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It is with great honor and excitement that I welcome readers to the inaugural issue of the *Research Journal of Critical Care Nephrology (RJCCN)*, one of the first international journals dedicated exclusively to the vital and rapidly expanding interface between nephrology and critical care medicine.

In recent years, the boundaries separating nephrology and intensive care have become increasingly blurred. Acute kidney injury, fluid and electrolyte disturbances, renal replacement therapy, and multiorgan dysfunction are central challenges in the management of critically ill patients. Yet, despite the profound overlap between these disciplines, there has been a striking lack of a dedicated academic platform to unify their scientific progress and clinical experience. The RJCCN was founded to fill this gap.

Our mission is to provide a rigorous and innovative venue for clinicians, researchers, and scientists who are shaping the future of critical care nephrology. We aim to highlight original research, clinical observations, and translational science that enhance understanding of kidney function and dysfunction in the critically ill; as well as to explore emerging technologies such as extracorporeal therapies, hemoadsorption, POCUS, biomarkers, and personalized renal support strategies.

The RJCCN is proud to be an international collaboration of experts and thought leaders

around the world. This diversity of perspectives reflects the global nature of the challenges we face and underscores our commitment to excellence, inclusivity, and scientific integrity.

We also recognize that critical care nephrology is not merely a subspecialty, it is a philosophy of integrated patient care. It demands that nephrologists understand the complexities of hemodynamics, sepsis, and organ support, while intensivists appreciate the nuances of renal physiology and extracorporeal therapy. The RJCCN seeks to bridge these worlds; to promote dialogue, foster innovation, and inspire new models of care that improve outcomes for our most vulnerable patients.

As we launch this first issue, I extend my deepest gratitude to our editorial board, reviewers, and contributors who have made this ambitious vision a reality. I invite nephrologists, intensivists, nurses, and researchers worldwide to join us in this endeavor to share knowledge, challenge paradigms, and collectively advance the science and art of critical care nephrology.

Welcome to the *Research Journal of Critical Care Nephrology*, where kidney and critical care meet at the frontiers of medicine.

Amir Ahmad Nassiri, MD
Editor-in-Chief, RJCCN



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The Evolving Role of the Nephrology Critical Care Nurse

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INTRODUCTION

Nephrology critical care nursing holds an interesting and demanding position where two specialty domains intersect. As the global prevalence of Acute Kidney Injury (AKI) and need for Renal Replacement Therapy (RRT) in critically ill patients continues to escalate, these nurses are at the forefront of a challenging healthcare conundrum.

Let's be realistic, the intensive care unit (ICU) is a high-stress environment where physiological instability and multi-organ dysfunction are the norm. In this setting, the kidneys are often among the first organs to suffer, with AKI striking over 50% of ICU patients in some studies and associated mortality rates sadly exceeding 20-30%. Managing these patients isn't just about medicine; it's about expertly weaving together knowledge from both critical care and nephrology. Central to it all stands the nephrology critical care nurse. This is the personnel who plays the critical link role, not only being responsible for the technical process of life-supporting equipment like CRRT machines but also providing whole person, compassionate care to highly vulnerable patients and families.

CORE RESPONSIBILITIES: MORE THAN JUST THE MACHINE

It's a misconception that this work begins and ends with the dialysis machine. Actually, it's a very holistic practice. The nurse's duties are vast and varied and shown in Figure 1.

The Art of Clinical Assessment

This is not just box ticking. It is all about careful, vigilant observation for those subtle, easily missed signs of fluid overload, impending electrolyte imbalance (e.g., life-threatening hyperkalemia), uremic complications, and the first indications of failing organ function.

Technical Competence Under Duress

They must become utter masters of the installation, priming, operation, and perhaps more than anything, repair of complex RRT technology, much of it CRRT. This entails a high-level understanding of anticoagulation algorithms, a demand for maintaining vascular access open, and a staid, professional response to an endless stream of machine beeps.

Navigating Through Medication Administration

AKI and RRT dramatically alter the body's management of medications. These nurses must be well-versed in pharmacokinetics to obtain medications properly dosed to avoid the twin dangers of toxicity and under-dosing.

Guardians of the Lifeline

Master care of central venous catheters is not a negotiable obligation. Their keen monitoring is the first line of defense against deadly catheter-related bloodstream infections (CRBSI).

Advocate and Guide

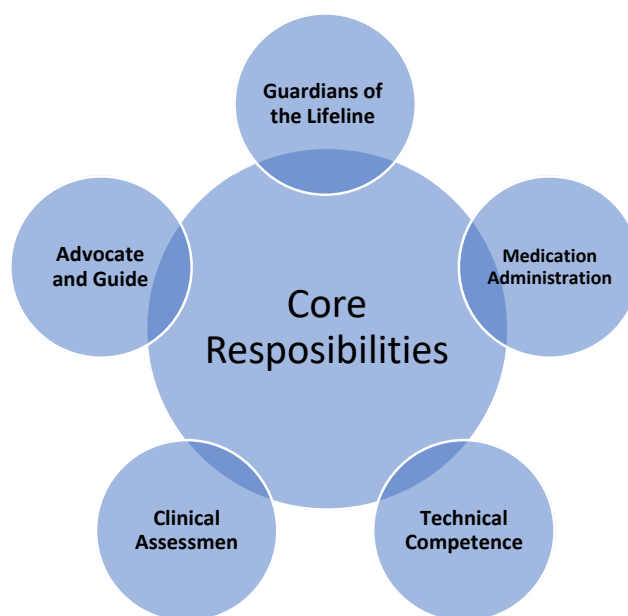
Primarily, they are comprehensive caregivers. They provide requisite education, emotional support, and straightforward, empathetic communication to patients and families as they make tough, oftentimes frightening, decisions about goals of care and an uncertain future.

BUILDING EXPERTISE: EDUCATION, COMPETENCIES, AND CERTIFICATION

With the complexity, it is not surprising that the profession needs strict, standard education. Even though international standards are dissimilar, the



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Core Responsibilities in Nephrology Critical Care Nursing

visible trend is towards formal post-registration training.

Core Knowledge

A comprehensive review of the sophisticated pathophysiology of AKI and CKD, the principles of extracorporeal therapy, and the subtle changes of acid-base and electrolyte balance are necessary.

Learning Through Doing (But safely)

High-fidelity simulation training is quickly becoming the new gold standard, allowing nurses to practice technical problem-solving and crisis management skills in a risk-free setting, build muscle memory and self-assurance without ever actually being in an emergency crisis.

THE TECH SHIFT: HOW INNOVATION IS RESHAPING PRACTICE

Smarter Machines

Integrated CRRT systems now feature easy-to-use interfaces, automatic alerts, and enhanced safety warnings, all of which reduce cognitive load and reduce the likelihood of human error.

Closing the Gap with Telemedicine

For rural nurses or units that lack specialist backup, tele-nephrology is a lifeline. It allows them to consult specialist teams in real time, an

approach of enormous potential to level the field and increase global equity of care provision.

Where does this leave us, then? It leaves us facing an undeniable fact: the nephrology critical care nurse is a critical pillar of the modern-day ICU team. They stand at the critical intersection of high-tech gadgetry and complicated human biochemistry, managing one of the most resource-intensive therapies in all of medicine. While the disparities of global resources paint two worlds that do not coexist, the mission of this nurse is unaltered: to offer skilled, compassionate, and safe medical care to gravely ill patients suffering from acute kidney injury. Its future relies on our continuing demand for standardized schooling, judicious investing in nursing skill and wise integration of technology with an eye to helping never replace the irreplaceable critical judgment of this. Their role was never just about operating a machine; it is about being the constant, knowledgeable guardian for the patient connected to it.

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Surviving Sepsis Is Not Enough, Time to Confront Post-sepsis Syndrome, A Narrative Review

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Keywords. sepsis, post-sepsis syndrome, survivorship, long-term outcomes, rehabilitation, critical illness recovery; quality of life

While global advances in sepsis care have reduced acute mortality, many survivors face a persistent burden of Post-Sepsis Syndrome (PSS), a complex condition encompassing physical, cognitive, psychological, immunologic, and social sequelae. Despite its prevalence, post-sepsis care remains fragmented and under-recognized within routine critical care pathways.

Relevant literature on post-sepsis outcomes was reviewed through major scientific databases, focusing on studies exploring the physical, cognitive, psychological, immunologic, and social consequences of sepsis. Observational, interventional, and review articles contributing to the understanding of post-sepsis syndrome were evaluated, and findings were synthesized narratively across key thematic domains. Recent multi-center and population-based studies reveal that over half of sepsis survivors experience at least one PSS component within the first year after discharge. Persistent fatigue, neuromuscular weakness, cognitive dysfunction, depression, anxiety, and increased susceptibility to infections are the most common manifestations. Hospital readmission and long-term functional decline remain frequent, while structured follow-up and rehabilitation services are scarce. Awareness among clinicians and policy frameworks addressing survivorship are limited. The reduction of in-hospital sepsis mortality has unveiled a new challenge; survivorship. Long-term recovery requires coordinated and multidisciplinary care extending beyond ICU discharge. Integrating PSS surveillance, rehabilitation programs, and patient education into national sepsis strategies is essential to improve functional outcomes and quality of life.

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At its core, sepsis is the dysregulation of the body's defenses against infection, triggering organ dysfunction and posing one of the greatest unresolved dilemmas in critical care medicine. A large multicenter cohort study involving over 426,000 intensive care unit (ICU) patients with sepsis in the United Kingdom found that hospital mortality rates decreased from 54.6% in the period

of 1988 to 1990 to 32.4% in 2017 to 2019. Notably, 8.8% of this absolute reduction, accounting for 40% of the overall decline, was due to advancements in treatment and critical care management.¹ However,



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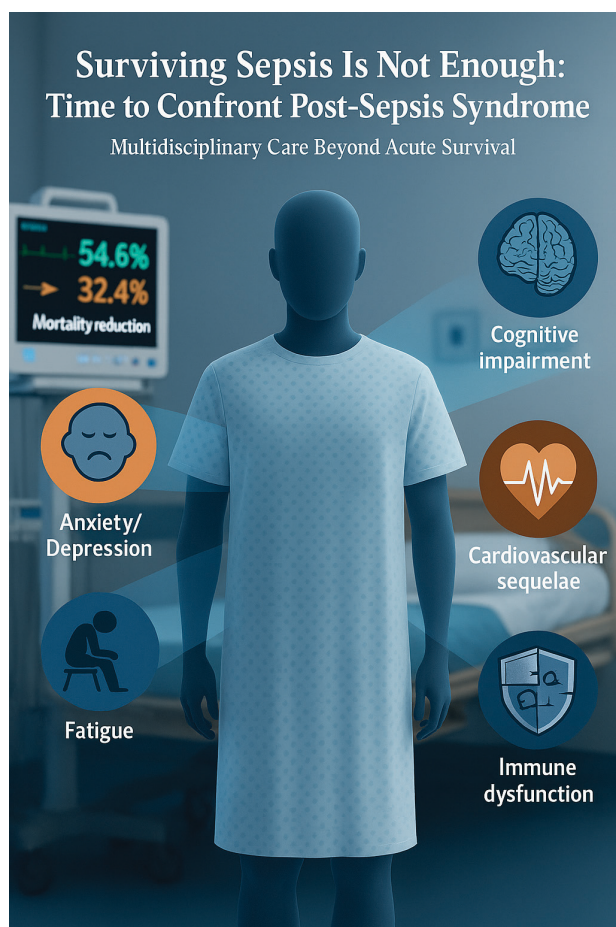
surviving the acute phase of sepsis is not the end of the story; for many patients, it marks the beginning of a new struggle with long-term sequelae that remain largely underrecognized in clinical practice.

Post-sepsis syndrome (PSS) is marked by prolonged immune dysregulation, chronic inflammation, and metabolic dysfunction, which increases survivors' risk of recurrent infections, cardiovascular complications, and neurocognitive decline (Figure).² In a German cohort of 159,684 survivors, 74% developed at least one new diagnosis within the first year following hospital discharge. The prevalence remained high in subsequent years, with 65.8 and 59.4% experiencing new medical, cognitive, or mental health conditions in the second and third years, respectively.³ As shown in Table, PSS manifests through a broad spectrum of long-term complications that extend far beyond the acute phase of illness. On the physical level, survivors often struggle with persistent muscle weakness, chronic fatigue, and reduced exercise tolerance, sometimes

compounded by residual organ dysfunction. Cognitive challenges are equally prominent, with many patients experiencing memory deficits, impaired attention, and difficulties in executive functioning. The psychological burden is also profound, encompassing depression, anxiety, post-traumatic stress disorder (PTSD), and persistent sleep disturbances. In addition, immunological alterations leave survivors more vulnerable to recurrent infections and, in some cases, even malignancies. Beyond these medical and psychological domains, PSS deeply affects social and functional reintegration, as individuals may become dependent on caregivers, face difficulties returning to their professional roles, and experience limitations in engaging with social activities. Collectively, these complications illustrate the pervasive and multidimensional impact of PSS on survivors' lives. Adult sepsis survivors have lower health related quality of life (HRQoL) compared with normal population but not worse than other ICU survivors.⁴ When a family member develops PSS, the economic and social impact on the family can be substantial. Families face direct costs such as repeated medical visits, medications, physiotherapy, and rehabilitation, as well as indirect costs including lost income, work absenteeism, and the need to provide long-term care. In addition, the emotional and social strain can disrupt daily routines and personal plans, significantly increasing stress levels for family members. PSS also places a considerable burden on the healthcare system. Survivors often require hospital readmissions, long term care including physiotherapy, psychological counseling, and regular medical follow ups, which increase overall healthcare costs. The syndrome also demands higher utilization of resources such as ICU beds, nursing care, medications, and home healthcare services. Given the points discussed, greater attention should be directed to the post sepsis condition, which has so far been overlooked.

The striking gaps revealed in recent studies raise a fundamental question: are we truly prepared to care for patients beyond the acute phase of sepsis?

Recent evidence highlights profound structural barriers in sepsis care that extend into the post-discharge period. Healthcare providers consistently reported deficits in sepsis knowledge, limited interdisciplinary communication, and fragmented



Clinical Domains and Reported Outcomes of PSS in Recent Studies

First author	Year	Domain	Sample size	Key findings	References
Sell S et al.	2025	Psychological	21,980 sepsis patients	Within 12 months, 54.8% diagnosed with any mental health impairment; 25.4% developed a new MHI; depression most common (32.2%), followed by anxiety (8.9%) and PTSD (0.6%); co-occurrence frequent; pre-existing psychiatric disorders were strongest risk factors (OR up to 8.9)	5
Halvorsen P et al.	2025	Quality of life / Functional	14,006 sepsis patients	Health-related quality of life was consistently lower than population norms up to 15 months after ICU discharge, with only partial improvement. Sick leave substantially increased after sepsis; 50% of working-age survivors had not regained work capacity by 20 months. Female sex, lower education, and comorbidities predicted poorer recovery, while severity of acute illness had minimal long-term impact	6
Liu et al.	2025	Social / Functional	339 sepsis patients	At 12 months, 65% of patients had died or developed PICS; among survivors, prevalence of PICS declined from 85% at discharge to 45% at 12 months. Only 44% of previously employed patients returned to work, ~40% were rehospitalized, and 31% required emergency care. Despite this burden, rehabilitation (15%) and psychiatric service use (7%) remained low, highlighting major gaps in follow-up support	7
Fleischmann-Struzek C et al.	2024	Physical / Cognitive / Psychological	753 sepsis patients	At 3-year follow-up: ~25% remained functionally dependent, ~30% regained independence, ~45% died; > 90% had new physical impairments, 58% cognitive deficits, ~41% psychological problems	8
Kattlun F et al.	2024	Cognitive	35 sepsis vs 35 controls	Survivors showed persistent deficits in working memory capacity ($P = 0.013$), with impairments in attention, memory, and executive functions; deficits independent of age, sex, depression, or anxiety	9

care transitions as critical shortcomings. Particularly concerning is the absence of standardized protocols for follow-up and aftercare, leaving primary care physicians, patients, and families without clear guidance. Providers also emphasized that information sharing between hospital and outpatient sectors is frequently incomplete, resulting in poorly coordinated rehabilitation, psychological support, and chronic disease management. Collectively, these deficiencies not only compromise recovery for survivors but also impose a significant burden on families and the healthcare system.¹⁰ These findings underscore systemic weaknesses, but they also highlight a more profound issue. PSS is still managed as an optional afterthought rather than being recognized as an essential dimension of critical care. The absence of standardized follow-up structures reflects a lack of prioritization at the policy level, where survival rates continue to

be the dominant outcome measure. This narrow focus risks neglecting the multifaceted disabilities and psychosocial burdens that define PSS for survivors and their families. Without a paradigm shift that embeds rehabilitation, mental health care, and chronic disease management into routine pathways, the healthcare system will continue to fail a growing population of sepsis survivors.

Addressing the profound unmet needs of sepsis survivors requires a paradigm shift toward structured, multidisciplinary, and patient-centered post-sepsis care. Evidence highlights the necessity of early and continuous rehabilitation that encompasses physical, cognitive, and psychological domains, complemented by nutritional guidance and speech-language therapy. To ensure equitable access, policy efforts must target both financial and structural barriers, while also expanding caregiver education and peer support initiatives. Furthermore, establishing dedicated

post-sepsis clinics, staffed by critical care specialists, rehabilitation experts, psychiatrists, and primary care providers, would provide a systematic framework for long-term follow-up. At a health systems level, integration of sepsis-specific screening protocols into routine outpatient care, coupled with sustainable funding models for rehabilitation services, represents a crucial step toward improving survivors' quality of life and reducing the long-term societal burden of sepsis.^{11,12}

Sepsis care has long been measured in lives saved, but survival alone is no longer a sufficient outcome. The growing recognition of PSS demands that we look beyond the ICU and confront the enduring physical, cognitive, and psychological scars left behind. Every unaddressed impairment represents not just an individual struggle, but a systemic failure to deliver truly comprehensive care. While continuous advances in acute-phase management and critical care remain vital to further reducing mortality, equal attention must now be directed toward enabling survivors to reclaim meaningful lives. The time has come for clinicians, researchers, and policymakers alike to embrace post-sepsis care as a central priority, because surviving sepsis should mark the beginning of recovery, not the start of another silent epidemic.

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Conflicts of Interest

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All authors contributed to the study and approved the final version of the manuscript.

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Association Between Lipid-related Parameters and the Carotid Intima-media Thickness, Relating to Type 2 Diabetes Mellitus

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Introduction. Higher carotid intima-media thickness (CIMT), indicates a greater burden of subclinical atherosclerosis (AS) and cardiovascular disease (CVD). The AS is related to insulin resistance and lipid oxidation. Detection of reliable and affordable surrogate markers and metabolic components for assessing the CVD risk is world-shaking. This study aimed to inspect the relationship between lipid-related parameters and CIMT, considering the impact of type 2 diabetes mellitus (T2DM).

Methods. This cross-sectional study was conducted on a total of 244 participants (113 men and 131 women), including 118 diagnosed with diabetes (DM) and 126 without diabetes (non-DM). Duplex ultrasonography parameters, demographic, physical, biochemical assessments, and lipid-related parameters were measured. Correlation and linear regression analyses assessed the relationship between the lipid-related parameters and CIMT.

Results. The DM patients' levels of triglyceride-glucose (TyG) index were significantly higher than the non-DM ones, however, the two groups demonstrated no statistically significant difference in CIMT levels. CIMT was correlated with low-density lipoprotein ($r = 0.33$, $P = .033$) in the DM group and with age ($r = 0.41$, $P < .001$) in the non-DM group. The multivariate linear regression model demonstrated age, TyG-BMI, and LDL/HDL ratio as the significant associates of CIMT, with age having the largest standardized regression coefficient of 0.311 ($P < .001$).

Conclusions. The current study revealed direct associations of CIMT with age, TyG-BMI, and LDL/HDL ratio, taking into account the DM/non-DM binary among the study participants.

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INTRODUCTION

Atherosclerosis (AS) is a chronic vascular disease characterized by the accumulation of fatty streaks in arterial walls, with possible progression into plaque formation (atheroma), plaque rupture, and eventually thrombotic occlusion of the vessels.¹ Accordingly, this process may cause mortality

and morbidity, such as ischemic heart disease, stroke, and peripheral arterial disease, which, in turn, impose significant burdens on the health of



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community members.² Thus, it is crucial for the early identification of high-risk people and the timely control of AS progression.³ It is known that some risk factors, including hypertension (HTN) and diabetes mellitus (DM), can accelerate the progression of AS at different levels,⁴ as well as endothelial dysfunction.⁵ Hence, HTN and DM are now considered essential parameters in the risk prediction of cardiovascular disease (CVD).⁶ In this context, it was also demonstrated that insulin resistance (IR) plays a staple role in the development of DM, HTN, and AS,^{1,7} and it is a well-known predictor of a wide range of CVDs.⁸ Given these facts, several studies have examined the predictive ability of different insulin resistance markers to achieve an accurate and non-invasive tool for the early detection of AS, particularly in high-risk groups.⁹

In recent years, some reliable and affordable surrogate markers for IR have been introduced, such as the triglyceride glucose (TyG) index, the TyG-modified indices (the TyG-body mass index (TyG-BMI) and TyG-waist circumference (TyG-WC)), triglyceride/ high-density lipoprotein cholesterol (TG/HDL) ratio, total cholesterol/ HDL (TC/HDL) ratio, low-density lipoprotein cholesterol/ HDL (LDL/HDL) ratio and TG minus HDL.¹⁰⁻¹³ Some of the mentioned parameters could predict IR more accurately than the homeostasis model assessment-estimated insulin resistance (HOMA-IR).^{14,15}

Given that both hypertriglyceridemia and impaired glucose metabolism are commonly related to IR and AS,¹⁶ growing attention is now attracted to assessing the association of the TyG index with AS.^{11,17} The studies demonstrated that higher TyG-BMI index, TG/HDL, TC/HDL, LDL/HDL ratios, and TG-HDL are associated with increased IR, metabolic dysregulation, and CVD.¹¹⁻¹³

Carotid intima-media thickness (CIMT) is a widely used imaging marker for the diagnosis of preclinical carotid AS,¹⁸ which was shown to have predictive value for future cardio/cerebrovascular events as well.¹⁹ Previous studies explored the positive relationship between some of the mentioned parameters and CIMT in different populations from the point of view such as of age, weight, and comorbidities,²⁰⁻²⁶ however, some controversial

results are present.^{17,27}

Moreover, to our knowledge, previously published research has not precisely compared the associations of lipid-related parameters totally and CIMT in individuals with and without diabetes mellitus.^{28,29} Consequently, the current research examined the mentioned relationship.

MATERIALS AND METHODS

Study Design and Participants

This cross-sectional study was conducted at the Endocrine Research Center, Iran University of Medical Sciences, and Firoozgar General Hospital, Tehran, Iran; from 2019 to 2021. The eligible participants were enrolled via convenience sampling, DM patients from the endocrine clinic, and non-DM patients from the neurologic clinic. The site of sampling was a referral center located in a metropolitan district of the middle socioeconomic status, which to some extent secures the generalizability of the findings.

The inclusion criteria were as follows: (DM group) T2DM, and the age range of 20 to 70 years old for both groups. The exclusion criteria for both groups were: smoking; substance abuse; pregnancy; taking corticosteroids, immunosuppressive medications, omega-3, lipid-lowering agents, and contraceptives; renal transplantation; systemic conditions (autoimmune diseases, chronic renal disease, chronic or acute infection); CV surgery; malignancy; and albuminuria (urine albumin to creatinine ratio > 30 mg/g). Diabetes mellitus was diagnosed according to criteria recommended by the American Diabetes Association (ADA).¹⁹

The research protocol was approved by the ethics committee of the Iran University of Medical Sciences (No: IR.IUMS.REC.1401.820), and all participants signed and provided written permission.

Clinical Measurements and Definitions

Data on demographic characteristics, clinical assessments, past medical history, and medications were collected via a standard questionnaire by a trained physician, who conducted a face-to-face interview at the initial appointment.

A calibrated stadiometer & digital scale (Seca GmbH & Co. KG, Germany) were used to measure standing height and weight, respectively. BMI

was demonstrated as the weight (kg) divided by the square of the height (m²). Participants' blood pressures were measured by a mercury sphygmomanometer (Riester, Exakta 1350, Germany) in the standard position (sitting position after a 10-minute rest).

The blood samples were collected in the tubes containing the clot activator after an overnight fast of at least 8 hours. The separated serum was then analyzed for evaluating the biochemistry panel, including fasting blood glucose (FBG), creatinine, and lipid profile. The samples were analyzed using the Enzymatic Calorimeter technique (Biorex).

The TyG index and modified TyG index were calculated using the following formulae:

TyG index: $\text{Ln} [\text{TG (mg/dl)} \times \text{FBG (mg/dl)} / 2]$ ³⁰ and TyG-BMI (TyG index $\times$ BMI). In addition, the other lipid-related parameters are as follows: TG/HDL-C ratio (TG divided by HDL-C), TC/HDL-C ratio (TC divided by HDL-C), LDL-C/HDL-C ratio (LDL-C divided by HDL-C), and TG minus HDL-C.

Additionally, e-GFR was determined by applying diet modification in renal disease (MDRD) formula.³¹

Assessment of Carotid Intima-media Thickness (CIMT)

An expert neurologist with certified neurosonology experience performed the carotid ultrasonography assessments. The mentioned neurologist was blinded to all participants' characteristics and laboratory results.

A high-resolution duplex ultrasound system (B-Mode) with an 8-Hz linear probe (Sonosite M Turbo, Fuji Film, Japan) measured CIMT. The CIMT was estimated by measuring the thickness of the innermost two layers of intima-media 10 mm before the bifurcation of the common carotid artery (CCA), where no atherosclerotic plaque was present. The left and right CIMT average was calculated and used in all analyses. Mean CIMT over the 75th percentile for age, race, and gender was considered a CV events risk factor, according to the American Echocardiographic Association criteria.³²

Statistical Analysis

Demographic and clinical characteristics of participants in the study groups are described

as proportions, means (standard deviation (SD)), or medians (interquartile range (IQR)). Between-group comparisons were conducted using an independent sample t-test and Mann-Whitney test for data with and without normal distribution. Categorical variables were compared using the χ^2 test. A Spearman's correlation analysis was performed to examine the correlations of CIMT with different clinical parameters.

Moreover, the associations of CIMT with lipid-related parameters were explored using univariate and multivariate linear regression analyses. The significance level was set at .05. The statistical analyses were performed using the statistical software Stata (ver. 13).

RESULTS

Data included 244 participants (113 men and 131 women) with a mean (SD) of age equal to 46.4 (10.4) years, consisting of 126 individuals without and 118 with T2DM (median (IQR) duration of DM = 7 (5 to 10) years). As presented in Table 1, the two groups of participants were comparable in terms of gender, BMI, serum TG, and HDL-C. Also, there was no significant difference between CIMT evaluated in the two groups. However, individuals with T2DM were older and had significantly higher BP, FBG, and TyG indexes and lower e-GFR, TC, LDL-C, LDL/HDL, and TC/HDL than those without diabetes (all *P* values < .05).

Next, the Spearman correlations were computed between CIMT and the variables assessed in Table 1, stratified for the diabetes status, and applying the Bonferroni multiple testing adjustment. Accordingly, in the DM group, LDL showed an association of 0.33 (*P* value = .033), and in the non-DM group, age, SBP, and TyG-BMI owned correlations of 0.41, 0.30, and 0.30 (*P* values of < .001, .085, .076; respectively).

Furthermore, considering the variables of *P* values lower than .1 in Table 1 and the Spearman correlations of *P* values lower than .1, the univariate regression models were fitted on CIMT as the response variable and adjusted for the diabetes status. The covariates included age, SBP, DBP, FBG, Total cholesterol, LDL-C, TyG, TyG-BMI, LDL/HDL, TC/HDL, and e-GFR. The findings reported in Table 2 indicated all covariates to be significantly

Table 1. Characteristics of the Study Participants, Compared in Terms of Diabetes Status

	Non-diabetic group (n = 126)	Diabetic group (n = 118)	P
Age, y (mean (SD))	42.7 (9.8)	50.3 (9.6)	< .001 ^a
Gender (female, n (%))	69 (54.8%)	62 (52.5%)	.730 ^b
BMI, kg/m ² (mean (SD))	26.2 (4.3)	26.6 (3.9)	.459 ^a
SBP, mmHg (median (IQR))	120 (110 to 120)	120 (120 to 130)	< .001 ^c
DBP, mmHg (median (IQR))	80 (70 to 80)	80 (70 to 80)	.004 ^c
FBG, mmol/l (median (IQR))	96 (92 to 103)	115 (103 to 138)	< .001 ^c
TG, mmol/l (median (IQR))	95 (75 to 148)	105 (89 to 124)	.288 ^c
TC, mmol/l (median (IQR))	149 (123 to 182)	132 (122 to 146)	.001 ^c
LDL-C, mmol/l (median (IQR))	95 (80 to 118)	70 (58 to 83)	< .001 ^c
HDL-C, mmol/l (median (IQR))	43 (41 to 48)	44 (41 to 48)	.567 ^c
TyG, median (IQR)	8.4 (8.2 to 8.9)	8.8 (8.5 to 9)	< .001 ^c
TG/HDL, median (IQR)	2.3 (1.8 to 3.5)	2.4 (2 to 2.9)	.616 ^c
TG-HDL, median (IQR)	51.5 (32 to 106)	60 (44 to 82)	.396 ^c
TyG-BMI, median (IQR)	223.2 (196.4 to 250.6)	230.1 (211.8 to 254)	.069 ^c
LDL/HDL, median (IQR)	2.3 (1.7 to 2.8)	1.5 (1.3 to 1.9)	< .001 ^c
TC/HDL, median (IQR)	3.5 (2.8 to 4.3)	3 (2.7 to 3.4)	< .001 ^c
e-GFR, mL/min/ 1.73m ² (median (IQR))	103.5 (82.9 to 130)	88.5 (74.4 to 106.3)	.001 ^c
CIMT, mm (mean (SD))	0.41 (0.11)	0.40 (0.13)	.506 ^a

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TyG, triglyceride glucose index; e-GFR, estimated glomerular filtration rate; CIMT, carotid intima-media thickness. a, t-test; b, χ^2 test; c, Mann-Whitney test.

Table 2. Univariate Regression Analyses of Carotid Intima-media Thickness

Variables	Coefficients	95% CI	P	Standardized Coefficients
Age, y	0.0039	0.0025, 0.0052	< .001	0.333
SBP, mmHg	0.0010	-0.0002, 0.0022	.101	0.108
DBP, mmHg	-0.0002	-0.0016, 0.0013	.839	-0.014
FBG, mmol/L	0.0010	0.0003, 0.0017	.005	0.208
TC, mmol/L	0.0007	0.0003, 0.0011	.002	0.207
LDL-C, mmol/L	0.0013	0.0008, 0.0018	< .001	0.320
TyG	0.0518	0.0248, 0.0788	< .001	0.216
TyG-BMI	0.0007	0.0003, 0.0011	< .001	0.229
LDL/HDL	0.0443	0.0223, 0.0664	< .001	0.272
TC/HDL	0.0215	0.0055, 0.0374	.009	0.168
e-GFR, mL/min/ 1.73m ²	-0.0005	-0.0009, 0.0000	.063	-0.126

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TyG, triglyceride glucose index; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; e-GFR, estimated glomerular filtration rate.

Table 3. Multivariate Regression Analyses of Carotid Intima-media Thickness

Variables	Coefficients	95% CI	P	Standardized Coefficients
Age, y	0.0036	0.0023, 0.0049	< .001	0.311
TyG-BMI	0.0005	0.0002, 0.0009	.005	0.172
LDL/HDL	0.0466	0.0215, 0.0716	< .001	0.285
TC/HDL	-0.0069	-0.0261, 0.0123	.478	-0.054

Abbreviations: TyG, triglyceride glucose index; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.

associated with CIMT, except for SBP, DBP, and e-GFR. Moreover, age and LDL-C had the highest standardized regression coefficients. Regarding the significant covariates and the interrelations

between them, the multivariate regression model was fitted, including the covariates of age, TyG-BMI, LDL/HDL, and TC/HDL, leading to the findings reported in Table 3. In this model, age,

TyG-BMI, and LDL/HDL remained significant correlates of CIMT and the largest standardized coefficient belonged to age.

DISCUSSION

This study examined the association of the lipid-related parameters totally with CIMT as an accepted marker for AS in a sample of the Iranian population with T2DM compared to that in non-diabetic people.

Our results highlighted a direct correlation between CIMT and age, TyG-BMI, and LDL/HDL ratio, evaluated in the diabetic and non-diabetic groups.

It is known that IR can accelerate AS progression through metabolic abnormalities, such as hyperglycemia and dyslipidemia.³³ Given both abnormalities,¹⁶ growing attention is now attracted to assessing the association of the TyG index with AS.^{11,17} Recently, the TyG-modified indices, TG/HDL, TC/HDL, LDL/HDL ratios, and TG minus HDL¹⁰⁻¹³ have been highlighted as reliable surrogate markers for IR, and their high values are associated with increased IR, metabolic dysregulation, and CVD.¹¹⁻¹³

In addition, existing evidence confirms the positive association of the mentioned parameters with obesity and atherogenic dyslipidemia¹⁴ and other CVD risk factors such as T2DM, HTN, and metabolic syndrome.³⁴⁻⁴⁰ TG/HDL ratio and TyG index are defined as a useful predictor of glycemic control in normal-weight and overweight patients with T2DM respectively.⁴¹ Furthermore, the TyG index, modified TyG indices and TG/HDL ratio have been suggested as reliable markers for predicting each aspect of CVD in different populations.^{12,13,42-44} The TC/HDL ratio is considered a probable biomarker for screening early peripheral arterial disease.⁴⁵ To some extent, controversies are present, a J-shaped relationship was detected between baseline TG/HDL and T2DM risk in Japanese.³⁴

CIMT as a predictive marker for the diagnosis of preclinical carotid AS and cardio/cerebrovascular events,^{18,19} is positively related to the TyG index;¹⁷ however, some controversial results are presented. For instance, it was revealed that a higher TyG index is linked to carotid AS measured by CIMT

in patients with ischemic stroke,³ this association is consistent with the role of IR in promoting AS and CVD. In another study on 2560 Korean subjects without a previous coronary artery disease and stroke history, the TyG index was associated with CIMT and arterial stiffness.⁴⁶ Furthermore, Lu *et al.* detected a direct association between the TyG index and abnormal CIMT in non-diabetic females after adjustment for AS traditional risk factors.⁷

Also, Jia *et al.* detected a U-shaped relationship between the TyG index and elevated CIMT in non-obese Chinese people.¹⁷ However, the TyG index was not significantly correlated with a high CIMT in another study conducted on the Chinese population.²⁷

Liu; demonstrated a direct association between TyG-WC and CIMT, reflecting a higher burden of subclinical carotid AS especially in middle-aged and older adults with normal weight.²¹

In addition, the other studies described positive associations between TG/HDL, TC/HDL, and LDL/HDL ratios with CIMT, AS, and carotid plaques in different populations,²²⁻²⁶ and also these correlations are confirmed in the diabetes population complicated by chronic kidney disease on peritoneal dialysis.²⁰

No previous published study has examined the relationship between lipid-related parameters and CIMT in individuals with T2DM compared to non-DM people. However, our findings partially align with the results of only one available preliminary report investigating the predictive ability of TyG concerning carotid atherosclerosis in individuals with T2DM without any control group.⁴⁷ Similarly, in another study by Gothwal *et al.*, the TyG index significantly correlated with CIMT in non-DM people.⁴⁸

The mechanism by which the mentioned parameters contribute to the development of AS is not fully demonstrated; however, it has been proposed that at the onset of IR, an increase of fatty acids in the liver, activates the pro-inflammatory pathways and consequently causes AS development and also increase the risk of coronary heart disease.⁴⁹⁻⁵¹ In addition, the elevated levels of fatty acids in pancreatic islets alter the metabolism of glucose and damage the beta cells.⁵² Another

suggested mechanism is that high glucose levels, which increase reactive oxygen radicals, exert injury to beta cells^{25,53} and cause endothelial dysfunction.²⁰

Our data also confirmed the direct effects of dyslipidemia and FBG on CIMT reported in previous studies.^{54,55} No correlation between BP and CIMT was detected from our data, possibly due to the aggressive hypertension treatment consistent with Oguntola *et. al.*²⁴

In the present manuscript, the references listed are based on studies of the Asian population (e.g., Chinese and Korean). In contrast, the results collected and presented here are based on results collected from the Iranian people, who are genetically closer to the Caucasian population. The differences between results may be due to the differences in the diet and lifestyles of the different populations.

Given the cheapness and simplicity of calculation, the TyG-BMI, and LDL/HDL may be regarded as a plausible and available indicator of subclinical carotid atherosclerosis. Although statin therapy is for the reduction of LDL-C level, a residual risk of carotid AS remains, so a combination therapy to control other lipid parameters, in addition to reducing the LDL-C level can be beneficial.⁵⁶ Accordingly, lifestyle modification (nutrition and exercise) and medical treatments are recommended for the primary prevention of CVD. So, these associations highlight the importance of assessing both metabolic and anthropometric factors in diabetic individuals for CVD risk stratification and management.

LIMITATIONS

Some limitations must be taken into account in this investigation. Firstly, recruiting the participants in the study was faced with the challenge of convincing them to go under the color-doppler sonography procedure. Besides, the lack of HbA1C measurements prevented us from achieving a more accurate estimate of the glycemic control status in the diabetic participants. In addition, the lack of medication analysis and categorization, limited us to prove the effect of insulin therapy beyond oral antidiabetic drugs or combination therapy on lipid profile. So the injectable therapies such as insulin could be a confounder variable.

CONCLUSIONS

In conclusion, the present study revealed direct relationships of carotid intima-media thickness with age, triglyceride glucose-body mass index, and low-density lipoprotein to high-density lipoprotein ratio, based on a sample composed of diabetic and nondiabetic patients. More comprehensive research with larger sample sizes and larger pools of covariates is required to authenticate these findings.

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DECLARATIONS

Ethical Approval

This project was accepted by the ethical committee of Iran University of Medical Sciences; ethical code: IR.IUMS.REC.1401.820. The study was conducted after obtaining ethical approval from the ethical committee of the Iran University of Medical Sciences (Ref. No: IR.IUMS.REC.1397.1118). Written informed consent was obtained from all subjects. The authors attest that the participants knew the study's purpose, risks, and benefits. Anonymity was maintained throughout the study period. All activities and methods for the study were carried out considering research ethics guidelines for Iran. All procedures performed in human participant studies followed the institutional and/or national research committee's ethical standards, the 1964 Helsinki Declaration, and its later amendments or comparable ethical standards.

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Conflict of Interest

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

Authors' Contributions

LN, AA, AKH, OAGH and ZM did the interventions, reviewed medical aspects, and participated in preparing the manuscript. LN, AA, AKH, OAGH and ZM drafted the manuscript. LN, AKH, OAGH and AA supervised the project and revised the manuscript critically. LN and AKH analyzed the manuscript. All authors read and approved the final version of the manuscript.

Abbreviations

ADA, American Diabetes Association; AS, Atherosclerosis; BMI, Body Mass Index; BP, Blood Pressure; CCA, Common Carotid Artery; CIMT, Carotid Intima-media Thickness; CV, Cardiovascular; CVD, Cardiovascular Disease; DBP, Diastolic Blood Pressure; DM, Diabetes Mellitus; e-GFR, Estimated Glomerular Filtration Rate; FBG, Fasting Blood Glucose; FRS, Framingham Risk Score; HbA1C, Hemoglobin A1C; HDL-C, High-density Lipoprotein Cholesterol; HOMA-IR, Homeostasis Model Assessment-estimated Insulin Resistance; HTN, Hypertension; IR, Insulin Resistance; LDL-C, Low-density Lipoprotein Cholesterol; MDRD, Modification of Diet in Renal Disease; SBP, Systolic Blood Pressure; TC, Total Cholesterol; T2DM, Type 2 Diabetes Mellitus; TG, Triglyceride; TyG, Triglyceride Glucose Index

The place where the study was performed

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Diagnostic Efficacy and Imaging Characteristics of MRI Combined with CT in Children with Duplex Kidney

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Keywords. duplication of kidney, MRI, CT, diagnostic performance, imaging characteristics

Introduction. To analyze the diagnostic efficacy and imaging characteristics of MRI combined with CT in children with duplication of kidney.

Methods. A retrospective analysis was conducted of the clinical data of 40 children with duplication of kidney admitted to our hospital between January 2019 and January 2024 and confirmed surgically. All patients underwent MRI and CT examinations, with surgery as the gold standard. The diagnostic efficacy of MRI and CT in children with duplication of kidney was analyzed.

Results. CT confirmed 32 cases of duplication of kidney, with a diagnostic rate of 80%. MRI confirmed 33 cases of duplication of kidney, with a diagnostic rate of 82.50%. CT combined with MRI confirmed 39 cases of duplication of kidney, with a diagnostic rate of 97.50%. The diagnostic rate of CT combined with MRI for duplication of kidney was higher than that of CT or MRI alone ($P < .05$). The diagnostic accuracy of CT combined with MRI for hydronephrosis duplication was 100%, significantly higher than the 77.27 and 81.82% rates of CT and MRI alone ($P < .05$). There was no significant difference in the diagnostic accuracy of CT or MRI alone for developmental and dysplastic duplication ($P > .05$).

Conclusions. MRI combined with CT has a high diagnostic efficacy for duplex kidney and its classification in children, which can provide a reference for clinical diagnosis and treatment and can be vigorously promoted in clinical practice.

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INTRODUCTION

Duplicated kidney is a common congenital urinary malformation in children. It refers to the presence of two renal segments and two collecting systems within one renal capsule.¹ It can cause urinary tract infection, hydronephrosis, renal insufficiency and other hazards, seriously affecting the health of the child.² At the same time, because it has no specific symptoms and signs, it often appears in the form of complications, which can easily lead to misdiagnosis, causing the child to miss the best treatment time and affect the prognosis.³

Therefore, timely and accurate diagnosis is crucial. In recent years, with the continuous development of science and technology and the continuous improvement of medical level, the diagnostic technology of duplicated kidney malformation has been developed, which has promoted the widespread clinical attention and attention to the treatment of this disease. The most commonly



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used examination methods at present are CT and MRI. Among them, CT has high density resolution and spatial resolution, which can clearly show the morphology, structure and pathological conditions of the kidneys, and can perform three-dimensional reconstruction, which helps to understand the pathological conditions more comprehensively, but it has poor soft tissue display.⁴ MRI has a high resolution for soft tissues, can image in multiple directions, can better display bones and soft tissues, and can evaluate the anatomical structure of the urinary system, but its examination time is longer and it is more sensitive to motion artifacts.⁵ At the same time, there are few detailed reports on the diagnostic value of MRI combined with CT in children with duplication of kidney. Therefore, in order to improve the diagnostic rate of duplication of kidney, this study combined the two for the diagnosis of duplication of kidney in children, aiming to provide a reference for clinical practice. The results are reported as follows.

MATERIALS AND METHODS

General Data Analysis

The clinical data of 40 children with duplication of kidney who were admitted to our hospital from January 2019 to January 2024 and confirmed by surgery were collected. Among them, there were 13 males and 27 females. The patients were aged 1 month to 13 years old, with an average age of (5.72 ± 1.26) years. Among them, 38 cases were unilateral (17 left-sided cases and 21 right-sided cases), and 2 cases were bilateral. There were 5 cases of developmental type, 22 cases of hydronephrosis type, and 13 cases of dysplasia type. Inclusion criteria: 1) confirmed by surgery; 2) aged 1 month to 13 years; 3) no contraindications for CT and MRI examination; 4) complete clinical data. Exclusion criteria: 1) patients with combined hypospadias, single kidney loss, and congenital megaureter; 2) patients with poor compliance. 28 patients had symptoms such as dysuria, fever, and hematuria, and the remaining 12 patients were found to have duplication of kidney due to other examinations.

Inspection Method

CT examination. It was performed using a Philips 64-slice volumetric CT scanner. Patients were

positioned supine, and scans were performed from the upper pole of the kidney to the pubic symphysis. After a plain scan, the contrast agent iohexol was injected via the antecubital vein. Parenchymal and excretory phase scans were performed 30 to 45 seconds and 5 minutes after contrast injection. Parameters included tube voltage 120 kV, tube current 180 to 260 mA, and slice thickness 5 mm. Data were transferred to a workstation for image post-processing using volume rendering, maximum intensity projection, multiplanar, and curved reconstruction, resulting in multi-dimensional 2D and 3D images of the urinary tract.

MRI Examination. A Philips 1.5 T MRI system was used with the patient in the supine position, using a standard abdominal coil. The costophrenic angles and pubic symphysis were covered. Axial scanning parameters were T1WI and T2WI sequences, with a 1-mm slice spacing, a 1-mm slice thickness, and a 256×256 matrix. Coronal and sagittal scans were performed with fat-suppressed signal sequences, and the fat-suppressed sequence was T2WI.

Diagnostic Criteria

Two chief physicians of the imaging department reviewed the films and compared the imaging results of the kidneys, ureters, and bladder with the postoperative results. If the preoperative imaging results were consistent with the postoperative results, it was confirmed; if some diagnostic results were inconsistent with the postoperative results, it was partially consistent; if all diagnostic errors were completely inconsistent; if some or all of them were inconsistent, it was undiagnosed. Classification criteria:⁶ 1) Developmental type: the upper renal cardia is well developed and similar to the lower renal cardia; 2) Hydronephrosis type: hydronephrosis of the upper renal cardia, ureteral obstruction, and combined with ureterocele; 3) Hypoplastic type: the upper renal cardia is small, partially vesicular or mulberry-shaped, with a small amount of fluid in the renal cardia and ectopic ureteral opening.

Statistical Analysis

SPSS 24.0 software was used to analyze the data. Enumeration data were expressed as (n). χ^2 test and Fisher's exact probability were used for analysis. $P < .05$ was considered significant.

RESULTS

Analysis of CT and MRI Diagnostic Results of Duplication of Kidney

Diagnosis rate of CT combined with MRI was higher than that of CT or MRI alone ($P < .05$), and there was no significant difference in the diagnosis rate between CT and MRI ($P > .05$) (Table 1).

Comparison of Diagnostic Accuracy of CT and MRI for Duplication of Kidney Types

The diagnostic accuracy of CT combined with MRI for hydronephrosis-type duplication of kidney was higher than that of CT or MRI alone ($P < .05$). There was no significant difference in the diagnostic accuracy of CT or MRI alone or in combination for developmental and dysplastic duplication of kidney ($P > .05$) (Table 2).

MRI and CT Imaging Features of Duplex Kidney in Children

MRI revealed that the duplicated kidney was longer in length than the normal kidney, with dilated renal pelvis and calyces exhibiting hydrops, which showed high signal intensity on T2WI and low signal intensity on T1WI. The upper renal segment was hydrocystically dilated, with the ureteral segment draining the dilated kidney exhibiting high signal intensity on T2WI and low signal intensity on T1WI. The lower renal segment was displaced outward. CT revealed that the ipsilateral kidney was larger than the

contralateral kidney, with thinning of the renal cortex and a cystic, low-density shadow within. Enhanced scans revealed enhanced cystic wall, and delayed scans revealed contrast agent retention in the low-hanging portion of the cystic shadow, forming a fluid-fluid surface.

Figure 1 shows a 2-year-8-month-old girl with duplication of kidney. Figure A is the delayed CT scan of the patient, showing two sets of renal pelvis and calyceal systems in the right kidney, hydronephrosis in the right upper hemisphere, and dilated hydroureter. Figure B is the MRU image of the patient, showing two sets of renal pelvis and calyceal systems in the right kidney, dilated hydroureter in the right upper hemisphere, and abnormal ureteral opening. Figure C is the laparoscopic surgery confirming the patient's right duplication of kidney, hydronephrosis in the right upper hemisphere, and low-positioned and dilated opening of the right duplication of ureter.

DISCUSSION

Duplicated kidney is a common collecting system anomaly of the upper urinary tract, with an incidence of 0.5 to 0.8%.⁷ It can be divided into developmental, hydronephrosis, and dysplastic types. Most duplicated kidneys have no obvious symptoms and are often discovered during examinations for other diseases.⁸ Different pathological classifications also have different treatment methods. Developmental types often have

Table 1. Analysis of CT and MRI Diagnostic Results of Duplication of Kidney ((n) %)

Inspection method	Number of cases	Confirmed diagnosis comparison	
		Confirmed	Undiagnosed
CT	40	32 (80.00)	8 (20.00)
MRI	40	33 (82.50)	7 (17.50)
CT combined with MRI	40	39 (97.50)	1 (2.50)
χ^2		5.000	
P		.025	

Table 2. Comparison of Diagnostic Accuracy of CT and MRI for Duplication of Kidney Types ((n) %)

Imaging examinations	Developmental type (n = 5)	Water accumulation type (n = 22)	Hypoplastic type (n = 13)
CT	4 (80.00)	17 (77.27)	11 (84.62)
MRI	4 (80.00)	18 (81.82)	11 (84.62)
CT combined with MRI	5 (100.0)	22 (100.0)	12 (92.31)
χ^2	-	8.238	0.377
P / Fisher exact probability	1.000	.016	.539

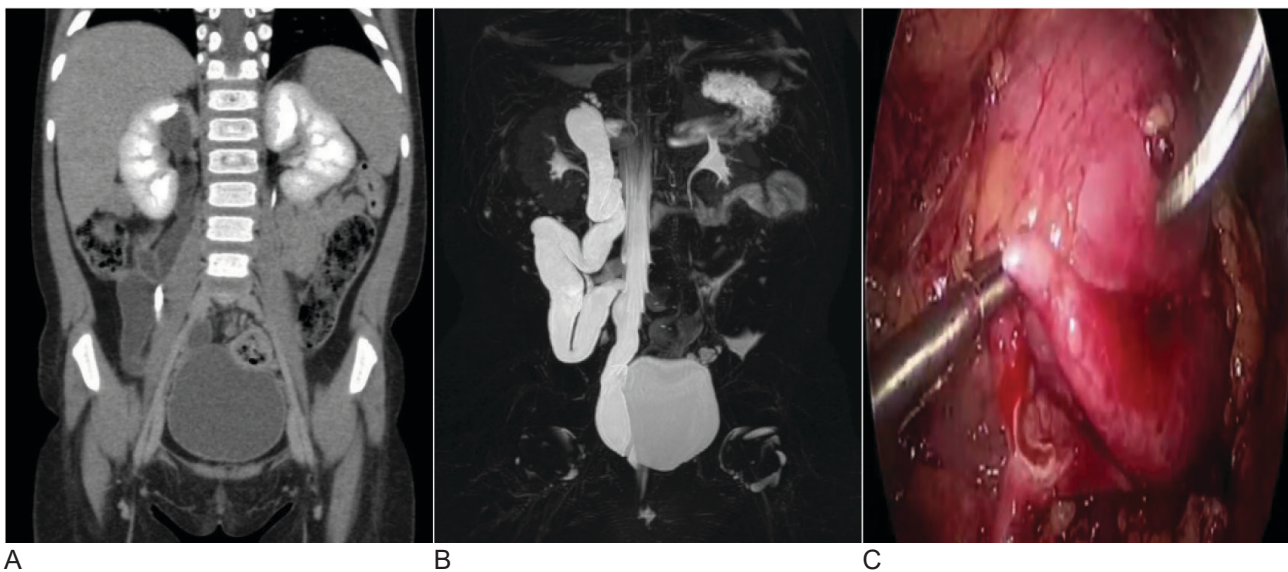


Figure 1. Images of MRI and CT in Diagnosing Duplication of Kidney in Children

no clinical symptoms and generally do not require surgical treatment; hydronephrosis and dysplasia types are often combined with ureterocele and ectopic opening, which can cause hydroureteral accumulation, compress renal tissue, and cause renal dysplasia. In the long term, it can lead to a gradual decline in renal function and even cause serious complications, requiring surgical treatment.⁹⁻¹⁰ Therefore, early diagnosis and surgical treatment are very important.

Ultrasound is easy to operate and can display the upper pole of the kidney in multiple sections. However, it is easy to misdiagnose when there is severe hydronephrosis, and it is not good at displaying the thin lower ureter, which has certain limitations.¹¹⁻¹² With the continuous improvement of diagnostic technology, CT and MRI are currently used to diagnose duplicated kidney in children. CT has a faster imaging speed and higher spatial resolution, and can avoid interference. It can display the anatomical structure and adjacent tissues of the renal parenchyma, renal calyx, renal pelvis and ureter. Enhanced scanning helps to more intuitively observe the three-dimensional structure of the kidney and its surrounding tissues, display the contents of the duplicated kidney, and can also track and scan the ureter to the bladder to determine whether the ureteral opening is ectopic. After reconstruction, the secretion and excretion function of the kidney can

be observed. However, the display of non-dilated duplicated ureters is not clear and intuitive.¹³ MRI does not have ionizing radiation and does not require the injection of contrast agents. It has a higher soft tissue resolution and can clearly display the anatomical structure and functional information of the kidney. MRI can provide a more accurate assessment of the subtle structure and morphological changes of the duplicated renal pelvis, renal calyx and ureter.¹⁴ In addition, MRI can also perform multi-directional scanning imaging, and after post-processing, it can display urinary system images in three dimensions, allowing for a more comprehensive observation of the kidneys and surrounding tissues, especially for the display of hydronephrosis and thickened ureters. However, the examination time is longer and it is more sensitive to motion artifacts.¹⁵ The results of this study showed that the diagnostic rate of CT combined with MRI for duplicated kidneys was higher than that of CT or MRI alone, while there was no significant difference in the diagnosis rate between CT and MRI. This indicates that MRI combined with CT can improve the diagnostic efficiency of duplicated kidneys in children. Since MRI and CT are combined, they are complementary in displaying duplicated renal pelvis, renal calyces and ureters, which can provide a more comprehensive understanding of the lesions and improve the accuracy of diagnosis.

However, one patient was missed in the combined diagnosis. The possible reason for this is that the anatomical complexity of the duplicated kidney and the problem of renal hypoplasia in children do increase the difficulty of diagnosis. Therefore, this study believes that it is necessary to comprehensively consider multiple factors when making a diagnosis and use multiple examination methods for comprehensive evaluation to improve the accuracy of diagnosis. The study also found that the diagnostic consistency rate of CT combined with MRI for hydronephrosis-type duplication of kidney was 100%, which was higher than the 77.27 and 81.82% of CT and MRI diagnosis alone, suggesting that CT combined with MRI has a higher diagnostic rate for hydronephrosis-type duplication of kidney and can provide a basis for clinical selection of treatment methods. However, there was no significant difference in the diagnostic consistency rate of CT and MRI alone and in combination for developmental and dysplastic duplication of kidney. The analysis was related to the small sample size included in this study.

MRI combined with CT has a high diagnostic efficacy for duplication of kidney and its classification in children and is worthy of clinical promotion and application. However, this study has certain limitations: the sample size is small, which may cause a certain bias in the results. The sample size will be expanded in the future for further demonstration.

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Immune Suppressive Medications Role in the Prognosis of COVID-19 Among Kidney Transplant Recipients

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Keywords. kidney transplantation,
COVID-19, prognosis, immune suppression

Introduction. Kidney transplant recipients are among the most critical individuals when facing COVID-19 pneumonia with increased risk of morbidities and mortalities. Immune suppressive medications are essential to prevent from rejection, while due to their immune-associated properties, these drugs are one of the major culprits for severe pneumonia. The current study aims to investigate the role of these agents in prognosis of COVID-19 pneumonia.

Methods. The current cross-sectional study was conducted on 139 kidney transplanted recipients hospitalized due to COVID-19 pneumonia. The transplant-related medications including angiotensin convertase enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs), corticosteroids, calcineurin inhibitors, mycophenolate mofetil, and mammalian targets of rapamycin inhibitors were recorded and their prognosticating role in the mortality and survival of the patients was evaluated through logistic and cox regression in crude and adjusted models: 1) age and gender, and 2) age, gender, medical diseases and COVID-19 severity.

Results. Based on logistic regression assessment, none of the consumed drugs by kidney transplant recipients had a preventive role in the mortality of the patients in either crude or adjusted models ($P > .05$). However, cox regression measures revealed that treatment with ACEI/ARB was accompanied by longer survival in the crude (HR = 0.532, 95% CI: 0.333 to 0.851, $P = .008$) and adjusted models 1 (HR = 0.515, 95% CI: 0.318 to 0.833, $P = .007$) and 2 (HR = 0.583, 95% CI: 0.349 to 0.975, $P = .040$), respectively.

Conclusions. Based on the findings of the current study, ACEI/ARB use was accompanied with decreased length of ICU stay among the kidney transplant patients with COVID-19 infection, while the other medications did not have any effect.

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INTRODUCTION

By the late days of 2019, the novel coronavirus 2019 disease (COVID-19) emerged in Wuhan, China and rapidly spread over the world.¹ Most of the infected individuals were asymptomatic or represented mild flu-like symptoms; however, approximately 20% of the patients presented

moderate to severe course of the disease and less than 5% progressed to critically-ill patients.² Risk factors for progression to the severe form of



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COVID-19 include old age, male gender, medical disease such as hypertension, diabetes mellitus, chronic kidney disease, cardiovascular disease, respiratory disease and obesity. Nevertheless, the rate of mortality variably differs from 1 to 7.2% in different communities and even reaches 49% among critical populations.³

Kidney transplantation requires lifelong immunosuppressive medications, drastically limiting the risk of organ rejection. Accordingly, due to immune suppression and comorbidities associated with chronic kidney disease, the kidney transplant individuals are at increased risk for severe COVID-19 infection, related adverse events and mortality compared with the general population.⁴

Severe course of COVID-19 infection might lead to requirement for ICU admission which is one of the alarm signs of probable devastating outcomes. It is yet unclear whether the presence of immunosuppression increases the complications of COVID-19 in kidney transplant individuals.⁵ Some experts highlight the incompetent immune of the patients representing increased risk of adverse events, while the others suggest that immunosuppression may reduce the frequency of cytokine storms, a significant cause of elongated hospitalization, ICU stay and mortality.^{2,4} Accordingly, the current study aims to dedicatedly investigate the effect of immunosuppressive agents applied in kidney transplantation on the length of ICU stay due to COVID-19 infection.

MATERIALS AND METHODS

Study Population

The current cross-sectional study was conducted on 139 kidney transplanted recipients coming down with COVID-19 admitted at Khorshid or Alzahra Hospitals affiliated with Isfahan University of Medical Sciences from April 2020 to December 2021.

The study protocol was primarily proposed to the Ethics Committee of Isfahan University of Medical Sciences and approved via code number "IR.MUI.MED.REC.1400.220". Then, the patients; their legal guardians got informed about the potential use of the medical data for scientific research, they were reassured regarding the confidentiality of their personal information and signed written consent

for participation in the study.

Over 18-year-old individuals with active medical records of kidney transplantation who had a positive real-time polymerase chain reaction (RT-PCR) test or clinical symptoms of COVID-19 infection along with CT scan compatible with COVID-19 infection⁶ were included in the study. Incomplete medical data, unavailability of high resolution chest CT scan and reluctance for participation in the study were considered as the exclusion criteria.

The patients entered into the study through convenience sampling until achieving the desired number of patients based on the biostatistician calculation.

Data Collection

The main scope of this study was to evaluate the influence of medications applied by the kidney transplanted recipients on the mortality of those who were infected with COVID-19.

Given that, the patients' medical records were retrieved from the archives of the index hospitals.

The demographic characteristics (age and gender) and medical data including hypertension, diabetes mellitus, and cardiovascular disease were recruited from the medical records.

Moreover, the medications including angiotensin convertase enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs), corticosteroids, calcineurin inhibitors (cyclosporine and tacrolimus), mycophenolate mofetil, mammalian targets of rapamycin inhibitors (mTORI) (sirolimus and everolimus), statins and insulin that the patients were currently applied, were recorded in the study checklist.

The glomerular filtration rate (GFR) of the patients was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). The measurement was done before discharge/ death.

COVID-19 Manifestations

Moreover, the severity of lung involvement due to COVID-19 infection was determined using a 4-score scale using the manifestations in lung HRCT: 1) normal stage: normal chest with score of zero, 2) mild stage: subpleural ground glass opacity and consolidation, nodular ground glass opacification mostly involving the lower or

middle lobes of the lungs bilaterally (score 1), 3) progressive stage: large and multiple involvements of the lungs with consolidation and increased interlobular presentation. Pleural effusion and lymphadenopathy are rare in this stage (score 2), and 4) severe stage: massive involvement in both lungs occupying more than 50% of the lungs with a white lung view (score 3).⁷

The next assessment of the study was the COVID-19 infection severity categorized as the following:

- Mild: fever with body temperature < 38 °C and no chest involvement in HRCT
- Moderate: evidence of chest involvement in HRCT (< 50%) but no fall in oxygen saturation ($\geq 94\%$)
- Severe: remarkable chest involvement in HRCT ($\geq 50\%$), oxygen saturation of less than 94% and respiratory rate > 30/min.⁸

Statistical Analysis

The obtained data were entered into the STATA version 14. Descriptive data were presented

in mean, standard deviation, percentages, and absolute numbers. The categorical data were compared using Chi-Square test or Fisher's exact test. Independent t-test or ANOVA were applied to compare the continuous variables. Univariate and multivariate logistic regression test was used to find the association between the length of ICU admission and type of medications in both crude and adjusted models. Given that, the adjusted models were primarily adjusted for age and gender. In the next step, they were adjusted for the previous variables as well as the medical diseases and COVID-19 infection severity. *P* value of less than .05 was considered as a significant level.

RESULTS

In the current study, data of 139 kidney transplanted patients admitted due to COVID-19 pneumonia were recruited. The study population predominantly consisted on males (54%) and had the mean age of 53.03 ± 14.06 years old. According to the hospitalization outcome, the patients were divided into two groups of deceased ($n = 18$) and

Table 1. Baseline Information

Variables	Vitality status		Total	<i>P</i>
	Deceased (<i>n</i> = 18)	Discharged (<i>n</i> = 121)		
Demographic characteristics				
Age, y (mean $\pm$ SD)	52.4 $\pm$ 13.93	57.67 $\pm$ 14.46	53.03 $\pm$ 14.06	.134 [€]
Gender (male), <i>n</i> (%)	11 (61.1)	53 (43.8)	75 (54.0)	.169*
Medical history, <i>n</i> (%)				
Diabetes mellitus	11 (61.1)	48 (39.7)	59 (42.4)	.086*
Hypertension	13 (72.2)	63 (52.1)	76 (54.7)	.109*
Cardiovascular disease	2 (11.1)	7 (5.8)	6 (6.5)	.329**
Current chronic medications, <i>n</i> (%)				
Statins	8 (44.4)	35 (28.9)	43 (30.9)	.182*
Insulin	9 (50)	25 (20.7)	34 (24.5)	.015**
ACEI/ARB	6 (33.3)	26 (21.5)	32 (23.0)	.366**
Corticosteroids	15 (83.3)	106 (87.6)	121 (87.1)	.705**
Calcineurin inhibitor	13 (72.2)	92 (76.0)	105 (75.5)	.771**
Mycophenolate	16 (88.9)	92 (76.0)	108 (77.7)	.362**
MTORI	4 (22.2)	21 (17.4)	25 (18.0)	.742**
CKD stage, <i>n</i> (%)				
1	0 (0.0)	2 (1.7)	2 (1.4)	.134**
2	1 (5.6)	26 (21.5)	27 (19.4)	
3	8 (44.4)	62 (51.2)	70 (50.4)	
4	6 (33.3)	15 (12.4)	21 (15.1)	
5	3 (16.7)	16 (13.2)	19 (13.7)	

*Chi Square **Fisher's Exact test [€]t-test

Abbreviations: ACEI, angiotensin convertase enzyme inhibitor; ARB, angiotensin receptor blocker; mTORI, mammalian targets of rapamycin inhibitors.

discharged (n = 121).

The studied groups were similar considering their demographic, medical history, current chronic medications (except for insulin ($P = .015$)) and stage of CKD ($P > .05$). Detailed information is demonstrated in Table 1.

Table 2 shows COVID-19 infection related clinical data in the studied patients. Accordingly, the medications applied to manage COVID-19 including remdesivir ($P = .561$) and corticosteroid use ($P = .999$) and requirement for hemodialysis ($P = .969$) during the hospitalization were similar between the groups, while the parameters including lung involvement in HRCT ($P < .001$), disease severity ($P < .001$) and intubation requirement ($P < .001$) were remarkably different between

deceased individuals and the survivors.

On-admission vital signs assessments revealed remarkable higher respiratory rate ($P = .018$) and lower oxygen saturation ($P = .022$) among those who did not survive. Except for CRP ($P = .005$), other laboratory measures were similar between the groups ($P > .05$) (Table 3).

Table 4 shows logistic regression models for the prognostic role of renal transplant medications to prevent from death due to COVID-19 pneumonia. Based on this table, none of the drugs had a preventive role in either crude or adjusted models ($P > .05$).

The mean duration of survival in the included patients was 9.85 ± 6.75 days (range: 2 to 33 days). Table 5 shows the survival duration of the

Table 2. COVID-19 Infection Related Clinical Information

Variables	Vitality status		Total	P
	Deceased (n = 18)	Discharged (n = 121)		
COVID-19 treatment, n (%)				
Remdesivir	3 (16.7)	31 (25.6)	34 (24.5)	.561**
Corticosteroids	17 (94.4)	112 (92.6)	129 (92.8)	.999**
Lung involvement in HRCT, n (%)				
Mild stage	0 (0)	69 (57.0)	69 (49.6)	< .001*
Moderate stage	13 (72.2)	46 (38.0)	59 (42.4)	
Severe stage	5 (27.8)	6 (5.0)	11 (7.9)	
Disease severity, n (%)				
Mild	0 (0.0)	31 (25.6)	31 (22.3)	< .001**
Moderate	4 (22.2)	83 (68.6)	87 (62.6)	
Severe	14 (77.8)	7 (5.8)	21 (15.1)	
In-hospital hemodialysis requirement	1 (5.6)	7 (5.8)	8 (5.8)	.969*
Mechanical ventilation requirement	7 (38.9)	2 (1.7)	9 (6.5)	< .001**

*Chi Square **Fisher's Exact test †t-test

Abbreviations: HRCT, high-resolution computed tomography.

Table 3. On-admission Vital Sign and Laboratory Measures

Variables	Vitality status		Total	P (independent t-test)
	Deceased (n = 18)	Discharged (n = 121)		
Respiratory rate, /min	25.72 ± 6.34	21.69 ± 6.70	22.21 ± 6.77	.018
Oxygen saturation (%)	82.72 ± 13.13	90.62 ± 6.30	89.60 ± 7.93	.022
Hemoglobin, g/dL	11.00 ± 2.98	11.87 ± 2.30	11.76 ± 2.40	.150
WBC, * × 10 ³ , μL	8.88 ± .51	8.71 ± .51	8.73 ± .51	.240
Lymphocyte, × 10 ³ , μL	6.25 ± .61	6.53 ± .65	6.49 ± .65	.089
Platelet*, × 10 ⁶ , μL	12.00 ± .44	12.06 ± .39	12.01 ± .43	.580
Sodium, meq	136.28 ± 5.69	136.87 ± 4.62	136.79 ± 4.75	.625
Potassium, meq	4.85 ± .71	4.61 ± .81	4.64 ± .80	.232
CRP, mg/dL	83.38 ± 37.10	53.26 ± 41.95	57.16 ± 42.46	.005
Creatinine, mg/dL	2.71 ± 1.72	2.20 ± 1.76	2.27 ± 1.76	.258

*calculated using Ln

Abbreviations: CRP, C-reactive protein; WBC, white blood cells.

Table 4. Logistic Regression Models to Prognosticate Kidney Transplantation Medications Role in the Prevention of COVID-19 Related Pneumonia

Variable	Crude model			Model 1*			Model 2**		
	OR	P	95% CI	OR	P	95% CI	OR	P	95% CI
ACEI/ ARB	0.621	.400	0.205 to 1.885	0.680	.503	0.220 to 2.100	0.957	.960	0.166 to 5.507
Corticosteroids	2.070	.345	0.458 to 9.362	1.944	.400	0.414 to 9.137	1.127	.920	0.109 to 11.644
Calcineurin inhibitors	1.306	.810	0.147 to 11.593	1.062	.957	0.120 to 9.429	2.264	.538	0.168 to 30.555
Mycophenolate mofetil	0.324	.200	0.058 to 1.816	0.337	.210	0.061 to 1.846	0.139	.156	0.009 to 2.115
mTORI	0.870	.906	0.086 to 8.830	0.605	.676	0.057 to 6.392	1.980	.648	0.106 to 37.147
Statins	0.524	.223	0.185 to 1.483	0.551	.276	0.188 to 1.612	0.448	.349	0.083 to 2.404

Abbreviations: ACEI, angiotensin convertase inhibitor; ARB, angiotensin receptor inhibitor.

*Model 1: Adjusted for age and gender

**Model 2: adjusted for age, gender, medical diseases and COVID-19 severity

Table 5. The Factors Associated With Survival Period of the Studied Population

Variable	Survival period (mean $\pm$ SD)	P	Variable	Survival period (mean $\pm$ SD)	P
Gender			mTORI		
Male	9.69 $\pm$ 6.70	.764*	Yes	11.36 $\pm$ 5.21	.205*
Female	10.03 $\pm$ 6.49		No	9.52 $\pm$ 6.80	
Diabetes mellitus			Remdesivir		
Yes	10.80 $\pm$ 6.40	.145*	Yes	9.15 $\pm$ 6.39	.476*
No	9.15 $\pm$ 6.64		No	10.08 $\pm$ 6.64	
Hypertension			Corticosteroids		
Yes	11.28 $\pm$ 7.01	.005*	Yes	9.88 $\pm$ 6.56	.862*
No	8.13 $\pm$ 5.56		No	9.50 $\pm$ 6.94	
Cardiovascular disease			In-hospital hemodialysis requirement		
Yes	10.78 $\pm$ 7.36	.663*	Yes	10.75 $\pm$ 8.10	.691*
No	9.78 $\pm$ 6.53		No	9.79 $\pm$ 6.50	
Statins			Mechanical ventilation		
Yes	10.95 $\pm$ 5.70	.186*	Yes	11.00 $\pm$ 7.12	.589*
No	9.35 $\pm$ 6.89		No	9.77 $\pm$ 6.55	
Insulin			CKD stage		
Yes	10.24 $\pm$ 4.78	.695*	1	3.50 $\pm$ 2.12	.342**
No	9.72 $\pm$ 7.06		2	8.85 $\pm$ 6.46	
ACE/ARB			3	9.60 $\pm$ 6.59	
Yes	12.78 $\pm$ 7.95	.016*	4	11.05 $\pm$ 6.89	
No	8.97 $\pm$ 5.85		5	11.53 $\pm$ 6.31	
Corticosteroids			Lung involvement in HRCT		
Yes	10.07 $\pm$ 6.60	.314*	Mild stage	9.70 $\pm$ 6.93	.675**
No	8.39 $\pm$ 6.27		Moderate stage	9.71 $\pm$ 6.18	
Calcineurin inhibitor			Severe stage	11.55 $\pm$ 6.57	
Yes	9.73 $\pm$ 6.50	.717*	Disease severity		
No	10.21 $\pm$ 6.85		Mild	8.84 $\pm$ 5.80	.463**
Mycophenolate mofetil			Moderate	9.90 $\pm$ 6.76	
Yes	9.99 $\pm$ 6.69	.637*	Severe	11.14 $\pm$ 6.88	
No	9.35 $\pm$ 6.21				

*Independent t-test

**ANOVA

evaluated patients considering different variables illustrating that among the medications, treatment with ACEI/ ARB ($P = .016$) was the only parameter that remarkably led to elongated survival time in the patients.

Cox regression showing the prognostic role of renal transplantation medications in survival of patients with COVID-19 pneumonia in Table 6 revealed that ACEI/ ARB were the only medications leading to increased survival of the patients in all

Table 6. Cox Regression

Variable	Crude model			Model 1*			Model 2**		
	HR	P	95% CI	HR	P	95% CI	HR	P	95% CI
ACEI/ ARB	0.532	.008	0.333 to 0.851	0.515	.007	0.318 to 0.833	0.583	.040	0.349 to 0.975
Corticosteroids	0.869	.646	0.477 to 1.583	0.790	.447	0.430 to 1.450	0.753	.382	0.399 to 1.421
Calcineurin inhibitors	0.949	.876	0.493 to 1.829	0.855	.641	0.444 to 1.647	0.728	.362	0.368 to 1.440
Mycophenolate mofetil	0.922	.723	0.588 to 1.446	1.006	.980	0.638 to 1.585	1.008	.973	0.622 to 1.634
mTORI	0.770	.469	0.379 to 1.565	0.635	.202	0.316 to 1.276	0.568	.127	0.275 to 1.174
Statins	0.756	.178	0.503 to 1.136	0.811	.326	0.535 to 1.232	0.918	.696	0.599 to 1.407

*Model 1: Adjusted for age and gender

**Model 2: adjusted for age, gender, medical diseases and COVID-19 severity

Abbreviations: ACEI, angiotensin convertase enzyme inhibitor; ARB, angiotensin receptor blocker; mTORI, mammalian targets of rapamycin inhibitors; HR, hazard ration.

crude and adjusted models. Accordingly, treatment with ACEI/ ARB caused decreased mortality for 47, 49, and 42% in the crude ($P = .008$), adjusted for age and gender ($P = .007$) and adjusted for age, gender, medical diseases and COVID-19 severity models ($P = .040$), respectively (Figure 1).

DISCUSSION

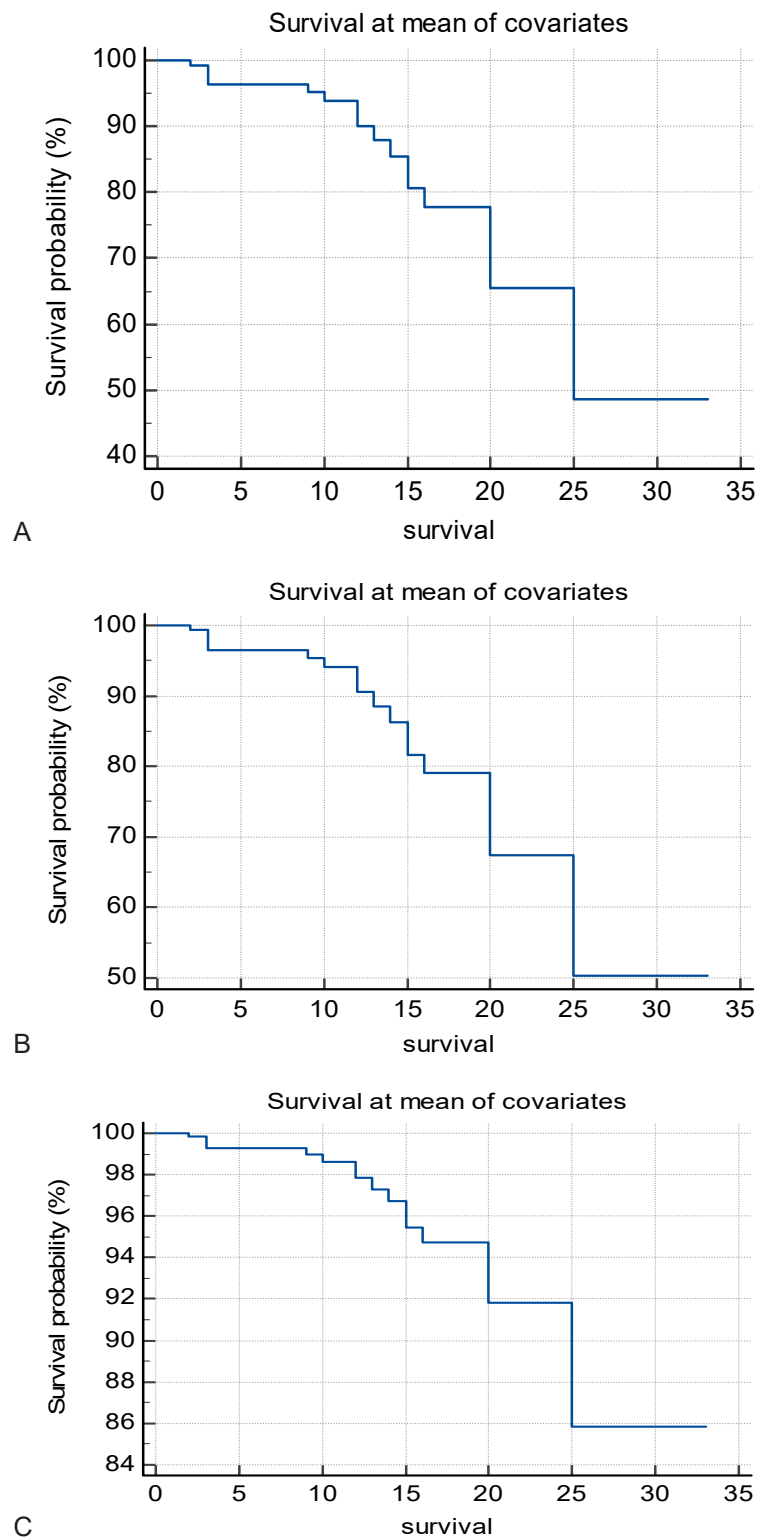
In the current study, we aimed to evaluate the contributing role of medications applied by the kidney transplanted patients in the mortality of patients came down with COVID-19 pneumonia. Accordingly, we found that except for ACEI/ ARB that significantly increased the longevity of the patients, none of the other medications including corticosteroids, calcineurin inhibitors, mycophenolate mofetil, mTORI, statins and insulin had affected the survival period in the studied cases. Moreover, none of the medications, even ACEI/ ARB, was a standalone determinant of the patients' prognosis.

Kidney transplanted patients are among the most critical individuals who are prone to remarkable adverse events than the general population following COVID-19 infection. This vulnerability occurs due to both immunocompromised status and impaired kidney function of these individuals. Nevertheless, the issue of continuing immune suppressive agents in this group of patients during COVID-19 infection has not been well-responded. Rarely have studies dedicatedly evaluated the effects of medications applied in kidney transplantation on the mortality and longevity in COVID-19 infection.

Rarity of knowledge is available regarding the effect of ACEI/ ARB use in kidney transplanted patients during COVID-19. Moreover, the applicable

data are controversial. In agreement with our findings, Soler *et al.* found a direct protective role for these agents to elongate survival of kidney transplanted patients; however, this findings was achieved in crude model of cox regression and the adjustment for COVID-19 severity revealed no association.⁹ Similarly, Mancina *et al.*¹⁰ and Soleimani *et al.*¹¹ found that the discontinuation of ACEI/ ARB in individuals with hypertension under medication with these agents increased risk of mortality, invasive ventilation, and acute kidney injury in COVID-19 infected patients. Nevertheless, most of the studies in the literature represented no role for ACEI/ ARB in kidney transplanted recipients to have a prognostic role for mortality prediction or a positive role in survival.^{2,12-14}

ACEI and ARB are the medications blocking renin-angiotensin system (RAS). Various studies have investigated the effect of RAS blockade on the outcomes of COVID-19 in CKD and kidney transplanted individuals. Although some studies on the general population stated no effect for RAS blockade on the severity and clinical outcomes of COVID-19,¹⁵⁻¹⁷ some presented that long-term use of RAS blocking agents might lead to lung involvement and renal failure.¹⁸ The reason for which the use of ACEI/ ARB in COVID-19 is a question refers to the pathophysiology of lung involvement in COVID-19 infection where the viruses use ACE2 as a receptor to enter type II pneumocytes or alveolar epithelial type II; therefore, the presence of ACE2 protein in lungs is important for virus cell entry.¹⁹ Preliminary studies reported that RAS blockade upregulates ACE2 expression in different organs and tissues; therefore, long-term use of ACEI/ ARB might deteriorate SARS-CoV-2 infection severity.



Cox regression model in (A) crude, (B) adjusted for age and gender and (C) adjusted for age, gender, medical diseases and COVID-19 severity

Thus, the advantage of RAS blocking agents use should be weighed over its potential effects on

COVID-19 infection in kidney transplant cases.²⁰ Although our results did not find that treatment

with steroids in kidney transplant recipients as a contributing factor to reduce mortality, the major body of evidence has supported to continue steroids in the individuals with solid organ transplantation who came down with severe COVID-19 requiring hospitalization, ICU admission and mechanical ventilation. These studies emphasized that steroid therapy as a cornerstone approach in solid organ transplantation was accompanied by less mortality among critically-ill patients as well as considerable response to COVID-19 treatment;²¹⁻²³ however, a review by Calderón-Parra *et al.* contrarily represented increased risk of adverse events due to COVID-19 infection in cases applying corticosteroids for a long period of time.²⁴ Given that, further investigations are required for responding to this question. It should not be forgotten that corticosteroid therapy is a critical treatment in approach to COVID-19.

Calcineurin inhibitors, cyclosporine and tacrolimus, are the basis of immune suppression in solid organ transplantation. It has been proposed that these agents can limit viral replication through binding to intracellular cyclophilins, inactivating peptidyl-prolyl cis/trans isomerase function.²⁵ Despite the study conducted by Cavagna and colleagues presenting promising data in terms of chronic calcineurin inhibitor use to reduce the severity of COVID-19 infection and lowering the probability of superinfection,²⁶ surfing the literature revealed consistent outcomes with our findings in terms of no significant role for this group of drugs in the severity of COVID-19 infection and its negative consequences such as ICU admission, duration of hospitalization and mortality rate.^{24,27}

Mycophenolate mofetil is one of the mainstays in the management of kidney transplantation; however, it seems that potent cytostatic effects of this agent on T and B lymphocytes, contributes to lymphopenia and compromising the humoral immune response to the virus.²⁸ Given that, Requião-Moura *et al.* represented higher rate of adverse events and mortality due to COVID-19 infection among the individuals under mycophenolate mofetil therapy.²⁹ Similarly, Kolla *et al.* in a large cohort study on more than 60400 patients represented increased risk of hospitalization and

mortality among the kidney transplant patients using mycophenolate mofetil.⁴ Although our results showed no effect for this agent to increase mortality rate, some experts proposed to cease or decrease the dose of mycophenolate mofetil considering the synergistic properties of the drug with the mechanism by which SARS CoV-2 induces impaired immune response.^{4,30} Further investigations might open better vision in this issue.

Regardless of our results detecting no role for mTORI to decrease the length of ICU stay, this group of drugs can potentially mitigate COVID-19 infection severity from two aspects. Primarily, mTORI agents inhibit the PI3K-AKT-mTOR pathway, required for intracellular virus replication, and increases the quality and functionality of memory T cells, ultimately modulating human innate response and mitigating immunosenescence. Secondly, these drugs can attenuate cytokine storm and reduce the severity and progression of the viral infection. Given that, Requião-Moura *et al.*²⁹ and de Andrade *et al.*³¹ favored to continue mTORI for kidney transplant recipients. However, other studies were in agreement with us representing neither protective nor deteriorative role for mTORIs in severe COVID-19 infection.^{2,12}

Regardless of subpopulation, statin use have been accompanied by reduced risk of ICU admission, ICU death and all-cause mortality among the patients with severe COVID-19. Various pathophysiological reasons have been proposed for statins to reduced adverse events following COVID-19 including cardioprotective, anti-inflammatory, immunomodulating and vasoprotective properties of these agents. In addition, statins can modulate SARSCoV-2 virus entry by acting on the ACE2 and CD147 receptors and lipid raft engagements.³²⁻³⁴

In summary, paucity of knowledge is available in terms of the influence of immune suppressive agents applied in kidney transplantation on the mortality in COVID-19 infection. Accordingly, this dedicated title in this study is a significant strength of the current investigation. However, small sample population is one of the limitations of our assessment. Furthermore, despite all the efforts made to control the potential confounding variables in logistic and cox regression analysis, there might be some neglected variables that could

have affected the outcomes such as the duration of each agent use, the interval between transplantation and COVID-19 infection and the anti-COVID-19 vaccination state.

CONCLUSIONS

Based on the findings of the current study, ACEI/ ARB use was accompanied with decreased length of ICU stay among the kidney transplant patients with COVID-19 infection, while the other medications did not have any effect.

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AUTHORS' STATEMENT

The manuscript has been read and approved by all the authors, and all agreed to submit the current manuscript in Current Transplantation Reports.

Ethics Approval

The study was proposed for the Ethics Committee of Isfahan University of Medical Sciences and approved via code number "IR.MUI.MED.REC.1400.220". Besides, its protocol was registered in Iranian Registry for Clinical Trials and accepted via code number 240051. The patients/ their legal guardians got informed about the potential use of the medical data for scientific research, they were reassured regarding the confidentiality of their personal information and signed written consent for participation in the study.

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Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.

Authors' Contribution

F. M. was contributed in literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review

M. M. was contributed in literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review

Sh. Sh. was contributed in literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review

M. M. was contributed in literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review

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Dexmedetomidine on the Prognosis of Patients With Sepsis-related Acute Kidney Injury

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Keywords. dexmedetomidine, sepsis,
acute kidney injury, mortality, intensive care

Introduction. To investigate the effect of dexmedetomidine (DEX) on the prognosis and renal function recovery in patients with sepsis-associated AKI (SA-AKI).

Methods. A prospective observational study was conducted, enrolling patients with SA-AKI admitted to the ICU of Suzhou Municipal Hospital from July 2021 to June 2023. Patients were divided into a DEX group and a non-DEX group according to the sedation regimen.

Results. After matching, a total of 204 patients (102 in each group) were included, with balanced baseline (SMD < 10%). The primary endpoint: DEX significantly reduced the risk of 28-day mortality (adjusted HR = 0.556, 95% CI: 0.317 to 0.975; $P = .041$), with a particularly significant benefit in patients with non-septic shock (HR = 0.372, $P = .016$) and AKI stage 1 (HR = 0.375, $P = .035$). Secondary endpoints: DEX significantly improved the rate of renal function recovery (adjusted OR = 2.841, 95% CI: 1.427 to 5.656; $P = .003$), and the efficacy was modified by AKI stage (P -interaction = .005) and shock status (P -interaction = .006). The benefit was most prominent in patients with AKI stage 1 ($P = .009$); the benefit was clear in patients with non-septic shock ($P = .011$). There was a strong trend toward benefit in patients with septic shock ($P = .054$). There was no difference in ICU length of stay between the two groups ($P > .05$).

Conclusions. DEX significantly improves survival and promotes renal function recovery in patients with SA-AKI, particularly in patients with stage 1 AKI and non-septic shock. The potentially significant benefit observed in patients with septic shock warrants further validation in a larger sample.

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INTRODUCTION

Acute kidney injury (AKI) is a clinical syndrome characterized by an acute decline in renal function. Over the past few decades, the incidence of AKI has increased, reaching 20 to 35 % among hospitalized patients^{1,2} and even higher in the intensive care unit (ICU), at approximately 40 to 60 %.^{3,4} Sepsis is the cause of 40 to 70% of ICU AKI patients,^{5,6}

termed sepsis-associated acute kidney injury (SA-AKI). The mortality rate for these patients further increases to 30 to 60%, and hospital stays are also prolonged.^{7,8}



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Dexmedetomidine (DEX) is a highly selective α_2 receptor agonist and a widely used sedative and analgesic drug in the ICU. DEX also has anti-inflammatory, anti-oxidative stress, and apoptosis-reducing properties, and its renal protective effects have been confirmed in animal studies.⁹⁻¹² In recent years, clinical studies examining the protective effects of DEX on renal outcomes have begun, primarily in small cohort or retrospective studies.¹³⁻¹⁴ However, high-quality prospective randomized controlled trials examining the effects of DEX on the prognosis of patients with SA-AKI are lacking. Therefore, this study aimed to investigate the effects of DEX on prognosis and renal function recovery in patients with SA-AKI through a prospective study.

MATERIALS AND METHODS

Prospective, observational study was used as the study design and ethics committee. This study was approved by the Ethics Committee of Suzhou Municipal Hospital (approval number: K-2021-GSKY20210201) and registered in the National Medical Research Registration and Filing Information System (registration number: MR-32-22-002262).

The research subjects included SA-AKI patients admitted to the ICUs of the three campuses of our hospital from July 2021 to June 2023 who agreed to participate in this study, and their families signed informed consent.

AKI diagnostic criteria: According to the 2012 KDIGO guidelines, AKI is diagnosed when one of the following three conditions is met: 1) Serum creatinine (SCr) increases by ≥ 0.3 mg/dL (≥ 26.5 μ mol/L) within 48 hours; 2) SCr increases by $\geq 50\%$ compared with the baseline value within 7 days; 3) Urine volume decreases [< 0.5 mL/(kg*h), lasting ≥ 6 hours].²

Diagnostic criteria for sepsis

Meet the following two conditions: 1) infection; 2) SOFA score ≥ 2 points.¹⁵

Diagnostic criteria for SA-AKI

Meeting both the diagnostic criteria for Sepsis and AKI.⁶

Inclusion Criteria

1) Age ≥ 18 years; 2) ICU hospitalization time ≥ 24 hours; 3) Meet the diagnostic criteria for SA-AKI; 4) Require sedation; 5) Have a physical examination or outpatient or inpatient renal function test report within 1 year before admission.

Exclusion Criteria

1) Chronic renal failure; 2) Bradycardia, II or III degree atrioventricular block; 3) Acute myocardial infarction, severe heart failure (NYHA grade 4); 4) Chronic liver failure (Child-Pugh B and C); 5) Drug addicts; alcohol addicts; 6) Mentally disabled patients; 7) Pregnant and lactating women.

Study Groups This study was divided into DEX group and non-DEX group; In the DEX group, a maintenance dose of 0.2 to 0.7 μ g·kg⁻¹·h⁻¹ was used in addition to conventional treatment, while in the non-DEX group, midazolam or propofol was used as sedative in addition to conventional treatment.

Data collected included gender, age, underlying diseases, type of ICU admission, primary infection site, APACHE II score, SOFA score, heart rate (HR), mean arterial pressure (MAP), white blood cell (WBC), high-sensitivity C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin (PCT), arterial lactate, albumin, alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine (SCr), cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), eGFR, mechanical ventilation (MV), continuous renal replacement therapy (CRRT), nephrotoxic drugs, vasoactive drugs, bacteremia, septic shock and AKI stage, 28-day survival, ICU stay time, and renal function recovery. Renal function recovery was defined as creatinine recovery to less than 1.5 times the baseline creatinine level or urine output > 0.5 mL/(kg*h).¹³

Statistical analysis was performed using STATA 18.0 software. Intergroup comparisons were performed using the chi-square test or Fisher's exact test. Normally distributed quantitative data were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$), and t -tests or t' tests were performed depending on homogeneity of variance. Data with non-normal distribution, as confirmed by the Shapiro-Wilk test, were expressed as medians (interquartile ranges). Intergroup comparisons were performed using the Wilcoxon rank-sum test or the Kruskal-Wallis test. Propensity score matching (PSM) was

performed to minimize the influence of confounding factors. A 1:1 nearest neighbor matching algorithm with a caliper width of 0.01 was used without replacement. Variables with a $P < .05$ and factors strongly associated with disease severity and treatment decision-making were selected to generate propensity scores. Standardized mean differences (SMDs) were calculated to evaluate the efficacy of PSM in reducing intergroup differences. Cox regression, linear regression plus bootstrap, and logistic regression were used to analyze the effects of dexmedetomidine on 28-day mortality, ICU length

of stay, and renal function recovery, respectively. All continuous variables were included in the models using their original units. Multivariate logistic regression with interaction terms (DEX $\times$ AKI stage, DEX $\times$ septic shock status) was used to assess heterogeneity in efficacy. Adjusted odds ratios (ORs) for stratified efficacy were calculated using linear combination analysis (LINCOM). A P value $< .05$ was considered statistically significant, and a P -interaction value $< .05$ was considered a significant stage effect.

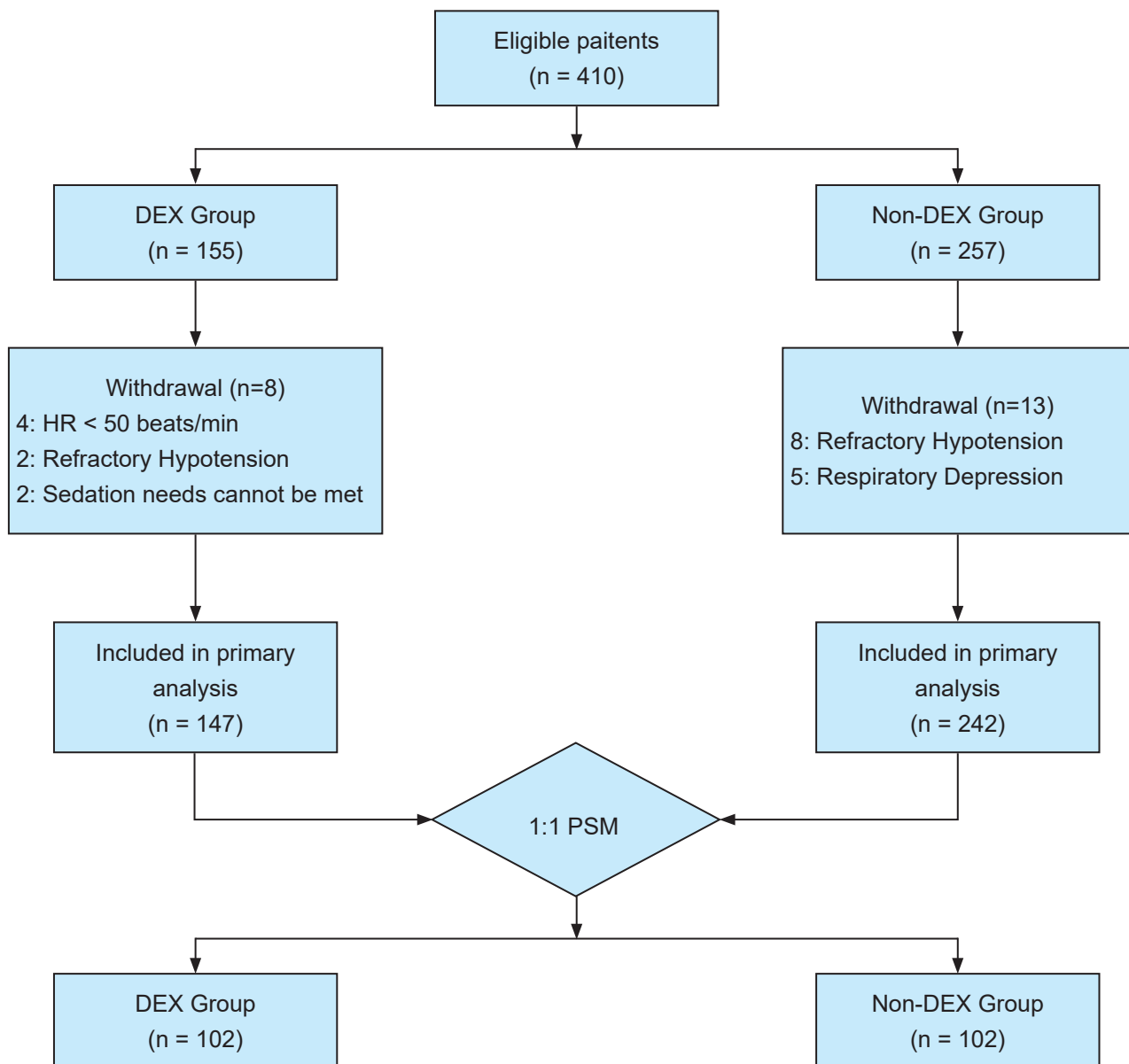


Figure 1. Flowchart of the SA-AKI Patient Study

RESULTS

General Information

A total of 389 patients with SA-AKI were included in the final analysis, with 147 in the DEX group and 242 in the non-DEX group (Figure 1). Of these, 276 were male and 113 were female, with an age range of 71.29 ± 15.81 years, a SOFA score of 6 (4, 8), and an APACHE II score of 21.20 ± 5.03 . There were 188 patients with AKI stage 1, 124 with AKI stage 2, and 77 with AKI stage 3. Patient and demographic characteristics and baseline data for the two groups are shown in Table 1. Significant differences in WBC, CRP, PCT, albumin, cystatin C, and NGAL between the two groups were observed ($P < .05$); no other differences were observed between the two groups ($P > .05$) (Table 1).

A total of 389 patients with SA-AKI were included in the final study analysis, including 147 patients in the DEX group and 242 patients in the Non-DEX group. After propensity score matching (1:1 nearest neighbor matching, caliper value = 0.01), 102 pairs of patients were successfully matched (204 cases).

After propensity score matching (1:1 nearest neighbor matching, caliper value = 0.01), 102 pairs of patients were successfully matched (204 patients). Forty-five patients in the DEX group were excluded due to a lack of sufficiently similar controls. After matching, the SMDs for all covariates were $< 10\%$ (Figure 2). The Rubin's B value decreased from 98.2% before matching to 27.5%, and the R value improved from 0.81 to 0.89, indicating that matching effectively eliminated baseline confounding. No statistically significant differences were found between the groups (all $P > .05$) (Table 1).

Comparison of Main Observation Indicators of Clinical Data Between the Two Groups

Univariate COX regression analysis compared the 28-day mortality rate between the DEX group and the non-DEX group. The results showed that the 28-day mortality risk in the DEX group was 0.528 times that of the non-DEX group, which means the risk was reduced by 47.2%, and this association was statistically significant ($P = .022$). After adjusting for age, APACHE II score, SOFA score, arterial lactate, MV, and CRRT, multivariate COX regression analysis showed that the 28-day mortality risk in the DEX group was still reduced

Table 1. Baseline Characteristics of Patients with SA-AKI in the Two Groups

Observation indicators	Before PSM			After PSM		
	DEX Group n = 147	Non-DEX group n = 242	P	DEX Group n = 102	Non-DEX group n = 102	P
Age, y	71.50 $\pm$ 17.01	71.15 $\pm$ 15.08	.397	71.69 $\pm$ 16.75	70.59 $\pm$ 14.95	.622
Gender (male), n (%)	99 (67.35)	177 (73.14)	.222	67 (65.69)	72 (70.59)	.452
Underlying diseases, n (%)						
Hypertension	81 (57.45)	137 (56.61)	.874	57 (55.88)	53 (51.96)	.574
Diabetes	57 (40.43)	94 (38.84)	.760	40 (39.22)	37 (36.27)	.665
chronic obstructive pulmonary disease	17 (12.06)	27 (11.16)	.790	12 (11.76)	9 (8.82)	.489
Heart failure	28 (19.86)	46 (19.01)	.688	20 (19.61)	17 (18.14)	.586
Cerebrovascular disease	25 (17.73)	46 (19.01)	.756	17 (16.67)	19 (18.63)	.713
Tumor	8 (5.67)	17 (6.53)	.606	6 (5.88)	7 (6.86)	.774
Type of ICU admission, n (%)			.704			.326
Emergency non-surgical admission	58 (39.46)	98 (40.50)		40 (39.22)	38 (37.25)	
Inpatient non-surgical transfer	51 (34.69)	84 (34.71)		34 (33.33)	37 (36.27)	
Emergency surgery admission	17 (11.56)	34 (14.05)		20 (19.61)	11 (10.78)	
Elective surgery transfer	21 (14.29)	26 (10.74)		14 (13.73)	10 (9.80)	

Table 1. Continued

Observation indicators	Before PSM			After PSM		
	DEX Group n = 147	Non-DEX group n = 242	P	DEX Group n = 102	Non-DEX group n = 102	P
Primary infection site, n (%)			.351			.100
Lungs	72 (48.98)	112 (46.28)		54 (52.94)	43 (42.16)	
Digestive system	32 (21.77)	42 (17.36)		24 (23.53)	19 (18.63)	
urinary system	19 (12.93)	32 (13.22)		9 (8.82)	14 (13.73)	
Skin and soft tissue	5 (3.40)	14 (5.79)		3 (2.94)	6 (5.88)	
central nervous system	1 (0.68)	9 (3.72)		0 (0.00)	5 (4.90)	
Other	18 (12.24)	33 (13.64)		12 (11.76)	15 (14.71)	
Bacteremia, n (%)	21 (14.29)	40 (16.53)	.555	15 (14.71)	15 (14.71)	.555
Septic shock, n (%)	49 (33.33)	89 (36.78)	.491	38 (37.25)	37 (36.27)	.885
SOFA	6 (4.8)	6 (4.8)	.056	6 (4.8)	6 (4.9)	.708
APACHE II	20.89 ± 4.97	21.38 ± 5.07	.347	21.32 ± 5.09	21.44 ± 5.28	.872
Heart rate, beats / min	101 (88,114)	99.5 (83,109)	.105	99.5 (86,112)	103 (88,112)	.607
Mean arterial pressure, mmHg	70 (59,77)	68 (58,77)	.261	70 (58,79)	70 (60,78)	.709
Mechanical ventilation, n (%)	91 (61.90)	157 (64.88)	.554	67 (65.69)	67 (65.69)	.554
CRRT, n (%)	40 (27.21)	67 (27.92)	.880	29 (28.43)	30 (29.41)	.877
Nephrotoxic drug use, n (%)			.983			.893
Vancomycin	15 (10.20)	23 (9.50)		9 (8.82)	10 (9.80)	
Polymyxins	6 (4.08)	11 (4.55)		4 (3.92)	4 (3.92)	
contrast agents	5 (3.40)	11 (4.55)		4 (3.92)	6 (5.88)	
Other	5 (3.40)	8 (3.31)		3 (2.94)	5 (4.90)	
Vasoactive drugs, n (%)	49 (33.33)	89 (36.78)	.491	38 (37.25)	37 (36.27)	.885
WBC, × 10 ⁹ /L	13.04 ± 4.72	14.10 ± 5.16)	.040	13.52 ± 4.76	13.80 ± 4.92	.696
CRP, mg/L	42.54 ± 6.42	40.42 ± 6.55	.002	41.82 ± 6.02	41.93 ± 6.08	.890
IL-6, pg/mL	99.91 (84.63,110.88)	99.06 (85.69,109.85)	.700	100.56 (87.77,109.98)	97.99 (84.32,110.39)	.446
PCT, ng/mL	5.31 (4.67,6.16)	5.02 (4.31,5.82)	.011	5.20 (4.61,6.01)	5.10 (4.58,5.76)	.426
Lactic acid, mmol/L	4.80 (3.43,6.60)	4.89 (3.41,8.40)	.246	4.89 (3.62,7.10)	4.08 (3.35,7.20)	.327
Albumin, g/L	30.49 (28.50,34.39)	31.67 (29.13,34.98)	.030	30.73 (28.63,34.73)	31.10 (28.25,34.07)	.837
ALT, U/L	56.16 (51.07,61.12)	56.08 (51.28,60.57)	.844	57.019 (52.26,60.76)	56.43 (50.96,60.36)	.424
BUN, mmol/L	9.42 (8.23,11.46)	9.51 (8.20,11.38)	.605	9.22 (8.26, 11.18)	9.18 (7.95,11.20)	.563
Creatinine, μmol/L	149.76 (125.26,203.33)	161.83 (131.63,208.42)	.168	153.46 (130.41,203.56)	160.52 (129.42,208.42)	.858
Cystatin C, mg/L	2.14 (1.68,2.59)	2.30 (1.86,3.47)	.003	2.21 (1.73,2.66)	2.06 (1.68,2.50)	.276
NGAL, ng/mL	206.78 (198.05,215.72)	202.98 (193.47,211.24)	.006	205.38 (196.53,212.61)	203.63 (194.88,212.63)	.673
eGFR, mL/min/ 1.73m ²	38.19 (27.44,47.34)	36.67 (27.43,45.01)	.334	37.00 (26.25,44.41)	37.73 (26.58,46.73)	.955
AKI stage, n (%)			.567			.672
AKI stage 1	76 (51.70)	112 (46.28)		49 (48.04)	50 (49.02)	
AKI stage 2	43 (29.25)	81 (33.47)		35 (34.31)	30 (29.41)	
AKI stage 3	28 (19.05)	49 (20.25)		18 (17.65)	22 (21.57)	

Abbreviations: APACHE II, acute physiology and chronic health evaluation score or acute physiology and chronic health evaluation II score; SOFA, sequential organ failure assessment; CRRT, continuous renal replacement therapy; NGAL, neutrophil gelatinase-associated lipocalin; AKI, acute kidney injury.

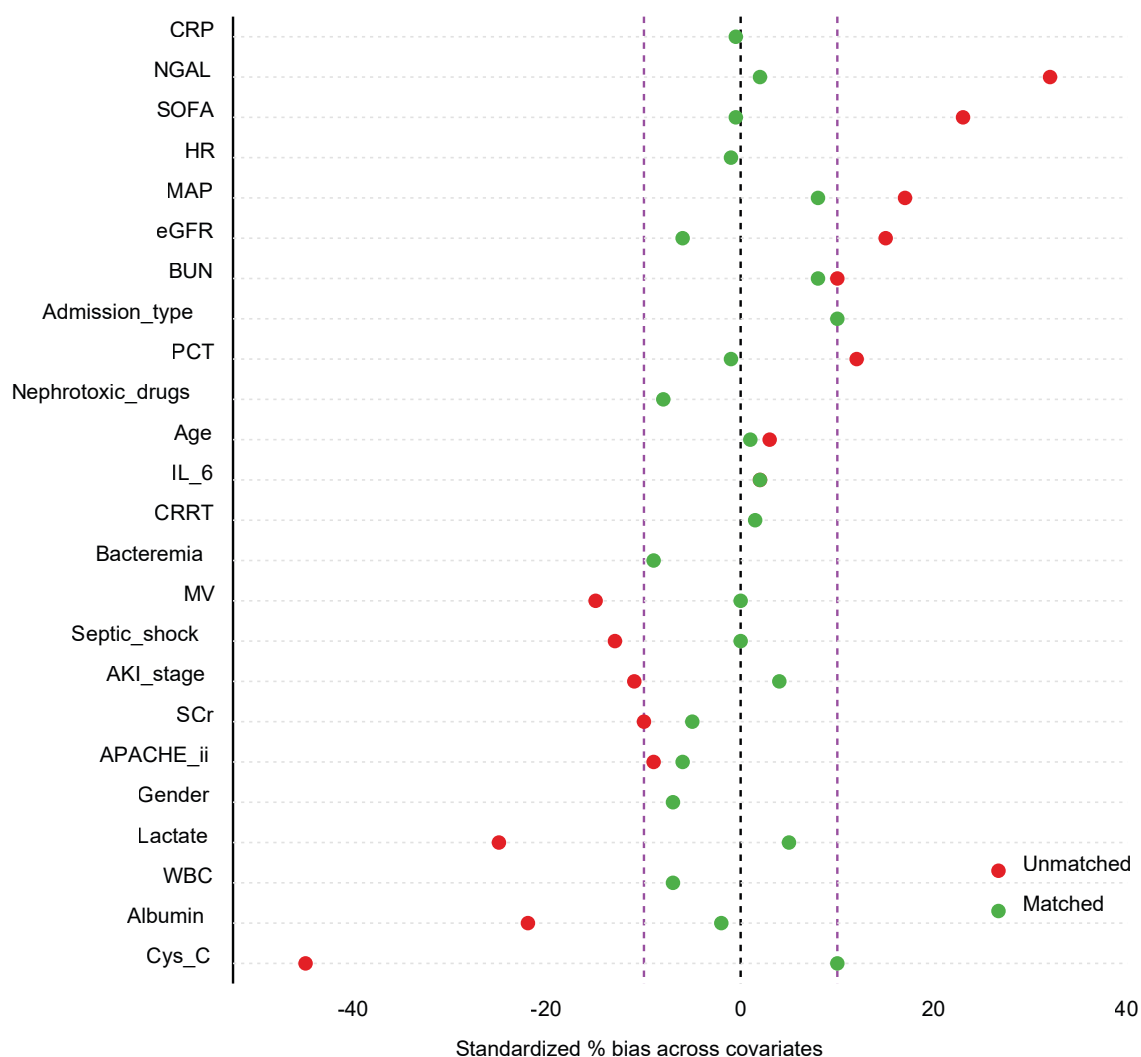


Figure 2. The standardized mean difference between the two groups before and after PSM. After propensity score matching (1:1 nearest neighbor matching, caliper value = 0.01), SMD of all covariates were less than 10%.

(HR = 0.556, 95% CI: 0.317 to 0.975 ; $P = .041$). Linear regression plus bootstrap analysis compared the ICU length of stay between the two groups. No statistically significant difference was found in ICU length of stay between the two groups in either univariate analysis or multivariate analysis with the inclusion of covariates (both $P > .05$). Univariate logistic regression analysis showed that the rate of renal function recovery was significantly higher in patients receiving DEX than in those not receiving it (OR = 2.117, 95% CI: 1.1193 to 3.757; $P = .001$). After adjusting for the above key covariates, multivariate analysis still showed that the favorable association of renal function recovery was further strengthened in the DEX group (OR = 2.841, 95%

CI: 1.427 to 5.656; $P = .003$) (Table 2).

Multivariate adjustment analysis revealed differences in 28-day mortality, ICU length of stay, and renal function recovery among subgroups according to AKI clinical stage and the presence or absence of septic shock. Among patients with AKI stage 1, the DEX group had a 62.5 % lower 28-day mortality compared with the non- DEX group (HR = 0.375, 95% CI: 0.151 to 0.931; $P = .035$). There was no statistically significant difference between the two groups in AKI stage 2 and stage 3 ($P = .461$). While DEX did not reduce 28-day mortality in patients with septic shock, the risk of 28 -day mortality in the DEX group was significantly higher at 62.8% in the non-septic

Table 2. Relationship Between Dexmedetomidine and Prognosis of Patients with SA-AKI

Prognostic indicators	Dexmedetomidine group		Non-dexmedetomidine group		Univariate analysis		Multivariate adjustment analysis*	
	n		n		Effect size (95% CI)	P	Effect size (95% CI)	P
Before PSM	n = 147		n = 242					
28-day mortality rate, n (%)	29 (19.73)		77 (31.82)		HR = 0.639 (0.417 to 0.980)	.040	HR = 0.629 (0.386 to 0.1.026)	.063
ICU stay,† d	9.0 (4.00 to 15.00)		9.0 (5.0 to 18.00)		GMR = 0.971 (0.809 to 1.135)	.738	GMR = 0.976 (0.795 to 1.156)	.797
Renal function recovery rate, n (%)	98 (66.67)		138 (57.02)		OR = 1.507 (0.983 to 2.310)	.060	OR = 1.841 (1.035 to 3.275)	.038
After PSM	n = 102		n = 102					
28-day mortality rate, n (%)	19 (18.63)		40 (39.22)		HR = 0.528 (0.306 to 0.913)	.022	HR = 0.556 (0.317 to 0.975)	.041
ICU stay,† d	8.0 (4.00 to 15.00)		8.0 (5.0 to 19.00)		GMR = 0.893 (0.672 to 1.115)	.374	GMR = 0.903 (0.702 to 1.113)	.403
Renal function recovery rate, n (%)	72 (70.59)		53 (51.96)		OR = 2.117 (1.193 to 3.757)	.001	OR = 2.841 (1.427 to 5.656)	.003

Note: Cox regression was used to analyze 28-day mortality; linear regression + Bootstrap was used to analyze ICU stay; and logistic regression was used to analyze renal function recovery rate. *Adjustment factors: Before PSM, age, sex, SOFA score, APACHE II score, HR, MAP, MV, CRRT, WBC, CRP, PCT, arterial lactate, albumin, BUN, SCr, cystatin C, NGAL, eGFR, and bacteremia, septic shock, and AKI stage were adjusted; after PSM, age, SOFA score, APACHE II score, arterial lactate, MV, and CRRT were adjusted.

†ICU length of stay was skewed and analyzed after natural logarithm transformation. The effect value was the geometric mean ratio (GMR), the 95% CI was calculated using the bootstrap percentile method (1000 replicates).

shock group (HR = 0.372, 95% CI: 0.166 to 0.833; $P = .016$) (Figure 3). There was no statistically significant difference in the ICU length of stay between the two groups at different AKI stages or with or without septic shock (all $P > .05$).

Multivariate COX regression was adjusted to analyze the difference in 28-day mortality between subgroups. The 28-day mortality of AKI stage 1 patients in the DEX group was 62.5% lower than that in the non-DEX group (HR = 0.375, 95% CI: 0.151 to 0.931; $P = .035$). There was no significant difference in AKI stage 2 and AKI stage 3 between the two groups ($P = .461$). For patients with septic shock, DEX did not reduce 28-day mortality, but in the non-septic shock group, the risk of 28-day mortality in the DEX group was 62.8%, and the difference was statistically significant (HR = 0.372, 95% CI: 0.166 to 0.833; $P = .016$) (Figure 4).

Multivariate logistic regression showed that AKI stage significantly modified the effect of DEX on renal function recovery (P -interaction = .005). Stratified analysis showed that in patients with AKI stage 1, DEX was independently associated with a significant increase in the rate of renal function recovery (adjusted OR = 4.814, 95% CI: 1.473 to 15.735; $P = .009$); no significant independent effect of DEX was observed in patients with AKI stage 2 (adjusted OR = 1.628, 95% CI: 0.517 to 5.126; $P = .405$); In patients with stage 3 AKI, the point estimate for DEX suggested a potential benefit (adjusted OR = 3.038), but the confidence interval (95% CI: 0.422 to 21.871) was wide and included 1, so the result did not reach statistical significance ($P = .270$). Septic shock status was also a significant modifier of the DEX effect (P -interaction = .006). In patients without septic shock, DEX was independently associated with a significantly increased rate of renal function recovery (adjusted OR = 3.048, 95% CI: 1.291 to 7.198; $P = .011$). In patients with septic shock, DEX showed a strong trend toward benefit (adjusted OR = 3.966), but the result was marginally statistically significant (95% CI: 0.978 to 16.079; $P = .054$) (Table 3 and Figure 5).

DISCUSSION

Sepsis-associated acute kidney injury (SA-AKI) is an important driver of high mortality in ICU patients, and its treatment strategy optimization urgently needs breakthroughs. This study systematically

evaluated the effect of dexmedetomidine on the prognosis of SA-AKI patients through a prospective

observational design. After PSM correction for confounding, we found that : DEX significantly

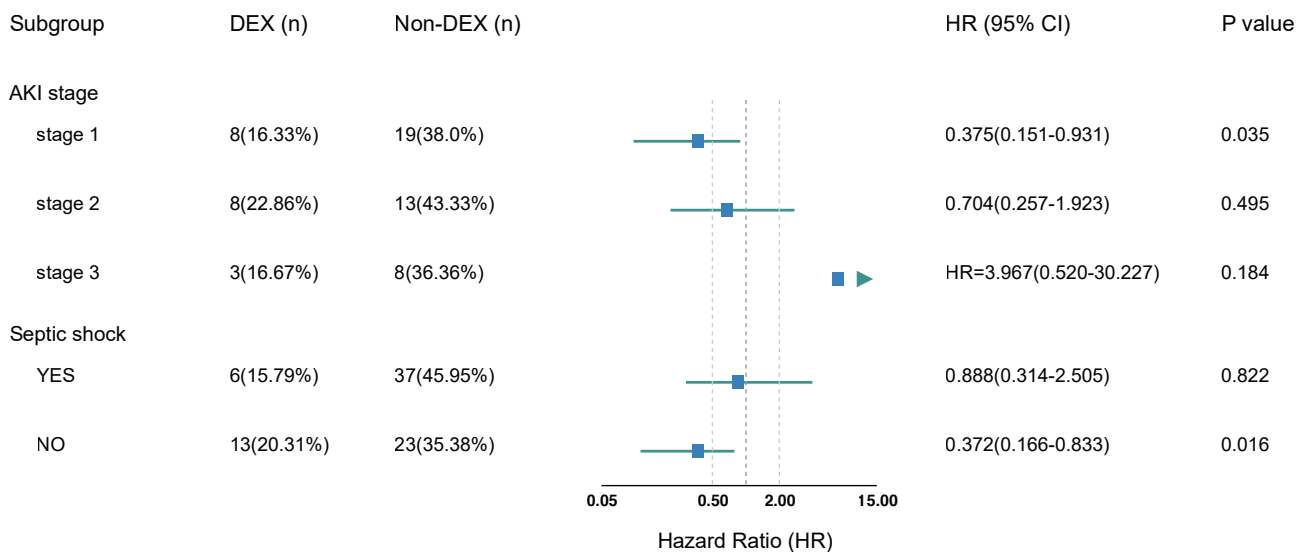


Figure 3. Risk of 28-day mortality risk in two groups of SA-AKI patients according to AKI stage and whether they had septic shock.

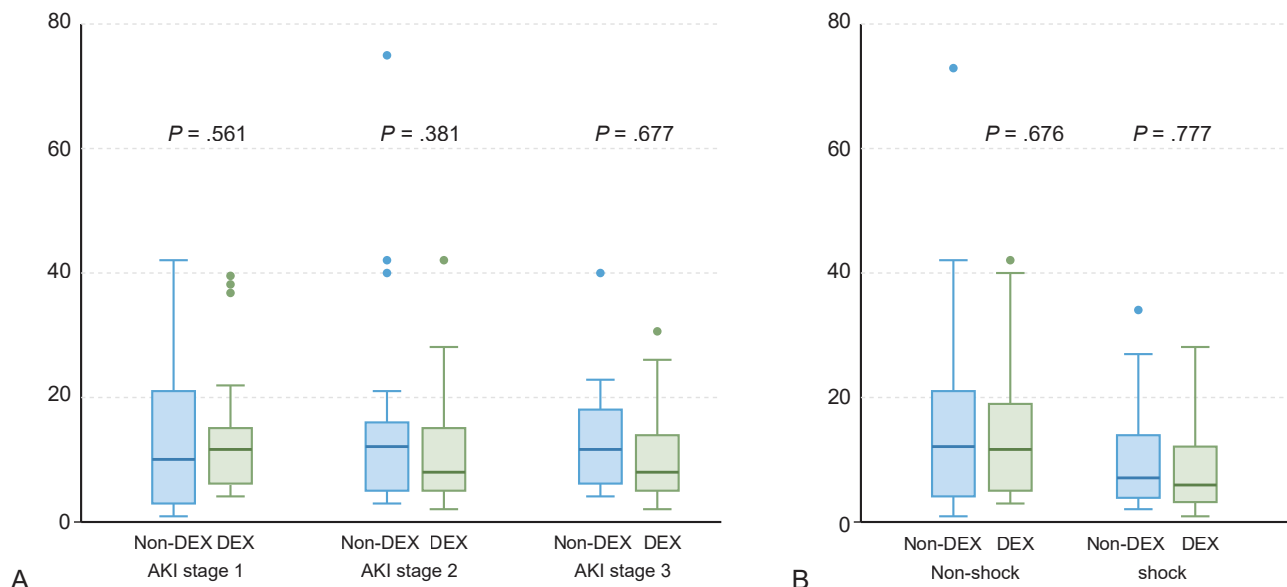


Figure 4. Comparison of ICU stay time between the two groups of SA-AKI patients with different AKI stages and whether they had septic shock: A) There was no significant difference in the length of ICU stay between the two groups of SA-AKI patients at different AKI stages ($P > .05$).

Table 3. Multivariate Logistic Regression Analysis of the Effect of DEX on Renal Function Recovery Rate in Patients with SA-AKI: Interaction Between AKI Stage and Septic Shock

Variable	OR (95% CI)	P
Dexmedetomidine × AKI stage interaction	4.384 (1.551 to 12.394)	.005
AKI stage 1	4.814 (1.473 to 15.735)	.009
AKI stage 2	1.628 (0.517 to 5.126)	.405
AKI stage 3	3.038 (0.422 to 21.871)	.270
Dexmedetomidine × septic shock interaction	3.461 (1.429 to 8.383)	.006
Septic shock	3.966 (0.978 to 16.079)	.054
Non-septic shock	3.048 (1.291 to 7.198)	.011

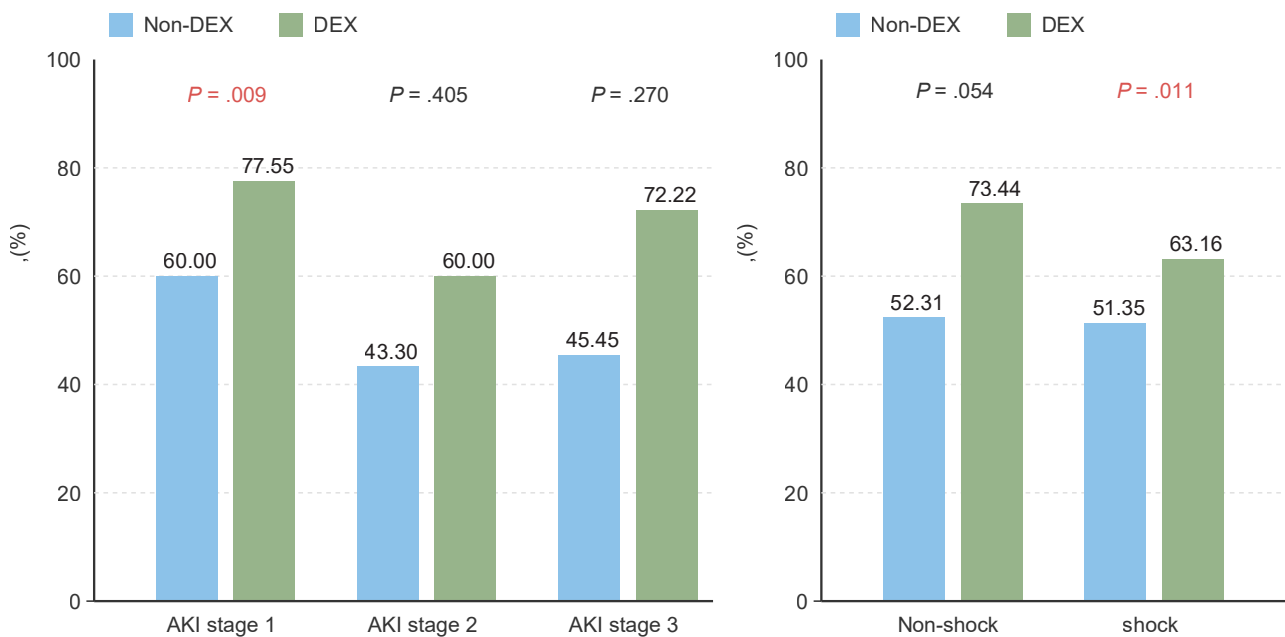


Figure 5. Comparison of renal function recovery rates in the two groups of SA-AKI patients with different AKI stages and whether they had septic shock. In AKI stage 1 patients, DEX was independently associated with a significantly increased rate of renal function recovery (adjusted OR = 4.814, 95% CI: 1.473 to 15.735; $P = .009$) (95% CI: 1.291 to 7.198; $P = .011$).

reduced the 28-day all-cause mortality of SA-AKI patients (adjusted HR = 0.556), and this survival benefit was particularly significant in patients with non-septic shock (HR = 0.372) and AKI stage 1 patients (HR = 0.375); DEX significantly improved the renal function recovery rate (adjusted OR = 2.841), and the efficacy was significantly modified by AKI stage and shock status. AKI stage 1 patients benefited the most (OR = 4.814), non-septic shock patients showed a clear benefit (OR = 3.048), and a strong benefit trend was also observed in septic shock patients (OR = 3.966, $P = .054$); DEX did not significantly shorten ICU length of stay. These results provide high-quality evidence for the use of DEX in personalized sedation therapy for SA-AKI.

The survival benefit of DEX in patients with SA-AKI may be due to its multiple protective mechanisms. The pathophysiological mechanism of sepsis-induced AKI has been preliminarily explored. Multiple mechanisms may lead to the occurrence of SA-AKI, including systemic and renal inflammation in sepsis, renal hypoperfusion and microcirculatory dysfunction, complement activation, RAAS dysregulation, mitochondrial dysfunction, etc.,⁶ among which renal inflammatory response and microcirculatory dysfunction are

crucial.¹⁶ Animal studies have shown that DEX prevents SA-AKI by inhibiting the expression of sepsis-induced inflammatory factors.^{10,17} The study by Yu-Chang *et al.* confirmed that DEX has the effect of improving the renal microcirculation of septic rats.¹⁸ Yuan Zhao *et al.* reported that DEX can protect LPS-induced acute kidney injury by affecting autophagy, apoptosis or ferroptosis.^{9,10,19,20} In recent years, clinical studies have also shown the renal protective effect of DEX. DEX can improve the prognosis of SA-AKI by reducing the level of norepinephrine in the blood, improving microcirculatory disorders, and weakening sympathetic nerve tension.¹⁴

Several studies have shown that SA-AKI is associated with a higher mortality rate,^{6,21,22} but the effect of DEX on the prognosis of patients with sepsis is still uncertain. A large retrospective cohort study²³ showed that DEX could reduce the 28-day mortality rate in mechanically ventilated patients with sepsis, but in another retrospective study of 331 patients with sepsis, DEX had no statistically significant effect on the 30-day mortality rate in patients with sepsis.²⁴ In another multicenter randomized controlled trial (DESIRE) of septic patients receiving mechanical ventilation, DEX had no statistically significant effect on the 28-day

mortality of patients (23 vs. 31%; HR = 0.69, 95% CI: 0.38 to 1.22, $P = .20$).²⁵ However, in a subgroup analysis of critically ill patients with APACHE II scores ≥ 23 , DEX could reduce the 28-day mortality and hospital mortality of patients with sepsis (22 vs. 42%, $P = .03$; 28% and 52%, $P = .01$).⁷ Consistent with our study, Hu's retrospective study also found that DEX can reduce the in-hospital mortality of SA-AKI patients (28.3 vs. 41.3%, HR = 0.56; $P < .001$), and is beneficial to shorten the ICU stay and hospital stay of SA-AKI patients (both $P < .001$). In addition, the renal function recovery rate in the DEX group was also higher (61.8 vs. 55.8%, HR = 1.35, $P = .01$).¹⁴ The failure to shorten the ICU stay in our study may be due to the fact that the average age of the patients included in this study was higher (71.29 years old) and the high proportion of stage 1 in the AKI stage (48.33 %), which may weaken the improvement effect of DEX on hospital stay. In addition, our study found that DEX had a significant effect on SA-AKI. The 62.5% reduction in mortality in stage 1 patients confirms the importance of early intervention: at this stage, renal injury is primarily functional, and DEX may inhibit AKI progression by improving renal perfusion and alleviating subclinical damage. The survival benefit was even more significant in patients with non-septic shock (adjusted HR = 0.372), suggesting that DEX may exert a stronger protective effect in SA-AKI in the setting of non-septic shock by stabilizing hemodynamics and alleviating non-infectious inflammatory responses.

This study reported that DEX significantly improved the renal function recovery rate in SA-AKI patients (adjusted OR = 2.841), and found key effect modifiers: the modifying effect of AKI stage (P -interaction = .005) and the modifying effect of shock state (P -interaction = .006). Among them, patients with AKI stage 1 benefited the most (adjusted OR = 4.814), which may be due to the fact that AKI stage 1 is mainly characterized by functional damage (insufficient renal perfusion, microcirculatory disorders), and DEX can reduce or even reverse early damage through α_2 receptor-mediated vascular regulation and anti-inflammatory effects; DEX can inhibit TLR4/NOX4/NF- κ B pathway, activate Keap1-Nrf2 pathway, enhance

AMPK/mTOR pathway, and other anti-oxidative stress, improve renal cortical perfusion, reduce renal damage, and promote its recovery.⁹ These mechanisms may play a key role in the reversible injury stage (AKI stage 1). The beneficial effect of DEX on the recovery of renal function in SA-AKI patients was weakened in AKI stages 2 and 3, and there was no statistical difference. This may be related to the irreversible increase in renal structural damage (such as tubular necrosis and interstitial fibrosis) in AKI stages 2 and 3, which makes recovery more difficult,²⁶⁻²⁸ suggesting that DEX still needs to be combined with renal repair strategies (such as stem cell therapy) in the sedation treatment of severe SA-AKI.²⁹ In addition, the study showed that DEX has a clear benefit in non-septic shock SA-AKI (OR = 3.048), while the benefit in septic shock SA-AKI is not significant, which may be related to the vascular regulation and anti-inflammatory effects of DEX. However, patients with septic shock have more severe inflammation and poor vasodilation ability, and DEX is difficult to correct such severe pathophysiological changes. However, there is still great potential for patients with septic shock SA-AKI (OR = 3.966, $P = .054$). Although it did not reach statistical significance, the effect size suggests its clinical importance. This is different from the report by Lulan Li³⁰ that DEX reduced the 90-day mortality rate in patients with septic shock (OR = 0.60, 95% CI: 0.37 to 0.94; $P = .030$). The complexity of the immune disorder in sepsis and the potential residual confounding in this study (such as pathogen virulence and antibiotic response) may have weakened the statistical power of our study.

In the study, DEX did not shorten the ICU stay of SA-AKI patients. It is possible that although DEX accelerates the recovery of renal function in SA-AKI patients, the overall recovery of critically ill patients is affected by the function of multiple organs, which is consistent with the findings of Hu *et al.*¹⁴ However, the mortality rate in the septic shock group was not significantly reduced. Severe sepsis is often complicated by immune paralysis and secondary infection. The immunomodulatory effect of DEX may have a "biphasic effect," and caution is warranted regarding the risk of DEX-induced

bradycardia or hypotension, which could offset its benefits in hemodynamically unstable patients.

This study avoided recall bias associated with retrospective studies through a prospective design. Strict PSM matching (SMD < 10%, Rubin's B < 30%) minimized confounding. Interaction analyses revealed a modifier effect of AKI stage and the presence of septic shock on the efficacy of DEX, promoting more precise treatment strategies for SA-AKI. However, this study was conducted in ICUs across three campuses of our hospital, not a truly multicenter study. Furthermore, the dose and duration of DEX were not analyzed, potentially leading to unmeasured confounding bias. Limited sample size in the subgroups of the study resulted in wide confidence intervals, requiring further validation in prospective, multicenter, and larger studies. Sedation in the non-DEX group was not performed using a single sedative agent, midazolam or propofol, potentially influencing the results. Furthermore, the study did not investigate long-term patient outcomes. Future studies may consider exploring the ultra-early application of DEX within 6 hours after the diagnosis of SA-AKI, which can be combined with new biomarkers (such as urinary NGAL and [IGFBP7·TIMP-2]) to dynamically evaluate the efficacy.³¹ More attention should be paid to the dosage and duration of DEX application in SA-AKI patients.

CONCLUSIONS

In summary, DEX significantly improves survival and renal function recovery in patients with SA-AKI, particularly those with stage 1 AKI and non-septic shock. The potentially significant benefit observed in patients with septic shock warrants further validation with a larger sample size. It is suggested that for hemodynamically stable patients with SA-AKI (especially those with KDIGO stage 1) requiring sedation, early use of dexmedetomidine may exert renal protection through multiple mechanisms, potentially becoming a key adjunctive strategy to improve prognosis.

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Conflict of Interest

All authors declare no conflicts of interest.

Author Contribution Statement

Zhou Sixuan, Sun Yanlin, and Zhuang Yue were responsible for patient recruitment, data collection, and paper writing. Zhou Biying was responsible for data analysis. Yang Aixiang was responsible for experimental design, paper guidance, and paper review.

Authors' Contributions

ZHOU Sixuan, SUN Yanlin, and ZHUANG Yue were responsible for patient recruitment, data collection, and academic paper writing. ZHOU Biying performed data analysis. YANG Aixiang provided experimental design, paper guidance, and manuscript review.

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Fluid Resuscitation in Sepsis and Septic Shock; What to Give and How Much to Give: A Systematic Review of Randomized Controlled Trials

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Keywords. sepsis, septic shock, fluid therapy, crystalloids, saline solution, albumins, resuscitation, vasoconstrictor agents, randomized controlled trials

Introduction. The optimal composition and volume of intravenous fluids for sepsis resuscitation remain uncertain. We conducted a systematic review focused on two core questions: what fluid to administer and how much to give in adult sepsis and septic shock.

Methods. We searched PubMed, Embase, Cochrane Library, and ClinicalTrials.gov for randomized controlled trials published from January 2020 to September 2025. Eligible trials enrolled adults with sepsis or septic shock and compared either fluid composition (e.g., balanced crystalloids, saline, albumin, plasma) or resuscitation volume/strategy (restrictive versus liberal or protocolized versus usual care). Two reviewers screened and extracted data; risk of bias was assessed using RoB 2. Owing to clinical heterogeneity and overlapping parent datasets, findings were synthesized qualitatively.

Results. We identified contemporary multicenter RCTs and prespecified or post hoc analyses spanning ED and ICU settings. Balanced crystalloids consistently reduced hyperchloremic acidosis and showed context-dependent signals for improved short-term outcomes versus saline; absolute mortality effects were modest. Albumin and plasma-based strategies produced transient physiologic gains without durable outcome benefits. Large trials comparing volume strategies (CLASSIC, CLOVERS) showed no overall mortality difference despite approximately two liters less fluid and earlier vasopressors in restrictive arms. Subgroup data suggested advantage for restrictive, vasopressor-prioritized care in advanced chronic kidney disease, while mechanistic sub-studies demonstrated no adverse effects on cardiac strain or endothelial glycocalyx. Feasibility trials targeting non-resuscitation fluids reduced administered volumes without safety concerns.

Conclusions. Current randomized evidence supports balanced crystalloids as default resuscitation fluids and indicates that clinically guided restrictive strategies are generally as safe as liberal ones, with potential benefit in fluid-intolerant phenotypes. Effectiveness depends less on a fixed fluid or volume and more on timing, patient context, and physiologic tolerance, reinforcing the paradigm of precision fluid therapy.

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INTRODUCTION

In the era of precision medicine, fluid resuscitation in sepsis and septic shock remains a paradoxical challenge. Despite decades of research, uncertainty persists regarding the optimal type, volume, and timing of fluid administration. Sepsis continues to impose a substantial global health burden, with approximately 48.9 million cases and 11 million deaths reported in 2017.¹ The age-standardized incidence has been estimated at 677 cases per 100,000 people, and mortality remains significantly higher in low- and middle-income countries compared with high-income regions.¹ These figures highlight that, despite scientific progress, sepsis remains one of the deadliest syndromes worldwide, underscoring the urgent need for more effective fluid resuscitation strategies.

At the dawn of the 21st century, Rivers *et al.* introduced the concept of Early Goal-Directed Therapy (EGDT). In this landmark trial, aggressive fluid administration during the first six hours of management significantly reduced mortality (from 46.5 to 30.5%) among patients with severe sepsis and septic shock.² This success led to the incorporation of high-volume fluid administration as a standard of care in international guidelines. However, subsequent multicenter studies yielded conflicting results and demonstrated that excessive fluid loading may cause volume overload and secondary complications. Consequently, the debate over the type, volume, and timing of resuscitation fluids remains ongoing.

The international Surviving Sepsis Campaign (SSC) continues to recommend an initial bolus of 30 mL/kg of crystalloids for patients with hypotension or elevated lactate levels. Nevertheless, this recommendation is supported by low-to-moderate quality evidence, and many experts now advocate for a more tailored approach. Intravenous fluids should be prescribed with the same rigor as pharmacologic agents (guided by the four principles of drug, dose, duration, and de-escalation) and adapted to the four dynamic phases of the ROSE model (Resuscitation, Optimization, Stabilization, and Evacuation). According to this model, fluid therapy should be adjusted to the phase of shock and patient-specific characteristics, replacing the outdated “one-volume-fits-all” paradigm with a

phase-based, individualized strategy.³

Over the past five years, a new wave of large-scale randomized controlled trials—including ANDROMEDA-SHOCK,⁴ BaSICS,⁵ PLUS,⁶ CLASSIC,⁷ and CLOVERS;⁸ has redefined the landscape of fluid resuscitation research in sepsis. These landmark studies have stimulated a gradual shift toward more individualized and physiology-informed approaches, challenging the traditional concept of uniform fluid administration. Yet, beyond these high-profile trials, numerous other RCTs have been conducted within the same period, each exploring different aspects of fluid type, timing, and hemodynamic endpoints. A comprehensive and comparative analysis of these studies is now essential to integrate their findings into a coherent framework and to achieve a clearer, evidence-based perspective on optimal fluid resuscitation strategies in septic patients. This growing body of evidence has not only reshaped trial-based understanding but has also deepened the physiologic perspective of fluid resuscitation.

Emerging physiologic concepts such as fluid responsiveness and fluid tolerance have further advanced this field. Clinicians are now encouraged to not only evaluate whether a patient will augment cardiac output following a fluid bolus but also to assess venous congestion as an indicator of intolerance. A 2024 multicenter proof-of-concept study demonstrated that venous congestion can coexist with fluid responsiveness, highlighting the need to balance perfusion optimization against the risk of interstitial edema and organ dysfunction. This integrative perspective reflects a nuanced evolution: fluid resuscitation should no longer be guided by static targets or rigid protocols but rather by individualized hemodynamic assessments and context-specific thresholds.⁹

Despite decades of research, the optimal composition and volume of intravenous fluids for sepsis resuscitation remain uncertain. This systematic review aimed to synthesize evidence from randomized controlled trials published between 2020 and 2025 investigating intravenous fluid resuscitation in adult patients with sepsis and septic shock. The review focused on two principal questions, what type of fluid to administer and how much fluid to give; to clarify how recent

evidence has shaped current understanding and practice of fluid therapy in sepsis.

MATERIALS AND METHODS

Study Design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.¹⁰

Search Strategy

A comprehensive literature search was performed in PubMed, Embase, Cochrane Library, and ClinicalTrials.gov to identify randomized controlled trials (RCTs) investigating fluid resuscitation in adult patients with sepsis or septic shock. The search covered publications from January 2020 to September 2025. Keywords and MeSH terms included combinations of: “sepsis”, “septic shock”, “fluid resuscitation”, “intravenous fluids”, “crystalloids”, “colloids”, “fluid restriction”, “fluid balance”, and “randomized controlled trial”; using Boolean operators (AND, OR, NOT) to optimize retrieval. Reference lists of included trials and relevant reviews were also screened to identify additional studies.

Eligibility Criteria

Eligible studies were randomized controlled trials enrolling adult patients aged 18 years or older with sepsis or septic shock who received intravenous fluid resuscitation. Trials were included if they investigated either the composition of fluids, such as crystalloids, colloids, or albumin, or the resuscitation volume and strategy, including restrictive versus liberal or protocolized versus usual care approaches. Comparators included standard care or alternative fluid regimens, and eligible outcomes encompassed mortality, hemodynamic parameters, organ dysfunction, renal outcomes, and other clinically relevant endpoints. Studies were excluded if they were non-randomized, conducted in pediatric populations, or designed as observational studies, case series, editorials, conference abstracts, or narrative reviews, or if they lacked primary data or did not specifically evaluate intravenous fluid resuscitation in sepsis.

Data Extraction

Two independent reviewers screened the titles and abstracts, followed by full-text assessment for eligibility. Data were extracted using a standardized template, capturing: first author, year, country, setting, sample size, intervention and comparator details, primary outcome, and key findings. Discrepancies were resolved by consensus with a third reviewer.

Quality Assessment

The methodological quality and risk of bias of included RCTs were appraised using the Cochrane Risk of Bias 2 (RoB 2) tool.¹¹ Each study was evaluated across five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Disagreements were resolved by discussion among the authors.

Data Synthesis

Given the heterogeneity in interventions and outcome measures, a qualitative (narrative) synthesis was performed. The included studies were organized around two core domains of fluid therapy: fluid type (“What to give”) and fluid volume or strategy (“How much to give”), with comparative analysis of clinical outcomes.

RESULTS

Our search identified contemporary randomized evidence on fluid resuscitation in adult sepsis and septic shock across ED and ICU settings from 2020 to 2025. We included pivotal multicenter RCTs comparing restrictive versus liberal or standard volume strategies (CLASSIC and CLOVERS) and feasibility trials targeting non-resuscitation or early ED restriction, alongside prespecified and post hoc analyses that interrogated phenotype-specific effects, endothelial and cardiac physiology, lactate kinetics, and site-level practice intensity. In parallel, we included RCTs and secondary analyses evaluating fluid composition, chiefly balanced crystalloids versus saline, albumin strategies, and plasma-based products. Across studies, primary outcomes were predominantly 90-day mortality and patient-centered days alive outcomes, with physiologic endpoints such as acid–base status,

microcirculation, glycocalyx biomarkers, and echocardiographic strain used in mechanistic sub-studies. Risk of bias by RoB-2 was generally low or raised some concerns mainly due to open-label designs and treatment cross-over; randomization and outcome measurement were usually low risk. Given heterogeneity in interventions, endpoints, and overlapping parent datasets (e.g., multiple CLOVERS and CLASSIC sub-studies), we performed a qualitative synthesis without meta-analysis.

DISCUSSION

The contemporary era of sepsis resuscitation was ushered in at the turn of the millennium, when Rivers and colleagues introduced EGDT.² This protocolised approach emphasised aggressive fluid resuscitation within the first six hours and dramatically reduced mortality. The success of EGDT led to widespread adoption of high-volume fluid administration, yet subsequent trials revealed that unchecked fluid loading causes volume overload and secondary complications. As evidence grew, clinicians began to treat intravenous fluids as potent therapeutics requiring stewardship; Malbrain *et al.* formalised this view by introducing the “four D’s” (drug, dose, duration and de-escalation) and four phases (resuscitation, optimization, stabilization and evacuation) of fluid therapy.¹²

This framework evolved as newer reviews highlighted that each phase of ROSE requires distinct tactics: after an initial bolus (e.g., 30 mL/kg over three hours), further resuscitation should be guided by dynamic assessments, and later phases focus on fluid minimization and active de-resuscitation with diuretics or ultrafiltration.¹³ Chen *et al.*’s 2025 narrative review underscored that the evacuation phase (first proposed in 2013) must be integrated throughout shock management to reverse fluid accumulation.¹⁴ Positive fluid balance is consistently associated with organ dysfunction and mortality, reinforcing the need for judicious fluid removal.¹⁵

Physiologic understanding has also expanded from mere fluid responsiveness to include fluid tolerance and venous congestion. Traditionally, any rise in cardiac output after a preload challenge justified further fluids; however, Kattan *et al.* defined “fluid tolerance” as the volume a patient can receive

without organ injury.¹⁶ This concept bridges the gap between responsiveness and fluid overload and balances arterial flow gains against venous congestion. A 2024 multicenter study found that markers of venous congestion often coexist with fluid responsiveness in mechanically ventilated septic patients, implying that clinicians must assess both responsiveness and tolerance (using tools like passive leg raise tests and venous ultrasound) to avoid worsening organ congestion.^{9,17}

This paradigm shifts from liberal, protocol-driven resuscitation to deliberately constrained, physiology-guided therapy challenges long-held assumptions and compels us to rethink our practice. Integrating the ROSE phases, the four-D stewardship principles and emerging ideas such as fluid tolerance and venous congestion marks only the beginning of this evolution. The real questions now lie ahead: which fluids truly matter, how much volume is enough, how should we titrate therapy and what endpoints should guide us, and when must we initiate or stop fluid administration? The following sections dissect these critical issues through the lens of recent clinical trials, tracing a roadmap toward precision fluid therapy in sepsis.

Fluid Composition: What to Give?

Fluid choice in sepsis resuscitation remains one of the most debated and clinically consequential questions in critical care. Early goal-directed therapy and the Surviving Sepsis Campaign guidelines positioned crystalloids as the first-line fluid for initial resuscitation, yet the fundamental question persists: does the type of fluid meaningfully alter patient outcomes, or are these differences largely physiologic rather than survival-defining? The answer requires integrating data from modern randomized controlled trials and meta-analyses, as summarized in Table 1, which compares recent trials published between 2021 and 2025.

Balanced Crystalloids Versus Saline

Over the past decade, multiple landmark trials have compared balanced solutions (such as lactated Ringer’s and Plasma-Lyte) with 0.9% saline. Collectively, evidence trends in favour of balanced crystalloids, although absolute survival benefit remains modest and context-dependent.

Table 1. Comparative Evidence from Randomized Controlled Trials on Fluid Type and Composition in Sepsis Resuscitation

First author	Year	Country	Setting	N	Intervention	Comparator	Primary outcome	Key results	R
Cusack et al.	2025	Ireland	ICU	103	20% Albumin (100 mL boluses to clinical effect)	Crystalloid	Change in microvascular density and flow at 15 min and 60 min (SDF imaging)	Albumin significantly improved microvascular density and flow at 15 and 60 min ($P < 0.005$) compared with crystalloids, without differences in fluid balance, vasopressor use, ICU stay, or mortality—suggesting selective benefit for microcirculatory optimization.	(18)
Gelbenegger et al.	2025	USA	ICU and ED	1563	Lactated Ringer's solution ($\geq 95\%$ of pre-randomization fluid)	0.9% Normal Saline	90-day mortality	In this secondary analysis of the CLOVERS trial, initial resuscitation with lactated Ringer's reduced 90-day mortality compared with saline (12.2% vs 15.9%; adjusted HR = 0.71, 95% CI 0.51–0.99; $P = 0.043$) and increased hospital-free days (adjusted mean difference = 1.6 days; $P = 0.009$). Patients receiving saline had higher chloride and lower bicarbonate levels, suggesting a possible role of balanced crystalloids in mitigating hyperchloremic acidosis.	(19)
Williams et al.	2025	Australia	ED	464	400 mL 20% Albumin + standard crystalloids	Standard crystalloids only	SBP at 24 hours	Early administration of concentrated albumin did not improve SBP at 24 h (mean 110.5 vs 110 mmHg), but increased SBP at 6 h, reduced total fluid volume and vasopressor use, and improved organ function scores without affecting mortality—suggesting feasibility and potential physiologic benefit warranting larger trials.	(20)
Zhang et al.	2024	China	ICU	143	Ringer's acetate solution (RAS)	Normal saline solution (NSS)	MAKE28 (Major Adverse Kidney Events within 28 days)	No significant difference in MAKE28 (23.3% vs 20.0%, OR 1.2, $P = 0.69$). Patients in the NSS group had longer mechanical ventilation duration ($P = 0.04$) and higher incidence of hyperchloremia ($P = 0.03$). No differences were found in mortality, AKI, or RRT—suggesting physiologic but not outcome-level advantages of balanced solutions over saline.	(21)
Gray et al.	2024	UK	ED	300	5% Human Albumin Solution (HAS)	Balanced crystalloids (Plasma-Lyte)	Recruitment rate and 30-day mortality	In this multicenter feasibility RCT, 5% HAS showed no clinical advantage over balanced crystalloids. Thirty-day mortality was numerically higher with HAS (21.1% vs 14.8%; adjusted OR 1.50, 95% CI 0.84–2.83). No differences were seen in ICU or hospital LOS, while critical care interventions and complications were less frequent in the crystalloid group. Findings suggest feasibility but no outcome benefit for albumin as a primary resuscitation fluid.	(22)
Clausen et al.	2024	Denmark	ICU	44	OctaplasLG® (pathogen-inactivated pooled plasma)	Ringer's acetate	Change in endothelial biomarkers and microvascular perfusion (baseline–24 h)	No significant improvement in microvascular perfusion or most endothelial biomarkers. VEGFR1 increased with OctaplasLG while it decreased with Ringer's acetate (mean diff = 0.36; $P = 0.003$). Patients receiving OctaplasLG had fewer CRRT-free days ($P = 0.015$). Fluid resuscitation with plasma was feasible but did not improve endothelial integrity or clinical outcomes.	(23)

Table 1. Continued

First author	Year	Country	Setting	N	Intervention	Comparator	Primary outcome	Key results	R
Maiwall et al.	2022	India	Liver ICU and ED	100	20% Albumin (0.5–1.0 g/kg over 3 h)	Plasma-Lyte (30 mL/kg over 3 h)	Reversal of hypotension (MAP >65 mmHg at 3 h)	20% albumin achieved target MAP more frequently (62% vs 22%; $P < 0.001$) and showed faster lactate decline ($P = 0.03$), with modest renal benefits but no difference in 28-day mortality (58% against 62%). Pulmonary complications were more frequent, requiring discontinuation in 22% of albumin-treated patients. Albumin improved hemodynamics but at the cost of increased adverse effects.	(24)
Zampieri et al.	2022	Brazil	ICU	10520	Balanced crystalloid (Plasma-Lyte 148)	0.9% saline (saline-only, mixed, or none pre-enrollment)	90-day mortality	In this post hoc analysis of the BaSICS trial, balanced crystalloids showed a low overall probability of mortality benefit (OR = 0.95; 89% CrI 0.66–1.51; probability = 0.58). However, patients who had received only balanced fluids before enrollment demonstrated a higher probability of survival benefit (OR = 0.78; CrI 0.56–1.03; probability = 0.92), particularly among unplanned septic admissions (OR = 0.70; CrI 0.50–0.97; probability = 0.96). These findings suggest pre-randomization fluid type may modulate treatment effect.	(25)
Cortegiani et al.	2021	Italy	ICU	304	20% Albumin (target ≥ 30 g/L) + crystalloid	Crystalloid alone	90-day mortality	In this ALBIOS secondary analysis of immunocompromised septic patients, albumin replacement (HR 0.94; 95% CI 0.69–1.29) did not reduce 90-day or 28-day mortality, nor improve SOFA scores, renal outcomes, or length of stay. Albumin showed no independent association with survival, supporting neutral effects in this subgroup.	(26)
Jackson et al.	2021	USA	ICU and ED	1641	Balanced crystalloids (Lactated Ringer's or Plasma-Lyte A)	0.9% Normal Saline	30-day in-hospital mortality	In this secondary analysis of the SMART trial, balanced crystalloids reduced 30-day mortality when fluid choice was controlled from both the ED and ICU (24.9% vs 30.6%; OR 0.68, 95% CI 0.52–0.89). No mortality difference was seen when fluids were controlled only in the ICU. Balanced fluids also increased ICU-, ventilator-, and vasopressor-free days, emphasizing the benefit of early initiation of balanced crystalloids in sepsis resuscitation.	(27)

Secondary analyses from large pragmatic trials, including SMART and BaSICS, demonstrated that balanced crystalloids may reduce mortality when administered consistently from the emergency department through the ICU phase.^{25,27} The CLOVERS secondary analysis confirmed this finding, showing that initial resuscitation with lactated Ringer's reduced 90-day mortality compared with saline (12.2 vs. 15.9%; adjusted HR = 0.71, 95% CI: 0.51 to 0.99; $P = .043$) and increased hospital-free days.¹⁹ Similarly, the SMART analysis by Jackson *et al.* reported lower 30-day mortality when balanced crystalloids were initiated early, emphasizing that timing of administration is as crucial as fluid composition.²⁷ By contrast, the post-hoc BaSICS analysis found no overall mortality difference but identified a higher probability of benefit among patients who had received only balanced fluids before enrollment (OR = 0.78, CrI: 0.56 to 1.03), especially in unplanned septic admissions.²⁵ This observation highlights that pre-randomization fluid exposure can modulate treatment effect, a pattern mirrored across several studies in Table 1. Smaller RCTs further clarified physiologic effects; Zhang *et al.* (2024) showed that patients resuscitated with saline developed more hyperchloremia and required longer mechanical ventilation without mortality differences.²¹ Collectively, these findings suggest that balanced crystalloids may not dramatically alter survival but consistently confer acid-base and renal advantages.

Meta-analytic data reinforce these trends. A 2025 network meta-analysis including 28 888 patients ranked balanced crystalloids highest for reducing all-cause mortality (SUCRA = 83%), outperforming saline (SUCRA $\approx$ 43%) and starch-based colloids.²⁸ Another 2022 systematic review and meta-analysis of 15 RCTs (20329 patients) likewise found reduced overall and 28/30-day mortality (RR = 0.88, 95% CI: 0.81 to 0.96) and lower acute kidney injury (RR = 0.85, 95% CI: 0.77 to 0.93) with balanced crystalloids.²⁹ However, neither analysis demonstrated a consistent benefit for 90-day mortality or renal replacement therapy, indicating that improvements are predominantly physiologic and short-term. Meanwhile, the FLUID cluster-randomized trial (> 43000 hospitalized

patients) found no significant difference in mortality or dialysis between hospitals primarily using lactated Ringer's and those using saline.³⁰ Yet, because only $\approx$ 15% of participants were ICU patients and adherence to the lactated Ringer's protocol was incomplete, the trial likely diluted any treatment effect.

Despite near-equipose in these large pragmatic studies, balanced crystalloids consistently reduce hyperchloremic metabolic acidosis, a mechanism associated with renal vasoconstriction and dysfunction. Consequently, current sepsis guidelines continue to favour balanced crystalloids as first-line resuscitation fluids.

Albumin and Other Colloids

The rationale for albumin administration derives from its oncotic properties and theoretical ability to restore the endothelial glycocalyx. Recent evidence, however, paints a nuanced picture.

As summarized in Table 1, Cusack *et al.* (2025) demonstrated that 20% albumin improved sublingual microvascular density and flow at 15 and 60 min versus crystalloids, but had no impact on vasopressor requirement, ICU stay, or mortality.¹⁸ Similarly, Williams *et al.* (2025) reported improved short-term hemodynamics and reduced vasopressor use, yet no sustained blood-pressure or survival benefit.²⁰ In cirrhotic septic patients, Maiwall *et al.* (2022) showed that 20% albumin achieved faster lactate clearance and earlier reversal of hypotension than Plasma-Lyte but increased pulmonary complications and did not improve 28-day survival.²⁴ The Cortegiani *et al.* (2021) sub-analysis of ALBIOS similarly found albumin to be outcome-neutral in immunocompromised patients.²⁶

Synthesizing these data, albumin appears to produce transient physiologic gains without durable survival benefit. The 2025 network meta-analysis ranked iso-oncotic albumin second to balanced crystalloids for mortality (SUCRA $\approx$ 71%), but credible intervals overlapped.²⁸ High cost, monitoring burden, and risk of pulmonary edema continue to restrict albumin use to select phenotypes (e.g., cirrhosis, severe hypoalbuminemia).

Plasma-based and Novel Fluids

Attempts to repair endothelial injury through

Table 2. Comparative Evidence from Randomized Controlled Trials on Fluid Volume and Resuscitation Strategies in Sepsis and Septic Shock

First author	Year	Country	Setting	N	Intervention	Comparator	Primary outcome	Key results	R
Sivapalan et al.	2025	Denmark	ICU	1366	Restrictive IV fluid therapy	Standard IV fluid therapy	90-day mortality	Secondary analysis of the CLASSIC trial using machine-learning-derived site intensity subgroups. Across five subgroups with varying standard-fluid volumes, restrictive and standard strategies yielded comparable 90-day mortality, SAEs, DAWOLS, and DAOH. No dose-response relationship was observed, suggesting that baseline variation in standard fluid intensity did not modify the treatment effect of fluid restriction.	(38)
Oshima et al.	2025	USA	ED, ICU, mixed hospital settings	574	Liberal crystalloid resuscitation strategy	Restrictive crystalloid resuscitation strategy	90-day mortality	Secondary biomarker analysis of the CLOVERS trial evaluating endothelial glycocalyx degradation (plasma heparan sulfate, syndecan-1). Higher baseline heparan sulfate strongly predicted mortality (adjusted HR 3.12, 95% CI 2.18–4.46), but assigned fluid strategy did not affect glycocalyx degradation or modify mortality across tertiles. Findings indicate that endothelial injury predicts outcome but is not altered by resuscitation volume.	(33)
Ahlstedt et al.	2024	Multinational (19 ICU sites)	ICU	777	Restrictive IV fluid strategy	Standard IV fluid therapy	Time to resolution of hyperlactatemia (within 72 h)	Post hoc analysis of CLASSIC participants with serial lactate data. Restrictive strategy did not significantly affect time to lactate normalization compared with standard care (HR 0.94 at day 1; 1.21 at days 2–3; both NS). Findings suggest that fluid restriction does not delay metabolic recovery in septic shock.	(39)
Lanspa et al.	2024	USA	ICU and ED	131	Restrictive fluid + vasopressor-priority strategy	Liberal fluid strategy	Left ventricular global longitudinal strain (LV GLS)	Prospective echocardiographic substudy of the CLOVERS trial. No significant differences between groups in LV GLS (coef. 1.22, P = 0.23), Δ LV GLS (–1.97, P = 0.27), or right ventricular free-wall longitudinal strain (P = 0.19). Restrictive fluid resuscitation did not impair short-term cardiac function.	(32)
Lindén A et al.	2024	Sweden	ICU	92	Protocolized restriction of non-resuscitation fluids	Usual care	Total IV fluid volume within 3 days of randomization	Median total fluid at 72 h was 6008 mL (IQR 3960–8123) vs 9765 mL (IQR 6804–12,401) in controls (P < 0.001), a reduction of ~3.6 L. No differences in 90-day mortality, ventilator-free days, or AKI events. Demonstrated feasibility of targeting non-resuscitation fluid reduction in septic shock.	(35)
Jorda et al.	2024	USA	ICU and ED	196	Restrictive fluid strategy with early vasopressor prioritization	Liberal fluid strategy	90-day all-cause mortality before discharge home	Restrictive fluid group had significantly lower mortality (21.7% vs 39.4%; HR 0.50, 95% CI 0.29–0.85; P = 0.009), more vasopressor-free days (mean diff +4.3; P = 0.01), and more ventilator-free days (mean diff +4.5; P = 0.015). Findings suggest benefit of conservative resuscitation in advanced CKD patients.	(31)
Shapiro et al.	2023	USA	ICU and ED	1563	Restrictive fluid strategy with early vasopressor prioritization	Liberal fluid strategy	90-day all-cause mortality before discharge home	No significant difference in 90-day mortality (14.0% vs 14.9%; P = 0.61). Restrictive group received 2.1 L less fluid and had earlier, longer vasopressor use. No significant differences in ventilator-, vasopressor-, or RRT-free days, nor in serious adverse events.	(8)

Table 2. Continued

First author	Year	Country	Setting	N	Intervention	Comparator	Primary outcome	Key results	R
Boulet et al.	2023	France	ICU	48	Restrictive fluid strategy targeting reduced maintenance and drug-dilution fluids	Standard fluid strategy	Cumulative fluid balance over first 5 days	Optimized restrictive protocol reduced total fluid intake modestly (mean diff -35.9 mL/kg; $P = 0.05$) but did not significantly change fluid balance, organ failure, LOS, or 28-day survival. Demonstrated safety and feasibility of stricter fluid limitation early in septic shock.	(34)
Jessen et al.	2022	Denmark	ED	123	Restrictive IV crystalloid strategy (boluses only if hypoperfusion criteria met)	Standard care (discretionary fluids)	Total IV crystalloid volume at 24 h post-randomization	Restrictive group received significantly less IV fluid (562 ± 1076 mL vs 1370 ± 1438 mL; mean diff -801 mL, 95% CI -1257 to -345; $P = 0.001$). No differences in adverse events, AKI, ventilation, vasopressor use, or mortality. Demonstrated feasibility and safety of restrictive fluid administration in non-shock sepsis.	(36)
Meyhoff et al.	2022	Multinational study (across Europe)	ICU	1544	Restrictive IV fluid therapy	Standard IV fluid therapy	90-day mortality	No significant difference in 90-day mortality (42.3% vs 42.1%; adj. diff 0.1%, 95% CI -4.7–4.9; $P = 0.96$). Serious adverse events and days alive without life support or out of hospital were similar. Restrictive strategy reduced cumulative fluid volumes (median 1.8 L vs 3.8 L) without increasing harm.	(7)
Semler et al.	2020	USA	ICU	30	Conservative fluid management protocol (restricted fluids + loop diuretic to maintain neutral balance)	Usual care	Mean daily fluid balance (Phase II) and ICU-free days (Phase III)	Conservative strategy did not achieve ≥ 500 mL/day reduction in mean fluid balance (-398 mL vs target -500 mL); cumulative input/output similar between groups. Hemodynamic, renal, and respiratory outcomes were comparable, confirming feasibility but limited efficacy.	(37)

plasma-derived or glycocalyx-restoring solutions have been largely unsuccessful. In the Clausen *et al.* (2024) phase IIa trial, pathogen-inactivated pooled plasma (OctaplasLG) did not improve endothelial biomarkers or sublingual microcirculation; VEGFR1 levels rose, and patients had fewer CRRT-free days.²³ Likewise, Gray *et al.* (2024) found that 5% human albumin offered no clinical advantage over balanced crystalloids and was associated with numerically higher 30-day mortality.²² Together, these findings show that plasma-based fluids remain feasible but not superior, echoing the prior withdrawal of starch and gelatin colloids due to renal injury and coagulopathy.

Volume and Strategy: How Much to Give?

Determining the optimal volume of intravenous fluids in sepsis remains one of the most contentious questions in critical care. For decades, aggressive fluid loading was equated with effective resuscitation, yet evidence now underscores that excess volume may induce venous congestion, organ edema, and delayed recovery.

Modern randomized trials have shifted this paradigm toward physiologic restraint. Both the CLASSIC and CLOVERS trials showed no significant mortality difference between restrictive and liberal fluid strategies despite a two-liter gap in cumulative volumes.^{7,8} This neutrality implies that within a clinically reasonable range, how much fluid is given may matter less than when, to whom, and under what physiologic guidance it is administered. Recent analyses have refined these findings by identifying subgroups in whom fluid intensity may have distinct consequences. Restrictive approaches appear beneficial in patients with impaired renal clearance,³¹ while no adverse cardiac³² or endothelial³³ effects have been linked to early vasopressor prioritization. Conversely, smaller feasibility trials focusing on post-resuscitation or non-resuscitation fluids reveal that much of avoidable overload occurs beyond the initial shock phase.^{34,35}

Collectively, these insights mark a conceptual evolution from fixed-volume resuscitation to individualized fluid stewardship. The future of sepsis management lies in tailoring volume therapy to dynamic hemodynamics, tolerance thresholds, and recovery phases. Liberal and restrictive

strategies can both be safe when applied judiciously, yet precision remains the true determinant of efficacy.^{36,37}

CONCLUSIONS

Over the past five years, the landscape of sepsis fluid resuscitation has transitioned from uniform, protocol-driven practice to a nuanced, evidence-informed science. Across randomized controlled trials, balanced crystalloids have consistently emerged as the most physiologically favorable resuscitation fluid, mitigating hyperchloremic acidosis and preserving renal function without incurring additional risk. Nonetheless, their superiority over saline in terms of mortality remains modest. Albumin and plasma-derived solutions may offer transient hemodynamic or endothelial benefits but have not demonstrated sustained outcome advantages, confining their role to selected clinical phenotypes rather than routine use.

Regarding fluid volume and strategy, recent multicenter trials such as CLASSIC and CLOVERS confirm that restrictive and liberal regimens achieve comparable survival, provided they are guided by continuous hemodynamic assessment. Restrictive approaches appear especially advantageous in patients with impaired renal clearance, while early vasopressor prioritization has not been associated with adverse cardiac or endothelial effects.

Taken together, current evidence underscores that the efficacy of fluid therapy in sepsis depends less on the specific fluid or absolute volume administered than on timing, patient context, and physiologic tolerance. The future of sepsis resuscitation lies in precision fluid therapy—a dynamic, patient-centered approach integrating advanced hemodynamic monitoring, endothelial biomarkers, and real-time decision support. In this evolving paradigm, the goal is no longer to give more or less, but to give appropriately—the right fluid, in the right amount, at the right time, for the right patient.

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Ethical Considerations

As this study is a secondary analysis of previously published data, no ethical approval or patient consent was required.

Conflicts of Interest

Ilad Alavi Darazam and Amir Ahmad Nassiri are a member of the editorial team of RJCCN. The authors have no involvement in the peer-review or editorial decision-making process for this manuscript.

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Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed to the study and approved the final version of the manuscript.

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Sepsis Management in Post-bariatric Surgery Patients Using Extracorporeal Blood Purification Treatment, A Case Series

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Keywords. sepsis, bariatric surgery, extracorporeal blood purification, continuous renal replacement therapy (CRRT)

Introduction. Bariatric surgery (BS) is among the most effective treatments for severe obesity. However, it is essential to acknowledge the risk of serious short-term complications following the procedure.

Case Presentation. We report four cases of Iranian patients admitted due to severe short-term complications following sleeve gastrectomy (SG), which included peritonitis, acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and sepsis. Based on their diagnoses and individual needs, two patients underwent exploratory laparotomy. All four cases were successfully treated with intravenous antibiotics, intensive supportive care, and continuous renal replacement therapy (CRRT) along with extracorporeal hemoperfusion.

Conclusions. SG is one of the most commonly performed metabolic procedures worldwide. However, it can lead to severe, life-threatening complications, such as sepsis resulting from peritonitis and pneumonia. These cases underscore the importance of early recognition and effective treatment strategies for this patient population. A strict postoperative follow-up is essential for the early detection and management of complications, ultimately reducing morbidity and mortality rates.

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INTRODUCTION

The global rise in obesity underscores the need for effective management strategies. Bariatric surgery (BS) is one of the most effective treatments for individuals with severe and morbid obesity. However, the inevitable risk of postoperative complications necessitates vigilant diagnosis and careful management. As the frequency of bariatric surgeries increases, so do concerns about postoperative complications and surgical effectiveness.^{1,2}

The American Society of Metabolic and Bariatric Surgery (ASMBS) categorizes complications

occurring within 30 days of surgery as short-term. Major complications include those requiring reoperation, prolonged hospitalization exceeding seven days, or anticoagulant therapy.³

Postoperative sepsis is one of the most life-threatening complications of BS.^{4,5} Sepsis often leads to AKI and necessitates CRRT for critically ill patients in the intensive care unit (ICU). In septic shock, an uncontrolled host response to



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infectious pathogens triggers a cytokine storm, resulting in cellular toxicity, organ failure, and increased mortality. CRRT can assist by removing inflammatory mediators using specialized adsorption membranes and sorbent cartridges.⁶

This study reports four cases of severe short-term complications following SG, including peritonitis, sepsis, ARDS, and AKI, all managed with CRRT.

CASE PRESENTATION

This retrospective case series includes four patients who presented with severe short-term complications following laparoscopic sleeve gastrectomy (SG) and were admitted to the ICU within 30 days post-surgery.

The surgical procedure was performed under general anesthesia with access through five trocars. Subsequently, cruroplasty was completed using 2/0 nonabsorbable sutures. A vertical gastrectomy

was then created with an 8-stapler device, and the stapler line was imbricated with Prolene 2/0 sutures. Omentopexy and gastropasty were carried out, followed by a leak test. Meticulous hemostasis was achieved, a drain was secured, and the remnant of the stomach was extracted.

Initial treatment for postoperative complications included hemodynamic management, broad-spectrum antibiotics (e.g., carbapenems and vancomycin), and ventilatory support according to standard protocols. Table 1 summarizes patient characteristics, symptoms, and laboratory results.

CytoSorb therapy was initiated at the onset of AKI, ARDS, or hyperinflammatory states, alongside hemodynamic instability requiring escalating vasopressor dosages over 12 to 24 hours. CytoSorb was used in addition to CRRT or independently when CRRT devices were unavailable. CRRT was performed using the Diapact system (B. Braun,

Table 1. Clinical Characteristic of Admitted Patients

	Case 1	Case 2	Case 3	Case 4
Age, y	61	36	39	27
Sex	Male	Female	Male	Male
Preoperative BMI, kg/m ²	47.5	45	41	45
Type of surgery	Sleeve Gastrectomy	Sleeve Gastrectomy	Sleeve Gastrectomy	Sleeve Gastrectomy
Number of hospital days (ICU)	4	6	10	12
Complications	Peritonitis, AKI, sepsis	AKI, sepsis	Peritonitis, Sepsis	ARDS, sepsis
CRRT mode	CVVH, CytoSorb	CVVH, CytoSorb	CVVH, CytoSorb	CVVH, CytoSorb
CRRT time, hours	60	48	12	42
Before CRRT, during, after				
WBC, ×10 ³	16.09, 21.83, 33.59	39.94, 28.66, 23.03	18.23, 23.02, 21.04	17.03, 16, 8.3
Platelet, ×10 ³	307, 243, 216	94, 73, 71	328, 464, 283	162, 158, 98
Urea	152, -, 101	86, -, 67	64, -, 47	37, -, 38
Creatine, mg/dL	4.9, -, 2.5	4.4, -, 2.1	1, -, 1	1.2, -, 1.04
PCT	112, 93, 30	13, 12, 4	6, 4, 1	3, 2, 0.7
PTT	34, 54, 50	59, 180, 38	31, 115, 87	33, 38, 36
INR	1.3, 1.4, 1.01	1.4, 1.3, 1.2	1.3, 1.2, 1.2	1.1, 1.2, 1.12
Bilirubin, mg/dL	3.2, -, 2.9	1.7, -, 0.9	0.4, -, 0.3	1.3, -, 0.4
Lactate	27, 23, 16	1.2, 0.8, 0.7	6.8, 6.2, 4.3	15, 44, 14.3
ESR	71, 51, 39	83, 67, 44	125, 99, 73	81, 35, 29
CRP	56.2, 43, 45	38, 29, 31	41, 37, 41	46, 46, 23
Albumin, g/dL	3.1, -, 2.7	2.4, -, 2.2	2.9, -, 3.1	3.7, -, 4.1
GCS	11, -, 15	14, -, 15	14, -, 15	13, -, 15
Blood pressure, mmHg	100/78 with norepinephrine ≤ 0.1 µg/ kg/ min, 100/70, 120/80	75/pulse, 100/70, 1112/75	117/75, 112/75/ 128/68	110/76, 115/75, 131/81
PaO ₂ /FiO ₂ , mmHg	< 200 and mechanically ventilated including CPAP, -, ≥ 400	< 400, -, ≥ 400	< 400, -, ≥ 400	< 200 and mechanically ventilated including CPAP, -, ≥ 400

Melsungen, Germany) in continuous venovenous hemodialysis/hemofiltration (CVVHD/CVVH) mode with heparin-based anticoagulation. The CRRT circuit included a CytoSorb adsorber before the dialyzer, with blood flow rates between 200 to 250 mL/min and 25 to 30 mL/kg/ hr dialysis doses. Adsorbers were replaced after 12 hours for the initial session and every 24 hr thereafter.

Treatment was discontinued upon clear signs of clinical improvement, including PaO₂/FiO₂ ratios > 250 mmHg, reduced vasopressor needs, and decreased inflammatory markers (e.g., WBC, ESR, CRP, lactate, procalcitonin). Lung function (PaO₂/FiO₂) and Sequential Organ Failure Assessment (SOFA) scores were monitored before and after CytoSorb therapy.⁷

Case 1

A 61-year-old man with a history of diabetes and chronic obstructive pulmonary disease (COPD) (preoperative BMI: 47.5 kg/m²) presented with decreased consciousness, abdominal pain, fever, and peritonitis five days after undergoing laparoscopic sleeve gastrectomy (SG) for weight loss. Paraclinical tests revealed leukocytosis (WBC count: 16,000/μL), elevated inflammatory markers (C-reactive protein: 150 mg/L), and acute kidney injury (AKI) with a serum creatinine level of 2.3 mg/dL. Diagnostic laparotomy confirmed a surgical site infection (SSI) with purulent peritoneal fluid and widespread peritonitis. The patient was treated with broad-spectrum antibiotics, including meropenem and vancomycin, and hemodynamic support using vasopressors. Despite experiencing hypotension, tachycardia, and hyperpyrexia indicative of septic shock, continuous renal replacement therapy (CRRT) combined with CytoSorb therapy over 60 hr led to gradual clinical improvement. He was discharged in stable condition after completing 10 days of intravenous antibiotics.

Case 2

A 36-year-old woman (preoperative BMI: 45 kg/m²) presented with fever (39.2 °C), severe abdominal pain, hematuria, and a history of multiple episodes of nephrolithiasis 20 days post-SG. Her past medical history included hypothyroidism managed with levothyroxine and recurrent

nephrolithiasis. Physical examination revealed low blood pressure (75 mmHg systolic) and tachycardia (heart rate: 120 bpm). An abdominopelvic CT scan demonstrated multiple stones in the distal and proximal portions of the left ureter, along with evidence of left hydronephrosis. Urgent lithotripsy was performed to clear the obstructing stones. Laboratory tests showed AKI with serum creatinine elevated to 3.1 mg/dL and markers consistent with urosepsis, including elevated procalcitonin levels. Broad-spectrum antibiotics, including piperacillin-tazobactam, were administered for 20 days, and CRRT was performed for 48 hours due to worsening kidney function. The patient made a full recovery and was discharged in stable condition.

Case 3

A 39-year-old man with a history of multi-drug addiction, type 2 diabetes, obstructive sleep apnea, and hypertension presented with fever (38.8 °C) and severe abdominal pain eight days after undergoing SG. He reported progressive abdominal distension and weakness. Diagnostic laparotomy revealed an infected abdominopelvic hematoma containing approximately 500 cc of old clot and purulent material, which was drained. Blood cultures were positive for methicillin-resistant *Staphylococcus aureus* (MRSA). Elevated inflammatory markers, including a C-reactive protein level of 180 mg/L, prompted the initiation of CRRT for 12 hr alongside intravenous antibiotics (linezolid and meropenem). The patient showed significant clinical improvement over the next week and completed a 20-day treatment course. He was discharged in stable condition.

Case 4

A 27-year-old man (preoperative BMI: 45 kg/m²) was admitted to the ICU a few hours post-SG with respiratory distress, hypoxemia, and reduced oxygen saturation (SpO₂: 75% on room air). A chest CT revealed bilateral coalescent opacities consistent with acute respiratory distress syndrome (ARDS). The patient required immediate endotracheal intubation and mechanical ventilation with protective lung strategies. Laboratory findings indicated leukocytosis, elevated procalcitonin, and evidence of systemic inflammatory response

syndrome (SIRS). CRRT was initiated for 42 hours due to fluid overload and worsening renal function. Despite the critical presentation, he gradually improved with supportive care, including diuretics, intravenous antibiotics (meropenem and vancomycin), and lung-protective ventilation. He was extubated on day 10 and discharged from the hospital after completing 12 days of intravenous antibiotics and supportive care.

DISCUSSION

Bariatric surgery is one of the most effective treatments for severe obesity and its comorbidities. However, SG, like any major surgical procedure, can lead to complications. While many individuals achieve significant weight loss and remission of comorbidities, rare cases of serious complications requiring early diagnosis and extensive care have been documented. Our case series underscores the necessity of early identification and appropriate treatment for patients experiencing significant postoperative complications.

Peritonitis, sepsis, ARDS, and AKI are severe complications that can be life-threatening. These cases demonstrate that, despite SG being a minimally invasive metabolic surgery, serious postoperative complications can arise and necessitate rapid intervention. In line with our study, Valera-Montiel reported a 54-year-old male who was admitted due to abdominal pain, hemodynamic instability, and altered consciousness, ultimately undergoing exploratory laparoscopy for SSI and septic shock seven days after SG.

Treatment with CRRT and CytoSorb proved beneficial for our patients. CRRT improved renal function and helped remove inflammatory cytokines that exacerbate sepsis and multi-organ failure. The efficacy of this treatment strategy highlights the importance of extracorporeal therapy in managing hyperinflammatory states caused by severe infections.

It is important to note that our patients had various risk factors, including diabetes, multi-drug addiction, hypertension, and respiratory disorders, which may have contributed to their postoperative complications. Consistent with our findings, Blair *et al.* reported that a history of hypertension, diabetes, and smoking can increase the risk of

postoperative sepsis. These cases illustrate the need for multidisciplinary coordination among surgeons, intensivists, and nephrologists in addressing such urgent situations.

These instances emphasize the importance of ongoing research and clinical experience exchange to understand better and manage the potential consequences of bariatric surgical procedures. While SG is a safe and effective treatment for obesity, heightened awareness of uncommon yet severe complications is crucial for ensuring optimal outcomes for individuals embarking on their weight loss journey.

CONCLUSIONS

Early recognition and effective management of short-term complications following SG, such as peritonitis, sepsis, ARDS, and AKI, are crucial for reducing morbidity and mortality. Postoperative follow-up and timely intervention are essential for improving outcomes in this patient population.

ABBREVIATIONS

- BS: Bariatric surgery
- SG: sleeve gastrectomy
- ARDS: acute respiratory distress syndrome
- AKI: acute kidney injury
- CRRT: continuous renal replacement therapy
- ASMBS: American Society of Metabolic and Bariatric Surgery
- ICU: intensive care unit
- CVVHD/CVVH: continuous venovenous hemodialysis/hemofiltration
- SOFA: Sequential Organ Failure Assessment
- COPD: chronic obstructive pulmonary disease
- SSI: surgical site infection
- MRSA: methicillin-resistant *Staphylococcus aureus*
- ARDS: acute respiratory distress syndrome
- SIRS: systemic inflammatory response syndrome

DECLARATIONS

Ethical Approval and Consent to Participate

All the procedures performed in the study were approved by the Research Ethics Committee of the Shahid Beheshti University of Medical Sciences and were in accordance with the ethical standards of the institutional Human Research Review Committee

and the 1964 Helsinki Declaration and its later amendments.

Patient Consent

The authors of this article hereby declare that informed consent was obtained from the patients described in this manuscript. The patient was fully informed about the nature of the study and its purpose. They were allowed to ask questions and were assured of their right to withdraw consent at any time without any impact on their future care. The patients have consented to the use of their data and any relevant medical information for this publication. Additionally, they understand that their identity will remain confidential and that any identifying details will be omitted or anonymized to protect their privacy. This declaration confirms our commitment to ethical standards in research and publication practices.

CONFLICT OF INTEREST

Kiana Entezarmahdi 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.

Availability of Data and Materials

The data supporting the findings of this study are available from the corresponding authors upon reasonable request. Due to privacy and ethical considerations, patient-related data have been anonymized, and individual records are not publicly accessible.

Competing Interest

The authors declare that they have no financial or non-financial competing interests.

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Author Contributions

Minoo Heidari Almasi and Amirahmad Nassiri conceptualized and designed the study, as well as oversaw data collection and manuscript preparation. Kiana Entezarmahdi and Antoine Schneider contributed to data collection and the evaluation of clinical cases. Maryam Barzin assisted with

manuscript preparation. All authors participated in drafting, critically revising, and approving the final version of the manuscript.

Consent for Publication

Not applicable.

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