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Umbilical Cord Blood versus Bone Marrow: A Comparative Review of Stem Cell Yield, Biological Properties, and Clinical Utility in Transplantation

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Abstract

Umbilical cord blood (UCB) has gained increasing recognition as a viable and potentially superior source of hematopoietic stem cells (HSCs) for transplantation. Since the first successful cord blood transplant in 1988, the field has expanded significantly, with over 50,000 UCB transplants done globally. UCB is now being used to treat a variety of hematologic, immunologic, metabolic, and neoplastic disorders. Its unique biological attributes, including immunological naivety, ease of collection, and lower risk of graft-versus-host disease, make it particularly advantageous in both paediatric and adult transplantation settings. Despite these benefits, a major limitation remains the relatively low yield of HSCs in a single unit, which can affect engraftment success, particularly in adults. Compared to bone marrow, UCB contains a higher concentration of primitive stem cells with greater proliferative potential, longer telomeres, and distinct cytokine profiles, but has reduced cytokine production and immune maturity. These differences have critical implications for transplantation outcomes and regenerative applications. This narrative review evaluates umbilical cord blood relative to bone marrow as sources of hematopoietic stem cells, synthesizing biological differences, clinical outcomes, limitations, and recent strategies to enhance UCB utility, such as ex vivo stem cell expansion, hybrid and public banking initiatives, and the standardization of collection and processing protocols.

Keywords: Umbilical Cord Blood, Hematopoietic Stem Cells, Bone Marrow, Transplantation

1.0 Introduction

Umbilical cord blood (UCB) transplantation has emerged as a valuable alternative to traditional hematopoietic stem cell sources over the past three decades. Since its first successful use in 1988, over 50,000 UCB transplants have been performed worldwide as of 2020, to treat various hematologic, metabolic, immunologic, and neoplastic disorders. Cord Blood (CB) transplantation has been used to successfully treat approximately 80 different diseases, including leukemia, lymphoma, myelodysplasia, aplastic anaemia, hemoglobinopathies, metabolic storage diseases, and immunodeficiencies (Mayani *et al*., 2020; Muhibi and Obeta, 2022).

The umbilical cord serves as the vital connection between the developing fetus and the placenta, facilitating nutrient and gas exchange during pregnancy. It contains a single umbilical vein and two arteries embedded in Wharton's jelly, a gelatinous connective tissue that provides structural protection and flexibility. Beyond its physiological role, the umbilical cord provides a convenient and non-invasive means of obtaining blood for stem cell collection, supporting its growing clinical relevance in transplantation and regenerative medicine (Brunelli *et al*., 2019).

Cord blood is a rich source of hematopoietic stem cells (HSC), functionally comparable to those obtained from bone marrow, and has been successfully used in transplantation for numerous hematologic and immunologic conditions. Following delivery, umbilical cord blood can be harvested using two principal techniques: the syringe method, involving direct aspiration from the umbilical vein, and the gravity-fed bag collection method, which allows blood to drain into a sterile collection bag (Ohnuma and Nishihira, 1999).

UCB stem cells are undifferentiated and possess pluripotent properties, meaning they have the capacity to develop into various specialized cell types. This makes them highly valuable for regenerative medicine and for the management of genetic and degenerative diseases. Notably, since these cells are collected at birth, they are free from exposure to environmental toxins, infections, and aging-related mutations, which enhances their viability and safety profile (Arien-Zakay *et al*., 2010).

The potential public health implications of CB use are profound. By intervening early and treating inheritable or life-threatening conditions with stem cell therapy, the intergenerational transmission of these diseases can be minimized, thereby reducing disease prevalence over time and contributing to long-term disease control and prevention (Shi *et al*., 2022).

In comparison, bone marrow has historically been the cornerstone of hematopoietic stem cell transplantation. It is the primary site of hematopoiesis, the process by which all blood cell types are produced. Transplants involving bone marrow-derived stem cells have been used for decades to treat a wide array of hematologic malignancies, with the donor's stem cells repopulating the recipient's hematopoietic system (Smith and Wagner, 2009). Additionally, mesenchymal stem cells and progenitor cells from bone marrow exhibit the capacity to differentiate into non-hematopoietic lineages, including cardiac, neural, hepatic, and vascular tissues (Charbord, 2010). Clinical investigations have demonstrated the potential benefits of bone marrow cell infusions in patients suffering from cardiac injury, stroke, liver failure, and peripheral artery disease. Preliminary evidence also suggests a promising, though still underexplored, role for bone marrow stem cells in the treatment of renal failure (Schächinger and Zeiher, 2005; Zubko and Frishman, 2009).

In this study, we aim to critically evaluate umbilical cord blood as a viable and potentially superior alternative to bone marrow for hematopoietic stem cell transplantation. The study seeks to explore the biological, immunological, and therapeutic advantages of cord blood, compare its cellular yield

and clinical outcomes with bone marrow, and examine its applicability in the treatment of various hematological and genetic disorders. By synthesizing recent findings, this review also aims to highlight the opportunities and limitations in the broader clinical adoption of cord blood transplantation.

2.0 Literature Search Strategy

Multiple electronic databases, including PubMed/MEDLINE, Google Scholar, the Directory of Open Access Journals (DOAJ), and Web of Science, were searched to identify relevant studies on umbilical cord blood and bone marrow stem cells. Medical Subject Headings (MeSH) terms and keywords such as "cord blood," "umbilical cord blood," "bone marrow," "hematopoietic stem cell," "stem cell," "stem cell transplantation," "cord blood stem cell transplantation," and "bone marrow transplant" were used. Boolean operators (AND/OR) and truncations were applied to refine the search and broaden coverage. The search was restricted to studies published between 2000 and February 2025. Titles and abstracts were reviewed for relevance, and information from eligible studies was extracted and summarized narratively.

3.0 Biological and Clinical Characteristics of Umbilical Cord Blood and Bone Marrow

3.1 Collection and Preservation of Umbilical Cord Blood and Bone Marrow

In order to provide UCB units that meet the standards for hematopoietic stem cell transplantation, specialized banking systems have been established to facilitate the collection, processing, and long-term storage of these cells under cryogenic conditions. Generally, there are three primary categories of UCB banking: (1) public banking, where cord blood is voluntarily donated for anonymous use by any matching recipient; (2) directed donor banking, where cord blood is collected from a neonate with the specific intent of treating a known relative with a disease amenable to HSC therapy; and (3) private or commercial banking, where families opt to store cord blood from a healthy newborn at their own expense, with the anticipation of possible future use for autologous or familial purposes (Armitage, 2016; Bień *et al*., 2024).

Cord blood collection typically occurs through one of two standard procedures following childbirth. The first involves collecting the blood immediately postpartum, while the placenta is still in utero. The second approach entails delivering the placenta with the umbilical cord clamped and subsequently transferring it to a technician or trained personnel who then performs the collection. Comparative analyses of these methods have not yielded consistent or clinically significant differences in terms of collected blood volume, $CD34^+$ cell concentration, or total nucleated cell counts (Pafumi *et al*., 2002; Solves *et al*., 2006)

Recent guidelines from NetCord, the World Marrow Donor Association (WMDA), and the Worldwide Network for Blood and Marrow Transplantation (WBMT) emphasize standardized procedures to optimize cord blood collection and $CD34^+$ recovery. Early cord clamping and prompt collection immediately after delivery are recommended to maximize blood volume and $CD34^+$ yield, as delays in clamping are associated with reduced stem cell numbers and clonogenic potential (Pafumi, 2013; Hare *et al*., 2021). Both in utero and ex utero collection techniques are acceptable, though in utero methods often yield higher total cell counts; combining both approaches can further optimize recovery (Bassiouny *et al*., 2015; Hare *et al*., 2021). The use of prefilled collection bags containing appropriate anticoagulants, such as citrate-phosphate-dextrose, is advised to prevent clotting and cell loss (Hare *et al*., 2021). Maternal and neonatal characteristics (including birth weight, gestational age, and male sex) have also been correlated with increased $CD34^+$ and total nucleated cell counts, and should be considered in optimizing collection outcomes (Hare *et al*., 2021).

The effectiveness of cord blood transplantation heavily relies on the integrity of the cryopreservation process (Akel *et al*., 2014). Volume reduction by centrifugation to deplete red cells and plasma is commonly used to minimize storage volume while maintaining high $CD34^+$ recovery rates—up to 87% in some reports (Hare *et al*., 2021). The addition of cryoprotectants such as 5–10% dimethyl sulfoxide (DMSO), coupled with a controlled cooling rate of approximately 1°C per minute, helps preserve $CD34^+$ cell viability during freezing (Strobel *et al*., 2017). Post-thaw viability should exceed 70–80%, and $CD34^+$ enumeration using harmonized flow cytometry protocols, as recommended by NetCord-FACT, ensures consistent unit selection across laboratories (Fournier *et al*., 2019; Liedtke *et al*., 2020).

Accreditation and quality management play crucial roles in maintaining the safety and reliability of cord blood units. Banks accredited by NetCord–FACT consistently demonstrate superior $CD34^+$ recovery and post-thaw viability compared to non-accredited facilities (Purtill *et al*., 2014). Current international standards emphasize rigorous quality systems, continuous staff training, and adherence to validated standard operating procedures to ensure compliance with WMDA, WBMT, and NetCord guidelines (Fournier *et al*., 2019; Liedtke *et al*., 2020).

An alternative preservation approach involves single-step volume reduction via centrifugation, which retains most leukocytes and erythrocytes before freezing. Historically, gradual dilution of thawed cord blood to reduce osmolality, followed by washing, was considered essential for maintaining cell viability. However, clinical evidence indicates that direct infusion of thawed cord blood, even without washing, can achieve comparable engraftment efficiency and patient safety (Halldorsdottir *et al*., 2018).

Bone marrow aspiration and biopsy are essential for diagnostic and therapeutic purposes, including hematopoietic stem cell transplantation. The posterior iliac crest remains the preferred harvest site due to its accessibility and safety, though the anterior iliac crest or, in infants, the tibia may be used as alternatives (Bhaskar, 2021). Sternal aspiration may be performed only by experienced operators when pelvic access is contraindicated, as it carries risks such as cardiac tamponade and is contraindicated in lytic bone diseases (Santavy *et al*., 2013).

Guidelines from NetCord, WBMT, and WMDA highlight the importance of multiple small-volume aspirations across different sites to minimize peripheral blood dilution and improve $CD34^+$ yield (Pati *et al*., 2008; Pabinger *et al*., 2022). Harvest volumes of approximately 15–20 mL/kg in adults and up to 20 mL/kg in pediatric donors are generally recommended, with adjustments based on age and weight (Furey *et al*., 2018; Tucci *et al*., 2019).

During bone marrow aspiration and processing, both manual and automated red cell depletion techniques yield comparable $CD34^+$ recovery, provided samples are promptly cryopreserved with validated cryoprotectant protocols (Bender *et al*., 2020; Qudeimat *et al*., 2023). Successful engraftment generally requires a $CD34^+$ dose of at least $2–3 \times 10^6$ cells/kg, with faster hematopoietic recovery observed at higher doses up to 5×10^6/kg (Tucci *et al*., 2019; Oyama *et al*., 2024). Standardized $CD34^+$ enumeration, as recommended by NetCord and WMDA, together with strict adherence to international accreditation standards and robust quality management systems, ensures consistency, safety, and optimal transplant outcomes (Jamal *et al*., 2022; Qudeimat *et al*., 2023).

3.2 Relativity in Stem Cell Yield

Hematopoietic stem cell transplantation has become a transformative therapy for a wide range of hematologic malignancies and non-malignant disorders, including immunodeficiencies, metabolic diseases, and genetic conditions. Among the major sources of hematopoietic stem cells, bone

marrow and umbilical cord blood remain the most established, each possessing distinct biological and clinical characteristics that determine their applicability and effectiveness in transplantation.

Umbilical cord blood, identified more recently as a viable source of hematopoietic stem cells, continues to gain recognition for its therapeutic value, particularly in patients without an available human leukocyte antigen (HLA)-matched donor (Wang and Metheny, 2023). It is collected at birth without risk to the donor and can be cryopreserved for future use. However, a key limitation of UCB transplantation typically contains an order of magnitude fewer nucleated cells per unit than a standard bone marrow harvest, which often results in slower engraftment and delayed immune recovery (Lund *et al*., 2015). This limitation is especially critical in adult recipients, who require higher total nucleated cell doses to achieve durable engraftment.

Bone marrow, by contrast, has long served as the traditional and most extensively studied stem cell source. It provides a higher concentration of hematopoietic and progenitor cells, which supports faster engraftment and immune reconstitution (Kiene *et al*., 2024). Nevertheless, bone marrow donation requires an invasive procedure under anesthesia, which poses certain risks and may deter potential donors.

Clinical comparisons have consistently shown that bone marrow transplantation results in faster engraftment compared with UCB. Neutrophil recovery following bone marrow transplantation typically occurs within 19 to 27 days, while in UCB transplants, engraftment often takes longer, around 19 to 23 days or more, accompanied by a higher risk of early graft failure and infection (Remberger *et al*., 2001; Takahashi *et al*., 2007; Kiene *et al*., 2024; Zhang *et al*., 2012; Kondo *et al*., 2021; Sanz *et al*., 2013).

Despite these challenges, relapse outcomes between bone marrow and UCB transplantation are generally comparable. Some registry analyses suggest that UCB may offer a slightly lower relapse risk in patients with high-risk or advanced disease, potentially due to its unique immunologic profile and greater tolerance for HLA mismatch (Takahashi *et al*., 2007; Van Besien *et al*., 2016; Ruggeri *et al*., 2022; Fuchs *et al*., 2020; Wang *et al*., 2019). However, the slower engraftment associated with UCB contributes to higher early non-relapse mortality, mainly resulting from infection and delayed hematopoietic recovery (Kondo *et al*., 2021; Zhang *et al*., 2012; Fuchs *et al*., 2020). Bone marrow transplantation generally achieves lower early mortality, reflecting its faster engraftment and more predictable recovery course (Remberger *et al*., 2001; Kiene *et al*., 2024).

GVHD remains another important clinical distinction between the two sources. UCB transplantation is consistently associated with lower rates of both acute and chronic GVHD compared with bone marrow, although this advantage is tempered by a greater susceptibility to early severe infections due to delayed immune reconstitution (Takahashi *et al*., 2007; Zhang *et al*., 2012; Fuchs *et al*., 2020; Sanz *et al*., 2013).

To improve the performance of UCB transplantation in adults, several strategies have been developed. Dual-unit cord blood transplantation was introduced to increase the total cell dose, but it has not consistently accelerated engraftment and may raise GVHD risk (Wang *et al*., 2019). More recently, haplo-cord transplantation, which combines a haploidentical graft with a cord blood unit, has shown encouraging results—achieving faster recovery and lower relapse rates while preserving the immunologic advantages of cord blood (Van Besien *et al*., 2016; Ruggeri *et al*., 2022).

Both umbilical cord blood and bone marrow have distinct advantages and limitations. Bone marrow remains the preferred source when rapid engraftment and predictable outcomes are essential, while UCB serves as a valuable alternative for patients lacking matched donors or at high risk for GVHD.

Continuous innovation in ex vivo expansion and hybrid transplant approaches is helping to bridge the engraftment gap between the two sources and may further expand the clinical utility of cord blood in the coming years.

3.3 Comparison of Stem Cell Number and Types

Cells derived from umbilical cord blood exhibit distinct biological and phenotypic characteristics when compared to those sourced from bone marrow, differing in cellular composition, abundance, and functional behavior. Among the hematopoietic cell population in cord blood, those possessing the CD34 marker and lacking CD38 expression are primarily found in the quiescent G0 phase of the cell cycle. This phase signifies a non-dividing, metabolically inactive state. However, despite being in this resting stage, these cells exhibit a significantly heightened proliferative response when exposed to cytokines and demonstrate reduced reliance on stromal support, in contrast to their bone marrow counterparts (Da Silva *et al*., 2009).

Investigations have identified hematopoietic stromal precursors within umbilical cord blood, indicating its capacity to support hematopoiesis independently (Gao *et al*., 2010). Cells with high proliferative potential that are capable of forming robust colonies are found in significantly greater numbers in cord blood, with their presence exceeding that observed in bone marrow by over eightfold (Kim *et al*., 2002). Detailed assessments of colony-forming cell concentrations reveal that approximately one milliliter of cord blood may contain up to 8,000 burst-forming units for erythroid lineage, roughly three times more than in bone marrow (Broxmeyer *et al*., 2006). Additionally, the concentration of granulocyte and macrophage colony-forming units ranges from 13,000 to 24,000, representing an estimated fifteenfold increase compared to bone marrow. Multipotent colony-forming units also exist in higher quantities, varying between 1,000 and 10,000 cells per millilitre (Hordyjewska *et al*., 2015).

Cord blood is particularly rich in primitive hematopoietic stem cells, exceeding those typically found in bone marrow. The percentage of cells expressing the CD34 surface marker in cord blood ranges from 0.02% to 1.43%, a value that approximates the levels seen in adult bone marrow but is considerably greater than in peripheral blood, where CD34 expression is minimal. Specific subpopulations such as CD34-positive but human leukocyte antigen DR-negative cells, as well as CD34-positive, CD38-negative cells, are also notably more abundant in cord blood, comprising approximately 4% of total cells, in contrast to 1% in bone marrow (Hordyjewska *et al*., 2015).

Surface molecule analysis reveals that CD34-positive cells in cord blood exhibit elevated expression of certain adhesion proteins, including CD44 and integrin-related molecules like CD49d and CD49f. Conversely, there is a lower expression of other adhesion-related molecules such as CD11 and CD18 compared to bone marrow-derived cells (Barbosa *et al*., 1998). A further distinction lies in the telomere length of these cells; cord blood cells possess longer telomeric DNA than cells from adult peripheral blood or bone marrow. This feature confers upon them a prolonged capacity for hematopoiesis, enabling a greater number of cell divisions and extended progeny production (Gammaitoni *et al*., 2004).

In terms of immunological profile, cord blood-derived immune cells also differ markedly from their bone marrow counterparts. Although the total counts of lymphocytes, monocytes, and B lymphocytes are generally comparable, differences emerge at the subpopulation level. A significant proportion of B lymphocytes in cord blood are phenotypically immature, exhibiting markers such as CD19 and CD5. The absolute number of T lymphocytes expressing CD4 and CD8 is reduced in cord blood, yet the CD4 to CD8 ratio is elevated relative to that seen in bone marrow. Cord blood contains

a unique population of T cell progenitors that are characterized by the absence of both CD3 and CD8 surface markers (Borrill *et al*., 2023).

Natural killer cells, which play a critical role in innate immunity, are present in lower proportions in cord blood, which correlates with diminished cytotoxic activity. This reduced function is thought to be intrinsic to the "naïve" status of neonatal immune cells and reflective of the developmental stage rather than external immunological influences (Basha *et al*., 2014). Hematopoietic progenitor cells in cord blood, particularly those expressing CD34, display increased resistance to staining with Pyronin Y dye, a property suggesting a heightened level of activation likely induced by the stress of parturition and sustained exposure to a milieu of cytokines (Hordyjewska *et al*., 2015). This resistance may render these cells less susceptible to environmental toxins or stressors.

The presence of mesenchymal stem cells in umbilical cord blood is well established. These cells are precursors to various specialized tissues, including bone, cartilage, adipose, and muscle. Investigations have demonstrated that, in addition to hematopoietic progenitors, cord blood also contains multipotent mesenchymal progenitor cells, akin to those found in bone marrow. These primitive cells exhibit the potential to differentiate into derivatives of all three germ layers. Morphological studies have identified two main subtypes of these progenitors in cord blood. One type displays a flattened, lobulated fibroblastic structure and constitutes the majority, while the other exhibits a more spindle-like fibroblast morphology (Hordyjewska *et al*., 2015).

Phenotypic analysis of these two cell types reveals the absence of hematopoietic and endothelial markers such as CD34, CD26, CD31, CD45, and major histocompatibility complex class II molecules. Instead, they express markers associated with mesenchymal lineage, including SH2, SH3, and SH4, as well as adhesion-related molecules such as CD29 and CD44. Both subtypes also express major histocompatibility complex class I molecules. A key distinguishing feature between the two populations is the expression of CD90, a surface protein highly expressed in the spindle-shaped cells but absent in the flattened type (Moraes, 2018).

3.4 Variations in Cytokine Composition and Production

The hematopoietic microenvironment serves as the primary site for cellular proliferation, differentiation, and maturation. Within this specialized niche, various cellular components, including fibroblasts, macrophages, osteoblasts, endothelial cells, and a subset of helper T lymphocytes, actively contribute to the synthesis and secretion of growth-promoting factors. The influence exerted by these factors is context-dependent, relying heavily on the identity of the target cell, the local concentration of the signaling molecules, and the simultaneous presence of other modulating cytokines (Hordyjewska *et al*., 2015).

Experimental investigations conducted under laboratory conditions have demonstrated that hematopoietic stem cells derived from umbilical cord blood, particularly those expressing specific surface markers indicative of stemness, exhibit an increased responsiveness to stromal cell-derived chemo-attractants compared to their counterparts residing within the adult bone marrow (Yong *et al*., 1999). This discrepancy extends beyond chemotactic behavior, influencing the overall quantity of cytokines synthesized, their resultant biological activity, and the population of cells engaged in cytokine production.

Cells such as T lymphocytes, natural killer cells, and macrophages sourced from umbilical cord blood have been observed to generate markedly lower levels of several key cytokines and colony-stimulating factors when compared to those found in adult peripheral blood. These include granulocyte-colony stimulating factor, granulocyte-macrophage colony stimulating factor,

interleukins responsible for hematopoietic support and immune modulation, and interferons critical for antiviral and immunoregulatory functions (Kim and Broxmeyer, 2011).

The limited ability of umbilical cord blood-derived immune cells to produce cytokines may stem from several interrelated factors. One contributing factor is the immunological immaturity of these cells, characterized by a lack of prior antigenic exposure, which renders them functionally "naïve". Additionally, this diminished cytokine production may be attributed to a reduced expression of messenger RNA transcripts encoding cytokine genes, leading to lower intracellular accumulation of these transcripts and increased susceptibility to degradation (Wang and Metheny, 2023).

Another potential explanation lies in the altered intracellular signaling dynamics unique to umbilical cord blood cells. These differences may reflect underdeveloped or inefficient signal transduction pathways necessary for cytokine gene activation. The capacity of these cells to transmit activation signals through specific receptor complexes may be impaired or insufficiently responsive, necessitating a stronger or more sustained stimulus to achieve activation thresholds. Some scientific interpretations suggest that these cells do not harbor intrinsic defects but rather require heightened levels of stimulation to initiate cytokine production (Brown and Boussiotis, 2008).

The presence of serum components with immunosuppressive properties in umbilical cord blood may also contribute to the overall downregulation of cytokine synthesis. These serum factors may exert inhibitory effects on the cellular machinery involved in cytokine expression, further compounding the reduced functional output observed in these immature immune cells (Tipnis *et al*., 2010).

Clinically, this immunological immaturity contributes to the delayed immune reconstitution commonly observed after UCB transplantation. Compared with bone marrow transplants, UCB recipients experience slower recovery of neutrophils, lymphocytes, and natural killer cells, which prolongs susceptibility to early bacterial and fungal infections (Takahashi *et al*., 2007; Zhang *et al*., 2012; Kondo *et al*., 2021; Fuchs *et al*., 2020). Median neutrophil engraftment typically occurs around 19–23 days for UCB versus 19–27 days for bone marrow, but functional immune recovery, particularly T-cell and B-cell reconstitution, may take several months longer in UCB recipients (Kiene *et al*., 2024; Ruggeri *et al*., 2022). Despite this slower early recovery, the long-term incidence of chronic GVHD and relapse rates are generally lower after UCB transplantation, reflecting its more tolerant and naïve immune profile (Van Besien *et al*., 2016; Wang *et al*., 2019).

Table 1: Quantitative and clinical comparison of cord blood and bone marrow for transplantation

Feature	Cord Blood (CB)	Bone Marrow (BM)	Citations
HSC concentration	Higher primitive HSCs, lower absolute	Lower primitive HSCs, higher absolute	(Ueda *et al*., 2001; Da Silva *et al*., 2009)
TNC per unit	~127 × 10^7/unit	2–5 × 10^8/kg recipient	(Barker *et al*., 2019; Remberger *et al*., 2015)
CD34+ per mL/unit	~44 × 10^5/unit	~1–2 × 10^6/kg recipient	(Barker *et al*., 2019; Remberger *et al*., 2015; Ueda *et al*., 2001)
T-regs/NK cells	More T-regs, rapid NK reconstitution	Fewer T-regs, mature NK cells	(Ueda *et al*., 2001; Dolstra *et al*., 2017)
HLA matching	1–2 mismatches tolerated	High-resolution match required	(Wagner *et al*., 2002; Morishima *et al*., 2023; Barker *et al*., 2019)
Acute GVHD (II–IV)	11–12% (severe)	37% (unrelated donor)	(Wagner *et al*., 2002; Cornelissen *et al*., 2003; Konuma *et al*., 2017; Zheng *et al*., 2013)
Chronic GVHD	10–21%	21–60%	(Wagner *et al*., 2002; Cornelissen *et al*., 2003; Konuma *et al*., 2017; Zheng *et al*., 2013; Mohty *et al*., 2003)
Neutrophil engraftment	21–28 days	14–21 days	(Wagner *et al*., 2002; Konuma *et al*., 2017; Kwon *et al*., 2014; Zheng *et al*., 2013)
Platelet engraftment	36–50 days	14–28 days	(Wagner *et al*., 2002; Konuma *et al*., 2017; Kwon *et al*., 2014; Zheng *et al*., 2013)
Collection	Non-invasive, banked, rapid	Invasive, donor-dependent	(Barker *et al*., 2019; Gaafar *et al*., 2025)

TNC: Total nucleated cell; NK: Natural Killer

4.0 Utilization of Umbilical Cord Blood and Bone Marrow in Therapeutic Applications

4.1 Hematopoietic Stem Cell Transplantation

4.1.1 Management of Leukemia

UCB transplantation has become an established option for hematopoietic stem cell replacement in leukemia, offering a viable source for marrow reconstitution after myeloablative therapy. Allogeneic cord blood, rather than autologous units, has demonstrated greater efficacy in malignant hematologic disorders due to its graft-versus-leukemia effect and broader donor availability (Milano and Boelens, 2015).

In pediatric leukemia, UCB transplantation is widely used due to its high engraftment success, lower rates of chronic GVHD, and tolerance for HLA mismatches. Comparative registry studies have shown that outcomes after UCB transplantation are broadly comparable to those of matched unrelated donor (MUD) bone marrow transplants, particularly in children and younger adults (Takahashi *et al*., 2007; Ruggeri *et al*., 2022). Median neutrophil recovery occurs within 19–23 days for UCB and 19–27 days for BM, while chronic GVHD remains lower with UCB (Zhang *et al*., 2012; Kondo *et al*., 2021).

In adults, UCB transplantation continues to show promise but remains influenced by several factors, including conditioning intensity, cell dose, and institutional experience. Myeloablative conditioning regimens and the use of double-unit or expanded UCB products (such as Omidubicel) have improved engraftment and reduced early infection-related mortality (Horwitz *et al*., 2021; Morse *et al*., 2024). Comparative analyses indicate that overall survival and relapse rates after UCB transplantation are similar to those achieved with bone marrow or peripheral blood stem cell grafts, though early non-relapse mortality remains slightly higher due to delayed immune recovery (Ruggeri *et al*., 2022; Fuchs *et al*., 2020).

Long-term outcomes suggest that UCB recipients experience reduced chronic GVHD and comparable relapse-free survival, resulting in similar or even improved graft-versus-host disease–free, relapse-free survival (GRFS) compared with BM or PBSC transplantation (Van Besien *et al*., 2016; Wang *et al*., 2019). These findings highlight UCB as a valuable alternative for patients lacking matched donors, especially in pediatric and minority populations.

4.1.2 Sickle Cell Disease

Sickle cell disease is an inherited hemoglobinopathy resulting from a single point mutation in the β-globin gene, producing structurally abnormal hemoglobin that polymerizes under hypoxic conditions. This process causes red cells to assume a rigid, sickled shape, leading to vaso-occlusion, chronic inflammation, multi-organ damage, and reduced life expectancy (Inusa *et al*., 2019). Despite advances in supportive care, including transfusion therapy and hydroxyurea, these approaches remain largely palliative and do not prevent cumulative organ injury (Brandow and Liem, 2022).

Hematopoietic stem cell transplantation using bone marrow from a HLA-identical sibling donor remains the gold-standard curative therapy (Cappelli *et al*., 2015). Early transplantation before irreversible organ damage offers the highest rates of event-free survival—often exceeding 90% in pediatric cohorts (Fitzhugh *et al*., 2017). However, most patients lack a matched sibling donor, prompting exploration of alternative graft sources such as UCB and haploidentical donors.

Outcomes with unrelated UCB transplantation have historically been variable, limited by low cell dose and delayed engraftment, leading to higher graft failure and early infection risk (Pawlowska *et al*., 2022). Advances in conditioning regimens, unit selection, and ex vivo expansion have improved outcomes, with multicenter analyses reporting overall survival rates of nearly 80% and event-free survival rates of 65–70% in well-matched pediatric transplants (Ruggeri *et al*., 2022; Wang *et al*., 2019).

Haploidentical HSCT, which uses half-matched family donors, has emerged as a promising alternative, showing comparable survival to matched donor transplants when post-transplant cyclophosphamide is used to prevent GVHD (Arcuri *et al*., 2019). Meanwhile, gene therapy and gene-editing strategies such as lentiviral β-globin addition and CRISPR-Cas9–mediated BCL11A disruption are transforming the therapeutic landscape, offering curative potential without donor dependence (Orkin & Bauer, 2019).

Although cord blood remains an appealing option due to rapid availability and relaxed HLA requirements, its role in adults is still limited by cell dose constraints. In contrast, bone marrow transplantation from matched siblings continues to yield the most reliable long-term outcomes. As cellular engineering and expansion platforms advance, UCB and gene-based therapies are expected to increasingly complement standard transplant approaches, broadening access to curative treatment for patients with sickle cell disease.

4.2 Non-Transplant Therapeutic Use

4.2.1 Blood Transfusion

Despite ongoing innovations in transfusion medicine and regenerative therapies, donor-derived blood transfusion remains an essential component of modern clinical care, particularly for neonates, elderly patients, and individuals with chronic or cardiovascular disease. UCB contains a mixture of fetal and adult hemoglobin, as well as functional platelets and hematopoietic progenitor cells (Mayani, 2024). Its high fetal hemoglobin concentration confers a greater oxygen affinity, theoretically improving tissue oxygenation efficiency (Bhattacharya, 2005).

While these biological properties have prompted interest in the potential therapeutic use of UCB for anemia and selected hematologic conditions, its practical application as a general transfusion product remains limited. The typical collection volume, often not exceeding 150–200 mL per placenta, is insufficient for most adult transfusion needs and restricts use to neonatal or pediatric settings. Additionally, the logistics of donor screening, consent procedures, and processing requirements make large-scale transfusion programs difficult to sustain.

UCB also carries distinct safety and quality considerations. The risk of microbial contamination during collection, especially in vaginal deliveries, remains a concern despite advances in aseptic protocols (Reuther *et al*., 2022). Furthermore, the need for maternal infectious disease testing, rapid processing, and short storage duration for unprocessed UCB all constrain its use for routine transfusion. Consequently, its role in transfusion medicine today is primarily investigational and restricted to specialized or emergency contexts rather than as a replacement for conventional blood donation.

Although the biochemical and immunologic properties of umbilical cord blood make it an intriguing adjunct in transfusion science, significant logistical, technical, and economic barriers currently limit its routine clinical use. Continued improvements in collection efficiency, contamination control, and storage technology may enhance its future applicability, but for now, UCB remains a niche rather than a general transfusion resource.

4.3 Limitations and Considerations in the Clinical Application of Umbilical Cord Blood

Umbilical cord blood has emerged as an essential alternative source of hematopoietic stem cells for transplantation, particularly following the initial clinical success recorded in the late 1980s (Kurtzberg *et al*., 2023). Since then, the field has witnessed a substantial increase in the number of cord blood transplants conducted globally, with tens of thousands of procedures utilizing this biological resource, including a significant proportion derived from unrelated donors. The development and proliferation of cord blood banks have made possible the storage of hundreds of thousands of units, which are now accessible for therapeutic use through numerous international registries and collaborative networks (Rocha, 2016).

Cord blood transplantation presents several clinical advantages, particularly in scenarios where conventional donor options are unavailable. One of its most notable benefits is the reduced necessity

for strict HLA compatibility between donor and recipient. This feature significantly broadens the pool of potential donors, making transplantation a viable option for a wider population, including those from underrepresented ethnic groups with historically lower donor match rates. In addition, patients who receive transplants using cord blood are generally at a lower risk of developing severe graft-versus-host disease, a complication that often arises following allogeneic transplantation procedures. This reduced risk has been attributed to the immunological immaturity of the lymphocyte populations found in cord blood and the relatively enriched presence of immune-modulatory cell types that may contribute to a more tolerogenic post-transplant environment.

Nevertheless, cord blood transplantation is not without its clinical challenges. A major concern is the limited quantity of stem and progenitor cells contained within a single unit of cord blood. This scarcity of cellular material can result in delayed hematopoietic recovery and prolonged periods of neutropenia, which, in turn, increase the susceptibility to infectious complications and other adverse outcomes. In pediatric recipients, the smaller body mass often allows for the successful use of a single unit; however, in adult patients, strategies such as the use of dual cord blood units or ex vivo expansion techniques are sometimes employed to compensate for the insufficient cell dose.

Despite the limitations in cell count, the ability of cord blood to tolerate higher degrees of HLA disparity has profound implications. Statistically, each cryopreserved unit of cord blood provides a significantly enhanced probability of locating a suitable match when compared to the likelihood of finding a compatible bone marrow donor (Gragert *et al*., 2014). This elevated matching potential is crucial in urgent clinical situations where rapid transplantation is necessary and time constraints limit the feasibility of extensive donor searches.

The global progress in cord blood transplantation has been largely supported by the establishment of national and international public cord blood banks. These facilities collect, process, and store donated cord blood at no cost to the donor, ensuring equitable access to high-quality grafts through globally connected donor search platforms. These public repositories operate under stringent regulatory standards that govern donor eligibility screening, collection protocols, cryopreservation procedures, and unit release criteria. In parallel, international organizations have contributed to the harmonization of banking operations by issuing detailed quality assurance frameworks and technical guidelines, ensuring the safety and efficacy of stored units (Jöris *et al*., 2021).

However, the landscape of cord blood banking also includes private institutions, where units are stored for potential autologous or familial use, typically in exchange for a fee. While private banks collectively store a larger number of units than their public counterparts, there are ongoing concerns about the actual utility of privately stored cord blood. Scientific and medical assessments have indicated that the probability of a child requiring their own stored cord blood for therapeutic use is extremely low, at 0.04% (Kaimal *et al*., 2009); however, public banking is generally considered more cost-effective because units are available to a broader pool of recipients. Moreover, the quality of privately banked units is sometimes questioned due to lower cell yields and a higher incidence of microbial contamination, likely resulting from variations in collection and processing standards (Frangoul and Domm, 2011).

Ethical and operational challenges in cord blood banking include concerns about informed consent, ownership rights, and equitable access to stored units. Inadequate regulatory oversight or inconsistent policy enforcement can lead to disparities in access and reduce public confidence in donation systems. Establishing transparent governance frameworks and fostering community engagement are essential to protect donors and ensure ethical and responsible banking practices

To address these challenges and harness the full therapeutic potential of cord blood, hybrid models of banking have been introduced. These frameworks aim to integrate the accessibility and public benefit of traditional public banks with the personalized focus of private storage. Regardless of the banking model employed, adherence to universally accepted operational standards is essential for maintaining the clinical integrity of stored grafts.

Countries seeking to expand their stem cell infrastructure should prioritize national public banking programs supported by clear regulatory policies, standardized collection networks, and cost-sharing partnerships between public health institutions and private partners to improve unit diversity and sustainability.

Ethical and medical discourse surrounding cord blood banking practices continues to evolve. Many experts advocate for the expansion of public donation programs, arguing that the collective benefit of increasing the global inventory of diverse and well-characterized cord blood units outweighs the largely speculative advantages of private storage. It is emphasized that certain conditions purported to be treatable with autologous cord blood may already be present at the time of birth, potentially compromising the therapeutic utility of the stored cells. Ultimately, the decision to bank cord blood is influenced by a multitude of personal, medical, and societal factors. As public awareness and education on the importance of donation improve, it is anticipated that participation in public banking will increase. This progression holds the promise of expanding global access to life-saving stem cell therapies and addressing disparities in transplant availability across different populations and healthcare systems (Bień *et al*., 2024).

5.0 Recommendations and Future Directions

Despite the significant progress made in the application of UCB for hematopoietic stem cell transplantation, several critical areas remain ripe for development and innovation. To fully harness the therapeutic potential of cord blood, future research and policy strategies should be directed at overcoming current limitations, particularly in stem cell yield, public accessibility, and storage infrastructure.

One of the principal challenges with CB transplantation is the relatively low quantity of stem cells available in a single cord blood unit, which can compromise successful engraftment, particularly in adult recipients. However, recent breakthroughs in ex vivo expansion technologies have begun to transform this limitation. The FDA approval of Omidubicel (Omisirge) in 2023 marked a major milestone in the field. Omidubicel, a nicotinamide-expanded UCB product, demonstrated superior clinical outcomes compared with standard UCB transplantation, including faster neutrophil engraftment (median 12 vs. 22 days), higher platelet recovery (55% vs. 35% by day 42), and lower rates of grade 2/3 bacterial or fungal infections (37% vs. 57%) in a Phase III randomized trial involving 125 patients (Horwitz *et al*., 2021; Morse *et al*., 2024). Earlier Phase I data reported similar advantages in engraftment speed and infection reduction (Anand *et al*., 2017). Long-term follow-up confirms durable trilineage hematopoiesis, sustained graft function, and stable immune reconstitution up to 10 years post-transplant, with no new safety concerns (Lin *et al*., 2023). These findings provide robust clinical and regulatory validation for expanded UCB transplantation, particularly benefiting patients from ethnic minorities who often lack matched donors (Morse *et al*., 2024; Lin *et al*., 2023).

Similarly, UM171, a small molecule that promotes robust ex vivo expansion of UCB hematopoietic stem cells, represents another promising innovation. While clinical evidence remains at the Phase I/II stage, trials have demonstrated rapid neutrophil recovery, enhanced T cell diversity, and reduced rates of chronic GVHD and severe infections, with outcomes comparable or superior to traditional stem cell sources (Dumont-Lagacé *et al*., 2021; Cohen *et al*., 2023). Mechanistic studies reveal that

UM171-expanded grafts display unique molecular and metabolic profiles supporting long-term repopulating potential (Fares *et al*., 2017; Papa *et al*., 2019). Importantly, UM171 expansion increases the proportion of usable cord blood units for adults from approximately 4–5% to over 50%, markedly improving donor access for racial and ethnic minorities (Dumont-Lagacé *et al*., 2021).

Omidubicel and UM171 expansion platforms directly address the long-standing challenge of low stem cell yield in UCB transplantation by enabling the use of smaller, better HLA-matched units and accelerating hematopoietic recovery. These advances signal a paradigm shift in cord blood transplantation, moving the field toward a new standard of care with faster engraftment, fewer infections, and broader donor availability (Horwitz *et al*., 2021; Pineault & Abu-Khader, 2015; Saiyin *et al*., 2022; Sica *et al*., 2020; Bari *et al*., 2015).

Table 2: Clinical outcomes for ex vivo expanded umbilical cord blood products

	Omidubicel	**UM171**
Expansion Mechanism	Nicotinamide-mediated stem cell expansion	Small-molecule–induced self-renewal (UM171)
Trial Phase	Phase III	Phase II
Sample Size (N)	125	52
Median Neutrophil Engraftment	12 days	17–18 days
Median Platelet Engraftment	33–42 days	37–42 days
Overall Survival (OS) / Non-Relapse Mortality (NRM)	No significant OS difference; reduced infections and NRM	67% OS / 19% NRM at 2 years
GVHD (Acute / Chronic)	Similar to standard UCBT	69% acute / 7% chronic GVHD
Regulatory Status	FDA-approved (2023)	Not yet approved
Key References	Horwitz *et al*., 2021; Lin *et al*., 2023; Shpall & Rezvani, 2021; Horwitz *et al*., 2023, 2025; De Koning *et al*., 2021; Majhail *et al*., 2021	Milano *et al*., 2023; Cohen *et al*., 2018, 2020, 2024; Dumont-Lagacé *et al*., 2021

Enhancing the quality of cells derived from cord blood remains an important objective. Investigative efforts should continue to explore novel cryoprotectants with reduced cytotoxicity, advanced cryopreservation methods such as vitrification, and standardized post-thaw processing techniques that improve cell recovery and functionality. Epigenetic reprogramming and metabolic conditioning may also prove beneficial in maintaining the primitive phenotype and pluripotency of cord-derived stem cells, making them more versatile for both hematopoietic and regenerative applications.

It is also imperative to establish robust cord blood banking systems in countries where they are currently lacking or underutilized. Governments should implement national policies that support public cord blood donation, ensure standardized regulatory oversight, and fund the establishment of accredited cord blood banks. Hybrid banking models integrating public access with the personalized storage offered by private banks could serve as a sustainable solution, especially in low-resource

settings. Public awareness campaigns that demystify cord blood donation and address cultural or religious concerns are essential to increase voluntary participation.

In strengthening cord blood banking systems, maintaining high-quality standards and increasing inventory diversity are equally important. Efforts should prioritize measures that expand HLA representation in public banks through inclusive donor recruitment, regional collaborations, and integration of underrepresented populations. Developing comprehensive digital registries linked across international networks can also enhance donor–recipient matching efficiency and improve equitable access to compatible grafts.

International collaboration is also needed to create a globally connected registry of cord blood units, improving the speed and efficiency of donor-recipient matching across borders. Investment in digital health platforms and artificial intelligence-based matching algorithms may help accelerate this process. Health policy frameworks should further incentivize clinical research into emerging uses of cord blood, including its application in neurodegenerative diseases, autoimmune disorders, and tissue regeneration.

6.0 Conclusion

Umbilical cord blood has proven to be a valuable and, in many respects, promising alternative to traditional hematopoietic stem cell sources such as bone marrow. Its ease of collection, lower immunogenicity, broader donor availability due to less stringent HLA matching requirements, and rich content of primitive, pluripotent stem cells underscore its growing clinical relevance. While its lower stem cell yield remains a critical limitation, particularly for adult recipients, this challenge is not insurmountable. Ongoing advancements in ex vivo expansion techniques and optimized collection protocols are poised to enhance both the quality and quantity of harvestable cells.

With sustained research, regulatory alignment, and infrastructural investment, especially in the public banking systems, digital registries, and novel cryopreservation technologies, cord blood transplantation is positioned to play an increasingly central role in hematopoietic stem cell therapy. However, its widespread clinical adoption will ultimately depend on cost-effectiveness, scalability, and confirmation of current results in larger randomized studies.

To this end, it is strongly recommended that efforts be intensified in developing cost-effective expansion strategies, implementing hybrid banking models, and promoting public education to increase donation rates. By combining scientific innovation with sustainable policy frameworks, cord blood can continue to evolve as a practical and equitable complement, rather than a complete replacement, to traditional stem cell sources in regenerative medicine and transplantation.

Conflicts of Interest

The authors declare that there is no conflict of interest

Ethical Consideration

Not applicable

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