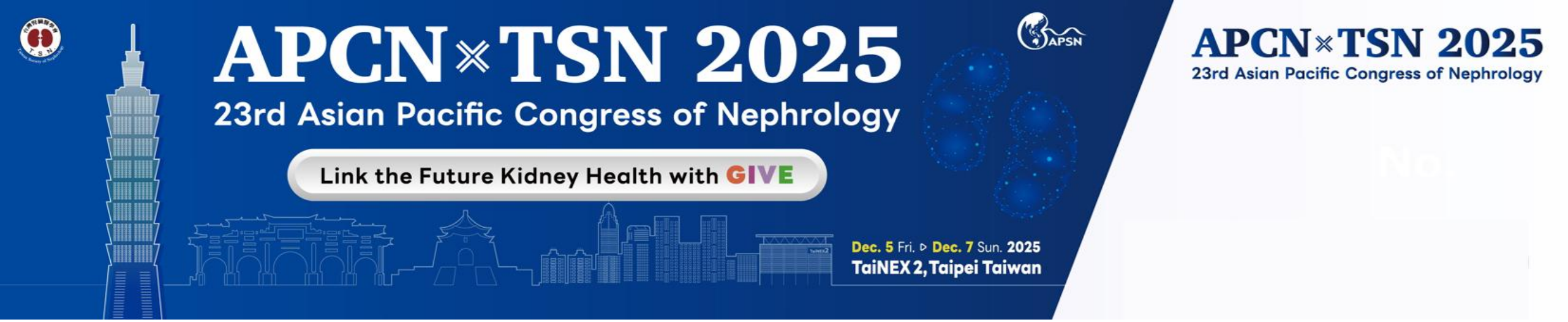

Mesenchymal Stem Cell Derived Exosomes Ameliorate Ischemia Reperfusion Induced Acute Kidney Injury: A Preclinical Meta-Analysis

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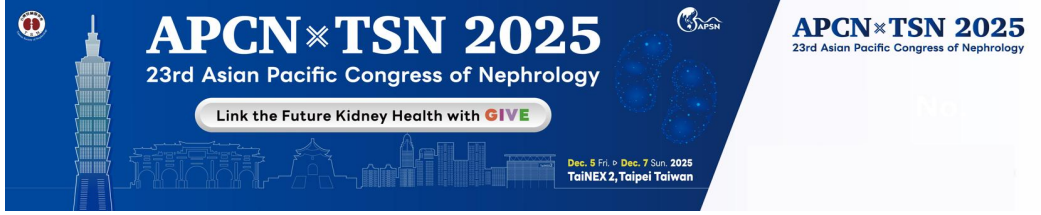


Background:

- Acute kidney injury (AKI) affects 10–15% of hospitalized patients and over 50% of ICU cases.
- Exosomes derived from mesenchymal stem cells (MSCs) have shown reno-protective effects in animal models mimicking AKI through ischemia reperfusion,
- yet their therapeutic efficacy has not been systematically and quantitatively evaluated.
- Purpose: This meta-analysis determines the overall effect of MSC-derived exosomes in ameliorating IRI-induced AKI.

METHODS:

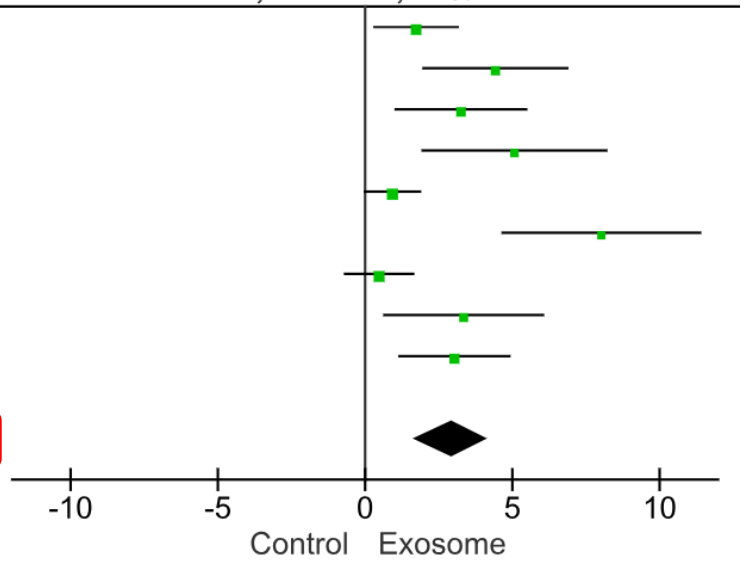
- A systematic review was performed across five major databases,
- A total of 362 were screened focusing on exosomes derived from mesenchymal stem cell therapy for IRI.
- Seven outcome parameters were measured:
  1. serum creatinine (SCr),
  2. blood urea nitrogen (BUN),
  3. tubular damage,
  4. apoptotic cells,
  5. inflammatory markers interleukin-6 (IL-6),
  6. tumor necrosis factor-alpha (TNF-α),
  7. the apoptotic marker caspase-3.
- Data were analyzed using Review Manager (RevMan version 5.4),

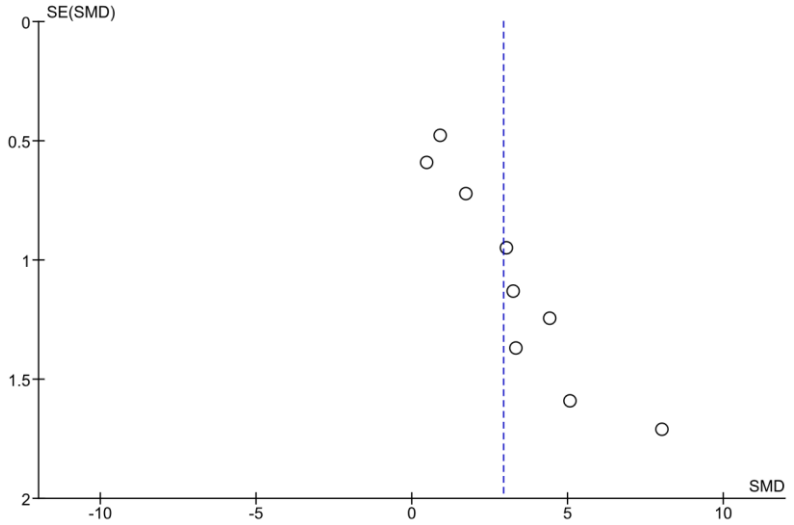
CREATININ

Study or Subgroup	Control Mean	Control SD	Control Total	Exosome Mean	Exosome SD	Exosome Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bing Shen 2016	147.73	12.3	6	124.55	12.41	6	13.4%	1.73 [0.32, 3.14]
Bo Shao 2025	250.11	34.69	6	122.03	14.98	6	10.1%	4.42 [1.99, 6.86]
Gong Min Zhu 2019	126.94	7.19	5	98.47	8.55	5	10.8%	3.26 [1.04, 5.47]
Jiahui He 2025	582.29	18.56	5	377.61	48.1	5	8.1%	5.07 [1.96, 8.18]
Jing Yuan Cao 2021	75.32	18.47	10	58.19	16.83	10	14.8%	0.93 [-0.00, 1.86]
Kun Chen Lin 2016	136.81	17.83	8	29.78	0.63	8	7.6%	8.02 [4.67, 11.37]
Long Li 2019	482.67	37.12	6	462.44	41.27	6	14.2%	0.48 [-0.68, 1.63]
Samin Taghavi 2025	3.84	0.36	4	2.83	0.09	4	9.3%	3.35 [0.66, 6.03]
Yonghong Wan 2023	33.08	3.21	6	22.65	3.14	6	11.9%	3.03 [1.17, 4.90]
Total (95% CI)			**56**			**56**	**100.0%**	**2.92 [1.66, 4.19]**

Heterogeneity: Tau² = 2.59; Chi² = 34.95, df = 8 (P < 0.0001); I² = 77%

Test for overall effect: Z = 4.53 (P < 0.00001)





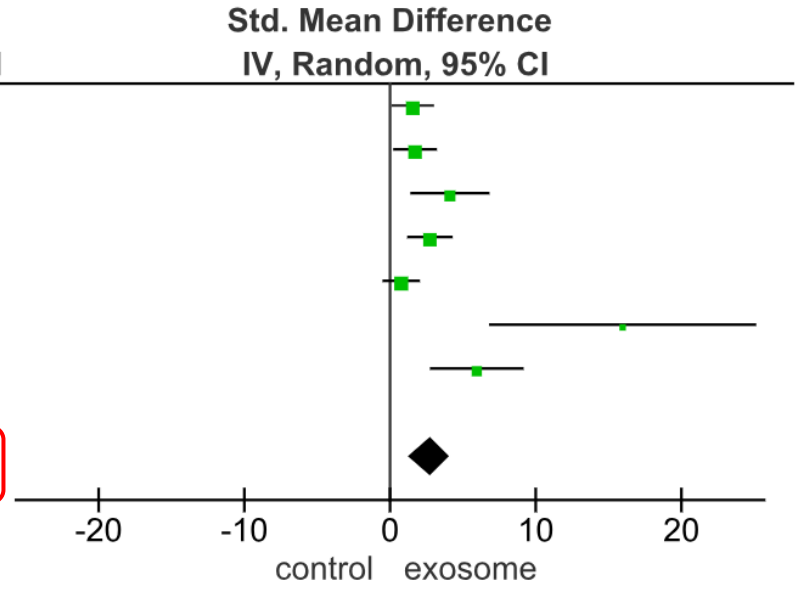
- a significant reduction in serum creatinine levels within 24 hours.
- Indicates clear improvement in glomerular filtration and early renal recovery.
- The effect was consistent across most included studies.

BUN

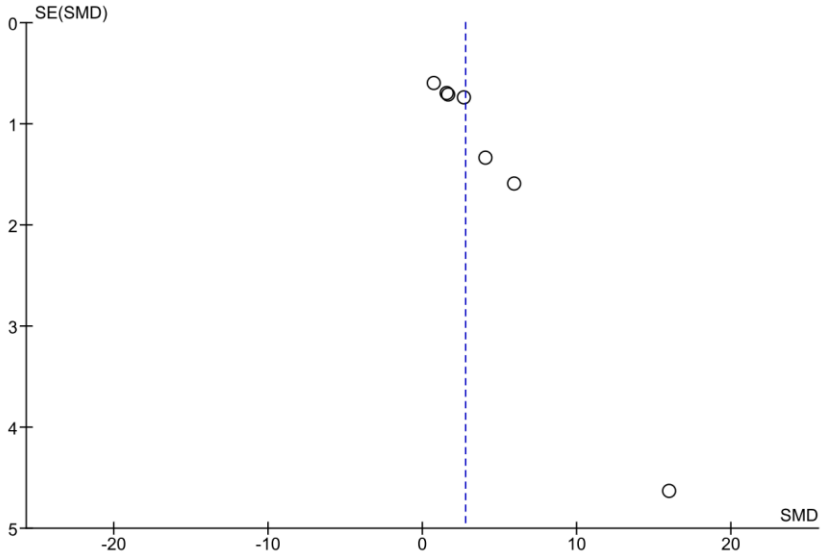
Study or Subgroup	Control Mean	Control SD	Control Total	Exosome Mean	Exosome SD	Exosome Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bing Shen 2016	40.82	4.13	6	33.26	4.78	6	18.6%	1.56 [0.20, 2.93]
Bo Shao 2025	34.19	3.88	6	28.74	1.45	6	18.4%	1.72 [0.31, 3.13]
Gong Min Zhu 2019	49.62	2.14	5	17.85	9.64	5	12.7%	4.11 [1.48, 6.73]
Kun Chen Lin 2016	17.14	5.36	8	6.07	0.71	8	18.1%	2.74 [1.27, 4.21]
Long Li 2019	45.42	2.73	6	42.78	3.56	6	19.4%	0.77 [-0.42, 1.96]
Xiaobing Ji 2025	2.21	0.14	5	0.39	0.04	5	2.2%	15.97 [6.89, 25.04]
Yonghong Wan 2023	13.47	0.58	6	7.35	1.21	6	10.7%	5.95 [2.83, 9.07]
Total (95% CI)			**42**			**42**	**100.0%**	**2.76 [1.34, 4.17]**

Heterogeneity: Tau² = 2.32; Chi² = 23.38, df = 6 (P = 0.0007); I² = 74%

Test for overall effect: Z = 3.82 (P = 0.0001)



- BUN levels were significantly reduced following exosome administration,
- Supports enhanced renal excretory function

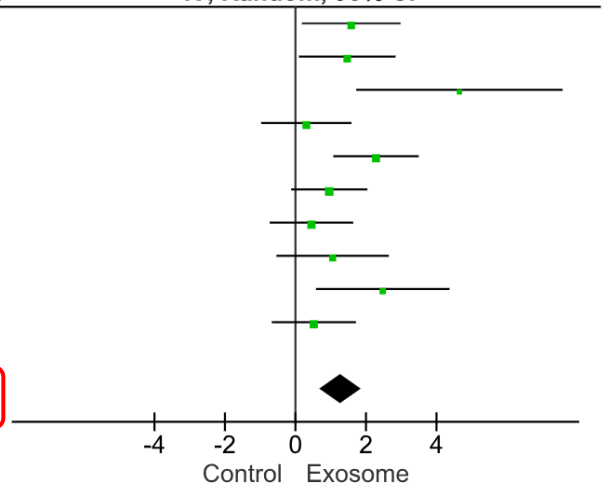


TUBULAR DAMAGE

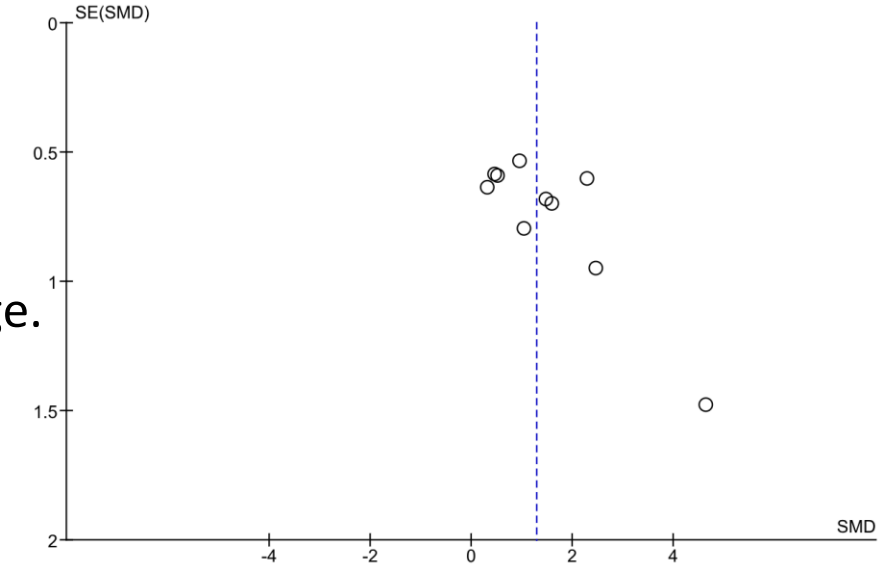
Study or Subgroup	Control Mean	Control SD	Control Total	Exosome Mean	Exosome SD	Exosome Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bing Shen 2016	3.21	0.43	6	2.49	0.41	6	10.1%	1.58 [0.21, 2.95]
Bo Shao 2025	4.43	0.46	6	3.78	0.35	6	10.4%	1.47 [0.13, 2.81]
Fengming Zhu 2017	3.8	0.34	5	2.1	0.32	5	3.4%	4.65 [1.75, 7.55]
Gong Min Zhu 2019	2.81	7.2	5	1.07	0.55	5	11.2%	0.31 [-0.94, 1.56]
Jing Yuan Cao 2021	2.86	0.6	10	1.38	0.64	10	11.9%	2.29 [1.10, 3.47]
Kun Chen Lin 2016	2.9	1.32	8	1.91	0.41	8	13.2%	0.96 [-0.09, 2.01]
Long Li 2019	3.84	0.55	6	3.56	0.59	6	12.2%	0.45 [-0.70, 1.61]
Samin Taghavi 2025	1.73	0.64	4	1.12	0.31	4	8.6%	1.05 [-0.51, 2.62]
Xiaobing Ji 2025	2.95	0.49	5	1.76	0.37	5	6.8%	2.48 [0.61, 4.34]
Yonghong Wan 2023	2.82	2.82	6	1.67	0.61	6	12.1%	0.52 [-0.64, 1.68]
Total (95% CI)			**61**			**61**	**100.0%**	**1.28 [0.70, 1.86]**

Heterogeneity: Tau² = 0.37; Chi² = 16.07, df = 9 (P = 0.07); I² = 44%

Test for overall effect: Z = 4.35 (P < 0.0001)



- Exosomes significantly decreased tubular injury scores,
- demonstrating structural preservation of renal tubular epithelium,
- Suggests potent cytoprotective effects against IRI-induced tissue damage.

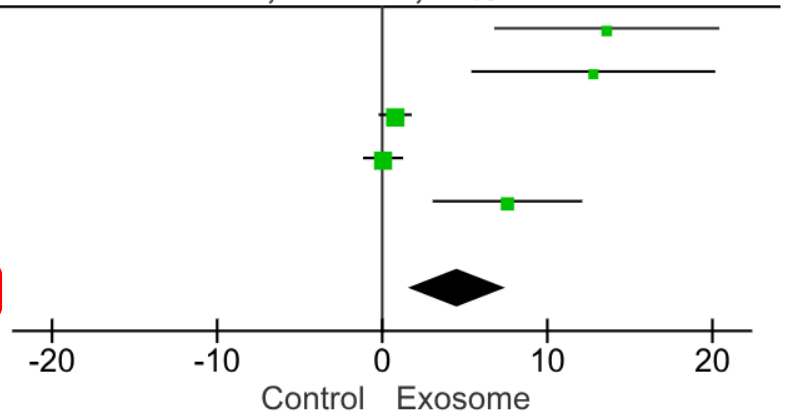


APOPTOTIC CELLS

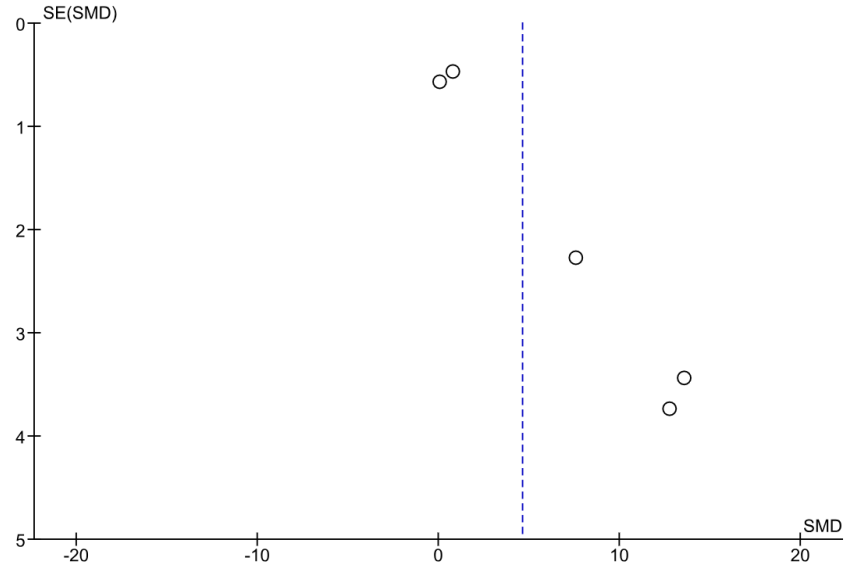
Study or Subgroup	Control Mean	Control SD	Control Total	Exosome Mean	Exosome SD	Exosome Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bo Shao 2025	79.01	4.02	6	24.82	3.3	6	11.9%	13.60 [6.87, 20.34]
Fengming Zhu 2017	53.72	2.65	5	20.24	2.04	5	10.7%	12.79 [5.48, 20.09]
Jing Yuan Cao 2021	60.01	25.04	10	44.27	10.06	10	29.9%	0.79 [-0.13, 1.71]
Long Li 2019	38.15	7.2	6	37.8	5.1	6	29.4%	0.05 [-1.08, 1.18]
Xiaobing Ji 2025	12.51	1.44	5	3.86	0.22	5	18.2%	7.58 [3.14, 12.03]
Total (95% CI)			**32**			**32**	**100.0%**	**4.61 [1.65, 7.57]**

Heterogeneity: Tau² = 7.43; Chi² = 34.72, df = 4 (P < 0.00001); I² = 88%

Test for overall effect: Z = 3.05 (P = 0.002)



- A marked reduction in apoptotic cell counts was observed in exosome-treated animals.
- Confirms the anti-apoptotic role of MSC-derived exosomes in attenuating IRI-induced cell death.



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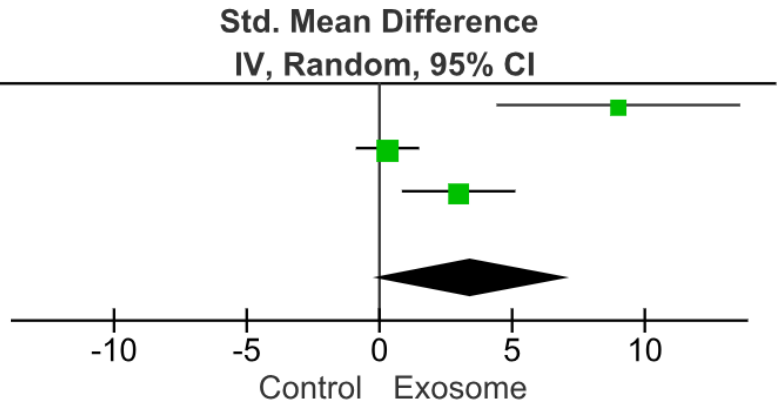
IL-6

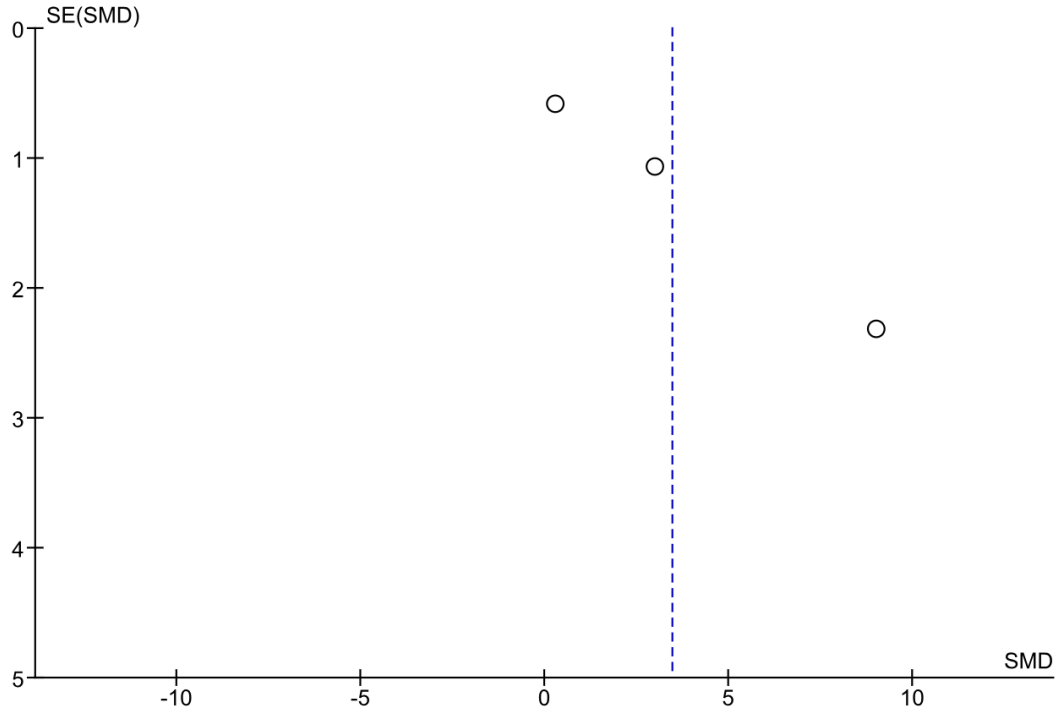
Study or Subgroup	Control Mean	Control SD	Control Total	exosome Mean	exosome SD	exosome Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bing Shen 2016	1.09	0.09	6	0.38	0.05	6	25.1%	9.00 [4.46, 13.54]
Bo Shao 2025	13.87	5.32	6	12.35	3.76	6	39.0%	0.30 [-0.84, 1.45]
Fengming Zhu 2017	13.12	2.8	5	5.87	1.34	5	35.9%	2.98 [0.90, 5.07]
Total (95% CI)			**17**			**17**	**100.0%**	**3.45 [-0.24, 7.15]**

Heterogeneity: Tau² = 8.78; Chi² = 16.49, df = 2 (P = 0.0003); I² = 88%

Test for overall effect: Z = 1.83 (P = 0.07)



- IL-6 levels were significantly lowered, indicating suppression of early systemic and local inflammatory responses.
- Reinforces the immunomodulatory of exosomal therapy.

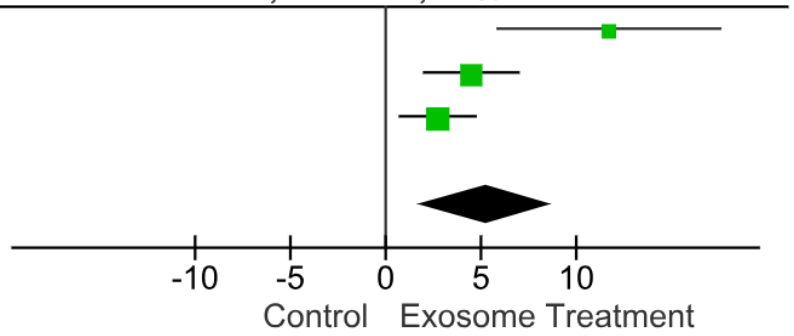


TNF-α

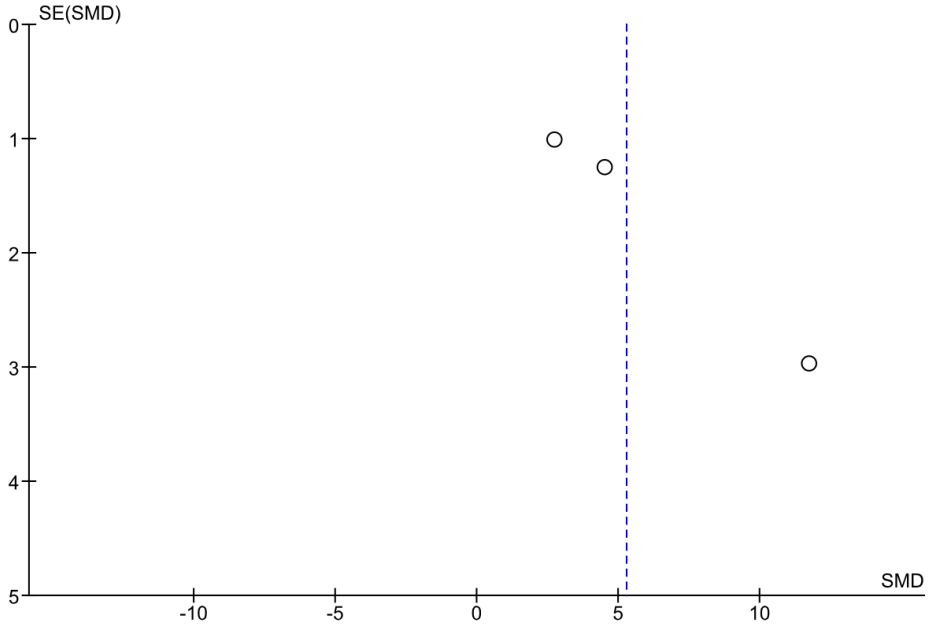
Study or Subgroup	Control Mean	Control SD	Control Total	Exosome Mean	Exosome SD	Exosome Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bing Shen 2016	1.06	0.08	6	0.32	0.02	6	20.7%	11.71 [5.89, 17.54]
Bo Shao 2025	4.3	0.52	6	2.18	0.33	6	38.3%	4.49 [2.03, 6.96]
Fengming Zhu 2017	8.04	0.56	5	6.76	0.21	5	41.0%	2.73 [0.76, 4.71]
Total (95% CI)			**17**			**17**	**100.0%**	**5.27 [1.72, 8.81]**

Heterogeneity: Tau² = 6.95; Chi² = 8.46, df = 2 (P = 0.01); I² = 76%

Test for overall effect: Z = 2.91 (P = 0.004)



- TNF-α, a key pro-inflammatory cytokine, was consistently reduced across studies.
- Demonstrates attenuation of IRI-associated inflammatory injury.



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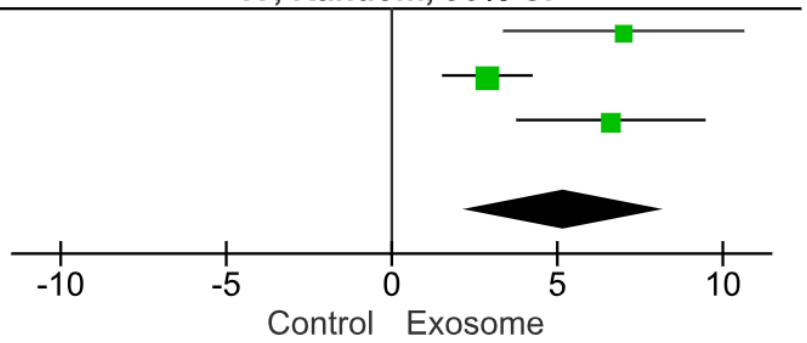
CASPASE 3

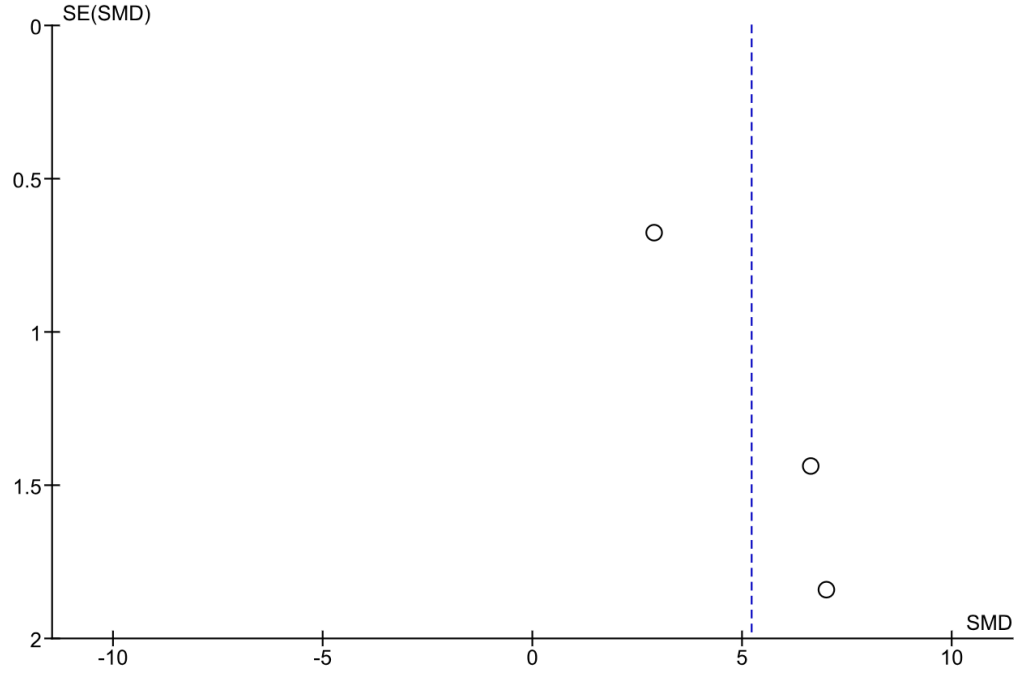
Study or Subgroup	Control Mean	Control SD	Control Total	Experiment Mean	Experiment SD	Experiment Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bo Shao 2025	0.15	0.02	6	0.03	0.01	6	27.2%	7.01 [3.40, 10.61]
Jing Yuan Cao 2021	2.04	0.34	10	1	0.35	10	40.8%	2.89 [1.56, 4.22]
Kun Chen Lin 2016	0.22	0.02	8	0.08	0.02	8	32.0%	6.62 [3.80, 9.44]
Total (95% CI)			**24**			**24**	**100.0%**	**5.20 [2.18, 8.22]**

Heterogeneity: Tau² = 5.35; Chi² = 8.67, df = 2 (P = 0.01); I² = 77%

Test for overall effect: Z = 3.38 (P = 0.0007)



- Exosome treatment reduced caspase-3 expression, confirming inhibition of downstream apoptotic pathways.
- Complements the reduction in apoptotic cell counts.



Discussion:

- A total of 11 in vivo studies published until 2025, involving 132 animals.
- Exosome doses ranged from 50 to 250 μg, with particle sizes of 120 - 140 nm.
- At 24 hours post-treatment, exosomes improved renal function and reduced tissue injury.
- Secondary analyses demonstrated attenuation of inflammatory markers:
  IL-6, TNF-α, apoptotic marker caspase-3.
- No exosome-related adverse effects were reported in any of the included studies.
- Highlighting their safety in preclinical settings.
- These findings strongly support exosomes as a promising future therapeutic for AKI.

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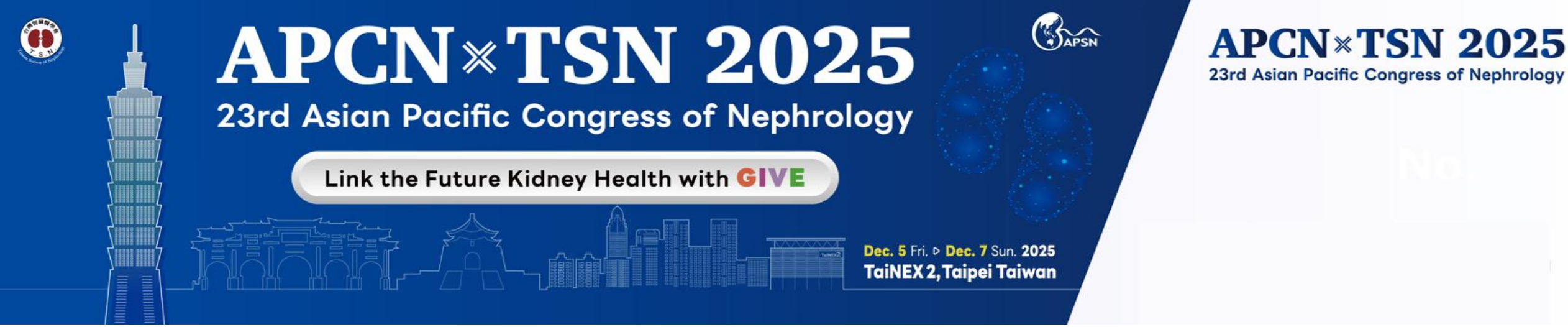
Conclusions:

- MSC-derived exosomes significantly improve renal function and attenuate tissue damage, apoptosis, and inflammation in preclinical models of ischemia reperfusion induced acute kidney injury.
- Provide robust preclinical evidence for exosomes as a novel regenerative and immunomodulatory therapy.
- Further translational and clinical studies are warranted to validate their therapeutic potential in humans.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