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Original Article

Efficacy and Challenges of Pediatric Cord Blood Transplantation: Insights from a Retrospective Single-Center Study

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Abstract

Background: Umbilical cord blood transplantation (UCBT) serves as a valuable alternative for pediatric patients without matched donors, particularly in urgent situations where timely transplantation is critical. While UCBT offers immunological benefits and broader donor availability, its clinical outcomes remain inconsistent, especially in non-malignant hematologic disorders.

Objective: To evaluate clinical outcomes of UCBT in pediatric patients with malignant and non-malignant hematologic conditions, focusing on transplant-related complications and survival rates.

Methods: In this retrospective single-center study, we analyzed 14 pediatric patients (aged 0.7–11 years) who underwent allogeneic UCBT at Mofid Children's Hospital between 2019 and 2024. Data were extracted from institutional registries and medical records, including patient demographics, disease classification, graft characteristics, conditioning regimens, engraftment status, incidence of graft-versus-host disease (GVHD), infections, and survival outcomes.

Results: Among the 14 patients, 85.7% had non-malignant disorders. Most received unrelated donor grafts, with HLA matching of 6/6 in 42.9%, 5/6 in 50%, and 4/6 in 7.1%. The median total nucleated cell dose was 4.95×10^7/kg, and the median $CD34^+$ cell dose was 1.7×10^5/kg. Neutrophil engraftment was achieved in 42.9% of patients, with a median of 19 days. Primary graft failure occurred in 50% of patients, and secondary graft failure in 7.1%. Acute GVHD developed in 14.3% of cases, while no chronic GVHD was observed. CMV reactivation occurred in 42.9% of patients, and bacterial infections were reported in 57.1%. The overall survival rate was 42.9%, with transplant-related mortality accounting for 57.1% of cases, due to infections and graft failure.

Conclusion: UCBT remains a feasible therapeutic option for pediatric patients lacking matched donors, particularly in urgent or resource-constrained settings. However, the high incidence of graft failure and infection-related mortality highlights the need for improved graft selection strategies, personalized conditioning protocols, and optimized post-transplant care to enhance patient outcomes.

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1. INTRODUCTION

AML Hematopoietic stem cell transplantation (HSCT) is a well-established, life-saving treatment for children with malignant and non-malignant hematologic disorders. In the pediatric population, the spectrum of conditions treated with HSCT differs significantly from that in adults and includes a variety of inherited anemias, such as congenital sideroblastic anemia and congenital dyserythropoietic anemia (1), as well as diverse inborn errors of immunity (IEI), including severe combined immunodeficiency (SCID), autoimmune lymphoproliferative syndrome (ALPS) (2), hemophagocytic lymphohistiocytosis (HLH) (3), and inborn errors of metabolism (IEM) (4).

One of the main challenges in HSCT is identifying a suitable donor, especially in cases requiring urgent transplantation. Umbilical cord blood (UCB) has emerged as a valuable alternative to traditional sources such as bone marrow (BM) and peripheral blood (PB), particularly for patients lacking fully HLA-matched donors (5). Since the first successful UCB transplantation in 1989, more than 40,000 procedures have been performed worldwide, highlighting its growing clinical relevance (6, 7). UCB possesses unique biological advantages, including a higher proportion of primitive hematopoietic stem cells (HSCs) with superior self-renewal capacity (8). Moreover, UCB transplantation demonstrates greater tolerance to HLA mismatches, thereby expanding donor availability and improving access for diverse and underserved patient populations (9).

Despite these benefits, several limitations remain. A major concern is the relatively low cell dose in a single UCB unit, which may delay neutrophil engraftment and immune reconstitution, leading to a higher risk of infections and extended hospital stays (5). Optimal unit selection must consider multiple variables, including total nucleated cell count, HLA compatibility, and overall graft quality. Although numerous studies have demonstrated the efficacy of UCB transplantation, long-term outcomes, particularly in pediatric patients, are still under investigation. Moreover, data specific to populations in resource-constrained settings remains limited, warranting further exploration (6, 8, 9).

This study aims to assess the efficacy and clinical outcomes of UCBT in pediatric patients (aged 0–18 years) treated at Mofid Children's Hospital between 2019 and 2024. The findings are expected to provide insights into optimizing donor selection, improving transplantation protocols, and enhancing post-transplant management, especially in urgent and resource-limited clinical settings.

2. MATERIALS AND METHODS

2.1. Study Design and Patient Population

This retrospective descriptive study evaluated the clinical outcomes of 14 pediatric patients (9 males, 5 females) who underwent umbilical cord blood transplantation at Mofid Children's Hospital, affiliated with Shahid Beheshti University of Medical Sciences in Tehran, Iran, between January 2019 and December 2024.

Eligible participants included children and adolescents (aged ≤18 years) who received allogeneic cord blood hematopoietic stem cell transplantation for malignant or non-malignant hematologic disorders. Malignant indications included acute lymphoblastic leukemia (ALL) and juvenile myelomonocytic leukemia (JMML). Non-malignant conditions comprised severe combined immunodeficiency (SCID), hyper-IgM syndrome, STAT3 deficiency, aplastic anemia, mucopolysaccharidosis, dyskeratosis congenita, Griscelli syndrome, and hemophagocytic lymphohistiocytosis (HLH). Patients who received stem cells from bone marrow or peripheral blood, or those who underwent haploidentical transplantation, were excluded.

2.2. Data Collection

Data were extracted from the "Data Registry of Hematopoietic Stem Cell Transplantation in Pediatric Group (0-18 years) in Shahid Beheshti University of Medical Sciences and Allied Centers" and supplemented with information from the patients' electronic medical records. The evaluated variables included patient characteristics such as demographics (age, sex), primary diagnosis, underlying disease classification (malignant vs. non-malignant), blood group, weight, and pre-transplant clinical status. Donor and graft characteristics included donor type (matched sibling donor [MSD], matched related donor [MRD], and matched unrelated donor [MURD]), HLA matching status (4/6, 5/6, 6/6), donor-recipient ABO compatibility, total nucleated cell (TNC) count ($\times 10^7$/kg), CD34+ cell dose ($\times 10^5$/kg), and cell viability percentage. Transplantation-related variables encompassed the conditioning regimen type (myeloablative vs. reduced-intensity), GVHD prophylaxis regimen, and supportive care protocols. Post-transplant outcomes were assessed based on neutrophil and platelet engraftment, donor chimerism, graft failure (primary or secondary), acute and chronic GVHD, infectious and non-infectious complications, survival status, and cause of death (if applicable).

2.3. Cord Blood Unit Selection and Processing

Cord blood units were selected based on HLA compatibility and cell dose, following established transplantation guidelines. Matching criteria varied depending on disease type, with a minimum 4/6 HLA match (HLA-A, HLA-B, and HLA-DRB1 loci) generally required for malignant conditions and a 5/6 match preferred for non-malignant disorders. Thresholds for unit selection included a minimum TNC dose of 1.5×10^7 cells/kg and a $CD34^+$ cell dose of at least 1.0×10^5 cells/kg (10).

Cord blood units underwent standardized processing, including controlled-rate cryopreservation and storage in accredited cord blood banks. On the day of transplantation, units were thawed using validated protocols to preserve cell viability. Pre-medications, including antihistamines and corticosteroids, were administered to prevent infusion-related reactions.

2.4. Transplantation Procedure

2.4.1. Conditioning Regimens

Combinations of Busulfan (BU), Cyclophosphamide (CPM), BU, Melphalan (MEL), or BU, Fludarabine (FLU), and Rabbit Anti-Thymocyte Globulin (ATG) were used in the myeloablative conditioning (MAC) regimen group.

Reduced-intensity conditioning (RIC) regimens were used to provide adequate immunosuppression for donor cell engraftment while minimizing toxicity. The typical RIC protocol included FLU, MEL, and R-ATG, with R-ATG administered at 2.5 mg/kg/day for three consecutive days. Alemtuzumab (anti-CD52) was not used in any patient, as it was not available in our setting. The selection of the conditioning regimen was individualized based on patient characteristics, underlying disease, and institutional protocols.

2.4.2. GVHD Prophylaxis and Supportive Care

GVHD prophylaxis was based on a calcineurin inhibitor (CNI)–based regimen. Cyclosporine A (CsA) was administered intravenously at 3 mg/kg/day in two divided doses starting from day –1. Target CsA levels were 200–300 ng/mL in non-malignant and 150–200 ng/mL in malignant conditions. Additional immunosuppressive agents, methotrexate (MTX), mycophenolate mofetil (MMF), or methylprednisolone (MP), were included depending on patient-specific factors.

In addition to agents that primarily target GVHD, all patients received supportive medications consistent with established practices in HSCT. These included prophylactic antivirals (acyclovir), antifungals (voriconazole or fluconazole), and antibacterial agents (ciprofloxacin), cotrimoxazole for Pneumocystis carinii, and ursodeoxycholic acid for prevention of sinusoidal obstructive syndrome (SOS). Also, G-CSF was administered at 5 μg/kg/day from day +5 until neutrophil engraftment in non-malignant disorders, and levetiracetam (for seizure prophylaxis in patients who received Busulfan) was used.

2.5. Study Endpoints and Definitions

- **Neutrophil engraftment:** Absolute neutrophil count (ANC) ≥ 0.5×10^9/L for three consecutive days.
- **Platelet engraftment:** Platelet count ≥ 20×10^9/L for seven consecutive days without transfusion.
- **Chimerism:** Full donor chimerism = ≥95% donor-derived cells; Mixed = 5% to <95%.
- **Primary graft failure:** ANC < 0.5×10^9/L by day +42 or <5% donor chimerism with no hematologic recovery.
- **Secondary graft failure:** Loss of engraftment or decline of donor chimerism to <5% after initial engraftment.
- **Acute GVHD:** Diagnosed per modified Glucksberg criteria (11).
- **Chronic GVHD:** Diagnosed and categorized based on NIH consensus.
- **Infectious complications:** Categorized as bacterial, viral, or fungal based on clinical, radiological, microbiological findings, and PCR assays.
  - **CMV reactivation:** Defined by detection of CMV DNA in peripheral blood.
  - **Fungal infections:** Classified per 2020 revised EORTC/MSG criteria as possible, probable, or proven (12).
- **Overall survival (OS):** Time from transplantation to death or last follow-up.

2.6. Statistical Analysis

Descriptive statistics were used to summarize patient demographics and clinical outcomes. Continuous variables were expressed as medians and ranges, while categorical variables were presented as frequencies and percentages. OS and EFS were estimated using the Kaplan–Meier method. Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY).

2.7. Ethical Considerations

The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RICH.REC.1401.035) and conducted in

accordance with the Declaration of Helsinki. Given the retrospective design and use of anonymized data, the requirement for informed consent was waived.

3. RESULTS

3.1. Patient and Transplant Characteristics

Patient and transplant characteristics are detailed in **Table 1**. A total of 14 pediatric patients underwent UCBT, including 9 males (64%) and 5 females (36%), with a median age of 4.9 years (range: 0.7–11 years). The majority of transplants were performed for non-malignant disorders (n=12, 85.7%), including SCID (n=2), ALD (n=2; monozygotic twins), HLH associated with Griscelli syndrome (n=2), AA (n=2), STAT3 deficiency (n=1), Hyper IgM (n=1), MPS II (n=1), and DC (n=1). Malignant conditions accounted for 14.3% of cases (n=2), comprising ALL (n=1) and JMML (n=1).

The median patient weight was 17.5 kg (range: 5–37 kg). Blood group distribution among recipients was as follows: A+ (n=6, 42.9%), B+ (n=4, 28.6%), O+ (n=2, 14.3%), AB+ (n=1, 7.1%), and A− (n=1, 7.1%).

3.2. Donor and Graft Characteristics

Most patients (n=13, 92.9%) received grafts from MURD, while one patient (7.1%) with AA received a graft from an MSD. HLA matching was 6/6 in 6 patients (42.9%), 5/6 in 7 (50%), and 4/6 in one (7.1%). Donor-recipient gender was matched in 7 cases (50%) and mismatched in 7 (50%). ABO compatibility was present in 6 patients (42.9%), while 8 (57.1%) received ABO-mismatched grafts.

The median infused TNC dose was 4.95×10^7/kg (range: 3.04–27.3 × 10^7/kg), and the median $CD34^+$ cell dose was 1.7×10^5/kg (range: 1.02–20.7 × 10^5/kg). Median graft viability was 91.35% (range: 67.60–98%).

3.3. Engraftment and Chimerism

Neutrophil engraftment was achieved in 6 patients (42.9%), with a median recovery time of 19 days (range: +15 to +22). Primary graft failure occurred in 7 patients (50%), defined as donor chimerism <5%. One patient (7.1%) experienced secondary graft failure following initial successful engraftment with high donor chimerism (**Table 2**).

Among patients with 4/6 HLA matches (n=4), two developed primary graft failure despite receiving adequate $CD34^+$ doses and high cell viability. One patient with a prior fungal infection achieved initial engraftment but succumbed to hepatic GVHD and invasive pulmonary infection. Another, who received the highest $CD34^+$ dose, also engrafted but died from pulmonary complications. These findings highlight the complex interplay between graft-related and patient-specific factors in determining engraftment success.

3.4. Conditioning Regimens, GVHD Prophylaxis, and Supportive Care

Eight patients (57.1%) received reduced-intensity conditioning (RIC), and six (42.9%) received myeloablative conditioning (MAC), tailored to their underlying diseases (**Table 1**). Details of conditioning and GVHD prophylaxis are summarized in **Table 1**. GVHD prophylaxis included cyclosporine A, with adjunctive agents such as methotrexate (MTX), mycophenolate mofetil (MMF), and methylprednisolone (MP), depending on clinical indication. Weekly PCR screening for CMV and EBV was conducted. CMV reactivation was managed with preemptive therapy (ganciclovir, valganciclovir, or foscarnet), while EBV reactivation was treated with immunosuppression taper and rituximab. Red blood cell transfusions were administered to maintain hemoglobin levels above 8 g/dL; all packed red blood cells were irradiated and leukodepleted. Platelet transfusions were administered when counts fell below 10×10^9/L or below 20×10^9/L in the presence of active bleeding.

3.5. Post-Transplant Complications

Post-transplant complications included acute GVHD in 2 patients (14.3%), with involvement of the skin and gastrointestinal tract. CMV reactivation was noted in 6 patients (42.9%), and EBV reactivation in one (Patient 4), who subsequently developed post-transplant lymphoproliferative disorder (PTLD) and T-cell lymphoma, with a poor response to chemotherapy. Bacterial infections were reported in 8 patients (57.1%), and one patient developed a probable fungal infection (7.1%). Other common but clinically less significant complications included electrolyte disturbances, thrombocytopenia, and gastrointestinal symptoms (**Table 2**).

3.6. Survival Outcomes

The overall survival rate was 42.9% (6/14), while transplant-related mortality occurred in 57.1% (8/14) (**Table 2**). Causes of death included a combination of severe hepatic GVHD, fungal and pulmonary complications (Patient 6); pulmonary complications (Patients 12 and 13); underlying disease progression (Patient 2); bleeding associated with graft failure (Patient 7); catheter-related event (Patient 8);

Table 1. Patient, Donor, and Transplantation Characteristics.

Patient number	Age at HSCT	Diagnosis	HLA match	Mismatch	Recipient Blood Group	CB Blood Group	Weight (Kg)	TNC Infused (107/kg)	CD34 (105/kg)	Viability	Conditioning regimen	GVHD prophylaxis
1	2	Jmml	5/6	HLA-B	A+	O+	10	14.31	2.71	96%	MAC (BU+MEL+FLU)	Cyclo +MTX
2	8	ALD	4/6	HLA-A & B	A+	O+	24	4.36	2.22	91.7%	MAC (BU+ FLU+ATG)	Cyclo +MMF
3	10y	Aplastic anemia	6/6	-	AB+	B+	25	3.38	1.04	94%	MAC (FLU+CPM+ATG)	Cyclo +MP
4	5	HLH+ Griscelli syndrome	5/6	HLA-B	A+	O+	19	4.10	1.02	89%	RIC (FLU+MEL+ATG)	Cyclo + MP
5	1y	SCID	6/6	_	A+	B+	8	10.67	1.38	95%	RIC (FLU+MEL+ATG)	Cyclo +Celcept
6	11y	Hyper IgM	4/6	HLA-A & B	O+	B+	20	8.00	2.50	88%	RIC (FLU+MEL+ATG)	Cyclo +Celcept
7	4y	Pancytopenia, Dyskeratosis Congenita	5/6	HLA-DRB1	A+	0+	10	17.40	12.00	98%	MAC (FLU+CPM+ATG)	Cyclo +MTX
8	4y8m	MPS II	6/6	_	O+	O+	24	3.85	1.08	97%	MAC (BU+ FLU+ATG)	Cyclo +Celcept
9	5y	Aplastic anemia	5/6	HLA-B	B+	B+	16	3.54	1.04	93%	MAC (FLU+CPM+ATG)	Cyclo+ MP
10	3y6m	ALL	6/6	_	B+	O+	13	5.54	1.05	80%	MAC (BU+CPM+MEL)	Cyclo +MTX
11	4y	STAT3 Deficiency	6/6	_	B+	O+	16	6.50	2.73	91%	RIC (FLU+MEL+ATG)	Cyclo +Celcept
12	1y8m	SCID	4/6	HLA-DRB1	B+	O+	5	27.30	20.70	75%	RIC (FLU+MEL+ATG)	Cyclo +Celcept
13	7y	ALD	4/6	HLA-A & B	A+	B+	22	3.04	1.60	77.80%	MAC (BU+ FLU+ATG)	Cyclo +MMF
14	7y	HLH+ Griscelli syndrome	5/6	HLA-A	A-	A-	37	4.06	1.23	67.60%	RIC (FLU+MEL+ATG)	Cyclo +MMF

Abbreviations: SCID: Severe Combined Immunodeficiency; **ALL:** Acute Lymphoblastic Leukemia; **JMML:** Juvenile Myelomonocytic Leukemia; **ALD:** Adrenoleukodystrophy; **MPS:** Mucopolysaccharidosis; **HLH:** Hemophagocytic Lymphohistiocytosis; **MURD:** Matched Unrelated Donor; **HLA:** Human Leukocyte Antigen; **TNC:** Total Nucleated Cell; **GVHD:** Graft-versus-Host Disease; **MAC:** Myeloablative Conditioning; **RIC:** Reduced-Intensity Conditioning; **BU:** Busulfan; **MEL:** Melphalan; **FLU:** Fludarabine; **CPM:** Cyclophosphamide; **ATG:** Anti-Thymocyte Globulin; **MTX:** Methotrexate; **MMF:** Mycophenolate Mofetil; **MP:** Methylprednisolone; **Cyclo:** Cyclosporine.

Table 2. Engraftment Outcomes and Post-transplant Complications.

Patient number	Chimerism %	Neutrophil Engraftment (Day)	Platelet Engraftment (Day)	Engraftment Status	Post-Transplant Complications		Current Status (Alive / Deceased)	Cause of death
					GVHD (Acute/chronic)	Other (Infectious/Non-Infectious)		
1	<5	-	-	Primary Graft Failure	-	CMV reactivation, Staphylococcus epidermidis,	Second transplant required	-
2	<5	-	-	Primary Graft Failure	-	CoNS	Death	Disease-related mortality
3	100	+21	+28	Engrafted	-	CMV reactivation	Alive	-
4	<5	-	-	Primary Graft Failure	-	EBV reactivation (PTLD), Staphylococcus epidermidis, and Pseudomonas bacteremia	Death	PTLD/T-cell lymphoma following EBV reactivation and HLH relapse
5	100	+17	+24	Engrafted	-	Staphylococcus aureus bacteremia	Alive	-
6	+100	+19	+25	Engrafted	Acute GVHD (Grade III-IV skin/GI/liver),	CMV reactivation, Pulmonary fungal infection, Sepsis	Death	Liver GVHD, Pulmonary, and fungal infection
7	94	+13	+22	Secondary Graft Failure	-	Severe skin rash (ATG-associated)	Death	Bleeding
8	<5	-	-	Primary Graft Failure	-	-	Death	CVL dislocation
9	<5	-	-	Primary Graft Failure	-	CMV reactivation skin rash (ATG-associated)	Second transplant required	-
10	100	+22	+38	Engrafted	Acute GVHD (Grade II skin)	CMV reactivation, Pseudomonas bacteremia,	Alive	-
11	<5	-	-	Primary Graft Failure	-	CoNS, Rash and diarrhea attributed to drug reaction	Death	Hepatic failure and infection
12	90	+19	+32	Engrafted	-	Enterococcus bacteremia	Death	Pulmonary complications
13	<5	-	-	Primary Graft Failure	-	Bacterial pneumonia	Death	Death on Day +24 due to pneumonia, sepsis, and refractory seizures
14	100%	+15	+20	Engrafted	-	CVL Infection, UTI	Alive	-

EBV-driven T-cell lymphoma (Patient 4); and hepatic failure (Patient 11).

Graft failure (primary or secondary) occurred in 57.1% (8/14). Among survivors, the majority achieved full donor chimerism (≥90%), with some showing mixed or low-level donor chimerism (<5%).

4. DISCUSSION

The UCBT has emerged as a valuable treatment modality for pediatric patients, especially in urgent settings where matched donors are not readily available (13).

In this study, we analyzed outcomes in 14 children who underwent UCBT at Mofid Children's Hospital, focusing on engraftment, complications, and survival. UCBT offers key advantages, including greater tolerance for HLA mismatches, which broadens donor availability for ethnically diverse populations. However, challenges such as delayed engraftment and impaired immune reconstitution, primarily due to the limited cell dose of single UCB units, persist (14). These limitations increase the risk of early infections and prolonged hospitalization, emphasizing the need for optimal donor selection and supportive strategies.

Engraftment remains a critical determinant of UCBT success, influenced by TNC and $CD34^+$ cell doses and HLA compatibility. In this study, successful engraftment occurred in only 42.9% of patients, with primary graft failure observed in 50%, highlighting the difficulty of achieving durable hematopoietic recovery despite meeting standard cell dose thresholds. This aligns with previous studies emphasizing the need for adequate cell dose and close HLA matching (14). Engraftment rates in our study were lower than those commonly reported in pediatric UCBT, which often exceed 80% (15). This discrepancy may be partly attributable to the high prevalence of non-malignant disorders, particularly immunodeficiencies, which are associated with underlying immune dysregulation (16, 17).

While HLA compatibility is a known predictor of engraftment (10), our data show it is not always sufficient. Some patients with 5/6 HLA matches and adequate $CD34^+$ doses failed to engraft, while others with 4/6 mismatches achieved full donor chimerism, possibly due to favorable graft features such as high stem cell counts and superior post-thaw viability (18).

Graft failure also occurred in recipients with acceptable HLA compatibility and cell dose thresholds, suggesting that additional factors such as reduced cell viability, pre-existing organ dysfunction, or early post-transplant complications (e.g., pulmonary events, hemorrhage) may significantly influence outcomes. These observations highlight the multifactorial nature of engraftment and support prior findings on the immunological flexibility of cord blood grafts in pediatric settings (19, 20). Ultimately, while HLA matching and cell dose are pivotal, they are insufficient as sole predictors; a comprehensive assessment of graft quality and recipient-specific factors is essential for individualized transplant planning (21).

The notably high rate of graft failure in our study may be explained by several interconnected factors characteristic of our resource-limited setting. Cell doses, although above the minimum thresholds, were frequently suboptimal relative to the patient's body weight, creating an unfavorable cell dose-to-recipient size ratio. Limited access to larger international cord blood bank inventories further restricted the ability to consistently select units with optimal cell content. In addition, the predominance of non-malignant disorders, particularly inborn errors of immunity, represents a recognized risk factor for graft failure due to underlying immune dysregulation and residual host immunity. These factors, taken together, may explain why graft failure occurred even in patients with acceptable HLA compatibility, while some with mismatches successfully engrafted, highlighting the pivotal role of cell dose and disease biology beyond HLA matching alone. Despite these challenges, several patients achieved durable engraftment and long-term survival, demonstrating that UCBT remains a viable and potentially curative therapy even under demanding clinical and logistical constraints. Our experience thus provides practical insights for centers facing similar limitations.

Conditioning regimens also appeared to influence outcomes. While 57.1% of patients received MAC, the remainder underwent RIC, selected based on disease type, age, and organ function. MAC was used for malignant or high-risk conditions, whereas RIC was preferred for immunodeficiencies or when intensive regimens were not tolerated. Despite the small sample size, successful engraftment and long-term survival were observed across both groups, suggesting regimen intensity alone was not a determining factor. All protocols included fludarabine, reflecting its central role in pediatric conditioning due to its potent immunosuppression and low organ toxicity (22, 23). The use of RIC in selected non-malignant cases yielded acceptable outcomes, supporting its use as a safer option in vulnerable populations.

The incidence of grade II–IV acute GVHD was 14.3%, lower than the 30–50% reported in prior pediatric UCBT studies. This may reflect the effectiveness of our GVHD prophylaxis, which included calcineurin inhibitors combined with methotrexate or mycophenolate mofetil, as clinically indicated. Notably, one severe case occurred in a

fully matched transplant, and another in a mismatched setting, indicating that factors beyond HLA disparity, such as minor histocompatibility antigens or immune kinetics, may play a role. The overall low GVHD rate may also be attributed to the immunologic immaturity of cord blood–derived T cells (24, 25).

No cases of chronic GVHD were observed, consistent with prior reports showing a lower incidence of long-term immune complications following UCBT in children. This is particularly advantageous in pediatric settings, where reducing long-term toxicity is critical for quality of life. Our findings align with larger studies, such as Ruggeri et al., reporting chronic GVHD rates below 20% (26). Biologically, this may be linked to the predominance of naïve T cells and the unique cytokine profile of cord blood (27). Despite >50% of patients receiving ≤5/6 matched grafts, no chronic GVHD occurred, suggesting cord blood's immunomodulatory properties may mitigate the impact of HLA mismatch. However, this should be interpreted with caution due to the small sample size of this study.

Infectious complications were the most frequent and serious adverse events, accounting for 50% of all deaths. This is consistent with international registry data identifying infection as the leading cause of non-relapse mortality in pediatric transplant settings (28) and with reports by Danby et al. (29). Delayed immune reconstitution and slow neutrophil recovery likely contributed to increased infection susceptibility (30).

CMV reactivation occurred in 42.9% of patients, comparable to existing pediatric data (31), and in some cases led to prolonged hospitalization or organ toxicity. Letermovir, recently approved for CMV prophylaxis in pediatric HSCT patients (32), was not available during our study period and did not influence these outcomes. Other complications, including metabolic and renal disturbances, were clinically manageable, likely reflecting the benefit of structured supportive protocols (33).

The overall survival rate was 42.9%, with follow-up ranging from under one month to 5 years. Although this rate falls within the range reported in pediatric UCBT studies, it remains suboptimal. A study by Spees et al. reported improved two-year mortality rates over time, attributed primarily to enhanced infection control (34). Despite standardized antimicrobial prophylaxis, our findings suggest that uniform protocols may not suffice in high-risk pediatric cases, supporting a shift toward personalized infection prevention.

Notably, four patients in this study achieved sustained engraftment and long-term survival despite clinical and immunological challenges typically associated with poor prognosis, highlighting the therapeutic potential of UCBT in complex pediatric settings. Patient 3 (aplastic anemia, 6/6 match) remains healthy 5 years post-transplant. Patient 5 (SCID) achieved immune recovery and continues to do well after three years. Patient 10 (ALL) maintained remission over five years despite CMV reactivation and vision loss from fungal infection. Patient 14 (HLH, 5/6 mismatch) achieved full donor chimerism and remains in remission. These cases highlight UCBT's potential even in complex settings, provided graft selection and post-transplant care are optimized.

Among eight deaths, transplant-related mortality (TRM) accounted for six (42.9%) and disease-related mortality (DRM) for two (14.3%). TRM causes included severe infections, hemorrhage from graft failure, catheter complications, pulmonary toxicity, and hepatic failure due to immunosuppressive therapy. One patient with Griscelli syndrome developed EBV-associated HLH progressing to post-transplant lymphoproliferative disorder (PTLD), which relapsed despite therapy and was fatal. These outcomes, though comparable to prior pediatric UCBT data (34), are concerning, particularly as 92.9% of patients received unrelated donor grafts. Factors such as HLA disparity, underlying disease, and low body weight may have compounded vulnerability. These findings highlight the need for stringent infection control, tailored conditioning, and consistent catheter management in high-risk pediatric populations.

Multiple factors appeared to influence post-transplant outcomes. Higher $CD34^+$ cell doses and better HLA compatibility generally correlated with engraftment and survival, in line with dose–response relationships described in previous studies (35).

However, primary graft failure still occurred in some patients with otherwise favorable graft metrics, suggesting other variables at play. The underlying diagnosis emerged as a key determinant. Patients with non-malignant diseases showed variable outcomes, consistent with registry data (36). Favorable long-term results were noted in SCID patients, likely due to their capacity for full immune reconstitution when treated early, while inherited metabolic disorders exhibited more complex post-transplant courses, possibly due to irreversible pre-transplant organ damage and limited response to HSCT.

4.1. Limitations

This study provides clinically relevant insights into pediatric UCBT; however, some limitations should be considered. A significant limitation of this study is its retrospective, single-center design with a small sample size (n=14). This

constraint prevents robust statistical comparisons between subgroups, such as patients with malignant versus non-malignant disorders, or those who received different conditioning regimens. Consequently, our findings should be interpreted as providing initial insights and observed trends rather than definitive conclusions. The generalizability of these results to other pediatric populations may be limited. Furthermore, as a retrospective study, some data points were not uniformly available across all patient records.

5. CONCLUSION

This study offers practical observations on the outcomes of umbilical cord blood transplantation in pediatric patients, particularly in a setting with limited resources. Engraftment and survival were influenced by factors such as HLA compatibility, $CD34^+$ cell dose, and underlying diagnosis. Cord blood remains a feasible donor source for children without matched unrelated donors. Based on these findings, careful donor selection, individualized transplant planning, and close post-transplant monitoring are recommended to improve clinical outcomes. Although the small sample size limits definitive conclusions, this work highlights key challenges and provides a foundation for future larger-scale, multicenter studies aimed at optimizing transplantation strategies and expanding access to effective treatment for high-risk pediatric populations.

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Conflict of interest

The authors declare that they have no conflicts of interest related to this study.

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Ethical statement

The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RICH.REC.1401.035) and conducted in accordance with the Declaration of Helsinki. Given the retrospective design and use of anonymized data, the requirement for informed consent was waived.

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