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Review

Urinary exosomes: Emerging biomarkers for urinary tract infection

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ABSTRACT

Urinary tract infections (UTIs) are among the most prevalent bacterial infections worldwide, often presenting diagnostic challenges owing to nonspecific symptoms and limitations of conventional biomarkers. Recent advances in EV research have highlighted urinary exosome nanosized vesicles secreted by renal and urothelial cells as promising noninvasive biomarkers for UTI detection and monitoring. These exosomes encapsulate a rich cargo of proteins, lipids, and nucleic acids reflective of the physiological and pathological state of the urinary tract. This review synthesizes current evidence on the diagnostic potential of urinary exosomes in UTIs, emphasizing their role in pathogen recognition, immune modulation, and inflammation signaling. We discuss emerging methodologies for exosome isolation and characterization and evaluate their clinical applicability in differentiating bacterial strains, predicting disease severity, and guiding antimicrobial therapy. By integrating molecular insights with translational perspectives, urinary exosomes may redefine the diagnostic landscape of UTIs and pave the way for precision urological care.

1. Introduction

Urinary tract infections (UTIs) represent a significant global health burden, affecting an estimated 150 million people annually [1]. These infections are the second most common type of infection globally and account for at least 11 million physician office visits and over 2 million emergency department visits in the United States each year. The economic impact of UTIs is substantial, with healthcare costs associated with UTIs in the US reaching approximately $2.3 billion annually [2]. Complicated UTIs (cUTIs), which occur in individuals with underlying urinary tract abnormalities or comorbidities, contribute to a large portion of this burden, leading to over 400,000 hospitalizations and costing between $340–$450 million annually in the U.S. alone [3]. The incidence of UTIs has increased by 60.40 %, from 252.25 million cases in 1990 to 404.61 million in 2019, with an associated increase in mortality from 98,590 deaths in 1990 to 236,790 in 2019 [1]. The demographic

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profile of UTI patients reveals a skewed distribution, with women being significantly more affected than men due to anatomical factors such as a shorter urethra and its proximity to the anus [4]. It is estimated that approximately half of all females will experience at least one UTI in their lifetime [5], and the prevalence in infants is 6.5 % in females compared with 3.3 % in males. However, UTIs are not exclusive to women; adult males are considered high risk, particularly after the age of 50, when the incidence increases [6]. Other key risk factors include advanced age, diabetes, pregnancy, catheter use, and conditions that obstruct urine flow, such as kidney stones or an enlarged prostate. For example, up to 80 % of nosocomial UTIs are catheter associated, and long-term catheterization can lead to polymicrobial bacteriuria in up to 95 % of cases. Recurrent UTIs, defined as two episodes in six months or three in a year, affect more than 20 % of patients and pose a particular challenge because of the formation of intracellular bacterial communities and quiescent reservoirs that evade standard diagnostic methods [2,7]. The current diagnostic paradigm for UTIs is centered on clinical evaluation, urinalysis, and urine culture. While useful, these conventional methods have significant limitations. Urine culture, often considered the gold standard, is notoriously slow, with results typically delayed by 2–3 days, contributing to empirical antibiotic use and subsequent antimicrobial resistance [8,9]. Furthermore, it lacks sensitivity and specificity, with a positivity threshold of >10^5 colony-forming units (CFU)/mL, which may lead to missed infections with lower bacterial loads or fastidious organisms [10]. This high threshold also fails to differentiate true symptomatic infection from asymptomatic bacteriuria (ASB), where bacteria are present in the urine without causing symptoms. Studies have shown that standard culture has a false-negative rate in up to 90 % of cases where molecular methods detect bacterial DNA. This diagnostic ambiguity leads to overtreatment, unnecessary antibiotic courses, and associated side effects. To address these shortcomings, researchers have focused on host-derived biomarkers that signal the presence of an active inflammatory response. Cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8) are promising candidates. IL-6 levels above 25 pg/mL can help distinguish symptomatic UTIs from ASBs in elderly patients, whereas an IL-8 concentration of 50 pg/mL is highly sensitive (97 %) for diagnosing UTIs in catheterized patients [11]. Other proteins, including neutrophil gelatinase-associated lipocalin (NGAL), lactoferrin (LF), heparin-binding protein (HBP), and myeloperoxidase (MPO), have also shown potential. For example, uNGAL has demonstrated 97.1 % sensitivity and 95.6 % specificity in children aged 3–24 months [12]. Despite their promise, a systematic review concluded that there is currently insufficient evidence to recommend any novel biomarker for routine clinical use, citing a lack of high-quality prospective studies and standardized thresholds [11]. This gap highlights the urgent need for more accurate, rapid, and specific diagnostic tools that can reliably distinguish infection from colonization, guide appropriate therapy, and monitor treatment response. This is precisely where urinary exosomes, which are nanosized vesicles that carry rich cargo of biological information, have emerged as powerful and promising frontiers in the fight against UTIs.

2. The biology and biogenesis of urinary exosomes

Exosomes are a class of extracellular vesicles (EVs) that play crucial roles in intercellular communication by transferring functional molecules between cells [13,14]. They are spherical, membrane-bound vesicles that typically range from 30 to 200 nm in diameter [15,16]. Their biogenesis originates within the cell from the endosomal system. The process begins with the inward budding of the plasma membrane to form early endosomes, which mature into multivesicular bodies (MVBs). During this maturation, portions of the endosomal membrane invaginate and form intraluminal vesicles (ILVs), which are then enclosed within the MVB [17]. The ultimate fate of the MVB is determined by its trafficking pathway: fusion with lysosomes leads to degradation of its contents, whereas fusion with the plasma membrane releases MVB ILVs into the extracellular space as exosomes. This intricate process is tightly regulated by a complex network of molecular machinery. Two primary pathways govern exosome biogenesis: the ESCRT-dependent pathway and the ESCRT-independent pathway [18]. The endosomal sorting complex required for transport (ESCRT) machinery, which is composed of sequential complexes (ESCRT-0 to ESCRT-III) and accessory proteins such as Vps4, recognizes ubiquitinated proteins on the endosomal membrane and facilitates the scission of the membrane to form ILVs [19]. An alternative pathway is driven by the lipid ceramide. The enzyme neutral sphingomyelinase 2 (nSMase2) converts sphingomyelin to ceramide, creating a curvature-inducing force that promotes membrane budding and exosome formation [20]. Tetraspanins, such as CD9, CD63, and CD81, are highly enriched in exosomes and organize into specialized domains called tetraspanin-enriched microdomains (TEMs), which facilitate cargo sorting and mediate interactions.

with other cells [21]. Rab family GTPases act as molecular switches that regulate the trafficking, docking, and fusion of MVBs with the plasma membrane, thereby controlling the final release of exosomes. For example, Rab27a and Rab27b are known to mediate MVB docking at the plasma membrane, whereas RAB11 regulates MVB transport of SNARE proteins, which form a complex that pulls. Finally, the fusion step itself is mediated by the vesicle and plasma membranes together for merger (Fig. 1). In the context of the urinary tract, exosomes are secreted by a variety of cell types throughout the nephron, including glomerular podocytes, proximal tubular cells, and renal collecting duct cells, as well as by the epithelial cells lining the bladder, ureters, prostate, and urethra [22]. This cellular origin provides a direct window into the physiological or pathological state of the urogenital system. Upon release, these vesicles travel through the renal tubules and the rest of the urinary tract, eventually becoming part of the urine sediment [23]. Owing to their protective lipid bilayer, urinary exosomes are remarkably stable and shield their internal cargo, primarily nucleic acids and proteins, from degradation by urinary RNases and proteases, making them ideal noninvasive biomarkers. A defining feature of exosomes is their distinct molecular composition. They are readily identified by a set of “general” marker proteins, primarily tetraspanins (CD9, CD63, and CD81), along with components of the endosomal sorting machinery, such as TSG101 and ALIX, and heat shock proteins (HSP70 and HSP90) [24]. The specific identity of an exosome can be further refined by its tissue of origin; for example, podocyte-derived exosomes carry podocin, whereas proximal tubular cell exosomes contain megalin and aquaporin-1. The cargo they carry reflects their parent cell’s state. The proteome of total urine includes over 3000 proteins, with approximately 0.6 % to 3 % of the total urinary protein content being associated with the EV fraction 17. The RNA cargo is predominantly noncoding, with microRNAs (miRNAs) constituting more than 42 % of the raw reads in exosomal RNA [25]. Other abundant cargoes include messenger RNAs (mRNAs), long noncoding RNAs (lncRNAs), and various lipids, including cholesterol and ceramide. This diverse and dynamic cargo allows exosomes to serve as sophisticated messengers capable of modulating immune responses, influencing cell behavior, and reflecting the health status of their tissue of origin. This unique biology makes urinary exosomes a treasure trove of information. They are not merely passive debris but also actively secreted vesicles containing a snapshot of gene expression, protein activity, and the metabolic state of their parent cells [26]. Understanding their biogenesis and composition is therefore fundamental to harnessing their potential as diagnostic and prognostic tools for UTIs.

3. Mechanisms of uropathogen interaction with host cells via exosomes

The pathophysiology of UTIs involves a complex interplay between invading uropathogens, particularly UPEC, and the host’s innate immune system, with exosomes emerging as critical players in this dynamic process. The initial event in UTI pathogenesis is the attachment of UPEC to the bladder urothelium. UPEC utilizes surface adhesins, such as

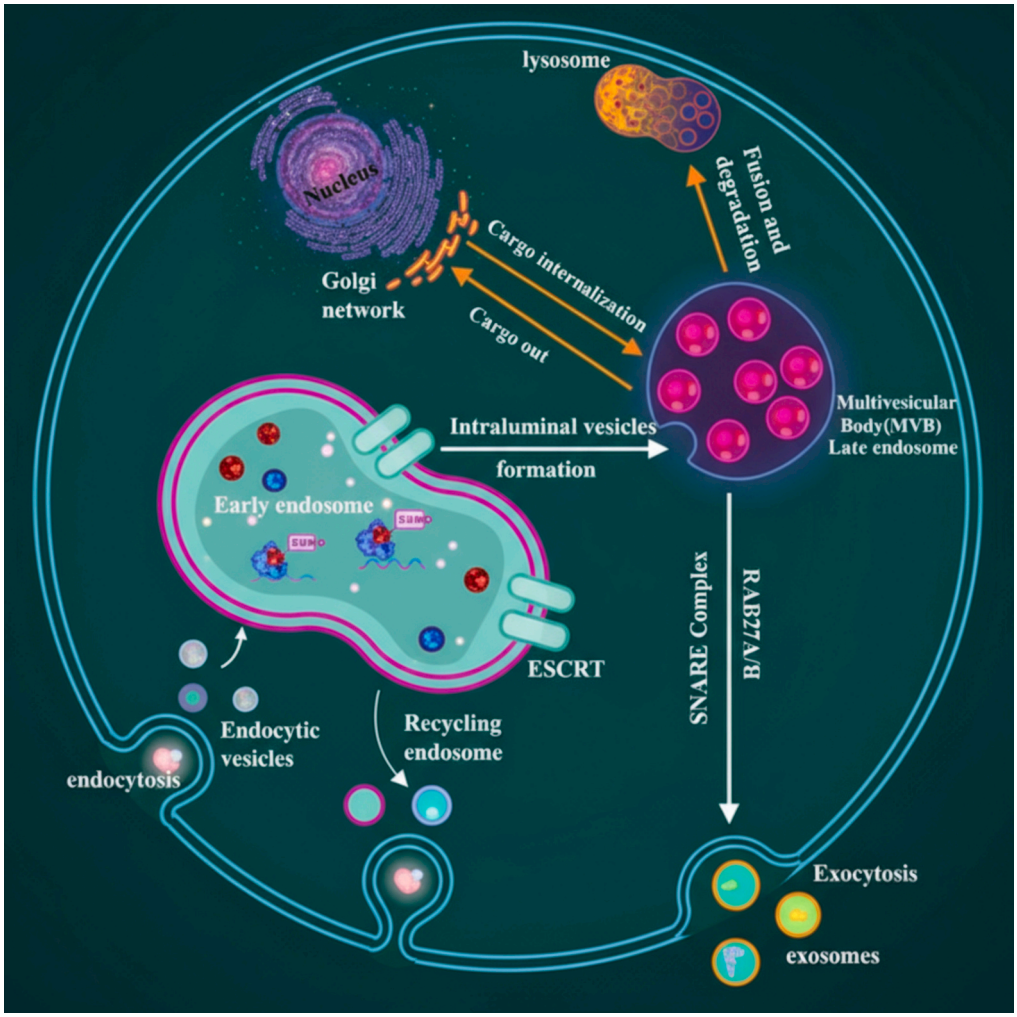

Fig. 1. Intracellular trafficking and processing of vesicles in a eukaryotic cell. The diagram illustrates the endocytic pathway and the formation and fate of multivesicular bodies (MVBs). Endocytic vesicles internalize cargo from the plasma membrane and deliver it to the early endosome, where sorting decisions are made. Cargo destined for degradation is incorporated into intraluminal vesicles via the ESCRT complex, where it forms MVBs. These MVBs either fuse with lysosomes for cargo degradation or undergo exocytosis to release exosomes. Recycling endosomes return selected cargo to the plasma membrane.

type 1 fimbriae containing the FimH lectin, to bind to glycoproteins such as uroplakin on the apical surface of umbrella cells [27,28]. This interaction triggers a robust intracellular signaling cascade, primarily through Toll-like receptor 4 (TLR4), which recognizes bacterial lipopolysaccharide (LPS) [29]. The activation of TLR4 in bladder epithelial cells initiates a defense program involving the production of proinflammatory cytokines (IL-6 and IL-8), chemokines (SDF-1 and CX3CL1), and antimicrobial peptides (AMPs). Neutrophils are rapidly recruited to the site of infection, guided by chemokine gradients, and work to phagocytose and kill invading bacteria. However, UPEC has evolved sophisticated countermeasures. One of the most elegant strategies involves manipulating the host's own vesicular trafficking system. Research has shown that UPEC infection induces bladder epithelial cells to secrete an increased number of exosomes [30]. These UPEC-induced exosomes are loaded with specific cargo, most notably the microRNA miR-18a-5p. When these exosomes are taken up by macrophages, the delivered miR-18a-5p targets the tumor suppressor gene PTEN, activating downstream MAPK/JNK signaling pathways. This activation paradoxically impairs the ability of macrophages to combat infection. It reduces their phagocytic activity, increases their production of the proinflammatory cytokine TNFα, and enhances their apoptosis. Consequently, in a mouse model of cystitis, the administration of these UPEC-induced exosomes exacerbated inflammation and tissue damage, while inhibiting their secretion with GW4869 or neutralizing TNFα with an antibody reduced both the bacterial burden and inflammation [30]. This finding highlights the fascinating hijacking of the host's natural exosome secretion machinery by UPEC to create a more permissive environment for its survival and proliferation. Another study revealed that exosomes isolated from the urine of UTI patients had significantly higher levels of the signaling molecule Akt than those from healthy controls did, suggesting that the Akt signaling pathway is activated during infection [31]. In addition to their pro-pathogenic role, exosomes also function as components of the host's innate immune defense. Human urinary exosomes possess potent antibacterial properties, effectively inhibiting the growth and inducing lysis of both pathogenic and commensal *E. coli*, a function dependent on their structural integrity and optimal at the acidic pH of urine [32,33]. These exosomes are enriched with antimicrobial proteins, including lysozyme C and myeloperoxidase (MPO), which are capable of bacterial lysis [34]. Further research has revealed that exosomes containing antimicrobial peptides such as cathelicidin-37 (LL-37) and beta-defensin 2 (HBD2), which are released from intestinal epithelial cells upon *Cryptosporidium* infection, directly bind to and reduce the infectivity of pathogens [35]. These findings suggest that epithelial cells can load exosomes with effector molecules as a first line of defense. The table below contrasts these opposing roles. Furthermore, UPEC employs a virulence factor, TcpC, which acts as a TIR domain-containing protein that mimics a host adaptor protein (MyD88) to disrupt TLR4 signaling, effectively dampening the host's

initial immune alarm. This highlights the evolutionary pressure on pathogens to evade detection. Interestingly, some host defense mechanisms involve exosomes. Pyroptosis, a lytic form of programmed cell death, is induced in bladder cells during UPEC infection. Exosomes released from these dying cells carry proinflammatory signals such as IL-1β and IL-18, which recruit mast cells. These recruited mast cells then release tryptase, which degrades tight junction proteins such as ZO-1, disrupting the urothelial barrier and facilitating the expulsion of infected cells [36]. These findings demonstrate a dual role for exosomes in both promoting inflammation and facilitating host defense through cell turnover. The intricate dance between UPEC and the host's exosome-mediated communication underscores their central role in UTI pathogenesis, positioning them as invaluable tools for understanding disease progression and therapeutic interventions.

4. Exosomal cargo reflecting UTI pathophysiology

The cargo contained within urinary exosomes serves as a dynamic record of the ongoing battle between uropathogens and the host immune system. The changes in this cargo provide a wealth of information that can be leveraged as biomarkers for UTIs. The analysis of exosomal content can be broadly categorized into protein and nucleic acid analyses, each offering unique insights into different facets of the disease. Protein cargo is a key indicator of cellular stress, inflammation, and signaling pathway activation. As previously discussed, the Akt signaling pathway is a prominent target for manipulation by UPEC-infected cells. Exosomes derived from these cells exhibit elevated levels of phosphorylated Akt, a reliable marker that distinguishes UTIs from asymptomatic bacteriuria. Similarly, the exosomal marker protein CD9 was found to be significantly increased in UTI patients, providing another potential diagnostic anchor point [31]. In addition to these specific markers, a broader analysis of the exosomal proteome would likely reveal a signature of acute inflammation, potentially including complement proteins, acute-phase reactants, and fragments of structural proteins indicative of tissue damage. The stability of proteins within the protected exosomal compartment makes them excellent candidates for detection in spot urine samples. The identification of specific protein signatures could lead to rapid, point-of-care tests analogous to those used for cardiac troponins. The most extensively studied cargo in the context of UTI is the nucleic acid content, particularly that of microRNAs (miRNAs). MiRNAs are small noncoding RNAs that regulate gene expression posttranscriptionally. In the context of UPEC infection, a specific miRNA, miR-18a-5p, is selectively packaged into exosomes. As detailed earlier, this miRNA is exported from bladder epithelial cells and delivered to macrophages, where it impairs their function, thereby facilitating bacterial persistence. The finding that urinary exosomal miR-18a-5p levels are significantly higher in UTI patients than in healthy controls suggests that urinary exosomal miR-18a-5p is a strong candidate for a UTI-specific diagnostic test [30]. Other miRNAs have been implicated in related renal inflammatory conditions, and their presence in the urinary exosome pool suggests that they could also be relevant in UTI. For example, miR-21 is a known promoter of fibrosis and was found to be upregulated in renal cells during hypertensive kidney injury, preceding traditional markers of kidney damage [37,38]. Given that pyelonephritis involves renal parenchymal involvement, urinary exosomal miR-21 could serve as a biomarker for the progression to a complicated infection. A panel of miR-21, miR-150, and miR-29c was previously identified to predict renal fibrosis in patients with lupus nephritis, highlighting the power of multimiRNA panels 27. A similar strategy could be employed to identify a panel of miRNAs that specifically characterize the unique inflammatory milieu of a UTI. The mechanistic link between exosomal cargo and UTI pathogenesis is increasingly clear. The transfer of miR-18a-5p represents a direct mechanism of immunomodulation by the pathogen. Conversely, the release of exosomes carrying antimicrobial peptides is a host-driven defense mechanism [35,39]. Other nucleic acids, such as lncRNAs and mRNAs, constitute a significant portion of the exosomal cargo and reflect the transcriptional response to infection. Analyzing these larger transcripts could provide a comprehensive view of the host's gene expression profile in response to UPEC. The stability of nucleic acids within the exosomal membrane is a major advantage over free-floating biomolecules in urine, ensuring that the cargo remains intact and delivers a clear signal [40]. The integration of proteomic and transcriptomic data from urinary exosomes promises to create a multidimensional picture of UTI pathology, capturing both the host's response and the pathogen's manipulative tactics.

5. Diagnostic potential of urinary Exos in the treatment of urinary tract infections

The unique properties of the abundance of urinary exosomes in urine, their stability, and their direct reflection of urogenital tract pathology position them as ideal candidates for revolutionizing UTI diagnostics. The primary advantage of using exosomes over conventional methods is their ability to provide a more specific signal of active disease. Standard urine culture can detect the presence of bacteria but cannot distinguish a clinically significant infection from simple colonization (asymptomatic bacteriuria). Similarly, dipstick tests for nitrite and leukocyte esterase are insensitive and nonspecific [1,2]. Exosomes, however, encapsulate proteins and nucleic acids that are products of the host's inflammatory response, offering a direct measure of the host–pathogen interaction. This distinction is paramount for guiding appropriate antibiotic use and combating antimicrobial resistance. The most compelling evidence for the diagnostic utility of exosomes lies in their ability to differentiate UTIs from asymptomatic bacteriuria (ABU). A landmark study demonstrated that urinary exosomes from UTI patients had significantly higher levels of the signaling molecule Akt and the general exosomal marker CD9 than did exosomes from ABU patients. Critically, this difference was maintained even after normalization to urine creatinine, addressing a major source of variability in urinary tests [31,41]. This finding is significant because ABU, characterized by the presence of bacteria without symptoms, does not require treatment; however, it is difficult to distinguish from uncomplicated UTI. The differential exosome signature offers a new way to make this critical distinction. Furthermore, the study revealed that Akt levels in exosomes from UTI patients decreased significantly following effective antimicrobial therapy, indicating that this exosome-based assay could be used to monitor treatment response in a manner completely absent from standard culture-based diagnostics. The discovery of exosomal miR-18a-5p as a sensitive and specific biomarker in a small cohort of UTI patients reinforces its potential. The ability to detect this miRNA in urine from UTI patients suggests that exosome-based liquid biopsies could replace invasive procedures and provide a precise diagnosis in hours rather than days. While the use of exosomes themselves is nascent, the principle of using their cargo for diagnosis has been validated by the success of other urinary biomarkers. For example, neutrophil gelatinase-associated lipocalin (NGAL) is a highly sensitive and specific marker for UTI, with a panel of NGAL, interleukin-1β, and interleukin-8 achieving 84 % sensitivity and 91 % specificity in a large cohort of older adults [42]. Similarly, the myeloperoxidase-to-creatinine ratio has shown 66 % sensitivity and 95 % specificity for UTIs. The analytical performance of exosome-based tests is poised to reach or exceed these metrics. The stability of the exosomal cargo means that a single, stable sample can be analyzed for multiple markers simultaneously, enabling the development of multimarker panels that capture the multifaceted nature of the inflammatory response. For example, a panel of exosomal proteins, such as Akt and CD9, and possibly other proteins, such as myeloperoxidase (MPO), could provide a highly accurate diagnostic tool. The analytical validation of exosomal miR-18a-5p in a small patient cohort is a crucial first step toward developing a rapid, quantitative PCR-based assay for UTI [30]. Such a test could be integrated into point-of-care platforms, allowing for immediate diagnosis in a clinical setting and eliminating

the delays associated with current standards. The potential to move beyond simple binary diagnosis to a nuanced understanding of infection severity or stage is also promising. For example, the level of exosomal sTLR4 has been proposed as a marker to differentiate cystitis from pyelonephritis, a critical distinction for determining the severity of illness. By providing a real-time readout of the host's response, exosome-based diagnostics could offer a more accurate and timely assessment of UTIs, moving the field away from culture-dependent paradigms toward a more mechanistically informative approach. The future of UTI diagnostics appears to lie in multiplexed assays that combine these different classes of biomarkers. An ideal test might integrate a panel of exosomal proteins (e.g., Akt and CD9) to confirm active infection with high specificity alongside a panel of free urinary metabolites (e.g., the acetate/creatinine ratio) to provide a rapid, cost-effective screen. This multimodal approach leverages the strengths of each biomarker type, resulting in a highly accurate and robust diagnostic platform. The successful translation of exosome-based testing for prostate cancer, such as the EPI test, serves as a powerful precedent for the clinical viability of this technology [41]. The journey from laboratory findings to clinical application is underway, with companies collaborating on manufacturing and researchers developing novel isolation and detection technologies, heralding a new era in infectious disease diagnostics.

6. Urinary exosomes: emerging biomarkers for diseases of the urinary system

Urinary exosomes, small extracellular vesicles released from cells lining the urinary tract and kidney, have emerged as potent noninvasive biomarkers for a broad spectrum of urinary diseases. Their unique molecular cargo, which encompasses proteins, nucleic acids, and lipids, reflects the physiological and pathological status of the cells of origin and signifies dynamic biological processes throughout renal and urothelial tissues [43]. Isolation of urinary exosomes has become increasingly feasible, utilizing techniques such as ultracentrifugation, size-exclusion chromatography, and affinity capture methods. Exosomes isolated from urine are ideal for biomarker discovery, as urine can be collected easily, serially, and without risk or discomfort to the patient. The lipid bilayer of exosomes shields fragile biomolecules from enzymatic degradation in urine, offering stability and reliability for downstream analyses [44]. The diagnostic potential of urinary exosomes is evident in kidney disease. In diabetic nephropathy, exosomal microRNAs such as miR-192 and miR-136–5p, as well as proteins such as nephrin and podocin, strongly correlate with disease severity and glomerular injury. In acute kidney injury (AKI) and drug-induced nephrotoxicity, early exosomal changes precede conventional biomarkers such as serum creatinine, allowing more timely interventions. Studies have demonstrated increased levels of aquaporin-2 and NGAL (neutrophil gelatinase-associated lipocalin) in urinary exosomes during early kidney damage, which aligns with histopathological findings [45]. Within urological cancers, urinary exosomes provide valuable molecular information. Meta-analyses have shown that the diagnostic accuracy of urinary exosome-based tests for bladder and prostate cancers is superior to that of many traditional methods, with area under the curve (AUC) values frequently exceeding 0.9, sensitivities up to 83 %, and specificities of 88 %. Exosomal cargo, including survivin, EDIL3, PCA3, and the TMPRSS2-ERG fusion transcript, has demonstrated remarkable discriminative power for early cancer detection, risk stratification, and recurrence monitoring. Furthermore, in renal cell carcinoma (RCC), proteins such as carbonic anhydrase IX and CD147 detected in urinary exosomes reflect alterations in the tumor microenvironment and offer promising avenues for noninvasive diagnosis [46]. Urinary exosomes are increasingly recognized as dynamic indicators of other renal and urinary tract disorders. For chronic kidney disease (CKD), exosomal panels enriched with fibrotic pathway proteins and complement factors provide insight into disease activity and progression. In inflammatory diseases such as lupus nephritis or interstitial cystitis, altered exosomal composition reveals underlying immune or fibrotic processes. Likewise, in kidney transplantation, donor-derived exosomal markers can indicate early graft rejection, guiding clinical management [47]. Despite their promise, the translation of urinary exosomes to routine clinical practice faces hurdles. Standardization of isolation, quantification, and normalization protocols is urgently needed. Variables such as urine dilution, timing of collection, and patient hydration can influence exosomal yield and composition. Large, multicenter validation studies are needed to define the specificity, reproducibility, and real-world value of urinary exosome biomarkers across diverse populations. Urinary exosomes encapsulate disease-specific molecular signatures and exhibit extraordinary promise for early diagnosis, prognosis, and treatment monitoring in urinary system diseases. As technological advances and rigorous validation studies unfold, urinary exosome analysis could revolutionize the landscape of noninvasive diagnostics in nephrology and urology (Table 1).

7. Therapeutic and prognostic implications of urinary exosomes

In addition to their diagnostic utility, urinary exosomes and engineered stem cell-derived exosomes hold profound therapeutic and prognostic potential, opening new avenues for managing UTIs and their complications. The prognostic value of exosomes extends to predict disease progression and recurrence. The ability of exosomes to carry specific miRNA profiles reflecting the state of the urogenital tract can be harnoted to predict outcomes. For example, in chronic kidney diseases, exosomal miRNA signatures are correlated with histopathological features such as renal fibrosis and tubular atrophy and have been used to predict progression to end-stage renal disease [68,69]. Applying this concept to UTIs, it may be possible to develop exosomal signatures that predict which patients with an initial infection are at high risk for developing recurrent UTIs, pyelonephritis, or long-term renal scarring. In children, renal scarring after acute pyelonephritis is a major concern, and factors such as age (>12 months) and high-grade vesicoureteral reflux are known risk factors [70]. Future studies could correlate exosomal profiles with these risk factors to stratify pediatric patients and tailor surveillance and intervention accordingly. The therapeutic applications of exosomes, particularly those derived from mesenchymal stem cells (MSC-Exos), represent a paradigm shift from fighting infection to modulating the host response to infection. In the context of cUTIs, the goal is not only to eradicate the pathogen but also to control the overwhelming inflammation that causes significant tissue damage and contributes to symptoms. MSC-Exos are perfectly suited for this task. They can be loaded with anti-inflammatory miRNAs, such as miR-146a, which downregulates TLR4/NF-κB signaling in macrophages, thereby reducing the production of proinflammatory cytokines. They can also polarize macrophages toward an anti-inflammatory M2 phenotype via miR-21-5p, a key step in resolving inflammation. Furthermore, MSC-Exos can inhibit the formation of neutrophil extracellular traps (NETs), which, while effective at trapping bacteria, can also cause collateral tissue damage e [71]. This immunomodulatory capacity makes them powerful therapeutic agents to mitigate the destructive phase of UTI. In addition to promoting inflammation, MSC-Exos promote tissue repair. They activate key regenerative pathways, such as the Wnt/β-catenin and ERK/AKT pathways, in urothelial cells, accelerating wound healing and regeneration of the damaged bladder lining [71]. Engineered exosomes can also deliver drugs directly to the site of infection. Loading of exosomes with antibiotics such as vancomycin has been shown to increase their ability to penetrate and disrupt bacterial biofilms, a major contributor to chronic and catheter-associated infections [71]. This targeted drug delivery system could overcome antibiotic resistance and improve therapeutic efficacy. Perhaps the most innovative therapeutic application is the use of exosomes as decoys to protect the host. UPEC produces cytotoxic necrotizing factor type 1 (CNF1), an exoenzyme that inactivates the host's innate immune response. Exosomes can be engineered to express receptors that bind to such toxins, effectively

Table 1
Urinary exosome biomarkers in kidney and urinary diseases.

Disease	Biomarker Type	Key Markers/Cargoes	Diagnostic Insight/Role	References
Acute Kidney Injury	Protein	Fetuin-A	Elevated in ICU patients with AKI; early diagnostic marker	[48]
Acute Kidney Injury	Protein	ATF3, WT1	ATF3 for tubular injury; WT1 for podocyte damage	[49]
Acute Kidney Injury	Protein	AQP1	Decreased postischemia; recovers over time	[50]
Acute Kidney Injury	Protein	AQP2	Altered in gentamicin-induced collecting duct injury	[51]
Acute Kidney Injury	Protein	Complement C3/C4, fibrinogen, galectin-3 BP, etc.	Inflammatory protein upregulation in vancomycin-induced AKI	[52]
Acute Kidney Injury	Protein	CD26	Prognostic marker for AKI recovery	[53]
Acute Kidney Injury	Protein	NGAL	Prognostic marker postrenal transplantation	[54]
Acute Kidney Injury	mRNA	Cystatin C	Reflects kidney tissue injury; elevated in UEs	[55]
Acute Kidney Injury	miRNA	miR-21	Correlates with leukocyte count and GFR in scrub typhus AKI	[56]
Acute Kidney Injury	miRNA	miR-16, miR-24, miR-200c	Upregulated during injury; linked to glomerular medulla mRNA suppression	[57]
Renal Fibrosis	Protein	TGF-β1, E-cadherin, N-cadherin, L1CAM	TGF-β1 correlates with fibrosis; cadherins altered in obstruction	[58]
Renal Fibrosis	mRNA	CD2AP	Negatively correlated with proteinuria and fibrosis severity	[59]
Renal Fibrosis	miRNA	miR-29, miR-200 family	Downregulated in CKD; potential noninvasive fibrosis markers	[60]
Renal Fibrosis	miRNA	miR-29c	Declines with fibrosis progression	[61]
Renal Fibrosis	miRNA	miR-200b	Strongly reduced in advanced fibrosis and IgAN/DKD	[62]
Diabetic Nephropathy	Protein	AMBP, MLL3, VDAC1	Differentially expressed in DN patients; early diagnostic potential	[63]
Diabetic Nephropathy	Protein	WT1	Detected in majority of DN patients; rare in healthy controls	[64]
Diabetic Nephropathy	Protein	PEPD, MUP1	PEPD upregulated; MUP1 downregulated in diabetic rats	[65]
Diabetic Nephropathy	Protein	Regucalcin	Downregulated in DN; reflects kidney tissue damage	[66]
Diabetic Nephropathy	miRNA	miR-145	Enriched in normoalbuminuric DM1 patients	[67]

neutralizing them before they can harm host cells. Another strategy involves coating medical devices. Urinary catheters are a primary source of CAUTIs. Coating these devices with exosomes or using exosome-inspired nanoplatforms could prevent bacterial adhesion and biofilm formation. For example, polydopamine-exosome hybrids have been explored as antimicrobial agents that combine the biocompatibility of exosomes with the inherent antimicrobial properties of the polymer PDA. While direct evidence in cUTI animal models is still lacking, preclinical data from other inflammatory conditions are highly promising [71]. By simultaneously delivering anti-inflammatory cargo and promoting tissue repair, exosome-based therapies could transform the management of severe UTIs, reducing morbidity and improving long-term outcomes, especially in vulnerable populations such as elderly individuals or those with recurrent infections. The dual role of exosomes as both harbingers of disease and potential therapeutic agents makes them a uniquely powerful tool in the clinical armamentarium against UTIs.

8. Technical challenges and the path to clinical translation

Despite the immense promise of urinary exosomes as biomarkers and therapeutics, several significant technical hurdles must be overcome to translate these discoveries into routine clinical practice. The most critical and widely cited challenge is the lack of standardized protocols for exosome isolation and characterization. The "gold standard," ultracentrifugation, is a time-consuming process that requires expensive equipment and often yields variable purity and yield. Contaminants such as protein aggregates, lipoproteins, and coisolated larger vesicles can confound downstream analyses. Alternative methods such as precipitation (e.g., ExoQuick™) are faster but can introduce polymer contamination and result in lower purity [72,73]. Emerging techniques such as size-exclusion chromatography, immunoaffinity capture, and microfluidic systems show great promise because they offer higher purity, speed, and automation potential, but they are not yet universally adopted. The International Society for Extracellular Vesicles (ISEV) has published the MISEV2018 guidelines to encourage rigorous reporting of methods, including details on particle size, concentration, and the presence of positive (e.g., CD9, CD63) and negative (e.g., nuclear or mitochondrial markers) controls [19,74]. Adherence to these guidelines is essential for generating comparable, reproducible data across different laboratories. Another major challenge is the standardization of sample collection, processing, and storage. Factors such as time to centrifugation, temperature fluctuations during transport, and repeated freeze–thaw cycles can affect the quantity and quality of exosomes. Multiple contaminants, including blood cells from hematuria, bacteria, and large glycoproteins such as uromodulin (Tamm-Horsfall protein), can interfere with exosome analysis. The ISEV Urine Task Force recommends rapid processing of urine samples on ice, cold storage at −70 °C or colder, and the use of protease inhibitors to preserve exosome integrity. The normalization of exosome concentrations for analysis is also a contentious area. While the use of substances such as urinary creatinine is common, this method can be misleading in states of altered glomerular filtration. More robust approaches, such as normalization to the total exosome number, are technically challenging but necessary for accurate longitudinal tracking of biomarkers [75]. Finally, the leap from a research tool to a clinically approved diagnostic requires extensive validation in large, prospective clinical trials. Most of the exciting findings regarding exosomal biomarkers for UTIs are based on small, retrospective cohorts. To be clinically useful, these markers must be validated in diverse populations, including children, pregnant women, and immunocompromised individuals. The clinical context is also critical. The same exosomal signature may look different in simple cystitis versus severe pyelonephritis or CAUTI. The successful implementation of exosome-based diagnostics will depend on navigating these complexities. This includes optimizing scalable and cost-effective isolation methods, establishing clear clinical guidelines for sample handling, and conducting head–to–head comparisons with existing and emerging technologies such as metagenomic next-generation sequencing (mNGS). The latter can identify the causative pathogen, but it does not capture the host's response. A truly transformative diagnostic will likely integrate both pathogen detection and host–response profiling. The development of integrated microfluidic biosensors that can perform both tasks simultaneously represents the ultimate goal. As seen with the approval of the ExoDx Prostate IntelliScore (EPI) test, which analyzes

exosomal RNA from urine sediments to avoid unnecessary biopsies, the path to clinical adoption is feasible with rigorous science and strategic collaboration between clinicians, engineers, and regulatory bodies [41]. The future of UTI management hinges on overcoming these technical bottlenecks to deliver reliable, rapid, and insightful exosome-based tests that can be seamlessly incorporated into clinical workflows.

9. Conclusion

Urinary exosomes represent a transformative frontier in the noninvasive diagnosis and monitoring of urinary tract infections. Their molecular cargo offers a dynamic snapshot of host–pathogen interactions, immune responses, and epithelial integrity within the urinary tract. As isolation and profiling technologies advance, exosome-based diagnostics may overcome the limitations of conventional urine tests, enabling earlier detection, pathogen-specific stratification, and personalized therapeutic guidance. Integrating urinary exosome analysis into clinical workflows holds promise for enhancing diagnostic precision and improving patient outcomes in urological infectious diseases.

Availability of data and material

Not applicable.

CRediT authorship contribution statement

Narbaev Zafar: Writing – original draft, Project administration, Methodology, Investigation, Conceptualization. **Umurzoqov Dilmurod:** Writing – original draft, Visualization, Methodology, Investigation. **Islom Kadirov:** Writing – original draft, Methodology, Investigation. **Eshchanova Gulbakhor:** Writing – original draft, Methodology, Investigation. **Sidikov Akmal:** Writing – original draft, Methodology, Investigation. **Gulomova Gulnora:** Writing – original draft, Methodology, Investigation. **Sharipov Rustam:** Writing – original draft, Methodology, Investigation. **Tadjibaeva Muyassar Karimbaevna:** Writing – original draft, Methodology, Investigation. **Ravshan Usmanov:** Writing – original draft, Methodology, Investigation. **Malokhat Abdukadirova:** Writing – original draft, Methodology, Investigation. **Makhbuba Ruzieva:** Writing – original draft, Methodology, Investigation. **Gavkhar Khudoyarova:** Writing – original draft, Methodology, Investigation. **Alisher Ishankulov:** Writing – original draft, Methodology, Investigation.

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Data availability

No data was used for the research described in the article.

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