

Extracellular Vesicles in Acute Kidney Injury: Mechanisms, Biomarkers, and Therapeutic Potential

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Abstract: Acute kidney injury (AKI) has a high morbidity and mortality rate but can only be treated with supportive therapy in most cases. The diagnosis of AKI is mainly based on serum creatinine level and urine volume, which cannot detect kidney injury sensitive and timely. Therefore, new diagnostic and therapeutic molecules of AKI are being actively explored. Extracellular vesicles (EVs), secreted by almost all cells, can originate from different parts of the kidney and mediate intercellular communication between various cell types of nephrons. At present, numerous successful EV-based biomarker discoveries and treatments for AKI have been made, such as the confirmed diagnostic role of urine-derived EVs in AKI and the established therapeutic role of mesenchymal stem cell-derived EVs in AKI have been confirmed; however, these related studies lack a full discussion. In this review, we summarize the latest progression in the profound understanding of the functional role of EVs in AKI caused by various etiologies in recent years and provide new insights into EVs as viable biomarkers and therapeutic molecules for AKI patients. Furthermore, the current challenges and prospects of this research area are briefly discussed, presenting a comprehensive overview of the growing foregrounds of EVs in AKI.

Keywords: extracellular vesicles, acute kidney injury, mesenchymal stem cells, therapeutic molecules, diagnostic biomarkers

Introduction

Acute kidney injury (AKI) is a renal injury syndrome characterized by a rapid decline in kidney function, mainly manifested as elevated serum creatinine and decreased urine volume, often caused by cell damage in the nephron.^{1,2} Due to population differences and inconsistencies in standardized AKI classification, estimates of AKI prevalence range from < 1% to 66%.³ Epidemiological data show that the incidence of AKI can reach more than 20% of the hospitalized population and exceed 50% in specific hospital units, resulting in approximately 1.7 million deaths worldwide.^{1,2} The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for Acute Kidney Injury summarized the causes of AKI based on many observational studies, which include sepsis, circulatory shock, cardiac surgery, nephrotoxic drugs, radiocontrast agents, burns, trauma and so on.⁴ AKI pathogenesis remains elusive but centers on proximal tubular epithelial cell (PTEC) injury. While initial damage triggers transient regenerative mechanisms involving dedifferentiation and proliferation, persistent damage triggers pathological cascades culminating in tubular atrophy, inflammatory infiltration, fibrotic remodeling, and irreversible progression to CKD.^{5,6} Despite the more profound understanding of AKI's diagnosis, pathogenesis, and treatment, the complexity and heterogeneity of its origin, pathophysiology, and clinical processes remain considerable barriers to overcoming the major global public health problem.⁷ The key pathophysiological processes of the progressive progression of AKI are caused by various causes, such as inflammation after renal tissue damage and renal fibrosis caused by abnormal damage repair.^{8,9}

Extracellular vesicles (EVs), defined by the International Society for Extracellular Vesicles (ISEV) as lipid bilayer-enclosed particles released from cells, serve as carriers of bioactive molecules (eg, proteins and nucleic acids).¹⁰ Owing

to their ubiquitous presence in biofluids and stable molecular composition, EVs exhibit remarkable potential as minimally invasive liquid biopsy tools for monitoring disease progression.¹¹ Complex intracellular pathways are regulated by the intrinsic properties of EVs, which enhance their potential utility in the therapeutic control of diseases.^{12,13} An increasing number of studies have demonstrated that EVs have emerged as a prominent research field, serving as potential diagnostic biomarkers and therapeutic molecules for multiple system diseases, including AKI,^{14,15} Alzheimer's disease,¹⁶ Parkinson's disease,¹⁷ prostate cancer,¹⁸ diabetes,¹⁹ lung injury²⁰ and so on. Meanwhile, EVs contain a variety of bioactive molecules, such as lipids, proteins, nucleic acids, and metabolites, which play a vital role in kidney disease by participating in inflammation and fibrosis processes.²¹ In addition, EVs can be regarded as paracrine factors that participate in cell-to-cell communication in AKI and induce epigenetic reprogramming of injured kidney cells. Various sources of EVs, including renal tubular epithelial cells (TECs), vascular endothelial cells, and mesenchymal stem cells (MSCs), have been shown to ameliorate the pathological status of AKI and delay its progression through a wide range of mechanisms.^{22–24} However, other studies have suggested that genetic material carried by EVs derived from TECs promotes the activation and proliferation of macrophages and fibroblasts, leading to kidney inflammation and fibrosis.^{1,2}

Much progress has been made in diagnosing and treating AKI, but it remains a non-negligible issue in medical treatment. Therefore, searching for more sensitive biomarkers and effective treatments is still crucial in future research. In this review, we highlight the updated advancement of EVs in AKI, focusing on their role in the diagnosis and treatment of AKI and their future development prospects. Furthermore, we critically evaluate persistent methodological challenges in EV research, particularly regarding standardization of isolation protocols, and hope to propose solutions to these problems in the future.

Extracellular Vesicles

General Characteristics and Biogenesis of EVs

EVs, which widely exist in almost all body fluids, including urine, blood, saliva, and cerebrospinal fluid, are recognized as critical components in intercellular communication by transporting biomolecules from the parental cells to the recipient cells.^{25,26} The biomolecules can not only represent the characteristics of the parental cells but also effectively alter the biological response of the recipient cells.²⁷ According to their size, biogenesis, and function, EVs can be classified into three main categories: exosomes (less than 150nm in diameter), microvesicles (150–1000nm in diameter), and apoptotic bodies (more than 1000nm in diameter).^{28,29} All three subtypes share comparable structural and compositional profiles, including surface molecule expression and cellular cargo mirroring their parental origins. Complete isolation remains technically challenging; however, exosomes demonstrate superior therapeutic efficacy, exhibiting enhanced anti-inflammatory properties compared to other subtypes.^{30,31} Of these, the most widely studied is exosomes, whose biogenesis consists of four steps: initiation, endocytosis, multivesicular bodies (MVBs) formation, and secretion of exosomes¹³ (Figure 1). First, plasma membrane (PM) invagination forms early endosomes (EE), which gradually develop into late endosomes (LE).³² LE transforms into intracellular MVBs with intraluminal vesicles (ILVs) by budding inward.³³ Subsequently, ILVs of MVBs are expelled from the cell through fusion with the PM or exocytosis after phagocytosis of various biomolecules and finally form exosomes.^{13,32,33} The lipid bilayer membrane comprising EVs contains surface proteins, tetraspanins (CD9, CD81, and CD63), and receptors, which regulate EVs' biological distribution and targeting ability and are used for their characterization^{34,35} (Figure 1).

In addition to humoral-derived EVs that have been extensively studied, the underlying applications of mesenchymal stem cells-derived EVs (MSC-EVs) and engineered EVs in diseases have attracted tremendous attention because of their higher biocompatibility and lower toxicity recently^{36–38} (Figure 2). EVs secreted by certain types of cells have a therapeutic effect of their own since they carry various cargo molecules from parent cells such as MSC-EVs, while modified EVs are supposed to have an extra therapeutic function because they contain additional therapeutically efficient materials such as engineered EVs.³⁹ A phospholipid bilayer structure modified with functional molecules allows the decoration of their initial framework by applying multiple approaches, including chemical procedures, direct parent cell membrane engineering, genetic engineering, and physical techniques.³⁸ An enclosed parental matrix attracts interest in

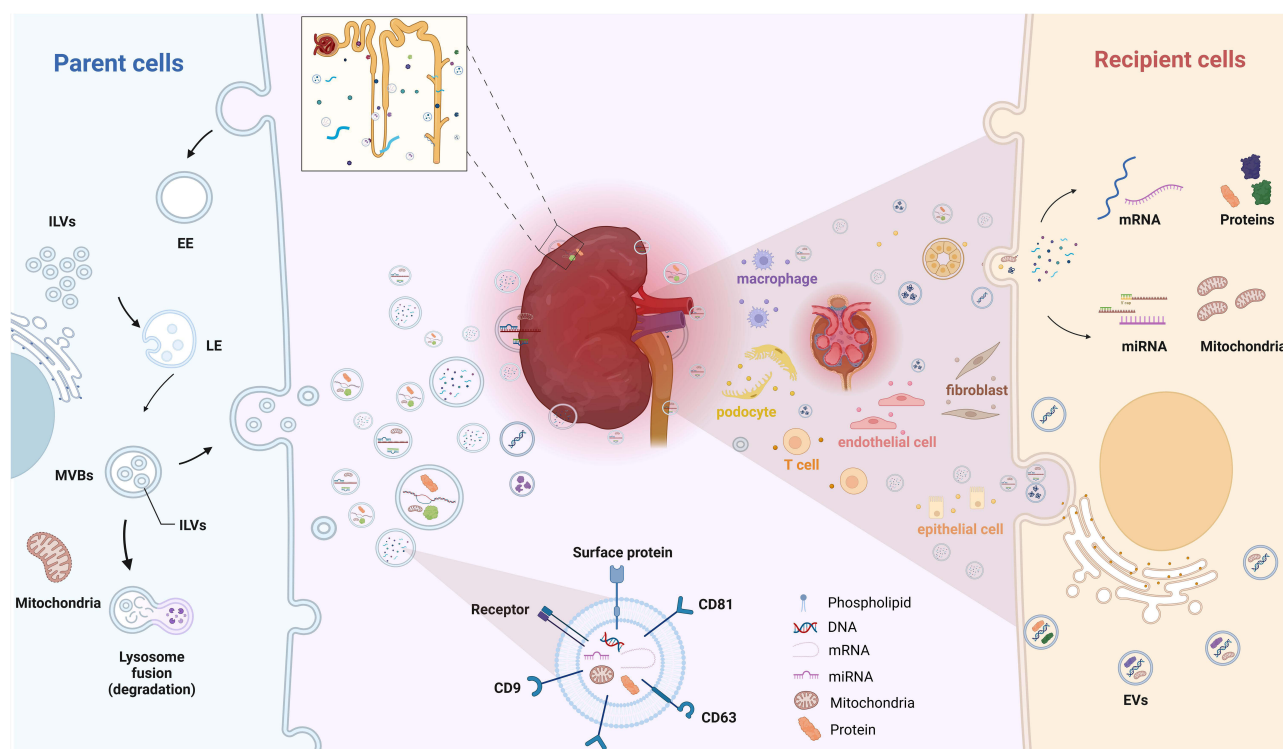


Figure 1 Role of EVs in intra-nephron communication. The EVs secreted by the parental cells reach the kidneys, transporting the carried biomolecules to the recipient cells. In the left half of the image, the parent cell section shows the process of EV formation. In the middle of the picture, the EVs secreted by the parental cells can interact with all the cells of the kidney and the EVs they secrete, and together affect the progression of kidney disease. At the bottom of the middle section is a microscopic amplification of EVs. In the right part of the image, the receptor cell receives the biomolecules carried by the parental cell-derived EVs. Created in BioRender. Yan, Q. (2025) <https://BioRender.com/194g381>.

Abbreviations: ILVs, intraluminal vesicles; EE, early endosome; LE, late endosome; MVBs, multivesicular bodies.

loading large amounts of siRNA, mRNA, or miRNA via lipofection, electroporation, calcium chloride treatment, or sonication.⁴⁰ More and more proofs indicate that EVs as therapeutic approaches are ideal for personalized medicine because of their diversity and multifunctionality.⁴¹

Isolation and Identification of Extracellular Vesicles

Obtaining EVs from complex and varied components with a high yield and exosome-like characteristic is a challenge and critical point for further clinical applications, which is susceptible to isolation procedures.³⁵ Unfortunately, there is no unified protocol or methodology for isolating and purifying EVs, as this step is determined by downstream analysis.³⁵ Based on the diverse biological properties of EVs, such as shape, size, surface proteins, and density, numerous conventional approaches have been applied for isolating EVs, including precipitation, differential ultracentrifugation (dUC), density gradient centrifugation (DG centrifugation), immunoaffinity capture-based technology, size exclusion chromatography (SEC), ultrafiltration, and microfluidics-based technology⁴² (Figure 2). Although separation techniques are diverse and have advantages, each approach has limitations (Table 1). Ultracentrifugation is the gold standard and most commonly used method for separating electric vehicles, which can extract high-purity EVs but cannot further distinguish the diverse populations of EVs.^{15,43} SEC is reproducible, cost-efficient, and requires no particular laboratory equipment or user expertise, but it is time-consuming.^{42,44} In addition, precipitation can bring a high yield, but it also loses the specificity and purity of EVs to a large extent.⁴⁵ On the contrary, immunoaffinity capture-based technology can ensure higher purity of EVs while reducing the yield.⁴⁶ Optimizing purity may improve experimental specificity, and increasing EV yield is elementary to augment experimental sensitivity. Therefore, given the respective characteristics of the techniques, the researchers combined and optimized them to obtain high-purity and high-yield EVs.⁴² The complexity and diversity of EV isolation methods, inevitable non-EVs components, as well as the heterogeneity of EVs are enormous obstacles to identifying the isolated EVs.^{35,42,47} Traditionally, the identification of EVs involved three parts (Figure 2):

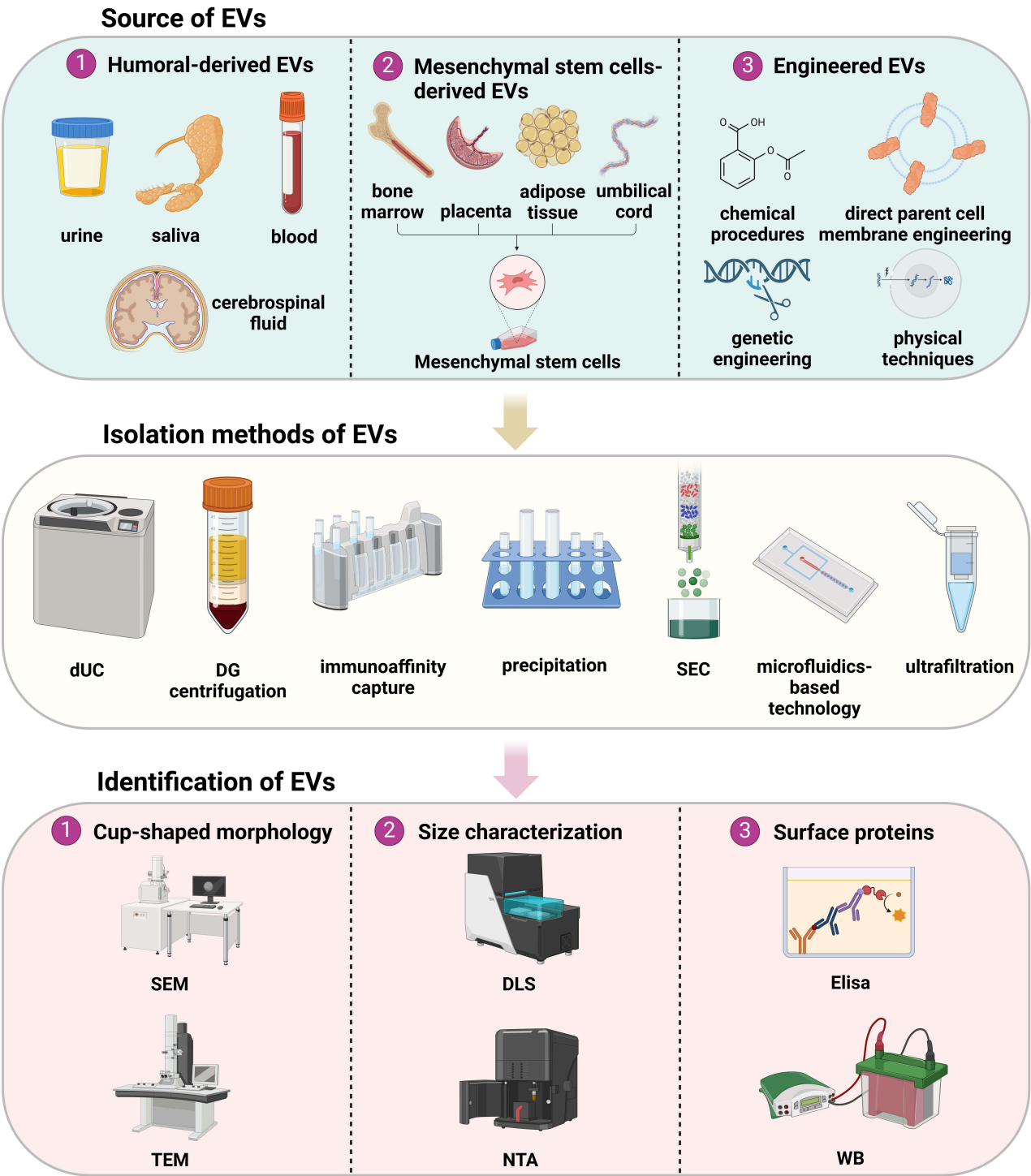


Figure 2 The extraction and characterization diagram of EVs. The three source EVs mentioned in the review must undergo a series of sequential processes to determine EVs, including the isolation and characterization of exosomes. Created in BioRender. Yan, Q. (2025) <https://BioRender.com/g4unxkb>.
Abbreviations: dUC, differential ultracentrifugation; SEC, size exclusion chromatography; DG centrifugation, density gradient centrifugation; SEM, scanning electron microscopy; TEM, transmission electron microscopy; DLS, dynamic light scattering (DLS); NTA, nanoparticle tracking analysis; ELISA, enzyme-linked immunosorbent assay; WB, Western blot.

Table 1 Comparison of the EV Isolation Methods

Method	Time	Principle	Samples	Purity	Advantages	Disadvantages	References
dUC	>4h	-According to density, size and shape.	Plasma, urine, milk, culture medium	Medium	1) Non-EVs component is low. 2) Low cost	1) Cannot distinguish the populations of EVs 2) Destroying the integrity of sEVs	[43,44,50]
SEC	0.3h	-Small particles can pass through the pores, while larger particles cannot.	Plasma, urine, milk, culture medium	High	1) Better than other techniques in the purity 2) Cost-efficient, with a 20 min average processing time per sample 3) Isolating EV preparations are superior integrity	1) Reduces total EV yield 2) The mRNA and protein yield of EVs is impacted 3) Low upper limit of sample volume 4) Time-consuming	[42,44]
Precipitation	0.3–12h	-Altering EVs' solubility or dispersibility, EVs can be settled out of biological fluids.	Serum, plasma, urine, cerebrospinal fluid, culture medium.	Low	1) High yield 2) Processing multiple samples simultaneously 3) Ease, faster, and low cost without damage to EVs.	1) The purity and specificity of EVs are largely lost 2) Low-quality	[51,52]
immunoaffinity capture-based technology	4–20h	-Using antibodies against specific EV surface markers.	Plasma, culture medium	High	1) High purity 2) Isolates specific EV subtypes	1) Low yield 2) Damage the integrity of EVs 3) Expensive 4) Suitable for small sample size	[53,54]
DG centrifugation	>16h	-Primarily based on particle density.	Plasma, culture medium, saliva, urine	High	1) The purity is improved compared with dUC	1) Complicated operation 2) Time-consuming	[55,56]
Ultrafiltration	<4h	-Based on particle size.	Serum, culture medium	Low	1) Simple operation	1) Low purity	[57,58]
Microfluidics-based technology	4–20h	-Based on the expression of surface proteins	Plasma, culture medium	High	1) High purity 2) Isolates specific EV subtypes	1) Low yield 2) Damages the integrity of EVs 3) Expensive 4) Fits a small sample size	[53,54,59]

Abbreviations: duc, differential ultracentrifugation; SEC, size exclusion chromatography; DG centrifugation, density gradient centrifugation.

characterizing cup-shaped morphology by scanning electron microscopy (SEM) and transmission electron microscopy (TEM), identifying size characterization using dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA), and recognizing EVs proteins by enzyme-linked immunosorbent assay (Elisa) and Western blot (WB).^{42,47,48} The ISEV recommends using transmembrane or GPI-anchored proteins to identify EVs. The purity of EVs can be determined by exploring the existence or absence of non-EVs proteins.^{42,49}

Role of EVs in Intra-Nephron Communication

EVs function in multiple biological processes and play a pathophysiological role in kidney diseases, including immune/inflammatory regulation, antibacterial effect, and kidney regeneration/repair.⁶⁰ Cellular communication between numerous nephron cells can be mediated by EVs, which amplify kidney damage⁶¹ (Figure 1). When stimulated by harmful factors, EVs derived from glomerular endothelial cells transfer miRNA to podocytes to impair podocyte function, while podocyte-derived EVs lead to renal TECs injury.^{62,63} Under high glucose conditions, mesangial cell-derived EVs damaged podocytes, and the interaction of EVs secreted by the two types of cells affected glomerular function.⁶⁴ In addition, EVs originating from upper segments of tubular cells deliver biomolecules to downstream cells and regulate their behavior, which are internalized by downstream cells.^{61,65} For example, renal proximal epithelial cells-derived EVs can go downstream through the urinary tract, arriving at distal tubules or collecting ducts.⁶⁶ Gidea et al found that distal tubule and collecting duct immortalized cell lines can ingest CD63-EGFP or CD9-RFP labeled EVs from human renal proximal tubule cells.⁶⁵ Furthermore, similar communication was found between renal tubule cells and interstitial cells. Proteinuria stimulates TECs to produce more EVs, in which loaded mRNA is transferred to macrophages and promotes their activation and migration, resulting in renal tubulointerstitial inflammation.⁶⁴

Urinary extracellular vesicles (uEVs) mainly originate from urogenital tract cells, including glomerular, tubular, prostate cells, and bladder cells, and can mediate communication between glomerular and tubular cells and between different segments of renal tubules.^{61,67} Lv et al isolated EVs released by podocytes from urine, whose structure was positive for the markers of podocyte.⁶⁸ Podocyte-derived EVs in urine may pass through the renal tubules to deliver the information to the TECs.⁶⁹ uEVs are promising biomarkers for reflecting renal tissue injury and predicting renal function progression.

EVs in AKI

EVs play a role in intercellular and interorgan crosstalk, potentially amplifying kidney damage and contributing to the progression of kidney disease⁶¹ (Figure 1). Based on EV-related studies, novel biomarkers and disease mechanisms have been identified in many kidney diseases, including AKI.⁷⁰ In addition, EVs are used not only as information molecules to report disease characteristics and progression but also to deliver therapeutic molecules to specific target cells to improve the progression of AKI.⁷¹ We will focus on the role of EVs in the diagnosis, treatment, and mechanism of AKI caused by various etiologies (Table 2) (Figure 3).

Ischemia/Reperfusion Injury-Related AKI

Ischemic/reperfusion injury (IRI), one of the primary causes of AKI, leads to significant morbidity and mortality.⁸⁸ With a complex pathogenesis, IRI-related AKI (IRI-AKI) still has few effective interventions or management.^{72,89} MSC-EVs may hold great promise for treating IRI, not just IRI-AKI, and many animal model experiments have shown their therapeutic potential.^{72,90,91} Cao et al used a noninvasive technique, accumulation-induced emission luminous (AIEgens), to demonstrate that MSC-EVs-transferred miRNA-200a-p activated the Keap1-Nrf2 signaling pathway in TECs, thereby restoring renal function in IRI-AKI mice (Figure 3).⁷² MSCs derived from multiple tissues, including the placenta, adipose tissue, bone marrow, and the umbilical cord, have beneficial anti-inflammatory and antifibrotic effects, and the EVs released from them are regarded as valuable cell-free therapies for treating renal IRI.^{92,93} All four sources mentioned above of MSC-EVs have been studied in IRI, and the results show that they have a therapeutic effect on IRI by alleviating renal fibrosis, reducing inflammatory cell infiltration, restoring renal structure, inhibiting renal cell apoptosis, and promoting vascular regeneration.^{48,94} For example, the human Wharton's jelly (hWJMSCs), a gel-like substance found in the umbilical cord, secreted EVs have renoprotective effects, such as improvement in renal function, cell

Table 2 Application of EVs in AKI

Types of AKI	Species	Source of EVs	Experimental Method	Main Findings	References
IRI-AKI	FVB mice	hP-MSCs-EVs	Intravenous injection	-MSC-EVs promoted the recovery of kidney function via activating the Keap1-Nrf2 signaling pathway.	[72]
	Rats	hWJMSCs-EVs	Intravenous injection	-hWJMSCs-EVs protect the kidney by alleviating the oxidative stress of kidney IRI through suppressing NOX2 expression.	[73]
	Rats	RTC-EVs	Intravenous injection	-Injections of EVs, given after 24 and 48 hours of reperfusion, preserved renal function and structure in both treatment groups.	[22]
S-AKI	C57BL/6 mice	FRC-EVs	Intravenous injection	-FRC-EVs attenuate S-AKI, with CD5L being the most abundant protein in FRC-EVs.	[74]
	C57BL/6 mice	Platelet-derived EVs	Intravenous injection	-Increased platelet-derived EVs during sepsis aggravated S-AKI through the ARF6 release to promote inflammation, apoptosis, and oxidative stress.	[75]
	Rats	Macrophage-derived EVs	Intravenous injection	-In S-AKI, macrophage-derived EVs are internalized by surrounding endothelial cells, resulting in endothelial cell injury.	[76]
CDDP-AKI	BALB/c mice	iMSC-EVs	Intravenous injection	-EVs secreted from pan-PPAR agonist-treated iMSCs have a greater renoprotective effect against AKI.	[77]
	CD1 mice	BMSCs-EVs	Intravenous injection	-The combination of pFUS and EVs is therapeutic in the setting of CDDP-AKI, superior to either EVs or pFUS alone.	[78]
	Rats	hucMSC-EVs	Renal capsule injection	-The activation of autophagy induced by hucMSC-Ex can effectively relieve the nephrotoxicity of cisplatin.	[79]
	C57BL/6 mice	Macrophage-derived EVs	Intravenous injection	-EVs miR-195a-5p mediate the communication between autophagy-deficient macrophage and TECs.	[80]
Glycerol-induced AKI	SCID mice	BMSCs-EVs	Intravenous injection	-BMSCs-EVs accelerate the recovery of glycerol-induced AKI in SCID mice.	[81]
	FVB mice	uEVs	Intravenous injection	-uEVs carrying Klotho improve the recovery of renal function in AKI.	[82]
Gentamicin-induced AKI	Rats	BMSCs-EVs	Intravenous Injection	-BMSCs minimized the gentamicin-induced renal damage through paracrine effects, most likely through the RNA carried by the EVs.	[83]
Post-transplant AKI	Human	uEVs	WB	-Determination of NGAL in uEVs is a better predictor of kidney dysfunction after KT than other urinary fractions.	[84]
	Rats	hWJMSCs-EVs	Intravenous injection	-The administration of EVs immediately after KT could ameliorate IRI in both the acute and chronic stages.	[85]
AKI after cardiac surgery	Human	uEVs	ELISA	-Monitoring alters in uEVs can forecast the onset of AKI in patients after cardiac surgery.	[86]
UUO-induced AKI	Rats	BMSCs-EVs	Intravenous injection	-BMSCs-EVs containing MFG-E8 attenuate renal fibrosis, partly through RhoA/ROCK pathway inhibition.	[87]

Abbreviations: IRI-AKI, ischemic/reperfusion injury related AKI; S-AKI, sepsis-associated AKI; CDDP-AKI, cisplatin-induced AKI; Glycerol-induced AKI; UUO-AKI, unilateral ureteral obstruction induced AKI; hP-MSCs-EVs, human placenta-derived MSCs-EVs; RTC-EVs, renal tubule cells derived- EVs; iMSC-EVs, induced mesenchymal stem cells; pan-PPAR, pan-peroxisome proliferator-activated receptor; pFUS, pulsed focused ultrasound; BMSCs-EVs, bone mesenchymal stem cells derived-EVs; hucMSC-EVs, human umbilical cord MSC-derived exosomes; uEVs, urine-derived EVs; WB, Western blot.

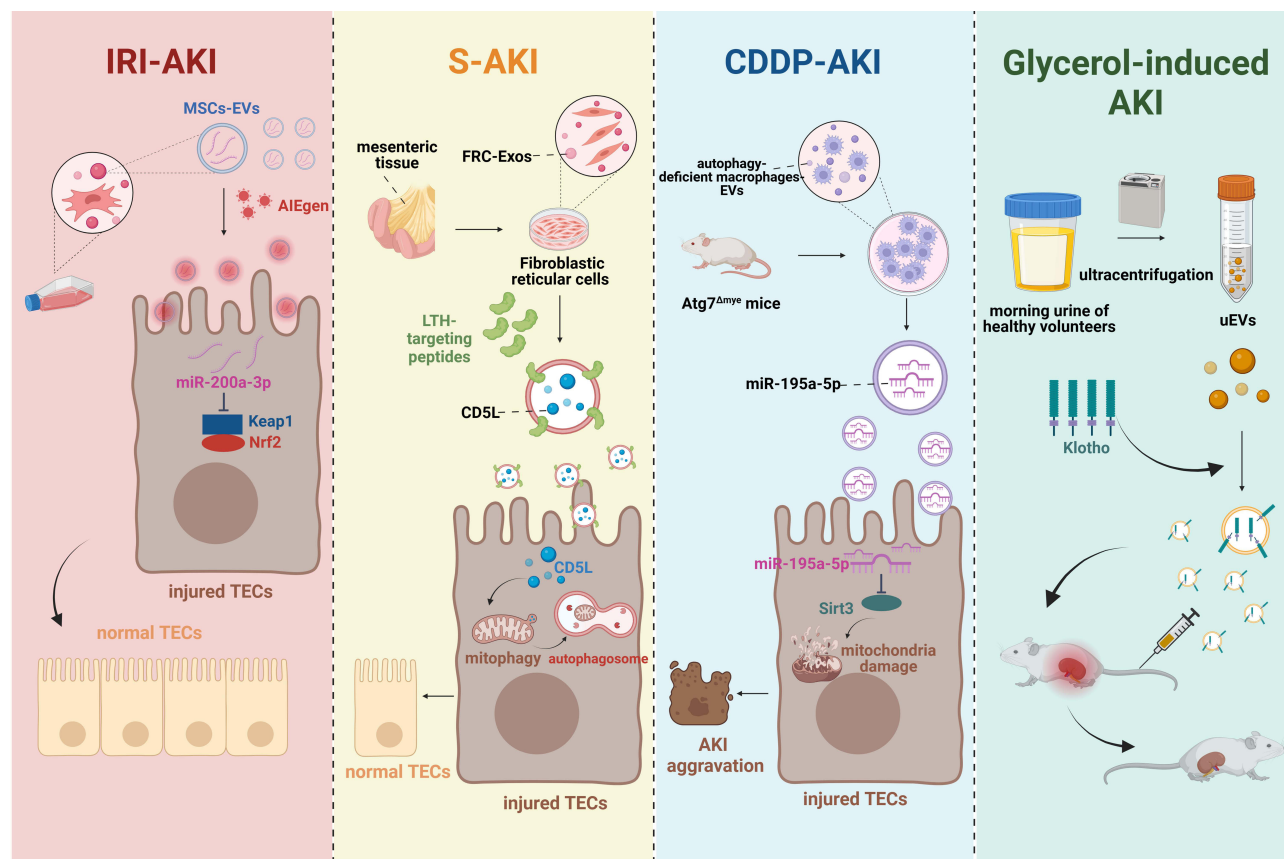


Figure 3 The mechanism of EVs in AKI. IRI-AKI: After using AIEgens to treat MSC-EVs, MSC-EVs-transferred miRNA-200a-p activated the Keap1-Nrf2 signaling pathway in TECs, thereby restoring renal function in IRI-AKI mice. S-AKI: FRC-EVs were modified with LTH-targeting peptides to navigate EVs to tubule cells, and CD5L in EVs was released into tubule cells to promote mitophagy, inhibit pyroptosis, and thus improve kidney injury. CDDP-AKI: The crosstalk between macrophages and TECs promotes disease progression in a CDDP-AKI mouse model, and autophagy-deficient macrophage (Atg7 Δ mye mice derived macrophage)-derived EVs damage the mitochondria of TECs in vitro, which possibly through the miR-195a-5p-SIRT3 axis. Created in BioRender. Yan, Q. (2025) <https://BioRender.com/x59y496>.

Abbreviations: Atg7 Δ mye, macrophages-specific depletion of ATG7; Glycerol-induced AKI, uEVs promote kidney regeneration by transferring the renal protective factor Klotho to damaged kidney tissue. AIEgens, accumulation-induced emission luminous; TECs, tubular epithelial cells; FRC-EVs, Fibroblastic reticular cells-derived EVs.

proliferation, cell survival, and tissue fibrosis inhibition in renal IRI, a process that is induced by mitigating oxidative stress (OS).^{73,92} In addition to MSC-EVs, EVs from healthy renal tubular cells can protect renal function as well. Renal endothelial and tubular-derived EVs are essential in IRI recovering and healing.⁹⁵ By intravenous administration of EVs derived from renal tubule cells, renal IRI was alleviated in rats, and the antioxidant capacity of the injured cells was enhanced.²²

The development of IRI-AKI involves various mechanisms, including cell injury, cell dysfunction, and multiple cell death, among which tubular cell necrosis and apoptosis are considered to be the main causes of IRI-AKI in previous studies.⁸⁹ EVs released from the apical and basolateral membranes of renal TECs can be isolated from plasma as a non-invasive biomarker monitoring AKI.⁹⁶ Damage-associated molecular patterns may transmit to renal TECs via EVs, hindering renal tubule recovery.⁴⁸ Moreover, once the immune response begins and IRI enters an initial inflammatory stage, renal tubular-derived EVs carrying biomolecules may activate and recruit innate immune cells, which promote the apoptosis of TECs and the damage of endothelial cells.^{48,97} Similarly, endothelial cells-derived EVs have pro-inflammatory functions, which can exacerbate vascular inflammation by attracting adaptive immune cells and inducing the production of autoantibodies.^{48,91–93,98} Biological factors delivered by endothelial progenitor cells (EPC-EVs) or MSC-EVs regulate inflammatory profiles and facilitate the repair of TECs and endothelial cells.⁹⁷ Plasma, serum, and platelet-derived EVs have been extensively studied as biomarkers or therapeutics for myocardial IRI.^{99–101} Unfortunately, we did not find these sources of EVs in renal IRI research. Given the protective effect of these EVs on myocardial IRI, do they have a palliative effect on renal IRI to treat IRI-AKI? It is hoped that future studies will answer this question.

Sepsis-Associated AKI

Sepsis, one of the major causes of death after trauma, burns, and severe surgery, is closely related to ~50% of AKI patients.¹⁰² At present, researchers are still exploring the pathophysiological mechanism of sepsis-associated AKI (S-AKI), so organ support and etiological treatment, such as antibiotics and resuscitation, are the primary options for its treatment.^{102,103} Similar to IRI-AKI, MSC-EVs also have a therapeutic efficacy in S-AKI. The specific mechanisms involved in the treatment of AKI from different sources of MSC-EVs are diverse. For example, adipose tissue MSCs-derived EVs (AMSCs-EVs) activate the Sirt1, human umbilical cord MSCs-derived EVs (hucMSCs-EVs) attenuate NF- κ B activity, and bone MSCs-derived EVs (BMSCs-EVs) block autophagy by the AMPK/mTOR pathway, the final result is the alleviation of S-AKI.^{104–106} Fibroblastic reticular cell-derived EVs (FRC-EVs), promising drug-delivery vehicles, can promote mitochondrial autophagy, restrict inflammasome activation, and accelerate the recovery of renal TECs to treat S-AKI.⁷⁴ FRC-EVs were modified with LTH-targeting peptides to navigate EVs to tubule cells, and CD5L in EVs was released into tubule cells to promote mitophagy, inhibit pyroptosis, and thus improve kidney injury (Figure 3).⁷⁴ Notably, approximately 70% of total plasma EVs in sepsis patients are derived from platelets, regarded as the major functional components of plasma EVs.⁷⁵ However, these platelet-derived EVs promote inflammation, apoptosis, and OS, possibly exacerbating S-AKI by activating the ERK/Smad3/P53 pathway.⁷⁵ S-AKI is also aggravated by macrophage-derived EVs, which have been shown to cause endothelial cell dysfunction and promote inflammation in vivo and in vitro.⁷⁶

Serum creatinine and urine volume have limitations in the diagnosis of AKI.^{103,107} In particular, sepsis reduces muscle perfusion, slowing the increase of serum creatinine concentration and ultimately preventing early diagnosis.¹⁰⁸ Although new biomarkers have been detected recently to diagnose S-AKI, they are low sensitivity.^{102,109} Consequently, there is an urgent need for non-invasive biomarkers with both sensitivity and specificity. uEVs, a non-invasive diagnostic modality, can reflect the molecular events of physiological and pathological changes in urinary diseases.¹¹⁰ So, uEVs activating transcriptional factor 3 (uATF3) may be an early indicator of S-AKI.¹¹¹ Li et al used integrative multi-omics analysis to describe the molecular dynamics landscape of serum-derived EVs during sepsis for the first time, ultimately finding 354 differentially expressed proteins and 332 differentially expressed RNAs in serum EVs of sepsis patients.¹¹² These differentially expressed molecules may provide valuable insights for diagnosing and treating S-AKI.

Drug-Induced AKI

Drug-induced kidney injury, a considerable pathogenic factor of AKI, has a clinical incidence of AKI as high as 60%.¹¹³ Drug-induced AKI is clinically manifested in various forms, the popular of which is tubular interstitial compartment injury.¹¹⁴ Among the drugs that can induce the AKI model, cisplatin and glycerol are commonly used.

Cisplatin-Induced AKI

Cisplatin (CDDP) is a chemotherapy drug widely used in the treatment of solid tumors, with the incidence of side effects of AKI achieving 30%.^{115,116} At present, the prevention of CDDP-induced AKI (CDDP-AKI) mainly includes diuretic hydration therapy and dose reduction or withdrawal of cisplatin.^{116,117} However, these measures cannot apply to patients with renal or cardiac dysfunction and hinder the treatment of tumors.^{116,117} Therefore, it is urgent to discover effective measures to prevent or treat CDDP-AKI. Kim et al found that a pan-peroxisome proliferator-activated receptor (PPAR) agonist can enhance the protective effect of induced mesenchymal stem cells derived EVs (iMSC-EVs) on kidney in CDDP-AKI mice.⁷⁷ Beyond reagents, the researchers also explored physical methods such as pulsed focused ultrasound (pFUS) processing of tissue to increase the therapeutic effect of MSCs-EVs on CDDP-AKI.⁷⁸ The possible reason is that pFUS enhances MSCs homing to save renal function safely and effectively.¹¹⁸ Ullah et al carried out a similar study. However, they denied the improved effect of pFUS on EVs homing to the kidney, suggesting that the better treatment outcome of this synergistic therapy was due to the up-regulation of the regenerative pathway (Sirt3, eNOS).⁷⁸ Apoptosis and necrotic apoptosis of proximal TECs are deemed to be the principal pathologic forms of CDDP-AKI.^{115,119} The therapeutic effect of hucMSCs-EVs on CDDP-AKI has been extensively studied, which involves several mechanisms, including reducing serum inflammatory cytokines, inhibiting TECs' mitochondrial apoptosis, and activating TECs' autophagy.⁷⁹ A recent study found that the crosstalk between macrophages and TECs promotes disease progression in the CDDP-AKI mouse model, and autophagy-deficient macrophage-derived EVs damage the mitochondria of TECs

in vitro, which possibly through the miR-195a-5p-Sirt3 axis (Figure 3).⁸⁰ EVs' role in the CDDP-AKI progression mechanism has not been fully elucidated, and relevant studies are limited. We call for more research to understand the pathophysiological mechanisms of CDDP-AKI in more detail.

Glycerol-Induced AKI

Myolysis and hemolysis can occur after intramuscular injection of glycerol, which exposes the kidneys to a mass of myoglobin and hemoglobin, resulting in ischemic tubular injury.^{81,120} Fifteen years ago, a mouse model of glycerin-induced AKI was used to demonstrate that EVs derived from human BMSCs stimulated the proliferation of TECs and accelerated the recovery of AKI.⁸¹ This process may be related to paracrine factors facilitating the proliferation of surviving intrinsic epithelial cells.⁸¹ Five years later, Maria conducted a similar experiment, reaffirming stem cells' therapeutic effect on glycerol-induced AKI and paracrine mechanisms (associated with the renal regenerative effect).^{120,121} Due to miRNA's pro-regeneration ability on the kidney, electroporation transiently transfected the specific miRNA into MSCs to obtain engineered EVs, which not only retained their pro-regeneration effect but also prominently improved renal function and morphology in glycerol-induced AKI mice.¹²² In consideration of the ethical issues, invasive sample collection, and limited donors of MSCs therapy, Zhang et al made the first attempt and succeeded in isolating a type of adult stem cell with excellent proliferation potential and multidirectional differentiation ability from urine for the first time, called urine-derived stem cells (USCs).¹²³ With Zhang's help, Li et al demonstrated that injecting USCs intravenously into glycerin-induced AKI mice promotes TECs proliferation.¹²⁴ Do uEVs have a therapeutic function on glycerin-induced AKI? Grange et al showed that uEVs promote kidney regeneration by transferring specific miRNA cargo to damaged kidney tissue and regulating the renal protective factor Klotho.⁸² The therapeutic effect of uEVs and MSCs-EVs on kidneys is similar, demonstrating their great potential in the future treatment of AKI.

Other drugs that can cause AKI contain antibiotics (gentamicin), contrast agents, and so on.¹¹⁴ Gentamicin, the most commonly used aminoglycoside drug, can cause kidney damage, which is mainly manifested as proximal tubular necrosis and glomerular hemodynamic changes.⁸³ Studies have shown that BMSCs mediate the recovery of kidney function in gentamicin-induced AKI mice through RNA carried in EVs.⁸³ Contrast-induced AKI is the third major cause of hospital-acquired AKI, whose exact pathogenesis remains unclear, and available treatments are minimal.¹²⁵ Unfortunately, we did not find any studies of contrast-induced AKI and EVs. Given the therapeutic effect of EVs on other types of AKI and the limited treatment options for contrast-induced AKI, initiating relevant research in this area may bring significant benefits. It is worth noting that renal injury caused by intramuscular injection of glycerol belongs to the rhabdomyolysis-induced AKI model. Rhabdomyolysis can be caused by a variety of causes, including trauma, burns, high fever, strenuous exercise, and the previously mentioned drugs (glycerin), causing rhabdomyolysis and disintegration, with AKI occurring in approximately 40% of patients.^{126,127} Next, we will introduce the role of EVs in burn and trauma-induced AKI.

Burns/Trauma-Induced AKI

Patients with severe burns and tissue trauma are at risk for AKI due to hypotension, fluid loss, intensive immune-pathophysiological responses, and rhabdomyolysis.^{128–130} After severe injury, about a quarter of patients are forcefully affected by trauma to develop AKI, resulting in them being at high risk of adverse outcomes.¹³¹ In particular, up to 58% of people with severe burns experience AKI, which is strongly related to 90-day mortality.^{130,132} Despite the most conventional treatment for burn-related AKI is renal replacement therapy (RRT), MSCs therapy may be more appropriate for some specific burn patients due to its comprehensive therapeutic capabilities.^{132–134} However, with significant progress, the clinical use of MSCs still needs to be improved due to several obstacles, including thrombosis, low survival in vivo, and tumorigenesis.^{135,136} MSCs-EVs, a novel approach for treating kidney disease, can overcome the limitations of MSCs while reserving the therapeutic characteristics of MSCs and may have great potential for burns- or trauma-induced AKI treatment.^{77,135} Regrettably, research on the function of MSC-derived EVs in burns-induced AKI is limited. More research in this area could be done in the future to benefit patients.

Post-Transplant AKI

Kidney transplantation (KT), the preferred treatment for end-stage kidney disease (ESRD), is associated with renal ischemia and exposure to toxins, which can lead to AKI.^{137,138} Existing injury indicators such as creatinine, which has a long half-life and is widely distributed, make it impossible to measure kidney function and injury in real time accurately.^{137,139} So, the researchers recommended uEVs as new biomarkers of renal function after KT.¹⁴⁰ The molecular components of uEVs can represent the pathophysiological state of the urinary system.⁸⁴ For instance, neutrophil gelatinase-associated lipocalin (NGAL) carried in uEVs was a better candidate for monitoring renal dysfunction after KT than other components in urine.⁸⁴ However, Peake et al suggested that the mRNA of kidney injury biomarkers in uEVs did not reflect or predict urinary biomarker levels after KT.¹³⁷ In addition, hWJMSCs-EVs improve survival rate and renal function after KT by reducing renal cell apoptosis and inflammation and promoting proliferation.⁸⁵ EVs have greatly interested researchers as a noninvasive way to diagnose or treat kidney diseases. If biomolecules in uEVs can predict or treat post-transplant AKI, KT's success probability will significantly increase.

AKI Induced by Other Methods

Many other factors can cause AKI, such as cardiac surgery, unilateral ureteral obstruction (UUO), and scrub typhus-associated AKI. The research found that monitoring alters in EV levels in urine can forecast the onset of AKI in patients after cardiac surgery.⁸⁶ BMSCs-EVs containing milk fat globule-epidermal growth factor-factor 8 (MFG-E8) improved kidney damage in UUO mice by inhibiting the RhoA/ROCK pathway.⁸⁷ Not only is miRNA-21 in urine a biomarker of AKI, but Yun et al also demonstrated that the level of miRNA-21 in uEVs has diagnostic significance for AKI in patients with scrub typhus.⁸⁴ The study of EVs and AKI caused by other factors needs to be more comprehensive. At the same time, studies on clarifying the relationship between EVs and AKI caused by these etiologies are insufficient, indicating a vast exploration space to fill the research gap in this area.

As a common refractory disease, the selection of multiple modeling methods for AKI should be based on the characteristics and objectives of the study, combining the advantages and feasibility of different models to make the research results credible. Coincidentally, most of the AKI studies involving EVs we collected focused on the role of MSCs-EVs. Moreover, most studies on MSCs-EVs focus on their therapeutic function in AKI. Due to the effects of reducing oxidative stress, anti-fibrosis, inducing renal tissue regeneration, and inhibiting renal cell apoptosis and inflammation, MSCs-EVs can be the next generation of cell-free therapies for AKI. Although MSCs-EVs are effective in treating AKI, these experimental conclusions are mainly derived from animal experiments, and the application of MSCs-EVs to humans is uncertain. It is worth noting that renal TECs injury is the central link causing AKI, but the number of studies of TECs-EVs in AKI has been unsatisfactory. Focusing on the potential role of TECs-EVs in the pathogenesis of AKI will greatly benefit the treatment of AKI. In addition, uEVs not only contain EVs secreted by all renal cells but also promote nephron cross-talk between the glomerular and renal tubular regions.¹⁴¹ Therefore, we have reason to believe that uEVs will have great value in the study of AKI in the future.

Challenges and Prospects of EVs in Clinical AKI Treatment

Although various experiments have shown the tremendous potential role of EVs in AKI, there are still many obstacles to their clinical application (Figure 4). First, the best way to deliver EVs into the body is still being determined. Most of the above animal experiments used intravenous (IV) injection to deliver EVs through the blood circulation to the kidney (Table 1). However, this method allows EVs to be retained by the upstream organ; thus, the uptake of EVs by the kidney is low.⁷ Intrarenal arterial (IA) injection can better increase the uptake of EVs to the kidney and transport therapeutic EVs directly to the injured kidney.¹⁴² In addition, IA injection can minimize systemic side effects and maximize the therapeutic efficacy, but it is an invasive procedure that may pose specific safety concerns.^{7,142} We only found one clinical trial in which MSCs-EVs were injected into the human internal renal artery. Although the results showed significant improvements in kidney function, more research is needed to demonstrate the safety of MSCs-EVs in clinical use.¹⁴³ In the case of systemic repeated administration, it is necessary to be vigilant about the immunogenicity of EVs.⁷ In addition, the dose of EVs applied to the human body at each time, the best time to inject EVs, the clearance in the

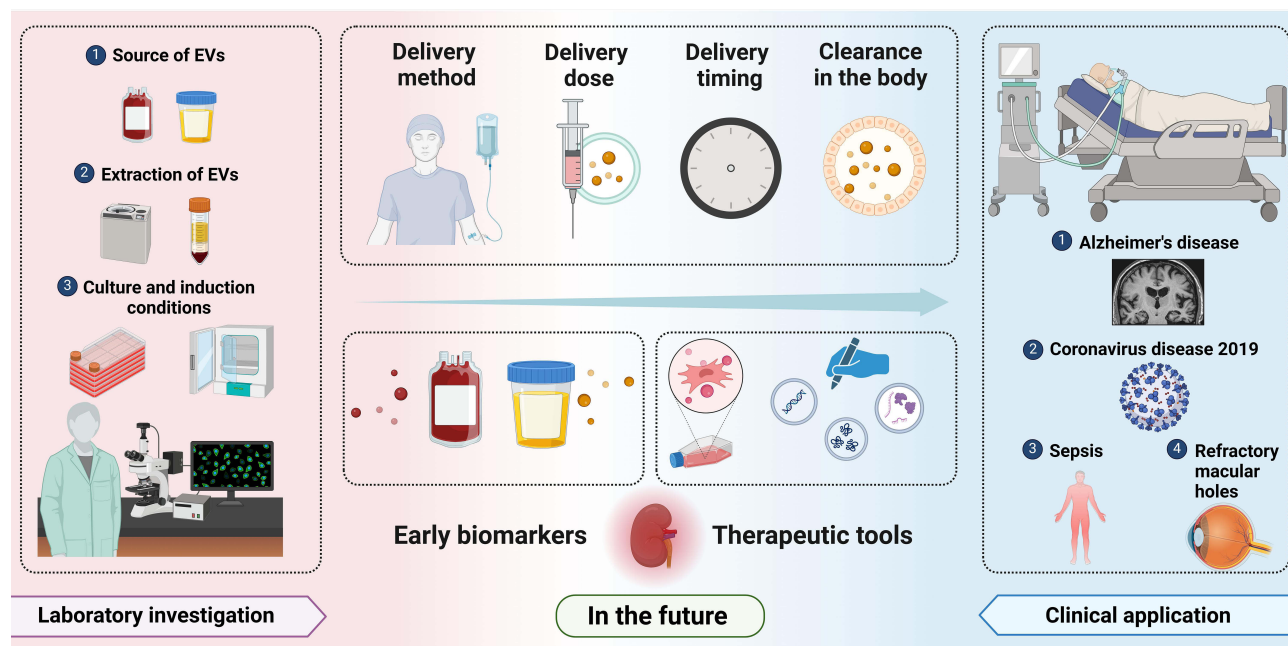


Figure 4 EVs from laboratory investigation to clinical application. The clinical application of EVs faces many challenges, but there have been studies on clinical patients. We believe that the clinical application of EVs in AKI can be realized in the near future. Created in BioRender. Yan, Q. (2025) <https://BioRender.com/u72t307>.

body, and whether it can be combined with other treatments are uncertain.⁷ Clinicians need to understand better the pharmacokinetics, pharmacodynamics, and biological distribution of every type of EV in the human body to determine the optimal dose and route of administration for each type of AKI.¹⁴⁴ The source, extraction and pretreatment methods, culture and induction conditions of EVs all change their properties and functions, and may affect the therapeutic effect of AKI.¹⁴⁵ Therefore, modifying EVs according to the different causes of AKI before the targeted treatment is wise.

There is no clinical precedent for using EVs to treat AKI, but the treatment of Alzheimer's disease, sepsis, refractory macular holes, and coronavirus disease 2019 (COVID-19) has entered early clinical trials using EVs.^{145–147} Based on the examples presented above, circulating system and urine-derived EVs may serve as potential early biomarkers of AKI, while MSCs-EVs and engineered EVs have feasibility as therapeutic tools, especially engineered EVs can be used as the specific treatment. Additionally, the difficulties in isolation and purification of EVs need to be overcome before realizing the clinical application of EVs in treating AKI. A simple and safe method for EV extraction should be developed to achieve both high-yield and high-purity EVs to meet clinical needs.¹⁴⁸ Finally, reliable criteria for evaluating the efficacy of EV therapies need to be established. Accurately evaluate the effect of EVs on AKI to determine the next course of treatment and avoid inconsistencies between preclinical studies and clinical applications. In any case, EVs hold promising prospects in the clinical application of AKI, whether as a treatment or a diagnostic method.

Conclusion

EVs hold considerable promise as a diagnostic or treatment tool for AKI. However, many challenges still need to be overcome before clinical applications are realized, such as establishing standard EV separation and purification procedures, determining the optimal dose, treatment timing, and infusion mode of EVs for use in humans, and confirming reliable criteria for evaluating the efficacy of EVs treatment. Future research is required to conduct additional clinical trials after determining EVs' safety and resolving other hindrances. This paper summarizes the potential application of EVs in various etiologies leading to AKI in recent years, emphasizing the excellent therapeutic value of MSCs-EVs. We are the first to summarize the application value of EVs in AKI caused by various etiologies, emphatically introducing IRI-AKI, S-AKI, and drug-induced AKI. Unfortunately, most studies focus on the therapeutic effect of MSCs-EVs on AKI, and few studies are exploring the functions of other sources of EVs in AKI.

In addition, the types of AKI we collected need to be more comprehensive. For some causes of AKI, such as contrast-induced AKI and burns/trauma-induced AKI, we do not find any studies related to EVs, although they are also common causes of AKI clinically. Overall, this paper emphasizes EVs' promising therapeutic and diagnostic potential as a clinical tool for AKI and underscores the need for further research in this domain. The clinical application of EVs is hoped to be realized soon, and the research based on EVs can find better diagnostic markers and provide the perfect treatment for AKI.

Author Contributions

We declare that all authors made substantial contributions to the study. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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