

Supplemental Material

Supplemental Table 1. Promising Biomarkers of Kidney Disease in Urinary EVs

Supplemental Table 2. Circulating EVs as Biomarkers in Kidney Disease

Supplemental Table 1. Promising Biomarkers of Kidney Disease in Urinary EVs

Biomarker		Origin	Isolation method	Disease	Source
EV type	Increased pEVs	Human	Total Exosome Isolation Reagent (Invitrogen)	Podocyte and early glomerular damage in hypertension	Kwon et al, ¹ 2017
	Increased p16 ⁺ EVs	Human	Total Exosome Isolation Reagent	Proximal tubular cellular senescence in hypertension	Santelli et al, ² 2019
	Increased pEVs	Swine; human	Total Exosome Isolation Reagent	Podocyte injury in MetS-related kidney disease	Zhang et al, ³ 2019
	Decreased urinary CD133 ⁺ EVs	Human	Ultra-centrifugation, filtration	Transplant recipients with slow graft function and vascular damage	Dimuccio et al, ⁴ 2014
	Increased urinary podocin ⁺ to nephrin ⁺ EVs ratio	Human	Direct analysis without EV isolation	Kidney injury in preeclampsia	Gilani et al, ⁵ 2017
	Decreased density of EVs	Human	Ultracentrifugation	Kidney function in patients with diabetes	Kaminska et al, ⁶ 2016

	Increased podocalyxin ⁺ micro-particles	Mice	Ultracentrifugation	Glomerular injury in DKD	Burger et al, ⁷ 2014
	Increased podocyte-released migrasomes	Human; mice	Sequential centrifugation, filtration	DKD	Liu et al, ⁸ 2020
	Increased annexin V ⁺ podocalyxin ⁺ micro-particles	Human	Ultracentrifugation	LN	Lu et al, ⁹ 2019
EV protein	Increased α_1 -antitrypsin	Human	Ultracentrifugation	DKD	Ning et al, ¹⁰ 2020
	Increased ELF3	Human	Sequential centrifugation	Podocyte injuries in DKD	Sakurai et al, ¹¹ 2019
	Decreased regucalcin	Human; rat	Ultracentrifugation in combination with DTT	DKD	Zubiri et al, ¹² 2015
	Increased dipeptidyl peptidase-IV	Human	Immunoprecipitation	Increased UACR in DKD	Sun et al, ¹³ 2012
	Increased uromodulin	Human	Filtration	DKD	Lou et al, ¹⁴ 2017

Increased CD3	Human	Ultracentrifugation	Kidney transplant rejection	Park et al, ¹⁵ 2017
Phosphoenolpyruvate carboxy-kinase	Human	Ultracentrifuga- tion, size exclusion chromatography	GFR after kidney transplant	Braun et al, ¹⁶ 2020
Decreased AQP2	Human	Ultracentrifugation	Acute disturbance in water homeostasis after kidney transplant	Oshikawa- Hori et al, ¹⁷ 2019
Increased NGAL	Human	Ultracentrifugation	Delayed graft function after kidney transplant	Alvarez et al, ¹⁸ 2013
Increased CP, MMP9, PODXL, CAIX, DKK4 Decreased CD10, EMMPRIN, DPEP1, syntenin1, AQP1	Human	Ultracentrifugation	RCC	Raimondo et al, ¹⁹ 2013
Increased periplakin, envoplakin, villin-1, C3, C9	Human	Ultracentrifugation	Autosomal dominant PKD	Salih et al, ²⁰ 2016

Decreased AQP-2 Increased APO-A1	Human	Double sucrose cushion ultracentrifugation	Impaired concentrating capability and decreased GFR in PKD	Pocsfalvi et al, ²¹ 2015
Decreased PC1:TMEM2 or PC2:TMEM2 ratio	Human	Ultracentrifugation	PKD	Hogan et al, ²² 2015
Decreased aquaporin-2	Rat	Sequential centrifugation	Cisplatin-induced kidney injury	Sonoda et al, ²³ 2019
Increased GluAp	Rat	Sequential centrifugation	Cisplatin-induced kidney injury	Quesada et al, ²⁴ 2017
Increased PTC-EMPs	Human	Total Exosome Isolation Reagent	Hypertensive micro-circulation kidney injury	Sun et al, ²⁵ 2018
Increased α_1 -antitrypsin, cerulo-plasmin Decreased amino-peptidase N, vasorin precursor	Human	Sucrose cushion ultracentrifugation	IgA nephropathy	Moon et al, ²⁶ 2011

Increased vasorin precursor	Human	Sucrose cushion ultracentrifugation	Thin basement membrane nephropathy	Moon et al, ²⁶ 2011
Increased TGF- β , L1CAM Decreased E-cadherin, N-cadherin	Human	Sequential centrifugation	Obstructive nephropathy	Trnka et al, ²⁷ 2012
Increased uroplakins and plakins	Human	Size exclusion chromatography	Calcineurin inhibitor-induced fibrosis of kidney	Carreras-Planella et al, ²⁸ 2020
Decreased CD133	Human	Filtration, ultracentrifugation	Acute and chronic glomerular damage	Dimuccio et al, ²⁹ 2020
Decreased β_1 subunit of V-ATPase	Human	Sucrose cushion ultracentrifugation	Distal tubular acidosis	Pathare et al, ³⁰ 2018
Increased osteoprotegerin	Human	Sucrose cushion ultracentrifugation with DTT	CKD	Benito-Martin et al, ³¹ 2013

	Increased cerulo-plasmin	Human; rat	Ultracentrifugation with DTT	Nondiabetic CKD	Gudehithlu et al, ³² 2019
	Increased podocin to nephrin ratio	Rat	Ultracentrifugation	Zucker diabetic fatty rats and PAN nephritis	Fujitaka et al, ³³ 2021
	Decreased AQP1, AQP2	Rat	Sequential centrifugation	IRI	Asvapromtada et al, ³⁴ 2018
	Increased caveolin-2	Rat	Ultracentrifugation	Bilateral ureteral obstruction and mercuric chloride-induced AKI	Bulacio et al, ³⁵ 2019
EV RNA	Increased miR-4534	Human	Exosome Isolation Kit (System Biosciences, LLC)	DKD	Zhao et al, ³⁶ 2020
	Increased miR-451-5p	Rat	Sequential centrifugation	DKD	Mohan et al, ³⁷ 2016
	Increased miR-362-3p, miR-877-3p, miR-150- 5p Decreased miR-15a-5p	Human	Sequential centrifugation	DKD	Xie et al, ³⁸ 2017

Increased miR-192	Human	Sequential centrifugation	Early-stage DKD	Jia et al, ³⁹ 2016
Increased miR-15b, miR-34a, miR-636	Human	Ultracentrifugation	DKD	Eissa et al, ⁴⁰ 2016
Increased miR-21-5p Decreased miR-30b-5p	Human	miRCURY Exosome Kit (Qiagen)	DKD	Zang et al, ⁴¹ 2019
Increased uromodulin mRNA	Human	EV collection tubes (Hitachi Chemical Diagnostics, Inc [now Minaris Medical America, Inc])	DKD	Yamamoto et al, ⁴² 2018
Increased WT1 mRNA	Human	Sucrose cushion ultracentrifugation	DKD	Abe et al, ⁴³ 2018
Increased mRNA of BMP7, CXCL14,	Human	EXOPRO Urine Clinical Sample	Transplant rejection	El Fekih et al, ⁴⁴ 2021

	CXCL11, B2M, IL32, C3, CD74, CD44, IFNAR2		Concentrator Kit (Exosome Diagnostics)		
	Increased miR-155-5p Decreased miR-223-3p, miR-1228-3p	Human	Filtration	Effect of tacrolimus therapy in kidney transplant	Freitas et al, ⁴⁵ 2020
	Increased BKV-miR-B1- 5p, bkv-miR-B1- 5p/miR-16	Human	Isolation of exosomal RNA from urine (exoRNeasy Serum/Plasma Midi Kits; QIAGEN)	BKV nephropathy in kidney transplant recipients	Kim et al, ⁴⁶ 2017
	Increased miR-21, miR- 150 Decreased miR-29c	Human	miRCURY Exosome Isolation Kit (Exiqon)	Kidney fibrosis in LN	Sole et al, ⁴⁷ 2019
	Decreased miR-29c	Human	Sequential centrifugation	Early kidney fibrosis in LN	Sole et al, ⁴⁸ 2015

Decreased let-7a, miR-21	Human	Sequential centrifugation	Active LN	Tangtanatakul et al, ⁴⁹ 2019
Increased miR-146a	Human	Sequential centrifugation	Active LN	Perez-Hernandez et al, ⁵⁰ 2015
Increased miR-31, miR-107, miR-135b-5p	Human	miRCURY Exosome Isolation Kit	Clinical response in LN	Garcia-Vives et al, ⁵¹ 2020
Increased miR-224-5p	Human	Sequential centrifugation	RCC	Qin et al, ⁵² 2021
Decreased GST- α 1, CEBPA, PCBD1 esRNA	Human	Sequential centrifugation, filtration	Clear cell RCC	De Palma et al, ⁵³ 2016
Decreased miR-30c-5p	Human	Sequential centrifugation, filtration	Early-stage clear cell RCC	Song et al, ⁵⁴ 2019
Increased miR-204-5p, miR-211-5p	Mouse	miRCURY Exosome Isolation Kit	Xp11.2 translocation RCC	Kurahashi et al, ⁵⁵ 2019

Decreased CD13 ⁻ exosomal miR-200b	Human	Sequential centrifugation, filtration	Kidney fibrosis	Yu et al, ⁵⁶ 2018
Decreased miR-29c	Human	PEG-based precipitation	Kidney fibrosis	Lv et al, ⁵⁷ 2018
Decreased CD2AP mRNA	Human	Sequential centrifugation	Deterioration in kidney function and fibrosis	Lv et al, ⁵⁸ 2014
Decreased miR-29c	Human	Sequential centrifugation	Kidney fibrosis	Lv et al, ⁵⁹ 2013
Decreased miRNA-181a	Human	Sucrose cushion ultracentrifuga- tion with DTT	CKD	Khurana et al, ⁶⁰ 2017
Increased miR-21	Human	Urine Exosome Purification and RNA Isolation Midi Kit (Norgen Biotek Corp)	CKD	Lange et al, ⁶¹ 2019

	Decreased miR-146a	Human	Ultracentrifugation and DTT	Early kidney injury in hypertension	Perez-Hernandez et al, ⁶² 2018
	Increased CCL2 mRNA	Human	Sequential centrifugation	Kidney damage and dysfunction in IgAN	Feng et al, ⁶³ 2018
	Decreased miR-192-5p, miR-194-5p, miR-30a-5p, miR-30d-5p, miR-30e-5p	Human	Sucrose cushion ultracentrifugation	Autosomal dominant PKD	Magayr et al, ⁶⁴ 2020
	Increased miR-1224, miR-21	Human; mouse	DTT, filtration, ultracentrifugation	Radiation-induced tubular injury in kidney	Bhayana et al, ⁶⁵ 2017
	Increased miR-1225-5p	Human	Isolation of exosome RNA from urine (RNA Isolation Kit; Norgen Biotek Corp)	Minimal change disease	Ramezani et al, ⁶⁶ 2015

Decreased miR-1915, miR-663 Increased miR-155	Human	Isolation of exosome RNA from urine (RNA Isolation Kit)	FSGS	Ramezani et al, ⁶⁶ 2015
Increased miR-26a	Human	Ultracentrifugation	Podocyte injury in autoimmune glomerulonephritis	Ichii et al, ⁶⁷ 2014
Increased mRNA of WT1	Mouse; human	Ultracentrifugation with DTT	Podocyte injury	Zhou et al, ⁶⁸ 2013
Increased miRNA-21	Human	Total Exosome Isolation Reagent	Scrub typhus-associated AKI	Yun et al, ⁶⁹ 2021
Increased desmin mRNA	Rat	Ultracentrifugation	PAN nephritis	Fujitaka et al, ³³ 2021
Increased cystatin C mRNA	Rat	Ultracentrifugation	PAN-induced podocyte injury	Spanu et al, ⁷⁰ 2014
Increased miR-16, miR- 24, miR-200c	Rat	Urine Exosome Purification and RNA Isolation	IRI	Sonoda et al, ⁷¹ 2019

			Kit (Norgen Biotek)		
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Abbreviations: AKI, acute kidney injury; AQP, aquaporin; B2M, β 2-microglobulin; BKV, BK virus; BMP, bone morphogenetic protein; CAIX, carbonic anhydrase IX; CCL, chemokine (C-C motif) ligand; CD, clusters of differentiation; CD2AP, CD2-associated protein; CEBPA, CCAAT/enhancer binding protein α ; CKD, chronic kidney disease; CP, ceruloplasmin; CXCL, chemokine (C-X-C motif) ligand; DKD, diabetic kidney disease; DKK, Dickkopf-related protein; DPEP, dipeptidase; DTT, dithiothreitol; ELF3, E74-like factor 3; EMMPRIN, extracellular matrix metalloproteinase inducer; EMP, endothelial microparticle; esRNA, exosomal shuttle RNA; EV, extracellular vesicle; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; GluAp, glutamyl aminopeptidase; GST- α 1, glutathione S-transferase α 1; IFNAR, interferon- α/β receptor; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IL, interleukin; IRI, ischemia-reperfusion injury; L1CAM, L1 cell adhesion molecule; LN, lupus nephritis; MetS, metabolic syndrome; MMP, metalloproteinase; mRNA, messenger RNA; NGAL, neutrophil gelatinase-associated lipocalin; PAN, polyarteritis nodosa; PC, polycystin; PCBD, pterin-4 α -carbinolamine dehydratase; PEG, polyethylene glycol; pEV, podocyte extracellular vesicle; PKD, polycystic kidney disease; PODXL, podocalyxin; PTC, peritubular capillary; RCC, renal cell carcinoma; TGF- β , transforming growth factor β ; TMEM, transmembrane protein; UACR, urine albumin to creatinine ratio; WT1, Wilms tumor 1.

Supplemental Table 2. Circulating EVs as Biomarkers in Kidney Disease

Biomarker	Origin	Isolation method	Disease	Source
Increased TIMPs mRNA	Human	Total Exosome Isolation Reagent (Invitrogen)	Decreased survival with clear cell RCC	Dias et al, ⁷² 2020
Increased GGT activity	Human	Sequential centrifugation, filtration	Advanced RCC	Horie et al, ⁷³ 2020
Increased miR-224	Human	Total Exosome Isolation Kit (Invitrogen)	Worse prognosis with clear cell RCC	Fujii et al, ⁷⁴ 2017
Increased miRNA-4525	Human	Immunoprecipitation with conjugated magnetic beads	Advanced RCC	Muramat-su- Maekawa et al, ⁷⁵ 2021
Increased miR-301a-3p Decreased miR-1293	Human	Total Exosome Isolation Kit	Metastatic clear cell RCC	Dias et al, ⁷⁶ 2020
Increased CAIX	Human	Not clearly described	Clear cell RCC	Vergori et al, ⁷⁷ 2021
Increased miR-210, miR- 1233	Human	Total Exosome Isolation Reagent	Clear cell RCC	Zhang et al, ⁷⁸ 2018
Increased miR-149-3p, miR-424-3p	Human	exoEasy Maxi Kit (Catalog No. 76064; QIAGEN)	RCC	Xiao et al, ⁷⁹ 2020

Decreased miR-92a-1-5p				
Decreased miR-126 e3p, miR-17e5p, miR-21e3p	Mouse	Ultracentrifugation	Cryoablation effects in RCC	Zhang et al, ⁸⁰ 2018
Increased miR-21	Human	PEG precipitation	Interstitial fibrosis and tubular atrophy; kidney transplant	Saejong et al, ⁸¹ 2020
Decreased endothelial microparticles	Human	Ultracentrifugation	Kidney transplant	Qamri et al, ⁸² 2014
Increased miR-30b, miR-30c, miR-34b, miR-34c, miR-342	Human	Isolation of exosomal RNA from urine (Exosomal RNA Isolation Kit; Norgen Biotek Corp)	Minimal change disease	Ramezani et al, ⁶⁶ 2015
Increased miR-4449	Human	ExoQuick isolation agent (System Biosciences)	DKD	Kim et al, ⁸³ 2019
Increased cystatin C and CD14	Human	Precipitation	Cardiorenal syndrome in patients with dyspnea	Verbree-Willem-sen et al, ⁸⁴ 2020

Abbreviations: CAIX, carbonic anhydrase IX; CD, clusters of differentiation; DKD, diabetic kidney disease; EV, extracellular vesicle; GGT, γ -glutamyltransferase; miRNA, microRNA; mRNA, messenger RNA; PEG, polyethylene glycol; RCC, renal cell carcinoma; TIMPs, tissue inhibitors of metalloproteinases.

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