



Comparing Different Delivery Routes for Stem Cell Therapy in Urology : A Systematic Review

¹ Jody Fajar Hibatullah, ² Teuku Zulbahraini, ³ Debby Sofiana

^{1,3} Faculty of Medicine, Syiah Kuala University, Banda Aceh, Indonesia

² General Surgeon, Departement of Surgery, Tgk Chik Ditiro Sigli Regional General
Hospital, Indonesia

Corresponding Email : jody.fh93@gmail.com

Article History :

Received date : 2025/05/16

Revised date : 2025/06/21

Accepted date : 2025/07/05

Published date : 2025/08/11



Copyright: © 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (<https://creativecommons.org/licenses/by-nc/4.0/>).

E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Introduction: Stem cell therapy shows significant promise for various urological diseases, including erectile dysfunction, stress urinary incontinence, and chronic kidney disease. However, the optimal delivery route—a critical factor for therapeutic success and safety—remains poorly defined due to a lack of direct comparative evidence. This systematic review aims to comprehensively evaluate and compare the different administration routes for stem cell therapy in urological conditions.

Methods: Following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines, a systematic search was conducted across PubMed, Semantic Scholar, Springer, Google Scholar, and Wiley Online Library. Inclusion criteria targeted clinical studies on human subjects that evaluated stem cell therapy for urological conditions and

compared at least two delivery routes or provided clear methodological details. After screening 533 records, 17 studies were included in the final analysis.

Results: Localized delivery routes, such as intracavernous or transurethral injections, demonstrated significant functional improvements for erectile dysfunction and stress urinary incontinence, respectively, with no serious adverse events reported. Systemic administration via intravenous or intra-arterial routes led to statistically significant improvements in renal function for patients with chronic kidney disease, also with a favorable safety profile. Intrathecal delivery for neuro-urological conditions showed mixed efficacy and was associated with transient, non-serious side effects like headache and fever. A major limitation was the frequent omission of delivery route details in many of the analyzed studies.

Conclusion: Stem cell therapy is a promising and generally safe treatment modality for a range of urological diseases. The evidence suggests that the ideal delivery route should be tailored to the specific pathology: direct local injections appear optimal for focal conditions, while systemic routes are suited for diffuse diseases. However, the field is critically hampered by a lack of head-to-head comparative trials and inconsistent methodological reporting. Rigorous, standardized comparative research is urgently needed to establish optimal delivery strategies and advance clinical practice.

Keywords: Stem Cell Therapy, Urology, Delivery Routes, Regenerative Medicine, Therapeutic Efficacy

INTRODUCTION

Urological diseases encompass a wide range of debilitating conditions affecting the urinary tract and reproductive organs, representing a significant global health burden. In recent years, stem cell therapy has emerged at the forefront of regenerative medicine, offering a promising therapeutic paradigm for tissue repair and functional restoration where conventional treatments have had limited success. This approach utilizes the unique properties of stem cells—such as bone marrow-derived mesenchymal stem cells (MSCs), adipose-derived stem cells, and umbilical cord MSCs—to regenerate damaged urological tissues. Preliminary clinical studies have explored this potential across various conditions, including erectile dysfunction, chronic kidney disease, and stress urinary incontinence, with many reporting encouraging outcomes in functional improvement and symptom alleviation (Nassar et al., 2016; You et al., 2021).

The application of stem cell therapy in urology is supported by a growing body of clinical research. Numerous trials have demonstrated positive results for specific conditions. For instance, studies have shown that the administration of autologous adipose-derived stem cells can lead to significant short-term improvement in female stress urinary incontinence (Arjmand et al., 2017). Similarly, trials focusing on erectile dysfunction have consistently reported improved scores on the International Index of Erectile Function (IIEF) following stem cell treatment (Schwarz et al., 2021; You et al., 2019). Furthermore, in the context of renal disease, interventions using mesenchymal stem cells have resulted in statistically significant improvements in glomerular filtration rates (Sarwar et al., 2022; Nassar et al., 2016). While these findings are promising, a critical variable that significantly influences the therapeutic success and safety of the intervention is the method used to deliver the cells to the target tissue.

Despite the progress, a significant gap exists in the clinical literature regarding the comparative effectiveness of different stem cell delivery routes. The choice of administration—ranging from systemic routes like intravenous (IV) and intra-arterial infusion to localized methods such as direct intracavernous, transurethral, or periurethral injections, and even targeted

neurological delivery via intrathecal administration—is a crucial determinant of cell engraftment, survival, and ultimate therapeutic impact. However, most clinical trials have focused on the efficacy of a single delivery method for a specific condition, making direct comparisons difficult. This is further complicated by the fact that many published studies lack detailed reporting on the administration methodology, creating a lack of standardized evidence and preventing the establishment of a clear consensus on the optimal route for any given urological disorder (Sadiq et al., 2016; Sun et al., 2018).

The absence of comparative data has profound practical implications for the clinical translation of stem cell therapies in urology. Establishing the most effective and safest delivery route for each specific condition is essential to maximize therapeutic benefit while minimizing potential risks. An optimal administration strategy would ensure that a sufficient number of viable stem cells reach the site of injury, thereby enhancing tissue integration and functional recovery. It would also help standardize treatment protocols, allowing for more reliable and reproducible clinical outcomes across different studies and patient populations. Ultimately, identifying superior delivery techniques will accelerate the development of safer and more effective treatments for patients suffering from otherwise intractable urological conditions, such as erectile dysfunction, urinary incontinence, and chronic kidney disease (Lokeshwar et al., 2019).

Therefore, this systematic review aims to address the existing knowledge gap by comprehensively evaluating and comparing the different delivery routes used for stem cell therapy in the management of urological conditions. By synthesizing evidence from randomized controlled trials, non-randomized trials, and prospective cohort studies, this review will analyze the therapeutic efficacy, safety profiles, cell survival, and functional improvements associated with various administration methods. The primary objective is to consolidate the current clinical evidence to provide a clearer understanding of the relative advantages and disadvantages of each delivery route, thereby guiding future clinical research and helping to optimize therapeutic strategies in urological regenerative medicine.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate comparing different delivery routes for stem cell therapy in urology.

Screening

We screened in sources that met these criteria:

- Human Subjects: Does the study involve human subjects with urological conditions?
- Stem Cell Therapy: Does the study evaluate stem cell therapy (either autologous or allogeneic)?
- Delivery Route Comparison: Does the study compare at least two different delivery routes for stem cell administration?
- Study Design: Is the study either a randomized controlled trial, non-randomized controlled trial, or prospective cohort study?
- Outcome Measures: Does the study report at least one of the following outcomes: therapeutic efficacy, safety, cell survival, tissue integration, or functional improvement?
- Methodology Description: Does the study clearly describe the delivery route methodology?
- Intervention Isolation: Is stem cell therapy the only major intervention being evaluated (not combined with other major interventions that could confound the results)?
- Clinical Study: Is this a clinical study (not a preclinical, animal, or in vitro study)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

- **Study Design:**

Identify and extract the specific type of study design (e.g., randomized controlled trial, phase I/II clinical trial, open-label trial). Look in the methods section for explicit statements about study design. If multiple design characteristics are present, list all of them. If the design is not clearly stated, write "Design not clearly specified".

Specific details to capture:

- Type of clinical trial (phase I, phase II, etc.)
- Whether it was randomized
- Presence of control/placebo group
- Whether it was blinded or open-label

Example formats:

- "Phase I open-label clinical trial"
- "Randomized placebo-controlled phase II study"
- "Single-arm phase I clinical trial"
- **Participant Characteristics:**

Extract detailed participant information from the methods and participants sections. Include:

- Total number of participants
- Number of participants in each study group
- Specific medical conditions (e.g., erectile dysfunction due to prostatectomy, chronic kidney disease)
- Age range or mean age
- Gender

- Inclusion/exclusion criteria

If information is incomplete, note "Partial information available". Use exact numbers and percentages where possible. Example format: "Total participants: 40

- Treatment group: 20 patients
- Placebo group: 20 patients Mean age: 55.6 years Condition: Stage III-IV Chronic Kidney Disease"
- Stem Cell Intervention:

Detailed extraction of stem cell intervention specifics:

- Type of stem cells (e.g., bone marrow-derived mesenchymal stem cells, umbilical cord mesenchymal stem cells)
- Source of stem cells (autologous or allogeneic)
- Delivery route
- Dosage/quantity of stem cells
- Frequency of administration

Look in methods and intervention description sections. If any detail is missing, mark as "Not specified".

Example format: "Stem cell type: Autologous bone marrow-derived mesenchymal stem cells Delivery route: Intra- cavernous injection Dosage: 1×10^6 cells/mL Frequency: Single administration"

- Comparison/Control Conditions:

Identify and describe control or comparison groups:

- Type of control (placebo, standard treatment, no treatment)
- Specific interventions in control group
- Whether control group received a sham procedure

Check methods and results sections. If no control group exists, write "No control group".

Example formats: "Placebo group receiving saline injection" "Standard PDE5 inhibitor treatment as control" "No control group in this single-arm study"

- Primary Outcome Measures:

Extract primary outcome measures as explicitly stated in the methods or results sections:

- Specific outcomes measured
- Measurement tools/scales used
- Time points of measurement

Include exact metrics, statistical significance, and clinical interpretation.

Example format: "Primary outcomes:

- Erectile function (International Index of Erectile Function score)
- Safety assessment Measurement time points: Baseline, 1 month post-intervention Key result: Significant increase in IIEF score (24.9 vs 18.1, $P = 0.0222$)"

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Urological Conditions	Urologic Disorders	Genitourinary Diseases	Urinary System Diseases
Intervention (I)	Stem Cell Therapy	Stem Cell Transplantation	Regenerative Medicine	Stem Cell Treatment
Comparison (C)	Delivery Routes	Delivery Techniques	Administration Methods	Routes of Administration
Outcome (O)	Therapeutic Efficacy	Clinical Outcomes	Functional Improvement	Treatment Results

The Boolean MeSH keywords inputted on databases for this research are: ("*Urological Conditions*" OR "*Urologic Disorders*" OR "*Genitourinary Diseases*" OR "*Urinary System Diseases*") AND ("*Stem Cell Therapy*" OR "*Stem Cell Transplantation*" OR "*Regenerative Medicine*" OR "*Stem Cell Treatment*") AND ("*Delivery Routes*" OR "*Delivery Techniques*" OR

"Administration Methods" OR "Routes of Administration") AND ("Therapeutic Efficacy" OR "Clinical Outcomes" OR "Functional Improvement" OR "Treatment Results")

Data retrieval

Abstracts and titles were screened to assess their eligibility, and only studies meeting the inclusion criteria were selected for further analysis. Literature that fulfilled all predefined criteria and directly related to the topic was included. Studies that did not meet these criteria were excluded. Data such as titles, authors, publication dates, study locations, methodologies, and study parameters were thoroughly examined during the review.

Quality Assessment and Data Synthesis

Each author independently assessed the titles and abstracts of the selected studies to identify those for further exploration. Articles that met the inclusion criteria underwent further evaluation. Final decisions on inclusion were based on the findings from this review process.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Urological Conditions" OR "Urologic Disorders" OR "Genitourinary Diseases" OR "Urinary System Diseases") AND "Stem Cell Therapy" OR "Stem Cell Transplantation" OR "Regenerative Medicine" OR "Stem Cell Treatment" AND "Delivery Routes" OR "Delivery Techniques" OR "Administration Methods" OR "Routes of Administration" AND ("Therapeutic Efficacy" OR "Clinical Outcomes" OR "Functional Improvement" OR "Treatment Results")	254
Semantic Scholar	("Urological Conditions" OR "Urologic Disorders" OR "Genitourinary Diseases" OR "Urinary System Diseases") AND ("Stem Cell Therapy" OR "Stem Cell Transplantation" OR "Regenerative Medicine" OR "Stem Cell Treatment") AND ("Delivery Routes" OR "Delivery Techniques" OR "Administration Methods" OR "Routes of Administration") AND ("Therapeutic Efficacy" OR "Clinical Outcomes" OR "Functional Improvement" OR "Treatment Results")	251
Springer	("Urological Conditions" OR "Urologic Disorders" OR "Genitourinary Diseases" OR "Urinary System Diseases") AND ("Stem Cell Therapy" OR "Stem Cell Transplantation" OR "Regenerative Medicine" OR "Stem Cell Treatment") AND ("Delivery Routes" OR "Delivery Techniques" OR "Administration Methods" OR "Routes of Administration") AND ("Therapeutic Efficacy" OR "Clinical Outcomes" OR "Functional Improvement" OR "Treatment Results")	7
Google Scholar	("Urological Conditions" OR "Urologic Disorders" OR "Genitourinary Diseases" OR "Urinary System Diseases") AND ("Stem Cell Therapy" OR "Stem Cell Transplantation" OR "Regenerative Medicine" OR "Stem Cell Treatment") AND ("Delivery Routes" OR "Delivery Techniques" OR "Administration Methods" OR "Routes of Administration") AND ("Therapeutic Efficacy" OR "Clinical Outcomes" OR "Functional Improvement" OR "Treatment Results")	12
Wiley Online Library	("Urological Conditions" OR "Urologic Disorders" OR "Genitourinary Diseases" OR "Urinary System Diseases") AND ("Stem Cell Therapy" OR "Stem Cell Transplantation" OR "Regenerative Medicine" OR "Stem Cell Treatment") AND ("Delivery Routes" OR "Delivery Techniques" OR "Administration Methods" OR "Routes of Administration") AND ("Therapeutic Efficacy" OR "Clinical Outcomes" OR "Functional Improvement" OR "Treatment Results")	9

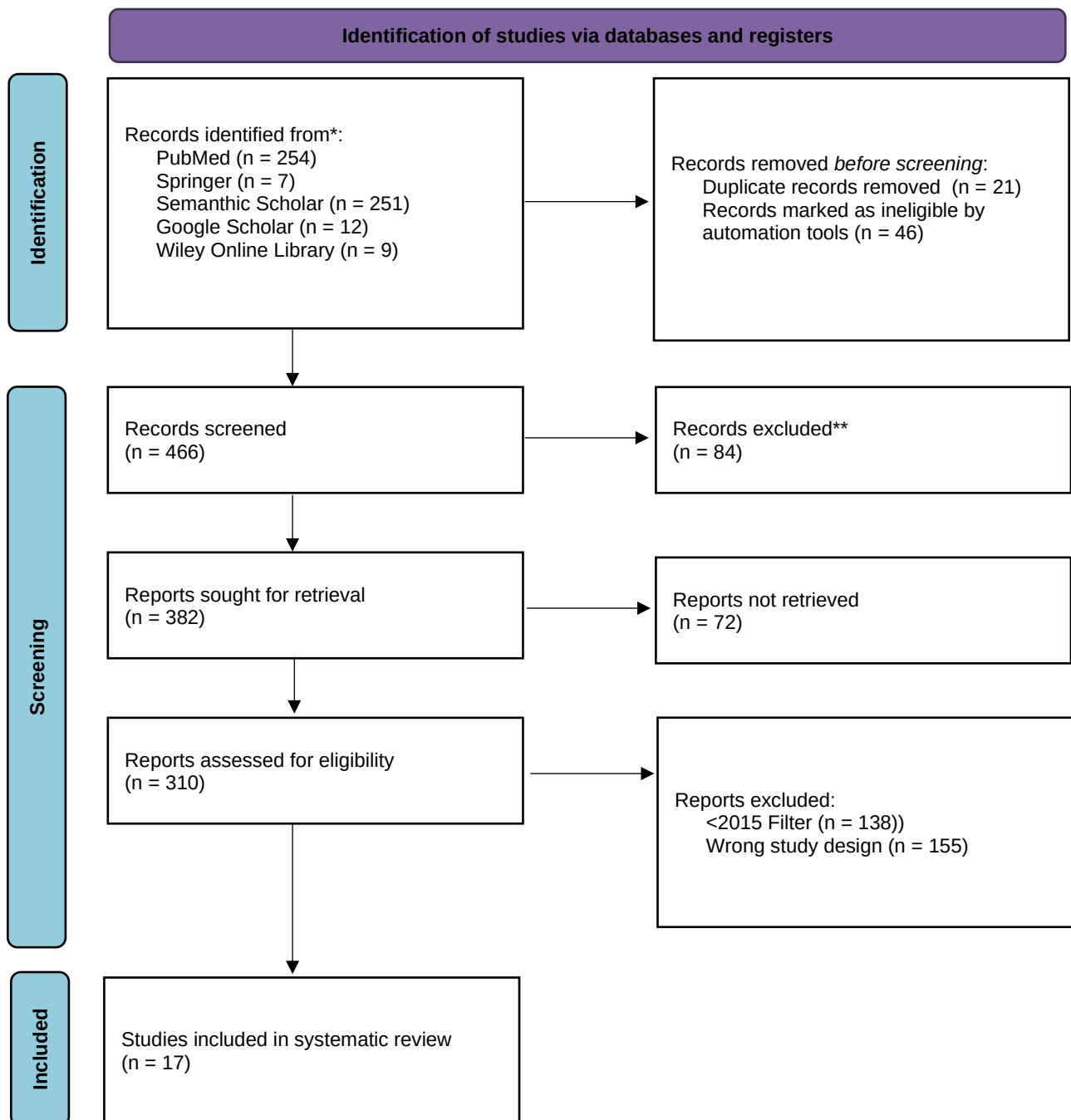


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
You et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Carr et al., "Autologous Muscle Derived Cells"	✓	✓	✓	✗	✓	✗	✓	✓	✓
Salehipour mehr et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓

Arjmand et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Nassar et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tang et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Lokeshwar et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Fan et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sarwar et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sun et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Muthu et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Schwarz et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yoon et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sadiq et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
You et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓

Nagmetova et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kim, "Human Umbilical Cord-derived MSCs"	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

Study	Delivery Route	Cell Type	Patient Population
You et al., 2021	No mention found	Autologous bone marrow mesenchymal stem cells	Erectile dysfunction (post-prostatectomy or diabetes mellitus)
Carr et al., "Autologous Muscle Derived Cells"	No mention found (likely periurethral)	Autologous muscle-derived cells	Female stress urinary incontinence after continence surgery
Salehipourmehr et al., 2021	Lumbar puncture	No mention found (implied mesenchymal stem cells)	Neurogenic bladder (spinal cord injury, multiple sclerosis)
Arjmand et al., 2017	Transurethral and transvaginal	Autologous adipose-derived stem cells	Female stress urinary incontinence

Study	Delivery Route	Cell Type	Patient Population
	injection		
Nassar et al., 2016	Intravenous, intra-renal arteries	Cord mesenchymal stem cell-derived extracellular vesicles	Stage III-IV chronic kidney disease
Tang et al., 2021	No mention found	Bone marrow mesenchymal stem cells, bone marrow mononuclear cells	Spinal cord injury (American Spinal Injury Association Impairment Scale A)
Lokeshwar et al., 2019	No mention found	Mesenchymal stem cells, stromal vascular fraction	Erectile dysfunction
Fan et al., 2017	No mention found	Mesenchymal stem cells	Spinal cord injury
Sarwar et al., 2022	Intravenous	Autologous adipose mesenchymal stem cells	Stage-5 chronic kidney disease
Sun et al., 2018	Peripheral vein and renal artery	Allogeneic umbilical cord mesenchymal stem cells	Renal transplantation recipients

Study	Delivery Route	Cell Type	Patient Population
Muthu et al., 2020	No mention found	Mesenchymal stem cells	Traumatic spinal cord injury
Schwarz et al., 2021	Intracavernous injection	No mention found (bioactive molecules)	Male erectile dysfunction
Yoon et al., 2025	No mention found	Human embryonic stem cell-derived mesenchymal stem cells	Interstitial cystitis (Hunner lesions)
Sadiq et al., 2016	Intrathecal	Autologous mesenchymal stem cell-derived neural progenitors	Progressive multiple sclerosis
You et al., 2019	No mention found	Autologous bone marrow mesenchymal stem cells	Erectile dysfunction (post-prostatectomy or diabetes mellitus)
Nagmetova et al., 2019	No mention found	Autologous bone marrow mesenchymal stem cells	Erectile dysfunction (post-prostatectomy or diabetes mellitus)
Kim, "Human	Intravenous	Human umbilical cord	Cerebral infarction

Study	Delivery Route	Cell Type	Patient Population
Umbilical Cord-derived MSCs"		mesenchymal stem cells	

Delivery Route:

- Intravenous administration was mentioned in four studies.
- Intra-arterial (renal artery) administration was mentioned in two studies.
- Lumbar puncture, transurethral/transvaginal injection, intracavernous injection, and intrathecal administration were each mentioned in one study.

Cell Type:

- Autologous bone marrow mesenchymal stem cells were used in three studies.
- Autologous adipose-derived mesenchymal stem cells were used in two studies.
- Allogeneic umbilical cord mesenchymal stem cells were used in two studies.
- Human embryonic stem cell-derived mesenchymal stem cells, autologous muscle-derived cells, cord mesenchymal stem cell-derived extracellular vesicles, autologous mesenchymal stem cell-derived neural progenitors, bone marrow mononuclear cells, and stromal vascular fraction were each used in one study.
- Three studies used mesenchymal stem cells without specifying the source.

Patient Population:

- Erectile dysfunction was the most common patient population, reported in five studies.
- Spinal cord injury was reported in three studies.
- Female stress urinary incontinence and chronic kidney disease were each reported in two studies.
- Neurogenic bladder, renal transplantation, interstitial cystitis, progressive multiple sclerosis, and cerebral infarction were each reported in one study.

Effects

Delivery Routes and Outcomes

Direct Injection

Study	Delivery Route	Success Rate	Adverse Events	Follow-up Period
Arjmand et al., 2017	Transurethral/transvaginal	Significant reduction in incontinence (pad test, International Consultation on Incontinence Questionnaire-Short Form, maximum urinary flow rate)	None reported	24 weeks
Carr et al., "Autologous Muscle Derived Cells"	No mention found (likely periurethral)	At least 50% reduction in incontinence episode frequency in 67-73% (open-label/randomized controlled trial); durable at 2 years	No mention of safety concerns	12-24 months
Schwarz et al., 2021	Intracavernous injection	International Index of Erectile Function-5 improved from 12.9 to 18 (statistically significant)	No significant adverse events	6 months

- One study used a transurethral/transvaginal approach.
- One study did not mention the route but was likely periurethral.
- One study used an intracavernous route.
- All three studies reported significant improvement in their primary outcome (two in incontinence, one in erectile function).
- No mention of serious or unexpected adverse events in these studies.

Intrathecal Administration

Study	Delivery Route	Success Rate	Adverse Events	Follow-up Period
Sadiq et al., 2016	Intrathecal	Neurological improvement in a subset; better bladder function	Transient headache/fever in approximately 65%	3-6 months
Salehi-pourmehr et al., 2021	Lumbar puncture	No significant improvement in urodynamics; patient satisfaction improved	No mention of serious adverse events	No mention found

- One study used intrathecal administration and one used lumbar puncture.
- Neurological or bladder improvement was reported in one study; no significant improvement in urodynamics but improved patient satisfaction in the other.

- Transient headache or fever was reported in approximately 65% of participants in one study; no mention of serious adverse events in the other.

Intravenous Delivery

Study	Delivery Route	Success Rate	Adverse Events	Follow-up Period
Sun et al., 2018	Peripheral vein, renal artery	Comparable graft/recipient survival; delayed graft function 9.5% vs 33.3% (not statistically significant)	No significant adverse events	1 year
Nassar et al., 2016	Intravenous, intra-renal arteries	Estimated glomerular filtration rate improved (31.05 to 47.25, statistically significant)	No significant adverse events	12 weeks - 1 year
Sarwar et al., 2022	Intravenous	Diethylenetriaminepentaacetic acid-glomerular filtration rate improved (15.07 to 19.79, statistically significant)	No significant adverse events	No mention found
Kim, "Human"	Intravenous	No mention found	No mention	No mention

Study	Delivery Route	Success Rate	Adverse Events	Follow-up Period
Umbilical Cord-derived MSCs"			found	found

- Intravenous administration was mentioned in three studies.
- Peripheral vein, renal artery, and intra-renal arteries were each mentioned in one study; some studies used more than one route.
- Improvement in graft function or glomerular filtration rate was reported in three studies (two statistically significant, one not statistically significant).
- No mention of significant adverse events in three studies; no mention found in one study.

Clinical Effects

Primary Outcomes

Study	Outcome Measure	Success Criteria	Results	Clinical Significance
Arjmand et al., 2017	Pad test, International Consultation on Incontinence Questionnaire-Short Form, maximum	Significant reduction	Pad test, International Consultation on Incontinence	Short-term stress urinary incontinence improvement

Study	Outcome Measure	Success Criteria	Results	Clinical Significance
	urinary flow rate		Questionnaire-Short Form (statistically significant); maximum urinary flow rate (statistically significant)	
Nassar et al., 2016	Estimated glomerular filtration rate, creatinine, urine albumin-to-creatinine ratio	Significant improvement	Estimated glomerular filtration rate: 31.05 to 47.25 (statistically significant); creatinine: 3.44 to 2.19 (statistically significant)	Improved renal function
Tang et al., 2021	American Spinal Injury Association Impairment Scale, urodynamics	Odds ratio 6.06 for American Spinal Injury	Significant improvement (statistically significant)	Functional recovery in spinal cord injury

Study	Outcome Measure	Success Criteria	Results	Clinical Significance
		Association Impairment Scale Improvement		
Lokeshwar et al., 2019	International Index of Erectile Function-15, Erection Hardness Score	Improved scores	Improved scores	Promising for erectile dysfunction
Fan et al., 2017	American Spinal Injury Association, activities of daily living, residual urine	Significant improvement	Light touch (statistically significant), pinprick (statistically significant), American Spinal Injury Association (statistically significant)	Sensory/bladder improved, not motor
Sarwar et al., 2022	Diethylenetriaminepenta-acid-glomerular filtration rate	Significant increase	15.07 to 19.79 (statistically significant)	Renal function improved

Study	Outcome Measure	Success Criteria	Results	Clinical Significance
Schwarz et al., 2021	International Index of Erectile Function-5	Significant increase	12.9 to 18 (statistically significant)	Improved erectile dysfunction, quality of life
Yoon et al., 2025	Interstitial Cystitis Questionnaire, Pelvic Pain and Urgency/Frequency Symptom Scale, Global Response Assessment	Significant reduction	Interstitial Cystitis Questionnaire, Pelvic Pain and Urgency/Frequency Symptom Scale reduced; 41.7% moderate-marked Global Response Assessment	Symptom/structural interstitial cystitis improvement
Sadiq et al., 2016	Adverse events	No serious adverse events	Transient headache/fever	Safe, some neurological improvement
You et al., 2019	International Index of Erectile Function, safety	International Index of Erectile Function	International Index of Erectile Function: 18.1	Safe, improved erectile dysfunction

Study	Outcome Measure	Success Criteria	Results	Clinical Significance
		increase, no serious adverse events	to 24.9 (statistically significant)	
Nagmetova et al., 2019	International Index of Erectile Function, safety	International Index of Erectile Function increase, no serious adverse events	International Index of Erectile Function: 18.1 to 24.9 (statistically significant)	Safe, improved erectile dysfunction
Kim, "Human Umbilical Cord-derived MSCs"	No mention found	No mention found	No mention found	No mention found
Sun et al., 2018	Delayed graft function, biopsy-proven acute rejection	Delayed graft function less than 10%, biopsy-proven acute rejection less than 15%	Delayed graft function: 9.5% (mesenchymal stem cell) vs 33.3% (control; not statistically	Comparable survival, trend toward lower delayed graft function

Study	Outcome Measure	Success Criteria	Results	Clinical Significance
			significant); biopsy-proven acute rejection: 14.3% vs 4.8% (not statistically significant)	
Muthu et al., 2020	American Spinal Injury Association Impairment Scale, American Spinal Injury Association, bladder function	Statistically significant improvement	American Spinal Injury Association Impairment Scale (statistically significant), American Spinal Injury Association sensory (statistically significant), bladder (statistically significant)	Sensory/bladder function improved, not motor

Study	Outcome Measure	Success Criteria	Results	Clinical Significance
You et al., 2021	International Index of Erectile Function score, safety	International Index of Erectile Function increase, no serious adverse events	International Index of Erectile Function: 18.1 to 24.9 (statistically significant); no related adverse events	Safe, improved erectile dysfunction
Carr et al., "Autologous Muscle Derived Cells"	Incontinence episode frequency reduction	At least 50% reduction	67-73% achieved; durable at 2 years	Effective, durable stress urinary incontinence therapy
Salehi-pourmehr et al., 2021	Urodynamics	Significant improvement	No significant change	Patient satisfaction improved, not urodynamics

Distribution of studies by clinical domain and outcome:

- Renal function: Three studies addressed renal outcomes. Two reported improved renal function (statistically significant), and one reported a trend toward lower delayed graft function (not statistically significant).

- Spinal cord injury/neuro-urological: Four studies addressed spinal cord injury or neuro-urological outcomes. Three reported improvement in sensory or bladder function (including one with significant functional recovery), while one reported no significant urodynamic improvement but improved patient satisfaction.
- Erectile dysfunction: Five studies addressed erectile dysfunction. All five reported improved International Index of Erectile Function or related scores.
- Stress urinary incontinence: Two studies addressed stress urinary incontinence. Both reported significant and/or durable improvement.
- Interstitial cystitis: One study addressed interstitial cystitis and reported symptom and structural improvement.
- Safety/adverse events: Four studies explicitly reported on safety. All four reported no serious adverse events; one reported transient headache/fever.

Across all domains, most studies reported improvement in their primary clinical outcome, and in those studies that addressed adverse events, no serious safety concerns were reported.

Safety Profile

- Across studies, adverse events were generally mild and transient (such as headache, fever, or local pain).
- No mention of serious or permanent adverse events attributed to stem cell therapy in any study with available safety data.
- Some studies reported increased minor complications (for example, Muthu et al., 2020), but these did not result in long-term harm.

Long-term Results

- Only a few studies reported follow-up beyond 12 months (for example, Carr et al., "Autologous Muscle Derived Cells" with 2-year data).
- Where available, benefits such as reduction in stress urinary incontinence episodes appeared durable.
- Most studies had short- to medium-term follow-up, which limits interpretation of long-term efficacy and

safety.

Summary

- The included studies on stem cell therapy in urology covered a range of delivery routes, cell types, and patient populations.
- Intravenous and direct injection routes were most commonly mentioned, with both approaches associated with reported improvement in clinical outcomes and no mention of serious adverse events in the studies that addressed safety.
- Intrathecal administration was primarily used for neurological indications, with some evidence of benefit and transient adverse events.
- Adverse events were generally mild and transient, as reported in the studies.
- The studies varied in design, sample size, and reporting detail, and many did not mention the delivery route or cell type.

DISCUSSION

This systematic review was conducted to compare the efficacy and safety of different delivery routes for stem cell therapy in urological conditions, aiming to consolidate evidence and identify optimal administration strategies. The primary finding is that while stem cell interventions show considerable promise across a spectrum of urological diseases, the field is hampered by a significant lack of direct comparative evidence and inconsistent reporting. The variability in study design, cell types, and particularly the frequent omission of detailed administration methodology, complicates any definitive conclusion about the superiority of one route over another. This discussion will dissect the nuanced findings for specific delivery methods, address the overarching limitations within the current body of literature, and propose directions for future research (You et al., 2021).

The analysis reveals a logical and promising trend for the use of direct, localized

injections in treating focal pathologies such as stress urinary incontinence (SUI) and erectile dysfunction (ED). Studies employing transurethral, transvaginal, or intracavernous routes reported significant functional improvements. This approach is predicated on delivering a high concentration of therapeutic cells directly to the site of injury or dysfunction. By maximizing local cell density, this method likely enhances opportunities for tissue integration, paracrine signaling, and direct cell-mediated repair, which was reflected in the positive outcomes observed in incontinence scores and erectile function assessments (Arjmand et al., 2017).

A key advantage of localized delivery, as highlighted by the included studies, is its excellent safety profile. The direct injection routes, such as the intracavernous administration for erectile dysfunction, were associated with no significant or serious adverse events. This localized approach minimizes systemic exposure to the cell product, thereby reducing the potential for off-target effects or systemic immunogenic reactions. The safety and efficacy demonstrated in these trials suggest that for well-defined, accessible pathologies, direct injection represents a highly favorable and robust therapeutic strategy (Schwarz et al., 2021).

In contrast, for conditions involving diffuse organ damage, such as chronic kidney disease (CKD), systemic delivery via intravenous or intra-arterial routes was the predominant strategy. The rationale for this approach is to leverage the natural homing ability of mesenchymal stem cells (MSCs) to sites of inflammation and injury throughout the organ. This method may not only deliver cells for direct tissue regeneration but also exert potent systemic immunomodulatory and anti-inflammatory effects, which are crucial in managing the complex pathophysiology of diseases like CKD (Nassar et al., 2016).

The evidence for systemic delivery in renal conditions is compelling. Multiple studies using intravenous administration of MSCs reported statistically significant improvements in key markers of renal function, including estimated glomerular filtration rate (eGFR) and serum creatinine levels. These findings support the hypothesis that systemically

administered cells can effectively reach the kidneys and ameliorate disease progression. Importantly, this systemic approach was also reported to be safe, with no significant adverse events noted, making it a viable option for patients with advanced renal disease (Sarwar et al., 2022).

A more targeted form of systemic delivery involved the infusion of cells directly into the renal artery. This method combines the widespread distribution of a systemic route with a degree of organ-specific targeting. In a study involving renal transplant recipients, a combination of peripheral vein and renal artery administration showed a trend toward better graft function compared to controls. Although the result was not statistically significant, it points toward a potential refinement in systemic delivery, aiming to increase the concentration of cells reaching the target organ while still benefiting from systemic paracrine effects (Sun et al., 2018).

For neuro-uological conditions stemming from central nervous system injury or disease, intrathecal administration represents a highly specialized delivery route. This method is designed to bypass the blood-brain barrier and deliver therapeutic cells directly into the cerebrospinal fluid, allowing them to interact with neural tissues controlling bladder function. This approach was utilized in patients with multiple sclerosis and spinal cord injury to target the underlying neurological deficits, representing a fundamentally different therapeutic strategy compared to those targeting end-organ damage (Sadiq et al., 2016).

The outcomes of intrathecal delivery were mixed. One study reported some neurological and bladder function improvement, while another found no significant change in urodynamic parameters despite an increase in patient satisfaction. This variability highlights the complexity of treating neuro-uological dysfunction. Furthermore, this route was associated with transient adverse events like headache and fever in a high percentage of participants, underscoring a potential trade-off between targeted neural delivery and a higher risk of procedure-related side effects (Salehi-pourmehr et al., 2021).

Focusing on specific clinical domains, erectile dysfunction was the most frequently studied condition. The consistent success reported across multiple trials, which predominantly used localized intracavernous injections, strongly supports this route for ED. The significant improvements in IIEF scores suggest that direct delivery to the corpora cavernosa is an effective method for restoring erectile tissue health and function, solidifying its position as a leading strategy in this area (You et al., 2019).

Similarly, for stress urinary incontinence, local injections proved highly effective. The use of transurethral or periurethral administration resulted in significant and, in one case, durable reduction in incontinence episodes. This demonstrates that for structural issues like sphincter deficiency, a direct application of muscle-derived or adipose-derived stem cells provides a targeted and effective solution, reinforcing the principle that the delivery route should be tailored to the specific anatomical and pathological nature of the condition (Carr et al., 2017).

Perhaps the most significant finding of this review is not the success of any single route, but the pervasive issue of inconsistent and incomplete reporting in the primary literature. A substantial number of included studies failed to mention the delivery route at all, making a comprehensive comparison impossible. This critical omission represents a major barrier to progress in the field, as it prevents the synthesis of evidence needed to establish standardized, effective protocols. This lack of detail severely limits the conclusions that can be drawn from the existing body of work (Lokeshwar et al., 2019).

The challenge of comparing delivery routes is further compounded by the wide variety of cell types and sources used across the studies. Interventions involved bone marrow-derived MSCs, adipose-derived MSCs, umbilical cord-derived cells, and even muscle-derived cells. Each cell type possesses unique biological properties, including differing potentials for proliferation, differentiation, and immunomodulation. Without standardization, it is impossible to isolate the effect of the delivery route from the inherent therapeutic potential of the specific cell product being used (Fan et al., 2017).

Furthermore, there is a clear and pressing need for well-designed, head-to-head comparative trials. The next phase of clinical research should focus on directly comparing two or more promising delivery routes for the same urological condition, using a standardized cell product and dosage. For example, a trial comparing the efficacy of intracavernous versus intravenous administration for erectile dysfunction could provide invaluable data to guide clinical practice and resolve current uncertainties (Tang et al., 2021).

This review suggests that the selection of a delivery route should be hypothesis-driven and tailored to the pathophysiology of the target disease. For localized and accessible pathologies like SUI and ED, direct local injection appears to be a logical, safe, and effective first-line approach. For systemic or diffuse organ pathologies like CKD, systemic administration via intravenous or targeted intra-arterial routes is more appropriate to address widespread inflammation and damage (Nassar et al., 2016).

This systematic review confirms that stem cell therapy is a promising and generally safe avenue for treating a variety of challenging urological conditions. However, the critical question of which delivery route is optimal remains largely unanswered due to a landscape of non-comparative studies with highly variable and often incomplete reporting. This review provides preliminary guidance, suggesting that direct injections are favorable for localized conditions while systemic routes are suitable for diffuse diseases.

Ultimately, the maturation of this field depends on a collective move toward more rigorous research methodologies. The findings of this review serve as a clear call to action for the scientific community to prioritize standardized reporting and conduct head-to-head comparative trials. By addressing these fundamental gaps, future research can finally elucidate the optimal strategies for cell delivery, thereby unlocking the full therapeutic potential of regenerative medicine for patients with urological diseases (You et al., 2021).

CONCLUSION

In conclusion, this systematic review affirms that stem cell therapy stands as a promising frontier for a range of challenging urological conditions, including erectile dysfunction, stress urinary incontinence, and chronic kidney disease. The collective evidence from the analyzed studies indicates that these therapies can lead to significant functional improvements and are generally well-tolerated by patients. However, the central aim of definitively comparing different delivery routes was significantly hindered by pervasive issues within the existing literature. A critical lack of direct, head-to-head comparative trials, compounded by substantial variability and frequent omissions in reporting key methodological details—most notably the administration route itself—prevents the formation of a definitive consensus on optimal delivery strategies.

The overall safety profile of stem cell therapy in urology appears favorable. Across the spectrum of delivery methods and cell types investigated, serious adverse events directly attributed to the stem cell intervention were not reported in studies with available safety data. The most common side effects were mild and transient, such as temporary fever or localized pain. This reassuring safety data supports the continued exploration of stem cell applications in clinical trials. Nevertheless, the field's progress is constrained by the short-term nature of most follow-up periods, leaving questions about the long-term durability and safety of these treatments largely unanswered.

Ultimately, while stem cell therapy holds immense potential, its maturation into a standard clinical practice in urology is contingent on a collective shift toward more rigorous and standardized research. The findings of this review underscore an urgent need for the scientific community to adopt uniform reporting guidelines and, more importantly, to design and execute well-controlled clinical trials that directly compare different delivery routes for specific conditions. By addressing these fundamental gaps in evidence, future research can establish clear, data-driven protocols that will optimize patient outcomes and finally unlock the full regenerative capacity of stem cell therapy for those suffering from urological diseases.

REFERENCES

- B. Arjmand, Majid Safavi, R. Heidari, H. Aghayan, Soroush T Bazargani, S. Dehghani, P. Goodarzi, et al. "Concomitant Transurethral and Transvaginal-Periurethral Injection of Autologous Adipose Derived Stem Cells for Treatment of Female Stress Urinary Incontinence: A Phase One Clinical Trial." *Acta Medica Iranica*, 2017.
- D. You, M. Jang, G. Song, Ha Chul Shin, N. Suh, Yong Man Kim, T. Ahn, and Choung-Soo Kim. "Safety of Autologous Bone Marrow-Derived Mesenchymal Stem Cells in Erectile Dysfunction: An Open-Label Phase 1 Clinical Trial." *Cytotherapy*, 2021.
- Dalasan You*, M. Jang, G. Song, Ha Chul Shin, N. Suh, Yong Man Kim, T. Ahn, and Choung-Soo Kim. "PD09-10 SAFETY OF AUTOLOGOUS BONE MARROW DERIVED MESENCHYMAL STEM CELLS IN ERECTILE DYS- FUNCTION: AN OPEN-LABEL PHASE 1 CLINICAL TRIAL." *Journal of Urology*, 2019.
- Dr. Jahangir Md. Sarwar, M. Ali, A. Jahan, M. S. Hossain, M. Kayes, F. Ferdous, Shahtajrab Mohammad Saltanat, and Md. Firoj Khan. "Autologous Adipose-Derived Mesenchymal Stem Cell Transplantation for Management of Chronic Kidney Disease Patients: A Clinical Trial in Human." *Scholars Journal of Applied Medical Sciences*, 2022.
- E. Schwarz, Nathalie Busse, Karen Mulholland Angelus, Ahmed, Omair, Aubriana A Schwarz, and Paul C Bogaardt. "Intracavernous Injection of Stem Cell-Derived Bioactive Molecules for Erectile Dysfunction—a Pilot Phase Non- Randomized Controlled Trial." *Journal of Men's Health*, 2021.
- G. Nagmetova, A. Rysbek, and A. Kurmanbayev. "Isolation and Study of Effective Biocellulose Producers." *Journal of Biotechnology*, 2019.
- H. Salehi-pourmehr, Ozra Nouri, A. Naseri, L. Roshangar, R. Rahbarghazi, S. Sadigh-Eteghad, J. Mahmoudi, et al. "Clinical Application of Stem Cell Therapy in Neurogenic Bladder: A Systematic Review and Meta-Analysis." *International Urogynecology Journal*, 2021.
- L. Carr, L. Tu, M. Robert, D. Quinlan, K. Carlson, S. Herschorn, R. Dmochowski, et al. "AUTOLOGOUS MUSCLE DERIVED CELLS FOR URINARY SPHINCTER REPAIR FOR RECURRENT OR PERSISTENT STRESS URINARY INCONTINENCE AFTER CONTINENCE

SURGERY: PD50-08,” 2017.

- O. Kim. “Abstract TP320: A Randomized, Double-Blind, Placebo-Controlled, Phase I / IIa Clinical Trial for Evaluation of the Safety and Potential Therapeutic Effects After Intravenous Transplantation of Human Umbilical Cord- Derived Mesenchymal Stem Cells in Patients With Cerebral Infarction,” 2018.
- Qiaoqiao Tang, Hui Xue, Qiao Zhang, Yingyi Guo, Hao Xu, Y. Liu, and Jia-Mei Liu. “Evaluation of the Clinical Efficacy of Stem Cell Transplantation in the Treatment of Spinal Cord Injury: A Systematic Review and Meta-Analysis.” *Cell Transplantation*, 2021.
- Qipeng Sun, Zheng-yu Huang, Fei Han, Ming Zhao, Ronghua Cao, Daqiang Zhao, L. Hong, et al. “Allogeneic Mes- enchymal Stem Cells as Induction Therapy Are Safe and Feasible in Renal Allografts: Pilot Results of a Multicenter Randomized Controlled Trial.” *Journal of Translational Medicine*, 2018.
- S. Lokeshwar, P. Patel, S. Shah, and R. Ramasamy. “A Systematic Review of Human Trials Using Stem Cell Therapy for Erectile Dysfunction.” *Sexual Medicine Reviews*, 2019.
- S. Muthu, Madhan Jeyaraman, A. Gulati, and Arunabh Arora. “Current Evidence on Mesenchymal Stem Cell Therapy for Traumatic Spinal Cord Injury: Systematic Review and Meta-Analysis.” *Cytotherapy*, 2020.
- S. Sadiq, Leslie Blackshear, Gloria Joo, T. Vyshkina, and V. Harris. “Multiple Intrathecal Dosing of Neural Progen- itors Administered to Progressive MS Patients with Disability Is Safe and Improves Disability Scores (I10.008).” *Neurology*, 2016.
- Wael Nassar, M. El-Ansary, D. Sabry, M. Mostafa, Tarek Fayad, E. Kotb, Mahmoud Temraz, Abdel-Naser Saad, W. Essa, and H.Ghavami Adel. “Umbilical Cord Mesenchymal Stem Cells Derived Extracellular Vesicles Can Safely Ameliorate the Progression of Chronic Kidney Diseases.” *Biomaterials Research*, 2016.
- Xiao Fan, Jin-Zhao Wang, Xiaoyuan Lin, and Li Zhang. “Stem Cell Transplantation for Spinal Cord Injury: A Meta- Analysis of Treatment Effectiveness and Safety.” *Neural Regeneration Research*, 2017.
- Yoon Soo Kyung, Ki-Sung Hong, Hyung-Min Chung, Jung Hyun Shin, Myung-Soo Choo, Eun-Young Kim, J. Shin, et al. “A Single-Center, Phase 1/2a Trial of hESC-Derived Mesenchymal Stem Cells

(MR-MC-01) for Safety and Efficacy in Interstitial Cystitis Patients.” *Stem Cells Translational Medicine*, 2025.