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Cell-Derived Therapies for Hypoplastic Left Heart Syndrome: A Meta-Analysis

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ABSTRACT

Background: Hypoplastic left heart syndrome is a severe single-ventricle congenital heart disease in which the right ventricle sustains systemic circulation after staged palliation. Cell-derived therapies have been investigated as adjunctive strategies to preserve ventricular function. This meta-analysis evaluated the safety and efficacy of cell-derived therapy in patients with hypoplastic left heart syndrome. Methods: PubMed, ScienceDirect, Wiley, and Cochrane were searched from inception to January 31, 2026. Database-specific search strings combined MeSH terms and free-text keywords for hypoplastic left heart syndrome, stem cells, cell-derived therapy, cardiosphere-derived cells, umbilical cord blood mononuclear cells, and mesenchymal precursor cells. Comparative human studies in HLHS or HLHS variants were included. Pooled odds ratios or mean differences with 95% confidence intervals were calculated using fixed-effect or random-effects models according to heterogeneity. Results: Six studies involving 218 patients were included. Cell-derived therapy improved right ventricular ejection fraction (mean difference, 4.61; 95% CI 0.28 to 8.94) and weight-for-age z score (MD 1.80; 95% CI 1.72 to 1.88). Mortality and hospital length of stay did not differ significantly between groups. Cardiopulmonary bypass time appeared shorter, but this finding was based on only two heterogeneous studies and should be interpreted cautiously. Conclusion: Adjunctive cell-derived therapy may improve ventricular function and somatic growth without a detectable early mortality signal, but the current evidence remains limited by small sample sizes, heterogeneity, and early-phase study designs.

INTRODUCTION

Hypoplastic left heart syndrome (HLHS) constitutes one of the most devastating phenotypes within the spectrum of congenital heart diseases (CHD), encompassing profound underdevelopment of the left-sided cardiac structures, including the left ventricle, mitral valve apparatus, and left ventricular outflow tract. As postnatal circulatory physiology becomes entirely dependent on the systemic pumping capacity of the morphologic right ventricle, this chamber is subjected to persistent systemic pressure overload from birth onward, rendering progressive ventricular dysfunction an almost inevitable consequence. In addition, diminished arterial oxygen saturation and impaired coronary perfusion compromise myocardial oxygen delivery, further exacerbating ventricular impairment.(1) HLHS is the most prevalent subtype of single-ventricle CHD, with an estimated incidence of 2–3 cases per 10,000 live births, accounting for approximately 3% of all congenital heart disease diagnoses in newborns.(2)

Patients with HLHS typically undergo staged palliation: the Norwood procedure in the neonatal period, bidirectional cavopulmonary connection in infancy, and Fontan completion later in childhood (18–48 months).(3) Although surgical and perioperative advances have improved survival, many patients still develop late morbidity, heart failure, or transplant need, highlighting the need for adjunctive strategies that may preserve systemic right ventricular function. Despite advances in surgical management, long-term outcomes remain suboptimal, with approximately 60% of patients with CHD

who have undergone the Fontan procedure surviving to 5 years following heart transplantation.[4] Considering the considerable technical complexity and procedural morbidity associated with both staged CHD reconstruction and cardiac transplantation, there is growing interest in developing innovative therapeutic strategies to improve right ventricular function in patients with hypoplastic left heart syndrome.

Regenerative cell-based therapies have attracted increasing attention as a promising therapeutic approach for various forms of congenital heart disease (CHD), owing to their capacity to promote myocardial repair, modulate adverse ventricular remodeling, and enhance functional cardiac recovery through multiple regenerative mechanisms. They may promote angiogenesis, paracrine signaling, and myocardial repair rather than relying on direct engraftment alone. In paediatric patients with HLHS, regenerative cell-based therapies have been investigated using umbilical cord blood-derived mononuclear cells (UCB-MNCs), cardiosphere-derived cells (CDC), and mesenchymal precursor cells administered during various stages of surgical palliation. Although the application of cell-based regenerative therapy has recently expanded into the field of congenital heart disease, its clinical development was initially driven by the need to restore myocardial function in adults with myocardial infarction and heart failure (HF).[5] Accumulating evidence from adult clinical trials has consistently demonstrated that these therapies possess a favourable safety profile while conferring meaningful improvements in cardiac structure and function among patients with myocardial infarction, chronic HF, and dilated cardiomyopathy. These encouraging findings have provided the biological and clinical rationale for translating regenerative cell-based strategies to paediatric patients with congenital cardiac anomalies, particularly those with hypoplastic left heart syndrome, in whom progressive systemic right ventricular dysfunction remains a major determinant of long-term morbidity and mortality.[6,7]

However, existing evidence remains fragmented across small early-phase studies with heterogeneous cell sources, delivery routes, and follow-up durations. Prior reviews have largely pooled broader congenital heart disease populations or provided descriptive summaries without HLHS-focused quantitative synthesis. Therefore, this meta-analysis was performed to evaluate the safety and efficacy of cell-derived therapy specifically in HLHS and to explore whether treatment effects vary by study design, cell platform, and operative timing.

RESEARCH METHODS

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8] No prospective registration of the review protocol was undertaken.

A comprehensive literature search was systematically undertaken across PubMed, ScienceDirect, Wiley, and the Cochrane Library from database inception through January 31, 2026. Search strategies were individually optimized for each database by integrating Medical Subject Headings (MeSH) with free-text terminology, including *"hypoplastic left heart syndrome," "HLHS," "stem cells," "cell-derived therapy," "cardiosphere-derived cells," "umbilical cord blood mononuclear cells,"* and *"mesenchymal precursor cells,"* linked using database-specific Boolean operators. Eligible publications consisted of English-language comparative studies involving human subjects published up to January 2026. Following removal of duplicate records, two independent reviewers screened titles and abstracts before conducting full-text eligibility assessments. Any discrepancies during study selection were adjudicated by a third reviewer. To maximise study capture, reference lists of all eligible articles were additionally scrutinised manually for potentially relevant publications.

Studies were considered eligible if they employed either interventional or observational comparative designs and enrolled patients diagnosed with hypoplastic left heart syndrome or closely related anatomical variants characterised by a functionally single systemic right ventricle. The intervention arm received a cell-derived or cell-based therapy, including mesenchymal stromal cells, progenitor cells, hematopoietic or UCB-MNCs, CDC, or cell-derived products. The comparator was placebo, no injection, or surgery alone. Studies without relevant outcomes, inaccessible full text, animal

models, reviews, protocols, editorials, letters, and adult studies of non-congenital cardiac disease were excluded.

The primary outcome was safety, evaluated by all-cause mortality and adverse events attributable to cell administration. Secondary efficacy endpoints comprised right ventricular ejection fraction (RVEF), weight-for-age *z*-score, cardiopulmonary bypass duration, and hospital length of stay. The methodological rigor of the included studies was critically appraised using the Cochrane Risk of Bias 2 (RoB 2) instrument for randomized controlled trials and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) framework for non-randomized investigations.[9]

Quantitative synthesis was conducted using Review Manager (RevMan) version 5.4. Binary outcomes were aggregated as odds ratios (ORs), whereas continuous variables were synthesised as mean differences (MDs) or standardized mean differences (SMDs), each accompanied by corresponding 95% confidence intervals (CIs). Statistical models were selected according to the magnitude of between-study heterogeneity, with either fixed-effect or random-effects approaches implemented as appropriate. Heterogeneity was evaluated using Cochran's Q statistic together with the I^2 index, whereby I^2 values exceeding 50% were interpreted as evidence of substantial inconsistency across studies. Statistical significance was defined by a two-sided P value <0.05.

RESULTS AND DISCUSSION

The database search identified 1,138 studies. After duplicate removal, title-abstract screening, and full-text assessment, six comparative clinical studies[10–16] were analysed, comprising 218 patients with hypoplastic left heart syndrome. Overall, 100 patients received cell-derived therapy and 118 were analyzed as controls. Figure 1 shown the PRISMA flow diagram.

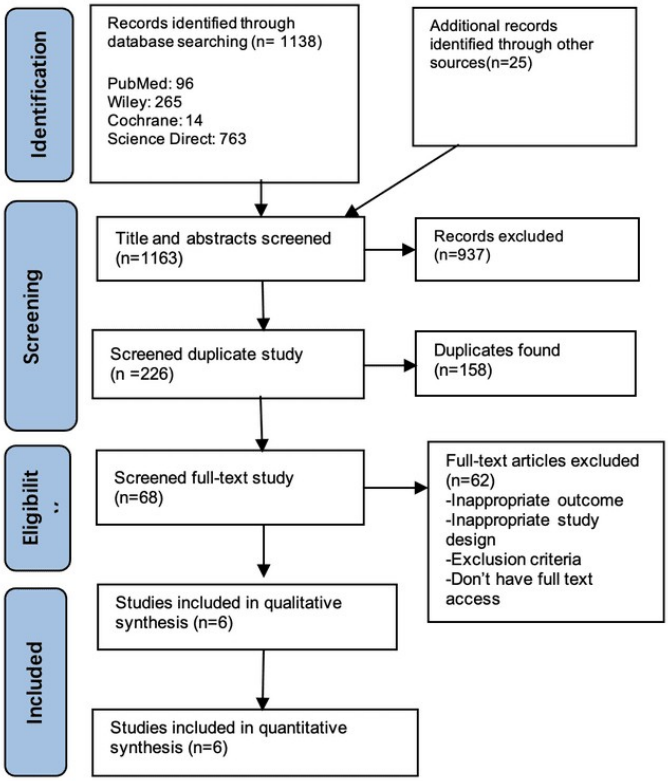

Figure 1. PRISMA Flow Diagram

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Included studies evaluated three main therapeutic platforms: UCB-MNCs, autologous CDC, and allogeneic mesenchymal precursor cells. Delivery routes varied across trials and included intracoronary infusion, intramyocardial injection, and subepicardial or direct myocardial administration. Timing also varied, ranging from neonatal Norwood palliation to stage II or stage III reconstruction and left ventricular recruitment procedures. These differences were clinically relevant and contributed to heterogeneity in several pooled outcomes.

Table 1. Characteristics Of The Included Clinical Studies

Study	Design	N (therapy/ control)	Age at operation	Cell therapy	Delivery/timing	Main clinical focus
Ishigami et al. (2015)	Prospective phase 1 controlled trial	7/7	Control: 1.5 ± 1.7 years; Therapy: 2.1 ± 1.2 years	Autologous cardiosphere-derived cells	Transcoronary infusion after staged palliation	Safety, feasibility, and early functional response
Tarui et al. (2015)	Long-term follow-up of TICAP	7/7	1.3 ± 1.5 years vs 2.0 ± 1.3 years	Autologous cardiosphere-derived cells	Transcoronary infusion with follow-up to 36 months	Durability of ventricular and somatic growth effects
Vincenti et al. (2021)	Comparative clinical impact study	7/17	5 (4-5) months in both groups	Autologous cell therapy from umbilical cord blood	Intramyocardial injection after bidirectional cavopulmonary anastomosis	Clinical impact after stage II palliation
Brizard et al. (2023)	Comparative feasibility study with matched controls	10/22	Therapy: 2.0 ± 0.7 days; Control: 2.8 ± 2.0 days	Autologous cord blood mononuclear cells	Intracoronary infusion during neonatal Norwood operation	Safety and feasibility of adjunct therapy during stage I palliation
Wittenberg et al. (2023)	Prospective randomized controlled trial	9/10	Baseline age reported at randomization. Therapy: 17.9 (6.1–27.0) months; Control: 9.0 (4.6–28.4) months	Allogeneic mesenchymal precursor cells	Direct intramyocardial injection during left ventricular recruitment surgery	Safety and feasibility in hypoplastic left heart variants
Gallego-Navarro et al. (2025)	Non-randomized controlled trial	50/45	Therapy: 4.7 (4.5–5.1) months; Control: 5.2 (4.4–6.2) months	Autologous umbilical cord blood mononuclear cells	Intramyocardial injection during staged palliation	Efficacy and safety of myocardial cell delivery

The overall risk-of-bias assessment indicated a moderate level of methodological concern across the included studies. Of the six studies evaluated, one was judged to have a low risk of bias, four were classified as having some concerns, and one was considered to be at high risk of bias. Most studies demonstrated an acceptable risk regarding missing outcome data and outcome measurement. Nevertheless, deficiencies in the randomization process together with deviations from the intended interventions emerged as the predominant methodological limitations, thereby diminishing the overall certainty and internal validity of the available evidence. In contrast, the remaining domains, including missing outcome data and outcome measurement, were generally judged to present a low risk of bias across most included studies. A comprehensive overview of the individual and overall risk-of-bias assessments is illustrated in Figures 2 and 3, whereas detailed domain-specific evaluations for each included study are summarized in Table 2.

Table 2. Risk of Bias Summary

Study	D1	D2	D3	D4	D5	Overall
Ishigami	Some	Low	Low	Low	Low	Some
Gallego-Navarro	Some	Low	Low	Low	Low	Some
Tarui	Some	Some	Low	Low	Low	Some
Brizard	High	High	Low	Low	Low	High
Vincenti	Some	Low	Low	Low	Low	Some

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Wittenberg	Low	Low	Low	Low	Low	Low

Note: D1 = randomization process; D2 = deviations from intended interventions; D3 = missing outcome data; D4 = measurement of outcome; D5 = selection of reported result.

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Weight	D1	D2	D3	D4	D5	Overall
	Ishigami	Ishigami	stem cells	control	1	!	+	+	+	+	!
	Gallego-Navarro	Gallego-Navarro	stem cell	control	1	!	+	+	+	+	!
	Tarui	Tarui	stem cell	control	1	!	!	+	+	+	!
	Brizard	Brizard	stem cell	control	1	-	-	+	+	+	-
	Vincenti	Vincenti	stem cell	control	1	!	+	+	+	+	!
	Wittenberg	Wittenberg	stem cell	control	1	+	+	+	+	+	+

+	Low risk		
!	Some concerns		
-	High risk		
D1	Randomisation process		
D2	Deviations from the intended interventions		
D3	Missing outcome data		
D4	Measurement of the outcome		
D5	Selection of the reported result		

Figure 2. Risk of Bias Graph

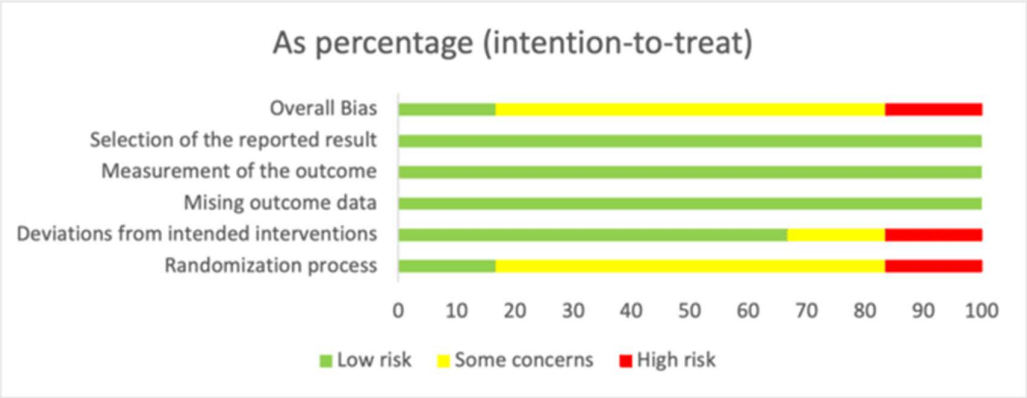

Figure 3. Risk of Bias Summary

Publication bias

Publication bias was not formally evaluated because the limited number of studies available for each pooled outcome precluded meaningful assessment using conventional methods. Specifically, the small evidence base rendered funnel plot inspection unreliable and substantially reduced the validity and interpretability of statistical approaches such as Egger's regression test and Begg's rank correlation test. Likewise, the certainty of evidence was not graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, as the modest number of included studies, considerable clinical and methodological heterogeneity among interventions, and predominance of early-phase clinical investigations, which limited the reliability of certainty-of-evidence grading.

Intervention characteristics

Source of cells varied with CDC cells (two studies) and umbilical cord blood (three studies). Intramyocardial injection (four studies) were the most frequent routes of cell delivery, and the remaining used intracoronary administration.

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Results of the indicator analyses

Death

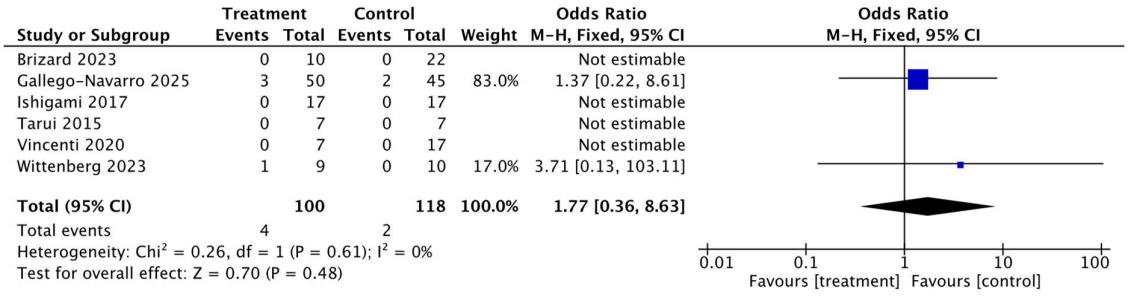

Figure 4. Forest Plot of the Treatment Group vs Control Group: Death

Mortality following cell-based therapy in HLHS patients was evaluated across six comparative studies, comprising 100 patients who received cell therapy and 118 control participants (Figure 4). The pooled estimate revealed no statistically discernible difference in all-cause mortality between treatment and control cohorts (OR = 1.77, 95% CI 0.36–8.63; $P = 0.81$), indicating that administration of cell-based therapy neither conferred a survival advantage nor increased mortality risk within the currently available body of evidence. Heterogeneity across studies was low ($I^2 = 0\%$), suggesting consistency in findings despite differences in study design or population.

Right Ventricular Ejection Fraction Improvement (RVEF, %)

Right ventricular ejection fraction (RVEF), a key indicator of systemic right ventricular performance, was assessed in four comparative studies evaluating the therapeutic efficacy of cell-based interventions in HLHS patients (Figure 5). Quantitative synthesis demonstrated a statistically significant improvement in RVEF among patients receiving cell-based therapy compared with those managed conventionally, with a pooled mean difference (MD) of 4.61 (95% CI 0.28–8.94; $P = 0.04$). These findings suggest that regenerative cell therapy may enhance systemic right ventricular systolic function, supporting its potential role in attenuating ventricular dysfunction in this high-risk population.

To further investigate whether the route of cell administration influenced treatment efficacy, subgroup analyses were performed according to delivery strategy. Intracoronary administration produced a more pronounced and statistically robust improvement in RVEF (MD = 5.32, 95% CI 2.70–7.94; $P < 0.0001$), whereas intramyocardial injection was not associated with a statistically significant increase in ventricular function (MD = 3.95, 95% CI –2.03 to 9.93; $P = 0.20$). Although substantial heterogeneity was observed across the overall analysis, the formal test for subgroup interaction was not statistically significant, indicating that the apparent differences in treatment effect between intracoronary and intramyocardial delivery were not sufficient to demonstrate a meaningful influence of the administration route on the overall therapeutic efficacy of cell-based therapy.

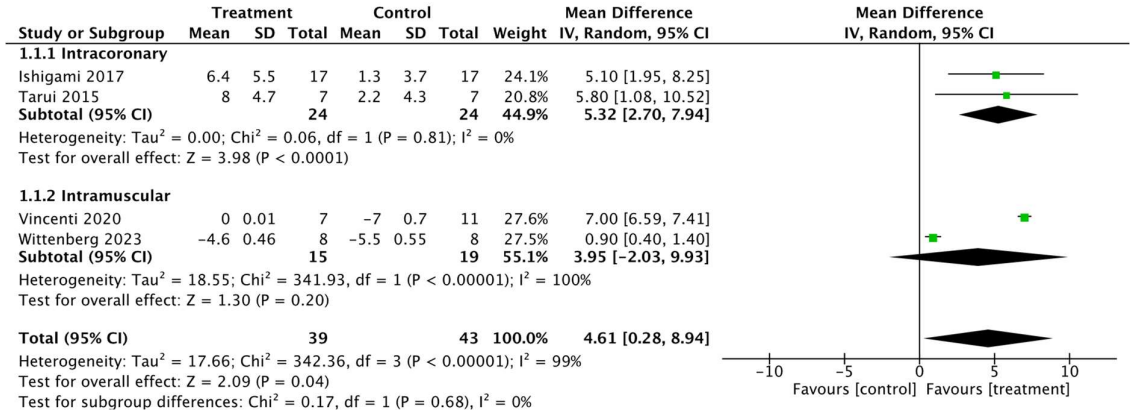

Figure 5. Forest Plot of the Treatment Group vs Control Group: RVEF improvement

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Body weight for age (z score)

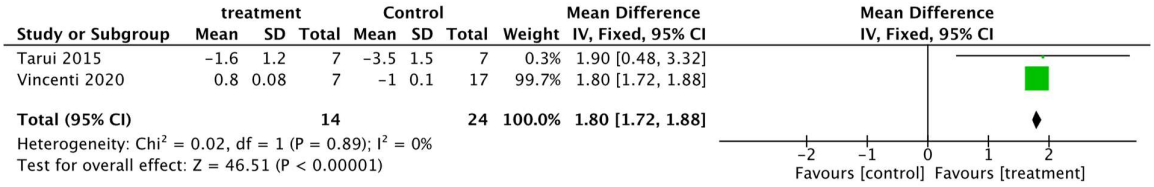

Figure 6. Forest Plot of the Treatment Group vs Control Group: Weight for Age (z score)

Somatic growth, assessed using weight-for-age *z*-scores, was evaluated during the follow-up period in two studies involving HLHS patients who received cell-based therapy compared with controls (Figure 6). The analysis included 14 patients in the treatment group and 24 in the control group. Pooled results demonstrated a significant improvement in weight-for-age *z*-scores among patients treated with cell-based therapy, with a MD of 1.80 (95% CI 1.72–1.88; $P < 0.00001$). There was superior somatic growth compared with the control group. Heterogeneity was low ($I^2 = 0\%$), indicating strong consistency between studies.

Cardiopulmonary bypass time (minutes)

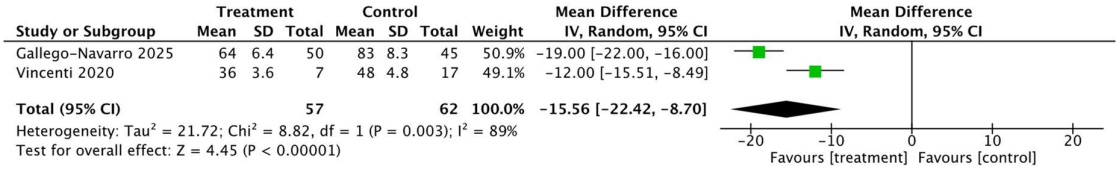

Figure 7. Forest Plot of the Treatment Group vs Control Group: Cardiopulmonary Bypass Time (minutes)

Cardiopulmonary bypass (CPB) duration was examined in two comparative studies involving 57 patients treated with cell-based therapy and 62 control patients undergoing standard management for HLHS (Figure 7). Quantitative synthesis demonstrated that recipients of cell-based therapy experienced a significantly shorter CPB duration than controls, with a pooled mean difference of –15.56 minutes (95% CI –22.42 to –8.70; $P < 0.00001$). These findings suggest that incorporation of cell-based therapy may contribute to a meaningful reduction in operative bypass time. However, because this outcome was informed by only two heterogeneous studies ($I^2 = 89\%$), the finding should be considered hypothesis-generating rather than practice changing.

Length of hospital stay

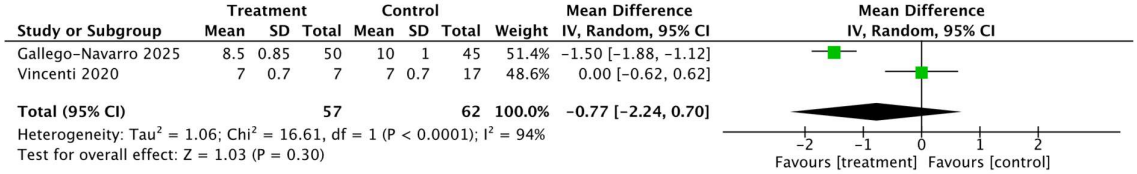

Figure 8. Forest plot of the treatment group vs control group: length of hospital stay

Hospital length of stay was examined in two comparative studies comprising 57 patients who received cell-based therapy and 62 patients managed with standard treatment (Figure 8). Pooled quantitative analysis demonstrated that the duration of hospitalization was comparable between the two

groups, with no statistically significant difference observed following administration of cell-based therapy (MD = –0.77 days, 95% CI –2.24 to 0.70; *P* = 0.30). Although the pooled estimate numerically favoured the cell therapy group, the confidence interval crossed the null value, indicating that the observed reduction in hospital stay did not reach statistical significance. These findings suggest that, based on the currently available evidence, adjunctive cell-based therapy does not appear to prolong postoperative recovery or increase hospitalization requirements compared with conventional management in HLHS patients.

Safety outcomes

Nonfatal safety outcomes were generally reassuring. No therapy-related deaths were reported in any study. Brizard et al. reported 36 serious adverse events, none related to cell-derived therapy; Gallego-Navarro et al. reported no cell-derived therapy-related deaths and no consistent excess of other safety outcomes; and Wittenberg et al. reported two serious adverse events, both unrelated to the investigational therapy.

DISCUSSION

This meta-analysis of 6 comparative studies involving 218 patients with HLHS suggests that cell-derived therapy may improve right ventricular function and somatic growth without a detectable increase in early mortality. The pattern of benefit was most consistent for intracoronary CDC strategies, whereas evidence for other platforms remained less certain.

The safety profile was generally reassuring. Across the included studies, therapy-related deaths were not reported, and serious adverse events were uncommon. In the TICAP and follow-up studies, no serious cell-related complications or tumor formation were observed; Brizard et al. reported that none of 36 serious adverse events were related to therapy; Gallego-Navarro et al. reported no product-related deaths; and Wittenberg et al. reported that the observed serious adverse events were unrelated to the investigational product.

Although the absolute gains in right ventricular ejection fraction (RVEF) and weight-for-age z score were modest, they are clinically relevant in HLHS because systemic right ventricular dysfunction and tricuspid regurgitation are major determinants of morbidity and mortality across staged palliation and after Fontan completion, and reduced right ventricular fractional area change or deformation before bidirectional cavopulmonary anastomosis predicts death or heart transplantation in medium-term follow-up. Likewise, somatic growth is a meaningful prognostic marker in HLHS, as poorer weight trajectories have been associated with worse outcomes after cavopulmonary surgery, whereas improved weight gain may reflect better physiologic reserve.[17,18] However, these findings should still be interpreted as surrogate signals rather than proof of durable clinical benefit, because long-term effects on transplant-free survival, Fontan failure, and quality of life remain insufficiently demonstrated.

The apparent reduction in cardiopulmonary bypass time should be interpreted cautiously. This outcome was derived from only two heterogeneous studies and is likely influenced by surgical technique, anatomy, and institutional practice rather than a direct effect of cell-derived therapy. For this reason, the CPB result should be considered hypothesis-generating rather than therapeutical outcomes.

Heterogeneity in cell source, dose, timing, and delivery route probably explains part of the variability in treatment effects. Autologous CDC were used in the TICAP and PERSEUS programs, umbilical cord blood-derived cells were evaluated in the Brizard and Vincenti studies, and allogeneic mesenchymal precursor cells were tested by Wittenberg et al. These are related but not interchangeable interventions, so pooled estimates should not be interpreted as if they represented a single standardized therapy.

Early clinical investigations have demonstrated that cell-based therapies are both feasible and biologically promising in patients with hypoplastic left heart syndrome (HLHS), with the most robust evidence derived from the TICAP and PERSEUS trials. In the TICAP study, intracoronary administration of autologous CDC following staged surgical palliation was shown to be safe and resulted in sustained improvements in right ventricular function, somatic growth, and heart failure status

over a 36-month follow-up period.[13] These findings were subsequently corroborated by the larger randomized PERSEUS trial, which reported significant enhancements in ventricular function, cardiac remodeling, somatic growth, and health-related quality of life, further supporting the therapeutic potential of CDCs in attenuating maladaptive remodeling of the systemic right ventricle in HLHS.[14,21] Comparable feasibility has also been reported with other cell sources, including autologous UCB-MNCs administered during stage II palliation and autologous cord blood mononuclear cells infused during the Norwood procedure. However, interpretation of the latter findings should be undertaken cautiously because the study employed a retrospective matched-control design, making it inherently more susceptible to selection bias.[10,15]

Despite differences in cell origin and delivery strategy, umbilical cord blood-derived cells, CDCs, and allogeneic mesenchymal precursor cells (MPCs) are all intended to mitigate systemic right ventricular maladaptation through complementary regenerative mechanisms, including myocardial remodeling, therapeutic angiogenesis, and paracrine-mediated immunomodulatory effects. UCB-derived mononuclear cells are rich in hematopoietic, mesenchymal, endothelial progenitor, and immune-modulatory cells, and can be obtained safely at birth with autologous compatibility. CDCs are thought to exert their effects predominantly via paracrine factors that stimulate resident cardiomyocytes, reduce fibrosis, and promote neovascularization. Preclinical studies suggest that neonatal-derived CDCs exhibit greater regenerative potential compared to those from older children, possibly due to preserved stemness and higher secretion of reparative exosomes.(20) MPCs are known to be immunoprivileged and secrete trophic factors that promote angiogenesis, inhibit apoptosis, and modulate fibrosis. The intramyocardial route ensures direct myocardial exposure, though it may limit scalability and poses procedural risks that require surgical access.[16]

Two trials are still ongoing. ELPIS is evaluating allogeneic mesenchymal stem cell injection during bidirectional cavopulmonary anastomosis, and APOLLON is examining autologous cardiac stem/progenitor cell infusion after reconstructive surgery.[21,22] Results from these studies should help define the optimal cell platform, timing, and target population for HLHS.

Cell-derived therapy in HLHS will depend on its practical feasibility within the narrow perioperative window. In the included HLHS trials, autologous products required antenatal or postnatal collection, central manufacturing, formal release review, controlled storage, and coordinated transport back to the operating room for timed administration during staged palliation, underscoring the need for a tightly organized multidisciplinary workflow and chain of custody. More broadly, cell-therapy manufacturing literature shows that process integration and automation are central to reproducibility, quality, cost-effectiveness, and scalability, while cost-of-goods planning must account for tissue procurement, materials, facility operation, production, and storage. Limited standardization across product characterization and platform components further complicates routine implementation.[23][24]

This review has several limitations. First, the number of randomized controlled trials was small, and most included studies were observational or early-phase clinical investigations. This design profile increases susceptibility to selection bias, confounding, and institutional practice effects. Second, HLHS is rare, making patient recruitment difficult and limiting statistical precision. Third, included studies differed in cell source, processing, dose, route of administration, timing relative to surgery, follow-up duration, and imaging modality. These differences explain the high heterogeneity observed for several outcomes. Fourth, some outcomes were available from only two studies, limiting certainty of pooled estimates and reducing the robustness of statistical inferences. Consequently, formal publication bias analyses, including funnel plot assessment, were not performed because the small number of included studies would render such analyses unreliable and potentially misleading. Fifth, a formal GRADE assessment was not conducted. Given the limited number of studies, heterogeneity of interventions, variation in study designs, and predominance of early-phase clinical investigations, the certainty of evidence could not be reliably graded.

The myocardium exhibits its greatest regenerative plasticity during early childhood. Consequently, paediatric patients may demonstrate enhanced responsiveness to the biological signals released by various stem cell populations, allowing the developing myocardium to derive greater therapeutic benefit from cell-based regenerative interventions.[20] The mechanism across cell-derived

therapies appears to be paracrine-mediated modulation of the myocardial microenvironment rather than direct engraftment or differentiation. Ongoing and future trials should clarify optimal cell type, dose, timing, route, and patient selection.

CONCLUSION

Cell-derived therapy as an adjunct to surgical palliation for hypoplastic left heart syndrome showed encouraging improvements in right ventricular function and somatic growth without a statistically detectable increase in early mortality. However, available evidence remains limited by small sample sizes, heterogeneous interventions, and early-phase study designs. Well-designed, adequately powered randomized trials with standardized cell processing, dosing, delivery routes, imaging endpoints, and long-term follow-up are required before routine clinical implementation can be recommended.

DECLARATIONS SECTION

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

All authors have agreeds to submit and publish the manuscript.

Originality

All authors declare that this manuscript have not been published or be under consideration for publication elsewhere.

Availability of Data and Material

The data underlying this article is available in the article.

Competing Interests

All authors and contributors (FDP, WW, MAS) to the study declare no conflict of interest.

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Author Contributions

FDP and WW developed the concept for the project and formulated the methodology. FDP managed the study protocol. FDP conducted the literature review, study selection, data collection, and bias risk assessment. FDP, WW, MAS carried out the formal data analysis. FDP created visual representations of the results. FDP, WW, MAS analyzed and interpreted the findings. FDP, WW, and MAS prepared the initial draft of the manuscript. They also collaboratively reviewed, validated, and finalized the manuscript. WW provided overall supervision for the project. All authors have reviewed and approved the final manuscript for submission.

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Not applicable.

Generative AI and AI-Assisted Technologies in the Writing Process

Authors acknowledge that Artificial Intelligence (AI) tools were only used to assist in language editing and did not generate or alter the scientific content, analyses, or conclusions presented in this manuscript. Any language refinement was reviewed and verified by the authors.

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