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Stem cell intervention and eGFR dynamics in chronic kidney disease, tracking renal function improvement: A systematic review and meta-analysis

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Abstract

Chronic kidney disease (CKD) poses a significant global health burden with limited therapeutic options to reverse renal function decline. This systematic review and meta-analysis evaluated the effectiveness of mesenchymal stem cell (MSC) interventions in CKD patients by analyzing changes in estimated glomerular filtration rate (eGFR). An electronic search of PubMed, Scopus, EBSCOhost, and ScienceDirect was performed for all articles about MSC therapy for CKD with eGFR as the primary outcome, from January 2015 to March 2025. Data were pooled for analysis with Stata. A total of 13 study groups from ten eligible studies were included, encompassing both controlled and single-arm trials with various MSC sources and dosages. Meta-analysis of controlled studies, which notably all shared the same etiology of diabetic kidney disease, demonstrated a significant improvement in eGFR following MSC therapy compared to controls (mean difference: 10.08 mL/min/1.73 m^2; 95% CI: 2.92–17.24; p=0.01), indicating a potential benefit of MSC in enhancing renal function. However, pooled single-arm analyses revealed a non-significant overall eGFR change (mean difference: 1.14 mL/min/1.73 m^2; p=0.62) with considerable heterogeneity across studies. MSC therapy shows promise for improving renal function in CKD, particularly in controlled settings with diabetic kidney disease, but further large-scale, standardized randomized trials are necessary to confirm its clinical utility and optimize treatment protocols.

Keywords: Mesenchymal stem cells, Chronic kidney disease, Glomerular filtration rate, Regenerative medicine, Meta-analysis.

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1. Introduction

Chronic kidney disease (CKD) represents a growing global health problem with increasing prevalence each year. Data from the International Society of Nephrology shows that 1 in 10 people worldwide suffered from CKD in 2017 [1]. The Indonesian Renal Registry in 2020 reported 130,931 CKD patients actively undergoing dialysis in Indonesia, with an increase of 3,551 hemodialysis procedures per year. In 2018, the prevalence of CKD in Indonesia was 3.8 per 1,000 population [2]. The Centers for Disease Control reported an increase in CKD prevalence from 11.8% in 1994 to 14% in 2023, with at least 1 in 7 Americans suffering from CKD [3]. This increasing prevalence coincides with the rise of metabolic diseases such as diabetes mellitus, hypertension, and obesity [1]. In CKD patients, chronic inflammation causes oxidative stress in nephrons, leading to peritubular capillary damage and myofibroblast activation, which induce fibrosis and create a vicious cycle of deteriorating kidney structure and function over time. Glomerular filtration rate (GFR) progressively decreases with worsening CKD stages according to the international stratification established by Kidney Disease: Improving Global Outcomes (KDIGO) [4, 5].

Current available CKD therapies cannot restore decreased GFR; therefore, new therapeutic options for CKD are needed that can improve CKD by increasing GFR. Glomerular filtration rate is an objective indicator for measuring kidney function and CKD progression, which has been internationally recognized based on the consensus established by KDIGO [5-7]. Stem cells are undifferentiated cells capable of self-regeneration and developing into various cell types that form different body tissues [8]. Stem cells can be obtained from two sources: embryos and adult human cells. Embryonic stem cells are closely associated with ethical and moral issues, so they are rarely used today; conversely, stem cells from adult human cells, especially mesenchymal stem cells (MSC) that can be obtained from various adult body tissues, have been widely used for medical therapy, including CKD [6].

Research into MSCs has confirmed their safety for human application, with minimal adverse effects observed. However, their therapeutic potential in CKD remains insufficiently explored, even as MSCs see broad use in other medical contexts. Preliminary searches of the PubMed database suggest that MSCs may enhance kidney function through diverse mechanisms, such as anti-inflammatory, immunomodulatory, and regenerative actions, mediated both by the cells themselves and their secreted factors [4, 6, 9, 10]. Although MSC therapy is becoming more accessible for a range of conditions including CKD its clinical effectiveness is still debated, largely due to the lack of standardized international treatment protocols or consensus guidelines.

This systematic review followed PRISMA guidelines and searched four databases (PubMed, Scopus, EBSCOhost, and ScienceDirect) from January 2015 to March 2025 using comprehensive search terms for CKD and MSC, ultimately including 10 studies with 13 treatment subgroups after applying strict inclusion/exclusion criteria. The researchers conducted both controlled and single-arm meta-analyses using random-effects models with the REML method, performed subgroup analyses based on MSC source and dosage, and assessed publication bias through funnel plots and Egger's test to evaluate the effectiveness of MSC interventions on estimated GFR (eGFR) changes in CKD patients. This study is designed to systematically review and meta-analyze the current literature to assess the efficacy of MSC therapy in CKD patients. The primary outcome is the change in eGFR before and after MSC administration or in comparison to control groups. Estimated GFR was selected as the main reference point for evaluating the effects of MSC therapy, reflecting international consensus on its use for CKD staging and its frequent application as an outcome measure in MSC research, thereby enabling a robust meta-analysis [5, 7].

2. Material and Methods

2.1. Study Selection and Eligibility Criteria

This study included all comparative studies and RCTs involving patients aged >18 years that assessed the therapeutic effects of various types of MSCs in CKD patients with different etiologies. The therapeutic effect of MSCs in CKD patients was evaluated based on changes in eGFR. No ethical approval was required for this study, as the data used were already published by the primary researchers. We also searched for additional studies from the references of articles obtained. Original research not published in English language, pediatrics subjects <18 years old, not available in full text, reviews, case reports, meta-analyses, comments, and letters were excluded from this study.

2.2. Search Strategy

We searched the PubMed, Scopus, EBSCOhost, and ScienceDirect databases from January 2015 through March 2025 for original papers that assessed the effect of MSC administration on CKD patients, without language restrictions. Keywords in this research included the following: ("chronic kidney disease"[Title] OR "chronic renal disease"[Title] OR "chronic kidney failure"[Title] OR "chronic renal failure"[Title] OR "CKD"[Title] OR "ADPKD"[Title] OR "diabetic nephropathy"[Title] OR "diabetic kidney disease"[Title] OR "focal segmental glomerulosclerosis"[Title] OR "lupus nephritis"[Title] OR "ESRD"[Title] OR "ESKD"[Title] OR "nephropathy"[Title] OR "nephrosclerosis"[Title]) AND ("stem cell"[Title] OR "stem cells"[Title] OR "mesenchymal"[Title] OR "MSC"[Title] OR "precursor"[Title] OR "stromal"[Title] OR "umbilical cord"[Title] OR "amnion"[Title] OR "placenta"[Title] OR "bone marrow"[Title] OR "ipscs"[Title] OR "pluripotent"[Title] OR "endothelial"[Title] OR "BM-MSCs"[Title] OR "AD-MSCs"[Title] OR "UC-MSCs"[Title] OR "AF-MSCs"[Title] OR "ESCs"[Title] OR "embryo"[Title]) AND ("GFR"[Title/Abstract] OR "EGFR"[Title/Abstract] OR "E-GFR"[Title/Abstract] OR "glomerular filtration rate"[Title/Abstract]). After eliminating duplicate entries, we screened the remaining studies for relevance based on titles and abstracts. We then conducted thorough evaluations of potentially relevant studies according to our predefined inclusion and exclusion criteria. This systematic review and meta-analysis

adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure comprehensive and transparent reporting. This study has been registered in the prospective register of systematic reviews (PROSPERO) with the registration number CRD420250596885.

2.3. Data Extraction

Two authors (KY, LP) independently extracted data using a standardized form capturing essential information, including publication details (PMID, first author, publication year, location), sample characteristics, study methodology, eGFR calculation formula, demographic information (age, gender), CKD staging, MSC classification, and outcome measurements. When specific data were not explicitly presented in a publication, we obtained the necessary information by analyzing charts within the paper or by directly contacting the original researchers. Any discrepancies in the extraction process were resolved through adjudication by a third and fourth author (AFT, RSY) to ensure data accuracy and consistency.

2.4. Statistical Analysis

Statistical analysis in this study was performed using Stata version 16. A random-effects meta-analysis model with the Restricted Maximum Likelihood (REML) method was applied to account for potential heterogeneity between studies. For controlled studies, pooled mean differences were calculated to compare changes in eGFR between intervention and control groups, while single-arm studies were analyzed by assessing mean differences in eGFR before and after MSC administration. Subgroup analyses were conducted based on MSC source and dosage using Q-tests to explore potential differences between groups. Publication bias was evaluated through funnel plot visualization and Egger's test, with a p-value <0.05 considered indicative of potential bias.

3. Results

3.1. Study Selection

Initially, 632 studies were identified, along with four additional studies from hand searching. After removing 61 duplicates, 555 studies were excluded following title and abstract screening. After full-text assessment of 16 studies, 6 were further excluded due to wrong intervention (n=2), wrong population (n=1), and unavailable outcomes (n=3). Ten studies were included in this meta-analysis, with three studies divided into multiple treatment subgroups based on different stem cell dosages. The study by Zheng et al. [11] was divided into three subgroups, Packham et al. [12] into two subgroups, and Tanaka et al. [13] into two subgroups, resulting in a total of 13 treatment subgroups. Of the ten included studies, three were randomized controlled trials, and seven were single-arm trials. The selection process is illustrated in the PRISMA flowchart in Figure 1.

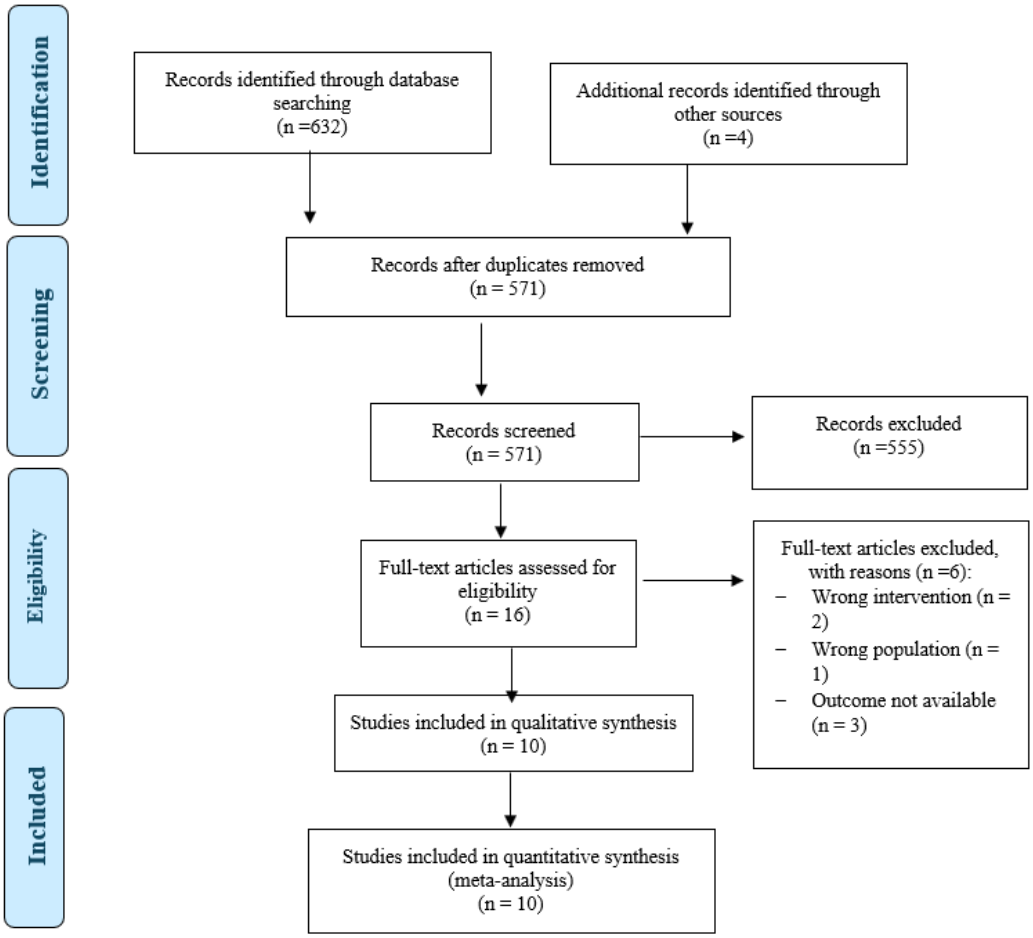

Figure 1.
PRISMA Flowchart.

Table 1.
Characteristics of included studies.

No	PID	Year	Author	Sub-group	Stem cell dosage*	CKD stage	CKD etiology	Country	Design	Intervention				Control				Stem cell type	Administration	Observation
										Sample	Age (year)	Male (%)	CKD stage	Sample	Age (year)	Male (%)	CKD stage			
1	31189223	2019	Villanueva et al. [14]	n/a	4.0 - 9.8	IIIb-IV	FSGS; CKD post AKI; HTN; RD; IgAN; SA	Chile	SAT	6	42.00	50	IIIb-IV	n/a	n/a	n/a	n/a	AD-MSC	IV	12 months
2	35415928	2022	Zheng et al. [11]	Group 1	6.4	IIIb-IV	CIN; DKD; HTN	Taiwan	SAT	3	54.30	66.7	IIIb-IV	n/a	n/a	n/a	n/a	AD-MSC	IV	12 months
3	35415928	2022	Zheng et al. [11]	Group 2	19.2	IIIb-IV	CIN; DKD; HTN	Taiwan	SAT	3	59.30	100	IIIb-IV	n/a	n/a	n/a	n/a	AD-MSC	IV	12 months
4	35415928	2022	Zheng et al. [11]	Group 3	32.0	IIIb-IV	CIN; DKD; HTN	Taiwan	SAT	6	49.80	83.3	IIIb-IV	n/a	n/a	n/a	n/a	AD-MSC	IV	12 months
5	27743903	2016	Packham et al. [12]	Group 1	15.0	IIIa-IV	DKD	Australia	RCT	10	70.50	90	IIIa-IV	10	74.8	80	IIIa-IV	BM-MSC	IV	3 months
6	27743903	2016	Packham et al. [12]	Group 2	30.0	IIIa-IV	DKD	Australia	RCT	10	64.80	70	IIIa-IV	10	74.8	80	IIIa-IV	BM-MSC	IV	3 months
7	29580865	2018	Makhlough et al. [15]	n/a	14.0	IIIb-IV	HTN; CIN; FSGS; nephrotic syndrome	Iran	SAT	7	39.00	71.4	IIIb-IV	n/a	n/a	n/a	n/a	BM-MSC	IV	18 months
8	37560967	2023	Perico et al. [16]	n/a	8.0	IIIa-IV	DKD	Italy	RCT	10	69.19	100	IIIa-IV	4	59.5	100	IIIa-IV	BM-MSC	IV	18 months
9	39186380	2024	Tanaka et al. [13]	Group 1	10.0	II-IIIb	Refractory IgA nephropathy	Japan	SAT	3	36.70	66.7	II-IIIb	n/a	n/a	n/a	n/a	AD-MSC	IV	13 months
10	39186380	2024	Tanaka et al. [13]	Group 2	20.0	II-IIIb	Refractory IgA nephropathy	Japan	SAT	6	52.80	83.3	II-IIIb	n/a	n/a	n/a	n/a	AD-MSC	IV	13 months
11	28535817	2017	Makhlough et al. [17]	n/a	18.0	IIIb-IV	ADPKD	Iran	SAT	6	42.30	50	IIIb-IV	n/a	n/a	n/a	n/a	BM-MSC	IV	12 months
12	36545894	2023	Carstens et al. [18]	n/a	3.2 - 19	III-V	CKDu	Nicaragua	SAT	18	44.50	100	III-V	n/a	n/a	n/a	n/a	AD-MSC	RAI	36 months
13	30290717	2018	Barbado et al. [19]	n/a	9.0	I-IIIb	Lupus nephritis	Spain	SAT	3	42.00	66.7	I-IIIb	n/a	n/a	n/a	n/a	BM-MSC	IV	9 months

Note: ADPKD: autosomal dominant polycystic kidney disease; CIN: chronic interstitial nephritis; CKDu: chronic kidney disease of unknown etiology; DKD: diabetic kidney disease; FSGS: focal segmental glomerulosclerosis; HTN: hypertensive nephrosclerosis; IgAN: IgA nephropathy; NS: nephrotic syndrome; RAI: renal artery infusion; PID: Pubmed ID; RCT: randomized controlled trial; RD: renal dysplasia; SA: sjogren associated; SAT: single arm trial. Age presented in mean. *Stem cell dosage in 10^7 cells.

3.2. Study Characteristics

A total of 91 patients from ten studies were included, with a mean age of 51 years. Male subjects predominated over females (77% vs 23%). Among all studies, CKD stages ranged from stage I to V. The etiologies of CKD included focal segmental glomerulosclerosis, hypertension, renal dysplasia, autoimmune disorders, interstitial nephritis, diabetes, IgA nephropathy, autosomal dominant polycystic kidney disease, and idiopathic causes. Diabetic kidney disease was the most common etiology, present in 46% of treatment subgroups, and in all randomized controlled trial.

The stem cells used in these studies were AD-MSC and BM-MSC. The administered stem cell doses varied from 3.2 to 32×10^7 cells, all delivered intravenously, except for one study by Carstens et al. [18] which utilized renal arterial infusion as the delivery method. Patient follow-up duration ranged from 3 to 36 months. The basic characteristics of the study are shown in Table 1.

3.3. Stem Cells and eGFR

We conducted a meta-analysis of three controlled study subgroups to assess differences in eGFR between patients receiving stem cell therapy and those in control groups. Importantly, all CKD cases included in these randomized controlled trials were exclusively attributed to diabetic kidney disease. These studies included 30 subjects in the intervention group and 24 comparable subjects in the control group, with data available for post-intervention eGFR change analysis. Results showed that stem cell therapy was associated with a mean eGFR increase of 10.08 mL/min/1.73 m² compared to controls, with a 95% confidence interval of 2.92 to 17.24 ($p = 0.01$). This statistically significant difference indicates a positive effect of stem cell intervention on kidney function. Among the three subgroups, Packham et al. [12] – Groups 1 and 2 showed eGFR differences of 7.70 (95% CI: -8.86 to 24.26) and 7.60 (95% CI: -11.10 to 26.30), respectively, neither reaching statistical significance individually. However, Perico et al. [16] demonstrated a statistically significant effect, with a mean difference of 11.29 (95% CI: 2.52 to 20.06), contributing the highest weight to the analysis (66.64%). Heterogeneity testing revealed no significant differences between studies, with values of $Tau^2 = 0.00$, $I^2 = 0.00\%$, and $H^2 = 1.00$, and a Q-test (chi-square) result of 0.22 ($p = 0.896$), indicating relatively homogeneous results across studies. Clinical implications suggest that stem cell therapy may provide clinical benefits in improving kidney function, as reflected by significant eGFR improvements. An average increase of 10 mL/min/1.73 m^2 can be considered clinically significant, especially in patients with chronic kidney function decline.

Single-arm meta-analysis was conducted on 13 treatment subgroups by comparing eGFR before and after stem cell administration. Based on a random-effects model using the REML approach, the mean eGFR change was 1.14 mL/min/1.73 m² with a 95% confidence interval between -3.31 and 5.59. Significance testing for the overall effect showed $p = 0.62$, indicating that stem cell therapy has not been proven to provide statistically significant kidney protective effects in improving glomerular filtration function. The high level of heterogeneity between studies ($I^2 = 73.63\%$) demonstrates substantial variability in response to stem cell therapy, which may be attributed to factors such as variations in stem cell types, administered doses, delivery methods, patient baseline characteristics, and differences in kidney function evaluation methods. Some studies, such as Packham et al. [12] and Barbado et al. [19], showed substantial eGFR improvements after intervention, while others, like Makhlough et al. [15] and Zheng et al. [11], Group 2 reported significant decreases. Although some individual studies reported eGFR improvements after stem cell administration, the cumulative results of this meta-analysis do not demonstrate consistency in protective benefits. Additionally, the confidence interval range crossing zero indicates uncertainty regarding the kidney-protective effect of this therapy. The results of the meta-analysis are summarized in Figure 2 and Figure 3.

Subgroup analysis (Figure 4) was performed to evaluate the influence of MSC dosage on treatment outcomes. Studies were stratified into low-dose ($<15\times10^7$ cells) and high-dose ($\geq15\times10^7$ cells) groups. The low-dose group showed a mean eGFR change of -1.88 mL/min/1.73m² (95% CI: -7.22, 3.46) with moderate heterogeneity (I^2=51.41%), while the high-dose group demonstrated a more favorable trend with a mean eGFR improvement of 3.53 mL/min/1.73m² (95% CI: -3.35, 10.41), albeit with higher heterogeneity (I^2=81.01%). Although this difference suggested a potential dose-response relationship, it did not reach statistical significance (test of group differences: QB(1)=1.48, p=0.22).

Subgroup analysis comparing the efficacy of different MSC sources revealed distinct response patterns (Figure 5). Adipose tissue-derived MSC showed a mean eGFR change of -1.35 mL/min/1.73m² (95% CI: -5.27, 2.57) with relatively moderate heterogeneity (I^2=33.81%), while BM-MSC demonstrated a more favorable trend with a mean eGFR improvement of 4.62 mL/min/1.73m² (95% CI: -5.85, 15.08), albeit with substantially higher heterogeneity (I^2=89.16%). Despite this numerical difference suggesting potentially superior efficacy of BM-MSC, the difference between cell types did not reach statistical significance (test of group differences: QB(1)=1.10, p=0.29). The lower heterogeneity in the AD-MSC group suggests more consistent, though generally neutral, treatment effects, while the higher heterogeneity in the BM-MSC group indicates more variable responses, ranging from strongly positive to negative outcomes.

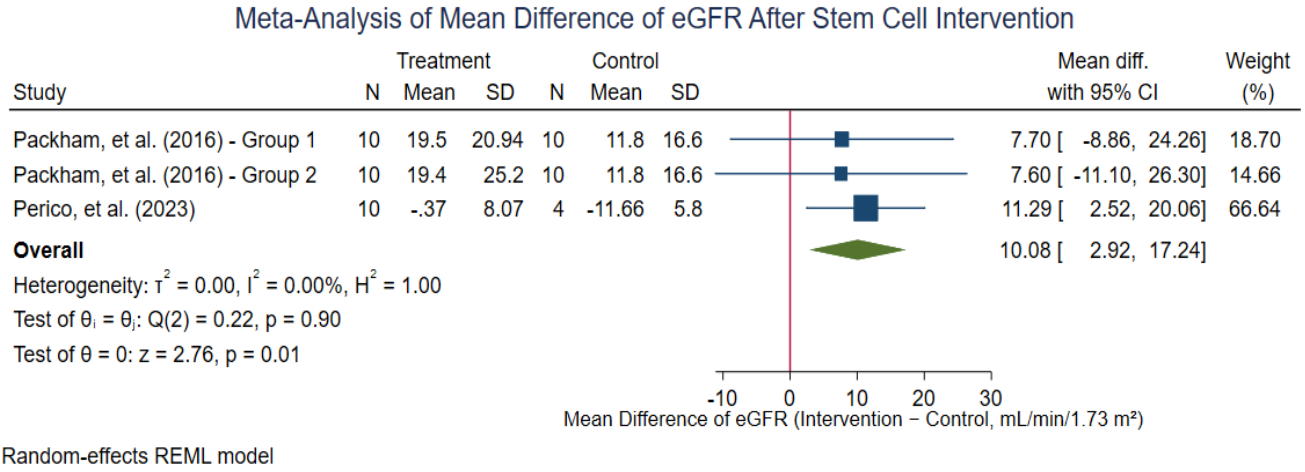

Figure 2.

Forest plot of the mean eGFR difference between the mesenchymal stem cell therapy and control groups. Meta-analysis using a random-effects REML model demonstrated a significant improvement in eGFR with stem cell therapy (mean difference: 10.08 mL/min/1.73m^2; 95% CI: 2.92, 17.24; p=0.01) with no significant heterogeneity between studies (I^2=0.00%).

Source: Packham et al. [12] and Perico et al. [16].

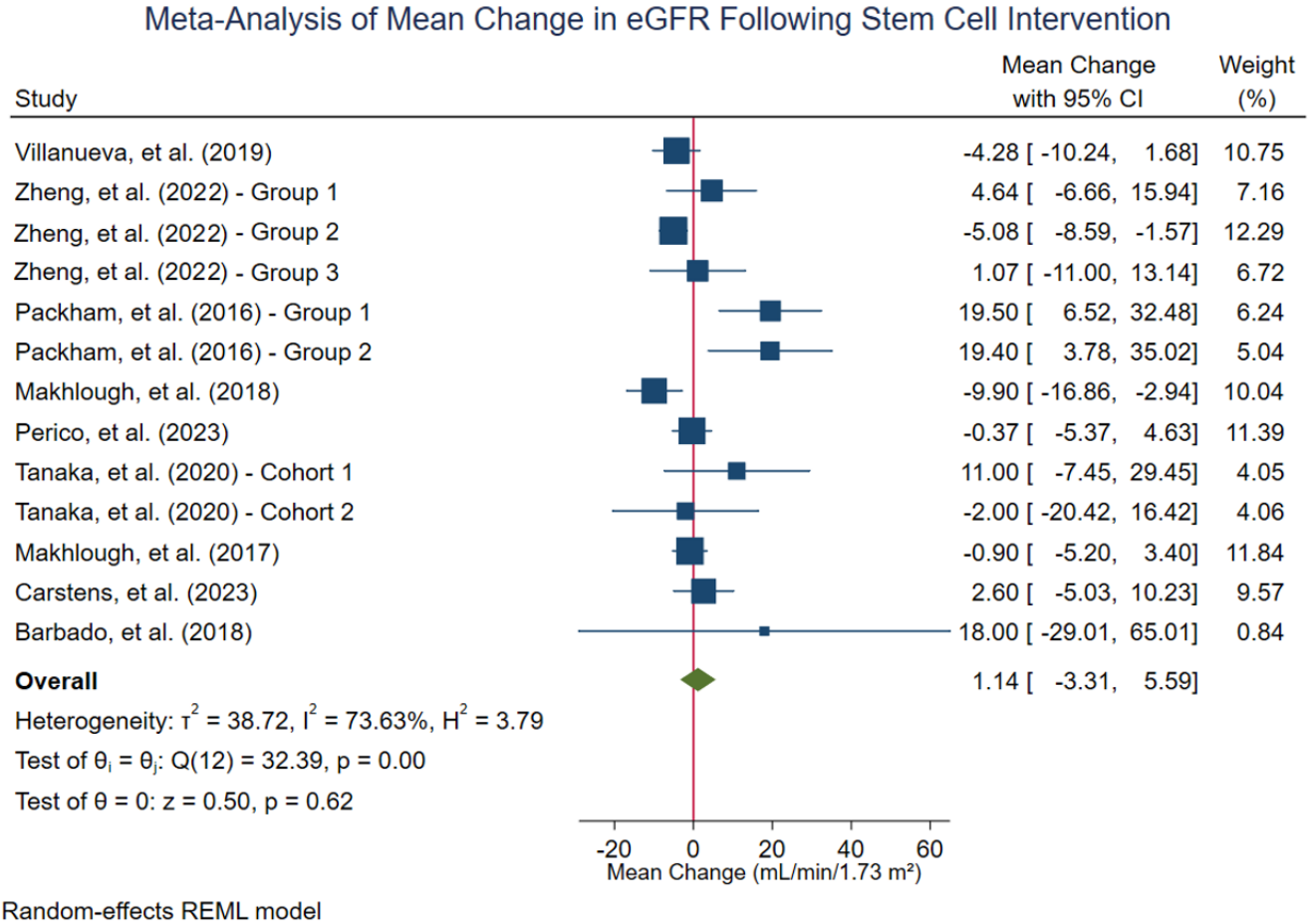

Figure 3.

Forest plot of mean eGFR changes following mesenchymal stem cell therapy. Single-arm meta-analysis of 13 treatment subgroups showed non-significant overall eGFR improvement (1.14 mL/min/1.73m²; 95% CI: -3.31, 5.59; p=0.62) with substantial heterogeneity between studies (I^2=73.63%).

Source: Villanueva et al. [14]; Zheng et al. [11], Packham et al. [12], Makhlough et al. [15], Perico et al. [16], Tanaka et al. [13], Carstens et al. [18] and Barbado et al. [19].

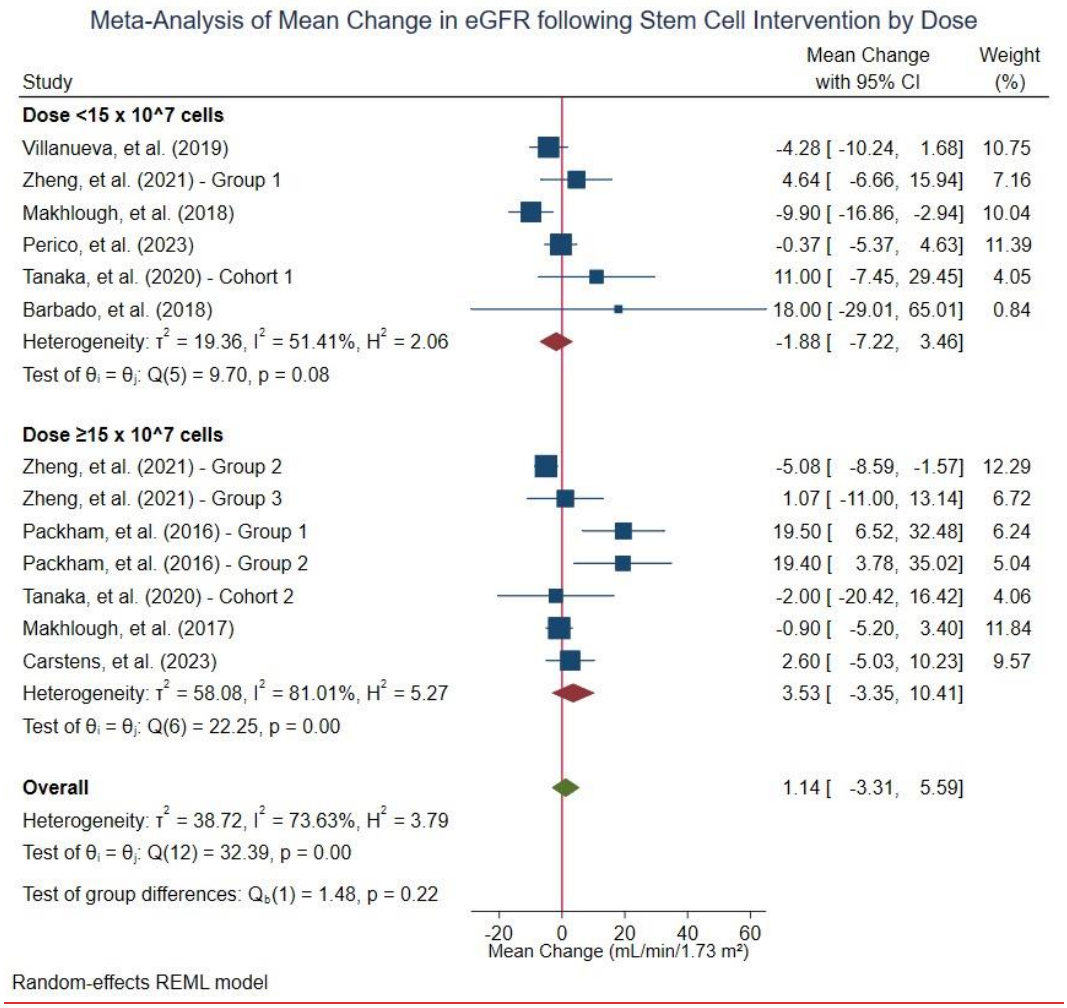

Figure 4.
Forest plot of mean eGFR changes following mesenchymal stem cell therapy stratified by cell dose.
Source: Villanueva et al. [14], Zheng et al. [11], Makhlough et al. [15], Perico et al. [16], Tanaka et al. [13], Barbado et al. [19], Packham et al. [12] and Carstens et al. [18]

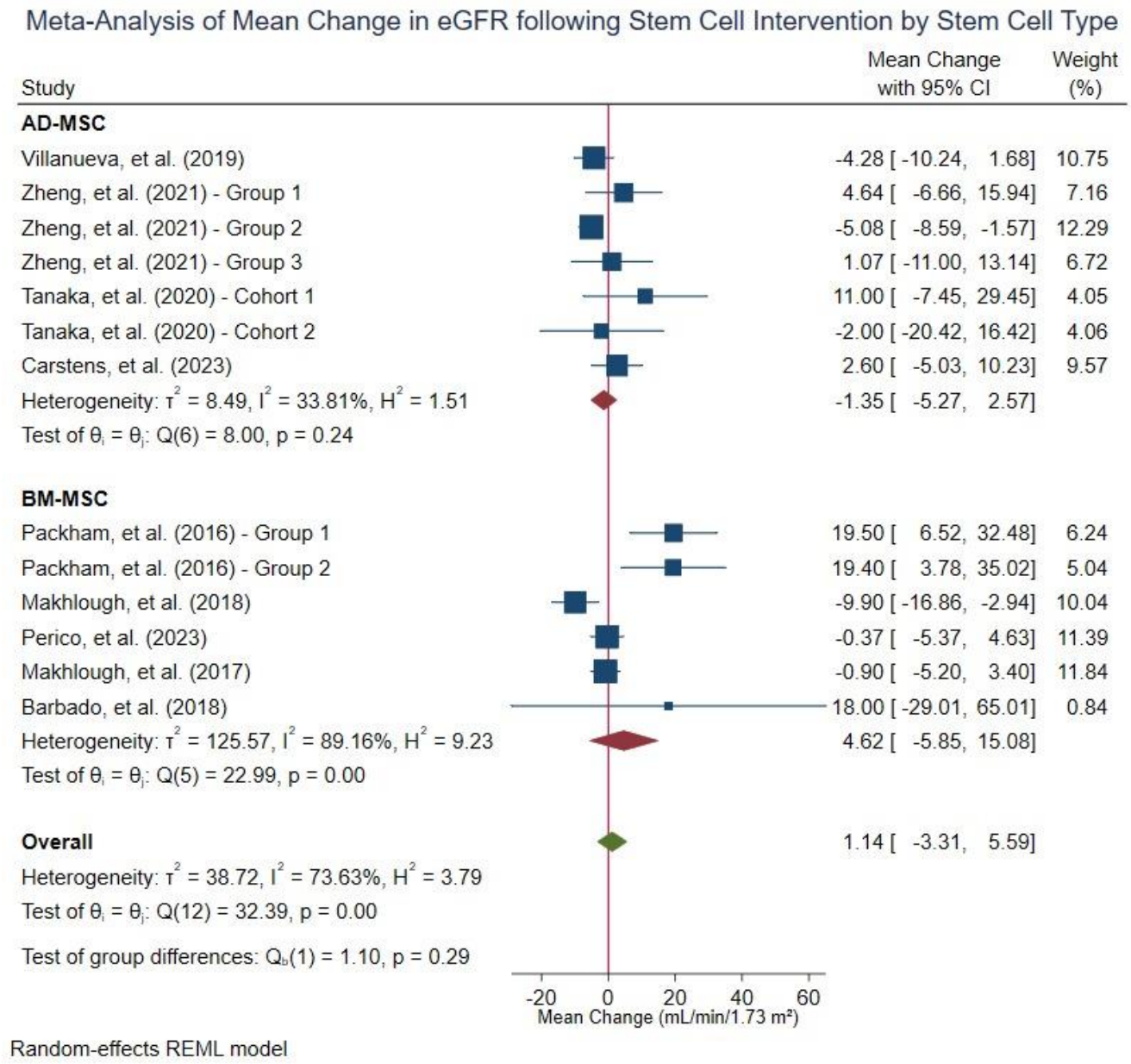

Figure 5.
Forest plot of mean eGFR changes following mesenchymal stem cell therapy stratified by cell type.
Source: Villanueva et al. [14], Zheng et al. [11], Tanaka et al. [13], Carstens et al. [18], Packham et al. [12], Makhlough et al. [15], Perico et al. [16], Makhlough et al. [17] and Barbado et al. [19].

3.4. Publication bias

The funnel plot (Figure 6) demonstrates modest asymmetry in study distribution, with several points deviating from the expected pattern of symmetry around the estimated effect size (θIV). Visual inspection reveals potential small-study effects, as evidenced by the asymmetric distribution of studies with larger standard errors. The presence of one notable outlier in the lower right quadrant with a substantial standard error suggests possible publication bias, though the relatively even distribution of studies with smaller standard errors near the apex provides some confidence in the overall effect estimate's reliability. Egger's test was subsequently performed to quantitatively assess the significance of this observed asymmetry. Egger's regression-based test for small-study effects revealed statistically significant asymmetry in the funnel plot (beta1 = 1.86, SE = 0.629, z = 2.95, p = 0.0032). This significant result ($p < 0.01$) indicates the presence of small-study effects, suggesting that smaller studies with larger effect sizes may be overrepresented in the literature. This finding supports the visual assessment of funnel plot asymmetry and suggests potential publication bias that should be considered when interpreting the overall results of the meta-analysis.

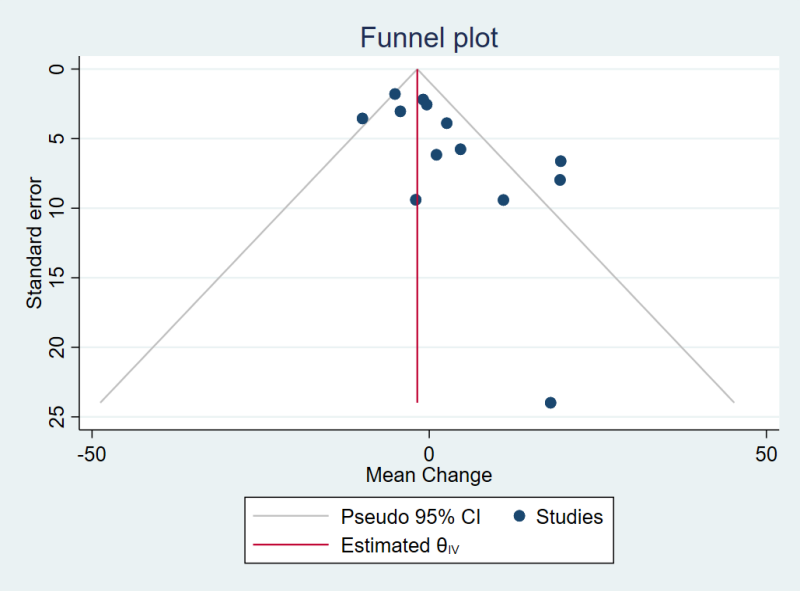

Figure 6.
Funnel plot of studies included in the meta-analysis of eGFR changes after stem cell therapy.

4. Discussion

Our meta-analysis provides important insights into the potential of MSC therapy for CKD, revealing both promising therapeutic benefits and significant challenges that must be addressed before widespread clinical implementation. The controlled studies analysis demonstrated a significant improvement in eGFR with MSC therapy compared to controls, suggesting therapeutic benefit. However, the single-arm analysis across 13 treatment subgroups showed variable responses with high heterogeneity, indicating that MSC therapy outcomes may depend on several factors, including cell type, dosage, and patient characteristics.

The observed improvement in eGFR by 10.08 mL/min/1.73m² in controlled studies represents a clinically meaningful change for CKD patients, particularly considering that CKD typically follows a progressive course with declining renal function over time. This magnitude of improvement is substantial when viewed in the context of natural disease progression, where CKD patients typically experience annual eGFR declines of 2 - 4.5 mL/min/1.73m² depending on underlying etiology and comorbidities. A comprehensive 10-year longitudinal study by Tsai et al. of 4,600 CKD patients in Taiwan provides crucial context for interpreting MSC therapy outcomes. In their cohort, 62.4% of patients experienced annual eGFR decline rates greater than 1 mL/min/1.73m², with the median decline rate being 4.42 mL/min/1.73m² per year for those classified as having disease progression. Importantly, patients with rapid CKD progression (>3 mL/min/1.73m²/year) showed dramatically worse outcomes, with 50% of stage 3 CKD patients entering end-stage renal disease within 5 years [20]. The Taiwan study also demonstrated that each 1 mL/min/1.73m² increase in annual decline rate was associated with a 17% higher risk of incident end-stage renal disease, suggesting that the magnitude of improvement seen with MSC therapy could translate into substantial long-term clinical benefits.

Furthermore, the Taiwan study identified diabetes and proteinuria as key predictors of rapid CKD progression, with odds ratios of 1.72 and 1.89, respectively, for developing decline rates >3 mL/min/1.73m^2/year. This aligns remarkably well with our finding that all controlled MSC studies were conducted exclusively in diabetic kidney disease patients, suggesting that this high-risk population may be particularly responsive to cellular therapy interventions. The convergence of these findings supports the hypothesis that MSC therapy may be most beneficial in patients with the greatest intrinsic risk of progression [20]. This finding is consistent with a recent systematic review by Liu et al. [21], which reported that MSC treatment significantly improved renal function in CKD patients compared to conventional therapy alone, with particular benefits observed in patients with diabetic nephropathy [21].

The high heterogeneity (I^2=73.63%) observed in our single-arm analysis warrants careful consideration. This variability likely reflects differences in CKD etiology and therapeutic protocols, including MSC source, dose, administration route, and follow-up duration. Individual studies reported widely divergent outcomes, with some showing substantial improvements [12]: +19.5 mL/min/1.73m²; [19]: +18.0 mL/min/1.73m²) while others demonstrated significant decreases [15]: -9.9 mL/min/1.73m²; [11] Group 2: -5.08 mL/min/1.73m²). These contradictory results highlight the complexity of MSC therapy and the need for standardized approaches to maximize therapeutic efficacy. Similar heterogeneity was noted in a comprehensive review by Hickson et al. [22], who identified considerable variability in study designs, MSC sources, and outcomes in clinical trials of cell-based therapies for kidney disease [22].

Dose-stratified analysis revealed an intriguing pattern wherein higher MSC doses (≥15×10^7 cells) tended toward more positive eGFR changes compared to lower doses (3.53 vs. -1.88 mL/min/1.73m²), though this difference did not reach statistical significance. This finding parallels observations by Wang et al. [23] in their systematic review, where they noted that higher MSC doses generally correlated with better outcomes, though optimal dosing remains undefined [23]. The considerable heterogeneity within the high-dose subgroup (I^2=81.01%) compared to the low-dose subgroup (I^2=51.41%) suggests that factors beyond dose alone influence treatment outcomes. The relationship between MSC dose and therapeutic

efficacy in CKD appears complex and may be influenced by cell viability, inflammatory microenvironment, and timing of administration, as reviewed by Rota et al. [6]. This complexity is further supported by Kabat et al.'s comprehensive analysis of 914 MSC trials, which identified a narrow minimal effective dose range of 100-150 million cells for intravenous delivery. Their findings suggest that both lower doses (200 million cells) may be less effective than this optimal range, indicating an inverted U-shaped dose-response relationship. This phenomenon may explain the heterogeneity observed in our high-dose subgroup, as doses exceeding the optimal threshold could potentially result in diminished therapeutic benefits [24].

Although not statistically significant, our subgroup analysis suggested that BM-MSC may provide more favorable outcomes compared to AD-MSC, with mean eGFR changes of 4.62 and -1.35 mL/min/1.73m², respectively. This trend aligns with findings from a preclinical meta-analysis by Papazova et al. [25], which found that BM-MSC demonstrated superior efficacy in improving renal function in animal models of CKD compared to other cell sources [25]. The different therapeutic potential of BM-MSC versus AD-MSC may be attributed to their distinct secretome profiles and immunomodulatory capacities, as demonstrated by comparative analyses conducted by Valencia et al. [26]. Based on Wang et al., BM-MSCs are identified as the most commonly used and optimal cell type for CKD treatment. Bone marrow-derived MSCs demonstrate superior effectiveness due to their low expression of MHC-I and MHC-II molecules, which helps them avoid allogeneic T-cell attacks, and their proven ability to differentiate into glomerular mesangial cells. Clinical evidence consistently shows that BM-MSCs are more effective at restoring kidney function compared to other MSC types, making them the gold standard for CKD therapy despite being challenging to purify quickly and effectively. However, AD-MSCs present compelling advantages, including easy purification, rapid proliferation, high cell viability, and convenient supply sources. Adipose tissue-derived MSCs exhibit stronger immunomodulatory effects than BM-MSCs due to higher production of IL-6 and TGF-β1 cytokines, though they are less effective at restoring kidney function. The optimal choice depends on specific clinical requirements, patient conditions, treatment objectives, and practical considerations such as availability and manufacturing capabilities [4].

Administration routes may also influence therapeutic efficacy, although our analysis was limited by the predominance of intravenous delivery in most studies. Only one study, Carstens et al. [18], utilized renal artery infusion, reporting a modest eGFR improvement of 2.6 mL/min/1.73m². This preference for systemic administration is consistent with the broader literature, as highlighted in a comprehensive review by Torres Crigna et al. [27] who noted that while direct renal delivery may theoretically enhance therapeutic effects through increased cell concentration at target sites, intravenous administration remains the most common approach in clinical trials due to its minimally invasive nature, established safety profile, and ability to reach both kidneys simultaneously [27]. Similarly, Gregorini et al. [28] reviewed various administration routes for cell-based therapies in kidney disease and concluded that, while site-specific delivery may increase therapeutic potential in certain contexts, systemic intravenous administration offers practical advantages in clinical settings and remains the standard approach for most trials [28]. Future comparative studies, specifically addressing administration routes, could help optimize therapeutic protocols for different CKD etiologies and disease stages.

4.1. Limitations

Several limitations of our study should be acknowledged. First, the relatively small number of included studies, particularly the limited number of controlled studies (n=3), restricts the generalizability of our findings. Second, the substantial heterogeneity in study designs, MSC sources, dosing protocols, and CKD etiologies makes direct comparisons challenging. Third, the predominance of diabetic kidney disease patients in the controlled studies potentially limits the applicability of findings to CKD from other causes. Furthermore, this meta-analysis demonstrates the presence of publication bias, as indicated by the asymmetry observed in the funnel plot. These findings suggest that studies with larger effect sizes are more likely to be published, which may influence the overall conclusions of the analysis.

5. Conclusion

Mesenchymal stem cell therapy shows promising potential for treating CKD, particularly in patients with diabetic nephropathy, although standardized protocols are needed to address variability in treatment responses.

Future research should focus on identifying optimal therapeutic parameters, including cell source, dosage, and administration route, while considering patient-specific factors that may influence outcomes. Large-scale RCTs with extended follow-up periods are essential to confirm these preliminary findings and establish MSC therapy as a viable treatment option in clinical practice.

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