RJCCN

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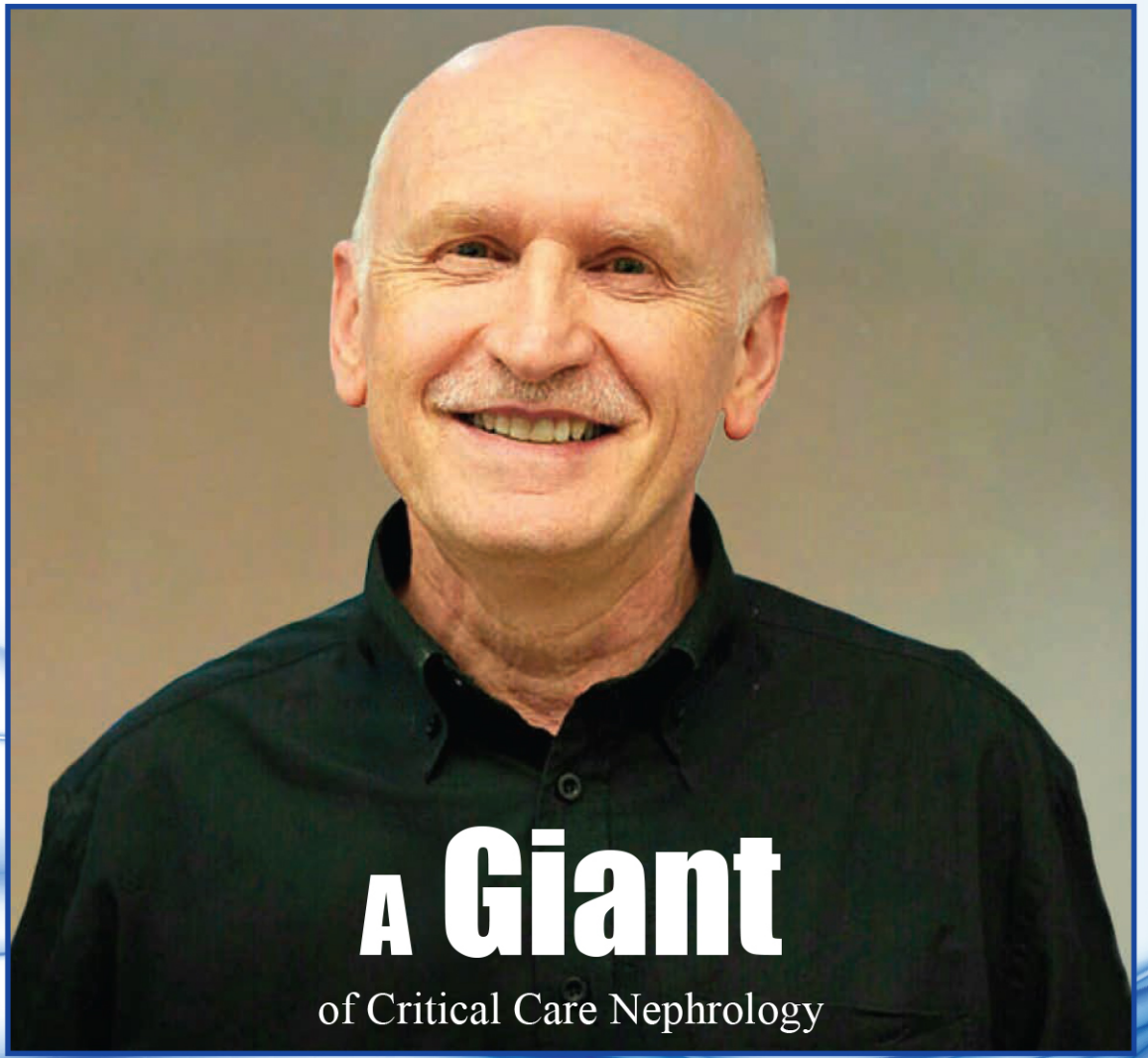

RESEARCH JOURNAL OF CRITICAL CARE NEPHROLOGY

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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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Research Journal of Critical Care Nephrology

INSTRUCTIONS TO AUTHORS

*Summarized Version**
August 2025

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.

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Manuscripts should be double-spaced, with 2.5-cm margins on all sides of the paper. All abbreviations must be spelled out the first time they are used, followed by the abbreviated form in parentheses. Units of measurement must be complied with the International System of Units (SI).

Original Research Papers. 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.

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

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

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

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Brief Communications. Original research papers can also be published in a brief format. Submitted papers that are of interest but are not acceptable as a full-length original contribution are offered by the editor to be published in this section. Also, the authors can primarily submit their papers for consideration of publication in this section. An unstructured abstract not longer than 150 words is required for this section. The body of the manuscript should not exceed 1500 words, and no heading or subheading should be used. Tables and/or Figures should be limited to 2 ones and references to 15 in maximum.

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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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Previous Publications

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In Memoriam: Vale, Professor Rinaldo Bellomo (1956 to 2025)

A Giant of Critical Care Nephrology, A Pioneer of Modern Medicine

RJCCN 2026; 2: 1-2
www.rjccn.org
DOI: 10.61882/rjccn.2.1.33

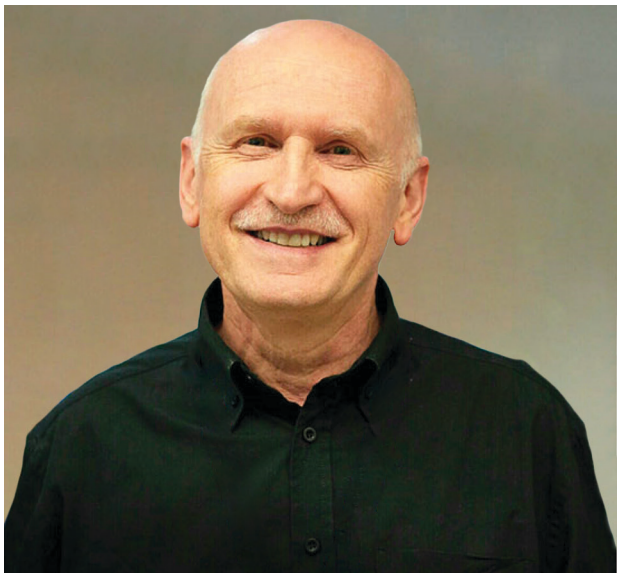
In May 2025, the global medical community lost one of its brightest minds, a visionary leader and one of the most influential figures in critical care nephrology: Professor Rinaldo Bellomo, a scholar whose name is synonymous with innovation, intellectual courage, and transformative impact. His passing leaves an irreplaceable void in the worlds of nephrology, intensive care medicine, and beyond. As we publish the second issue of the *Research Journal of Critical Care Nephrology*, we humbly dedicate these pages to the memory of a man whose influence helped shape the very foundation of our field.

Professor Bellomo was not only a towering academic figure; he was a force of nature-brilliant, curious, compassionate, and relentlessly driven by a desire to improve patient care. He often reminded us: "Medicine is not just about treating organs-it is about understanding people, questioning assumptions, and never stopping the pursuit of better care (by *Rinaldo Bellomo)*."

Few individuals have transformed a specialty the way he did. His contributions defined and redefined modern critical care nephrology, bringing clarity to the complexities of acute kidney injury and elevating the science of renal support in the ICU to new heights.

From introducing and refining critical concepts in AKI, to helping establish the modern understanding of continuous renal replacement therapy (CRRT), to leading groundbreaking work on sepsis, fluid management, clinical trials, and evidence-based practice, Professor Bellomo's intellectual fingerprints remain everywhere. His scholarship sparked movements, shaped guidelines, and set standards of care that have saved countless lives.

But beyond the science, those who had the privilege of knowing Professor Bellomo will forever



remember his humanity. He was a mentor who listened deeply, challenged gently, and inspired effortlessly. His generosity toward young clinicians and researchers helped cultivate a generation of leaders who now carry his torch. His trademark blend of sharp intellect and warm humor made him a colleague whose presence lifted every room. His humility, despite the magnitude of his accomplishments, remains one of his most enduring lessons.

In truth, his legacy cannot be measured by citations alone. It lives in the patients who received kinder, safer, and more thoughtful care because of his work. It lives in the countless physicians and scientists he shaped. It lives in the spirit of curiosity, rigor, and compassion that he modeled for all of us.

Please cite this article as: Nassiri AA. In Memoriam: Vale, Professor Rinaldo Bellomo (1956 to 2025). RJCCN 2026; 2(1): 1

As we reflect on the passing of this extraordinary man, we also celebrate a life lived with purpose and impact. Professor Bellomo leaves behind a scientific heritage that will stand the test of time and a personal memory that will remain cherished across continents.

In honoring Professor Bellomo, we reaffirm our commitment to advancing the field he helped build. May his brilliance continue to guide us, his compassion inspires us, and his legacy remind us that great medicine begins not only with knowledge, but with humanity.

With profound respect, admiration, and gratitude,

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

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Critical Care Nephrology: From the Original Vision to Today's Reality

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In 2025 Professor Rinaldo Bellomo, the most representative figure in the history and development of the discipline of Critical Care Nephrology, passed away. Of Italian origin, Rinaldo Bellomo moved to Australia in 1980 where eventually became director of intensive care at Austin and repatriation medical center, in Melbourne, and foundation chair of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG). Besides the numerous achievements and awards, Rinaldo was a man of incredible curiosity, extremely sensible to all aspects of human culture. He cultivated history, politics and philosophy trying to learn from the contact with different cultures, colleagues and disciplines.

One day in the early 90's he entered unexpected my small office in Vicenza and candidly told: "Dr. Ronco I want to learn from you about continuous therapies". Since then, we spent hours together in Vicenza, Pittsburgh, and Melbourne discussing about science, research, and philosophy, and we published the very first editorial on our vision on the multidisciplinary approach to acute kidney injury in the critically ill patient.[1] Together we pioneered critical care nephrology as a discipline and we described our vision for the future development of this area of medicine.

In our editorial we described many problems affecting the limited interaction between critical care and nephrology. However, we clearly stated why the times for a more intense collaboration were mature. The two previous decades had seen major changes in the practice of medicine, with the establishment of intensive care medicine as a structured discipline. Its evolution also produced major implications for clinical nephrology with advances in the understanding of pathophysiology and management of severe acute renal failure (ARF).

In our mind, it was clear that management of this type of disorder demanded knowledge and application of new technologies and skills that were not part of standard training in intensive care medicine nor in nephrology. Such expertise could only come from a multidisciplinary approach in which nephrologist and intensivist were willing to work side by side to achieve optimal care for the critically ill patient. In other words: "The formal development of a specialty area called *Critical Care Nephrology* was something whose time had come". Our vision was certainly ahead of times, however; while this topic was certainly spurred by the emergent role of continuous renal replacement therapies,[2] several obstacles and problems appeared immediately evident underlining the reasons for delays in the implementation of the visionary plan.

First of all, postgraduate medical training was historically specialty-oriented leading to an adversarial "us and them" mentality. Specialists were consulted for organ-specific problems while a patient's global view was never really implemented. This approach often resulted in inadequate communication with relatives and inappropriate therapeutic strategies. Physicians had often a sort of antagonism rather than a true cooperation. The intensivists were often unresponsive to sound advice by the nephrologists, while the latter often reached the intensive care unit too late for an effective and useful consultation. The clash of these cultures has significantly impeded the development of a combined strategy in the management of patients with ARF.

Another reason for a clash instead of cooperation was the desire to "control" the patient in the system, seeking an increased perception of the importance of this or that specialty and relevant

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services in the hospital. Financial issues and budget requirements were also frequent reasons to make units and specialties one against the other. This of course had implications on resource allocation and personnel assignment. The question about control and reimbursement for procedures or extracorporeal therapies was also at the base of the eternal discussion in those times between continuous and intermittent renal replacement therapies, especially in regions and countries were a "fee for service" policy was in place.

Professor Bellomo and myself wanted to disrupt the inertia and the immobilism due to the above-mentioned reasons and we strongly advocated a closer cooperation between intensive care and nephrology. We clearly stated that this new deal was definitely needed and ultimately inevitable. To corroborate this vision, it became progressively clear that acute renal failure was part of a more complex syndrome with significant organ interactions. Thus, the participation of different specialists to the decision process about diagnosis and treatment was considered almost mandatory. To make a practical step forward we decided to apply what later was called the "Vicenza model":[3] a practical approach to the critically ill patients were different specialists were called at the bedside of the patient for a collegial discussion and a shared management strategy. The nephrologist was going to ICU several times a day even without request, while the intensivist was actively participating in the nephrological and dialytic procedures. Starting from this experience we founded a consensus group called ADQI (Acute Dialysis Quality Initiative) that utilized the achieved results to establish recommendations and to pursue a thorough research agenda.[4-6] Results became soon evident while outcomes of critical kidney patients definitely improved.[7] Based on this, prof. Bellomo and myself suggested a sort of pathway for Critical care Nephrology implementation in various continents and facilities:

All nephrology fellows who intend to be involved in the care of acute renal failure should spend at least a year in an intensive care fellowship program.

1. All critical care medicine fellows who intend to take an active role in the management of acute renal failure should spend at least a year in a nephrology fellowship.
2. It is desirable, in large institutions, for one or some individuals to have completed a full fellowship in both specialties.
3. A tertiary institution should have a 'task force' allocated to the combined management of ARF and to the development of a research program dealing with multiple aspects of this condition.
4. An integrated critical care nephrology training program should be made available in large institutions for those who wish to pursue an academic
5. Specific courses and educational events should be planned with dedicated faculty and scientific agenda (clear reference was made to the conferences in San Diego, Melbourne and Vicenza).
6. The intense effort in this direction even resulted in multiple editions of a huge textbook entitled "Critical care Nephrology".[8]

Our original vision has become today a reality. Universities, hospitals and scientific societies have taken into consideration these recommendations and have structured curricula and courses for training and implementation of Critical Care Nephrology programs even utilizing the new possibilities offered by artificial intelligence.[9] Postgraduate training in intensive care and nephrology include collaborative courses and events aiming at a true collegial management of the patients with acute kidney injury (in the past defined as acute renal failure) and related syndromes including cardiorenal syndrome, hepatorenal syndrome etc.[10]

This is the legacy of professor Rinaldo Bellomo, a scientist, a great physician and a friend. The vision of more than thirty years ago has become a reality. All young fellows and investigators in the field of Critical Care Nephrology should be aware of the contribution of Rinaldo to this field. He has populated the journals and books with his articles, studies and wisdom: a legacy that cannot be forgotten in the years to come.

Claudio Ronco, MD

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RJCCN COMMENTARY

Point-of-Care Ultrasonography in Nephrology and Critical Care: A New Era of Bedside Precision

Abhilash Koratala

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

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Keywords. POCUS, ultrasound, nephrology, hemodynamics, critical illness

INTRODUCTION

Point-of-care ultrasonography (POCUS), performed by clinicians at the bedside, has rapidly evolved from a niche skill practiced by early adopters into a widely recognized extension of the physical examination.[1] Across medicine, but particularly in nephrology and critical care, POCUS has emerged as a tool that sharpens clinical reasoning, reduces diagnostic uncertainty, and accelerates actionable decisions.[2,3] Once confined to procedural guidance, POCUS is being increasingly incorporated into hemodynamic assessment to guide resuscitative strategies aimed at optimizing organ perfusion. Its growing presence reflects not only technological progress, but a broader shift toward bedside physiology-centered diagnostics and management.

As the Research Journal of Critical Care Nephrology inaugurates its POCUS feature, it is an opportune moment to consider where the field stands today, how it has evolved, and where it is headed. The intersection of nephrology and critical care offers a uniquely compelling perspective: both disciplines rely on timely and accurate assessment of hemodynamics and other dynamic physiologic processes, areas in which the traditional physical examination is often insensitive. POCUS bridges this gap, enabling clinicians to discern why a patient is deteriorating and to judge whether a given intervention is likely to help or harm.

POCUS AS AN EXTENSION OF THE PHYSICAL EXAMINATION

Traditional bedside assessment depends on indirect, externally observable or elicitable signs of disease, such as pulmonary crackles, peripheral edema, and jugular venous distension, which often appear late in the disease course and are prone to substantial interobserver variability. Multiple studies have shown that clinicians frequently overestimate their proficiency in physical examination, while the examination itself has limited sensitivity for detecting early pathology or hemodynamic aberrations.[4,5] By extending the clinician's physical senses through direct visualization of internal organs, POCUS provides objective information that surpasses what can be inferred from inspection, percussion, palpation, and auscultation alone. This direct visualization markedly improves diagnostic yield and accuracy and enables quantitative assessment at the bedside. In this way, POCUS revitalizes the physical examination by adding a previously inaccessible dimension, real-time visualization. For example, with a limited number of focused views, clinicians can assess cardiac function, evaluate pulmonary aeration, interrogate venous flow patterns suggestive of elevated right-sided pressures, and identify hydronephrosis or potential sources of sepsis. Importantly, POCUS does not replace clinical judgment but rather supports it. The clinical question remains central, and each ultrasound view helps answer it with greater precision. Accordingly, POCUS represents a shift away from reliance on surrogate markers and toward direct assessment of bedside physiology.

Please cite this article as: Koratala A. Point-of-Care Ultrasonography in Nephrology and Critical Care: A New Era of Bedside Precision. RJCCN 2026; 2(1): 6-10

USE-CASES IN NEPHROLOGY: FROM URINARY OBSTRUCTION TO HEMODYNAMICS

Nephrology has quietly emerged as one of the disciplines in which POCUS adds substantial value, in part because nephrologists routinely navigate diagnostic uncertainty and rely on nuanced clinical inference. Acute kidney injury (AKI), for example, encompasses a broad range of hemodynamic, obstructive, and intrinsic etiologies that are often difficult to disentangle using laboratory data and physical examination alone.

Bedside renal ultrasound enables rapid evaluation for hydronephrosis, identification of nephrolithiasis through acoustic shadowing or twinkle artifact, and assessment of bladder distention or Foley catheter dysfunction. In kidney transplant recipients, POCUS aids in differentiating physiologic collecting system dilation from true obstruction and facilitates detection of extrinsic compressive processes such as lymphoceles or hematomas.[6] Together, these assessments streamline clinical decision-making, minimize delays in care, and reduce unnecessary downstream imaging.

Beyond obstruction, POCUS can provide early clues about the chronicity of kidney disease. Findings such as increased cortical echogenicity, cortical thinning, and reduced renal size make a reversible intrinsic process less likely, helping clinicians contextualize an episode of AKI. Timely access to this information can shape the diagnostic trajectory and prevent unwarranted interventions.

Its most transformative impact lies in clarifying hemodynamic kidney injury. Bedside evaluation of cardiac function, pericardial effusion, pulmonary congestion, inferior vena cava dynamics, and venous Doppler flow patterns enables a more integrated assessment of renal perfusion and an individual patient's tolerance to fluid therapy. The increasing use of the term "hemodynamic AKI" reflects a broader recognition that kidney dysfunction commonly results from multiple mechanisms, often in combination, including low-flow states, elevated venous pressures, and impaired autoregulation, rather than an almost reflexive attribution to a "prerenal" process often equated with volume depletion and treated with intravenous fluids.[7,8]

Evidence from heart failure and dialysis populations shows that lung ultrasound can detect pulmonary congestion well before clinical signs become apparent, and that POCUS-guided adjustments in volume management improve blood pressure control and reduce recurrent decompensation.[9,10] Similarly, assessment of systemic venous congestion using hepatic, portal, intrarenal and femoral vein Doppler has been linked to increased risk of AKI, incomplete decongestion, and hospital readmissions, while improvement in these waveform patterns can be leveraged to track the effectiveness of decongestive therapy.[11-3]

Taken together, these applications underscore how POCUS allows nephrologists to look beyond the laboratory data and interrogate the broader cardiorenal axis, integrating information on perfusion, venous outflow, and dynamic response to therapy at the bedside.

POCUS IN CRITICAL CARE: RAPID ANSWERS IN HIGH-STAKES SETTINGS

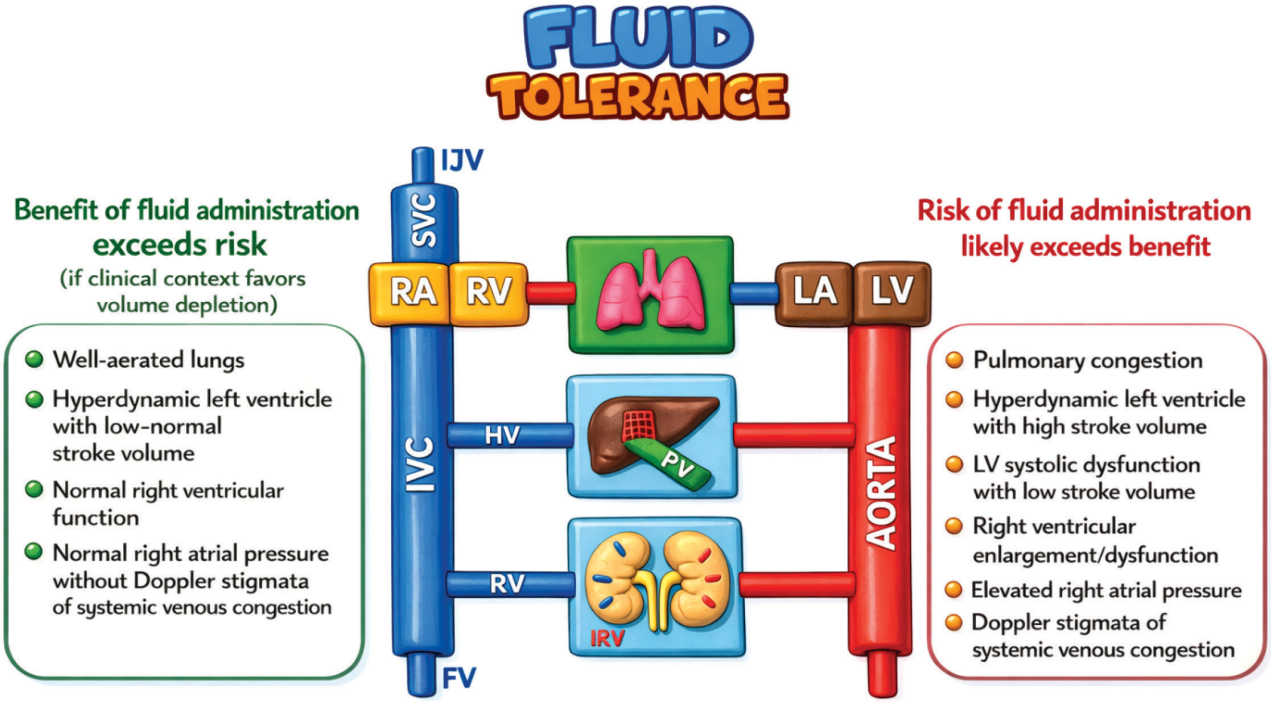
Point-of-care ultrasound has become an indispensable tool in critical care because it delivers rapid, repeatable physiologic insights in settings where diagnostic uncertainty carries immediate consequences. Intensivists routinely navigate scenarios ranging from rapid response activations on hospital wards to the management of complex, multi-organ failure in the intensive care unit, and the appeal of POCUS lies in its speed, portability, and capacity for iterative bedside assessment. In patients presenting with undifferentiated shock, POCUS helps clarify whether circulatory collapse is driven by reduced cardiac output, obstructive physiology, distributive vasodilation, or profound hypovolemia, distinctions that are essential because early therapeutic pathways diverge sharply depending on the underlying mechanism.[14] Further, ultrasound guidance is well known to enhance the safety and accuracy of routine procedures, including vascular access, thoracentesis, and paracentesis.

Bedside cardiac ultrasound allows rapid evaluation of left ventricular function, right ventricular strain, pericardial effusion with tamponade physiology, and gross valvular abnormalities, enabling clinicians to quickly prioritize interventions. Visual estimation of

myocardial contractility provides immediate, actionable information, while more quantitative measures such as left ventricular outflow tract velocity–time integral permit serial tracking of cardiac output trends and response to therapy. Complementing this cardiac assessment, lung ultrasound has emerged as a cornerstone of bedside respiratory evaluation, consistently outperforming auscultation and chest radiography in the detection of pulmonary edema, pneumothorax, and consolidation. The presence, distribution, and morphology of B-lines offer granular insight into thoracic fluid tolerance and the underlying etiology, helping guide management decisions.[15]

With respect to the common ICU dilemma of volume assessment, more accurately described as *hemodynamic evaluation*, reliance on inferior vena cava ultrasound alone is increasingly recognized as insufficient. Instead, comprehensive Doppler-based assessment of the entire hemodynamic circuit is emerging as a critical bedside skill. This approach helps determine which intervention a given patient is most likely to benefit from, including fluid administration, vasoactive agent support, diuretics, or ultrafiltration, and allows clinicians to monitor the response to these therapies over time. Such an integrative assessment includes estimation of stroke volume, evaluation of left ventricular filling pressures and right ventricular systolic pressure, and assessment of systemic venous congestion using Doppler interrogation of hepatic, portal, and intrarenal veins, commonly referred to as the Venous Excess Ultrasound framework.[16,17]

One of the most important conceptual advances enabled by POCUS-guided care is the distinction between fluid responsiveness and fluid tolerance (Figure). Fluid responsiveness addresses whether stroke volume or cardiac output will increase following fluid administration, whereas fluid tolerance asks whether the patient can safely accommodate that volume without harm.[18] Traditional resuscitation strategies have emphasized the former, often at the expense of the latter, effectively treating fluid responsiveness as a



POCUS-based Assessment of Fluid Tolerance
Integrated cardiac, pulmonary, and venous ultrasound findings are used to weigh the potential benefit versus risk of fluid administration. Favorable fluid tolerance is suggested by well-aerated lungs, preserved right ventricular function, and absence of venous congestion, whereas pulmonary congestion, ventricular dysfunction, elevated right atrial pressure, and Doppler evidence of systemic venous congestion indicate limited fluid tolerance and higher risk from additional fluids.
Abbreviations: RA, right atrium; RV (yellow), right ventricle; LA, left atrium; LV, left ventricle; IJV, internal jugular vein; SVC, superior vena cava; HV, hepatic vein; RV (blue), renal vein; FV, femoral vein; IRV, intrarenal vessels.

mandate for continued fluid loading. However, emerging evidence highlights that even fluid-responsive patients may experience adverse effects from additional fluids due to venous congestion, capillary leak, and impaired lymphatic drainage. The concept of fluid tolerance reframes resuscitation by shifting attention upstream to the venous side of the circulation and the vulnerability of individual organs to congestion-related dysfunction. Through bedside assessment of cardiopulmonary interactions and early sonographic markers of congestion, POCUS offers a practical means to identify patients who are fluid responsive but no longer fluid tolerant, allowing clinicians to individualize resuscitation strategies that preserve tissue perfusion while minimizing fluid-induced organ injury.

Further, POCUS provides rapid, bedside physiologic assessment across multiple organ systems that complements clinical examination. For example, diaphragm ultrasound enables noninvasive evaluation of diaphragmatic excursion and thickening, offering insight into respiratory muscle function during acute respiratory failure, ventilator weaning, and detection of ventilator-associated diaphragmatic dysfunction. Ocular ultrasound, particularly measurement of the optic nerve sheath diameter, serves as a practical adjunct for identifying patients at risk of elevated intracranial pressure when invasive monitoring is unavailable. During cardiac arrest and peri-arrest states, POCUS facilitates the rapid identification of potentially reversible causes including tamponade, massive pulmonary embolism, severe hypovolemia, and tension pneumothorax while also assisting in confirmation of cardiac activity and guiding resuscitative priorities without delaying chest compressions. In parallel, focused abdominal sonography for trauma (FAST) remains a cornerstone for the rapid detection of pericardial, pleural, and intraperitoneal free fluid in hemodynamically unstable patients. Additionally, bedside venous compression ultrasound adds important diagnostic value in the ICU by allowing rapid detection of deep vein thrombosis, reinforcing the likelihood of pulmonary embolism when CT chest imaging is delayed but right heart strain is present on cardiac ultrasound, thereby guiding timely therapeutic decisions.[19,20]

THE COMPETENCY GAP AND THE PATH FORWARD

Despite growing interest, POCUS training remains heterogeneous, with many clinicians relying on fragmented exposure through short courses or self-directed learning, an imbalance that is particularly evident in nephrology, where clinical demand has outpaced formal training infrastructure. Recent position statements underscore that competency requires not only image acquisition and interpretation but also disciplined clinical integration and an appreciation of limitations. Addressing these gaps will require intentional, multispecialty collaboration across nephrology, critical care, emergency medicine, anesthesia, and cardiology, leveraging shared expertise rather than siloed ownership of ultrasound domains. As technology continues to evolve and research increasingly refines physiologic phenotyping, the central challenge is no longer demonstrating that POCUS enhances care, but ensuring it is used consistently, safely, and meaningfully. Structured curricula, supervised longitudinal scanning, image archiving, and quality assurance must therefore become collective priorities, allowing POCUS to mature from an individual skillset into a shared clinical language that supports nuanced, physiology-driven decision-making at the bedside.

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Pregnancy-related Acute Kidney Injury: A Narrative Review of Epidemiology, Pathophysiology, and Clinical Management

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Pregnancy-related acute kidney injury (Pr-AKI) is a severe complication of obstetric medicine that remains a significant cause of maternal and fetal morbidity and mortality. Although the burden has declined in many low- and middle-income countries (LMICs) following improvements in prenatal and obstetric care, its incidence has risen in high-income nations, due to older maternal age, the growing prevalence of diabetes and chronic hypertension, as well to more sensitive definition criteria and improved diagnostic tools. Physiological changes during pregnancy can lower the baseline serum creatinine level and may delay diagnosis.

This review summarizes current evidence on the epidemiology, pathophysiology, etiologic mechanisms, diagnostic difficulties, management, and outcomes of Pr-AKI. Globally, the condition demonstrates a paradox, i.e., decreasing incidence but persistent mortality in LMICs and increasing incidence in developed countries. Hypertensive disorders of pregnancy, particularly preeclampsia, eclampsia, and the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, have become the predominant causes worldwide. Distinct trimester-specific patterns, overlap with thrombotic microangiopathies and acute fatty liver of pregnancy, and the need to balance maternal and fetal health make Pr-AKI uniquely complex.

Improving Pr-AKI outcomes requires early recognition, pregnancy-specific diagnostic biomarkers, and coordinated multidisciplinary care. Strengthening antenatal surveillance, expanding access to renal replacement therapy in resource-limited settings, and providing structured postpartum follow-up are essential to reducing the global burden of Pr-AKI.

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INTRODUCTION

Pregnancy-related acute kidney injury (Pr-AKI) refers to a sudden loss of renal function during gestation or in the postpartum period. It is a sentinel event that reflects the quality of maternal health services. Despite progress in obstetric and nephrology practice, Pr-AKI remains a leading cause of preventable maternal death and a precursor to

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chronic kidney disease.[1-4]

Normal pregnancy produces extensive cardiovascular and renal adaptations. Glomerular filtration rate increases by roughly 50%, plasma volume expands, and systemic vascular resistance declines.[5-7] As a result, serum creatinine falls to about 0.4 to 0.6 mg/dL, therefore; a level of around 1 mg/dL, normal for a non-pregnant individual, may already indicate substantial impairment in a pregnant women. Awareness of these physiological changes is crucial to timely diagnosis and intervention.[8-10]

This review integrates findings from international studies to describe trends, mechanisms, clinical syndromes, management strategies, and outcomes of Pr-AKI. It highlights the differences between regions and underscores the importance of early detection and long-term follow-up.[11-23]

EPIDEMIOLOGY AND GOLBAL TRENDS

The epidemiology of Pr-AKI varies markedly across regions. In high-income countries, the incidence has risen over the past two decades due to delayed childbearing, higher rates of chronic disease, and improved case recognition.[10,24-7] In contrast, many LMICs have experienced a decline, although the overall burden remains far greater. In India, for example, septic abortion once accounted for more than half of Pr-AKI cases but now represents < 5% after the legalization of abortion and broader access to prenatal care. This is in contrast to the United States, where the incidence increased from about four to twelve per ten thousand deliveries between 2005 and 2015.[1,3,28-35]

Racial and socioeconomic disparities remain a significant factor in the incidence of Pr-AKI among different populations. Black and Native American women in the United States experience roughly 50% higher odds of Pr-AKI and 60% higher mortality than White women.[35-59] Structural barriers to timely prenatal evaluation, as well as differences in comorbidity profiles, contribute to this inequity.

Estimating the true incidence of Pr-AKI is challenging. Traditional definitions such as RIFLE, AKIN, and KDIGO are not validated in pregnancy and rely on relative rises in serum creatinine. Because physiologic creatinine levels are lower during gestation and baseline values are often unknown, many cases go unrecognized until renal dysfunction is advanced.[60-7] Routine measurement of renal indices during early pregnancy, particularly among those with higher risk facotrs or those who experience events such as hypertensive crises, bleeding, or sepsis, can improve surveillance.

PHYSIOLOGICAL ADAPTATIONS AND DIAGNOSTIC CHALLENGES

Pregnancy induces profound renal and systemic changes. Vasodilation increases cardiac output, and hormonal modulation by estrogen, progesterone, and relaxin leads to an expanded plasma volume and enhanced renal blood flow. Glomerular hyperfiltration begins early and peaks by mid-pregnancy, resulting in a physiological reduction in serum creatinine and urea concentrations.[68-71] Mild hydronephrosis or pyelocaliectasis is common in pregnancy due to progesterone-induced smooth muscle relaxation and mechanical compression of the ureters by the enlarging uterus.[68-70] Differentiating these physiologic changes from true renal pathology requires careful interpretation of laboratory parameters. Even minor elevations in serum creatinine may signify genuine kidney injury, as baseline creatinine levels are typically lower during pregnancy. Although monitoring urine output can provide useful information, its reliability is limited because of altered maternal fluid dynamics and potential therapeutic interventions. Notably, diuretics are generally avoided during pregnancy, as their use may precipitate oligohydramnios and compromise fetal well-being.[72,73]

Several biomarkers, including neutrophil gelatinase–associated lipocalin, soluble fms-like tyrosine kinase-1, and placental growth factor, have shown potential for differentiating pre–eclampsia–related dysfunction from intrinsic renal disease; however, their clinical validation and application remain limited.[73] Evaluation should include serial laboratory tests, assessment for proteinuria, and renal ultrasonography to rule out obstruction. Renal biopsy may be considered before approximately twenty-five weeks of gestation when histologic results would alter management; after this time, it is typically postponed until after delivery due to procedural risk.[68,69,74,75]

ETIOLOGY AND RISK FACTORS

The causes of Pr-AKI differ by trimester and socioeconomic contexts. In early pregnancy, dehydration from hyperemesis gravidarum and infection following unsafe abortion are predominant. Later in pregnancy, hypertensive disorders such as preeclampsia and eclampsia, the HELLP syndrome, acute fatty liver of pregnancy, and thrombotic microangiopathies become the principal etiologies.[76-84] Intra- and postpartum hemorrhages, puerperal sepsis, and amniotic-fluid embolism contribute during the peripartum period.

Advanced maternal age, chronic hypertension, diabetes mellitus, prior preeclampsia, and preexisting chronic kidney disease markedly increase susceptibility to develop Pr-AKI.[80,85-9] Socioeconomic deprivation, limited access to emergency obstetric care, and delayed referral further elevate the Pr-AKI risk. Early-pregnancy complications tend to be reversible with prompt rehydration or control of infection. In contrast, late-pregnancy and postpartum forms are often more severe and carry a greater risk of residual renal damage (Table 1).

Hypertensive disorders of pregnancy constitute the most frequent cause of Pr-AKI worldwide. Preeclampsia is defined by new-onset hypertension after twenty weeks of gestation with proteinuria or evidence of end-organ dysfunction.[81,83,90-3] When seizures develop, the condition is called eclampsia. The HELLP syndrome, which includes hemolysis, elevated liver enzymes, and low platelets, represents the most severe form of this disease spectrum. Renal involvement results from endothelial injury, vasospasm, and glomerular endotheliosis.[88,94-8]

Acute fatty liver of pregnancy typically occurs in the third trimester and is characterized by microvesicular fatty infiltration of hepatocytes due to defects in mitochondrial fatty acid oxidation. It presents with nausea, vomiting, abdominal pain, jaundice, and hypoglycemia. Because it shares clinical features with HELLP, the two disorders may coexist. Prompt delivery and supportive management can usually result in a full recovery.

Thrombotic Thrombocytopenic Purpura (TTP) and HELLP syndrome are important thrombotic microangiopathies (TMAs) leading to Pr-AKI. Although their clinical features overlap, differentiating them is crucial for management and prognosis. TTP, typically occurring in the late second or third trimester, results from severe ADAMTS13 deficiency (< 10% activity), which predisposes to microvascular platelet aggregation.[71,88,94-103]

It is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and neurologic dysfunction, while renal involvement is usually mild to moderate but can cause severe AKI in up to 10% of cases. Plasma exchange is the mainstay of therapy, as delivery does not improve outcomes. In contrast, HELLP syndrome, a severe variant of preeclampsia, is marked by hemolysis, hepatic injury, and thrombocytopenia, often accompanied by hypertension and proteinuria. AKI occurs in 3 to 15% of affected women and may reach over 60% in severe cases. Prompt delivery of the fetus is the definitive treatment, typically leading to rapid maternal recovery and favorable renal outcomes. Compared with TTP or atypical HUS, HELLP-related AKI generally resolves completely after delivery, and absence of relapse on follow-up supports its distinction from TMAs persisting beyond pregnancy.[84,89,104-8]

CLINICAL MANAGEMENT AND THERAPEUTIC APPROACH

During the management of Pr-AKI, stabilization of both maternal physiology and protection of fetal health are required. A multidisciplinary team, including a nephrologist, obstetrician, intensive care specialist, pharmacist, and neonatologist, is often required to optimize care.[109-11] Initial treatment focuses on optimizing and maintaining hemodynamic stability and adequate renal perfusion. Hypovolemia should be corrected with isotonic balanced crystalloid fluids, while volume overload must be avoided in pre-eclamptic patients. Blood products are administered as necessary, and severe metabolic acidosis or hyperkalemia should be corrected promptly.[6,112-4]

In cases of severe preeclampsia, eclampsia, or HELLP syndrome, expedited delivery remains the definitive therapy. Antihypertensive medications, such as beta-blockers or hydralazine, are used to control blood pressure without compromising uteroplacental blood flow. Magnesium sulfate is given for seizure prophylaxis but requires close

Table 1. Treatments of Choice for the Syndromes Associated with Pr-AKI Risk

Condition	Specific Treatment
Preeclampsia (severe) / HELLP / AFLP	Prompt delivery of the fetus
TTP	Plasma exchange (initiated while ADAMTS13 levels are pending); Rituximab for refractory cases (with caution in the third trimester)
aHUS	Eculizumab, Plasma exchange
Septic abortion / UTI	Antibiotics; surgical removal of products of conception for septic abortion
Glomerulonephritis	Steroids and immunosuppressants (e.g., azathioprine, calcineurin inhibitors). Note that mycophenolate and cyclophosphamide are contraindicated.
Hemorrhage (Placental Abruption/PPH)	Control bleeding, volume resuscitation, and delivery
Obstructive Uropathy	Analgesics, stent, or nephrostomy

Abbreviations: TTP; thrombotic thrombocytopenic purpura, aHUS; atypical hemolytic uremic syndrome

monitoring because, in the case of declining kidney function, magnesium retention and potential toxicity risk increase.[7,115,116] When thrombotic thrombocytopenic purpura is suspected, plasma exchange should begin immediately. For cmHUS, early administration of complement inhibitors, such as antibodies targeting the membrane attack complex, could be lifesaving. Septic abortion and puerperal sepsis need broad-spectrum antibiotics and surgical evacuation of uterine contents when indicated (Table 1).[117-20]

Renal replacement therapy is initiated for the standard indications of refractory fluid overload, metabolic acidosis, hyperkalemia, or uremic symptoms. Both intermittent hemodialysis and continuous modalities are considered safe during pregnancy.[121] Evidence suggests that intensive dialysis improves fetal growth and extends gestational duration in women with advanced renal failure. Immunosuppressive therapy with corticosteroids or calcineurin inhibitors may be used when glomerulonephritis is confirmed, whereas agents such as cyclophosphamide and mycophenolate are avoided due to their teratogenicity.[6,109-11,116,120]

MANAGEMENT PRINCIPLES

The management of Pr-AKI is complex, requiring a multidisciplinary team and careful consideration of both maternal and fetal well-being. The core principles involve supportive care, management of complications, and treatment of the underlying cause (Table 2).[71,109,117,121]

MATERNAL AND FETAL OUTCOME

Pr-AKI remains closely linked to poor maternal and fetal outcomes.[76,89,98,100,122] Reported maternal mortality ranges from 4% to nearly 30%, depending on regions and their resource availability. The highest incidence of Pr-AKI-associated poor outcomes is observed in low- and middle-income countries where delayed referral and limited access to dialysis are common. In contrast, mortality in tertiary centers of high-income nations is usually < 5%. Cortical necrosis, often resulting from massive hemorrhage or sepsis, predicts irreversible renal failure and accounts for a disproportionate share of deaths.[84,88,94-8,100,104,105,123]

Renal recovery after Pr-AKI varies widely. Observational studies suggest that approximately two-thirds of survivors achieve complete recovery within six weeks of delivery, whereas up to one-quarter have partial recovery with persistent proteinuria or mild reductions in glomerular filtration rate. About 8% of patients with Pr-AKI show progress to chronic dialysis. Temporary renal-replacement therapy does not preclude recovery. Indeed, many women who require short-term dialysis regain full renal function postpartum. Even so, the episode carries long-term consequences: women with a history of Pr-AKI are nearly three times more likely to develop chronic kidney disease and twice as likely to experience cardiovascular events later in life.[84,98,99,103,124,125] Consequently, postpartum evaluation should include measurement of serum creatinine and urine protein, as well as counseling regarding hypertension, weight control, and lifestyle modification.[109,113]

Fetal outcomes mirror the severity of maternal illness. Perinatal mortality remains high, ranging from 25 to 35% globally. Prematurity, intrauterine growth restriction, and stillbirth are

Table 2. General Management Approach to Pr-AKI

Management Aspect	Key Principles and Actions
General Supportive Care	● Medication Review: Withhold potentially nephrotoxic drugs (e.g., NSAIDs, aminoglycosides), or replace with other agents. ● Dose Adjustment: Adjust maintenance doses of renally cleared medications (e.g., magnesium sulphate for preeclampsia). ● Treat Underlying Cause: Address hemorrhage with fluid/blood resuscitation, treat sepsis with antibiotics, and relieve any urinary tract obstruction.
Fluid Management	● Crucial but Challenging: The primary goal is to restore and maintain renal perfusion without causing fluid overload, a major iatrogenic risk. ● Hypovolemia: ○ Prioritize cautious isotonic fluid resuscitation to restore effective blood volume and renal perfusion. ○ Guide therapy by maternal hemodynamics, urine output trends, and resolution of clinical signs of hypoperfusion. ○ Avoid excessive fluid administration, as it increases the risk of pulmonary edema and worsens outcomes in preeclampsia and capillary leak states ● Acute Tubular Injury: ○ Restrict fluids to prevent volume overload once euvolemia is achieved. ○ Replace insensible losses and maintain even or slightly negative fluid balance based on output and weight changes. ○ Continue close monitoring for evolving electrolyte abnormalities or indications for renal replacement therapy
Pharmacological Interventions	● Diuretics (Furosemide): No proven benefit on renal outcomes and may worsen prognosis. Use should be limited to managing documented fluid overload, and it must be avoided in preeclampsia unless pulmonary edema is present. ● Low-Dose Dopamine: No evidence of benefit and carries substantial side effects. It plays no to minimal role in managing Pr-AKI.
Treatment of Underlying Obstetric Conditions	● Prompt Delivery: This is the treatment of choice for Pr-AKI caused by preeclampsia, HELLP syndrome, and acute fatty liver of pregnancy (AFLP) ● Targeted Therapies: Thrombotic microangiopathies (TMAs) do not necessarily require delivery and are treated with plasma exchange (TTP) or complement inhibition with complement inhibitors (cmHUS).
Renal Replacement Therapy (Dialysis)	■ Indications: ● Initiate RRT for standard maternal indications, as pregnancy does not alter thresholds for dialysis initiation. ● Specific indications include: ○ Refractory volume overload unresponsive to diuretics. ○ Hyperkalemia or metabolic acidosis not controlled with medical therapy. ○ Severe uremic complications such as pericarditis, bleeding diathesis, or encephalopathy. ○ Persistent severe AKI with marked azotemia (e.g., blood urea nitrogen >112 mg/dL) or prolonged oliguria/anuria despite conservative management. ■ Dialysis Strategy in Pregnancy: ● The standard of care is intensified dialysis, typically daily or near-daily sessions totaling >20 hours/week. ● Increased dialysis frequency improves maternal metabolic control and reduces fetal exposure to uremic toxins, leading to: ○ Higher live birth rates. ○ Greater birth weights and improved fetal growth outcomes. ● Dialysis prescriptions should be individualized to maintain optimal volume status, acid-base balance, and electrolyte homeostasis, while minimizing hemodynamic instability. ● Close maternal-fetal monitoring (including ultrasonography and fetal heart rate assessment) is essential throughout RRT.
Specialized Procedures	● Transcatheter Arterial Embolization (TAE): For uncontrollable postpartum hemorrhage, TAE is a safe and effective procedure. One study found that no patients (0 out of 47) developed post-contrast AKI after emergency TAE.
Renal Biopsy	● Rarely Necessary: Reserved for severe cases without a clear diagnosis where the results would change management during pregnancy, such as differentiating preeclampsia from other proteinuric diseases in the second trimester.

the most common complications. Many preterm births are iatrogenic, undertaken to preserve maternal health in severe preeclampsia or HELLP syndrome.[76,94,94,97,99,100,106] Neonates frequently

require intensive care for respiratory distress and low birth weight. Long-term follow-up of offspring from affected pregnancies suggests a higher lifetime risk of hypertension, chronic kidney diseases, and metabolic disorders, underscoring the intergenerational influence of maternal kidney injury.[76,89,98,100,103,104,126]

GLOBAL DISPARITIES IN CARE

Despite significant improvements in obstetric medicine, outcomes remain deeply unequal worldwide. In high-income countries, universal antenatal screening, rapid laboratory testing, and immediate access to dialysis have made Pr-AKI relatively rare and usually reversible. In contrast, in low-resource settings, a similar condition continues to be associated with preventable maternal death.[2,5,6,76,77,80-2,85,93,95] Many facilities lack basic laboratory capacity, dialysis equipment, or trained nephrologists. Women may travel long distances to reach tertiary centers, often arriving with advanced multi-organ failure.

Socioeconomic and cultural barriers compound the problem. In several regions, women delay seeking care because of limited autonomy, transportation costs, or fear of stigma. Unsafe abortion, still prevalent in some countries, remains a major driver of septic AKI. Broader determinants of health, including education, nutrition, and gender inequality, shape both the risk and the outcome of renal complications.[76-8,80-2,85,93,95,96,100-3,122,123,125,127,128]

Global initiatives, such as the International Society of Nephrology's 0by25 campaign, aim to eliminate preventable deaths from acute kidney injury by 2025. These initiatives emphasize that timely diagnosis and affordable dialysis must be available in every country.[76,78,96,102] Achieving this requires collaboration between governments, academic institutions, and professional societies. Investment in rural obstetric care, training of mid-level providers, and establishment of regional perinatal-nephrology networks are critical steps toward narrowing the gap.

EXPANDED EVIDENCE SUMMARY OF REPORTED CASES AND COHORTS

A synthesis of more than forty observational cohorts, representing thousands of pregnancies, provides a comprehensive picture of Pr-AKI worldwide. The incidence among hospital deliveries ranges from one in ten thousand in high-income regions to nearly 20% of obstetric admissions in some low-resource hospitals. Hypertensive disorders account for roughly half of all cases, followed by sepsis (15 to 20%) and hemorrhage (10 to 15%). Among women who require dialysis, approximately 70% recover renal function within six weeks postpartum, 10% remain dialysis-dependent, and the rest experience partial recovery.[76,78-80,85,129-32]

Regional trends highlight dramatic shifts over time. In India, septic abortion once represented the leading cause of Pr-AKI but now contributes to < 5% of cases, reflecting legal reform and improved infection control. Hypertensive disorders, particularly preeclampsia and HELLP syndrome, have become the dominant etiologies. In the United States, national datasets indicate a threefold increase in Pr-AKI incidence between 2005 and 2015, primarily attributed to older maternal age and comorbid conditions.[76-9,127] Maternal mortality in well-resourced centers is < 5%, whereas it exceeds 30% in hospitals lacking dialysis capacity. Fetal survival similarly varies, ranging from 90% in tertiary institutions to less than 60% in resource-limited environments. These differences demonstrate that Pr-AKI is not merely a biological disease but also a measure of social and systemic inequality.[76-80,83,85,94,124,127]

CONCLUSIONS

Pr-AKI remains a formidable challenge at the intersection of obstetrics, nephrology, and public health. Although incidence has declined in many developing regions, the persistence of high mortality and the rising trend in developed nations highlight its global relevance. Early recognition, prompt delivery when indicated, and coordinated multidisciplinary management are key to reducing complications. Preventive strategies should emphasize universal access to prenatal care, effective control of hypertension and diabetes before conception, and immediate management of obstetric emergencies.

In high-income countries, attention should focus on long-term follow-up after delivery to detect chronic kidney disease and cardiovascular risk.

In low- and middle-income regions, investment in health infrastructure, workforce training, and dialysis availability is essential to prevent avoidable deaths. Research priorities include the development of pregnancy-specific diagnostic criteria for acute kidney injury, validation of novel biomarkers, and investigation of long-term outcomes for both mothers and offspring.

In conclusion, Pr-AKI is a multifactorial disorder that reflects the broader landscape of maternal health. Its prevention and management demand not only clinical vigilance but also commitment to social equity and global cooperation. Through timely diagnosis, evidence-based care, and sustained investment in women's health, the burden of pregnancy-related acute kidney injury can be substantially reduced.

AUTHORS CONTRIBUTIONS

Mehdi Kashani, MD: Conceptualization, literature review, data synthesis, drafting of the manuscript, figure and table preparation, and critical revision

Juxiang Wang, MD: Literature review, regional and international data collection, and critical revision for intellectual content

Jiong Cui, MD: Methodological guidance, data verification, comparative analysis between LMIC and high-income settings, and manuscript editing

Kianoush B. Kashani, MD, MS: Senior supervision, conceptual design, expert input on nephrology and critical care aspects, and final approval of the manuscript

All authors read and approved the final version of the manuscript.

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Not applicable

Consent to Participate

Not applicable

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Conflict of Interest

The authors declare no competing interests.

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Inhibition of FSP1-MYH9 Interaction Reduces TGF-β-induced Podocyte Injury: Potential Therapeutic Role of Trifluoperazine

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Keywords. FSP1, MYH9, podocyte injury, trifluoperazine

Introduction. Podocytes are crucial for maintaining the glomerular filtration barrier, and their injury is a major contributor to kidney diseases. FSP1 (Fibroblast-specific protein 1) has been implicated in various pathological conditions but its role in podocyte injury, especially under TGF-β (Transforming Growth Factor-Beta) stimulation, is not well understood. This study aims to explore the involvement of FSP1 and its interaction with MYH9 in TGF-β-induced podocyte damage and assess the therapeutic potential of Trifluoperazine (TFP).

Methods. Human podocytes were treated with TGF-β, followed by FSP1 knockdown using siRNA. A series of assays including CCK8, wound healing, F-actin staining, and CO-IP were performed to assess podocyte injury, migration, and FSP1-MYH9 interactions. The effects of TFP on these interactions and podocyte health were also evaluated.

Results. TGF-β increased FSP1 expression in podocytes, leading to cell damage. FSP1 knockdown reduced injury by improving cell viability and cytoskeletal integrity. CO-IP revealed that FSP1 interacts with MYH9 to promote podocyte injury. TFP treatment reduced FSP1-MYH9 interaction, alleviating podocyte damage.

Conclusion. FSP1 promotes TGF-β-induced podocyte injury through its interaction with MYH9, activating the P38 MAPK pathway. TFP disrupts this interaction, offering a promising therapeutic approach for treating podocyte-related kidney diseases.

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INTRODUCTION

Podocytes are essential components of the glomerular filtration barrier, which plays a critical role in the initiation and progression of glomerulopathies.[1] Podocyte injury is a key pathophysiological process in many kidney diseases, such as diabetic kidney disease, IgA vasculitis nephritis, and glomerulonephritis.[2-5] Injured podocytes can undergo cell death, foot process effacement, and proteinuria, leading to kidney dysfunction.[6] Therefore, identifying novel targets to mitigate podocyte injury is crucial for improving treatment outcomes.

Podocytes express specific proteins, such as

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nephrin and podocin, which form part of the slit diaphragm, a structure essential for filtration.[7,8] These proteins are used as markers to assess podocyte health and functional integrity.[9] In this study, we demonstrate that the podocytes exhibit protein expression patterns typical of healthy podocytes, reinforcing their relevance in studying disease-related damage.

One of the challenges in studying podocytes is their limited proliferative capacity, which makes detecting cellular responses to injury challenging.[10] CCK8 assays, which measure cell viability, have been shown to be effective in assessing podocyte injury, as they provide insight into the metabolic activity of these cells.[11] The CCK8 assay is appropriate for this study as it accurately reflects the degree of injury in cells with low proliferative potential.

FSP1 (Fibroblast-specific protein 1), also known as S100 calcium-binding protein A4, belongs to the S100 family of proteins and is involved in various biological processes.[12] It has been reported that secreted FSP1 activates the VEGFA pathway, inducing epithelial barrier dysfunction and inflammation.[13] In lung cancer, serum FSP1 can act as a biomarker to guide treatment strategies.[14] Additionally, FSP1 + cells can activate macrophages and the Notch signaling pathway, promoting renal fibrosis and inflammation in kidney diseases.[15] The expression of FSP1 in podocytes is associated with epithelial-to-mesenchymal transition (EMT)-like changes and has been recognized as a biomarker in tubulointerstitial fibrosis.[16] However, the role of FSP1 in TGF-β-treated podocytes remains unexplored.

MYH9 (myosin heavy chain 9) encodes the protein NMIIA, which acts as a molecular motor and plays a key role in cell migration, division, and polarization. MYH9 expression is elevated in various cancers, including gastric, lung, and colorectal cancers.[17,18] It has been shown that MYH9 interacts with MYH10 to recruit USP45, promoting cancer progression in ovarian cancer.[19] In acute kidney injury, APE2 interacts with MYH9 to induce mitochondrial fragmentation.[20] However, the interaction between MYH9 and FSP1 in podocyte injury remains unknown.

Given that this study is conducted entirely in vitro, it is important to note the limitations of such experiments. While we demonstrate the interaction between FSP1 and MYH9 in podocyte injury under controlled conditions, we have yet to establish whether these proteins exhibit similar functional relevance in vivo. It remains to be determined whether the expression of FSP1 and MYH9 changes in actual disease states or under conditions that induce podocyte damage. Further research is needed to assess the potential of these proteins as therapeutic targets in vivo.

MATERIALS AND METHODS

Cell Culture and Treatment

Human podocytes were purchased from Xuanke Biotechnology (Shanghai, China). The cells were cultured in RPMI 1640 medium (Hyclone, Utah, USA), supplemented with 10% fetal bovine serum (FBS; Gibco, USA), and maintained in a humidified atmosphere containing 5% CO_2 at 37°C. Podocytes were exposed to different treatments, including medium alone, TGF-β (10 ng/ml; Promega, Madison, Wisconsin, USA), or Trifluoperazine (TFP) (20 μM). The duration of treatments and experimental conditions were standardized for consistency across assays.

Transfection

Small interfering RNAs (siRNAs) targeting FSP1 and MYH9 were obtained from GenePharma (Shanghai, China). Cells were transfected with siRNA using Lipofectamine 3000 (Invitrogen, USA) according to the manufacturer's protocol. Successful transfection and knockdown efficiency were confirmed through RT-qPCR and Western blot analyses.

CCK8 Assay

A CCK8 assay kit (Sigma, USA) was employed to assess cell viability, an important indicator of podocyte injury. Briefly, the kit was used to measure the metabolic activity of living cells. The absorbance was recorded at 450 nm using a microplate reader, reflecting the degree of podocyte viability under different experimental conditions. The CCK8 assay is particularly suitable for podocytes, which are cells with limited proliferative capacity, providing a robust measure of injury by capturing changes

in their metabolic activity.

Wound Healing Assay

Cells (2×10^5) were seeded into six-well plates and cultured until they reached 70 to 80% confluence. Following treatment, a scratch was made using a pipette tip to create a straight wound across the monolayer. The progress of wound healing was observed and recorded at specific time points to assess the migration ability of podocytes. This assay helped demonstrate changes in cellular motility associated with podocyte injury.

F-actin Staining

To examine cytoskeletal changes in podocytes, cells were fixed with a 3.7% (v/v) formaldehyde solution and permeabilized using a 0.2% (v/v) Triton X-100 solution. After several washes with PBS, the cells were stained with either fluorescein or rhodamine-labeled phalloidin to visualize F-actin structures. DAPI was used to stain cell nuclei. This assay provided insight into actin stress fiber patterns, which are critical for maintaining podocyte structure, especially under TGF-β-induced injury.

CO-IP Assay

For co-immunoprecipitation (CO-IP) experiments, treated cells were lysed using a buffer containing 40 mM HEPES (pH 7.4), 0.5% Triton X-100, 2 mM EDTA, and protease inhibitors. Cells were subjected to gentle shaking, followed by centrifugation at 12,000 × g for 10 minutes to separate the supernatant. The supernatant was incubated with a specific antibody overnight at 4 °C, followed by incubation with A/G agarose beads for 4 hours the next day. The samples were then separated by SDS-PAGE and analyzed by Western blotting to detect the protein-protein interactions.

Western Blot

Protein was extracted from treated cells using RIPA buffer (Byotime, China) supplemented with protease inhibitor cocktail tablets and phosphatase inhibitor PMSF (both from Roche, Switzerland). P38 and phosphorylated-P38 (p-P38) antibodies were obtained from CST. Protein samples were separated via SDS-PAGE, transferred to PVDF membranes, and detected using the appropriate antibodies to assess the expression levels of target proteins.

RT-qPCR

Total RNA was extracted from treated cells using TRIzol reagent. cDNA was synthesized using the HiScript III All-in-One RT SuperMix (Vazyme, China), following the manufacturer's instructions. Quantitative real-time PCR (qRT-PCR) was performed to measure gene expression levels using specific primers. GAPDH was used as the internal control, and relative gene expression.

Statistical Analysis

Statistical analyses were performed using Student's *t*-test or one-way ANOVA to compare differences among experimental groups. A *P* value of less than .05 was considered statistically significant. Data are presented as mean ± standard deviation (SD) for all experiments.

RESULTS

FSP1 Expression is Increased in TGF-β-Treated Podocytes

To evaluate the expression of FSP1 in podocytes under TGF-β treatment, we treated podocytes with TGF-β for 24 hours and assessed FSP1 mRNA levels using RT-PCR. The results showed a significant increase in FSP1 expression in TGF-β-treated podocytes compared to the untreated control (Figure 1A). Western blot analysis further confirmed the upregulation of FSP1 at the protein level in TGF-β-treated podocytes (Figure 1B). These results suggest that FSP1 plays a role in the TGF-β-induced changes in podocytes, indicating its potential involvement in podocyte injury.

FSP1 Knockdown Alleviates Podocyte Injury

To assess the functional role of FSP1 in podocyte injury, we knocked down FSP1 expression using siRNA and examined several markers of podocyte health. The CCK8 assay was used to evaluate cell viability. TGF-β treatment significantly reduced cell viability, while FSP1 knockdown reversed this effect, indicating a protective role for FSP1 knockdown in podocyte injury (Figure 2A).

We also performed TUNEL staining to assess cell apoptosis. The results showed that TGF-β

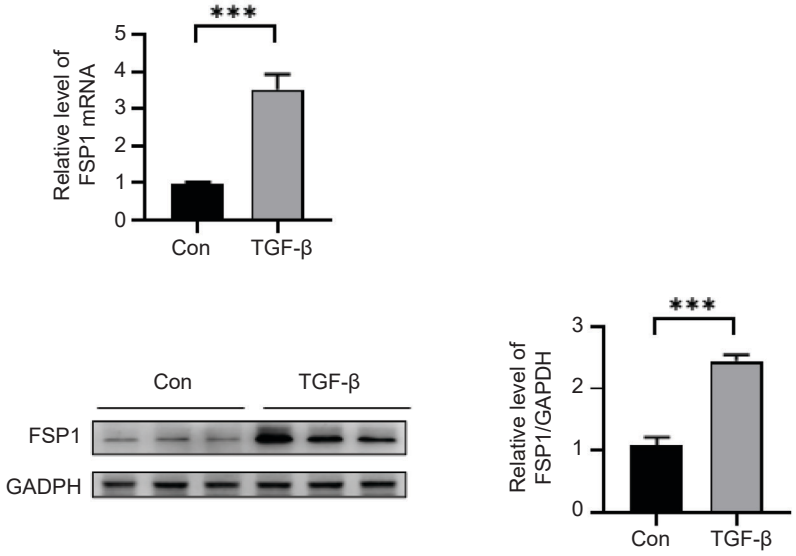


Figure 1. FSP1 Expression is increased in TGF-β-Treated Podocytes. FSP1 mRNA level evaluation by RT-PCR after TGF-β treatment. FSP1 protein level detection by western blot after TGF-β treatment (n = 3) (*P < .05, **P < .01, ***P < .001)

treatment increased podocyte apoptosis, but FSP1 knockdown significantly reduced the number of apoptotic cells (Figure 2B). Additionally, a wound healing assay was used to evaluate cell migration. TGF-β treatment promoted podocyte migration, but this effect was mitigated by FSP1 knockdown (Figure 2C).

Given that the integrity of podocyte foot processes is crucial for maintaining glomerular function, we examined actin stress fiber patterns using F-actin staining. TGF-β-treated podocytes displayed disrupted F-actin fibers, indicative of foot process injury. However, FSP1 knockdown restored the normal stress fiber structure, suggesting its role in protecting podocyte cytoskeletal integrity (Figure 2D). Collectively, these findings demonstrate that FSP1 knockdown reduces podocyte injury caused by TGF-β treatment.

FSP1 Binds to MYH9 and Exacerbates Podocyte Injury

To investigate the molecular mechanisms underlying FSP1-mediated podocyte injury, we used the STRING database to predict potential binding partners of FSP1(Figure 3A). MYH9, a protein known to be involved in cancer invasion and metastasis, was identified as a candidate binding partner of FSP1. To confirm this interaction, we performed a CO-IP assay, which demonstrated that FSP1 binds to MYH9 in podocytes (Figure 3B-C).

Next, we examined the effect of MYH9 knockdown on podocyte injury. MYH9 knockdown reduced cell viability, which had been increased by TGF-β treatment. Similarly, TUNEL staining indicated that MYH9 knockdown decreased cell apoptosis (Figure 3D), and wound healing assays showed a reduction in cell migration (Figure 3E). Furthermore, MYH9 knockdown reduced P38 phosphorylation, a key signaling event in podocyte injury (Figure 3F). These results indicate that FSP1 promotes podocyte injury through its interaction with MYH9, potentially by activating the P38 MAPK signaling pathway[21].

TFP Reduces FSP1-MYH9 Binding and Alleviates Podocyte Injury

Given that TFP has been reported to improve renal function in models of lupus nephritis, we investigated whether TFP could mitigate podocyte injury by targeting the FSP1-MYH9 interaction[22]. CO-IP assays showed that TFP treatment reduced the binding between FSP1 and MYH9 (Figure 4A-B).

We then assessed the effects of TFP on podocyte health. TFP treatment reduced cell viability, which had been elevated by TGF-β treatment. TUNEL staining confirmed that TFP decreased

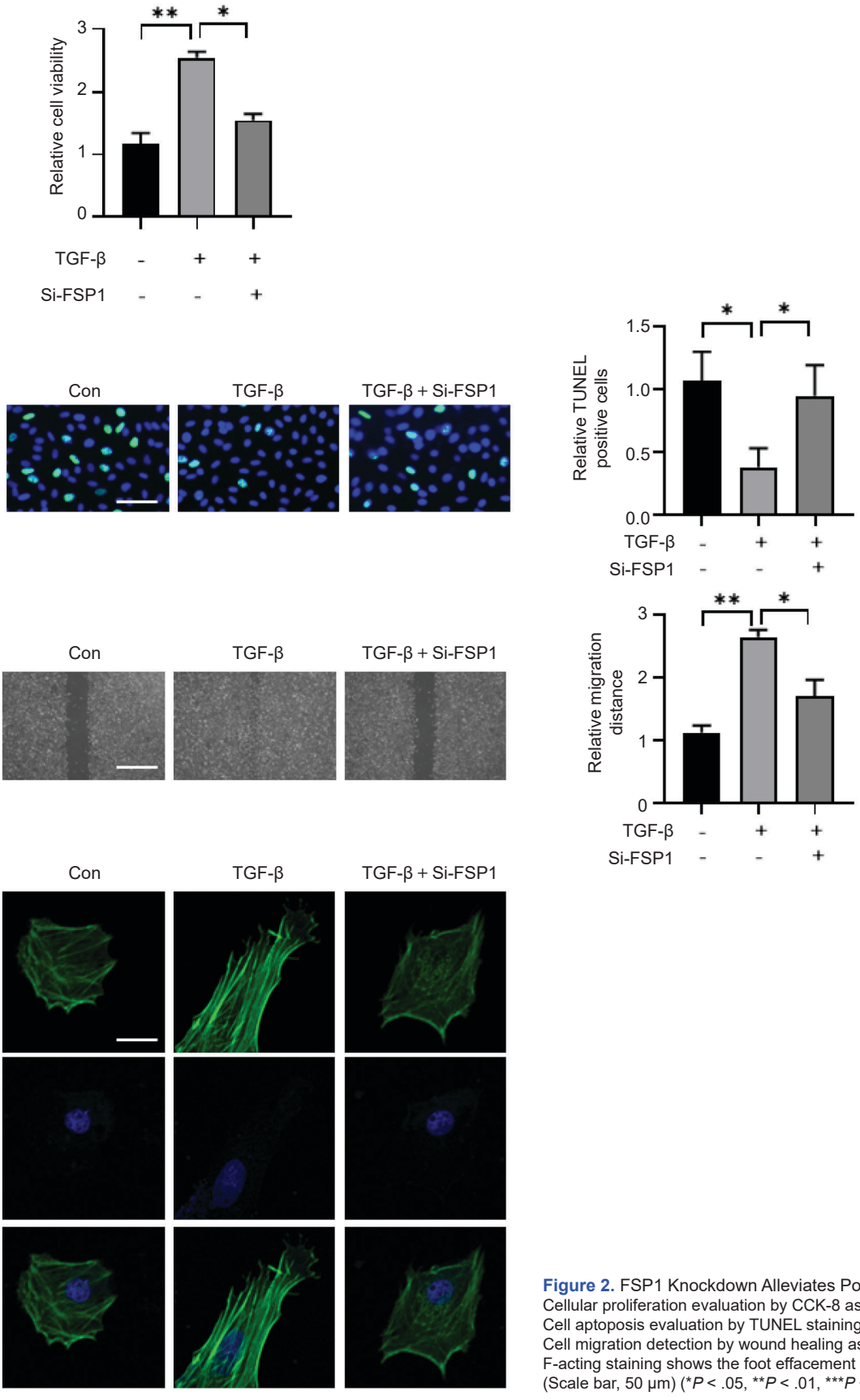
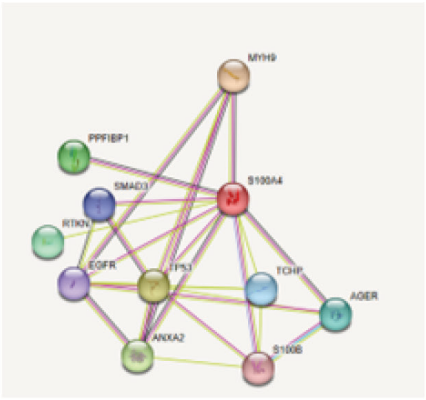
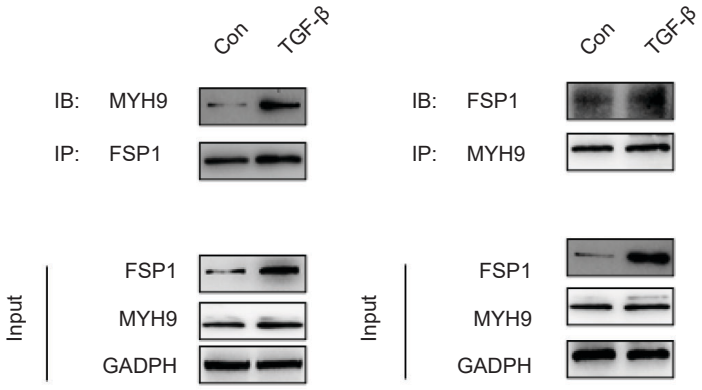
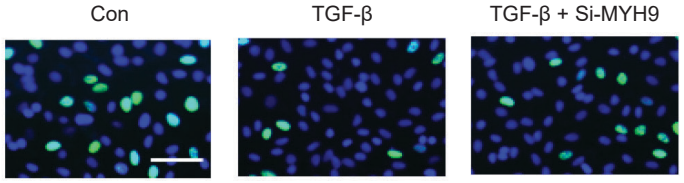
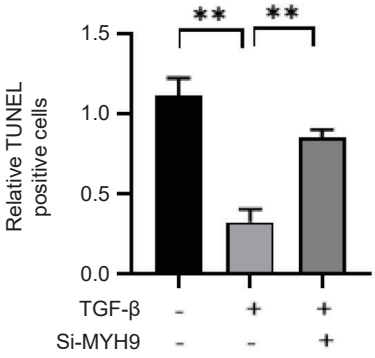


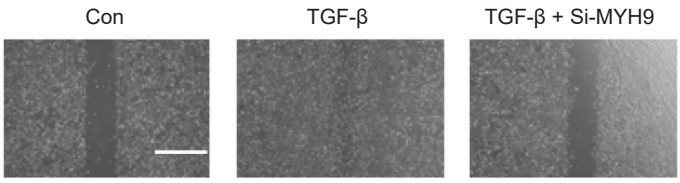
Figure 2. FSP1 Knockdown Alleviates Podocytes Injury
Cellular proliferation evaluation by CCK-8 assay
Cell aptoposis evaluation by TUNEL staining
Cell migration detection by wound healing assay
F-acting staining shows the foot effacement
(Scale bar, 50 μm) (*P < .05, **P < .01, ***P < .001)

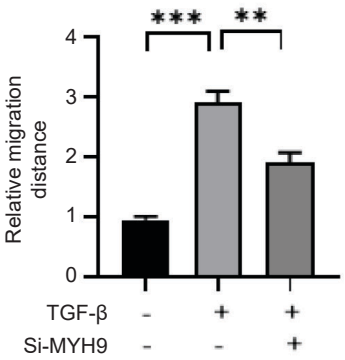


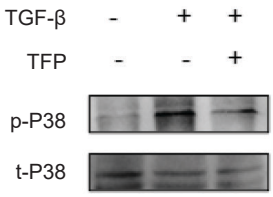












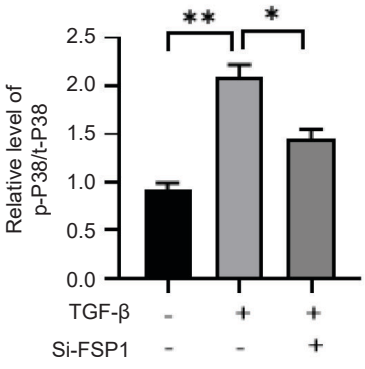


Figure 3. FSP1 Binds to MYH9 and Exacerbates Podocyte Injury
A. String database use to predicate the interaction between FSP1 and MYH9
B-C. Use of CO-IP to indicate that FSP1 could interact with MYH9
D. Cell apoptosis evaluation by TUNEL staining
E. Cell migration was detection by wound healing assay.
F. p-P38 level detection by western blot
(Scale bar, 50 μm) (*P < .05, **P < .01, ***P < .001)

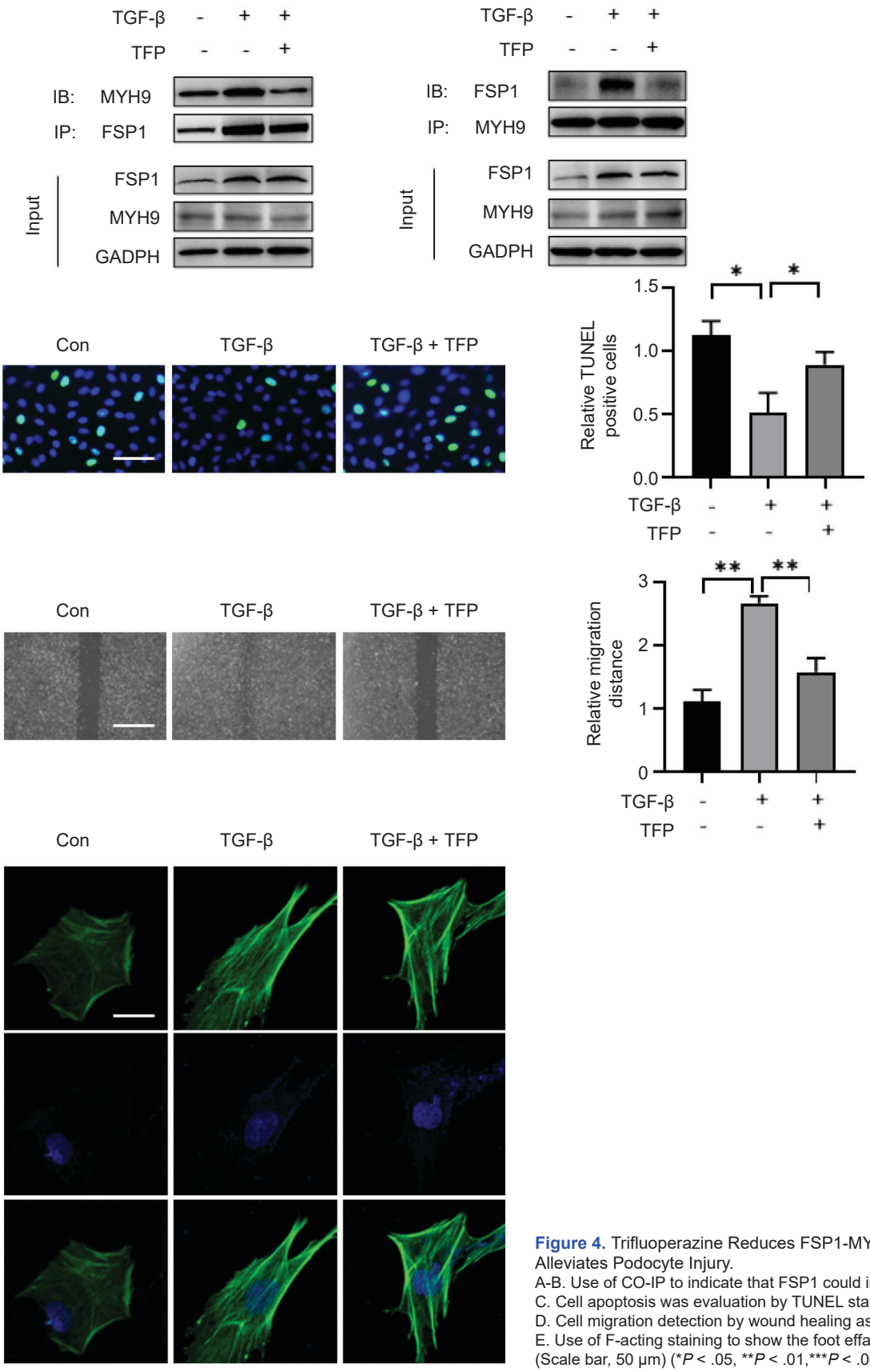


Figure 4. Trifluoperazine Reduces FSP1-MYH9 Binding and Alleviates Podocyte Injury.
A-B. Use of CO-IP to indicate that FSP1 could interact with MYH9.
C. Cell apoptosis was evaluation by TUNEL staining.
D. Cell migration detection by wound healing assay
E. Use of F-acting staining to show the foot effacement
(Scale bar, 50 μm) (**P* < .05, ***P* < .01,****P* < .001)

cell apoptosis (Figure 4C), and wound healing assays showed a reduction in podocyte migration following TFP treatment (Figure 4D). Additionally, F-actin staining demonstrated that TFP treatment restored the normal actin stress fiber structure in podocytes, which had been disrupted by TGF-β treatment (Figure 4E). These results suggest that TFP alleviates podocyte injury by reducing the interaction between FSP1 and MYH9.

DISCUSSION

Podocyte injury is a key contributor to kidney diseases, leading to outcomes such as cell apoptosis, foot process effacement, and eventual kidney dysfunction.[23-5] Increasing evidence has demonstrated that TGF-β plays a central role in regulating cell migration, proliferation, and adhesion in kidney diseases. It has been reported that TGF-β1 activates the Smad and MAPK signaling pathways, promoting integrin-β3 expression.[23,26] Our study further expands on these findings by showing that TGF-β treatment leads to significant changes in podocyte viability, migration, and actin cytoskeleton integrity.

We demonstrated that FSP1 expression is upregulated in podocytes following TGF-β treatment. FSP1 has been recognized as a biomarker in tubulointerstitial fibrosis due to its association with epithelial-to-mesenchymal transition (EMT)-like changes.[27] Previous studies have indicated that FSP1 expression is elevated in high glucose-treated podocytes via the RAC/PAK1 signaling pathway.[28] Our results are consistent with these findings, confirming that FSP1 is upregulated in response to TGF-β in podocytes, contributing to injury.

The role of FSP1 in promoting podocyte injury was further explored through knockdown experiments. We found that FSP1 knockdown significantly reduced podocyte injury by restoring cell viability, reducing apoptosis, and improving cytoskeletal integrity. This suggests that FSP1 may be a key mediator of TGF-β-induced podocyte damage, making it a promising therapeutic target.

Mechanistically, our study identifies MYH9 as a critical binding partner of FSP1 in podocytes. MYH9 is known to play important roles in cell migration, division, and polarization in various cancers. In kidney diseases, MYH9 has been linked to the promotion of mitochondrial fragmentation in acute kidney injury.[29,30] One study showed that MYH9 could activate GSK3β/β-Catenin Signaling to promote esophageal squamous cell carcinoma.[29] However, the interaction between FSP1 and MYH9 in podocyte injury has not been previously described. Our co-immunoprecipitation experiments confirmed that FSP1 binds to MYH9, and MYH9 knockdown reduced podocyte injury by decreasing cell viability and migration. Furthermore, MYH9 knockdown suppressed P38 phosphorylation, a signaling event associated with podocyte injury, implicating the FSP1-MYH9 axis in the activation of the P38 MAPK pathway.

Although our study focuses on in vitro experiments, the relevance of FSP1 and MYH9 in vivo remains to be fully elucidated. The expression of these proteins in actual disease states or conditions that induce podocyte damage has not yet been established. Future studies should explore the expression of FSP1 and MYH9 in clinical samples from patients with kidney diseases such as diabetic nephropathy or lupus nephritis. This will help determine whether these proteins play a functional role in disease progression and whether they could serve as biomarkers or therapeutic targets in vivo.

TFP, a phenothiazine derivative used in clinical practice as an antipsychotic agent, has shown potential in renal protection. TFP has been reported to mitigate doxorubicin-induced cardiotoxicity via the NF-κB pathway and to improve renal function in nephritis models.[30] Our findings suggest that TFP alleviates podocyte injury by disrupting the interaction between FSP1 and MYH9. This reduction in binding between FSP1 and MYH9 resulted in improved podocyte viability, reduced apoptosis, and restored cytoskeletal integrity, highlighting TFP as a potential therapeutic agent for podocyte-related kidney injuries.

Limitations and Future Directions

One limitation of this study is that it was conducted entirely in vitro, which may not fully reflect the complexities of in vivo kidney disease. While we demonstrated the importance of the FSP1-MYH9 interaction in podocyte injury, it

is essential to validate these findings in animal models or clinical samples. Investigating the expression levels of FSP1 and MYH9 in patients with kidney diseases, such as diabetic nephropathy, glomerulonephritis, or lupus nephritis, would provide further insight into their potential as therapeutic targets. Additionally, the pathways downstream of the FSP1-MYH9 interaction, including P38 MAPK activation, warrant further investigation to determine their role in disease progression and treatment.

Our study identifies FSP1 as a critical mediator of TGF-β-induced podocyte injury through its interaction with MYH9. FSP1 knockdown mitigates podocyte damage, while TFP disrupts the FSP1-MYH9 interaction, offering a novel therapeutic strategy for treating podocyte-related kidney injuries. Further in vivo studies are required to establish the clinical relevance of these findings and explore the potential of FSP1 and MYH9 as biomarkers and therapeutic targets.

CONCLUSION

In this study, we demonstrated that FSP1 expression is upregulated in TGF-β-treated podocytes, contributing to podocyte injury. Knockdown of FSP1 significantly alleviated this injury by restoring cell viability, reducing apoptosis, and improving cytoskeletal integrity. Mechanistically, we identified MYH9 as a critical binding partner of FSP1, and the interaction between these two proteins plays a key role in activating the P38 MAPK signaling pathway, exacerbating podocyte damage.

Moreover, we showed that TFP, a clinically available antipsychotic agent, reduces the interaction between FSP1 and MYH9, thereby mitigating podocyte injury. This highlights the potential therapeutic value of TFP in the treatment of podocyte-related kidney injuries.

While our findings offer new insights into the molecular mechanisms of podocyte injury, further in vivo studies are needed to establish the clinical relevance of FSP1 and MYH9 as therapeutic targets and to explore their potential as biomarkers in kidney disease. Overall, our study provides a foundation for developing novel strategies to treat podocyte injury and kidney diseases.

ETHICAL APPROVAL

This study was approved by the Ethics Committee of Nanjing Medical University, approval number IACUC-036594.

INFORMED CONSENT TO PARTICIPATE

Informed consent was not required in this study.

COMPETING INTERESTS

The authors declare that they have no competing interests

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

FUNDING

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Restoration of Monocyte HLA-DR in Sepsis: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Keywords. sepsis, monocyte HLA-DR, immunosuppression, immunomodulatory therapy, meta-analysis

Introduction. Sepsis usually develops into an immunosuppressive state characterized by a reduction in monocyte HLA-DR expression. There have been many immunomodulatory and extracorporeal treatment options proposed to overcome this malfunction, but their overall effectiveness has not been determined.

Methods. Randomized controlled trials were meta-analysed and systematically reviewed to evaluate therapies to restore monocyte HLA-DR expression in patients with sepsis in the adult population. Trials reporting quantitative post-treatment monocyte HLA-DR at an early follow-up time point were included. A random-effects model was used to pool standardized mean differences to control the heterogeneity among assay platforms.

Results. Seven randomized clinical trials included eight treatment groups to be analyzed (a total of 329 subjects). All interventions (cytokine-based interventions, granulocyte-macrophage colony-stimulating factor, interferon-γ, extracorporeal modalities, polymyxin-B hemoperfusion, continuous hemofiltration, hemofiltration–hemoadsorption) resulted in an increase in monocyte HLA-DR expression compared to control conditions. The overall effect size was large and statistically significant (SMD = 1.79, 95% CI: 1.18 to 2.40**).** Heterogeneity was high **(**$I^2 \approx 78\%$**);** however, leave-one-out sensitivity analyses demonstrated the robustness of the results, and the direction of the effect was always positive across all studies.

Conclusions. Immunomodulatory and extracorporeal therapies consistently increase monocyte HLA-DR expression in sepsis, supporting the reversibility of sepsis-induced immunosuppression, with cytokine-based therapies showing the strongest effects. HLA-DR emerges as a key biomarker and therapeutic target, but evidence is limited by small, heterogeneous studies and reliance on surrogate endpoints. Larger, standardized trials with patient-centred outcomes are needed to determine whether HLA-DR restoration improves survival.

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INTRODUCTION

Sepsis is a major cause of mortality across the globe with an estimated 49 million cases and 11 million deaths every year.[1] In spite of the improvement in

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antimicrobial therapy, organ support, and practice of critical-care, mortality in septic shock is still highly persistent. This phenomenon resides to a great extent in the complicated, two-phase nature of immune response that is typical of sepsis, which changes to an initial, hyperinflammatory stage to the next phase of severe immunosuppression.[2-4]

A range of coordinated immune dysfunctions characterizes the immunosuppressive milieu. These include massive lymphocyte apoptosis, which is a hallmark of immune failure caused by sepsis[5,6] and T-cell exhaustion, as indicated by an increase in inhibitory receptors, including PD-1 and impaired effector potential.[7-9] There is also an innate immunity defect: monocyte dysfunction, characterized by a lack of HLA-,DR surface expression and an impaired antigen-presentation capacity, is closely associated with secondary infection rates and poor outcomes.[10-2] Taken together, these aberrations result in a significantly increased vulnerability to nosocomial infections and end-of-life mortality.[13,14]

The most reproducible and informative clinical indicator of innate immune competence among the immunologic biomarkers at present is the monocyte HLA-DR expression. Persistent HLA-DR low levels provide predictive value of secondary infections, extended organ dysfunction, and death in heterogeneous groups of patients with sepsis. As a result, HLA-DR has become one of the major biomarkers of patient with the so-called immunoparalysis caused by sepsis, which has become a new pharmacological target in the sign of immunomodulation.[10-2,14,15] Treatments like granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-γ, and lipopolysaccharide-adsorptive hemoperfusion have been tested on the ability to restore monocyte HLA-DR expression.[16-20] However, there is variability in the results of randomized controlled trials (RCTs); sample sizes are small, and assay methodologies are variable which prevents aggregation of effect size estimates. The consistency of these therapies in restoring HLA -DR expression is still inconclusive.

In addition to interventional studies, there is a larger body of observational evidence which links early low expression of HLA-DR with higher mortality and high risk of secondary infection. The prospective cohort studies and nested analyses continue to show that patients with the lowest HLA-DR levels on postoperative days 1 and 2 are the most susceptible to immunoparalysis, secondary infections, and death. This prognostic aspect of HLA-DR provides a necessary background of explaining its biological and clinical significance and supplements the knowledge gained in the course of interventional studies.[11,12,15]

Here we carried out a study focused on randomized controlled trials evaluating HLA-DR restoration. We conducted a meta-analysis of randomized controlled trials in a systematic manner to detect all the studies that assessed therapeutic interventions that were aimed at modulating monocyte HLA-DR expression. Standardized mean differences (SMDs) were used to normalize disparate assay methodologies. This aspect answers the following research question: Can immune-modulating therapies restore monocyte HLA-DR in sepsis?

Our objective was to: 1) measure therapeutic outcomes in early HLA-DR recovery; and 2) clarify the biological and clinical relevance of HLA-DR restoration within sepsis immunotherapy. Collectively, these analyses aim to elucidate the biological and clinical relevance of HLA-DR in sepsis and outline future directions for personalized immunotherapy.

MATERIALS AND METHODS

Study Design and Protocol

The current study was performed as a systematic review and meta-analysis of randomized controlled trials (RCTs) considering the effects of immunomodulatory therapy on monocyte human leukocyte antigen DR (HLADR) expression in sepsis or septic shock patients. The methodology was followed by PRISMA, and predefined literature identification, screening, eligibility assessment, and inclusion procedures were included. Eligible studies enrolled adults (≥18 years) with sepsis, severe sepsis, or septic shock, and compared an immune-targeting interventions such as granulocyte–macrophage colony-stimulating factor (GM-CSF), interferon-γ, polymyxin-B hemoperfusion (PMX-HP), continuous venovenous hemofiltration (CVVH), hemofiltration with adsorption, or related immunomodulatory strategies to placebo or standard care. Trials were required to report

quantitative post-treatment monocyte HLA-DR values at an early follow-up time point, which served as the outcome for effect-size calculation.

Eligibility Criteria

The eligible trials were randomized controlled trials with a prospective design that enrolled adult patients with sepsis or septic shock and tested an immunomodulatory intervention and reported quantitative HLA -DR outcomes. Excluded were non-randomized or quasi-experimental design, those studies without extractable HLA-DR data, pediatric population, as well as preclinical or conference-only abstracts.

Search Strategy

A comprehensive literature search of PubMed/MEDLINE was performed covering publications from January 1, 2008 through January 2025, without language restrictions. The following Boolean string was used:

((sepsis[MeSH Terms] OR sepsis[Title/Abstract] OR "septic shock"[Title/Abstract])

AND

("HLA-DR"[Title/Abstract] OR "monocyte HLA-DR"[Title/Abstract]

OR mHLA-DR[Title/Abstract] OR "HLA-DR Antigens"[MeSH]))

AND

(randomized controlled trial[Publication Type] OR randomized[Title/Abstract]

OR randomised[Title/Abstract] OR placebo[Title/Abstract] OR trial[Title/Abstract])

Reference lists of included studies and prior systematic reviews were screened manually for additional eligible trials.

Study Selection

Titles and abstracts were first independently screened by two reviewers and then full-text assessment of potentially relevant articles was carried out. The discrepancies were identified by discussion. The process of identifying and screening and including were recorded in a PRISMA flow diagram (Figure 1).

Data Extraction and Harmonization

Extracted data included study characteristics, sepsis definitions, intervention type and dosage, sample sizes, timing of HLA-DR measurement, quantitative assay method (e.g., percentage HLA-DR$^+$ monocytes, antibody-binding capacity, Quantibrite mAb/cell), and reported HLA-DR values with measures of variability. Although baseline values were recorded for contextual comparison, effect-size calculations were based solely on post-treatment HLA-DR measurements at the earliest follow-up time point. The numerical means and standard deviations were extracted by using high-resolution figure digitization when HLA-DR data were reported in the form of graphical data only. In studies that provided medians that had interquartile ranges, the mean and standard deviation were estimated through proven procedures (Wan *et al.*, 2014, Luo *et al.*, 2018). Internal consistency cross-validation of all of the extracted values was conducted.

Handling of Non-Standardized HLA-DR Reporting

Since studies that were included used a variety of HLA-DR measurement platforms, unit systems and statistical forms, a great deal of harmonization was necessary. Standardization of digitized data was done across assays and medians derived values converted to approximate means to allow comparison. All the data of percentages based immunophenotyping, fluorescence intensity and data of the antibody-binding capacity were converted to the standardized mean differences to be used in the meta-analysis.

Risk of Bias Assessment

The Cochrane Risk of Bias 2.0 (RoB 2) tool was used to determine the methodological quality. Each trial was evaluated across domains including the randomization process, deviations from intended intervention, completeness of outcome data, validity of outcome measurement, and selective reporting. Domain-level findings.

Effect Size Calculation

Given the inconsistency of HLA-DR reporting units across studies, treatment effects were quantified using the standardized mean difference (SMD, Hedges g). Variance and standard error estimates were calculated from group sample sizes and pooled

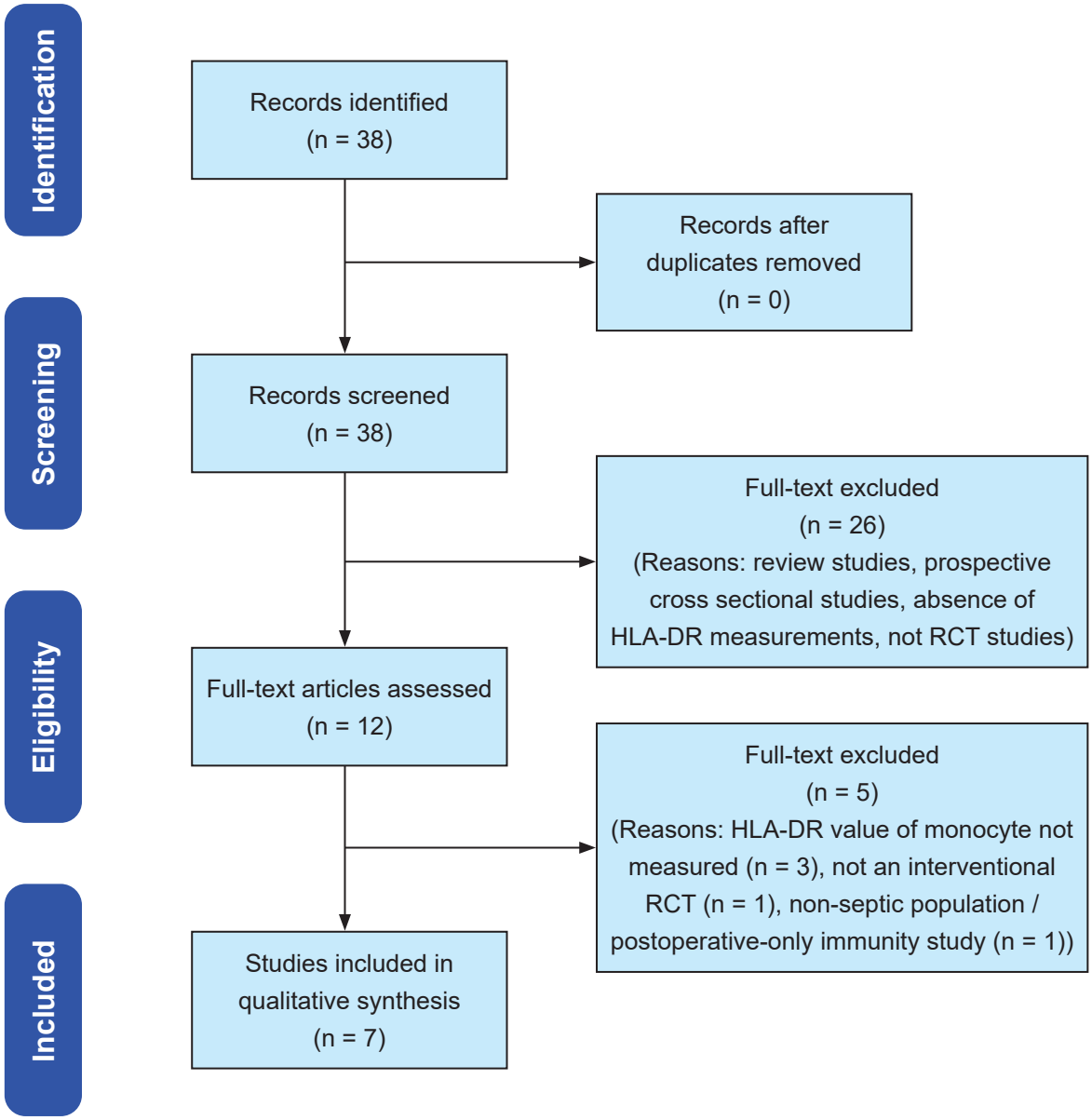

Figure 1. PRISMA flowchart showing the number of records identified, screened, excluded, and assessed for eligibility. A total of 7 studies met the inclusion criteria and were included in the qualitative synthesis.

standard deviations, enabling uniform effect-size comparison despite heterogeneous assays.

Statistical Analysis

A DerSimonian–Laird random-effects model was applied to pool effect sizes. Heterogeneity was quantified using Cochran's Q, the I^2 statistic, and τ^2, reflecting expected clinical and methodological diversity across interventions.

Statistical and Diagnostic Analyses

A meta-regression model was constructed to examine the possible sources of heterogeneity where intervention class (cytokine-based vs. extracorporeal therapies) was used as a moderator. The interpretation was in accordance with standard recommendations which realized the low statistical power of meta-regression with fewer than ten studies. The sensitivity analysis based on leave-one-out sensitivity analysis was used to assess the robustness of the pooled effect estimate by repeating the calculation of the pooled SMD after the removal of each study one by one. The diagnostic of graphical influence was applied to find out whether any of

the trials had disproportionate leverage on pooled outcome. The visual method of determining potential publication bias was to use a funnel plot of effects size versus standard error. According to Cochrane recommendations, funnel plot asymmetry (e.g., Egger regression) is not the subject of formal tests, since less than ten studies are included. Python was used to run all statistical operations and include numeric analyses with numpy and pandas and visualization with matplotlib.

RESULTS

Study Selection

The search process found 40 records in PubMed. Title and abstract screening were conducted after which 12 full-text articles were evaluated to determine their eligibility. Among them, 7 randomized controlled trials were eligible to a quantitative synthesis. The other 5 were omitted because of:

HLA-DR value of monocytes (n = 3) no measurement.

Not an interventional RCT (n = 1)

Non-septic population / postoperative-only immunity studies (n = 1).

Figure 1 presents the PRISMA flow diagram outline of the process of selecting.

Characteristics of Included Studies

The seven included randomized controlled

Table 1. Summary of Study Characteristics, Interventions, HLA-DR Measurement Methods, and Risk of Bias

Study (Author, Year)	Country	Sample Size (I/C)	Intervention Type	Timing / Dose	HLA-DR Measurement Method	Primary Endpoint	Risk of Bias Summary
Meisel, 2009	Germany	18 / 18	GM-CSF	4 μg/kg/d × 5 days, then 4 to 8 μg/kg/d (response-guided)	mHLA-DR (mAb/cell by flow cytometry)	Restoration of monocyte HLA-DR; reversal of immunosuppression	Low–moderate (adequate randomization; open-label design)
Pinder, 2018	UK	13 / 18	GM-CSF	3 μg/kg/d s.c. × 5 days	mHLA-DR (Quantibrite, mAb/cell ×10^3)	Change in HLA-DR at Day 2	Low risk (adequate randomization; blinded laboratory assessment)
GRID, 2023	France	54 / 44	GM-CSF	125 μg/m^2/d s.c. × 5 days	mHLA-DR (standardized flow cytometry, ABC calibration)	Improvement of immune status based on HLA-DR trajectory	Low–moderate (good allocation procedures; open-label design)
Srisawat, 2018	Thailand	26 / 20	PMX-HP (Polymyxin-B hemoperfusion)	Two PMX-HP sessions within 24 h	mHLA-DR (% positive monocytes)	Change in HLA-DR and organ dysfunction	Moderate risk (open-label; unclear allocation concealment)
Lijun, 2015	China	30 / 30	Hemofiltration + HA-330 adsorption	CVVH + HA-330 for 1 to 3 days (4 L/h predilution)	mHLA-DR (% positive monocytes)	HLA-DR recovery and clinical outcomes	Moderate–high risk (open-label; limited protocol standardization)
Peng, 2010	China	20 / 20	CVVH (Hemofiltration)	Early CVVH using HF2000 hemofilter	mHLA-DR (% positive monocytes)	Post-treatment changes in HLA-DR and cytokine levels	High risk (open-label; unclear randomization; incomplete reporting)
Leentjens, 2012 (IFN-γ)	Netherlands	6 / 3	IFN-γ cytokine immunotherapy	IFN-γ 100 μg s.c. daily × 3 days (LPS-challenge human model)	mHLA-DR (% positive monocytes)	Reversal of endotoxin-induced immunoparalysis	Low risk (randomized, objective laboratory endpoints)
Leentjens, 2012 (GM-CSF)	Netherlands	6 / 3	GM-CSF	GM-CSF 3 μg/kg s.c. daily × 3 days (LPS-challenge human model)	mHLA-DR (% positive monocytes)	Reversal of endotoxin-induced immunoparalysis	Low risk (randomized, objective laboratory endpoints)

trials enrolled a total of 329 participants with sepsis or septic shock and evaluated a diverse range of immunomodulatory interventions. Three trials investigated granulocyte–macrophage colony-stimulating factor (GM-CSF)[17,18,20] and one multi-arm trial[21] included both an IFN-γ arm and an additional GM-CSF arm analyzed as separate comparisons. Extracorporeal approaches were represented by polymyxin-B hemoperfusion (PMX-HP),[19] continuous veno-venous hemofiltration (CVVH),[22] and hemofiltration combined with HA330 hemoadsorption.[23] In total, these seven RCTs contributed eight analyzable study arms to the meta-analysis.

Study characteristics-including sample size, intervention details, sampling time points, and HLA-DR measurement platforms-are summarized in Table 1. Because the included trials used heterogeneous laboratory methods (percentage HLA-DR$^+$ monocytes, antibody-binding capacity, and fluorescence-based quantification), all outcomes were expressed as standardized mean differences (SMDs) for comparability. The study-level descriptive statistics (means, standard deviations, and derived values where applicable) and the corresponding effect sizes used in the quantitative synthesis are presented in Table 2.

Effect of Interventions on Monocyte HLA-DR Expression

In eight arms of included randomized controlled trials (329 participants), a heterogeneous mix of immunomodulatory interventions (granulocyte-macrophage colony-stimulating factor and interferon-g), extracorporeal blood-purification methods (polymyxin-B hemoperfusion and continuous veno-venous haemofiltration) and a combination of both hemofiltration and

Table 2. Study-level Quantitative Inputs for the Meta-analysis, Including Effect Size Estimates (Hedges g), Variances, Standard Errors, and Inverse-variance Weights Used in the Pooled Models

Study	Intervention	n (I/C)	HLA-DR Measurement	Timepoint Used	Intervention Mean ± SD (with ranges if applicable)	Control Mean ± SD (with ranges if applicable)	Hedges g	Variance (v)	SE	Weight (1/v)
Meisel 2009	GM-CSF	18 / 18	mHLA-DR (mAb/cell ×10^3)	Day 5	47.3 ± 21.4	19.2 ± 11.2	1.52	0.1451	0.381	6.89
Pinder 2018	GM-CSF	13 / 18	mHLA-DR (mAb/cell ×10^3)	Day 2	56 ± 36.1 (Mean 54–58, SD 33–39)	7 ± 8.5 (Mean 6–8, SD 7.5–9.5)	1.98	0.2001	0.447	5.00
Vacheron 2023 (GRID)	GM-CSF	54 / 44	mHLA-DR (ABC)	Day 3	35,667 ± 20,741 (34k–37.5k; SD 18.5k–22.9k)	7,667 ± 5,926 (7.3k–8k; SD 5.3k–6.6k)	1.65	0.0554	0.235	18.04
Srisawat 2018	PMX-HP	26 / 20	% mHLA-DR	Day 3	37.4 ± 13.8	29.0 ± 12.8	0.62	0.0928	0.305	10.77
Peng 2010	CVVH (Hemofiltration)	20 / 20	% mHLA-DR	Post-treatment	65 ± 12 (Mean 62–68; SD 10.8–13.2)	28 ± 7 (Mean 27–29; SD 6.3–7.7)	3.69	0.2792	0.528	3.58
Leentjens 2012 (IFN-γ)*	IFN-γ	6 / 3	% mHLA-DR	Visit 2 (0 h)	97 ± 3.7 (Median 98 [94–99])	76 ± 5.9 (Median 76 [72–80])	3.92	1.5976	1.264	0.63
Leentjens 2012 (GM-CSF)*	GM-CSF	6 / 3	% mHLA-DR	Visit 2 (0 h)	90.3 ± 9.6 (Median 94 [82 to 95])	76 ± 5.9 (Median 76 [72 to 80])	1.65	0.6945	0.833	1.44
Lijun 2015	Hemofiltration + HA330 adsorption	30 / 30	% mHLA-DR	Day 3	38.9 ± 8.6	29.3 ± 7.1	1.18	0.0787	0.280	12.71

*Leentjens et al. (2012) included two intervention arms (IFN-γ and GM-CSF) sharing a single control group. In accordance with Cochrane recommendations for multi-arm trials, the control group was divided equally across comparisons for variance and weight calculation to avoid double-counting participants.

hemoadsorption protocols consistently boosts monocyte HLA-DR expression compared to control conditions. The reported effect sizes (Hedges g) ranged between 0.62 and 3.92 with consistently positive immunorestorative results regardless of methodological heterogeneity. The therapies based on cytokines had the strongest effects: in three GM-CSF studies, the effect sizes were 1.52, 1.98, and 1.65; and in interferon-g the effect size was 3.92. There were moderate to large effects with polymyxin -B hemoperfusion of 0.62, continuous veno -venous haemofiltration of 3.69, and hemofiltration with HA330 adsorption of 1.18. Collectively, these results support the strong possibilities of both cytokine and blood-purification approaches to restore monocyte HLA-DR expression in immunosuppression related to sepsis (Figure 2).

Pooled Effect Size

Random-effects meta-analysis showed that there was a significant and statistically significant increase in early monocyte HLA-DR expression following immunomodulatory or extracorporeal interventions (pooled SMD = 1.79, 95% CI: 1.18 to 2.40; $P < .001$). This degree of effect is indicative of a powerful, clinically significant sepsis-associated immunosuppression attenuation across a range of therapeutic approaches, including cytokine-based (GM-CSF and interferon-g) and extracorporeal blood-purification (polymyxin-B hemoperfusion, continuous veno-venous haemofiltration, and hemofiltration-hemoadsorption) strategies. Regardless of the patient group and intervention process heterogeneity, the direction of the effect was always positive. The pooled estimate and accompanying prediction interval are illustrated in Figure 2, highlighting the expected range of treatment effects in future comparable studies. Subgroup analyses comparing cytokine therapies with extracorporeal modalities are presented in Table 3 and visualized in Figure 2, demonstrating larger pooled effects for cytokine treatments and moderate-to-large effects for extracorporeal approaches.

Heterogeneity

A random-effects model revealed significant between-study heterogeneity across the eight included treatment arms (Cochran's Q = 32.06, df = 7; $P < .0001$), corresponding to an I^2 of 78.1%

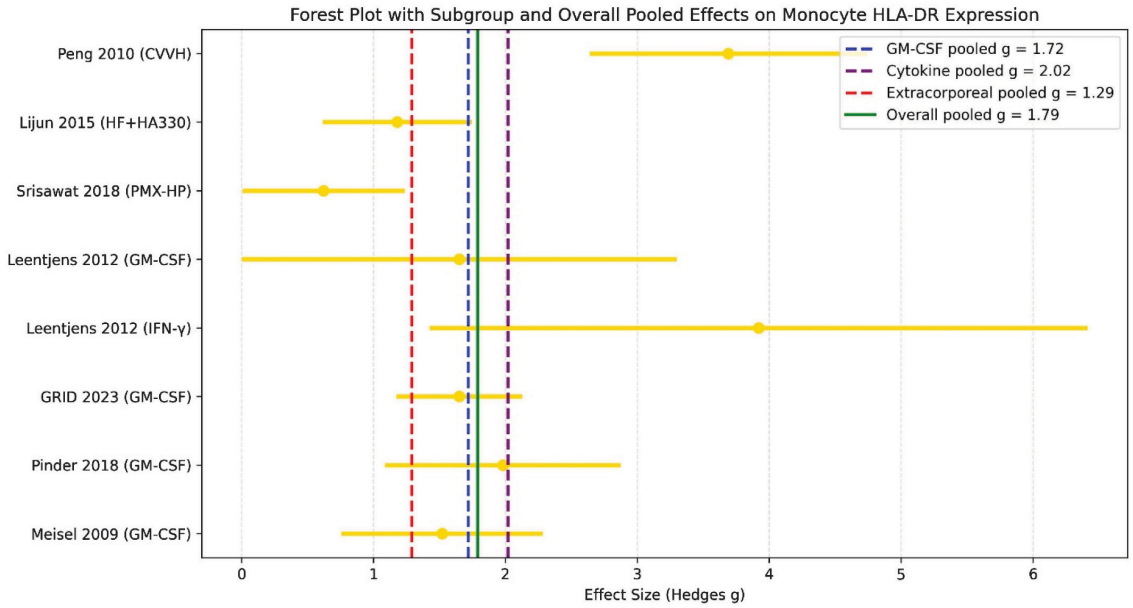

Figure 2. Forest plot showing standardized mean differences (Hedges g) for the effect of cytokine-based immunotherapies (GM-CSF and IFN-γ) and extracorporeal blood purification techniques (PMX-HP, hemofiltration with HA330 adsorption, and CVVH) on monocyte HLA-DR expression across eight randomized trials. Error bars represent 95% confidence intervals. Dashed vertical lines indicate pooled subgroup effects for GM-CSF therapies, all cytokine interventions, and extracorporeal modalities, while the solid green line denotes the overall pooled effect across all studies (g = 1.79). Cytokine therapies showed the largest pooled improvement in HLA-DR expression, followed by moderate-to-large effects from extracorporeal approaches. Positive effect sizes reflect enhanced restoration of monocyte HLA-DR compared with control.

Table 3. Subgroup Analyses of Pooled Standardized Mean Differences (SMDs) for Monocyte HLA-DR Restoration Across Intervention Types, Measurement Methods, and Sampling Time Points

Subgroup	Included Studies	Pooled SMD	Interpretation
Cytokine therapies (GM-CSF, IFN-γ)	Meisel 2009; Pinder 2018; GRID 2023; Leentjens 2012 (IFN-γ, GM-CSF)	≈ 2.02	Largest pooled effect; strongest immunorestorative signal
Extracorporeal therapies (PMX-HP, CVVH, HF+HA330)	Srisawat 2018; Lijun 2015; Peng 2010	1.29	Large effect; consistent but more heterogeneous
Measurement: ABC / mAb per cell	Meisel 2009; Pinder 2018; GRID 2023	1.68	Large pooled effect among quantitative fluorescence assays
Measurement: % HLA-DR$^+$ monocytes	Srisawat 2018; Lijun 2015; Peng 2010; Leentjens 2012	1.39	Large effect across percentage-based immunophenotyping
Day 3 sampling	GRID 2023; Srisawat 2018; Lijun 2015	≈ 1.50*	Moderate-to-large early immune restoration effect
Day 4–5 sampling	Meisel 2009	—	Only one study; pooled estimate not calculable

and a between-study variance of $\tau^2 = 0.53$ under a random-effects model. This difference is likely to be attributed to differences in intervention modality, timing and dose, severity of illness at baseline, and laboratory methods used to measure monocyte HLA-DR expression. The positive treatment effect was however observed in all studies, which was a support of a consistent biological signal in various immunomodulatory and extracorporeal strategies. A Cochrane Risk of Bias 2 tool was used to assess the methodological quality, and domain-level assessments are presented in Table 1. Randomised trials based on cytokines generally imposed a low-low to moderately risk of bias which was accepted given proper randomisation, allocation processes and objective laboratory outcomes of monocyte HLA-DR. On the other hand, trials of extracorporeal therapies showed a high risk of bias in a variety of areas, which can be explained by open-label designs, poor reporting of allocation concealment, variation among procedures, and insufficient protocol standardisation. Although such limitations in the methodology occurred, outcome assessment was mostly objective and there was no selective reporting in any of the trials.

Meta-regression Analyses

A meta-regression that included intervention class as a modulator (cytokine versus extracorporeal therapy) did not find any statistically significant determinant of the heterogeneity observed ($\beta = 0.43$, $P = .49$; $R^2 = 8.4\%$). Although cytokine therapies tended to show larger effects, intervention type accounted for only a small proportion of between-study variance. This finding suggests that heterogeneity more likely reflects differences in study design, timing of intervention, baseline immune suppression, and laboratory quantification methods rather than treatment class alone (Figure 3).

Sensitivity Analyses

Leave-one-out sensitivity analyses demonstrated that the pooled effect was highly robust to the removal of any single study. Excluding the highest-effect trial (Leentjens 2012, IFN-γ) yielded a pooled SMD of 1.74 (95% CI: 1.10 to 2.38), whereas excluding the lowest-effect study (Srisawat 2018, PMX-HP) increased the pooled estimate to 1.90 (95% CI: 1.25 to 2.55). Across all permutations, the pooled effect size remained large in magnitude, directionally consistent, and statistically significant, indicating that no individual study exerted undue influence on the overall result. The complete set of leave-one-out recalculations is displayed in Figure 4, with corresponding numerical outputs summarized in Table 4.

Publication Bias

Visual inspection of the funnel plot (Figure 5) showed no marked asymmetry or small-study clustering. As recommended for analyses with < 10 studies, formal statistical tests for funnel plot asymmetry were not performed.

DISCUSSION

This meta-analysis and systematic review shows that a variety of immunomodulatory interventions, such as cytokine therapy and extracorporeal

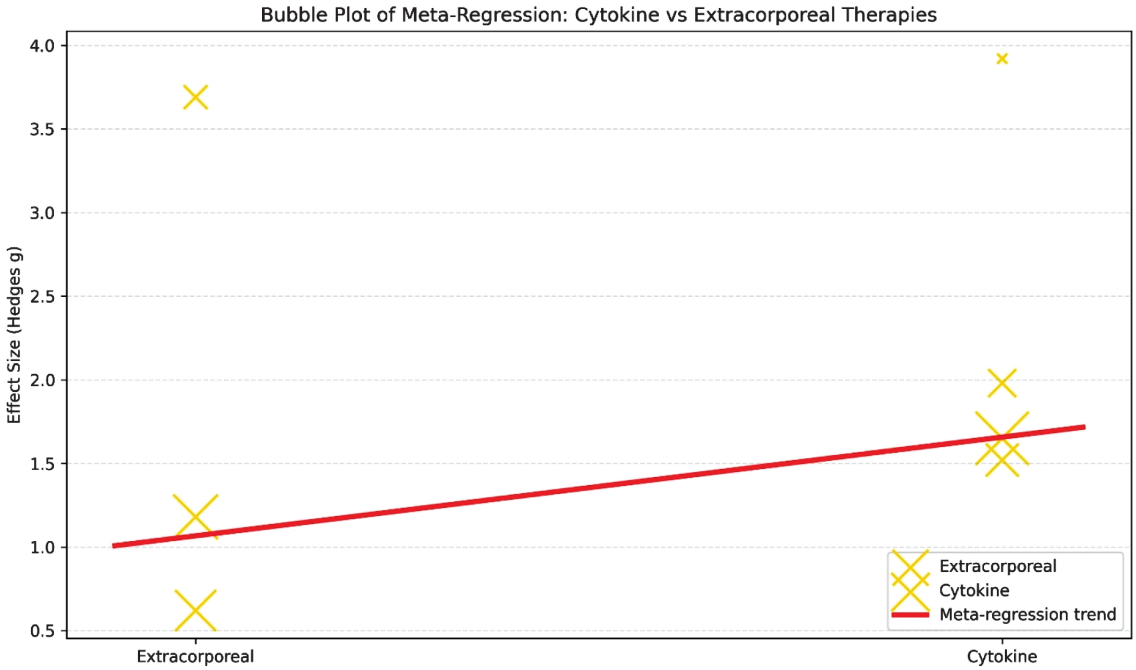

Figure 3. Bubble plot illustrating the meta-regression analysis evaluating whether intervention class (cytokine-based vs. extracorporeal therapies) moderates the effect of treatment on monocyte HLA-DR expression. Each circle represents a study arm, with bubble size proportional to study precision (inverse variance). The red line depicts the weighted regression trend. Cytokine therapies tended to demonstrate larger effect sizes than extracorporeal approaches; however, the moderator effect was not statistically significant (β = 0.43, SE = 0.58; *P* = .49), and intervention class accounted for only a small proportion of between-study heterogeneity (R^2 = 8.4%).

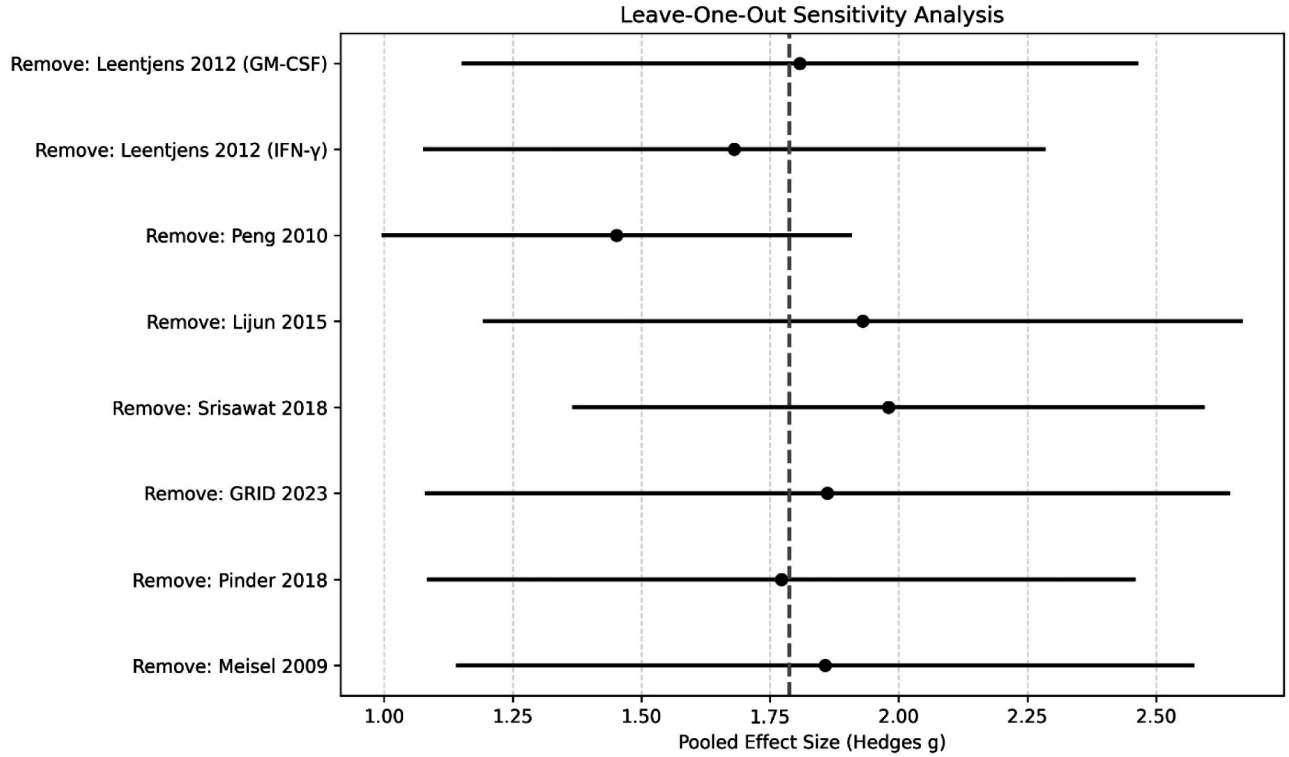

Figure 4. Leave-one-out sensitivity analysis showing the influence of individual studies on the overall pooled effect of immunomodulatory and extracorporeal interventions on monocyte HLA-DR expression. Each point represents the random-effects pooled estimate after removal of the indicated study, with horizontal bars showing 95% confidence intervals. The dashed vertical line indicates the overall pooled effect from all included studies. The pooled estimate remained stable across all iterations, indicating that no single study disproportionately influenced the overall effect.

Table 4. Leave-One-Out Sensitivity Analysis of Pooled Effect Sizes

Study Removed	Pooled SMD	95% CI	Change vs Full Model (1.79)
Meisel, 2009	1.80	1.18 – 2.41	+0.01
Pinder, 2018	1.76	1.14 – 2.38	–0.03
GRID, 2023	1.75	1.12 – 2.38	–0.04
Leentjens, 2012 (IFN-γ)	1.74	1.10 – 2.38	–0.05
Leentjens, 2012 (GM-CSF)	1.78	1.16 – 2.40	–0.01
Srisawat, 2018 (PMX-HP)	1.90	1.25 – 2.55	+0.11
Lijun, 2015 (HF + HA330)	1.85	1.21 – 2.49	+0.06
Peng, 2010 (CVVH)	1.60	1.02 – 2.18	–0.19

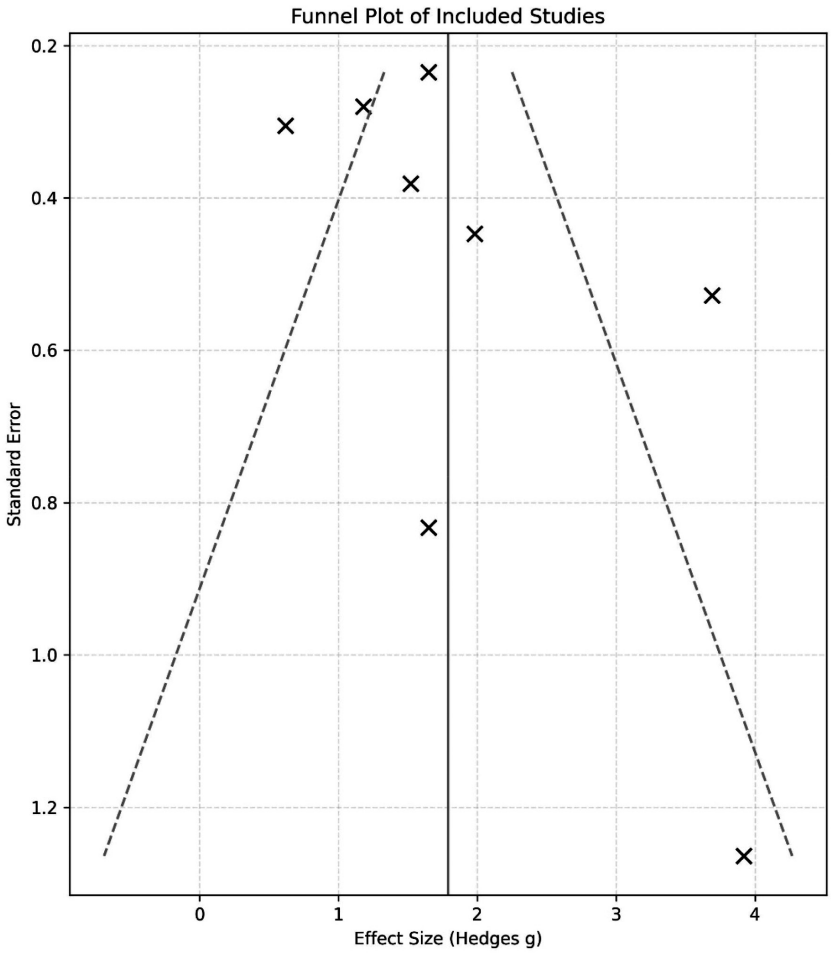

Figure 5. Funnel plot of included study arms showing effect size (Hedges g) plotted against standard error. The vertical line represents the random-effects pooled estimate, and dashed lines indicate the 95% pseudo-confidence limits. Visual inspection suggests some asymmetry; however, interpretation is limited by the small number of studies and substantial between-study heterogeneity.

blood purification, are all capable of enhancing the monocyte HLA-DR expression in adult sepsis patients. In seven randomized controlled trials with eight arms, each of the interventions enhanced HLA-DR compared to control and the combined effect size (standardized mean difference = 1.79) showed a significant reversal of sepsis-induced impairment of antigen-presenting capacity. This evidence supports the idea that sepsis-associated immunosuppression is a manipulable biological phenotype and that HLA-DR is a responsive immune early biomarker of immune restoration.[12,17-24]

Nonetheless, the level of heterogeneity ($I^2 \approx 80\%$) points to the fact that the analyzed studies vary significantly in terms of design, patient population, intervention, and measurement. Though the direction

of effect was similar, the magnitude was significantly different, which limited the interpretability of one pooled estimate. To explore this variability, a meta-regression was undertaken in which intervention class served as a moderator. The larger effect sizes were more often with cytokine therapies, although the type of intervention only explained a modest fraction of the heterogeneity, and thus it is probable that variation in the timing of sampling, the approach of measuring the assays, the underlying immune status, and clinical severity also play a role. Notably, this result is relevant to mention the major limitation: the pooled effect implicitly assumes biological and clinical similarity between interventions- a premise that is hardly likely to hold.

Further analysis of the quality of the studies only confirms the issue. The trials assessing extracorporeal therapies were characterized by a greater risk of bias, which could be explained by the open-label design, lack of clarity with regard to randomization methods, or lack of completeness in reporting.[19,22,23] Conversely, cytokine-based randomized controlled trials, especially those experiments that focused on granulocyte-macrophage colony-stimulating factor, were generally better designed and thus more valid.[17,18,20,21] Therefore, despite the fact that both of therapeutic classes enhanced the HLA-DR expression, there is much more evidence provided in favor of cytokine therapies than in extracorporeal modalities.

Mechanistically, these approaches differ fundamentally. Cytokines such as GM-CSF and IFN-γ are direct biological signals that stimulate monocyte differentiation, antigen-presenting ability and sensitivity to microbial stimuli.[14,25-7] The IFN-γ study by Leentjens *et al.* demonstrated the largest immunorestorative effect in the dataset,[21] highlighting the potency of targeted cytokine signaling. In contrast, extracorporeal therapies function indirectly, primarily through removal of endotoxins and inflammatory mediators that inhibit monocyte function. Such detoxification or mediator-modifying effects alter the inflammatory environment and create conditions permissive for endogenous immune recovery rather than directly stimulating immune activation. These mechanistic distinctions warn against considering any evidence of improvement in HLA-DR to mean that there is any therapeutic equivalence between these radically different modalities-particularly in terms of feasibility, cost, scale and clinical advantage.

The most evident constraint is, probably, the dependence on a surrogate biomarker. Reduced monocyte HLA-DR expression is closely linked with high mortality, secondary infections, and inability to recover organ dysfunction.[12,14,24] However, it is not clear because it is still undecided whether interventions that restore HLA-DR eventually enhance clinical outcomes. The majority of the trials that were incorporated were small and short term with early immunological end points being reported instead of infection rates, organ recovery, or survival. Thus, in spite of the biological signal, the evidence cannot be generalized to say that patient-centered outcomes have been improved, and such a generalization may lead to overinterpretation of surrogate markers, which is a well-established drawback of critical care studies.

The strong points of this analysis are that it only uses randomized evidence, standardizes measurements of heterogeneous HLA-DR into standardized effect sizes, and it contains multiple mechanistically distinct therapies. However, weaknesses should also be considered: the minimal sample sizes, discrepancy in assay methodologies, and incomplete blinding in a few studies and the use of digitized or reconstructed data to obtain some results. These considerations explain why bigger, strictly designed multicenter trials using standardized flow cytometry protocols and assessing clinically meaningful endpoints are necessary.

Future Directions

Further studies should concentrate on the validation of biomarker-based immunotherapy interventions, which involve the use of HLA-DR in determining patients with immunoparalysis that is related to sepsis. There is an urgent necessity of standardizing monocyte HLA-DR quantification by having harmonized flow cytometry protocols and calibration materials to allow cross-centre comparison. Comparative trials will be crucial to compare the efficacy of cytokine-based and extracorporeal intervention, mechanism of action, and clinical applicability. Finally, multicenter

randomized trial with patient outcome powered but not solely using surrogate biomarkers is necessary to assess the meaningfulness of immunorestorative therapies in terms of their effect on the outcomes of infection, organ recovery, and survival.

CONCLUSIONS

Altogether, immunomodulatory treatments, such as cytokines, extracorporeal modalities, are regularly associated with enhanced monocyte HLA -DR expression in adult sepsis patients, which suggests that the immunosuppressive effects of sepsis are a reversible biological phenomenon. Even though the response of this biomarker is strong regardless of the type of intervention, cytokine-based interventions have higher levels of evidence, and HLA-DR improvement is not yet a factor that can be converted into clinical benefit. There exist important heterogeneity, methodological constraints, and dependence on surrogate endpoints, and therefore, there is a necessity to conduct rigorously designed trials with harmonized immune monitoring and meaningful clinical outcomes. These discoveries have formed the basis of future accuracy immunotherapy interventions that are intended to restore immune competence in sepsis.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article and its supplementary materials. Extracted numerical data derived from published figures were obtained using validated digitization methods and are available from the corresponding author upon reasonable request.

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AUTHORS CONTRIBUTIONS

F.J.G. conceived the study, designed the protocol, performed data extraction, statistical analysis, and drafted the manuscript.

I.A.D. independently screened studies, verified extracted data, and contributed to interpretation of results. All authors critically revised the manuscript for important intellectual content and approved the final version.

ETHICS APPROVSL AND CONSENT TO PARTICIPATE

Not applicable. This study is a systematic review and meta-analysis of previously published data and did not involve new data collection from human participants.

CONFLICT OF INTEREST

Ilad Alavi Darazam is a member of the editorial team of RJCCN. The author had no involvement in the peer-review or editorial decision-making process for this manuscript.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Artificial intelligence–assisted tools were used to support language editing, data visualization, and computational scripting. All scientific decisions, analyses, and interpretations were performed by the authors, who take full responsibility for the content of this manuscript.

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Acute Kidney Injury in Adult Patients Receiving Extracorporeal Membrane Oxygenation: A Systematic Review

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Keywords. extracorporeal membrane oxygenation, ECMO, acute kidney injury, renal replacement therapy, CRRT, mortality

Introduction. Acute kidney injury (AKI) is a frequent and clinically important complication in adults receiving extracorporeal membrane oxygenation (ECMO), yet reported incidence and associated outcomes vary widely due to differences in populations, ECMO configuration, and AKI definitions. We systematically reviewed full-text studies reporting AKI and related outcomes in adult patients supported with veno-arterial (VA) and/or veno-venous (VV) ECMO.

Methods. A systematic search of PubMed identified 661 records; 660 remained after deduplication. Full texts available for assessment were screened for eligibility (n = 126). We included original adult ECMO/ECLS studies reporting extractable AKI and/or renal replacement therapy (RRT/CRRT) outcomes.

Results. Forty-five studies were included in qualitative synthesis. AKI incidence was extractable in 29 studies and ranged from 2.3% to 89.0% (median 50.5%). RRT/CRRT use was extractable in 29 studies and ranged from 1.8% to 91.0% (median 53.3%). Mortality was extractable in 37 studies (ICU, in-hospital, or 30-day) and ranged from 6.0% to 95.0% (median 53.3%). KDIGO was the most frequently referenced AKI definition (reported in 26 studies), followed by RIFLE (19) and AKIN (11), with overlap across studies.

Conclusions. AKI and RRT/CRRT use are common in adults receiving ECMO, with substantial variability driven by clinical heterogeneity and inconsistent AKI definitions and outcome reporting. Standardized AKI definitions and harmonized reporting of renal and mortality outcomes are needed to improve comparability and guide future ECMO–kidney research.

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INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) has become an established form of temporary life support for adults with refractory respiratory failure (veno-venous, VV-ECMO) and/or circulatory collapse (veno-arterial, VA-ECMO), particularly when conventional therapies fail.[1] Over the last decade, adult ECMO utilization has expanded substantially worldwide, supported by improved technology, increasing clinician experience, and growing guidance from international societies.[2] This growth is also reflected in large registry data: the Extracorporeal Life Support Organization (ELSO) Registry reports continuing increases in adult

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ECMO activity across participating centers and provides contemporary benchmarks for outcomes and complications.[3] Randomized and comparative evidence in severe acute respiratory distress syndrome (ARDS)—including the CESAR trial and the EOLIA trial—has further shaped modern ECMO practice and contributed to broader adoption, especially in high-volume referral centers.[4,5]

Acute kidney injury (AKI) is one of the most common and clinically significant complications experienced with ECMO support. AKI as it is known in this context is usually multifactorial and results in a complex interaction of critical illness physiology and ECMO-specific factors. First, many patients are started on ECMO because they are suffering from profound hemodynamic and/or respiratory failure; systemic hypoperfusion, venous congestion, exposure to vasopressors, and shock-inflammation all predispose the kidney to injury.[6] Second, ECMO may alone contribute to injury by interactions between blood and surfaces that increase inflammation and complement activity, hemolysis and pigment nephropathy, non-pulsatile bloodflow (especially relevant to VA-ECMO physiology) and conflicting clinical priorities (anticoagulation, transfusion, and bleeding).[7] Third is that fluid overload is prevalent among ECMO patients due to capillary leak, large-volume resuscitation and transfusion requirements; and a positive fluid balance is consistently linked to poor outcomes and is tightly interwoven with AKI development and renal replacement therapy (RRT) requirement.[8] Finally, concomitant exposures such as sepsis, nephrotoxic antimicrobials, iodinated contrast and rhabdomyolysis predispose a population that is already susceptible to multi-organ dysfunction to AKI.[6]

The clinical significance of AKI during ECMO is high. AKI is associated with increased mortality, longer intensive care unit (ICU) hospital stays and increased resource utilisation, especially if RRT is necessary.[9,10] The long-term consequences of severe AKI, besides the acute hospitalization, survivors may continue to be at high risk for chronic kidney disease (CKD), end-stage kidney disease and long-term mortality consequences that further amplify the individual and health system burden of ECMO-associated renal injury.[9] Because RRT is often utilised during ECMO for indications that include refractory fluid overload, severe AKI, electrolyte/acid-base disturbances, and uremia, the interface of ECMO and RRT has emerged as a critical practical domain in critical care nephrology.[7] One of the most challenging issues is that AKI incidence is reported widely across the literature in the adult ECMO population. Such variability is in part accounted for by heterogeneous patient populations (VA vs. VV ECMO, different case-mix and severity of illness), different time windows used to identify AKI (e.g., at the time of cannulation, during the ECMO run, or after decannulation), and inconsistencies in the estimation of baseline creatinine and urine output expression[6]. Importantly, the AKI definition chosen has a material impact on the estimate of occurrences. Previous consensus systems like the RIFLE criteria and Acute Kidney Injury Network (AKIN) classification were proposed to standardize the diagnosis and severity of this type of illness and subsequently, the Kidney Disease: Improving Global Outcomes or KDG - a contemporary guideline - incorporated parts of both systems into a widely accepted and applied framework.[11,12] Nonetheless, ECMO studies often use mixed definitions, use modified criteria or omit important components (especially urine output), so comparability may be limited and synthesis of the evidence may be complicated. This heterogeneous approach is causing uncertainty amongst clinicians and researchers concerned about obtaining robust estimates of AKI prevalence, RRT utilisation and associated outcomes in adult ECMO populations.

Study Aim

The primary aim of this systematic review is to summarize the incidence and definitions of AKI among adult patients receiving VA-ECMO and/or VV-ECMO. Secondary aims are to describe the reported use of RRT/continuous RRT (CRRT) and mortality outcomes (e.g., ICU, in-hospital, or short-term mortality as reported), and to identify key reporting gaps that limit cross-study comparability and clinical translation.

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.[13] A review protocol was developed before screening and data extraction. The protocol was not registered in PROSPERO (International Prospective Register of Systematic Reviews).

Eligibility Criteria

Studies were eligible if they met the following criteria:

Population. Adult patients (≥ 18 years) receiving ECMO/extracorporeal life support (ECMO/ECLS), including veno-arterial (VA) and/or veno-venous (VV) configurations

Study Types. original research (e.g., cohort studies, registry analyses, case-control studies, or clinical trials)

Outcomes. reported extractable data for at least one of the following—AKI incidence and/or AKI definition, renal replacement therapy (RRT) or continuous renal replacement therapy (CRRT) utilization, and mortality outcomes (ICU mortality, in-hospital mortality, or 30-day mortality as reported). Studies were excluded if they focused on pediatric or neonatal populations, were review articles/meta-analyses/editorials/letters, were case reports or small case series, lacked extractable renal outcome data, or clearly represented overlapping cohorts where a more complete or larger dataset was available (in which case the most comprehensive report was retained).

Information Sources

The primary information source was PubMed (National Library of Medicine). Additional free full-text sources were used only for retrieval of articles when available (e.g., PubMed Central, publisher "free full text" links, and publicly accessible PDFs). The final search was performed on 20/12/2025.

Search Strategy

The search strategy combined terms for: 1) ECMO/ECLS (e.g., "extracorporeal membrane oxygenation," ECMO, ECLS, and related terms), and 2) kidney outcomes (e.g., "acute kidney injury," AKI, "renal replacement therapy," RRT, CRRT, dialysis).

Study Selection Process

All records retrieved from PubMed were exported and imported into Zotero for reference management and screening. Duplicate records were identified and removed within Zotero. Screening was performed in two stages: 1) Title/abstract screening to identify potentially eligible studies, and 2) Full-text eligibility assessment for those advanced to retrieval. Full texts were obtained using open-access links and web-based retrieval where available. Screening was conducted by two reviewer using predefined criteria; uncertain eligibility decisions were resolved through discussion among the authors to ensure consistency.[13]

Data Extraction

A standardized extraction form was used to collect the following information from each included study: study design, setting, publication year, sample size; ECMO configuration (VA, VV, or mixed) and primary clinical indication when reported; AKI definition (e.g., KDIGO, RIFLE, AKIN, or other); AKI incidence (n/N and/or %); RRT/CRRT use (n/N and/or %); and mortality outcomes (type and rate, including ICU, in-hospital, or 30-day mortality). When outcomes were not reported in extractable numeric form, they were recorded as not reported (NR) or not extractable, and denominators were allowed to vary across outcomes.

Risk of Bias Assessment

Risk of bias for observational studies was planned to be assessed using the Newcastle–Ottawa Scale (NOS), evaluating domains of selection, comparability, and outcome assessment. Studies were to be categorized as low, moderate, or high risk of bias based on overall NOS domain performance. If any randomized trials were identified, an appropriate randomized trial risk-of-bias tool (e.g., RoB 2) would be applied.[14]

Synthesis Approach

A narrative synthesis with tabulation of study characteristics and outcomes was performed. Meta-analysis was not undertaken because of substantial heterogeneity across studies in patient populations (VA vs. VV and differing indications),

AKI definitions (KDIGO/RIFLE/AKIN or unspecified), and outcome windows (timing of AKI ascertainment and mortality endpoints), which limits statistical comparability and interpretability of pooled estimates.[15]

RESULTS

Study Selection

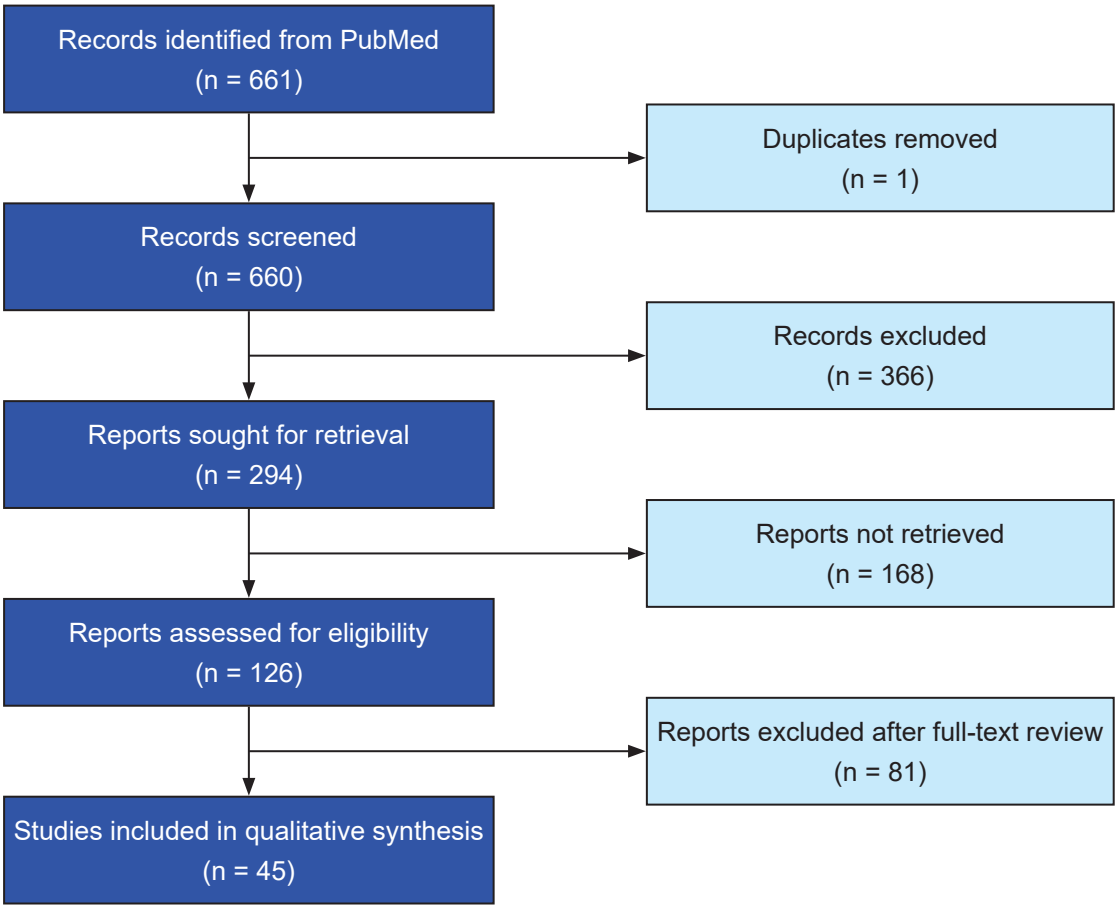
The PubMed search identified 661 records. After deduplication in Zotero, 660 records remained for title/abstract screening. Following screening, 366 records were excluded and 294 reports were sought for full-text retrieval. Because of access limitations, 168 reports could not be retrieved. In total, 126 full-text articles were assessed for eligibility, and 81 were excluded after full-text review. Finally, 45 studies were included in the qualitative synthesis. Not all studies reported each outcome in an extractable form; therefore, denominators vary across outcomes (Figure).

Characteristics of Included Studies

The included studies were predominantly observational (most commonly retrospective cohorts and registry-based analyses) of adult patients receiving VA-ECMO, VV-ECMO, or mixed ECMO configurations in ICU and cardiothoracic critical care settings. Indications reflected typical adult ECMO practice (e.g., severe respiratory failure/ARDS for VV-ECMO and cardiogenic shock or post-cardiotomy support for VA-ECMO), although case-mix and reporting varied across studies (Table 1).

AKI Definitions Used

AKI definitions were heterogeneous. KDIGO criteria were most frequently referenced, followed by RIFLE and AKIN, with overlap in some reports. Several studies did not clearly specify a standardized AKI definition in readily extractable text. Variability in definition choice and ascertainment windows likely contributed to the wide range of AKI incidence reported.



PRISMA Flow Diagram for Study Selection

Table 1. Characteristics of Included Studies (Adult VA/VV ECMO) and AKI Definitions

Study (first author, year)	Title	Journal	DOI	ECMO configuration (detected)	AKI definition (detected)
Lau, 2025	Kidney replacement therapy during extracorporeal membrane oxygenation: pathophysiology, technical considerations, and outcomes	Renal Failure	10.1080/0886022X.2025.2486557	Mixed (VA+VV)	KDIGO, RIFLE, AKIN
Chu, 2024	Risk factors for mortality in patients with sepsis on extracorporeal membrane oxygenation and/or continuous renal replacement therapy: a retrospective cohort study based on MIMIC-IV database	Renal Failure	10.1080/0886022X.2024.2436106	Mixed (VA+VV)	KDIGO
Li, 2024	Acute kidney injury and cardiogenic shock severity for mortality risk stratification in patients supported with VA ECMO	ESC heart failure	10.1002/ehf2.14967	VA	KDIGO, RIFLE, AKIN
Gao, 2023	Extracorporeal membrane oxygenation and acute kidney injury: a single-center retrospective cohort	Scientific Reports	10.1038/s41598-023-42325-5	Mixed (VA+VV)	KDIGO, RIFLE, AKIN
Askenazi, 2012	Renal replacement therapy in critically ill patients receiving extracorporeal membrane oxygenation	Clinical journal of the American Society of Nephrology: CJASN	10.2215/CJN.12731211	Mixed (VA+VV)	RIFLE
Chen, 2023	Independent risk factors of acute kidney injury among patients receiving extracorporeal membrane oxygenation	BMC nephrology	10.1186/s12882-023-03112-6	VA	KDIGO
Coelho, 2023	Factors associated with acute kidney injury in patients undergoing extracorporeal membrane oxygenation: retrospective cohort	Revista Da Escola De Enfermagem Da U S P	10.1590/1980-220X-REEUSP-2022-0299en	Mixed (VA+VV)	KDIGO, RIFLE
Gaisendrees, 2021	Gender-related differences in treatment and outcome of extracorporeal cardiopulmonary resuscitation-patients	Artificial Organs	10.1111/aor.13844	VV	Creatinine/urine output criteria (unspecified)
Shin, 2023	Higher Rates of Dialysis and Subsequent Mortality in the New Allocation Era for Heart Transplants	The Annals of Thoracic Surgery	10.1016/j.athoracsur.2022.07.017	VA	KDIGO, RIFLE
Forker, 2019	Postreperfusion plasma endothelial activation markers are associated with acute kidney injury after lung transplantation	American Journal of Transplantation	10.1111/ajt.15402	Unclear	KDIGO, RIFLE, AKIN
Kim, 2021	Risk factors and mortality of acute kidney injury within 1 month after lung transplantation	Scientific Reports	10.1038/s41598-021-96889-1	Unclear	KDIGO, RIFLE, AKIN
Yeh, 2015	Use of Extracorporeal Membrane Oxygenation to Rescue Patients With Refractory Ventricular Arrhythmia in Acute Myocardial Infarction	Medicine	10.1097/MD.0000000000001241	VA	KDIGO, RIFLE
Lin, 2017	Extracorporeal membrane oxygenation support in post-traumatic cardiopulmonary failure: A 10-year single institutional experience	Medicine	10.1097/MD.0000000000006067	Mixed (VA+VV)	KDIGO, RIFLE
Marella, 2020	Effectiveness of Vancomycin Dosing Guided by Therapeutic Drug Monitoring in Adult Patients Receiving Extracorporeal Membrane Oxygenation	Antimicrobial Agents and Chemotherapy	10.1128/AAC.01179-20	Mixed (VA+VV)	RIFLE, AKIN
Huang, 2023	Risk factors for mortality in surgical patients on combined continuous renal replacement therapy and extracorporeal membrane oxygenation: single-center retrospective study	Renal Failure	10.1080/0886022X.2023.2282019	Mixed (VA+VV)	KDIGO
Chen, 2023	One-Year Survival for Developing Acute Kidney Injury in Adult Patients with AMI Cardiogenic Shock Receiving Venoarterial Extracorporeal Membrane Oxygenation	International Journal of General Medicine	10.2147/IJGM.S427999	Mixed (VA+VV)	KDIGO

Table 1. Continued

Study (first author, year)	Title	Journal	DOI	ECMO configuration (detected)	AKI definition (detected)
Lumlertgul, 2022	Long-term outcomes in patients who received veno-venous extracorporeal membrane oxygenation and renal replacement therapy: a retrospective cohort study	Annals of Intensive Care	10.1186/s13613-022-01046-0	Mixed (VA+VV)	KDIGO
Dado, 2020	Outcomes among Patients Treated with Renal Replacement Therapy during Extracorporeal Membrane Oxygenation: A Single-Center Retrospective Study	Blood Purification	10.1159/000504287	Mixed (VA+VV)	KDIGO, RIFLE
Graw, 2022	The role of cell-free hemoglobin and haptoglobin in acute kidney injury in critically ill adults with ARDS and therapy with VV ECMO	Critical Care (London, England)	10.1186/s13054-022-03894-5	VV	KDIGO
Kuo, 2019	Analysis of survival after initiation of continuous renal replacement therapy in patients with extracorporeal membrane oxygenation	BMC nephrology	10.1186/s12882-019-1516-6	Mixed (VA+VV)	Creatinine/urine output criteria (unspecified)
Austin, 2018	Retrieval of critically ill adults using extracorporeal membrane oxygenation: the nine-year experience in New South Wales	Anaesthesia and Intensive Care	10.1177/0310057X1804600608	Mixed (VA+VV)	KDIGO
Chen, 2011	Prognosis of patients on extracorporeal membrane oxygenation: the impact of acute kidney injury on mortality	The Annals of Thoracic Surgery	10.1016/j.athoracsur.2010.08.063	Unclear	RIFLE, AKIN
Liu, 2021	Comparison of Clinical Outcomes of Different Connection Modes of Extracorporeal Membrane Oxygenation Combine with Continuous Renal Replacement Therapy	The Heart Surgery Forum	10.1532/hsf.4335	VA	KDIGO, RIFLE
Lee, 2015	Risk Factors for Acute Kidney Injury and In-Hospital Mortality in Patients Receiving Extracorporeal Membrane Oxygenation	PloS One	10.1371/journal.pone.0140674	Mixed (VA+VV)	KDIGO, RIFLE, AKIN
Bidar, 2021	Renal replacement therapy in extra-corporeal membrane oxygenation patients: A survey of practices and new insights for future studies	Anaesthesia, Critical Care & Pain Medicine	10.1016/j.accpm.2021.100971	Mixed (VA+VV)	KDIGO
Hou, 2024	Risk factors associated with hospital mortality in non-surgical patients receiving extracorporeal membrane oxygenation and continuous renal replacement treatment: a retrospective analysis	Renal Failure	10.1080/0886022X.2024.2398711	Mixed (VA+VV)	KDIGO
Pabst, 2020	Predictors for acute and chronic renal failure and survival in patients supported with veno-arterial extracorporeal membrane oxygenation	Perfusion	10.1177/0267659119889521	VA	KDIGO, RIFLE
Lepère, 2020	Risk Factors for Developing Severe Acute Kidney Injury in Adult Patients With Refractory Postcardiotomy Cardiogenic Shock Receiving Venoarterial Extracorporeal Membrane Oxygenation	Critical Care Medicine	10.1097/CCM.0000000000004433	VA	KDIGO, RIFLE
Thyagarajan, 2021	Renal Recovery in Critically Ill Adult Patients Treated with Veno-Venous Or Veno-Arterial Extra Corporeal Membrane Oxygenation: a Retrospective Cohort Analysis	Journal of Critical Care Medicine	10.2478/jccm-2021-0006	Mixed (VA+VV)	RIFLE, AKIN
Ceresa, 2025	Acute Kidney Injury, Renal Replacement Therapy, and Extracorporeal Membrane Oxygenation Treatment During the COVID-19 Pandemic: Single-Center Experience	Medicina (Kaunas, Lithuania)	10.3390/medicina61020237	VV	KDIGO
Alsahow, 2025	Outcomes of acute kidney injury in patients receiving extracorporeal membrane oxygenation during the COVID-19 pandemic: a prospective, observational, and multi-center study	Renal Failure	10.1080/0886022X.2025.2570817	Mixed (VA+VV)	KDIGO, RIFLE
Bateman, 2016	36th International Symposium on Intensive Care and Emergency Medicine : Brussels, Belgium. 15-18 March 2016	Critical Care (London, England)	10.1186/s13054-016-1208-6	Unclear	AKIN

Table 1. Continued

Study (first author, year)	Title	Journal	DOI	ECMO configuration (detected)	AKI definition (detected)
Toinet, 2019	Renal outcome after simultaneous heart and kidney transplantation	Clinical Transplantation	10.1111/ctr.13615	Unclear	KDIGO, MAKE
Kim, 2023	High incidence of acute kidney injury in extracorporeal resuscitation, Leading to poor prognosis	Heliyon	10.1016/j.heliyon.2023.e22728	Mixed (VA+VV)	KDIGO
Pilarczyk, 2022	Acute Kidney Injury in Patients with Severe ARDS Requiring Extracorporeal Membrane Oxygenation: Incidence, Prognostic Impact and Risk Factors	Journal of Clinical Medicine	10.3390/jcm11041079	Mixed (VA+VV)	KDIGO, MAKE
Holub, 2024	[Pharmacokinetic and pharmacodynamic considerations of antibiotic therapy among critically ill adult patients with sepsis]	Orvosi Hetilap	10.1556/650.2024.33001	VA	KDIGO
Franco, 2024	Factors associated with post-hospitalization dialysis dependence in ECMO patients who required continuous renal replacement therapy	Renal Failure	10.1080/0886022X.2024.2343810	Mixed (VA+VV)	AKIN
Joannidis, 2020	Lung-kidney interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup	Intensive Care Medicine	10.1007/s00134-019-05869-7	Mixed (VA+VV)	KDIGO
Sagoschen, 2022	Case Fatality of Hospitalized Patients with COVID-19 Infection Suffering from Acute Respiratory Distress Syndrome in Germany	Viruses	10.3390/v14112515	Unclear	KDIGO
Na, 2018	Using additional pressure control lines when connecting a continuous renal replacement therapy device to an extracorporeal membrane oxygenation circuit	BMC nephrology	10.1186/s12882-018-1172-2	Mixed (VA+VV)	RIFLE
Qian, 2020	Clinical Characteristics and Outcomes of Severe and Critical Patients With 2019 Novel Coronavirus Disease (COVID-19) in Wenzhou: A Retrospective Study	Frontiers in Medicine	10.3389/fmed.2020.552002	Unclear	KDIGO
Perez-Garzon, 2025	Analysis of factors associated with the initiation of renal replacement therapy in patients on veno-arterial extracorporeal membrane oxygenation: a case-control study	BMC nephrology	10.1186/s12882-025-04395-7	Mixed (VA+VV)	KDIGO, RIFLE, AKIN
Kubo, 2025	Impact of early initiation of renal replacement therapy in patients on venoarterial ECMO using target trial emulation with Japanese nationwide data	Scientific Reports	10.1038/s41598-025-85109-9	Mixed (VA+VV)	RIFLE
Schönfelder, 2025	Comparison of integrated versus parallel continuous renal replacement therapy combined with veno-venous extracorporeal membrane oxygenation in patients with COVID-19 ARDS	BMC anesthesiology	10.1186/s12871-024-02818-w	Mixed (VA+VV)	Creatinine/urine output criteria (unspecified)
Lin, 2007	Evaluation of outcome scoring systems for patients on extracorporeal membrane oxygenation	The Annals of Thoracic Surgery	10.1016/j.athoracsur.2007.05.045	Unclear	RIFLE

AKI Incidence During ECMO

AKI incidence was variably reported across studies, reflecting heterogeneity in populations, baseline kidney function, timing of AKI assessment, and whether urine output criteria were included. Some studies stratified AKI by severity (e.g., KDIGO stages), but severity reporting was inconsistent.

RRT/CRRT Use

Use of renal replacement therapy (including CRRT) was frequently reported but varied substantially. When modality was specified, continuous modalities were common, consistent with hemodynamic instability and the need for fluid management. Reporting of timing, modality, and indications was inconsistent across studies.

Mortality Outcomes

Mortality endpoints varied (ICU, in-hospital, or 30-day). Many studies reported worse outcomes among patients with AKI and/or those requiring RRT, although associations were often confounded by illness severity and ECMO indication (Table 2).

Risk of Bias

Overall, the included evidence base was predominantly observational (mostly retrospective cohorts and registry analyses). Using the Newcastle–Ottawa Scale (NOS) and scoring conservatively based on what was explicitly reported, the overall risk of bias was low in 34 studies, moderate in 5 studies, and high in 6 studies (Table 3). The most common limitations were: 1) Confounding due to illness severity and ECMO indication (with incomplete or inconsistent multivariable adjustment), 2) Selection bias related to single-center designs and referral/ECMO candidacy practices, and 3) outcome reporting heterogeneity, including variable AKI definitions (KDIGO/RIFLE/AKIN), inconsistent timing windows for AKI ascertainment, and variation in mortality endpoints (ICU, in-hospital, or 30-day). Many studies relied on secure clinical records/registries for exposure and outcome ascertainment, supporting stronger performance in exposure/outcome domains, but comparability was frequently limited when adjustment for key confounders was absent or incompletely described.

DISCUSSION

Principal Findings

In this systematic review of adult studies with VA- and/or VV-ECMO, we provided evidence of a steady high burden of kidney complications. Among those studies for which data were extractable, AKI incidences varied widely but were often significant and more than half of the reporting studies described the use of RRT/CRT in a significant proportion of ECMO patients. Mortality was still high in all studies, but with huge variabilities according to the indication of ECMO, configuration of the ECMO and outcome window. These results are consistent with the wider ECMO literature, which shows that despite growing utilisation and increased technical skills organ complications, in this case AKI, remain frequent and clinically important.[1,6] A key reason for heterogeneity between studies in our review was methodological heterogeneity, specifically inconsistent AKI definitions (KDIGO vs. RIFLE vs. AKIN or unspecified), inconsistency in ascertainment of baseline creatinine, and varying time periods of AKI and mortality reporting. Similar issues have been highlighted in previous reviews focusing on critical care nephrology and ECMO which quote the inconsistent definition and reporting of outcomes as limiting comparability and synthesis.[6,16]

Across included studies, many authors reported worse outcomes in those patients who developed AKI and/or were on RRT/CRRT. While the direction of association was generally consistent, interpretation must be cautious as ECMO patients who develop AKI are often sicker at baseline, have more exposure to hemodynamic instability and are at greater risk for multi-organ dysfunction, all of which may be confounds in observed associations between AKI, RRT and mortality in observational studies.[6] Nevertheless, the recurrence of signal that AKI and RRT go together with worse outcomes provides weight for the clinical emphasis on early recognition and prevention strategies as feasible, and standardized reporting.

Interpretation and Plausibility of Biological Causes

The mechanisms of association of ECMO and AKI are biologically plausible and multifactorial.

Table 2. Renal Outcomes and Mortality Reported in Included Studies

Study (first author, year)	AKI incidence	RRT/CRRT use	Mortality
Lin, 2007	74.0%	43/35	Mortality (unspecified): 71.0%
Shin, 2023	2554 (12.3%)	5/6	Mortality (unspecified): 52.0%
Toinet, 2019	67.0%	74.5%	Mortality (unspecified): 22.0%
Askenazi, 2012	71.0%	70.0%	Mortality (unspecified): 95.0%
Gaisendrees, 2021	80.0%	80.0%	ICU: 47 (78.0%)
Gao, 2023	81 (61.0%)	53 (65.0%)	In-hospital: 133 (70.0%)
Kim, 2023	1177/8850	67.0%	Mortality (unspecified): 95.0%
Bateman, 2016	130/0 (20.0%)	17/7	ICU: 181 (29.1%)
Chen, 2011	0/1	56/46	In-hospital: 62 (61.0%)
Kim, 2021	29/33 (22.2%)	7.4%	Mortality (unspecified): 9/26 (34.6%)
Lau, 2025	74.0%	1080/8860	Mortality (unspecified): 74.0%
Chen, 2023	53.6%	20.0%	Mortality (unspecified): 70.2%
Holub, 2024	6 (12.2%)	22.0%	In-hospital: 987 (79.5%)
Lee, 2015	1/1 (14.1%)	2/1	In-hospital: 11/15 (33.0%)
Forker, 2019	57 (45.0%)	118 (77.0%)	In-hospital: 180 (84.3%)
Austin, 2018	71.0%	83 (70.3%)	Mortality (unspecified): 13.0%
Lin, 2017	70.0%	7/17 (41.2%)	In-hospital: 70.0%
Yeh, 2015	45.0%	24 (49.0%)	Mortality (unspecified): 22 (45.0%)
Bidar, 2021	60.0%	3/88	Mortality (unspecified): 25.0%
Coelho, 2023	5144/256	17.0%	In-hospital: 55.0%
Joannidis, 2020	128/100	44.0%	Mortality (unspecified): 10.0%
Kuo, 2019	34.20%	71.8%	Mortality (unspecified): 95.0%
Li, 2024	182 (84.3%)	11.8%	In-hospital: 182 (84.3%)
Marella, 2020	34.0%	77 (66.0%)	Mortality (unspecified): 56.0%
Pabst, 2020	108/196 (55.1%)	108/196 (55.1%)	In-hospital: 23 (54.0%)
Sagoschen, 2022	25.0%	2936 (1.8%)	In-hospital: 37.4%
Franco, 2024	20 (39.0%)	20 (39.0%)	Mortality (unspecified): 54.4%
Graw, 2022	21 (40.3%)	71.8%	Mortality (unspecified): 25.0%
Qian, 2020	6 (16.2%)	7 (18.9%)	Mortality (unspecified): 13 (35.1%)
Chen, 2023	44/103 (42.7%)	30 (80%)	In-hospital: 44/103 (42.7%)
Dado, 2020	1159/50	48 (53.3%)	Mortality (unspecified): 48 (53.3%)
Na, 2018	60.0%	118 (77.0%)	In-hospital: 48.3%
Pilarczyk, 2022	2/3 (2.3%)	2/3	Mortality (unspecified): 2/3 (95.0%)
Liu, 2021	78.0%	25.0%	In-hospital: 67 (33.0%)
Ceresa, 2025	134 (34.0%)	134 (34.0%)	ICU: 140 (35.0%)
Lumlertgul, 2022	91 (41.2%)	91 (41.2%)	ICU: 65 (21.7%)
Thyagarajan, 2021	109 (89.0%)	58 (91.0%)	Mortality (unspecified): 3 (6.0%)
Alsahow, 2025	3/4 (5.0%)	3/4 (5.0%)	Mortality (unspecified): 111 (8.1%)
Huang, 2023	16 (15.2%)	77 (73.3%)	Mortality (unspecified): 1097/3
Kubo, 2025	85.0%	997 (79.5%)	In-hospital: 997 (79.5%)
Perez-Garzon, 2025	50.5%	44.9%	ICU: 26.5%
Schönfelder, 2025	5/11	3/6	Mortality (unspecified): 89.0%
Hou, 2024	85.0%	1080/8860	Mortality (unspecified): 77/105 (73.3%)
Lepère, 2020	65.0%	60.7%	30-day: 124/257 (48.2%)
Chu, 2024	1159/49	1177/2676	In-hospital: 1097/1

First, ECMO is usually initiated in situations that are characterized by deep shock and/or profound hypoxemia. Renal hypoperfusion, exposure to vasopressors, microcirculatory dysfunction, and venous congestion may play a role in ischemic and congestive kidney injury, especially in VA-ECMO patients with cardiogenic shock physiology.[6] Second, the extracorporeal circuit has the ability to increase inflammation and complement activation via blood-surface interactions that aid in systemic inflammatory response and endothelial dysfunction, which can increase renal injury. Third,

Table 3. Risk of Bias Assessment of Included Observational Studies (Newcastle–Ottawa Scale Summary)

Study (first author, year)	Selection (0–4)	Comparability (0–2)	Outcome (0–3)	Total (0–9)	Overall judgment
Lau, 2025	4	2	3	9	Low risk
Chu, 2024	3	2	3	8	Low risk
Li, 2024	4	2	3	9	Low risk
Gao, 2023	4	2	3	9	Low risk
Askenazi, 2012	4	2	2	8	Low risk
Foley, 2022	3	2	3	8	Low risk
Hsu, 2022	4	2	3	9	Low risk
Gaisendrees, 2021	2	0	2	4	High risk
Shin, 2023	4	1	1	6	Moderate risk
Chen, 2021	4	2	3	9	Low risk
Austin, 2018	4	2	3	9	Low risk
Giraud, 2012	3	2	3	8	Low risk
Giraud, 2013	3	2	3	8	Low risk
Marella, 2020	3	0	1	4	High risk
Lumlertgul, 2021	4	2	3	9	Low risk
Haneya, 2015	4	2	3	9	Low risk
Chou, 2021	4	2	3	9	Low risk
Foo, 2020	4	2	3	9	Low risk
Graw, 2022	1	2	2	5	Moderate risk
Huan, 2022	3	1	2	6	Moderate risk
Kalbhenn, 2022	4	2	3	9	Low risk
Liu, 2021	2	0	2	4	High risk
Bidar, 2021	0	0	2	2	High risk
Jeon, 2021	4	2	3	9	Low risk
Kim, 2021	4	2	3	9	Low risk
Kimmoun, 2019	3	2	3	8	Low risk
Kram, 2020	4	2	3	9	Low risk
Lunz, 2014	4	2	3	9	Low risk
Luu, 2020	4	2	3	9	Low risk
McCaffrey, 2021	4	1	3	8	Low risk
Neri, 2016	4	2	3	9	Low risk
O'Neill, 2020	4	2	3	9	Low risk
Toinet, 2019	0	0	0	0	High risk
O'Neill, 2021	4	2	3	9	Low risk
Holub, 2024	3	0	2	5	Moderate risk
Paden, 2020	4	2	3	9	Low risk
Park, 2022	4	2	3	9	Low risk
Qian, 2020	2	0	3	5	Moderate risk
Reich, 2022	4	2	3	9	Low risk
Schmidt, 2014	4	2	3	9	Low risk
Schönfelder, 2025	2	0	2	4	High risk
Sutter, 2014	4	2	3	9	Low risk
Thongprayoon, 2019	4	2	3	9	Low risk
Tsai, 2020	4	2	3	9	Low risk
Zangrillo, 2013	4	2	3	9	Low risk

hemolysis-which is related to circuit shear stress, cannula positioning and pump dynamics-should be considered as a cause of pigment nephropathy and tubular injury and can accompany coagulation disturbances which create problems with fluid and transfusion management.

Fluid balance is a particularly important and modifiable factor. ECMO patients frequently receive large-volume resuscitation and blood products, and positive fluid balance can both reflect and worsen kidney dysfunction.[8] In observational data, positive fluid balance during ECMO has been associated

with higher mortality, and the need for CRRT is commonly driven by fluid overload rather than classical uremic indications alone.[8] This supports a conceptual model in which kidney injury, capillary leak, and fluid overload act as mutually reinforcing processes during ECMO, with renal support often integrated to achieve net fluid management and metabolic control.

VA versus VV configuration may also influence the "kidney risk profile." VA-ECMO is typically used for circulatory support and may be more strongly linked to renal injury via hemodynamic instability, nonpulsatile flow, and congestion, whereas VV-ECMO is primarily a gas exchange support modality in which renal injury may be more tightly coupled to underlying critical illness (e.g., sepsis, ARDS severity) and the consequences of prolonged mechanical ventilation, inflammation, and fluid management.[1,6] In practice, however, the distinction is not absolute because many patients have combined cardio-pulmonary dysfunction, and study-level reporting frequently does not permit clean stratification.

Clinical Implications

A number of practical implications flow from this. First, there is a strong need of standardizing AKI definitions in ECMO research and clinical reporting. KDIGO provides a harmonized and widely adopted framework which incorporates serum creatinine and urinary output criteria and can reduce the risk of definitional variability between studies.[17] Earlier consensus definitions (RIFLE and AKIN) comprised critical steps in milestones however mixed usage within ECMO studies makes comparison difficult and may over- or under-estimate AKI incidence depending on operationalization and time point.[12,18] Adoption of KDIGO-based reporting, ideally with information on severity staging, occurrence in relation to cannulation/decannulation, and baseline creatinine strategy would lead to better cross study interpretability and enhanced evidence synthesis in the future.

Second, early monitoring is still imperative in ECMO patients: close attention to urine output, changes in creatinine, acid-base status and net fluid balance can serve as a warning signal for progressive biophase (kidney) injury and the basis of integrated cardio-pulmonary-renal management.[6,16] Given that fluid overload is both a cause for poorer outcomes and a common trigger for initiation of CRRT, a proactive strategy to fluid stewardship is likely to be of benefit, even in the absence of any definitive evidence concerning strategies such as timing.[8]

Third, RRT integration requires a deliberate planning. ECMO - CRRT could be achieved with a separate venous access or integrated into the ECMO circuit; each option has technical and safety trade -offs around pressures in the circuit, the management of anticoagulant use, and the filter lifetime. A pragmatic implication is the value of standardized institutional protocols and common decision making between ECMO teams and nephrology/critical care nephrology services, specifically around issues such as indications (i.e. fluid overload vs. metabolic indications, start time, anticoagulation strategy and net ultrafiltration targets).

Research Issues and Directions

The evidence base would be enhanced by the adoption of better reporting standards and prospective study designs. Future ECMO studies should report (at minimum) the AKI definition used (preferably KDIGO), the temporal window around which AKI ascertainment occurred, how the baseline creatinine was ascertained, whether urine output criteria were used, and how the severity distribution is distributed. For those studies reporting renal support, the inclusion of the clear indications for RRT/CRRT, timing in relation to ECMO initiation, modality, and the inclusion/noninclusion of RRT in the ECMO circuit should be mentioned. Because of the heterogeneity between VA and VV indications, a stratified reporting based on configuration of ECMO and primary indication would enable better interpretability and more meaningful comparisons.[1,6]

In addition, kidney-centered endpoints are under-reported. Beyond hospital survival, the field would benefit from standardized reporting of renal recovery, CKD progression, dialysis dependence at discharge and follow-up, and patient-centered functional outcomes. Registry efforts and international datasets, such as those

coordinated through ELSO, provide an opportunity to enhance standardized complication reporting and facilitate large-scale evaluation of kidney outcomes (Extracorporeal Life Support Organization).

Strengths and Limitations

This review has several strengths: a systematic approach, a focused adult ECMO population including VA and VV configurations, and full-text extraction of renal and mortality outcomes with transparent handling of non-extractable data. However, limitations include reliance on a single primary database (PubMed), incomplete full-text retrieval due to access constraints, heterogeneity in study populations and outcome definitions, and the observational nature of most included evidence. Finally, some outcomes could not be extracted numerically from all studies, resulting in varying denominators across outcomes; summaries therefore reflect only studies with extractable data.

CONCLUSION

AKI is a frequent and clinically important complication in adults supported with veno-arterial and/or veno-venous ECMO. In this systematic review, many included studies reported substantial AKI burden and frequent use of renal replacement therapy/continuous renal replacement therapy, reflecting the close physiologic interaction between cardio-pulmonary failure, critical illness, and renal vulnerability during ECMO. Mortality also remained considerable across studies, although reported rates varied because endpoints differed (ICU, in-hospital, or 30-day) and because patient case-mix and indications for ECMO were heterogeneous.

A central finding of this review is that inconsistency in AKI definitions and reporting practices continues to limit comparability across the ECMO literature. Mixed use of KDIGO, RIFLE, and AKIN criteria—often with incomplete reporting of urine output criteria, baseline creatinine determination, timing of AKI ascertainment, and AKI severity staging—likely contributes to the wide range of AKI incidence and RRT use observed. Future research should adopt standardized KDIGO-based definitions with clearly defined assessment windows and severity reporting, and should provide transparent detail on RRT indications, timing, and modality. More consistent reporting, including kidney-centered longer-term outcomes such as renal recovery and chronic kidney disease progression, will strengthen evidence synthesis and better inform integrated ECMO–renal support strategies in critical care practice.

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Full PubMed Search Strategy

Database. PubMed (National Library of Medicine)

Last search date. [20/12/2025]

Filters applied. None

PubMed search string. ("Extracorporeal Membrane Oxygenation"[Mesh] OR ECMO OR ECLS OR "extracorporeal life support") AND ("Acute Kidney Injury"[Mesh] OR "acute kidney injury" OR AKI OR "renal failure" OR "kidney failure") AND (adult[Mesh] OR adults)

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RJCCN ORIGINAL PAPER
NURSING

The Impact of Nurse-Led Continuous Renal Replacement Therapy Management on Clinical Outcomes in Adult Critically Ill Patients: A Systematic Review

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Keywords. acute kidney injury, continuous renal replacement therapy, critical care nursing, intensive care units, nurse-led care, adult

Introduction. Continuous renal replacement therapy (CRRT) is a cornerstone treatment for hemodynamically unstable critically ill patients with acute kidney injury (AKI). Despite technological advances, CRRT outcomes remain variable, and the impact of nursing leadership in CRRT delivery has not been sufficiently synthesized. This study aims to evaluate the effect of nurse-led CRRT management on clinical and treatment-related outcomes in adult critically ill patients.

Methods. A systematic review was conducted according to PRISMA 2020 guidelines. PubMed/MEDLINE, Embase, Scopus, CINAHL, and the Cochrane Library were searched for studies involving adult ICU patients receiving CRRT where nurse-led management was explicitly described. Primary outcomes included mortality, circuit lifespan, and unplanned circuit interruption or clotting. Secondary outcomes included delivered CRRT dose, treatment downtime, and CRRT-related complications.

Results. Fifteen eligible studies were identified, including randomized and non-randomized designs evaluating nurse-led CRRT models compared with standard or physician-led care. Nurse-led CRRT management was associated with prolonged circuit lifespan and reduced unplanned interruptions in most studies. Mortality effects were variable. Heterogeneity across studies reflected differences in staffing models, protocols, and outcome definitions.

Conclusions. Nurse-led CRRT management appears to improve key treatment-related outcomes and care continuity in adult ICU patients. These findings have important implications for workforce development and care models, particularly in low- and middle-income countries (LMICs).

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INTRODUCTION

Acute kidney injury (AKI) is a prevalent and severe complication among patients in intensive care units (ICUs), affecting 40 to 60% of this population. AKI significantly increases morbidity, mortality, hospital length of stay, and healthcare expenditures.[1-3] In patients with severe AKI and hemodynamic instability, continuous renal

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replacement therapy (CRRT) is the preferred modality for renal support. CRRT facilitates gradual solute clearance and fluid removal, thereby minimizing abrupt intravascular volume shifts and cardiovascular stress compared to intermittent hemodialysis.[4-7]

Despite advancements in CRRT technology, membranes, and anticoagulation strategies, patient outcomes remain highly variable.[2,4-6] Suboptimal outcomes are often attributable to operational factors rather than device limitations. These include frequent treatment interruptions, premature circuit clotting, inadequate anticoagulation management, and failure to deliver the prescribed dialysis dose-all of which compromise efficacy and contribute to adverse clinical outcomes.[8-11]

Nursing practice is central to the delivery and success of CRRT.[8-10] Nurses manage continuous bedside operations, including vascular access surveillance, circuit monitoring, anticoagulation titration, and alarm troubleshooting. Given the continuous nature of CRRT, nursing competence and vigilance directly influence circuit lifespan and therapeutic target achievement. Frequent interruptions and dose deviations are often linked to workflow inefficiencies that fall within the nursing domain.[1,8,11]

Consequently, nurse-led CRRT management models have emerged. In these models, specially trained critical care or nephrology nurses assume primary responsibility for CRRT operations within standardized protocols, often with consultative rather than continuous physician oversight. These approaches aim to enhance efficiency, prolong circuit lifespan, and optimize delivered doses while maintaining patient safety. While several observational studies have suggested benefits, findings have yet to be comprehensively synthesized.

The relevance of nurse-led CRRT is particularly pronounced in low- and middle-income countries (LMICs), where access to nephrology specialists may be limited. In such settings, empowering nurses through structured training and protocol-driven autonomy may represent a cost-effective and scalable strategy to improve patient outcomes.[13-5]

Despite growing interest, uncertainty remains regarding the impact of these models on clinical outcomes and safety. This systematic review aims to evaluate the effect of nurse-led CRRT management on clinical and treatment-related outcomes, with a focus on circuit lifespan, treatment continuity, delivered dose, and patient safety.[8-12]

MATERIALS AND METHODS

Protocol and Reporting

This review followed the Preferred Reporting Items for Systematic Reviews (PRISMA) 2020 guidelines. The protocol was developed a priori.

Eligibility Criteria

Study Designs. Randomized controlled trials (RCTs), prospective and retrospective cohort studies, and before-after interventional studies included. Reviews, editorials, case reports, and conference abstracts were excluded.

Population. Adult patients (≥ 18 years) in ICUs receiving CRRT

Exposure. Nurse-led CRRT management (nurses holding primary responsibility for bedside management via institutional protocols).

- **Comparator:** Physician-led models, Mixed-management models, or Standard care
- **Outcomes:** Primary outcomes were mortality, circuit lifespan, and unplanned interruptions. Secondary outcomes included delivered dose, downtime, and complications.

Search Strategy

PubMed/MEDLINE, Embase, Scopus, CINAHL, and the Cochrane Library were searched for English-language studies using terms related to "CRRT," "critical care nursing," and "nurse-led management."

Data Extraction and Quality Assessment

Two reviewers independently screened titles and extracted data using standardized forms. Disagreements were resolved via consensus. Risk of bias for non-randomized studies was assessed using the ROBINS-I tool.

RESULTS

Of the 15 included studies, five directly evaluated nurse-led CRRT models. These studies consistently demonstrated improved circuit lifespan and reduced

unplanned interruptions. Mortality outcomes were inconsistently reported and could not be conclusively linked to the management model. (See Table 1 for study classifications).

Only Studies 8 to 12 directly evaluate nurse-led or nursing-driven CRRT management and outcomes (Table 1). The remaining studies provide contextual and mechanistic support, not primary outcome comparisons (Table 2).

Study Selection

The systematic database search identified 1,247 records. After removing 312 duplicates, 935 records were screened by title and abstract. Of these, 862 records were excluded for failing to meet the inclusion criteria. Seventy-three full-text articles were assessed for eligibility, of which 58 were excluded due to pediatric populations, absence of a nurse-led CRRT description, use of non-CRRT modalities, or insufficient outcome data (Figure). Ultimately, 15 eligible articles were included in the review.

Study Characteristics

The included studies varied in ICU settings, geographic locations, and specific nurse-led CRRT implementation models. Most studies assessed protocol-driven nursing management versus standard or physician-led care. Notably, although 15 studies were included in the overall review, only five (Studies 8 to 12) directly examined nurse-led or nursing-driven CRRT management and its specific impact on outcomes. The other studies offered essential contextual and mechanistic support rather than primary outcome comparisons.

Primary Outcomes

Nurse-led CRRT management was consistently associated with longer circuit lifespan and a reduction in unplanned interruptions. In contrast, mortality outcomes were inconsistently reported across the literature and demonstrated no uniform direction of effect (Table 3).

Nurse-led or nursing-intensive CRRT models

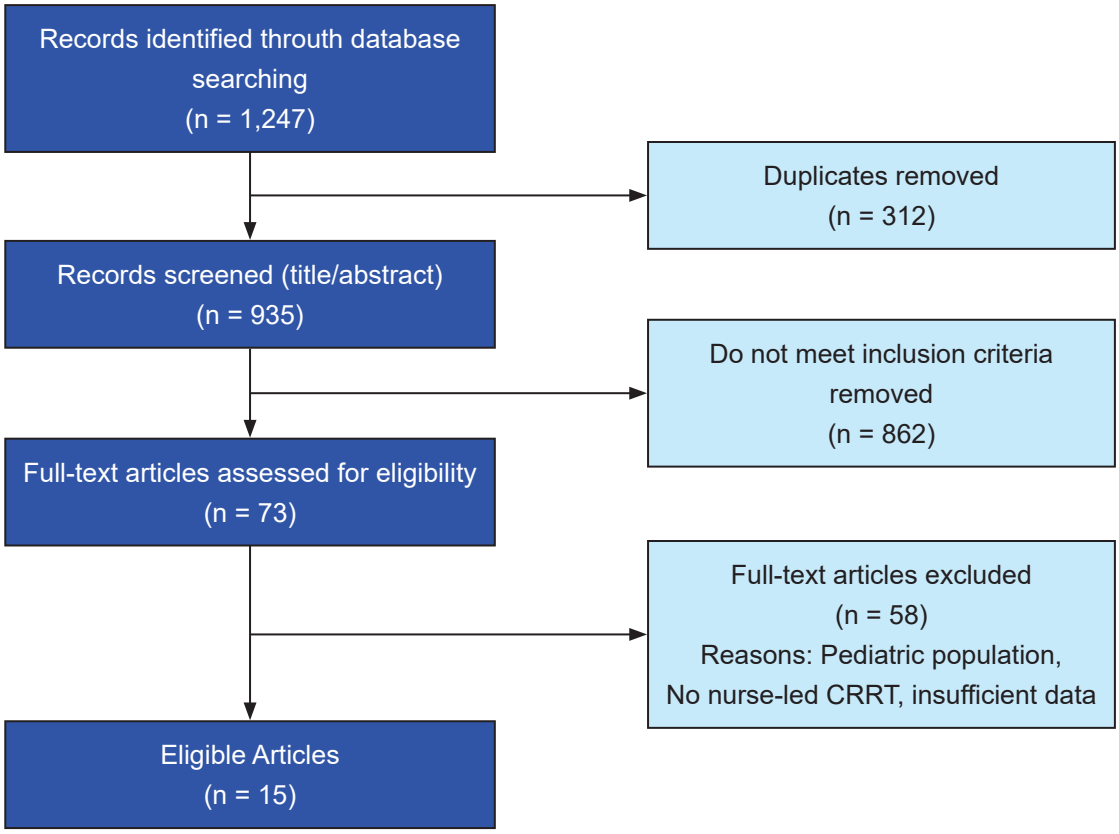
Table 1. Classification and Relevance of Included Studies (n = 15)

(Author, Year)	Study Type	Primary Relevance to Review Question
Kellum & Lameire, 2013[1]	Guideline	AKI context; CRRT indications
Hoste et al., 2015[2]	Epidemiological study	AKI burden in ICU
Bellomo et al., 2012[3]	Narrative review	AKI outcomes and CRRT role
Ronco et al., 2019[4]	Narrative review	CRRT principles
Ricci & Ronco, 2018[5]	Narrative review	Evolution of CRRT
Uchino et al., 2005[6]	Multicenter cohort	AKI outcomes; CRRT utilization
Tolwani, 2012[7]	Clinical review	CRRT implementation
Baldwin et al., 2007[8]	Multicenter observational	Nursing-based CRRT management
Mottes & Goldstein, 2018[9]	Nursing review	Nursing responsibilities in CRRT
Villa et al., 2016[10]	Observational / review	Nursing role & patient safety
Clark et al., 2014[11]	Observational cohort	Circuit lifespan & nursing practice
Vandijck et al., 2013[12]	Observational study	Nurse staffing/training impact
Tandukar & Palevsky, 2019[13]	Review	CRRT indications & delivery
Murugan et al., 2016[14]	Observational / review	CRRT fluid management
WHO, 2020[15]	Global report	Nursing workforce & training

Note. Only Studies 8 to 12 directly evaluate nurse-led or nursing-driven CRRT management and outcomes. The remaining studies provide contextual and mechanistic support, not primary outcome comparisons.

Table 2. Contextual Studies Supporting CRRT and Nursing Models (Non-Outcome)

Study	Key Contribution to Review
Kellum & Lameire, 2013[1]	Defines AKI severity guiding CRRT initiation
Bellomo et al., 2012[3]	Describes AKI morbidity and mortality
Ronco et al., 2019[4]	Establishes CRRT principles requiring bedside expertise
Ricci & Ronco, 2018[5]	Highlights complexity of CRRT delivery
Tolwani, 2012[7]	Emphasizes need for skilled CRRT management
Tandukar & Palevsky, 2019[13]	Reinforces protocol-based CRRT delivery
Murugan et al., 2016[14]	Demonstrates precision needs in CRRT
WHO, 2020[15]	Supports investment in nursing education and leadership



PRISMA 2020 Flow Diagram of Study Selection (Flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies evaluating nurse-led continuous renal replacement therapy management in adult critically ill patients. Records were identified through database searching, duplicates were removed, and studies were screened by title and abstract. Full-text articles were assessed for eligibility, with reasons for exclusion documented).

Table 3. Primary Outcomes Linked to Individual Studies

Study	Circuit Lifespan	Interruptions / Downtime	Mortality Outcomes	Contribution
Baldwin et al., 20078	↑ Longer filter survival	↓ Unplanned interruptions	Not primary endpoint	Multicenter evidence of nursing-based CRRT management improving circuit performance
Clark et al., 201411	↑ Prolonged circuit lifespan	↓ Premature clotting	No independent effect	Identified nursing practices as determinants of circuit longevity
Vandijck et al., 201312	Indirect improvement	↓ Downtime	Not reported	Demonstrated impact of nurse staffing and training on CRRT delivery quality
Villa et al., 201610	Not quantified	↓ Adverse events	Not reported	Linked nursing vigilance to patient safety
Mottes & Goldstein, 20189	Conceptual	Conceptual	Not applicable	Synthesized nursing-specific CRRT responsibilities

are consistently associated with improved circuit performance, while the effects on mortality remain inconclusive or unmeasured.

Secondary Outcomes

Several studies reported improved delivered CRRT dose and reduced downtime with nurse-led models. Complication rates were comparable or reduced (Table 4).

DISCUSSION

This systematic review demonstrates that nurse-led CRRT management is associated with significant improvements in key treatment-related outcomes, particularly circuit lifespan and treatment continuity.[8,10-2] These findings highlight the pivotal role of nursing leadership in optimizing CRRT delivery and quality. Furthermore, they reinforce the concept that effective CRRT is highly dependent

Table 4. Secondary Outcomes by Study

Study	Delivered Dose	Complications	Safety / Quality Indicators
Baldwin et al., 2007[8]	↑ Dose consistency	↓ Filter clotting	Improved protocol adherence
Clark et al., 2014[11]	Indirect	↓ Clotting	Nursing technique influenced outcomes
Vandijck et al., 2013[12]	↑ Effective delivery	↓ Technical failures	Staffing adequacy critical
Villa et al., 2016[10]	Not reported	↓ Errors & alarms	Improved patient safety
Mottes & Goldstein, 2018[9]	Conceptual	Addressed	Education reduced adverse events

on bedside expertise and continuous clinical oversight, rather than solely on initial prescription parameters. By enhancing circuit performance and minimizing interruptions, nurse-led models ensure that the prescribed therapy dose is delivered more reliably—an essential factor for maintaining metabolic stability and fluid balance in critically ill patients.[4,7]

The observed benefits are likely attributable to the unique position of bedside nurses, whose constant presence enables continuous monitoring, early identification of circuit dysfunction, timely anticoagulation adjustments, and prompt troubleshooting of access-related issues.[9-11] These competencies are critical, as circuit clotting and unplanned downtime remain the primary limitations of CRRT, often leading to increased blood loss, higher costs, and reduced treatment efficiency.[4,11] Standardized, protocol-driven nurse-led approaches may also mitigate practice variability, which has been identified as a key contributor to adverse events and suboptimal CRRT delivery in intensive care settings.[5,9]

The implications of these findings are particularly significant for low- and middle-income countries (LMICs), where the scarcity of nephrologists and intensivists often necessitates a greater reliance on nursing staff for the delivery of complex therapies.[13-5] In such settings, nurse-led CRRT models represent a pragmatic and cost-effective strategy to expand access to renal support while maintaining safety and quality of care. Investment in specialized nursing education, competency-based training, and standardized protocols has the potential to reduce circuit wastage and optimize resource utilization.[12,15] Furthermore, empowering nurses through expanded roles and structured autonomy may enhance job satisfaction and workforce retention—factors critical to sustaining services in resource-constrained environments.[15]

Limitations

Several limitations of the current evidence must be acknowledged. The majority of included studies were observational, introducing risks of selection bias and residual confounding. Additionally, significant heterogeneity in study designs, CRRT modalities, anticoagulation strategies, and outcome definitions limited direct comparisons and precluded a quantitative meta-analysis.[8,10-2] Patient-centered outcomes—including mortality, renal recovery, and long-term kidney function—were inconsistently reported, restricting definitive conclusions regarding the downstream clinical impact of nurse-led management.[4,6]

CONCLUSIONS

Despite these limitations, the consistent treatment-related benefits observed across diverse settings support the value of nurse-led CRRT management as a core component of high-quality ICU renal support. Future research should prioritize prospective, multicenter studies with standardized outcome measures to evaluate the impact of nurse-led models on patient-centered outcomes, cost-effectiveness, and long-term renal recovery. From a clinical perspective, these findings support the integration of structured nurse-led programs that emphasize specialized training and protocol-driven autonomy. Rather than a substitute for physician expertise, nursing leadership should be positioned as an essential element of multidisciplinary, safe, and effective CRRT delivery. Nurse-led CRRT management seems to enhance important process-related outcomes in adult critically ill patients and offers a promising approach to improve care delivery. Future research should emphasize standardized outcome reporting and prospective assessment of nursing-led CRRT models.

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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.

CONFLICT OF INTEREST

Behrang Alipour Abedi is a member of the editorial team of RJCCN. The author had no involvement in the peer-review or editorial decision-making process for this manuscript.

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RJCCN CASE REPORT
KIDNEY DISEASE

Plasmacytoma in Membranoproliferative Glomerulonephritis: A Case Report

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Keywords. plasmacytoma, membranoproliferative glomerulonephritis, multiple myeloma, monoclonal gammopathy of undetermined significance, acute kidney injury

Multiple myeloma is a prevalent disease, whereas bone plasmacytoma is a localized neoplasm of monoclonal plasma cells, constituting a distinct plasma cell disorder that falls between monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM). We present a 63-year-old woman who exhibited proteinuria and acute kidney injury (AKI), subsequently diagnosed with membranoproliferative glomerulonephritis (MPGN) of unknown etiology. One year later, the patient developed a lytic bone lesion and diagnosed as having a solitary bone plasmacytoma. MPGN may be caused by immunological complexes or associated with monoclonal gammopathy; therefore, it is essential to assess individuals with MPGN to identify any typical or atypical etiologies of the condition.

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INTRODUCTION

Multiple myeloma (MM) is a common malignancy, constituting almost 1% of all malignancies and 10% of all hematologic cancers, with more cases occurring in men. The major clinical manifestations are the osteolytic bone lesions, anemia, hypercalcemia, renal failure, and an increased risk of infection. Extramedullary disease (EMD) is reported in 1 to 2% of patients at the time of initial diagnosis, increasing to 8% upon disease progression.[1]

Plasmacytoma, a localized neoplasm, is diagnosed based on the fulfillment of four specific criteria: Biopsy-confirmed clonal plasma cells in an isolated lesion of bone or soft tissue, no sign of clonal plasma cells in the bone marrow standard skeletal examination of the spine and pelvis, lack of end-organ damage, renal failure, anemia, or bone lesions. Plasma cell disorders, including plasmacytomas, may lead to kidney failure (Ig); the mechanisms of renal damage in plasma cell malignancies may be either immunoglobulin-dependent or immunoglobulin-independent.[2,3]

Membranoproliferative glomerulonephritis (MPGN) can occur in the context of plasma cell neoplasms such as plasmacytoma or MM or as a paraneoplastic glomerulopathy due to deposition of monoclonal immunoglobulins or light chains. These monoclonal proteins can also act as autoantibodies or form immune complexes that deposit in the glomeruli, activating complement pathways and causing the characteristic MPGN pattern.[4]

MPGN associated with monoclonal gammopathies is considered a component of the spectrum of monoclonal gammopathy of renal significance (MGRS), wherein the kidney damage is solely attributable to the monoclonal protein, in the absence of overt MM.

CASE PRESENTATION

A 63 years old woman was admitted to

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Hasheminejad kidney center due to peripheral edema and elevated serum creatinine. She had a recent history of non-steroidal anti-inflammatory drugs (NSAID) usage due to low back pain for two weeks before admission. On admission the serum creatinine level was 3.2 mg/dL (increased to 5 mg/dL), and she had proteinuria (5900 mg/24h) and microscopic hematuria. The result of Anti-nuclear antibody (ANA), Anti-double stranded DNA (Anti-ds DNA), C3, C4, and CH50 tests were all normal. A kidney ultrasound showed 137 mm for the right kidney and 147 mm for the left kidney, with normal parenchymal thickness. Serum and urine protein electrophoresis immunofixation was ordered.

The patient underwent five sessions of hemodialysis and a kidney biopsy was done, which revealed mostly enlarged and hypercellular glomeruli with increased mesangial cellularity and endocapillary proliferation making lobular accentuation; two glomeruli showed fibro-cellular crescents. Tubular atrophy and interstitial fibrosis were about 5%. Immunofluorescence study showed 3+ IgG, 3+ C3, 2+ C1q, and 1+ Kappa and Lambda deposition.

The diagnosis of type I MPGN was made according to the pathologic findings. Treatment was initiated with five sessions of plasmapheresis, three pulses of 500 mg methylprednisolone, and 500 mg cyclophosphamide; after which the serum creatinine level reduced to 1.7mg/dL. The patient was administered two grams of mycophenolate mofetil (MMF) daily as maintenance therapy. After two months serum creatinine was 1.18 mg/dL and the urine protein was 750 mg/24h. Re-check of serum and urine immunofixation and electrophoresis were normal.

One year following the first admission the patient was readmitted due to recurrence of low back pain. A lumbar MRI revealed a 35 to 37 mm solid intraosseous mass lesion in the posterior aspect of the ninth thoracic vertebra necessitating surgical excision (Figure 1); the pathology indicated plasmacytoma characterized by CD 138 positive cells (Figure 2). Bone marrow aspiration and biopsy showed mildly hypercellular marrow (45 to 50% cellularity) with less than 1% plasma cells (Figure 3).

According to the pathology report of bone plasmacytoma a local radiotherapy was considered in conjunction with lenalidomide, while prednisolone and MMF were tapered and ultimately discontinued gradually over two months; serum creatinine was 0.7 mg/dL and 24h urine protein was 123 mg.

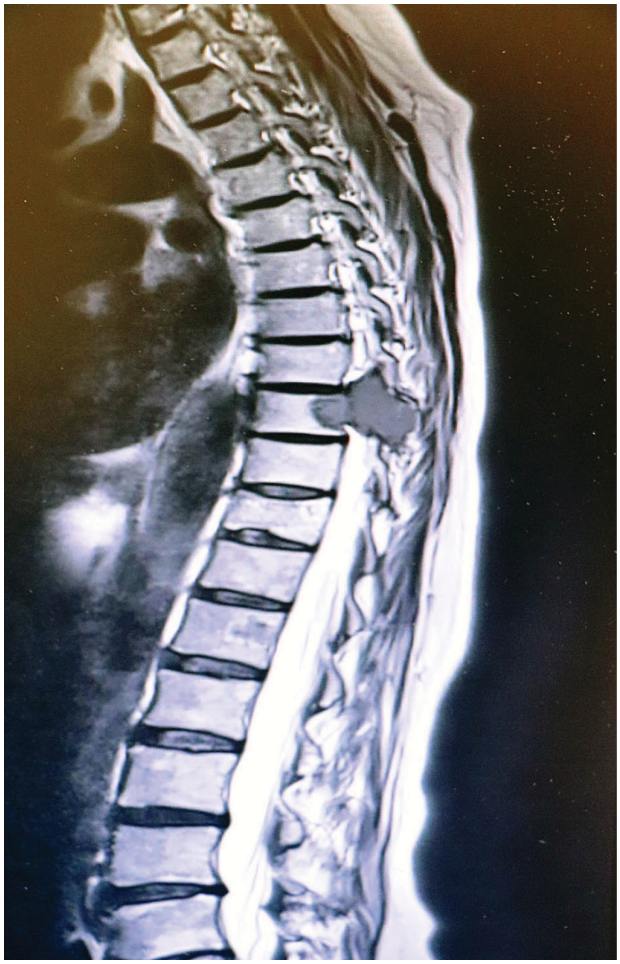

Figure 1. Thoracic MRI shows a mass lesion in posterior aspect of ninth thoracic vertebra.

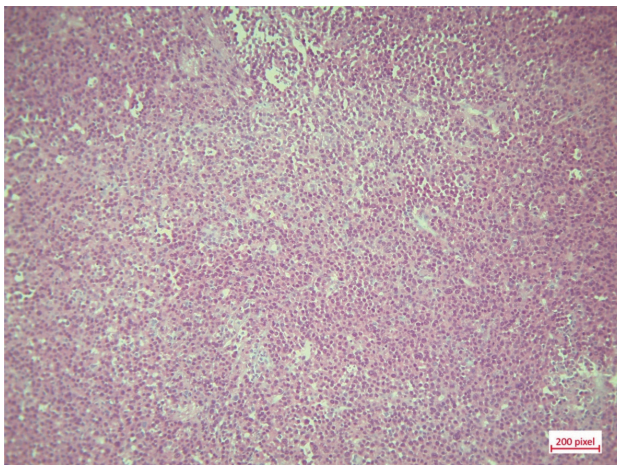

Figure 2. Plasmacytoma of Thoracic Lesion.

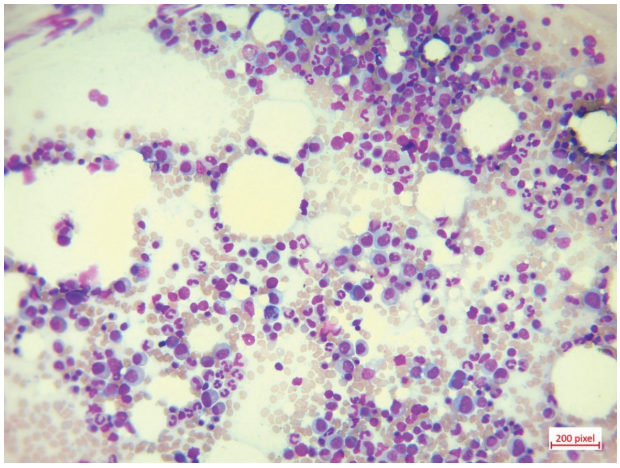

Figure 3. Bone marrow biopsy shows less than 1% plasma cells.

DISCUSSION

Bone plasmacytoma is a localized neoplasm of monoclonal plasma cells that typically manifesting as a solitary mass in bone, predominantly in the vertebrae or other skeletal sites. Bone marrow infiltration comprises fewer than 10% clonal plasma cells. This tumor can induce local bone destruction, lytic lesions, and pathological fractures. The risk of progression of bone plasmacytoma to multiple myeloma is high, with studies suggesting progression rates up to 60 to 85% over 10 years, particularly when clonal plasma cells are detected in the bone marrow or when abnormal serum kappa to lambda free light chain ratios are present. Localized radiotherapy is the mainstay of treatment, sometimes supplemented by surgery, with careful long-term monitoring due to risk of systemic progression.[5-7]

MPGN is a pattern of glomerular injury classified into immune complex-mediated and complement-mediated types and can be associated with infections, autoimmune disorders, or monoclonal gammopathies. In the context of plasma cell disorders, monoclonal gammopathy can drive complement activation or immune complex deposition that leads to MPGN-type injury in the kidneys.[8,9] Early detection and management of plasmacytoma are crucial to prevent progression to multiple myeloma and related complications.

CONCLUSION

Solitary bone plasmacytoma and solitary extramedullary plasmacytoma represent rare subgroup of plasma cell dyscrasias. In our case bone plasmacytoma was diagnosed a year after clinical presentation of MPGN however, a potential causal relationship between plasmacytoma and MPGN may exist. Therefore, when diagnosing MPGN in a patient, it is imperative to investigate not only the common etiologies but also the rarer ones.

CONFLICT OF INTEREST

Atefeh Amouzegar is a member of the editorial team of RJCCN. The author had no involvement in the peer-review or editorial decision-making process for this manuscript.

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