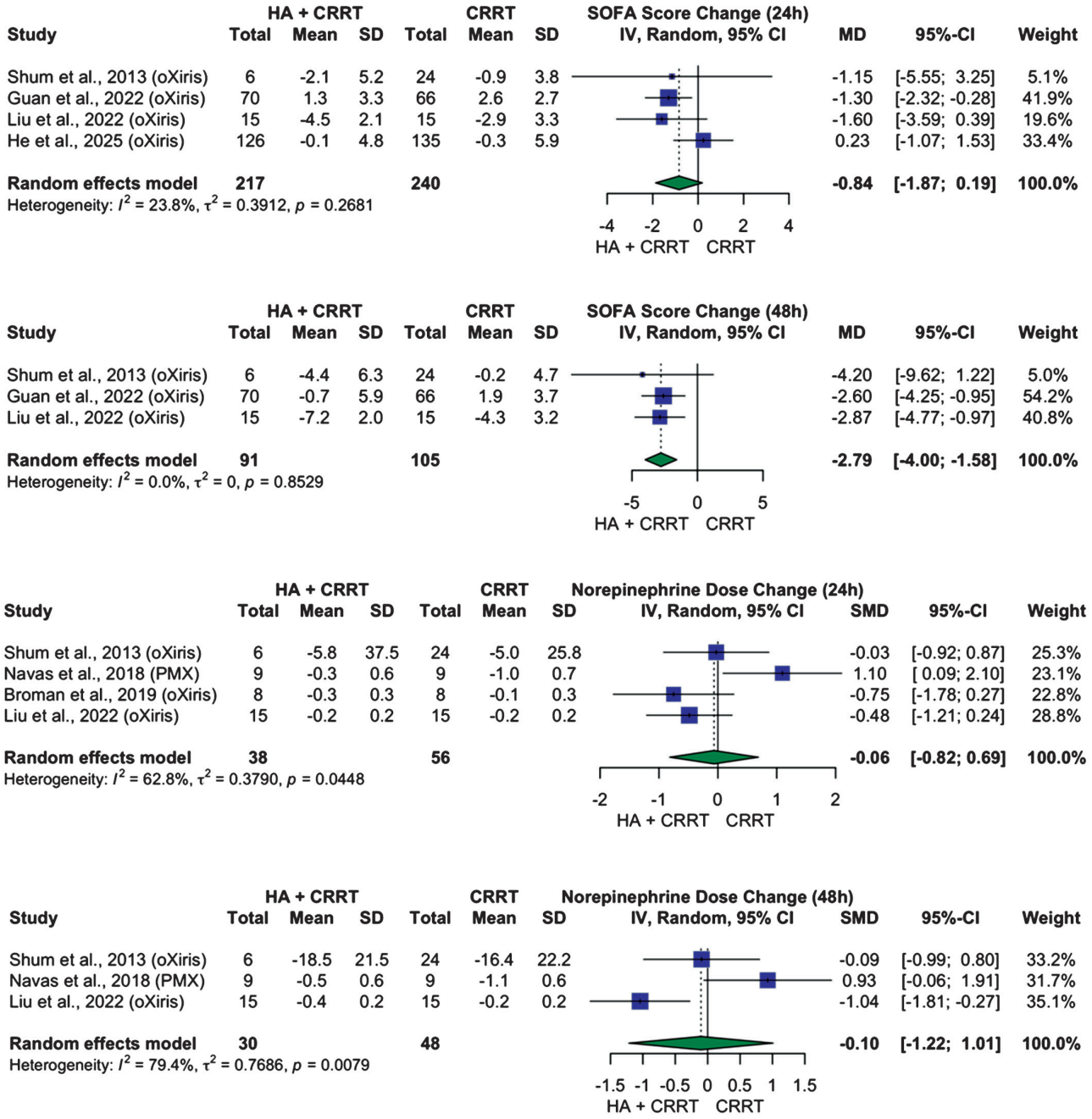


Figure 4. Forest Plot of the SOFA Score and Norepinephrine Dose Changes Mean Difference, 24 and 48 Hours After CRRT, Between hemoadsorption + CRRT and CRRT

mechanical ventilation duration between CVVH + oXiris and CVVH alone were found.[44] Notably, patients in the hemoadsorption with PMX group required a longer duration of mechanical ventilation compared to controls.[39] The changes in CRP levels were contradictory between studies.[13,39,43,44,47,48]

Endotoxin and Cytokine Levels. Only two studies measured endotoxin levels and reported that endotoxin levels had a significantly greater decline in the oXiris[40] and PMX group[36] compared to the standard filter group. Broman *et al.* revealed that TNF-α levels declined more rapidly and to a greater extent in the oXiris group (70% reduction), compared with the standard CRRT therapy (20% reduction).[40] Zheng *et al.* showed that TNFα and IL-10 levels were lower in the oXiris group compared

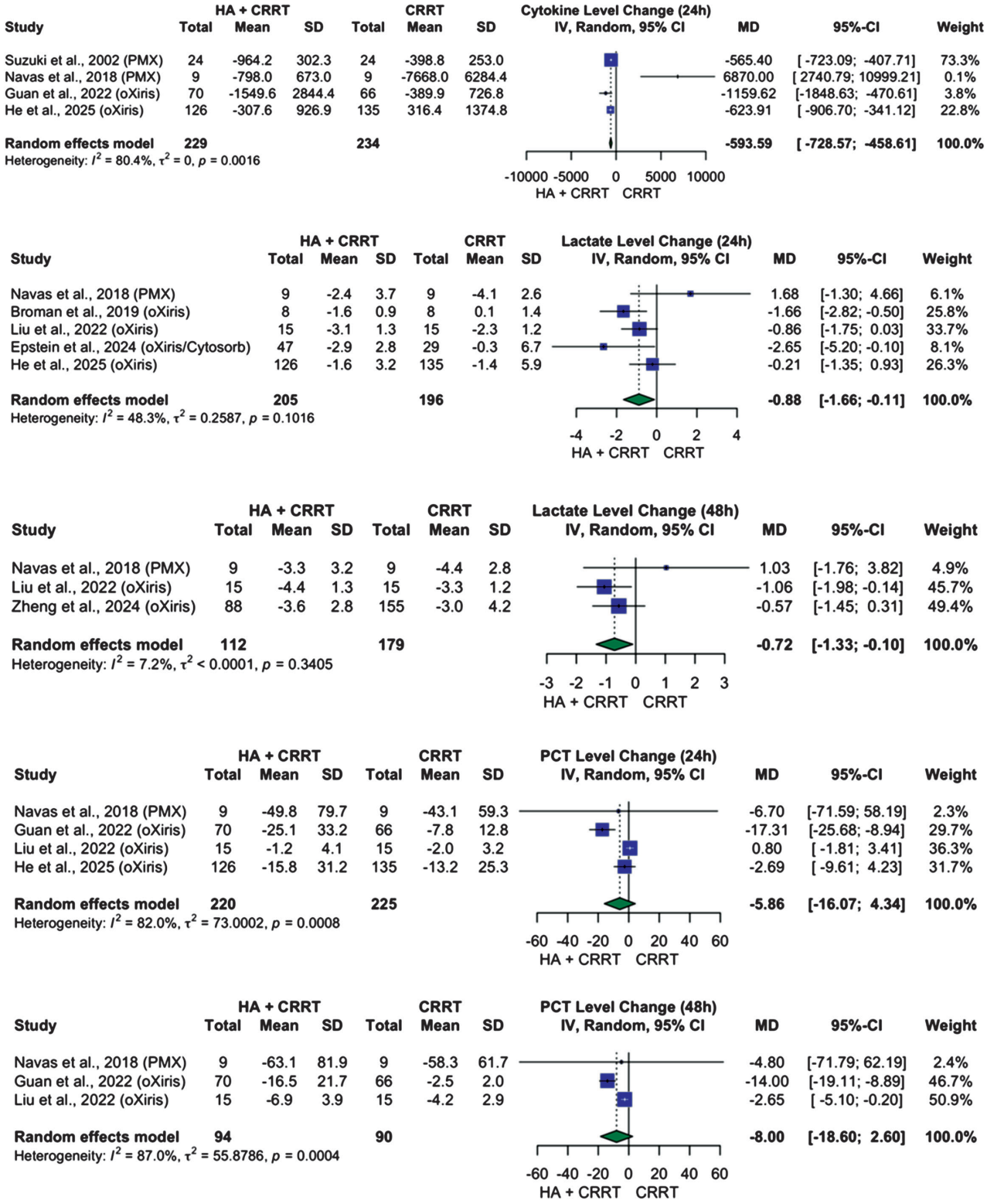


Figure 5. Forest Plot of IL-6, Lactate, and PCT Level Changes Mean Difference, 24 and 48 Hours After CRRT, Between hemoadsorption + CRRT and CRRT

to the control group.[46] However, other studies reported no significant differences between the two groups in changes of IL-2, IL-10, and TNF-α after the first treatment with oXiris,[43] IL-1β, IL-8, IL-10, and TNF-α after treatment with PMX,[39] and IL-1β and TNFα after treatment with HA330-II.[47]

DISCUSSION

In our analysis of SA-AKI patients requiring intensive care, the use of hemoadsorption techniques, when added to CRRT, did not demonstrate a statistically significant difference across primary mortality outcomes compared to conventional CRRT alone. No significant differences were observed in primary endpoints, including 28-, 60-, and 90-day mortality, as well as ICU and in-hospital mortality. Similarly, secondary outcomes, such as length of ICU stay, total hospital length of stay, and duration of CRRT, were comparable between patients treated with hemoadsorption-based strategies and those receiving standard CRRT. Importantly, our analysis demonstrated that adding hemoadsorption to CRRT was associated with a significant reduction in SOFA score at 48 hours and a significant decrease in IL-6 concentrations at 24 hours, alongside significant reductions in lactate levels at both 24 and 48 hours. Subgroup analyses further suggested a significant reduction in 28-day mortality with specific adsorption modalities, including oXiris, the combination of oXiris with CytoSorb, and HA330-II. Moreover, when combined with hemoadsorption, no difference was found between CVVH and CVVHDF modalities for CRRT.

Non-significant differences in primary mortality outcomes may be due to short follow-up durations and multifactorial drivers of mortality in SA-AKI, which are strongly influenced by disease severity and comorbidities. Also, secondary outcomes, including ICU length of stay, hospital length of stay, and CRRT duration, were not inferior to CRRT alone, suggesting that the addition of hemoadsorption did not increase treatment duration or healthcare resource use and may therefore be feasible without increasing healthcare burden. This finding was further supported by subgroup analysis, which showed no improved efficacy of CVVHDF compared to CVVH and no need for higher costs. Also, our analysis demonstrated that the addition of hemoadsorption to CRRT was associated with a significant reduction in SOFA score at 48 hours, suggesting a more rapid short-term improvement in organ dysfunction compared with CRRT alone. This early stabilization effect is biologically plausible, given that hemoadsorption membranes can clear circulating cytokines and endotoxins, key drivers of sepsis-related vasodilation and impaired tissue perfusion.[50] This interpretation is supported by prior studies reporting similar early improvements in organ function and hemodynamics using adsorptive filters like oXiris.[50-2]

In parallel, lactate levels were significantly lower at both 24 and 48 hours in the hemoadsorption group. Lactate is a core component of the current definition of septic shock and represents an objective marker of tissue hypoperfusion that is less influenced by clinician judgment than vasopressor titration. Experimental and clinical data have linked persistent hyperlactatemia in sepsis to microcirculatory dysfunction, endothelial injury, and impaired oxygen utilization, highlighting its relevance as a surrogate of microvascular recovery.[53] In contrast, no significant differences were observed in vasopressor dose reduction between groups, a finding that may reflect the subjective nature of vasopressor management, which depends on physician preference, different protocols, and target blood pressure strategies. Taken together, these findings suggest that hemoadsorption may preferentially improve objective markers of perfusion, such as lactate, and early organ dysfunction, which may help limit early progression from sepsis toward septic shock.

Hemoadsorption is an extracorporeal blood purification strategy designed to remove circulating inflammatory mediators and pathogenic substances involved in the dysregulated immune response of sepsis and SA-AKI.[9,10] Broad-spectrum adsorption devices such as oXiris, CytoSorb, and HA330-II can remove a wide range of cytokines, pathogen-associated and damage-associated molecular patterns, and selected toxins, thereby addressing multiple inflammatory pathways beyond renal solute clearance alone.[16,51,54] In contrast, polymyxin B hemoperfusion is primarily intended to selectively bind circulating lipopolysaccharide and is therefore most relevant in endotoxemia related to gram-

negative bacterial infections.[10,16] These mechanistic differences are reflected in our subgroup findings, which demonstrated a significant reduction in 28-day mortality with oXiris, the combination of oXiris plus CytoSorb, and HA330-II, but not with polymyxin B hemoperfusion. Consistently, sensitivity analyses showed that exclusion of either the Suzuki *et al.* or Lee *et al.* studies resulted in a statistically significant reduction in 28-day mortality, a finding that is plausibly explained by the predominant use of polymyxin B in those trials. Taken together, these observations suggest that inclusion of PMX-based studies where efficacy may be confined to a narrower, endotoxin-driven septic phenotype can dilute pooled mortality effects in heterogeneous SA-AKI populations, whereas broader adsorption modalities may be better suited to the complex inflammatory environment of critically ill patients.

Our findings align with the most recent meta-analyses and reviews focused on CytoSorb or similar broad-spectrum hemoadsorption in sepsis, which have not demonstrated a significant mortality reduction despite improvements in inflammatory mediator clearance or hemodynamics.[55,56] Notably, these studies also described inconsistent effects on secondary clinical outcomes, with some reporting modest or transient reductions in lactate levels or vasopressor requirements, while others found no meaningful differences in ICU length of stay or duration of organ support.[17,55,56] Similarly, we observed significant improvements in objective metabolic and organ dysfunction markers, such as lactate reduction and SOFA score at 48 hours, without corresponding changes in vasopressor dose or ICU length of stay. In contrast, a network meta-analysis of blood purification techniques in septic patients reported heterogeneous results across modalities, suggesting that potential benefits in clinical or surrogate outcomes may be driven by specific adsorption filters rather than hemoadsorption as a uniform intervention.[17]

Most of the previous studies focused on individual hemoadsorption devices, mostly CytoSorb, and enrolled heterogeneous septic populations without specifically focusing on patients with SA-AKI.[52,55,56] In contrast, our meta-analysis exclusively evaluated ICU patients with SA-AKI undergoing CRRT and systematically assessed hemoadsorption as an adjunctive therapy across short-term and intermediate-term mortality endpoints.

LIMITATIONS

This meta-analysis has several limitations. Most included studies were conducted in Asia, with limited representation from North America, Africa, and other regions, which may restrict generalizability. The majority of studies were single-center with relatively small sample sizes, and hemoadsorption dose and duration were not consistently reported. In addition, study populations were largely restricted to ICU patients, and outcomes predominantly focused on short-term mortality, particularly 28-day mortality, with limited data on long-term outcomes.

CONCLUSION

In critically ill patients with sepsis-associated AKI, the addition of hemoadsorption to CRRT was associated with significant short-term improvements in organ dysfunction and metabolic markers, including reductions in SOFA score, IL-6, and lactate levels. However, it didn't cause significant improvements in short- or intermediate-term mortality, nor did they affect ICU or hospital length of stay or CRRT duration. Larger, well-designed multicenter trials with standardized hemoadsorption protocols and longer follow-up are needed to clarify whether specific patient subgroups or adsorption modalities may derive meaningful clinical benefit.

CONFLICT OF INTEREST

Amir Ahmad Nassiri and Ilad Alavi Darazam serve as members of the RJCCN editorial team. The authors had no involvement in the peer-review or editorial decision-making processes for this manuscript.

FUNDING

This study received no specific funding from public, commercial, or not-for-profit funding agencies.

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Received January 2026
Revised February 2026
Accepted March 2026

Diagnostic Accuracy of Serum and Urinary Neutrophil Gelatinase-associated Lipocalin for Predicting Sepsis-associated Acute Kidney Injury: A Systematic Review and Meta-Analysis

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Keywords. sepsis-associated acute kidney injury, neutrophil gelatinase-associated lipocalin, NGAL, biomarkers, diagnostic accuracy, systematic review, meta-analysis, sepsis, early detection

Introduction. Sepsis-associated acute kidney injury (SA-AKI) is a frequent and serious complication among critically ill patients and is associated with substantial morbidity and mortality. Conventional diagnostic markers such as serum creatinine and urine output often detect kidney injury only after functional decline and may be confounded in septic states. Neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a potential early biomarker of tubular injury; however, its diagnostic performance in sepsis remains uncertain. This systematic review and meta-analysis evaluated the diagnostic accuracy of serum and urinary NGAL for predicting SA-AKI in adults with sepsis.

Methods. A systematic search of the PubMed database was conducted from inception to 2025 to identify studies evaluating serum, plasma, or urinary NGAL in adult patients with sepsis. Eligible studies reported diagnostic accuracy for AKI defined according to KDIGO, AKIN, or RIFLE criteria. Data extraction was performed independently by two reviewers. Pooled sensitivity, specificity, diagnostic odds ratios (DORs), and summary receiver operating characteristic (SROC) curves were estimated using a bivariate random-effects model. Subgroup analyses explored differences according to clinical setting and timing of biomarker measurement.

Results. Seventeen studies met the inclusion criteria. For serum NGAL, the pooled sensitivity was 0.77 (95% CI: 0.63 to 0.86) and pooled specificity was 0.68 (95% CI: 0.52 to 0.80), with an AUC of 0.773 and a diagnostic odds ratio of 6.15 (95% CI: 4.38 to 8.64). Urinary NGAL demonstrated comparable but slightly higher diagnostic performance, with pooled sensitivity of 0.75 (95% CI: 0.66 to 0.82), specificity of 0.71 (95% CI: 0.64 to 0.78), an AUC of 0.782, and a diagnostic odds ratio of 7.12 (95% CI: 4.17 to 12.16). Subgroup analyses suggested modestly improved diagnostic performance in ICU populations.

Conclusions. Both serum and urinary NGAL demonstrate moderate diagnostic accuracy for predicting SA-AKI in adult patients with sepsis. Urinary NGAL showed slightly better discriminatory performance in several clinical contexts. Rather than replacing established KDIGO-based diagnostic criteria, NGAL may serve as a complementary biomarker to support early risk stratification. Larger prospective studies with standardized assay methods and diagnostic thresholds are needed before routine clinical implementation.

RJCCN 2026; 2: 133-48
www.rjccn.org
DOI: 10.66224/rjccn.2.2.47

Please cite this article as: 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. RJCCN. 2026;2(2):133-48.

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction resulting from a dysregulated host response to infection and continues to represent a major cause of morbidity and mortality worldwide.[1] Among the complications associated with sepsis, acute kidney injury (AKI) is particularly common and clinically significant. It occurs in approximately 30 to 50% of critically ill septic patients and is associated with prolonged hospitalization, increased need for renal replacement therapy, and a higher risk of death.[2-4] Sepsis-associated acute kidney injury (SA-AKI) arises through a complex interplay of mechanisms, including microvascular alterations, inflammatory responses, oxidative stress, mitochondrial dysfunction, and apoptosis of tubular epithelial cells.[5-7]

In clinical practice, AKI is typically diagnosed using changes in serum creatinine levels and urine output according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[8] These markers, however, have important limitations. Serum creatinine is an indirect indicator of renal function and often rises only after substantial kidney injury has already occurred, sometimes 24 to 48 hours later.[9] In addition, creatinine levels can be influenced by several factors such as age, muscle mass, fluid balance, and hemodynamic instability—conditions frequently present in patients with sepsis.[10] Because of these limitations, there has been growing interest in identifying biomarkers including cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinase 2, and insulin-like growth factor–binding protein 7 that can signal kidney injury earlier in the disease process.

One candidate that has received considerable attention is neutrophil gelatinase-associated lipocalin, also referred to as lipocalin-2.[11] NGAL is a 25-kDa protein belonging to the lipocalin family and is rapidly produced and expressed by neutrophils and various epithelial cells, including renal tubular epithelial cells following ischemic or inflammatory injury.[12,13] Both plasma and urinary NGAL concentrations can increase within a few hours of kidney injury, often before detectable changes occur in serum creatinine.[14,15] Experimental studies further suggest that NGAL expression reflects tubular stress and inflammatory activation, which are central components of the pathophysiology of SA-AKI.[5,16]

A number of clinical investigations have evaluated NGAL as a predictor of AKI in different settings, including cardiac surgery, critical care, and emergency department populations.[17-9] Nevertheless, its diagnostic value in patients with sepsis remains uncertain. Because sepsis is characterized by systemic inflammation and neutrophil activation, circulating NGAL levels may increase even in the absence of kidney injury, potentially reducing diagnostic specificity.[20,21] In addition, differences among studies—including assay methods, cutoff thresholds, timing of biomarker measurement, definitions of AKI (RIFLE, AKIN, or KDIGO), and study design—have contributed to substantial variability in reported diagnostic performance.[22,23]

Another unresolved question is whether NGAL measured in serum or plasma performs differently from NGAL measured in urine in this setting. Circulating NGAL can originate not only from the kidneys but also from other tissues during systemic inflammation, whereas urinary NGAL is generally thought to more closely reflect tubular injury.[24,25] In addition, NGAL has a relatively small molecular weight (~25 kDa), which means it can pass through the glomerular filtration barrier. Under normal conditions, filtered NGAL is largely reabsorbed and degraded by proximal tubular cells, but changes in glomerular filtration or tubular function may alter urinary NGAL levels and complicate its interpretation as a marker of intrinsic tubular damage.[13,26] The diagnostic performance of NGAL may also depend on the clinical context, such as whether patients are evaluated in the intensive care unit or the emergency department, as well as the timing of biomarker measurement during the course of sepsis.[27,28] Furthermore, the source of sepsis itself may influence NGAL levels. For instance, sepsis caused by urinary tract infection or pyelonephritis—conditions that may already involve renal injury—could produce different NGAL patterns compared with sepsis originating from non-renal sources such as skin, pulmonary, or intra-abdominal infections. Taken together, these factors highlight the need for a comprehensive synthesis of the available evidence.

In light of these considerations, we conducted a systematic review and bivariate random-effects meta-analysis to evaluate the diagnostic accuracy of serum and urinary NGAL for predicting sepsis-associated acute kidney injury in adult patients. Subgroup analyses were also performed according to clinical setting to explore potential sources of heterogeneity.

MATERIALS AND METHODS

Study Design and Reporting Standards

This systematic review and diagnostic meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines. The aim of the study was to assess the diagnostic performance of serum and urinary neutrophil gelatinase-associated lipocalin (NGAL) for predicting sepsis-associated acute kidney injury (SA-AKI) in adult patients.

Search Strategy

A systematic search of the PubMed database was conducted from inception through 2025. The following Boolean search strategy was applied:

("Neutrophil Gelatinase-Associated Lipocalin"[Mesh] OR "neutrophil gelatinase-associated lipocalin"[Title/Abstract] OR NGAL[Title/Abstract] OR "lipocalin-2"[Title/Abstract]) AND ("Sepsis"[Mesh] OR sepsis[Title/Abstract] OR septic[Title/Abstract] OR "septic shock"[Title/Abstract]) AND ("Acute Kidney Injury"[Mesh] OR "acute kidney injury"[Title/Abstract] OR AKI[Title/Abstract]) NOT (review[Publication Type] OR meta-analysis[Publication Type]) NOT ("cardiac surgery"[Title/Abstract] OR "cardiopulmonary bypass"[Title/Abstract] OR transplant[Title/Abstract]) AND (predict* OR prognos* OR associat* OR "risk factor*" OR ROC OR AUC OR odds OR hazard)*

The search excluded review articles, meta-analyses, cardiac surgery populations, cardiopulmonary bypass studies, and transplant-related studies to focus specifically on sepsis-associated AKI in medical populations. Reference lists of eligible studies were also screened to identify additional relevant articles.

Eligibility Criteria

Studies were included if they:

1. Included adult patients diagnosed with sepsis or septic shock.
2. Evaluated serum, plasma, or urinary NGAL.
3. Assessed NGAL for prediction or diagnosis of acute kidney injury.
4. Reported sufficient data to construct 2×2 contingency tables (TP, FP, FN, TN).
5. Used recognized AKI definitions (KDIGO, AKIN, or RIFLE).

Studies were excluded if they:

1. Were non-human or mechanistic studies.
2. Included pediatric or neonatal populations.
3. Did not evaluate NGAL as a diagnostic test for AKI.
4. Focused exclusively on mortality, chronic kidney disease progression, or non-AKI outcomes.
5. Were reviews, editorials, bibliometric studies, or conference abstracts without extractable data.
6. Lacked sufficient diagnostic accuracy information.

Study Selection

Titles and abstracts were first screened to remove clearly irrelevant records. Full-text versions of potentially eligible articles were then reviewed in detail against the predefined inclusion criteria. Although the review protocol was not prospectively registered, the eligibility criteria, outcomes of interest, and statistical methods were defined before data extraction began. Two reviewers independently screened the titles and abstracts of retrieved articles to identify potentially relevant studies. Full-text articles were then evaluated according to the predefined inclusion and exclusion criteria. Any disagreements were resolved through discussion and consensus, and when necessary, a third reviewer was consulted to reach a final decision.

Data Extraction

Data extraction was performed independently using a standardized collection form. The following information was recorded for each study: first author, year of publication, country, study design, and clinical setting. Additional data included total sample size, diagnostic criteria used for sepsis and AKI, type of NGAL measured (serum/plasma or

urine), and the reported NGAL cutoff value. Across the included studies, the diagnostic criteria used to define sepsis varied and included Sepsis-3, Surviving Sepsis Campaign criteria, ACCP/SCCM definitions, and earlier consensus frameworks. Definitions of acute kidney injury were primarily based on KDIGO criteria, although some earlier studies applied AKIN or RIFLE classifications.

Serum and plasma NGAL measurements were analyzed together under the category of "serum NGAL," as these matrices have comparable analytical characteristics and are frequently used interchangeably in clinical studies. When multiple NGAL cutoff values were reported, the threshold identified by the study authors as the optimal diagnostic cutoff—typically based on receiver operating characteristic (ROC) analysis or Youden's index—was selected. If measurements were reported at multiple time points, the earliest clinically relevant value used for AKI prediction was extracted to ensure consistency across studies.

Diagnostic accuracy data were collected as true positives, false positives, false negatives, and true negatives. When these values were not directly reported, 2 × 2 contingency tables were reconstructed from the available sensitivity, specificity, and sample size information whenever possible.

Quality Assessment

The methodological quality of included studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. This framework assesses potential risk of bias across four domains: patient selection, index test, reference standard, and flow and timing. In addition, concerns regarding the applicability of each study to the review question were considered. Each domain was judged as having low, high, or unclear risk of bias based on predefined signaling questions.

Statistical Analysis

All statistical analyses were performed using RStudio (R Foundation for Statistical Computing, Vienna, Austria). Diagnostic meta-analyses were conducted using the mada and metafor packages. A bivariate random-effects model was used to jointly estimate pooled sensitivity and specificity while accounting for the correlation between these measures and potential heterogeneity among studies. Summary receiver operating characteristic (SROC) curves were constructed, and the area under the curve (AUC) was calculated to summarize overall diagnostic performance. The pooled diagnostic odds ratio (DOR) with 95% confidence intervals was also estimated using a random-effects model. Between-study heterogeneity was assessed using the Zhou and Dendukuri I^2 statistic, which extends conventional heterogeneity measures to bivariate diagnostic test accuracy models and incorporates the correlation between sensitivity and specificity.

Subgroup and Sensitivity Analyses

Prespecified subgroup analyses were conducted according to:

- Clinical setting (ICU vs. ED/ER)
- Leave-one-out sensitivity analyses were performed to evaluate the influence of individual studies on pooled estimates.

Publication Bias

Publication bias was assessed using Deeks' funnel plot asymmetry test. A P value < .10 was considered indicative of potential small-study effects.

RESULTS

Study Selection

The literature search identified 133 records in the PubMed database. No duplicate records were detected. After screening titles and abstracts, 101 studies were excluded for reasons such as non-human or mechanistic design, pediatric populations, absence of NGAL evaluation, non-sepsis cohorts, intervention studies, or lack of diagnostic accuracy outcomes. The remaining 32 articles underwent full-text review. Of these, 15 studies were excluded because they did not provide extractable diagnostic accuracy data, included mixed or non-sepsis populations, evaluated biomarker models without reporting standalone NGAL performance, or represented small pilot datasets with unstable estimates. Ultimately, 17 studies met the eligibility criteria and were included in the quantitative meta-analysis. The study selection process is summarized in Figure 1.

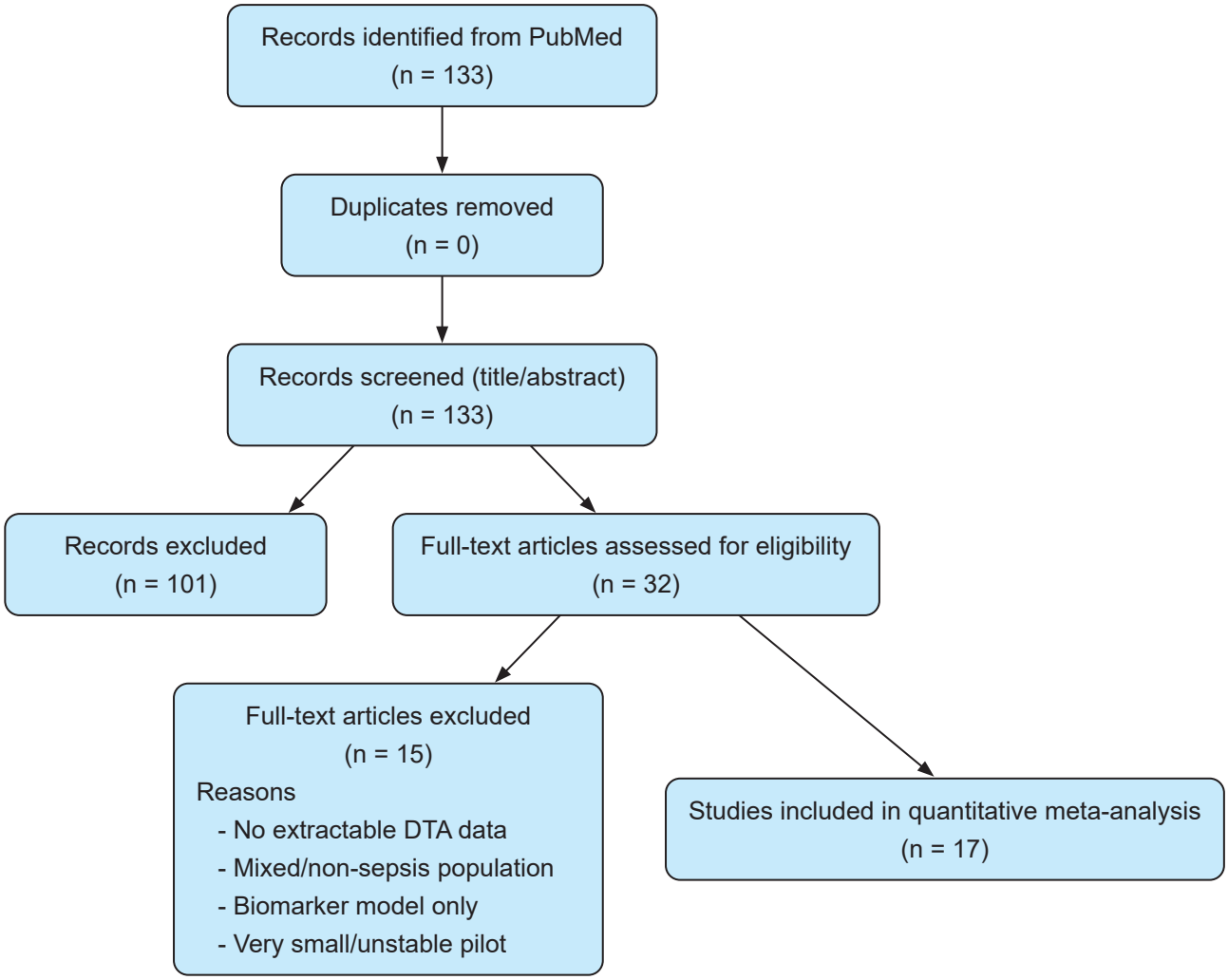


Figure 1. PRISMA flow diagram of the study selection process (A total of 133 records were identified through PubMed database searching. No duplicate records were found. After title and abstract screening, 101 records were excluded. Thirty-two full-text articles were assessed for eligibility, of which 15 were excluded for predefined reasons (no extractable diagnostic accuracy data, mixed/non-sepsis population, biomarker model only, or very small/unstable pilot studies). Ultimately, 17 studies met the inclusion criteria and were included in the quantitative meta-analysis)

Study Characteristics

A total of 17 studies published between 2010 and 2025 were included in the final analysis. These investigations were conducted across diverse geographic regions, including China, Korea, Brazil, Egypt, Malaysia, the Netherlands, Sweden, Turkey, the Czech Republic, Japan, and the United States. Most studies used a prospective design, although one retrospective study and one cross-sectional study were also included. The majority of studies were conducted in intensive care unit (ICU) settings, with several enrolling patients from emergency departments (ED) or emergency rooms (ER). Sample sizes varied substantially, ranging from 25 to 661 participants.

With respect to biomarker type, seven studies evaluated plasma NGAL, eight assessed urinary NGAL, and two reported both plasma and urine measurements. Studies reporting both sample types contributed separate datasets to the serum and urine analyses. NGAL cutoff values varied widely across studies, reflecting methodological heterogeneity. Detailed characteristics of the included studies are summarized in Table 1.

Diagnostic Accuracy of Serum NGAL

Nine datasets evaluating serum (plasma) NGAL were included in the pooled analysis. Using

Characteristics of the Studies Included in the Meta-analysis

Author	Year	Country	Design	Clinical Setting	Total Sample Size	AKI Cases	Non-AKI Cases	AKI Definition	Sepsis Definition	NGAL Type	Cut-off Value	Time of Measurement	Assay Method
Hu[40]	2022	China	Prospective	ICU	110	33	77	KDIGO	Sepsis-3	Urine	170 ng/mL	ICU admission, 24h, 48h, 72h (ROC at 24h)	Immunoturbidimetric assay (NORMAN-2 analyzer)
Klementa[41]	2024	Czech Republic	Prospective	ICU	46	31	15	KDIGO 2012	Sepsis-3	serum	290 ng/mL	Day 1, Day 7 (ROC at Day 1)	Immunoturbidimetric assay (BioPorto NGAL kit)
Kim[42]	2017	Korea	Retrospective registry study	ED/ICU	167	41	126	KDIGO	Surviving Sepsis 2012 / Sepsis-3 reclassified	Plasma	493 ng/mL	At enrollment (single timepoint)	Triage NGAL fluorescence immunoassay (Alere)
Nga[43]	2015	Brazil	Prospective	ER	168	121	47	AKIN	Surviving Sepsis 2012	Urine	3.36 ng/mg creatinine*	< 24 h after admission	ELISA
Zaitoun[44]	2024	Egypt	Prospective	ICU	166	100	66	KDIGO	Sepsis syndrome	Both	Serum = 250 ng/mL / Urine = 475 ng/mL	≤ 2 h after admission	ELISA (Bioassay Tech Lab)
Pei[45]	2022	China	Prospective	ED	162	60	102	KDIGO 2012	Sepsis-3	Serum	95.6 ng/mL	At admission (first time when sepsis diagnosed)	ELISA (Abcam kit)
Fan[46]	2014	China	Prospective	ICU	126	58	68	RIFLE	Sepsis consensus	Urine	402 ng/mL	Peak uNGAL during hospitalization	Polyclonal antibody-based radioimmunoassay (RIA)
Ralib[47]	2015	Malaysia	Prospective	ICU	129	67	62	KDIGO	ACCP/SCCM Sepsis	Plasma	454 ng/mL	Within 24 hours of ICU admission	ARCHITECT chemiluminescent microparticle immunoassay (CMIA)
Qiu[48]	2021	China	Prospective	ICU	90	44	46	KDIGO	Sepsis-3	Urine	181.71 ng/mL	At ICU admission	Legend Max™ ELISA kit (BioLegend)
de Geus[49]	2013	Netherlands	Prospective	ICU	75	50	25	AKIN	ACCP/SCCM	Plasma	304 ng/mL	ICU admission	Triage® immunoassay (Biosite/Alere)
Park[50]	2019	Korea	Retrospective	ED	85	19	66	KDIGO	Sepsis-3	Urine	359 ng/mL	At emergency department presentation	Chemiluminescent microparticle immunoassay (Abbott Architect analyzer)
Li[51]	2024	China	Prospective	ICU	80	40	40	KDIGO	Sepsis-3	Urine	155.19 ng/mL	12 h after admission	ELISA (Abcam kit)

Table continued

Author	Year	Country	Design	Clinical Setting	Total Sample Size	AKI Cases	Non-AKI Cases	AKI Definition	Sepsis Definition	NGAL Type	Cut-off Value	Time of Measurement	Assay Method
Teker[52]	2025	Türkiye	Cross-sectional	ICU	101	66	35	KDIGO	Sepsis-3	Serum	39.25 ng/mL	First day	Not reported
Martensson[53]	2010	Sweden	Prospective	ICU	25	18	7	RIFLE/ AKIN	ACCP/SCCM	Plasma & Urine	Plasma = 120 ng/mL / Urine = 68 ng/mL	Twice daily sampling starting at ICU admission	ELISA (BioPorto Diagnostics, Denmark)
Aydogdu[54]	2013	Turkey	Prospective	ICU	129	63	66	RIFLE	2001 Sepsis Definition	Urine	29.5 ng/mL	On admission	ELISA (Human Lipocalin-2/ NGAL ELISA BiovendorTM).
Shapiro[29]	2010	USA	Prospective multicenter	ED	661	24	637	Creatinine +0.5 mg/ dL	SIRS-based	Plasma	150 ng/mL	At ED presentation (time 0, before treatment)	Fluorescent point-of-care immunoassay (Triage NGAL Test; Biosite Diagnostics, San Diego CA)
Shimoyama[55]	2020	Japan	Prospective	ICU	44	20	24	KDIGO ≥ 1	Sepsis-3	Urine	438.5 ng/mL	Immediately after ICU entry (Day 1)	ARCHITECT uNGAL assay (Abbott Japan)

*The cutoff value “3.36 ng/mg creatinine” represents urine NGAL normalized to urine creatinine concentration (uNGAL/Cr ratio).
Note: The table summarizes the main characteristics of the 17 studies evaluating NGAL for the early detection of AKI in patients with sepsis. Reported variables include the first author and publication year, country, study design, clinical setting, total sample size, number of AKI and non-AKI patients, definitions used for AKI and sepsis, type of NGAL measured (serum/plasma or urine), diagnostic cut-off values (ng/mL), timing of biomarker measurement, and the assay methods used for NGAL determination.

random-effects meta-analysis models, the pooled sensitivity was 0.77 (95% CI: 0.63 to 0.86) and the pooled specificity was 0.68 (95% CI: 0.52 to 0.80) (Figure 2A and 2B).

The summary receiver operating characteristic (SROC) curve demonstrated an area under the curve (AUC) of 0.773 (Figure 3), indicating moderate diagnostic performance for predicting sepsis-associated acute kidney injury. The pooled diagnostic odds ratio (DOR) was 6.15 (95% CI: 4.38 to 8.64), indicating that patients who developed AKI had over six times higher odds of elevated serum NGAL levels compared with those who did not develop AKI.

Between-study heterogeneity was moderate according to the Zhou and Dendukuri I^2 statistic (I^2 = 43.2%), suggesting that a moderate proportion of the variability across studies reflects true differences rather than chance. Leave-one-out sensitivity analysis showed that removal of any individual study did not meaningfully change the pooled sensitivity, specificity, or DOR estimates

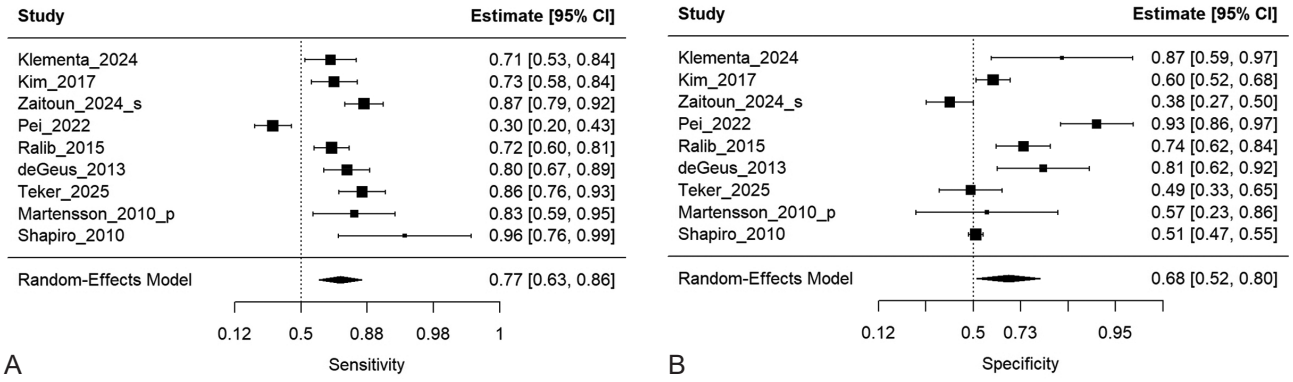


Figure 2. A) Forest Plot of Pooled Sensitivity for Serum/Plasma NGAL (Forest plot showing the sensitivity estimates of individual studies and the pooled sensitivity of serum/plasma NGAL for the detection of AKI in patients with sepsis. Each square represents the sensitivity estimate for an individual study, and the horizontal lines indicate the corresponding 95% confidence intervals (CIs). The size of the square reflects the relative study weight. The diamond represents the pooled sensitivity estimated using a bivariate random-effects model (pooled sensitivity = 0.77, 95% CI: 0.63 to 0.86)). B) Forest Plot of Pooled Specificity for Serum/Plasma NGAL (Forest plot showing the specificity estimates of individual studies and the pooled specificity of serum/plasma NGAL for the detection of AKI in patients with sepsis. Squares represent study-specific estimates, and horizontal lines indicate the corresponding 95% confidence intervals (CIs). The diamond represents the pooled specificity derived from the bivariate random-effects model (pooled specificity = 0.68, 95% CI: 0.52 to 0.80)).

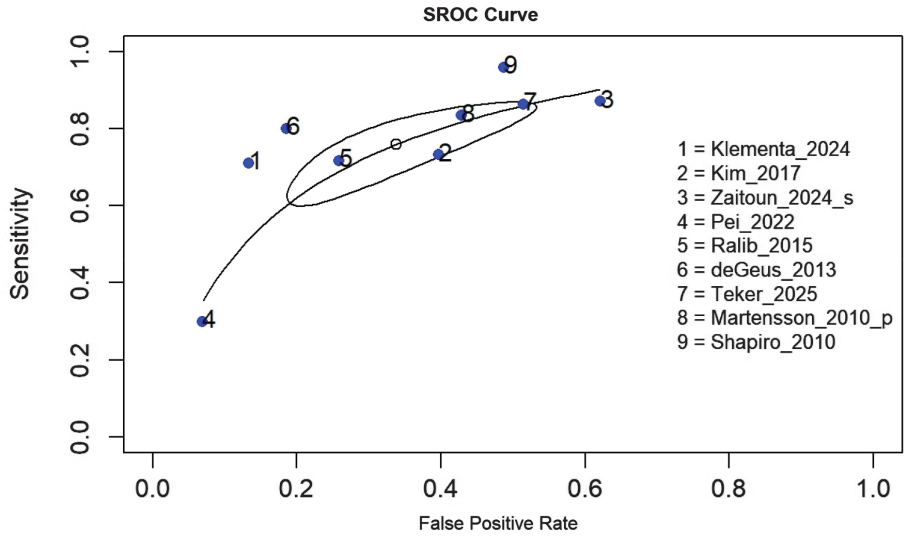
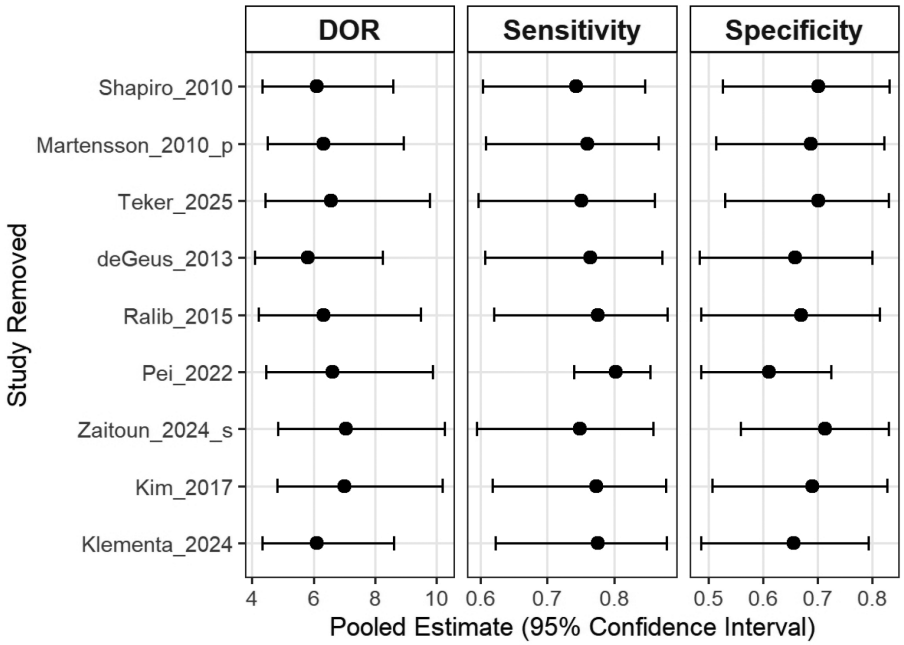


Figure 3. Summary ROC (SROC) Curve for Serum/Plasma NGAL (The SROC curve illustrates the overall diagnostic performance of serum/plasma NGAL for the detection of sepsis-associated AKI (Each point represents an individual study included in the meta-analysis. The solid curve represents the summary ROC estimated using the bivariate random-effects model, while the ellipse indicates the 95% confidence region around the summary operating point).



Supplementary Figure 1. Leave-one-out Analysis Showing the Change in Pooled Diagnostic Odds Ratio, Sensitivity, and Specificity After Sequential Removal of Each Individual Study (Excluding any single study did not materially alter the pooled estimates, indicating robust serum NGAL results).

(Supplementary Figure 1), indicating that the overall results were stable. The regression test for funnel plot asymmetry conducted on the serum/plasma NGAL studies indicated statistically significant evidence of potential publication bias (z = 2.03, P = .042). This suggests that small-study effects may have influenced the pooled diagnostic odds ratio for serum/plasma NGAL. The limit estimate of the intercept as the standard error approaches zero was 0.81 (95% CI: -0.24 to 1.87), indicating some degree of asymmetry in the funnel plot (Figure 4).

Diagnostic Accuracy of Urine NGAL

Ten datasets evaluating urinary NGAL were

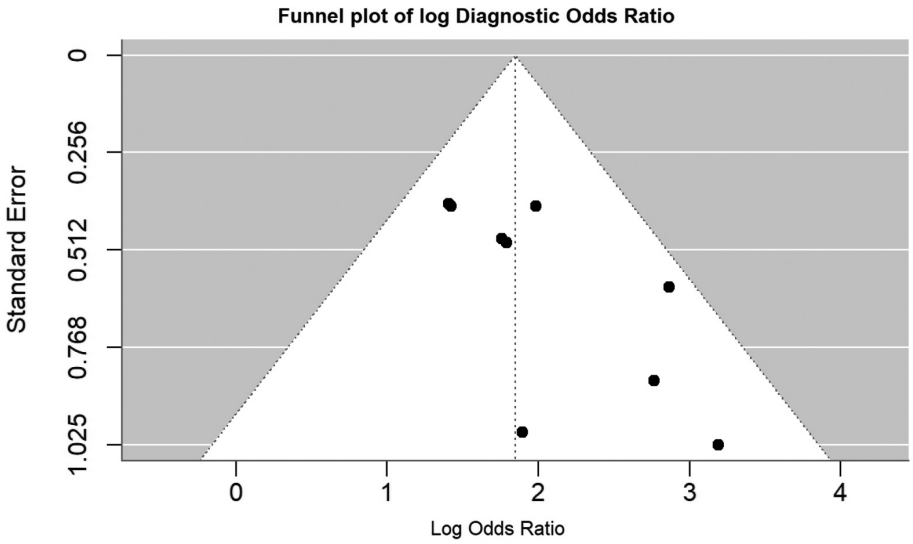


Figure 4. Funnel Plot of the Log Diagnostic Odds Ratio (DOR) Versus Standard Error for Studies Evaluating Serum/Plasma NGAL in Predicting Sepsis-associated AKI (Each point represents an individual study; the vertical dashed line indicates the pooled log DOR and the triangular region represents the expected 95% confidence limits. Deeks' regression test suggested significant funnel plot asymmetry (z = 2.03, P = .042), indicating potential publication bias.

included in the pooled analysis. The random-effects model yielded a pooled sensitivity of 0.75 (95% CI: 0.66 to 0.82) and a pooled specificity of 0.71 (95% CI: 0.64 to 0.78) (Figure 5A and 5B).

The SROC analysis produced an AUC of 0.782 (Figure 6), again indicating moderate diagnostic accuracy for predicting sepsis-associated acute kidney injury. The pooled diagnostic odds ratio (DOR) for urinary NGAL to predict acute kidney injury was 7.12 (95% CI: 4.17 to 12.16), suggesting that patients with AKI had over sevenfold higher odds of elevated urinary NGAL compared to those without AKI.

Between-study heterogeneity was low to moderate according to the Zhou and Dendukuri I^2 estimate (I^2 = 19.6%). Leave-one-out sensitivity analysis demonstrated that the pooled estimates remained stable when individual studies were excluded (Supplementary Figure 2). Regression test of funnel plot asymmetry for urine NGAL showed no statistically significant evidence of publication bias (z = 1.73, *P* = .08), suggesting the pooled diagnostic odds ratios are unlikely distorted by small-study effects (Figure 7).

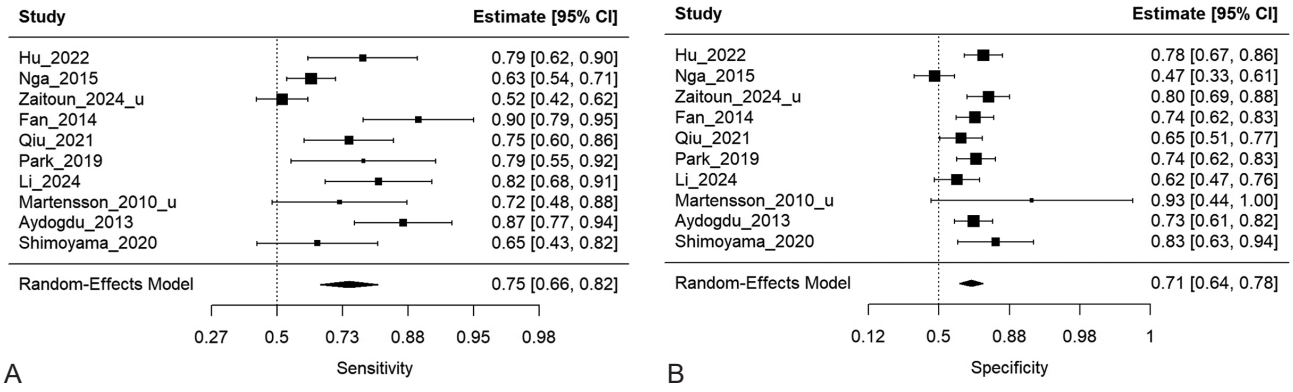


Figure 5. A) Forest plot displaying the sensitivity estimates of individual studies evaluating urinary NGAL for the detection of sepsis-associated AKI. Each square represents a study-specific estimate, with horizontal lines indicating 95% confidence intervals (CIs). Square size reflects the relative weight of each study. The diamond at the bottom depicts the pooled sensitivity derived from the bivariate random-effects model (pooled sensitivity = 0.75, 95% CI: 0.66 to 0.82). B) Forest plot showing the specificity estimates of individual studies assessing urinary NGAL for predicting sepsis-associated AKI. Study-specific estimates are shown as squares with 95% CIs indicated by horizontal bars. The size of each square corresponds to the study weight. The pooled specificity calculated using the bivariate random-effects model is shown as a diamond (pooled specificity = 0.71, 95% CI: 0.64 to 0.78).

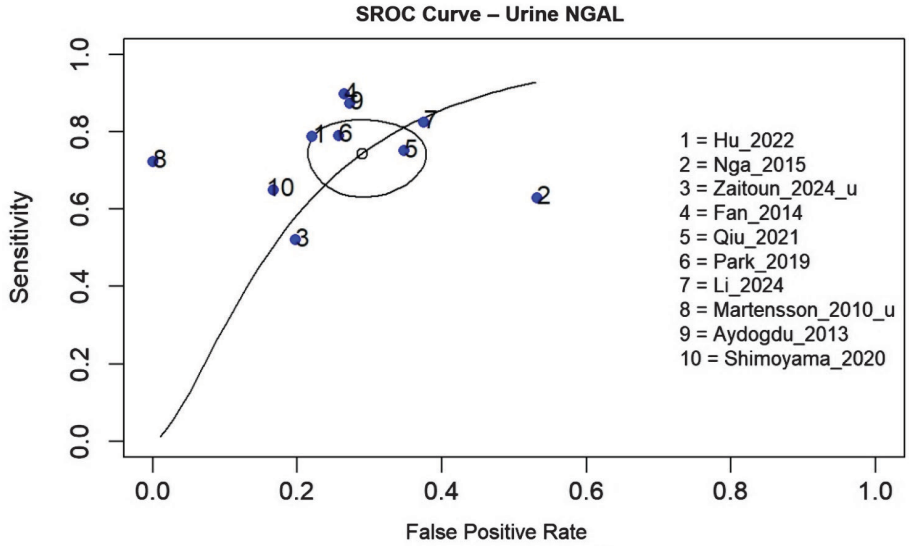
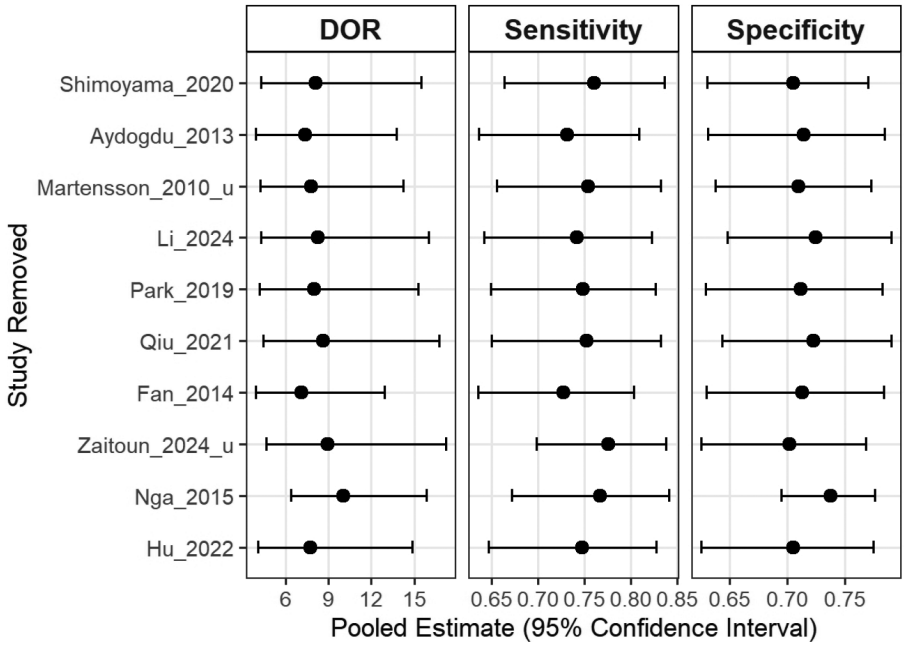


Figure 6. Summary ROC (SROC) Curve Depicting the Overall Diagnostic Performance of Urinary NGAL for Identifying Sepsis-associated AKI (Each point represents an individual study from the meta-analysis. The solid curve shows the summary ROC estimated using a bivariate random-effects model, and the ellipse indicates the 95% confidence region around the summary operating point).



Supplementary Figure 2. Leave-one-out Analysis Evaluating the Influence of Individual Studies on Pooled Urinary NGAL Diagnostic Performance (Sequential study exclusion produced minimal changes in sensitivity, specificity, and diagnostic odds ratio, demonstrating strong robustness of the urinary NGAL findings).

Subgroup Analyses

Clinical Setting.

Serum NGAL

In ICU populations (6 studies), serum NGAL demonstrated a pooled sensitivity of 0.80 (95% CI: 0.73 to 0.86) and a pooled specificity of 0.64 (95% CI: 0.46 to 0.79). The summary ROC curve showed an AUC of 0.81, indicating good diagnostic accuracy. Between-study heterogeneity was negligible (I^2 = 0In non-ICU settings (3 studies), including emergency department and mixed ED/ICU populations, serum NGAL demonstrated a

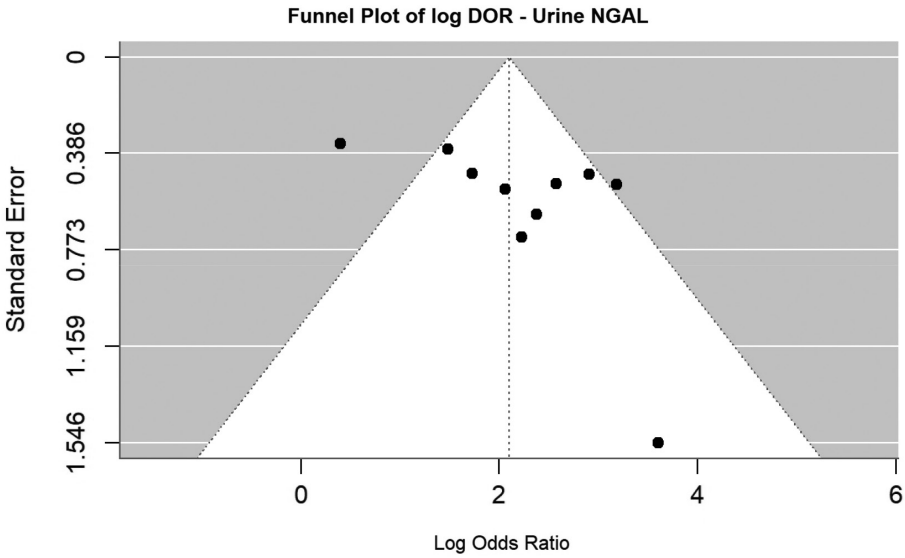


Figure 7. Funnel Plot of the Log Diagnostic Odds Ratio (DOR) Against Its Standard Error for Studies Evaluating Urinary NGAL in the Detection of Sepsis-associated AKI. Each point represents an individual study, with the vertical dashed line indicating the pooled log DOR and the triangular region representing the expected 95% confidence limits in the absence of publication bias. Visual inspection demonstrated no substantial asymmetry, and Deeks' regression test did not indicate statistically significant publication bias.

pooled sensitivity of 0.66 (95% CI: 0.28 to 0.90) and a pooled specificity of 0.73 (95% CI: 0.38 to 0.92). The summary ROC analysis yielded an AUC of 0.75, indicating moderate diagnostic accuracy. Between-study heterogeneity was minimal ($I^2 \approx 0\%$), although interpretation is limited by the small number of studies and wide confidence intervals

Urinary NGAL

In ICU populations (n = 8), urinary NGAL demonstrated a pooled sensitivity of 0.76 (95% CI: 0.65 to 0.84) and a pooled specificity of 0.74 (95% CI: 0.69 to 0.79). The summary ROC analysis yielded an AUC of 0.78, indicating moderate diagnostic accuracy. Between-study heterogeneity was low ($I^2 \approx 0\%$)."

In ED/ER settings (n = 2), urinary NGAL demonstrated a pooled sensitivity of 0.71 (95% CI: 0.51 to 0.85) and a pooled specificity of 0.62 (95% CI: 0.33 to 0.84), with an area under the curve (AUC) of 0.719. Due to the small number of included studies, these findings should be interpreted with caution.

DISCUSSION

In this systematic review and meta-analysis of adult patients with sepsis, both serum and urinary NGAL showed moderate accuracy for predicting sepsis-associated acute kidney injury (SA-AKI). Serum NGAL demonstrated a pooled sensitivity of 0.77 and specificity of 0.68, corresponding to an AUC of 0.773. Urinary NGAL showed slightly stronger overall diagnostic performance, with pooled sensitivity of 0.75, specificity of 0.71, and an AUC of 0.782. The pooled diagnostic odds ratio was also somewhat higher for urinary NGAL (7.12) than for serum NGAL (6.15), indicating modestly better overall performance. Subgroup analyses suggested that diagnostic performance was improved in ICU populations. Taken together, these findings support the concept that NGAL reflects evolving tubular stress and inflammatory injury during the progression of sepsis.

From a clinical standpoint, an AUC approaching 0.78 indicates that NGAL provides meaningful, though not definitive, diagnostic discrimination for early detection of SA-AKI. In practice, biomarkers with this level of performance are often most useful for early risk stratification rather than for establishing a definitive diagnosis. This may be particularly relevant in patients with evolving renal dysfunction, where serum creatinine changes often occur relatively late in the course of injury.

Our results are broadly consistent with prior large meta-analyses reporting moderate diagnostic performance of NGAL for AKI detection across diverse patient populations. Haase *et al.* reported pooled AUC values between 0.75 and 0.80 for NGAL among critically ill and surgical patients.[17] Bagshaw *et al.* observed higher NGAL concentrations in septic AKI compared with non-septic AKI, although overall diagnostic discrimination remained moderate.[20] Similarly, Shapiro *et al.* found that plasma NGAL provided moderate predictive value for AKI in emergency department patients with suspected sepsis.[29] The present analysis aligns with these findings, with pooled AUC values of 0.773 for serum NGAL and 0.782 for urinary NGAL, while incorporating more recent datasets and performing structured subgroup analyses.

The biological rationale for NGAL as an early biomarker of SA-AKI is well established. NGAL is released from renal tubular epithelial cells in response to ischemic and inflammatory injury and is also produced by activated neutrophils during systemic inflammation. In sepsis, microcirculatory disturbances, cytokine activation, and endothelial dysfunction can lead to early tubular stress before measurable changes in serum creatinine occur.[7] This pathophysiological sequence supports the potential value of NGAL as an early marker of kidney injury. At the same time, NGAL expression increases in systemic inflammatory states even in the absence of direct renal injury, which may limit specificity in septic populations.[30] This inflammatory confounding may partly explain the moderate specificity observed in the present pooled analyses, particularly for serum NGAL.

Sepsis-associated AKI remains strongly linked to increased morbidity and mortality.[1] Current KDIGO diagnostic criteria rely primarily on serum creatinine and urine output, both of which may lag behind the onset of structural kidney injury.[8] The findings of this study suggest that NGAL—particularly urinary NGAL—may serve as a useful

adjunct for early risk stratification in critically ill patients. However, the moderate specificity and variability in reported assay thresholds indicate that NGAL should not be used as a standalone diagnostic test. Instead, it is likely to be most informative when interpreted alongside clinical assessment and established diagnostic criteria.

Methodologically, this meta-analysis employed a bivariate random-effects model, which accounts for the inherent correlation between sensitivity and specificity and is widely recommended for diagnostic accuracy studies.[31,32] Reporting followed PRISMA-DTA guidance,[33,34] and risk-of-bias considerations were informed by QUADAS-2 principles.[35] Deeks' funnel plot asymmetry test suggested potential publication bias for serum NGAL (P = .042), whereas no statistically significant asymmetry was observed for urinary NGAL (P = .08). However, diagnostic meta-analyses that include fewer than 20 studies have limited statistical power to detect publication bias; therefore, these findings should be interpreted with caution.[36]

Across the included studies, reported NGAL cut-off values for predicting SA-AKI varied widely. Serum or plasma NGAL thresholds ranged approximately from 40 to nearly 500 ng/mL, while urinary NGAL cut-offs ranged from about 30 to over 400 ng/mL. This substantial variability likely reflects differences in assay platforms, timing of sample collection, patient populations, and AKI definitions across studies. Consequently, these values cannot be interpreted as universal diagnostic thresholds. In clinical practice, NGAL measurement may be most useful in several scenarios, including septic ICU patients with early oliguria, cases in which creatinine kinetics are unclear, and situations where rapid AKI risk stratification is required. Integration of NGAL measurements with KDIGO criteria or sepsis management bundles could potentially facilitate earlier nephrology consultation or more timely adjustment of fluid and vasopressor management.

An important consideration when evaluating novel biomarkers is whether earlier detection translates into improved clinical outcomes. Although NGAL has been shown to detect acute kidney injury several hours earlier than serum creatinine, current evidence mainly demonstrates improved diagnostic performance rather than clear reductions in mortality or long-term renal outcomes. Most studies evaluating NGAL have focused on diagnostic accuracy rather than biomarker-guided therapeutic interventions. Nevertheless, earlier identification of patients at risk for SA-AKI may facilitate closer hemodynamic monitoring, earlier nephrology consultation, and more timely adjustment of fluid management and nephrotoxic medications.[17,37,38]

Practical issues also influence the clinical applicability of NGAL testing. The cost of biomarker assays and the availability of standardized laboratory platforms may limit widespread implementation. In addition, variability among assay methods—including ELISA-based laboratory tests and automated immunoassays—can lead to differences in measured NGAL levels and reported diagnostic thresholds across studies. Although point-of-care NGAL assays have been developed and may provide faster results in emergency or intensive care settings, broader clinical adoption will likely depend on improved assay standardization, cost-effectiveness, and integration into routine laboratory workflows.[21,26,39]

LIMITATIONS

Several limitations should be considered when interpreting these findings. First, variability in the definitions of AKI (KDIGO, AKIN, and RIFLE) and sepsis (Sepsis-3 versus earlier criteria) may have introduced clinical heterogeneity across studies.[1,8] Second, NGAL cutoff values and assay platforms varied substantially among studies, potentially contributing to threshold effects. Third, subgroup analyses for emergency department settings and delayed-measurement cohorts were based on relatively small numbers of studies, which may limit the robustness of these estimates. Fourth, NGAL levels can increase in systemic inflammatory conditions independent of kidney injury, potentially reducing diagnostic specificity in septic populations.[30] Fifth, the literature search was primarily conducted in PubMed, and although reference lists were manually screened, relevant studies indexed exclusively in other databases such as Embase or Web of Science may have been missed. Finally, the wide variation in reported

diagnostic thresholds prevented the identification of a universally applicable NGAL cutoff value.

CONCLUSIONS

Both serum and urinary NGAL demonstrate moderate diagnostic accuracy for the prediction of sepsis-associated acute kidney injury. Urinary NGAL showed slightly better discriminatory performance than serum NGAL, particularly in ICU settings. However, given the variability in assay methods, diagnostic thresholds, and study populations, NGAL should be considered an adjunctive biomarker within established KDIGO-based diagnostic frameworks rather than a standalone diagnostic test. Further large-scale prospective studies using standardized assay platforms, consistent cutoff values, and clearly defined sampling time points are required to better define its clinical utility in the early detection of sepsis-associated AKI.

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.

CONFLICT OF INTEREST

Ilad Alavi Darazam and Amir Ahmad Nassiri serve as members of the RJCCN editorial team. The authors had no involvement in the peer-review or editorial decision-making processes for this manuscript.

FUNDING

This study received no specific funding from public, commercial, or not-for-profit 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.

A.A.N. Conceptualization, Supervision, Manuscript review

I.A.D. Conceptualization, Supervision, Manuscript review & editing and Correspondence with journal

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Received February 2026
Revised March 2026
Accepted April 2026

Kidney Health for All: Caring for People, Protecting the Planet

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The current kidney care model—focused on late-stage disease and in-center hemodialysis—is unsustainable, because of costs, environmental burden, poor outcomes, and reduced quality of life. The 78th World Health Assembly's recognition of kidney disease as a serious health threat presents a critical opportunity to reshape kidney care. Aligned with this, the 2026 World Kidney Day theme, "Kidney Health for All: Caring for People, Protecting the Planet," calls for a systematic change. A sustainable model must prioritize early detection and prevention, reducing the need for kidney replacement therapy. Transplantation and home dialysis benefit people with kidney failure, environment, and society. Dialysis itself must become more ecofriendly without compromising care quality, recognizing that planetary perturbations in turn affect kidney health. Conservative care should also be considered, particularly for elderly and frail patients, if the quality-of-life benefits outweigh the perspectives offered by dialysis. Achieving this shift requires coordinated action across all stakeholders; education and engagement of the public, policy makers, and health professionals to raise awareness about the threat of kidney disease; and an urgent move toward patient-centered care.

RJCCN 2026; 2: 149-60
www.rjccn.org
DOI: 10.66224/rjccn.2.2.44

Keywords. environment, green nephrology, prevention, screening, sustainable kidney care, World Kidney Day

INTRODUCTION

Chronic kidney disease (CKD) is[1] of the most common noncommunicable dis eases globally,[1,2] linked to significant comorbidities, particularly cardiovascular dis ease; premature mortality; societal costs; reduced productivity; and a considerable environmental footprint.[3] CKD disproportionately affects disadvantaged

Please cite this article as: Vanholder R, Abdellatif D, Cesar Soares Dos Santos Jr A, Correa-Rotter R, Gopalakrishnan N, Wang B, Roumeliotis S, Balducci A, Haris A´, Yadla M, Hsiao L. Kidney Health for All: Caring for People, Protecting the Planet. RJCCN. 2026;2(2):149-60.

populations and minority groups.[4] Advanced CKD causes distressing symptoms, social isolation, and, in children, growth and development delays. Despite its wide-ranging impact, CKD remains underrecognized as a global health threat. Recently, CKD's profile was raised by the World Health Organization Resolution on Kidney Health, approved at the 78th World Health Assembly.[5] The Resolution urges governments to integrate prevention, early detection, and management of kidney disease into national noncommunicable disease strategies, and to expand access to equitable, sustainable, high-quality kidney including dialysis, care, progressively transplantation, and conservative care within universal health coverage. In addition, World Kidney Day (WKD) was acknowledged as key for raising public awareness and promoting kidney health. Sponsored and championed by Guatemala, the Resolution marked a pivotal step in establishing kidney disease as a global health priority. Guatemala's leadership was pivotal in mobilizing broad support, particularly from those countries most affected by the growing burden of CKD and care access inequities. It also recognized the strong influence of environmental factors on kidney health, high lighting the disproportionate impact of climate change on developing countries and small island States, as emphasized in the 77th WHA Resolution (see below). These milestones form the policy foundation for the 2026 WKD theme, "Kidney Health for All: Caring for People, Protecting the Planet," which underscores the need to safe guard kidney health, to address the environ mental effect on kidney health but also of kidney care on the environment, and to pivot health care models from a focus on late-stage treatment to early risk reduction and detection (Figure 1). This editorial calls for urgent, integrated action across early detection, prevention, equitable care, and environmental steward ship to advance both kidney and planetary health (Table 1),[6] underscoring the need for a more sustainable kidney care model with prevention and eco-friendliness as 2 main pillars (Figures 1 and 2),[6] to which all other attention points are linked. We offer a general outline of measures that can be taken by communities and governments, although it is merely impossible

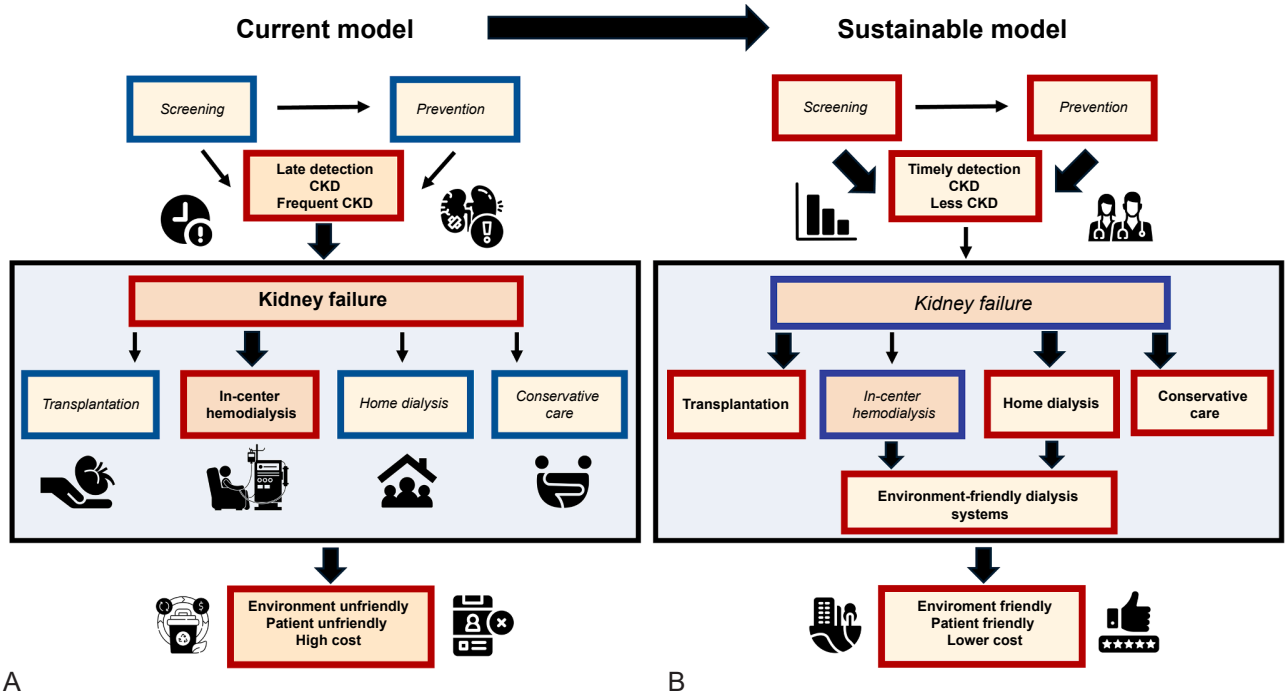

Figure 1. A) Current model of kidney care. B) Sustainable model of kidney care. Elements that are less or insufficiently prominent in that specific model are in italics with a blue frame; elements that are prominent in a specific model are in bold with a red frame. Yellow background indicates if beneficial for sustainability, and orange background indicates disadvantageous. Light blue–shaded box with black frame is used for kidney replacement therapy. The thickness of the arrows indicates the degree of impact on the following element. CKD, chronic kidney disease; home dialysis, peritoneal dialysis and/or home hemodialysis.

Different actions to make kidney care sustainable, according to the topic and target

Topic	Target population	Action
Prevention	People with diabetes	- Timely diagnosis - Adequate treatment
	People with hypertension	- Timely diagnosis - Adequate treatment
	Lifestyle errors jeopardizing kidney function	- Promote healthy lifestyle and offer advice for correction (e.g., no smoking, sedentarism, nutrition errors, and alcohol consumption) - Limit exposure to nephrotoxins - Health-promoting taxation (e.g., salt, sugar, or fat taxes) - Education campaigns
	Unfavorable living conditions; difficulties to reach quality care	- Correct living conditions (e.g., social measures to reduce insufficient cooling of buildings, food insecurity, and poverty) - Correction of inequities (e.g., ethnic/gender disparities [gender refers to social or cultural rather than biological identity], health illiteracy, discrimination, and disadvantages of remote areas)
Early detection	People with risk factors of CKD General population aged > 45 yr	- Urine testing - Albuminuria testing - Screa/eGFR - Screening for CKD risk factors (mainly hypertension, diabetes, cardiovascular disease, and obesity) - Education of public and caregivers - Ensure that appropriate therapy reaches all valid candidates
Environmental kidney threats	Global warming	- Urgent: decrease GHG emission - Adapt working conditions (adapt hydration and protection against pollution and nephrotoxins) - Adapt living conditions (building cooling and greenery)
	Floods, hurricanes, and typhoons	- Urgent: decrease GHG emission - Prevent floods - Avoid diseases propagated by floods (e.g., malaria and dengue) - Ensure safe water storage - Forestall water contamination risks in flood-prone areas
	Fine particulate matter pollution	- Decrease and prevent generation of fine particulate matter (industry, transport, and forest fires) - Minimize pollution and particulate matter release
Transplantation	Promotion of organ donation	- Provide clear guidelines on organ donation and transplantation - Act against donor and recipient exclusion based on questionable criteria - Stimulate application of all donor types (deceased, living, and after cardiac death) - Promote preemptive transplantation - Technical and institutional support on organization transplantation programs in areas with poor transplantation rates - Guidelines on how to react to paid donation - Education, press campaigns, and social media campaigns
	Promotion of organ transplantation	- Provide clear guidelines on organization of organ donation and transplantation programs - Technical and institutional support for organization transplantation programs - Education - Press and social media campaigns
	Declining graft function over time, post- transplantation complications	- Research and innovation to improve graft longevity (e.g., organ preservation, immunosuppression, and antifibrosis approaches)
Dialysis	Ecofriendly dialysis[a]	- Transparency about manufacturing and transport emissions - Spent dialysate and RO reject recycling - Decrease manufacturing and transport emissions - Register and diminish emissions at unit level - Recycling material - Decrease water wastage - Waste triage - Peritoneal dialysis - Home hemodialysis
	Simpler and more compact dialysis systems	- Peritoneal dialysis - Research and innovation

Table continued

Topic	Target population	Action
Comprehensive conservative care	Preserve quality of life, particularly in frail and elderly patients	- Discuss possibility of conservative care with patients - Shared decision-making - Awareness creation among candidates for KRT and health professionals
Patient empowerment	All people with CKD	- Promote correct and appropriate information delivery to all KRT candidates - Shared decision-making - Facilitate patient-friendly units and hospitals - Nurse involvement in patient contacts - Kidney care discussion groups - Patient involvement in research and registries - Patient training in communication skills
Kidney care in crises	All people with CKD All crisis situations All crisis-prone countries and regions	- Inclusion of kidney care in crisis preparedness plans - Awareness creation among authorities - Development of less resource-dependent therapies - Development of own disaster preparedness plans if kidney care is excluded from official plans
Advocacy	Entire community involved in kidney care	- Awareness creation about kidney health and burden of kidney disease at all society levels - Education and information

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GHG, greenhouse gas; KRT, kidney replacement therapy; RO, reverse osmosis; Screa, serum creatinine. a For more details, see Figure 2 and the study by Vanholder et al. 6
The table summarizes several examples but is not exhaustive.

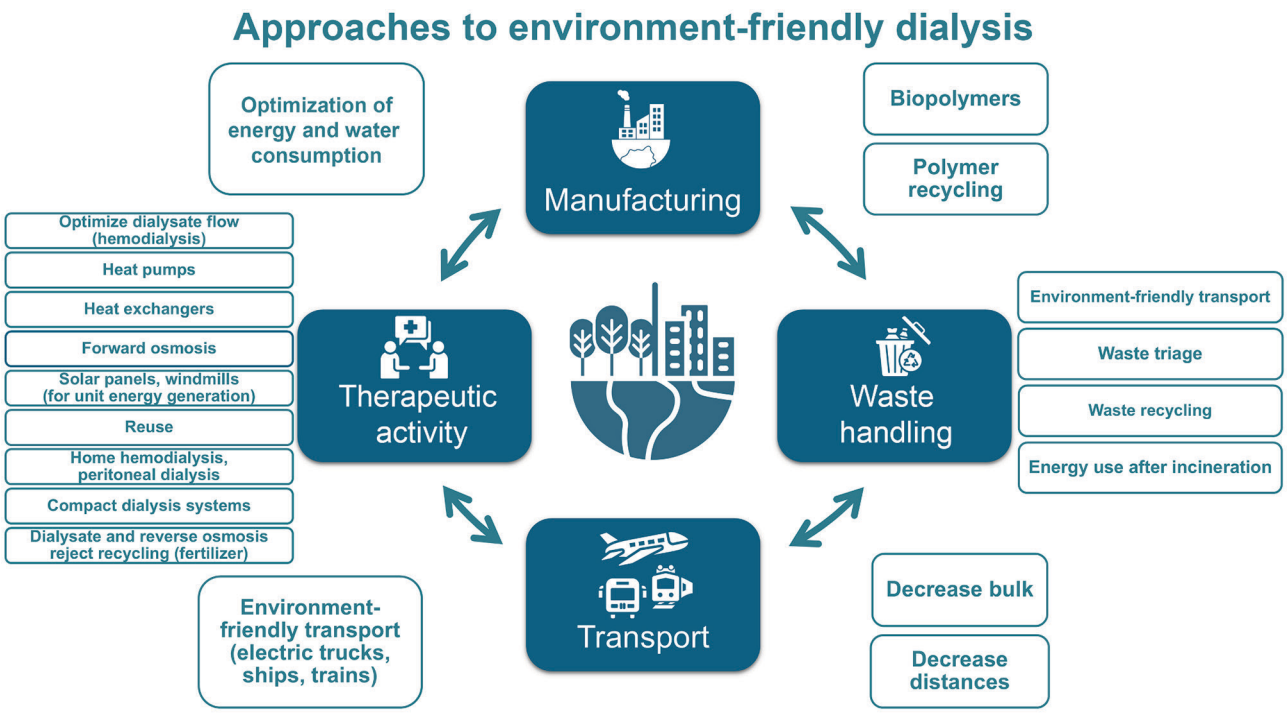

Figure 2. Approaches toward environment-friendly dialysis, categorized for manufacturing, transport, therapeutic activity, and waste handling. The list is not exhaustive. For more detailed lists, see the study by Vanholder et al. 6 Environment friendliness should not be pursued at the expense of patient quality of life or clinical status. Compact dialysis systems consume less water or recycle dialysate over sorbents.

to propose a ready-made outline that fits all. Kidney health plans need to be developed, aiming for a sustainable model, but might necessitate adaptations depending on the local possibilities and circumstances.

PREVENTION: THE FOUNDATION OF KIDNEY HEALTH

Beyond general primary and secondary preventive measures for all kidney conditions, prevention may require targeted therapies,

including rare kidney diseases.[7] Diabetes and hypertension—the leading causes of CKD—remain widely underdiagnosed and undertreated.[8] Kidney function is further compromised by modifiable lifestyle factors, including smoking, unhealthy nutritional habits (notably, excess sugar and salt), alcohol use, obesity, exposure to nephrotoxins, physical inactivity, exposure to heat, environmental pollution, and agrochemicals. Addressing these could significantly reduce the CKD burden.[9] Prevention is beneficial across all country wealth levels but is especially critical where costly CKD therapies are inaccessible or inadequately reimbursed, resulting in premature death and catastrophic out-of-pocket health expenditures.

A shift toward prevention as the corner stone to sustainable kidney care calls for simple, yet effective, public health strategies, such as promoting healthy diets or introducing health-oriented taxation (e.g., salt, sugar, or fat taxes).[9] Currently, governments invest mani fold more in cure than in prevention, and a more balanced distribution among both fac tors is needed. Several governments take steps in that direction, sometimes in the context of a global cardiovascular health plan, but approaches differ depending on the local conditions.

WKD promotes Eight Golden Rules for kidney health—simple, actionable lifestyle measures:[10] regular physical activity, healthy diet, adequate hydration, blood glucose control, blood pressure management, avoiding smoking, using medications as prescribed, and regular kidney function testing. These principles provide a framework for kidney health promotion across populations and health care settings. Because unfavorable living conditions and difficulties to reach quality care have a negative impact on outcomes of noncommunicable diseases, including CKD,[11] prevention must also address social dimensions. These include food insecurity, poor food quality, poverty, remoteness (rural vs. urban), inadequate access to services, red lining, unfavorable living conditions (unhygienic and unsafe housing, inadequate building cooling, and polluted living areas), and lack of neighborhood greenery. Public understanding of how the kidney functions and its threats is poor. Informative campaigns, like the European Renal Association's ABCDE initiative, highlighting albuminuria, blood pressure, cholesterol, diabetes, and estimated glomerular filtration rate as key warning signs, should be widely disseminated.[12] The public is to be encouraged to ask their primary care providers about these fac tors, like people currently do for their glucose and cholesterol. However, educational outreach often misses those at highest risk of CKD: individuals with limited health literacy, language or cultural barriers, or lower socioeconomic status. Tailored approaches (videos, social media campaigns, and cartoons) are vital to reach these deprived populations regarding all aspects and levels of CKD.

EARLY DETECTION: A CRITICAL, UNDERUTILIZIED TOOL

CKD symptoms typically emerge at advanced stages, when therapies often only can delay, not prevent, kidney failure.[13,14] Serum creatinine remains the most widespread marker for routine assessment and monitoring of CKD but lacks sensitivity for early detection,[15] although this is essential to timely and effectively prevent progression. Albuminuria stands out as a simple, low-cost, and reliable early indicator of kidney microvascular damage and CKD, but also of related conditions, such as hypertension, diabetes, and dyslipidemia.[16] However, urinary screening assessments, including albuminuria checks, are rarely per formed, even in well-developed health care systems.[17] Albuminuria testing can thus detect hidden cases across the entire cardio-kidney-metabolic spectrum,[16] serving as an alarm for conditions that, if untreated, lead to irreparable organ damage, including the kidneys. The progression of all conditions thus detected can be decelerated therapeutically, with the potential to reduce the pressing individual and societal burden of CKD and kidney failure. Modeling suggests that population-wide timely albuminuria screening and treatment could lower the lifetime incidence of dialysis or trans plantation by 21.8% and of cardiovascular disease by 12%.[18,19] Implementing universal screening from age 45 years or even 35 years onward has been suggested to enhance cost effectiveness and health care resilience.[18] Programs like the US Kidney Disease Screening and Awareness Program help to promote early screening and detection of CKD.[20] In addition,

kidney disease should be a central attention point also outside nephrology, particularly in diabetes, hypertension, cardiovascular disease, and obesity, as a negative outcome accelerator in these conditions.[21,22] Underlining this threat needs continued advocacy of the nephrological community,[23] particularly as there are now several novel therapies to delay progression.[24] For screening to have impact, it must be paired with education of the public and of frontline providers, such as general practitioners, nurses, pharmacists, and, particularly in low resource settings, community health workers. Detection of CKD and its risk factors should be followed by effective therapies, given their wide-ranging benefits, but these should be made universally accessible and affordable. Despite its growing burden, awareness and early detection of CKD remain limited in low and middle-income countries. A 2024 pilot study in high-risk groups in India reported 60% prevalence but extremely low awareness (16.5% in rural areas, 1.4% in urban areas).[25] In Brazil, serum creatinine and albuminuria testing remains below recommended levels, limiting early CKD detection and opportunities for timely intervention.[26] These gaps underscore the urgent need to integrate essential screening tests, like albuminuria and serum creatinine, into routine primary care, especially in regions where people often present with advanced disease.

ENVIRONMENTAL RISKS: AN EMERGING CHALLENGE FOR KIDNEY HEALTH

We are witnessing rapid environmental and climatologic changes with profound health consequences. The kidneys—which are central to maintaining volume homeostasis—are especially vulnerable for these shifts. Global warming raises the risk of heat stress and dehydration, which are major contributors to acute kidney injury and kidney stone development,[27,28] and eventually progression to CKD.[29] Outdoor workers exposed to extreme heat are particularly at risk, especially when hydration is inadequate or working conditions are insufficiently adapted, as in Mesoamerican nephropathy, a rapidly progressing form of CKD identified in agricultural workers in (sub)tropical climates.[30] Climate change also intensifies extreme weather events, such as floods, hurricanes, and typhoons. These, combined with the rising temperatures, increase the spread of tropical diseases, like malaria or dengue, as well as water borne disorders, like leptospirosis or infectious diarrhea[31] —all of which can cause acute kidney injury. Flood waters may also become nephron-toxic when contaminated with industrial or natural pollutants. Additionally, fine particulate matter from industry, transport, and forest fires has been linked to prevalence of CKD.[32] Vulnerable populations bear the brunt of these risks, often living in inadequately protected environments, with limited access to cooling, greenery, and safe working conditions. In 2024, the 77th World Health Assembly adopted a landmark Resolution on Climate Change and Health, recognizing the environ mental crisis as a major threat to human well-being and calling for climate-resilient, low-car bon health systems. The Resolution pressed Member States to incorporate health into national climate strategies and endorsed mechanisms, such as the Alliance for Transformative Action on Climate and Health, to support implementation.[33] Building on this momentum, the 78th Resolution specifically emphasized coordinated global action on environmental threats to overall and kidney health. Together, these Resolutions create a compelling dual mandate: to place kidney health at the intersection of noncommunicable disease control and environmental stewardship, and to guide Member States toward more integrated, equitable, and sustainable health responses. Addressing environmental risks, however, must go hand in hand with reducing the ecological footprint of kidney care itself (see below).

ECO-FRIENDLY KIDNEY FAILURE CARE: TOWARD GREENER NEPHROLOGY

The ideal approach to forestall the negative impact of interventions is taking measures, ensuring that they are no longer needed. Accordingly, prevention of kidney disease sup ports planetary sustainability by delaying or avoiding dialysis or reducing the use of pharmaceuticals, the production of which also has an environmental footprint. However, if drugs delay the progression of CKD and the need for kidney replacement therapy (KRT), this may compensate for the carbon footprint of drug production. A real-data secondary analysis of the

placebo-controlled CREDENCE study, investigating the impact of canaglifozin on outcomes, found a 20 to 25% greenhouse gas reduction during 2.6 years of follow-up in patients with type 2 diabetes not yet on KRT.[34,35]

Transplantation: Advancing Access and Sustainability

Among KRTs, transplantation offers the best outcomes—lower societal costs, improved survival, enhanced quality of life, and significantly less environmental impact compared with dialysis.[36,37] Yet, access to kidney transplantation varies widely across and within countries, influenced by health care infrastructure, socioeconomic status, and geography (rural vs. urban).[4] Donation practices also differ: some countries rely heavily on living donors, whereas others focus mainly on deceased donation. In many areas, donation after cardiac death or preemptive transplantation remains underutilized, despite favorable outcomes.[38,39] Furthermore, potential donors and recipients are frequently disqualified on the basis of arbitrary criteria or prejudices, with the exclusion of specific social groups, age categories, women, individuals with nonessential comorbidities, or borderline donors. Excluding borderline donors also reduces the donor pool, despite evidence that kidneys from borderline donors are safe, provided careful assessment, long-term follow-up, and treatment of risk factors.[40] In low-resource settings, kidney transplantation programs are often underdeveloped or absent, further deepening health in equities and enhancing economic burden. Reducing transplantation disparities re quires clear, globally endorsed guidelines on program design, ethical and legal frameworks on how to react to paid donation, and both technical and institutional support from countries or units with advanced trans plantation programs. Efforts should also include public education programs to expand the donor pool, and to address cultural, religious, and societal concerns.

Sustainability Dialysis: Reducing Environmental Impact While Improving Access

Most people on KRT receive dialysis despite the many dis advantages mentioned above.[37,41] In recent years, the environmental burden of dialysis has emerged as an added concern. The health care sector heavily impacts environmental degradation.[42] Dialysis is one of the main contributors, because of its repetitive and long-lasting water and energy consumption, greenhouse gas emission, and plastic waste generation.[6] Although therapeutic activities are a direct part of this process, approximately 70% of health care–related greenhouse gas emissions stem from the supply chain, largely related to manufacturing, transport, and waste handling.[6,43,44] In addition, substantial volumes of spent dialysate and reverse osmosis reject are usually discarded through the drain system, a particular issue in arid regions or during droughts.[6,45] Urgent action is needed: investment in eco-friendly dialysis technologies, which must prioritize patient safety by reducing toxicity from microplastics and eluates, while also improving the treatment experience by addressing stressors, like excessively noisy machines; critical review of the clinical procedures to reduce environmental footprint without affecting treatment quality; and greater transparency about the burdens of manufacturing and transport and how they are addressed (Figure 2).[6] This responsibility re quires collaboration among industry, physicians, patients, nurses, engineers, chemists, and environmental scientists. Home-based therapies—peritoneal dialysis and most home hemodialysis regimens, except daily extended dialysis—offer environmental advantages versus in-center hemodialysis, including reduced patient and personnel transportation needs, lower energy consumption for room temperature control, lower reverse osmosis plant electricity consumption, and, with compact hemodialysis systems and peritoneal dialysis, less water consumption. Peritoneal dialysis has a smaller footprint than in-center hemodialysis,[43,46,47] even if transporting its bulkier supplies may still generate substantial emissions, particularly when transport distance is high.[46] Most home hemodialysis regimens are also suggested to show a benefit versus in-center hemodialysis, except for 6 × 8-hour extended hemodialysis (300 mL/min dialysate flow).[47] In cremental dialysis may further decrease environmental burden, together with dialysate flow optimization,[48] if this is clinically suitable, and provided informed

consent is obtained. Peritoneal dialysis and existing compact hemodialysis systems can also help expand dialysis access in low-resource settings and in crises. In addition, several systems regenerating dialysate over sorbents are currently under development or undergoing preliminary clinical testing but are not yet available for widespread clinical use.[49] However, to achieve availability in emerging countries, barriers like import taxes or transport costs must be addressed (e.g., through local manufacturing).

Comprehensive Conservative Care: Indispensable But Often Forgotten

Comprehensive conservative or palliative care is the third option for treating kidney failure, next to transplantation and dialysis. This approach focuses on maximizing quality of life through full medical support, without initiating KRT.[50] Conservative care is particularly appropriate for frail and elderly people, many of whom show a rapid decline in functional status and increased mortality in the first year after dialysis start.[51] People with CKD stages 3 to 5 preferred conservative care if dialysis implied an increase in hospital visits or restricted travel capacity.[52] Despite this, conservative care often remains underutilized.[50,53] Educational initiatives aimed at both people with kidney disease and health care professionals should increase awareness and understanding of conservative care. Promoting this approach more broadly can ensure people receive treatments aligned with their values, circumstances, and wishes, while reducing unnecessary medical, economic, and environ mental burdens.

PATIENT EMPOWERMENT: THE ELEPHANT IN THE ROOM

Many people report that the information provided before starting KRT is of average to poor quality, particularly in countries with lower gross domestic product.[54] Paternalistic decision-making remains common, overlooking opportunities for early modality planning, vascular access creation, and elective KRT initiation. By contrast, shared decision-making actively engages patients in treatment choices, enhancing satisfaction, quality of life, outcomes, transplantation, and home dialysis rates, and reducing reliance on in-center hemodialysis.[54,55] The current hospital structures remain highly patient unfriendly, making even vocal people poorly heard. Readily accessible smaller hospital-independent outpatient units, increased nurse involvement in consultations, and discussion groups with active patient participation are possible innovative options, next to several educational and informative initiatives elaborated throughout this text. Support by patient organizations could help to advance these evolutions. Effective pre-dialysis care, accurate risk prediction, and strategic modality planning are crucial for improving outcomes and reducing health care costs, but could be optimized, particularly in lower-resource areas, by fore stalling late referral, fragmented care, inadequate patient education, poor adherence, and limited communication. Patient involvement is also crucial in research design, data interpretation, and registry development, helping to steer efforts in directions that really matter to them. Patients also should be encouraged to participate in training programs that build confidence and communication skills, empowering them to become active care partners and shape the future of kidney health.[56]

KIDNEY CARE IN CRISIS SITUATIONS: ADAPTING TO A CHANGINH WORLD

The number of people affected by crisis situations is steadily increasing, driven by population growth, climate change, and increasing geopolitical instability. These crises range from natural disasters (earthquakes, floods, extreme weather, and pandemics) to human-made emergencies, particularly armed conflicts.[57] People with kidney diseases are particularly vulnerable as they depend on specialized medication and resource-intensive treatments, like dialysis. These require skilled staff, clean water, electricity, functional machines, trans port possibilities to supply stock, and reliable infrastructure—resources typically compromised in crises.[57] Missing dialyses can quickly lead to life-threatening complications, such as hyperkalemia, which may require urgent evacuation.[58] Interruption of drug therapies may accelerate CKD progression or cause kidney graft rejection. Despite these risks, people with kidney diseases are rarely considered in official disaster plans. With crises becoming more frequent and severe, kidney health should

be integrated in disaster planning and emergency protocols. Authorities should be made aware of the nephrological community's specific needs through strong coordinated advocacy. In case of noninclusion of kidney care in gen eral disaster plans, the nephrology commu nities and nephrologists should develop their own. Simultaneously, there is an urgent need for less resource-dependent treatment strategies.

CALL TO ACTION: A COLLECTIVE AND GLOBAL RESPONSIBILITY

The traditional kidney care model aligned around in-center hemodialysis is no longer sustainable—ecologically, economically, and ethically (Figure 1). People living with CKD urgently need better quality of life and care. Transformation requires a holistic approach (Table 1), with all stakeholders considering each of the key areas discussed above—adapted to local situations, infrastructure, and resources.

WKD 2026 amplifies this need, issuing a call to global action:

- The public should be educated to ask care providers about their kidney parameters and function.
- Workers, particularly those employed out doors in agriculture and construction, should be sensitized about occupational threats of heat and environmental pollution and how to mitigate these to preserve kidney health.
- People with kidney disease and their com munities should be empowered to take an active role in shaping care pathways that serve their needs to their benefit.
- Health care professionals must shift emphasis toward integrated, preventive, and community-based care that enhances well-being and environmental responsibility, with focus on early disease and out-of-hospital approaches.
- Researchers and industry must challenge the status quo and prioritize innovation, striving toward equity, flexibility, patient friendliness, and sustainability.
- Policy makers and administrators need to recognize the cardio-kidney-metabolic cluster as a critical public health threat, prompting system redesign, and promoting sustainable kidney care by funding and reimbursement initiatives.
- Patient advocacy organizations must be recognized as essential partners in design, implementation, and evaluation of policy initiatives to ensure the system is built around patient-specific needs. However, active advocacy is a responsibility of the entire kidney care community.
- Global health partnerships should link these efforts, advocating at all levels for cohesive future-ready kidney care and global health.

Widespread lack of awareness—among the public, policy makers, and even health professionals—contributes to persistent in equities across socioeconomic, gender (social or cultural rather than biological identity), ethnic, national, and regional lines. Tackling this re quires robust education that highlights the public health threats and general burden imposed by kidney damage and kidney diseases. Given the demographic and geopolitical trends, appropriate well-planned screening, early detection, and prevention are the first and fore most steps to reach sustainability goals. These measures reduce complications, progression to advanced kidney disease, and the need for KRT. Prevention will ultimately also favor global health by mitigating the course of diseases frequently causing or complicating CKD and/or accelerated by CKD, significantly decreasing personal and societal problems, which emerge already in robust social security systems. In the absence of universal coverage, this will have even more important benefits, by avoiding early fatal outcomes and devastating financial consequences for many.

CONCLUSION

Aligning Kidney Health with Global Health and Sustainability Agendas

The recognition of kidney diseases as a global priority by the World Health Organization at the 78th World Health Assembly marks a pivotal moment.[5] It provides a comprehensive mandate for urgent action and a strong foundation for national and international advocacy. The 2026 WKD theme catalyzes the embed ding of kidney health and care within broader health and sustainability. This shift to patient centered models must be championed

by all stakeholders who share this responsibility to realize this model, across health, environment, labor, and policy sectors, through partnership aligned movements and coalitions with groups with parallel interests across organ specialties. This publication and WKD 2026 issue an urgent, united call to prioritize kidney health as a pillar of a healthier, fairer, and more sustainable future. The decisions made now will determine the life of millions for decades to come.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGEMENT

This article is being published in Kidney International and reprinted concurrently in several journals. The articles cover identical concepts and wording, but vary in minor stylistic and spelling changes, detail, and length of manuscript in keeping with each journal's style. Any of these versions may be used in citing this article.

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Received February 2026

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Volume 2, Number 2, April 2026