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REVIEW

Hussein: Umbilical cord MSCs and regeneration

Advancing regenerative therapies with umbilical cord–derived mesenchymal stem cells: A review

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ABSTRACT

Umbilical cord–derived mesenchymal stem cells (UC-MSCs) are a clinically attractive regenerative and immunomodulatory platform that combines ethical accessibility, low immunogenicity, rapid expansion, genetic stability, and a potent paracrine secretome. This study aimed to synthesize evidence on safety, efficacy, and translational readiness by conducting a focused PubMed review (2014–2024) restricted to clinical studies and trials, using predefined inclusion and exclusion criteria and structured data extraction. Across indications, UC-MSCs show a consistent safety profile and signals of benefit mediated by tissue repair and immune regulation: in musculoskeletal disease they improve osteoarthritis pain and function and may slow osteonecrosis; in hepatology they sustain gains in decompensated cirrhosis, mitigate acute allograft rejection, and aid recovery from ischemic-type biliary lesions; as induction in renal transplantation they are feasible with early graft benefits; in type 2 diabetes responders improve glycemic control and inflammation, while maternal and obstetric factors can shape intrinsic cell properties; in neurology, studies in cerebral palsy, chronic spinal cord injury, and traumatic optic neuropathy report motor, sensory, and visual improvements; in COVID-19–related acute respiratory distress syndrome (ARDS) trials show better oxygenation, radiological recovery, quality of life, and modulation of the TNF–sTNFR2 axis; in immune-mediated and transplant settings they reduce graft-versus-host disease, with signals in systemic lupus erythematosus, refractory immune thrombocytopenia, Crohn's fistulas, and as cotransplant support in aplastic anemia. The limitations of this study encompass small sample sizes, single-center designs, and short-duration trials. Additionally, there is significant heterogeneity concerning the source, manufacturing processes, dosage, administration routes, and endpoints. Other challenges include adherence to good manufacturing practices (GMP), issues related to potency, biobanking, logistical constraints, cost factors, and regulatory obstacles. Large multicenter randomized trials with standardized protocols and long-term follow-up, and combination strategies with biomaterials, gene engineering, and extracellular vesicle or exosome products, are needed to confirm durable benefit and enable routine clinical integration.

Keywords: Regenerative medicine, clinical studies, immunomodulation, anti-inflammatory therapy, tissue repair and regeneration.

INTRODUCTION

Mesenchymal stem cells (MSCs) are multipotent stromal cells with the remarkable ability to self-renew and differentiate into a variety of cell types, including fat, cartilage, and bone. These properties make them highly attractive for applications in regenerative medicine, tissue engineering, and immunotherapy[1]. MSCs are defined by their lack of hematopoietic markers such as CD34 and CD45, their expression of markers including CD73, CD90, and CD105, and their ability to adhere to plastic surfaces in culture[2]. Beyond differentiation, MSCs also exert strong immunomodulatory effects through interactions with immune cells such as T cells, B cells, and macrophages[3]. MSCs can be derived from several tissue sources, each with distinct advantages and limitations. Bone marrow is the most established source, offering high differentiation potential, though collection is invasive and yields decline with age. Adipose tissue provides a less invasive alternative with good availability, though with somewhat reduced osteogenic capacity[4]. Umbilical cord tissue, particularly Wharton's jelly, offers an abundant and non-invasive source, though these cells may have lower self-renewal potential compared with other sources. Amniotic fluid and membranes also show promise due to pluripotent-like properties, but raise ethical considerations. Additional sources such as peripheral blood, dental pulp, synovial fluid, liver, lung, and skeletal muscle have been studied, but are often limited by low yield and restricted accessibility[5] Figure 1. Among these options, UC-MSCs are emerging as a leading candidate for clinical use. Obtained from Wharton's jelly, cord blood, or perivascular tissue, UC-MSCs can differentiate into multiple lineages while being readily available from tissue usually discarded after birth. Their collection is safe, non-invasive, and ethically acceptable, making them an especially valuable resource for advancing regenerative therapies and immune-based treatments[6,7].

UC-MSCs are gaining increasing attention in regenerative medicine because they combine accessibility, safety, and biological strength[8]. They can be collected easily and non-invasively, as the umbilical cord is typically discarded after childbirth, eliminating both ethical concerns and donor risk[9]. This makes them a widely available and ethically sound source of stem cells. One of the defining advantages of UC-MSCs is their "youthful" biology. Originating from neonatal tissue, they exhibit rapid proliferation, long-term genetic stability, and resistance to cellular aging[10]. These qualities allow them to be expanded into large, clinically useful cell

populations without compromising their integrity. Functionally, UC-MSCs can differentiate into multiple lineages including, bone, cartilage, and fat, and secrete a diverse range of bioactive molecules that regulate immune responses and suppress inflammation[11]. Such immunomodulatory properties make them especially promising for the treatment of inflammatory and immune-related diseases, where conventional therapies often have limited impact[12]. Another critical advantage is their strong safety profile. Because they are derived from newborn tissue, UC-MSCs carry fewer accumulated genetic mutations compared with adult-derived stem cells, lowering concerns about malignant transformation[13]. In contrast to embryonic stem cells, they also avoid significant ethical controversy, as their source material would otherwise be discarded as medical waste. Altogether, UC-MSCs represent a highly reliable and versatile platform for advancing cell-based therapies. Their combination of ethical accessibility, robust biological performance, and proven immunomodulatory effects positions them as a cornerstone resource for the future of regenerative medicine and immune-targeted treatments[14] Figure 2.

METHODS

A comprehensive literature search was conducted in PubMed to identify studies on umbilical cord-derived mesenchymal stem cells (UC-MSCs) published between 2014 and 2024. The search combined Medical Subject Headings (MeSH) and free-text terms, including “Umbilical cord-derived mesenchymal stem cells,” “UC-MSCs AND therapy,” and “UC-MSCs AND immune disorders,” with Boolean operators and field tags ([Title/Abstract], [MeSH Terms]) to refine results. Filters were applied to capture only clinical studies and trials, with additional restrictions on disease-specific topics such as liver cirrhosis, immune disorders, COVID-19, and metabolic disease. The time frame of 2014–2024 was selected to cover a decade of rapid growth in UC-MSC research, reflecting major advances in clinical translation and the publication of large-scale trials. PubMed was chosen as the primary database because it provides the most comprehensive coverage of biomedical and clinical research, particularly peer-reviewed journal articles indexed in MEDLINE, ensuring reliability and quality of the sources. Retrieved records were imported into Excel, duplicates were removed, and titles and abstracts were screened for relevance, followed by full-text assessment for eligible studies. Inclusion criteria consisted of clinical studies (randomized controlled trials, pilot studies, and phase I–III trials) involving UC-MSCs as a therapeutic

intervention and reporting outcomes on efficacy, safety, or therapeutic potential. Exclusion criteria ruled out preclinical or in vitro research, reviews, meta-analyses, conference abstracts, editorials, and studies lacking methodological detail. Data were extracted and categorized by study design, patient population, UC-MSC source and administration, and clinical outcomes, ensuring a focused dataset by excluding irrelevant studies.

RESULTS AND DISCUSSION

Findings from clinical research point to the broad therapeutic promise of umbilical cord–derived mesenchymal stem cells (UC-MSCs). With a strong safety record and the ability to both regenerate tissue and regulate immune responses, UC-MSCs stand out as a valuable option for treating conditions ranging from musculoskeletal disorders to immune-related diseases. Still, results are not uniform; they vary with the type of disease studied, the design of clinical trials, and patient-specific factors. This variation highlights the need for more standardized approaches and larger multicenter studies to confirm and refine their use. To set the stage for the discussion, Table 1 outlines the main therapeutic areas investigated, the benefits reported, and the current limitations.

UC-MSCs in musculoskeletal regeneration

Clinical studies increasingly show that umbilical cord–derived mesenchymal stem cells (UC-MSCs) offer meaningful potential in treating musculoskeletal disorders, though the strength of the evidence varies between trials. In a phase I dose-escalation study, Javiera Matas et al.[15] found that intra-articular UC-MSC injections in knee osteoarthritis were safe and improved both pain and joint function, offering early proof of concept for their use in degenerative joint disease. These results are echoed by Indra H. Dilogo et al.,[16] whose open-label study reported similar benefits, further supporting the feasibility of UC-MSC therapy in osteoarthritis. Extending the evidence base, Chen Chen et al.[17] provided three-year follow-up data in patients with osteonecrosis of the femoral head, showing not only symptom relief but also slower disease progression, suggesting a more durable regenerative effect. Beyond joint disease, Widodo et al.[18] explored UC-MSCs in late-onset brachial plexus injury and demonstrated that either the cells or their secretome improved functional

recovery and tissue repair, pointing to a wider role in complex neuromuscular injuries. Together, these studies emphasize the safety, regenerative potential, and versatility of UC-MSCs in musculoskeletal medicine. Still, comparisons are complicated by differences in trial design, patient populations, and treatment protocols. Improvements in osteoarthritis outcomes have been consistent across short-term studies, while the longer-term benefits seen in osteonecrosis require additional confirmation. The brachial plexus findings are promising but remain preliminary and need validation in larger trials. Overall, the evidence suggests UC-MSCs could reshape treatment for musculoskeletal disorders, provided that future multicenter studies refine dosing strategies, standardized methods, and confirm both safety and lasting efficacy.

UC-MSCs in liver disease

Clinical studies examining (UC-MSCs) in liver disease suggest broad therapeutic potential across cirrhosis, transplantation, and biliary complications. In a long-term follow-up study, Shi et al. [19]demonstrated that UC-MSC therapy in patients with decompensated cirrhosis led to sustained improvements in liver function scores and overall clinical status, highlighting both the regenerative and immunomodulatory effects of the therapy. These findings provide important long-term evidence that UC-MSCs can stabilize chronic liver disease, a condition with limited effective treatment options outside of transplantation. Complementing this, Shi et al. [20]reported in a pilot trial that UC-MSC infusion was safe and clinically beneficial in patients experiencing acute liver allograft rejection. Here, MSCs not only reduced inflammatory activity but also appeared to support graft survival, suggesting that their immunoregulatory properties can be harnessed in the transplant setting where rejection remains a critical challenge. Extending to biliary complications, Zhang et al.[21] explored UC-MSCs in patients with ischemic-type biliary lesions following transplantation. Their findings indicated improved biliary repair and function, with the therapy being well tolerated. Taken together, these studies demonstrate that UC-MSCs act through a combination of regenerative and immunomodulatory mechanisms to improve outcomes across diverse liver-related conditions. While the long-term cirrhosis trial underscores their potential in chronic disease management, the transplant-focused studies highlight their role in addressing acute immune-mediated injury and post-transplant complications. However, the evidence base remains relatively small, with pilot studies and single-center trials predominating. Larger,

multicenter randomized studies are needed to confirm efficacy, standardize treatment protocols, and establish where UC-MSC therapy can be integrated into existing liver disease and transplantation frameworks. Nonetheless, current data point to UC-MSCs as a versatile tool capable of addressing both chronic degeneration and acute immune-driven injury in hepatology.

UC-MSCs in renal transplantation

Research on the use of umbilical cord–derived mesenchymal stem cells (UC-MSCs) in renal transplantation has primarily focused on their potential as induction therapy to improve graft survival and reduce immune complications. Sun et al. [22] first outlined a detailed study protocol investigating whether allogeneic MSCs could prevent delayed graft function and acute rejection in recipients of deceased donor kidneys. This protocol established the scientific rationale for introducing MSCs at the time of transplantation, aiming to leverage their immunomodulatory and anti-inflammatory properties during the critical early post-transplant phase. Building on this framework, Sun et al.[23] later published pilot results from a multicenter randomized controlled trial, showing that UC-MSC induction therapy was both safe and feasible in renal allografts. Importantly, early findings indicated improvements in graft function and reduced immune-mediated injury compared to standard care. Taken together, these studies illustrate a careful progression from conceptual design to clinical application. The protocol paper laid the groundwork for methodological rigor, while the subsequent clinical trial provided preliminary evidence that UC-MSCs may improve short-term transplant outcomes without introducing significant safety concerns. However, both works remain early in scope, with small sample sizes and short follow-up limiting conclusions about long-term efficacy. Larger, multicenter trials with extended monitoring will be essential to confirm whether UC-MSC therapy can reduce rejection rates, improve long-term graft survival, and ultimately be incorporated into standard transplantation protocols.

Metabolic applications of the UC-MSCs

Research into the metabolic applications of the (UC-MSCs) reveals both their direct therapeutic potential and the influence of maternal and obstetric factors on their biological properties. In patients with type 2 diabetes mellitus, Wang et al.[24] identified predictive factors that influenced the clinical efficacy of UC-MSC therapy,

showing that treatment improved glucose control, insulin sensitivity, and systemic inflammation in responders. This study emphasizes that patient-specific characteristics may shape therapeutic outcomes, highlighting the importance of precision in applying UC-MSC therapy for metabolic disorders. In parallel, maternal factors have been shown to affect the biological function of UC-MSCs. Jevtovic et al.[25] demonstrated that maternal exercise during pregnancy positively influenced glucose and lipid metabolism in offspring stem cells, suggesting that lifestyle factors can program neonatal cell biology in ways that may enhance their regenerative and metabolic potential. Similarly, Avercenc-Léger et al.[26] reported that certain obstetric conditions predicted UC-MSC proliferation and chondrogenic differentiation capacity, providing further evidence that the perinatal environment directly impacts stem cell quality and function. Together, these studies expand the understanding of UC-MSCs beyond their therapeutic effects in established disease to include the maternal and perinatal factors that shape their baseline biology.

UC-MSCs for neurological disorders

Clinical investigations into (UC-MSCs) for neurological disorders highlight their potential to promote functional recovery, although findings vary depending on the condition and study design. In cerebral palsy, Boyalı et al.[27] provided preliminary evidence that allogeneic MSC therapy may be a viable treatment, reporting improvements in motor function with good tolerability. These results were reinforced by Gu et al.,[28] who conducted a randomized controlled trial showing significant gains in gross motor function compared with controls, underscoring the therapeutic promise of UC-MSCs in pediatric neurorehabilitation. Adding nuance, Wang et al.[29] studied identical twins with cerebral palsy and observed improvements in motor function, while also suggesting that hereditary factors may influence the degree of clinical response, an important consideration for tailoring treatment strategies. Spinal cord injury has also been a major focus of UC-MSC research. Awidi et al.[30] demonstrated in a phase I/II trial that expanded stromal cells from both bone marrow and umbilical cord were safe and feasible in chronic spinal cord injury, with some patients experiencing neurological improvement. Similarly, Albu et al.[31] investigated intrathecal administration of Wharton's jelly–derived MSCs and reported improvements in sensory and motor recovery, further confirming both safety and therapeutic potential in this challenging patient population. Extending the scope to

neuro-ophthalmology, Li et al.[32] combined optic canal decompression with UC-MSC transplantation for traumatic optic neuropathy. Their phase I results showed that the procedure was safe and provided preliminary signals of visual function improvement. Taken together, these studies suggest that UC-MSCs exert neuroprotective and regenerative effects across a range of neurological conditions, from developmental disorders such as cerebral palsy to traumatic injuries of the spinal cord and optic nerve. While improvements in motor and sensory outcomes appear consistent, the magnitude of benefit varies, and long-term durability remains to be fully established. Variability in cell sources, administration routes, and patient populations further complicates direct comparison. Nonetheless, the convergence of evidence across multiple indications highlights UC-MSCs as a versatile therapeutic platform for neuroregeneration. Future research should focus on larger randomized trials, standardized treatment protocols, and long-term follow-up to clarify the extent and durability of neurological recovery achievable with UC-MSC therapy.

UC-MSCs for respiratory disorders

Clinical research into (UC-MSCs) for respiratory disorders, particularly acute respiratory distress syndrome (ARDS) associated with COVID-19, has shown promising safety and early efficacy signals, though results vary across trials. In a multicenter randomized double-blind trial, Sitbon et al. [33]demonstrated that UC-MSC therapy was safe and improved respiratory function and quality of life in subsets of patients, suggesting meaningful long-term benefits. Similarly, Shi et al.[34] confirmed sustained improvements in pulmonary outcomes in their one-year follow-up study of severe COVID-19 patients, reinforcing the therapy's durability and safety profile. Earlier work by Shi et al.[35] also indicated that UC-MSC treatment reduced lung damage and improved radiological outcomes, providing mechanistic evidence of repair. At the pilot level, Meng et al.[36] reported in a phase I trial that UC-MSC infusions were well tolerated and associated with signs of clinical improvement, while Kaffash Farkhad et al.[37] also observed improvements in oxygenation and disease severity in a controlled phase I study, strengthening the feasibility of UC-MSC use in acute respiratory injury. Complementing these clinical outcomes, Kouroupis et al.[38] explored immunological mechanisms, showing that UC-MSCs modulated TNF and soluble TNF receptor 2 levels in patients with COVID-19 ARDS, supporting the hypothesis that their therapeutic benefits are mediated through immunomodulation

and dampening of hyperinflammatory pathways. When compared collectively, these studies highlight several consistent themes: UC-MSCs are safe across diverse patient populations, they improve short-term oxygenation and radiological findings, and they may contribute to longer-term recovery of lung function. However, trial heterogeneity includes differences in sample size, dosing regimens, and outcome measures limit definitive conclusions. While phase I and pilot studies provide encouraging feasibility data, larger multicenter randomized trials such as those led by Sitbon et al.[39] are critical for validating efficacy and informing clinical guidelines. Overall, UC-MSCs appear to offer a dual benefit in ARDS by reducing inflammation and supporting lung repair, but robust evidence from large-scale studies is still required before their integration into standard respiratory care.

UC-MSCs in immune-mediated and transplant-related disorders

Clinical studies investigating (UC-MSCs) in immune-mediated and transplant-related disorders demonstrate consistent safety and notable immunomodulatory benefits, though with variability in outcomes depending on disease context. In graft-versus-host disease (GVHD), Niu et al.[40] reported durable clinical responses in patients with severe, steroid-refractory GVHD, with long-term follow-up confirming sustained improvements and manageable safety concerns. Expanding on this, Gao et al.[41] conducted a multicenter randomized controlled trial and found that prophylactic use of UC-MSCs significantly reduced the incidence and severity of chronic GVHD, highlighting their potential role in prevention as well as treatment. Similarly, Nagamura-Inoue et al.[42] provided mechanistic insight, showing that serum-free manufactured UC-MSCs shifted immunological responses in steroid-resistant GVHD without increasing infection risk, underscoring their capacity to restore immune balance safely. Beyond transplantation, UC-MSCs have been tested in autoimmune and inflammatory diseases. Chen et al.[43] demonstrated that infusion in refractory immune thrombocytopenia improved platelet counts and reduced bleeding events in a subset of patients, while Kamen et al.[44] showed reductions in disease activity indices in systemic lupus erythematosus, confirming both safety and immunological benefit. Complementing these clinical findings, Ma et al.[45] provided in vitro evidence that UC-MSCs suppressed pathogenic immune activity in autoimmune hemolytic anemia, reinforcing the rationale for their use in autoimmune conditions. In inflammatory bowel disease, Wei et al.[46] reported higher closure rates of complex

perianal fistulas in Crohn's disease patients treated with UC-MSCs, demonstrating benefits in tissue repair alongside immune regulation. UC-MSCs have also been explored as supportive therapy in hematologic transplantation. Zu et al.[47] combined UC-MSCs with reduced-dose cyclophosphamide and peripheral blood stem cells in patients with severe aplastic anemia, reporting encouraging engraftment and improved GVHD control with acceptable toxicity. This study highlights how UC-MSCs function synergistically in cotransplant settings to enhance outcomes. When considered together, these studies consistently highlight the ability of UC-MSCs to modulate immune responses across diverse conditions, from GVHD and autoimmune cytopenias to Crohn's disease and SLE, while maintaining a strong safety profile.

Critical barriers to the clinical integration of umbilical cord–derived mesenchymal stem cells

Although the accumulated evidence highlights the therapeutic promise of umbilical cord-derived mesenchymal stem cells (UC-MSCs), several important limitations must be acknowledged before their clinical use can be fully established. The findings across studies are not always consistent. For instance, clinical trials in neurological disorders such as cerebral palsy and spinal cord injury have reported variable outcomes: some demonstrated substantial gains in motor function and quality of life, while others noted only modest or short-lived improvements. Such discrepancies are likely influenced by differences in the origin of the cells (e.g., Wharton's jelly versus cord blood), the methods of expansion and preparation, the delivery route (intravenous, intrathecal, or scaffold-based), and heterogeneity in patient characteristics such as age, disease stage, and comorbidities. Likewise, trials in liver and renal disorders have shown promising but uneven results, underscoring the importance of developing standardized protocols for cell preparation, dosing, and administration. Without harmonization, direct comparison between studies remains challenging, and conclusions about efficacy are tentative[48].

Another critical limitation of the current body of literature is its reliance on small, early-phase clinical studies. Most trials enroll fewer than 50 patients and follow them for less than a year. While these studies demonstrate safety and short-term efficacy, they cannot provide definitive evidence of long-term outcomes, including durability of therapeutic benefit or the risk of late adverse effects such as unwanted immune reactions, fibrosis, or tumorigenicity. Moreover, inconsistencies in reporting methods

and outcome measures hinder meaningful meta-analyses and systematic reviews, which are essential to translating preclinical and early clinical findings into widely accepted treatment guidelines. At present, the absence of uniform standards in trial design, patient selection, and clinical endpoints remains a significant obstacle to progress[49]. In addition, several translational and regulatory barriers must be addressed before UC-MSCs can move from experimental therapy to mainstream clinical practice. Large-scale production under good manufacturing practice (GMP) conditions requires rigorous quality control to ensure product consistency, viability, and potency. The regulatory landscape is fragmented, with differing approval processes and safety requirements across regions, which complicates global commercialization. There are also logistical challenges related to biobanking, cryopreservation, transport, and cost-effectiveness, all of which must be resolved for UC-MSC therapy to be scalable and accessible. Addressing these issues will require coordinated international efforts, multicenter randomized controlled trials with long-term follow-up, and continued innovation in cell engineering and delivery strategies. Only then can UC-MSCs progress from promising experimental interventions to standardized, evidence-based therapies that transform routine clinical care[50].

CONCLUSION

Umbilical cord-derived mesenchymal stem cells stand out as one of the most exciting developments in regenerative medicine, offering promise across a wide range of conditions. Evidence to date suggests that they can support immune regulation, tissue repair, and recovery in both chronic and acute diseases, including autoimmune disorders, liver cirrhosis, neurological injuries, chronic kidney disease, osteoarthritis, and even COVID-19-related acute respiratory distress syndrome. Their distinct biological advantages, such as low risk of immune rejection, strong paracrine signaling, and high proliferative capacity, make them a particularly valuable option for patients whose needs are not met by current therapies. At the same time, the field is still in its early stages. Much of the available data comes from small pilot or Phase I/II studies with relatively short follow-up periods. This makes it difficult to fully assess the long-term safety and durability of treatment effects. In addition, differences in how UC-MSCs are sourced, prepared, and delivered along with variations in patient populations, create inconsistencies that limit direct comparison across trials. Beyond the scientific hurdles, challenges in large-scale manufacturing, cost, and

differing international regulatory pathways also slow the pace of clinical adoption. For UC-MSCs to move from experimental use to routine medical care, the next step will be large, multicenter randomized controlled trials built on standardized protocols and extended follow-up. Stronger global regulatory alignment and better manufacturing systems will also be essential. Looking forward, pairing UC-MSC therapy with advances in biomaterials, gene editing, or exosome-based approaches may unlock even greater therapeutic potential. With these developments, UC-MSCs could progress from promising experimental treatments to a foundation of future regenerative and personalized medicine, offering lasting benefits for conditions that remain some of the most difficult to treat.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Summary of UC-MSC clinical applications across disease areas

Title of the study	Year	Category	References
A Phase I Dose-Escalation Clinical Trial to Assess the Safety and Efficacy of Umbilical Cord-Derived Mesenchymal Stromal Cells in Knee Osteoarthritis. Stem Cells Translational Medicine	2024	Musculoskeletal disorders	Matas J, et al. [15]
Umbilical cord-derived mesenchymal stem cells for treating osteoarthritis of the knee: a single-arm, open-label study.	2020	Musculoskeletal disorders	Dilogo IH, et al.[16]
Efficacy of umbilical cord-derived mesenchymal stem cell-based therapy for osteonecrosis of the femoral head: A three-year follow-up study.	2016	Musculoskeletal disorders	Chen C, et al. [17]
Functional outcome and histologic analysis of late onset total type brachial plexus injury treated with intercostal nerve transfer to median nerve with local umbilical cord-derived mesenchymal stem cells or secretome injection: a double-blinded, randomized control study.	2024	Musculoskeletal disorders	Widodo W, et al. [18]
A Pilot Study of Mesenchymal Stem Cell Therapy for Acute Liver Allograft Rejection.	2017	Liver diseases	Shi M, et al. [19]
Mesenchymal stem cell therapy in decompensated liver cirrhosis: a long-term follow-up analysis of the randomized controlled clinical trial.	2021	Liver diseases	Shi M, et al. [20]

Therapeutic potentials of umbilical cord–derived mesenchymal stromal cells for ischemic-type biliary lesions following liver transplantation.	2017	Liver diseases	Zhang YC, et al. [21]
Allogeneic mesenchymal stem cell as induction therapy to prevent both delayed graft function and acute rejection in deceased donor renal transplantation: study protocol for a randomized controlled trial.	2017	Kidney diseases / transplantation	Sun Q, et al. [22]
Allogeneic mesenchymal stem cells as induction therapy are safe and feasible in renal allografts: pilot results of a multicenter randomized controlled trial.	2018	Kidney diseases / transplantation	Sun Q, , et al. [23]
Predictive factors that influence the clinical efficacy of umbilical cord–derived mesenchymal stromal cells in the treatment of type 2 diabetes mellitus.	2024	Metabolic / endocrine disorders	Wang Y, et al. [24]
Effects of Maternal Exercise Modes on Glucose and Lipid Metabolism in Offspring Stem Cells.	2023	Metabolic / endocrine disorders	Jevtovic F, et al. [25]
Umbilical cord-derived mesenchymal stromal cells: predictive obstetric factors for cell proliferation and chondrogenic differentiation.	2017	Obstetrics / perinatal biology	Avercenc-Léger L, et al. [26]
Allogeneic mesenchymal stem cells may be a viable treatment modality in cerebral palsy.	2024	Neurological disorders	Boyalı O, et al. [27]
Therapeutic evidence of umbilical	2020	Neurological	Gu J, et al. [28]

cord-derived mesenchymal stem cell transplantation for cerebral palsy: a randomized, controlled trial.		disorders	
Effect of umbilical cord mesenchymal stromal cells on motor functions of identical twins with cerebral palsy: pilot study on the correlation of efficacy and hereditary factors.	2015	Neurological disorders	Wang X, et al. [29]
Safety and potential efficacy of expanded mesenchymal stromal cells of bone marrow and umbilical cord origins in patients with chronic spinal cord injuries: a phase I/II study.	2024	Neurological disorders	Awidi A, et al. [30]
Clinical effects of intrathecal administration of expanded Wharton jelly mesenchymal stromal cells in patients with chronic complete spinal cord injury: a randomized controlled study.	2021	Neurological disorders	Albu S, et al. [31]
Treatment of Optic Canal Decompression Combined with Umbilical Cord Mesenchymal Stem (Stromal) Cells for Indirect Traumatic Optic Neuropathy: A Phase 1 Clinical Trial.	2021	Neurological disorders	Li J, et al. [32]
Treatment of COVID-19-associated ARDS with umbilical cord-derived mesenchymal stromal cells in the STROMA-CoV-2 multicenter randomized double-blind trial:	2024	Respiratory disorders / COVID-19	Sitbon A, et al. [33]

long-term safety, respiratory function, and quality of life.			
Effect of human umbilical cord-derived mesenchymal stem cells on lung damage in severe COVID-19 patients: a randomized, double-blind, placebo-controlled phase 2 trial.	2021	Respiratory disorders / COVID-19	Shi L, et al. [34]
Human mesenchymal stem cells treatment for severe COVID-19: 1-year follow-up results of a randomized, double-blind, placebo-controlled trial.	2022	Respiratory disorders / COVID-19	Shi L, et al. [35]
Human umbilical cord-derived mesenchymal stem cell therapy in patients with COVID-19: a phase 1 clinical trial.	2020	Respiratory disorders / COVID-19	Meng F, et al. [36]
Mesenchymal stromal cell therapy for COVID-19-induced ARDS patients: a successful phase 1, control-placebo group, clinical trial.	2022	Respiratory disorders / COVID-19	Kaffash Farkhad N, et al. [37]
Umbilical Cord-derived Mesenchymal Stem Cells modulate TNF and soluble TNF Receptor 2 (sTNFR2) in COVID-19 ARDS patients.	2021	Respiratory disorders / COVID-19	Kouroupis D, et al. [38]
Treatment of COVID-19-associated ARDS with umbilical cord-derived mesenchymal stromal cells in the STROMA-CoV-2 multicenter randomized double-blind trial: long-term safety, respiratory function, and quality of life.	2024	Respiratory disorders / COVID-19	Sitbon A, et al. [39]

Human umbilical cord-derived mesenchymal stromal cells for the treatment of steroid refractory grades III-IV acute graft-versus-host disease with long-term follow-up.	2024	Hematology / immune disorders	Niu J wen, et al. [40]
Phase II Multicenter, Randomized, Double-Blind Controlled Study of Efficacy and Safety of Umbilical Cord–Derived Mesenchymal Stromal Cells in the Prophylaxis of Chronic Graft-Versus-Host Disease After HLA-Haploidentical Stem-Cell Transplantation.	2016	Hematology / immune disorders	Gao L, et al. [41]
Immunological influence of serum-free manufactured umbilical cord-derived mesenchymal stromal cells for steroid-resistant acute graft-versus-host disease.	2022	Hematology / immune disorders	Nagamura-Inoue T, et al. [42]
Efficacy and safety of human umbilical cord-derived mesenchymal stem cells in the treatment of refractory immune thrombocytopenia: a prospective, single arm, phase I trial.	2024	Hematology / immune disorders	Chen Y, et al. [43]
Safety, immunological effects and clinical response in a phase I trial of umbilical cord mesenchymal stromal cells in patients with treatment refractory SLE.	2022	Hematology / immune disorders	Kamen DL, et al. [44]
In vitro Immunomodulatory Effects of Human Umbilical Cord-Derived Mesenchymal Stem Cells on	2022	Hematology / immune disorders	Ma C, Feng Y, Yang L, Wang S, Sun X, Tai S, et al. [45]

Peripheral Blood Cells from Warm Autoimmune Hemolytic Anemia Patients			
Efficacy and safety of allogeneic umbilical cord-derived mesenchymal stem cells for the treatment of complex perianal fistula in Crohn's disease: a pilot study.	2023	Gastrointestinal disorders	Wei J, , et al. [46]
Feasibility of reduced-dose posttransplant cyclophosphamide and cotransplantation of peripheral blood stem cells and umbilical cord-derived mesenchymal stem cells for SAA	2021	Hematopoietic disorders	Zu Y, et al. [47]

Abbreviations: ARDS: Acute respiratory distress syndrome; TNF: Tumor necrosis factor; sTNFR2: Soluble tumor necrosis factor receptor 2; HLA: Human leukocyte antigen; SLE: Systemic lupus erythematosus; SAA: Severe aplastic anemia; STROMA-CoV-2: Multicenter randomized double-blind trial acronym in COVID-19–associated ARDS.

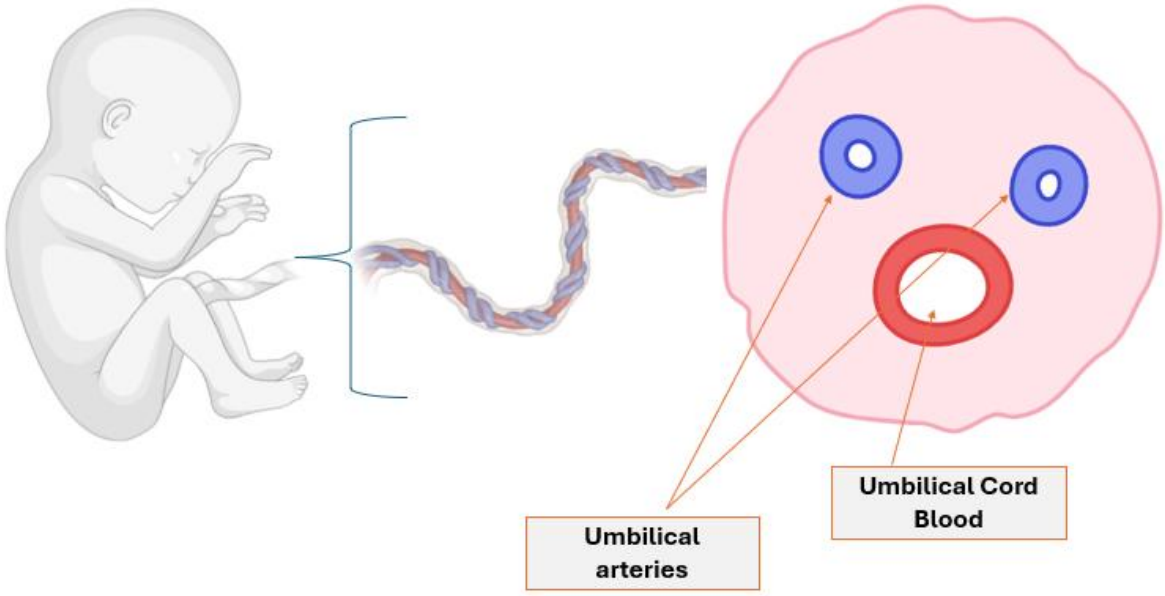

Figure 1. Cross-sectional schematic of the human umbilical cord highlighting the anatomical source of Wharton's jelly and umbilical cord–derived mesenchymal stem cells (UC-MSCs). The illustration depicts a cross-section of the umbilical cord, highlighting two umbilical arteries and a central umbilical vein containing cord blood, all encapsulated within Wharton's jelly. Wharton's jelly serves as a rich extracellular matrix that supports the presence of UC-MSCs, which can be efficiently isolated for regenerative and therapeutic purposes. This schematic underscores the vascular structures and the adjacent stromal compartment, identifying them as the primary niche for UC-MSCs.

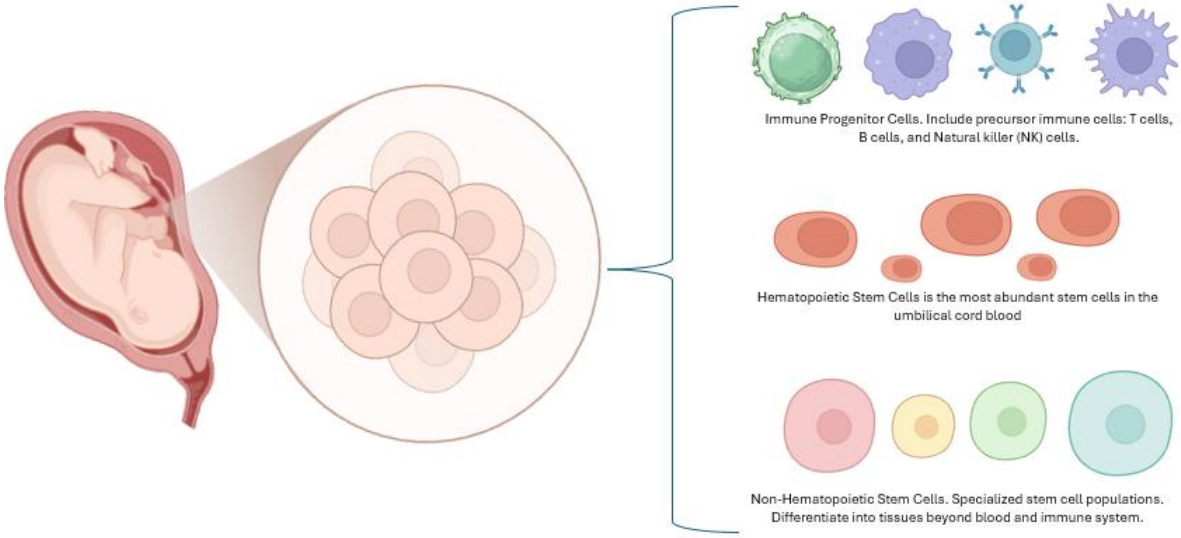

Figure 2. **Illustration of the umbilical cord as a rich source of diverse stem and progenitor cells with significant therapeutic potential.** Hematopoietic stem cells (HSCs) generate all types of blood cells and are extensively utilized in hematologic therapies. Immune progenitor cells, which differentiate into T cells, B cells, and natural killer (NK) cells, play a pivotal role in immune regulation and transplantation. Mesenchymal stem cells (MSCs) can differentiate into various tissues while exerting significant immunomodulatory and regenerative effects. Additionally, non-hematopoietic stem cells contribute to neural and cardiac repair. Collectively, these cell populations underscore the umbilical cord's potential as an ethically accessible and versatile source for regenerative medicine, immunotherapy, and hematologic treatments.