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From Preservation to Regeneration: Stem Cell-Derived Therapies in Machine-Perfused Kidney Transplants – A systematic Review and Meta-analysis

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Abstract
Introduction: Ischemia-reperfusion injury (IRI) remains a critical determinant of graft outcomes in kidney transplantation, contributing to delayed graft function and reduced long-term survival. Machine perfusion has emerged as a dynamic preservation strategy offering a therapeutic window to condition organs prior to implantation. The integration of stem cells and extracellular vesicles (EVs), known for their immunomodulatory and cytoprotective properties, into perfusion protocols represents a novel and potentially synergistic approach. However, the evidence base remains limited and heterogeneous.

Methods: This systematic review and meta-analysis evaluated the therapeutic potential of stem cell-based interventions during machine perfusion, following PRISMA guidelines. PubMed, Embase, and Scopus were searched for experimental studies using stem cells or EVs during hypothermic or normothermic machine perfusion in animal or discarded human kidneys. Outcomes included renal function, injury biomarkers, inflammation, and histology.

Results: Nine studies were included, seven in meta-analysis. Several reported reductions in inflammatory cytokines (IL-6, IL-1β) and biomarkers (NGAL) following stem cell or EV administration. However, meta-analysis showed no significant effects on creatinine clearance (SMD: 0.00; 95% CI: −0.54 to 0.55), urine output (SMD: 0.54; 95% CI: −0.46 to 1.55), or NGAL (SMD: −1.68; 95% CI: −5.60 to 2.25). Stem cell retention was limited, mechanisms of action remain incompletely understood, and only one study assessed post-transplant function.

Conclusion: Despite potential immunomodulatory and cytoprotective effects, consistent functional benefits were not demonstrated. Standardized studies incorporating transplant models and long-term outcomes are needed to clarify therapeutic potential and optimize delivery strategies.

Introduction

Despite advances in kidney transplantation in recent years, the demand for donor organs continues to significantly exceed supply, resulting in prolonged waitlist durations.(1–3) The ongoing shortage of organs has led to significant efforts to expand the donor pool and increase graft use, driving the development of innovative preservation techniques such as machine perfusion (MP).(4–7) Although widely used, conventional static cold storage has limitations, such as ischemia-induced cellular damage, suboptimal graft recovery, and high organ discard rates. To overcome these challenges, alternative preservation modalities such as hypothermic and normothermic machine perfusions have been introduced.(8–11) These dynamic preservation techniques aim to improve organ viability by providing continuous oxygenation. Normothermic perfusion additionally supports active metabolism by delivering nutrients and metabolic substrates, while clearing of waste products throughout the preservation period.(12–14) Simultaneously, regenerative medicine has become a promising complement to organ preservation, with stem cell-based therapies introducing new strategies to reduce ischemia-reperfusion injury and promote graft repair mechanisms.(15–20) Specific stem cell populations, along with their bioactive derivatives such as extracellular vesicles (EVs), display powerful regenerative and immunomodulatory capacities that hold promise for enhancing kidney graft preservation and function.(11,21–23) Although mesenchymal stromal cells (MSCs) represent the most frequently studied cell population in this context, other progenitor cell types and stem cell-derived products have also been investigated and were therefore included in this review. Combining these cell-based approaches with advanced perfusion technologies may improve transplant outcomes and bridge the gap between organ supply and demand. This systematic review investigates the therapeutic potential of stem cell-derived products within machine perfusion systems, specifically focusing on their ability to reduce renal ischemia-reperfusion injury and enhance creatinine clearance. The current body of literature on this topic remains highly heterogeneous, notably in terms of perfusion modalities, timing of interventions, analytical methodologies, and types of cellular products. This variability underscores the importance of a comparative analysis of existing studies to elucidate the relative advantages and limitations of each approach. By synthesizing current evidence, our systematic review and meta-analysis aim to provide insights into emerging strategies that could improve kidney graft preservation and post-transplant outcomes.

Methods

1.1. Search Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.(24,25) A comprehensive literature search was performed in PubMed, Embase, and Scopus on 25 February 2025, using the concepts “stem cell”, “machine perfusion”, and “kidney”, with additional perfusion and stem cell-related terms. The detailed search strategy is presented in Table S1 and further described in Supplemental Methods.

1.2. Study Selection and Data extraction

Studies investigating the effect of stem cell-based therapies combined with MP vs. MP alone on graft function or injury in animal models or patients undergoing kidney transplantation were considered. Studies were included if they met the following criteria: (1) published in English or French, (2) original research articles, (3) focusing on kidney transplantation, (4) conducted in a machine perfusion model, and (5) investigating stem cell-based therapies. Studies were excluded if they did not meet these criteria or were unavailable in full-text format. Details are in the Supplemental Methods.

1.3. Risk of Bias and Quality Assessment

The Systematic review center for laboratory animal experimentation (SYRCLE’s) risk of bias tool for animal studies was used to evaluate study methodologies, with quality assessment of the reported articles based on animal experiments (details in the Supplemental Methods).(26) For studies on

human organs, methodological quality was assessed using the National Institutes of Health (NIH) scoring tools.

1.4. Statistical Analysis

Renal function was assessed using creatinine clearance during perfusion, after perfusion or after transplantation, and mean urine output during perfusion. Renal blood flow and fractional excretion of sodium were also considered. Renal injury was assessed through Neutrophil Gelatinase-Associated Lipocalin (NGAL) levels. For each outcome, when available, means and standard deviations were extracted for control and treatment groups, along with sample sizes (details in the Supplemental Methods). All analyses were performed using the metafor package in R (v4.3.0; R Core Team, Vienna, Austria). Although substantial methodological heterogeneity was anticipated across studies—including differences in experimental models, perfusion protocols, and cellular products—a meta-analysis was performed to provide an exploratory quantitative synthesis of available functional outcomes. Funnel plots were generated to explore potential publication bias for the outcomes included in the meta-analyses.

Results

1.1. Study Selection

A total of 1,862 studies were identified through the database search (Pubmed, Embase and Scopus). After removal of duplicates identified by Covidence (n=681), 874 studies were screened with titles and abstracts.(27) During full-text review, 110 of the 119 articles were excluded for the following reasons: five did not involve kidneys, 40 were review articles or conference abstracts, 53 did not involve machine perfusion, and 12 did not involve stem cell–based therapy or derivatives. Thus, nine experimental studies met the predefined inclusion criteria and were included in the qualitative analysis of this systematic review.(15,28–35) Of these, four studies reported sufficient results for aggregated data analysis on the effect of MSCs treatment during MP on creatinine clearance, five on urinary output and three on NGAL levels. The study selection process is summarized in the PRISMA flow diagram (Figure S1).

1.2. Quality and risk of bias assessment

Risk of bias was mostly “unclear” for animal studies due to insufficient methodological reporting, particularly in relation to selection bias (Figure S2, Tables S2 and S3). Specifically, all studies failed to clearly report on the method of allocation sequence generation and concealment. Baseline group similarity was reported in only one study,(35) while adjustment for potential confounders remained largely unaddressed. Performance bias was variably reported: random housing of animals is not applicable to most included studies, as they were conducted ex vivo rather than involving live animals.(28–31,34) Nevertheless, only one study explicitly reported blinding of caregivers and investigators, while the others did not provide sufficient information for assessment.(35) Detection bias was poorly mitigated, with limited reporting on random outcome assessment and assessor blinding. Due to a lack of reporting on the handling and justification of missing data, attrition bias was judged unclear in the majority of studies, except for two studies.(29,35) Reporting bias was considered low in studies with available protocols or comprehensive outcome reporting.(28–31,35) Other sources of bias were minimal across studies, with most publications demonstrating freedom from confounding factors such as unit of analysis errors or funding-related influence.(28–31,34,35) For human studies, the overall quality was better, most often “good” or “not reported” (Figure S2, Table S4).

1.3. Study Characteristics

Nine experimental studies met the inclusion criteria, all exploring stem/progenitor cell therapies delivered during ex vivo kidney machine perfusion. Table 1 and Figure 1 summarize key parameters: species, model design, sample size, and ischemia times.

Four studies employed porcine kidneys(28,30,31,35), three human discarded kidneys(15,32,33), one a rat model(29), and one included all three.(34) Porcine kidneys were exposed to controlled warm

ischemia (20-75 minutes) via renal artery clamping or circulatory arrest (n=6 studies).(28–31,34,35) In human studies, warm ischemia was uncontrolled, reported in one case as 9-18 minutes.(32) Most studies used static cold storage, with durations ranging from 2h to 37h (n=6 studies).(15,31–35) Perfusion protocols varied: typically, kidneys underwent Normothermic Machine perfusion (NMP, at ~37°C) either alone (n=3 studies)(15,31,32) or following an initial phase of hypothermic machine perfusion (HMP) or oxygenated hypothermic perfusion (HOPE) (n=5 studies).(28,30,33–35) A single study investigated HMP alone.(29) NMP duration ranged from 2 to 7 hours, while HMP/HOPE phases lasted 2-24 hours. Only one study included transplantation and 14-day follow-up.(35)
Cell types investigated were MSCs from adipose tissue (n=1 study),(35) bone marrow (n=2 studies)(29,34) or both (n=2 studies)(30,31) (Table 2). One study tested EVs from MSCs as a cell-free therapy alternative.(29) Others used neonatal kidney stem progenitor cells (nKSPCs)(32), multipotent adult progenitor cells (MAPCs)(15) or EVs from porcine urine progenitor cells (UPCs) or MSCs.(28,33) Most studies compared cell-based therapy to machine perfusion alone (n=8 studies),(15,28–30,32–35) with additional groups such as porcine vs. human MSCs (n=1 study),(35) adipose-derived MSCs (A-MSCs) vs. bone marrow-derived MSCs (BM-MSCs) (n=1 study),(30) or EVs combinations (HMP/EVs + NMP vs. HMP/EVs + NMP/EVs, n=1 study)(28). Cell dosing varied: two studies used labelled cells at different concentrations (n=2 studies),(31,34) three used 10 million cells based on safety data;(30,32,35) two used arbitrary doses (50 million and 3 million).(15,29) EVs doses were either arbitrarily set (28.5×10^9 EVs)(33) or based on secretion from cultured cells (6.5×10^9 EVs from 12 million cells).(28) Administration was mostly via the renal artery during perfusion, often 60 min after NMP initiation;(15,28,30,31,35) some studies did not specify timing but followed a similar approach. Despite model and protocol heterogeneity, studies shared outcome measures: perfusion parameters, renal function (e.g., urine output, creatinine clearance), and cytokine levels. Mechanistic insights were obtained via biochemical, histological, and immunological analyses, including injury biomarkers (e.g., NGAL, IL-6, IL-10), cytokine profiling, advanced imaging (Magnetic Resonance Imaging (MRI), Contract-Enhanced Ultrasound (CEUS)), cell tracking, and transcriptomics.

1.4. Composition of the perfusate

Table 3 summarizes the composition of the perfusate used during HMP and NMP, highlighting substantial heterogeneity in both base solutions and pharmacologic additives. Among the perfusion devices used across the included studies, two employed an adapted pediatric cardiopulmonary bypass system.(15,32) Four studies utilized a custom-made device based on the LifePort® system (Organ Recovery Systems, Itasca, IL, USA).(28,30,31,35) One study used the VitaSmart® device from Bridge to Life (London, UK),(33) another employed the RM3 system (Waters Medical Systems, Rochester, MN, USA),(34) and the remaining study did not specify the device used.(29) Most HMP strategies employed University of Wisconsin-based machine perfusion solutions (UW-MPS, Bridge to Like Ltd., Columbia, SC, USA), typically perfused at 4°C and low pressures ranging from 25 to 50 mmHg (n=5 studies).(29,30,33–35) Exception included the use of KPS-1® (Organ Recovery System, Itasca, IL, USA) for one study.(28) Notably, HMP perfusates were acellular and not supplemented with pharmacologic additives beyond the base solution. In contrast, NMP protocols consistently incorporated oxygenated, red cell-based perfusates, either with autologous whole blood (n=1 study)(34) or packed red blood cells (n=7 studies).(15,28,30–33,35) The perfusate was enriched with additives targeting metabolic support (e.g., glucose, insulin, calcium gluconate, sodium bicarbonate), antimicrobial prophylaxis (e.g., amoxicillin-clavulanate, cefuroxime), and vascular modulation (e.g., verapamil, mannitol). Most protocols operated at physiological temperatures (36–37°C) and perfusion pressures between 70 and 120 mmHg, with oxygenation ensured via carbogen (95% O_2/5% CO_2) at flow rates of 0.2–0.5 L/min. While the core components were similar, differences emerged in the complexity of additives—ranging from basic formulations (e.g., creatinine, glucose, antibiotics) to more elaborate mixtures including multivitamins, Nutriflex® (B. Braun Melsungen AG, Melsungen, Germany) and dexamethasone.(15) Overall, NMP protocols displayed a convergence toward physiologically active, cell-rich perfusates with targeted metabolic and pharmacologic supplementation.

1.5. Functional Outcomes

All studies showed no significant differences in perfusion-related parameters such as renal blood flow, intrarenal resistance, and oxygen consumption between treated and control groups.(15,28,30–35) Notably, one study reported enhanced cortical and medullary perfusion in MAPCs-treated kidneys after 4 hours of NMP, as measured by CEUS—a non-invasive imaging technique that evaluates microvascular blood flow in real time.(15) Creatinine clearance during perfusion and fractional sodium excretion were generally similar across groups, though some studies observed modest improvements. For example, one study reported improved creatinine clearance in kidneys perfused with A-MSCs although this difference was not statistically significant.(30) Two studies observed increased urine output in treated kidneys, (15),(32) but only one reported a statistically significant difference.(15) One study reported kidney function measurements over a 14-day period following transplantation, demonstrating significant elevated levels of plasmatic creatinine in control groups compared to the HOPE and NMP+hMSCs groups.(35) However, others found no significant differences in renal function endpoints after machine perfusion, including urine production.

Meta-analysis on aggregated results concerning creatinine clearance was performed on four studies reporting creatinine clearance during NMP,(28,30,32,35) and one reporting post-HMP values.(34) The pooled effect size was not significant (SMD: 0.00; 95% CI: –0.54 to 0.55), indicating no measurable impact. Heterogeneity was low (I^2 = 0.0%, τ^2 = 0.00), and Cochran's Q test did not suggest significant variability between studies (p = 0.81). Results from Lohmann et al., who measured creatinine clearance at day 14 post-transplantation, were consistent with the findings during perfusion (Figure 2).(35) Mean urine output during perfusion was reported in five studies, which were all included in the meta-analysis (Figure 3).(15,28,30,32,34) The pooled analysis yielded an SMD of 0.54 (95% CI: –0.46 to 1.55), with no statistically significant difference between treated and control groups. Heterogeneity was moderate (I^2 = 66.5%, τ^2 = 0.84), and Cochran's Q test indicated significant between-study variability (p = 0.031). In summary, the aggregated results do not demonstrate a consistent link between stem cell-based interventions and functional improvement during perfusion. Meta-analyses with standardized mean differences revealed non-significant pooled effects of stem cell or stem cell-derived product on renal blood flow and fractional sodium excretion with low heterogeneity, as detailed in Supplementary Results (Figure S3, S4). Funnel plots were generated to explore potential publication bias and are presented in Supplementary Figure S5.

1.6. Injury Markers

Biomarker-based assessment of kidney injury yielded conflicting results. Several studies evaluated NGAL and Kidney Injury Molecule-1 (KIM-1) as primary markers. Three reported decreased NGAL levels in urine or perfusate after treatment with nKSPCs, MAPCs, or MSCs, suggesting potential renoprotection.(15,30,32) Conversely, other investigations failed to detect significant differences in NGAL or KIM-1 levels between treated and control groups.(28,34,35) One study noted a progressive rise in plasma NGAL with progressive reduction thereafter although not reaching basal levels over 14 days post-transplantation in all groups, with no intergroup differences.(35)

A meta-analysis of NGAL levels was performed on three studies.(15,28,34) The study by Lohmann et al., measuring NGAL at day 2 post-transplantation, were analysed separately.(35) Due to large differences in absolute values between studies, only SMD were used. The pooled SMD was –1.68 (95% CI: –5.60 to 2.25), indicating no statistically significant difference between treated and control groups (Figure 4). Heterogeneity was substantial (I^2 = 95.5%, τ^2 = 11.14), and Cochran's Q test confirmed significant between-study variability (p < 0.001). Post-transplant NGAL results were consistent with perfusion-phase findings. Overall, meta-analysis showed no significant impact of stem cell-based therapies on NGAL levels during or after perfusion.

One study reported reduced ischemic injury in kidneys treated with HOPE plus EVs compared to controls. In the same study, renal caspase-3 expression—an apoptosis marker—was significantly higher in controls than in EV-treated kidneys.(33) Another study observed no significant difference in leukocyte infiltration between MAPCs-treated and control kidneys, but found reduced flavin mononucleotide (FMN) release, a mitochondrial injury marker, in the treated group.(15) In HMP

settings, another group reported lower levels of tissue injury markers (lactate dehydrogenase, lactate) and oxidative stress, in MSCs- or EVs-treated kidneys compared to controls.(29) A subsequent study confirmed reduced oxidative stress, as evidenced by decreased glutathione levels, in kidneys treated with both HMP and NMP combined with EVs.(28)

1.7. Inflammatory Response

A consistent pattern across studies was the modulation of inflammatory responses following stem cell or EVs administration. Two studies reported a reduction in the pro-inflammatory cytokine interleukin-6 (IL-6) in kidneys subjected to NMP with either nKSPCs or A-MSCs, compared to controls. However, only one of these studies demonstrated a statistically significant decrease.(30) A separate investigation reported a significant decrease in IL-6 levels two hours post transplantation in the HOPE group relative to controls. However, in the same study, IL-6 secretion increased in all NMP groups to similar levels.(35) The expression of the pro-inflammatory marker interleukin-1 beta (IL-1β) was significantly decreased in studies using nKSPCs and MAPCs combined with NMP, or HMP/NMP plus EVs, when compared to control groups.(15,28,32) In contrast, an upregulation of IL-1β was observed in kidneys treated with MSCs in an HMP model, although this increase did not reach statistical significance.(34) The pro-inflammatory chemokine interleukine-8 (IL-8) levels were found to be significantly reduced in nKSPCs-treated kidneys in one study,(32) whereas another study reported significant higher IL-8 expression in kidneys treated with BM-MSCs and A-MSCs compared to controls.(30) Furthermore, one study reported a non-significant reduction in interleukin-18 (IL-18), a pro-inflammatory cytokine, in kidneys treated with HMP or NMP combined with EVs, compared to control groups.(28) At the mRNA level, IL-10, IL-8, and transforming growth factor-beta (TGF-β)—a cytokine involved in fibrosis and immune regulation—were all significantly reduced in the HOPE group one hour after transplantation, compared to controls.(35)
The anti-inflammatory cytokine interleukin-10 (IL-10) was significantly increased in MAPCs-treated kidneys, but not in other models.(15) Data from another study showed a significant increase in interleukin-1 receptor antagonist (IL-1RA), an anti-inflammatory mediator, suggesting a potential shift toward an anti-inflammatory profile following treatment with HMP or NMP combined with EVs.(33) One study also assessed Hepatocyte Growth Factor (HGF) and Vascular Endothelial Growth Factor (VEGF)—key in regeneration and angiogenesis—reporting significantly increased expression in HOPE plus EVs-treated kidneys compared to controls.(33) Additionally, transcriptomic analyses revealed activation of immunomodulatory genes such as FOXP3, SOCS5, and ISG15, as well as metabolic regulators including Idh2, Ndufs8, and Pdhb, reinforcing the molecular basis for observed immunologic changes.(28,29)

1.8. Histological findings

Histological assessment of tissue injury was performed in six out of nine included studies. Across all experimental groups, and independently from the experimental group, common histopathological features included inflammation, tubular atrophy, and varying degrees of fibrosis. Two studies reported significantly reduced tissue damage in kidneys treated with MSCs, EVs, or HOPE combined with EVs compared to controls. Specifically, treated groups exhibited decreased tubular epithelial cell flattening, tubular necrosis, and luminal obstruction compared to control groups.(29,33) Another study demonstrated improved structural preservation in kidneys treated with HMP/EVs or NMP/EVs, with enhanced tissue integrity observed after 5 hours of NMP. However, histological lesions such as tubular dilation, epithelial detachment, and inflammatory infiltrates were still evident following NMP in this study.(28)

1.9. Cell tracking and Localization

Several studies employed tracking techniques to confirm cell delivery and localization within renal tissues. Among them, three studies used fluorescent labelling methods,(15,32,34) while one study assessed cell retention by quantifying the presence of the Y chromosome in the renal cortex.(35) MSCs and MAPCs were frequently found in the renal cortex, glomeruli, or peritubular spaces following perfusion.(15,34,35) One study reported that nKSPCs remained detectable in the renal cortex for up to six hours.(32) Cell delivery appeared limited in another study.(31) Only the highest

dose (10 million MSCs) led to detectable retention, primarily within glomerular capillaries. However, many of these cells were disintegrated, with fluorescent labelling indicating membrane fragments rather than intact MSCs. Kinetic data further showed that most cells disappeared rapidly from the perfusion circuit, especially when no kidney was connected, suggesting trapping outside the organ. Even with a kidney, only minimal retention occurred after the first passage. No quantification per high-power field was provided, and flow cytometry detected very few MSCs in renal tissue, reinforcing the conclusion that cell engraftment was low and largely ineffective.(31)

Discussion

This is the first systematic review and meta-analysis assessing the therapeutic potential of combining stem cell-based therapies with dynamic organ preservation to reduce renal ischemia-reperfusion injury and enhance creatinine clearance. Regardless of stem cell source or perfusion temperature, the studies included in this systematic review and meta-analysis did not provide conclusive evidence of a significant impact of stem cell-based intervention during machine perfusion on renal injury and function, although it should be noted that there was considerable methodological variation between studies. Several studies reported decreased levels of pro-inflammatory cytokines and increased anti-inflammatory mediators, suggesting a potential immunomodulatory effect, although a meta-analysis of these outcomes was not possible. Nevertheless, these changes did not translate into a significant functional improvement during perfusion in preclinical studies. One possible explanation for this apparent discrepancy relates to the temporal dynamics of tissue repair following ischemia–reperfusion injury. Most studies included in this review performed normothermic perfusion for relatively short periods, typically between two and seven hours. While this time-frame may be sufficient to detect early molecular or inflammatory changes, it may be insufficient for these biological effects to translate into measurable functional recovery. Experimental models of renal ischemia–reperfusion injury indicate that tissue repair processes, including tubular regeneration and endothelial recovery, occur over time scales of days to weeks following reperfusion. Tubular cell proliferation begins within 24–48 hours, peaks around 72 hours to day 4, and functional recovery is largely achieved by day 7–14 (36,37), while endothelial repair involving pro-angiogenic signaling may extend beyond 7 days post-reperfusion.(38,39) Consequently, reductions in inflammatory mediators observed during *ex vivo* perfusion may represent early biological signals whose functional consequences would only become apparent after transplantation and/or prolonged *in vivo* reperfusion. Consequently, reductions in inflammatory mediators observed during *ex vivo* perfusion may represent early biological signals whose functional consequences would only become apparent after transplantation and/or prolonged *in vivo* reperfusion.(16,23)

The biological mechanisms underlying the potential benefits of stem cell-based therapies during machine perfusion remain incompletely understood. Increasing evidence suggests that the therapeutic activity of stem cells is largely mediated through paracrine signaling rather than durable engraftment within the target tissue. Stem cells secrete a wide range of bioactive molecules—including cytokines, growth factors, and extracellular vesicles—that can modulate inflammatory pathways, reduce oxidative stress, and promote tissue repair processes.(40,41) Experimental studies in kidney and other solid organ models have shown that stem cell-derived extracellular vesicles can reproduce many of the immunomodulatory and cytoprotective effects attributed to the cells themselves.(22,23,42) These vesicles contain regulatory proteins, lipids, and microRNAs capable of influencing endothelial integrity, mitochondrial function, and immune cell activation during ischemia-reperfusion injury. Importantly, several studies included in this review indicate that cell retention within the kidney is limited, with many infused cells entrapped within glomerular capillaries or rapidly cleared from the perfusion circuit.(31) These findings support the hypothesis that the observed biological effects may primarily reflect transient paracrine interactions rather than sustained cellular integration into renal tissue.

Although machine perfusion has gained clinical relevance, most clinical studies to date have focused on comparing perfusion modalities (e.g., HMP vs. NMP, with or without oxygen), while the

integration of regenerative therapies into these platforms remains largely experimental.(43–46) Protocols across studies show marked heterogeneity, involving various cell types (e.g., MSCs from bone marrow or adipose tissue, MAPCs, urine-derived progenitors, or EVs) and different ischemic durations, perfusion temperatures, devices, pressures, and perfusate compositions. This variability limits the ability to draw definitive conclusions regarding efficacy or optimal conditions for therapeutic delivery. Moreover, cell dosing remains highly heterogeneous across studies. Few investigations have compared different doses with standardized endpoints, and no consensus has emerged regarding the optimal number of stem cells to use. While higher doses (e.g., 10 million cells) appear necessary for detectable renal retention, even at this level, only a minority of glomeruli show MSCs presence.(31) In many cases, fluorescent labeling indicated cell debris rather than intact MSCs, suggesting that cell death occurs shortly after infusion. These observations strongly indicate that cell viability and biodistribution are critical challenges. Quantitative data on how many stem cells reach the renal parenchyma remain insufficient. The rapid decline of MSCs counts from the perfusate, particularly when kidneys are not connected to the circuit, further suggests that many cells are trapped or lost outside the graft. This could explain the absence of a dose-response relationship and reinforce the hypothesis that therapeutic effects are likely mediated via paracrine signaling rather than sustained engraftment.(40–42,47) As for the type of therapeutic agent, both stem cells and EVs have been tested, but direct comparisons are rare. Only a few studies assessed different MSCs sources (e.g., bone marrow vs. adipose-derived), and no one provided conclusive evidence favoring one over another. Similarly, comparisons between stem cells and EVs are limited and inconclusive, making it difficult to recommend one strategy over another. Another source of heterogeneity relates to the experimental models used across studies, which should be considered when interpreting translational relevance. While rodent models are useful for mechanistic investigations, porcine models more closely resemble human renal anatomy and transplantation conditions, which may influence the interpretation and translational relevance of the reported outcomes.

A major gap in the current body of evidence is the lack of post-transplantation data. Notably, only one study included in this review evaluated the impact of stem cell administration during machine perfusion in a transplantation setting with post-operative follow-up.(35) In this porcine autotransplantation model, kidneys treated with MSCs during NMP were subsequently transplanted and monitored for 14 days. Although the intervention was technically feasible and safe, no significant improvement in post-transplant renal function was observed compared with controls. Despite these neutral findings, this study provides important proof-of-concept for integrating cell-based therapies into *ex vivo* perfusion platforms prior to transplantation. The absence of functional improvement may reflect the limited sample size, the complexity of post-transplant injury mechanisms, or insufficient exposure time to the therapeutic intervention. These observations highlight the need for future studies to incorporate transplant models with clinically relevant endpoints, including delayed graft function, graft survival, and long-term renal function.

Finally, the quality of evidence is limited. Risk of bias was often assessed as unclear due to poor reporting of key methodological aspects, such as randomization, blinding, or allocation concealment. Small sample sizes, inconsistent reporting of cell characterization and viability, and variability in perfusion protocols further limit the strength of conclusions that can be drawn. Standardization of delivery protocols, systematic cell tracking, and robust functional assessment in transplant models will be essential to advance the field. Beyond biological efficacy, the clinical translation of stem cell-based therapies during machine perfusion raises important logistical and economic challenges. The production of clinical-grade MSCs requires specialized GMP-compliant facilities, rigorous quality control, and regulatory oversight, which increase both costs and implementation complexity.(48) Future translational studies should therefore assess not only biological efficacy but also the scalability and cost-effectiveness of these approaches. To support future study design, Table 4 summarizes the key parameters that should be considered in experimental protocols investigating stem cell therapies during machine perfusion.

This study has some limitations. Publication bias is possible, as studies with negative or non-significant results are less likely to be published. Outcome heterogeneity may affect the robustness of pooled results. The quality of included studies varied, with some showing methodological limitations. Differences in study design, animal species and donor conditions, and outcome definitions may further limit comparability. In the present study, pooled analyses were therefore intended to complement the qualitative synthesis and to provide an overview of potential effect directions across studies investigating stem cell-based interventions during machine perfusion. Given the limited number of studies and methodological variability, the results of the meta-analysis should be interpreted cautiously and primarily considered as an exploratory summary of the currently available evidence rather than definitive estimates of therapeutic efficacy. Moreover, funnel plots were generated to explore potential publication bias; however, because fewer than ten studies were included in the meta-analyses, interpretation of funnel plot asymmetry should be considered with caution.

In summary, this systematic review and meta-analysis of preclinical studies on stem cell-based therapies during machine perfusion did not demonstrate significant improvement in renal injury or function during perfusion, regardless of stem cell source or perfusion protocol. However, such interventions might be associated with immunomodulation and increased anti-inflammatory cytokines. Clinical translation will likely depend on overcoming challenges in delivery efficiency, mechanistic understanding, and rigorous validation in transplant models. In particular, the relative contribution of viable cells, paracrine signaling, and the release of bioactive molecules following cell apoptosis remains incompletely understood and warrants further investigation.

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Statement of Ethics
A statement of ethics is not applicable because this study is based exclusively on published literature.
Conflict of Interest Statement
All authors declare no conflict of interest.

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Author Contributions
Margaux Navez: Conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript
Elisa Dos Santos Barata: Collection and assembly of data, final approval of manuscript
Nathalie Maes: Data analysis
Elena Levtchenko, Fanny Oliveira Arcolino, Perrine Burdeyron and Clara Steichen: Provision of study data, final approval of manuscript
Olivier Detry, Nicholas Gilbo and François Jouret: Conception, Administrative support, manuscript writing, final approval of manuscript

Data Availability Statement
All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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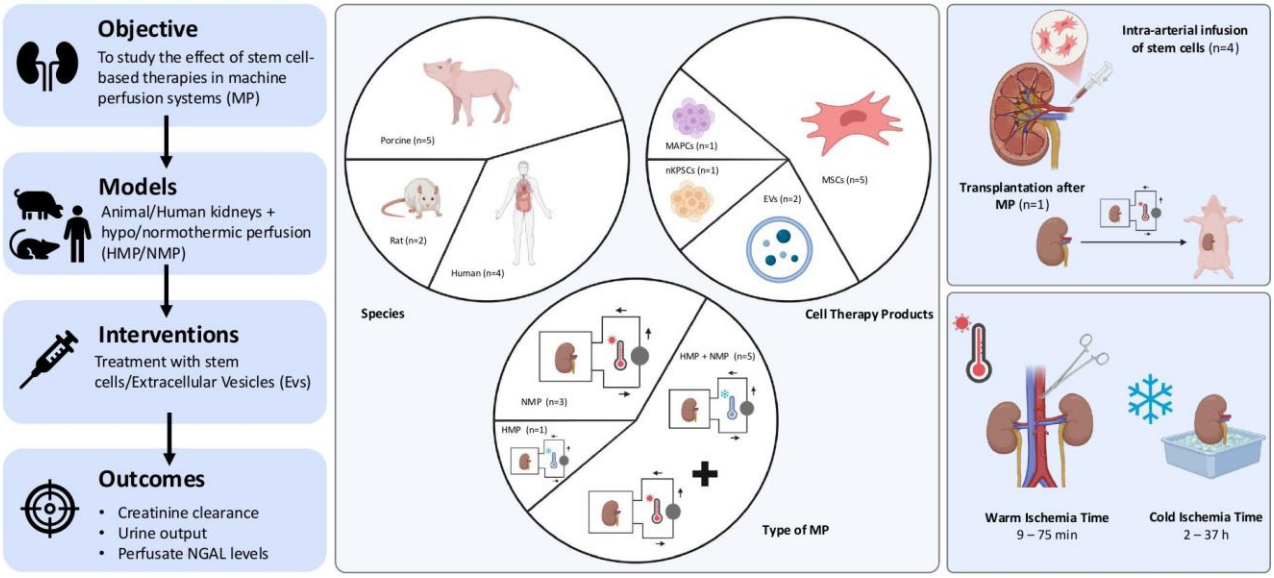
Figure Legends

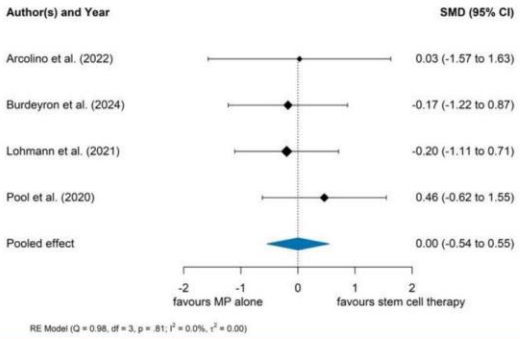
Fig 1. Overview of experimental designs investigating stem cell-based therapies in kidney machine perfusion models. This schematic summarizes key aspects of 9 translational studies evaluating the effects of stem cell–derived therapies in ex vivo kidney perfusion systems. (Left) The primary objective is to assess how stem cells or extracellular vesicles (EVs) influence kidney function using animal (porcine, rat) and human kidneys subjected to hypothermic (HMP) and/or normothermic (NMP) machine perfusion. Reported outcome measures include creatinine clearance, urine output, and perfusate neutrophil gelatinase-associated lipocalin (NGAL) levels. (Center) Studies vary in species used (porcine, rat, human), cell therapy products applied [multipotent adult progenitor cells (MAPCs), kidney progenitor cells (nKPSCs), mesenchymal stromal cells (MSCs), or EVs], and type of machine perfusion (MP) strategy. (Right) Delivery approaches include intra-arterial infusion of stem cells, and organs are subjected to variable warm ischemia times (9–75 min) and cold ischemia times (2–37 h) before perfusion.

Fig 2. Creatinine Clearance During Perfusion: Meta-Analysis of Standardized Mean Differences. This figure summarizes the results of four studies reporting creatinine clearance during machine perfusion.(28,30,32,35) The pooled effect size is not statistically significant, with the standardized mean difference (SMD [95% CI]) estimated at 0.00 (–0.54 to 0.55), indicating no effect of stem cell or stem cell-derived product administration on creatinine clearance during perfusion. Heterogeneity across studies was low ($I^2 = 0.0\%$), with Cochran's Q test indicating no significant heterogeneity ($p = 0.81$), and between-study variance $\tau^2 = 0.0$. Results from Lohmann et al. (2021), assessing creatinine clearance 14 days post-transplantation, and from Vallant et al. (2024), reporting outcomes post-reperfusion are analyzed separately. These findings are consistent with those observed during perfusion.

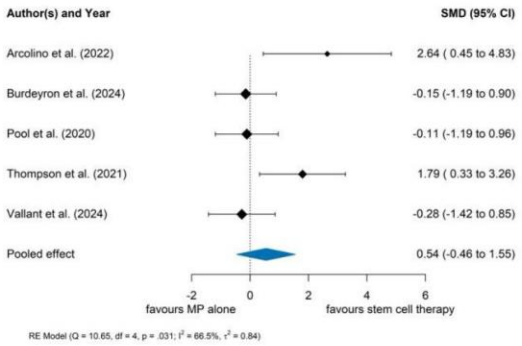
Fig 3. Mean Urine Output During Perfusion: Meta-Analysis of Standardized Mean Differences. This figure presents the pooled analysis of five studies reporting mean urine output during machine perfusion.(15,28,30,34,35) The overall effect of stem cell or stem cell-derived product administration on urine output is not statistically significant, with a standardized mean difference (SMD [95% CI]) of 0.54 (–0.46 to 1.55). Assessment of heterogeneity revealed moderate variability across studies ($I^2 = 66.5\%$), with Cochran's Q test confirming the presence of heterogeneity ($p = 0.031$) and a between-study variance τ^2 of 0.84. These results suggest that stem cell-based interventions during machine perfusion do not significantly influence urine output.

Fig 4. NGAL Levels During or at the End of Perfusion: Meta-Analysis of Standardized Mean Differences. This figure presents a meta-analysis of three studies reporting NGAL levels during or at the end of machine perfusion.(15,28,34) NGAL levels reported by Lohmann et al. (2021) at day 2 post-transplantation are analysed separately.(35) Due to substantial differences in absolute mean values across studies, only standardized mean differences are presented, not mean differences. The pooled effect is not statistically significant, with an SMD [95% CI] of –1.68 (–5.60 to 2.25), indicating no clear impact of stem cell or stem cell-derived product administration on NGAL levels during or at the end of perfusion. Heterogeneity among studies was high ($I^2 = 95.5\%$), supported by Cochran's Q test ($p < 0.001$) and a between-study variance τ^2 of 11.14. Results for NGAL measured two days post-transplantation are consistent with findings during perfusion.

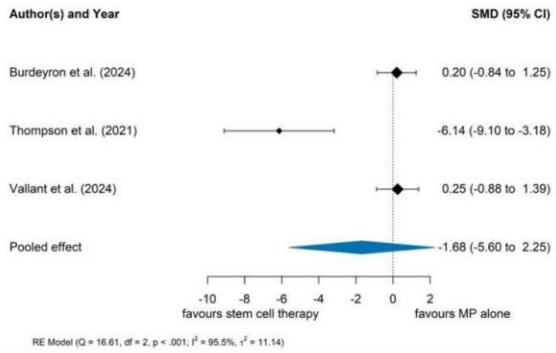




Study	Control group		Treated group		Effect		Weight
	N_C	$Mean_C \pm SD_C$	N_T	$Mean_T \pm SD_T$	MD (95%CI)	SMD (95%CI)	
During Perfusion							
Arcolino et al. (2022)	3	7.56 ± 9.32	3	7.81 ± 4.24	0.25 (-11.3 to 11.8)	0.028 (-1.57 to 1.63)	11.6 %
Burdeyron et al. (2024)	5	0.63 ± 0.64	12	0.52 ± 0.55	-0.10 (-0.75 to 0.54)	-0.17 (-1.22 to 0.87)	27.2 %
Lohmann et al. (2021)	7	0.97 ± 0.83	14	0.80 ± 0.83	-0.17 (-0.92 to 0.58)	-0.20 (-1.11 to 0.71)	36.0 %
Pool et al. (2020)	5	2.68 ± 0.37	10	4.40 ± 4.21	1.72 (-0.90 to 4.35)	0.46 (-0.62 to 1.55)	25.2 %
Pooled effect						0.00 (-0.54 to 0.55)	100 %
Heterogeneity : Q=0.98, df=3, p=0.81, I^2(95%CI)=0.00% (0.00 to 75.8%) , τ^2(95%CI)=0.00 (0.00 to 1.01)							
Post-reperfusion							
Vallant et al. (2024)	6	2.59 ± 0.42	6	2.40 ± 0.44	-0.19 (-0.68 to 0.30)	-0.41 (-1.55 to 0.74)	
Day 14 after transplant.							
Lohmann et al. (2021)	14	48.5 ± 15.9	14	50.0 ± 8.33	1.50 (-7.90 to 10.9)	0.11 (-0.63 to 0.86)	



Study	Control group		Treated group		Effect		Weigth
	N_C	$Mean_C \pm SD_C$	N_T	$Mean_T \pm SD_T$	MD (95%CI)	SMD (95%CI)	
Arcolino et al. (2022)	3	824 ± 245	3	1448 ± 105	624 (322 to 926)	2.64 (0.45 to 4.83)	12.6 %
Burdeyron et al. (2024)	5	211 ± 194	12	180 ± 201	-31 (-236 to 174)	-0.15 (-1.19 to 0.90)	23.4 %
Pool et al. (2020)	5	165 ± 120	10	152 ± 106	-13 (-137 to 111)	-0.11 (-1.19 to 0.96)	23.0 %
Thompson et al. (2021)	5	960 ± 189	5	1436 ± 281	476 (180 to 773)	1.79 (0.33 to 3.26)	18.7 %
Vallant et al. (2024)	6	510 ± 224	6	446 ± 190	-64 (-299 to 171)	-0.28 (-1.42 to 0.85)	22.3 %
Pooled efect						0.54 (-0.46 to 1.55)	100 %
Heterogeneity : Q=10.7, df=4, p=0.031, I^2(95%CI)=66.5% (0.00 to 97.1%) , τ^2(95%CI)=0.84 (0.00 to 14.2)							



Study	Control group		Treated group		Effect	Weigth
	N_C	$Mean_C \pm SD_C$	N_T	$Mean_T \pm SD_T$	SMD (95%CI)	
During Perfusion						
Burdeyron et al. (2024)	5	2.66E+11 ± 1.34E+11	12	3.10E+11 ± 2.27E+11	0.020 (-0.84 to 1.25)	35.1 %
Thompson et al. (2021)	5	12400 ± 1014	5	7196 ± 379	-6.14 (-9.10 to -3.18)	29.9 %
Vallant et al. (2024)	6	121.0 ± 25.81	6	129.8 ± 37.56	0.25 (-0.88 to 1.39)	35.0 %
Pooled efect					-1.68 (-5.60 to 2.25)	100.0 %
Heterogeneity : Q=16.61, df=2, p<0.0001, I^2(95%CI)=95.5% (79.6 to 99.5%) , τ^2(95%CI)=11.14 (2.03 to 111.4)						
Day 2 after transplant						
Lohmann et al. (2021)	14	1747167 ± 810818	14	5153500 ± 6073633	0.76 (-0.00 to 1.53)	