Combined Heart and Liver Transplantation in the Failing Fontan: Systematic Review and Single-arm Meta-analysis

Vanessa Karlinski Vizentin, MD,[1] Vanio Antunes,[2] Iuri Ferreira Felix, MD,[3] Cynthia Florencio de Mesquita,[4] Elísio Bulhões,[5] Rebecca K. Ameduri, MD,[6] and Jonathan N. Johnson, MD[6]

Background. The Fontan procedure has transformed the management of congenital heart defects characterized by single ventricle physiology, yet it predisposes individuals to Fontan-associated liver disease. Combined heart and liver transplantation (CHLT) emerges as a therapeutic option, but evidence of its efficacy and safety remains limited. This study aimed to comprehensively evaluate CHLT in Fontan patients, focusing on patient characteristics, perioperative outcomes, and posttransplant morbidity and mortality. **Methods.** Following Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines, a systematic search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials was conducted. Studies meeting the intervention of CHLT in Fontan patients were included, and data were collected and synthesized using proportion meta-analysis techniques. Statistical analysis was carried out using R software. **Results.** Four studies met inclusion criteria, comprising 67 Fontan patients undergoing CHLT. All included studies were observational retrospective cohorts performed in the United States. The 1-y survival rate post-CHLT was 88% (95% confidence interval [CI], 70%-98%). Liver graft rejection rates were low, 4% (95% CI, 0%-22%), and no heart graft rejection greater than mild was reported. Postoperative complications included acute kidney injury 75% (95% CI, 50%-93%), temporary dialysis 27% (95% CI, 9%-51%), neurologic events 7% (95% CI, 0%-26%), infection 23% (95% CI, 3%-55%), and unplanned medical procedures 40% (95% CI, 23%-59%). **Conclusions.** CHLT in Fontan patients demonstrates promising survival rates, but graft rejection and postoperative complications pose challenges. The rate of renal complications is particularly notable and requires further evaluation. Future research should prioritize comparative different management strategies and long-term follow-up to refine protocols and optimize outcomes.

(*Transplantation* 2025;00: 00–00).

INTRODUCTION

The Fontan procedure has revolutionized the management of congenital heart defects characterized by single ventricle physiology, providing a palliative solution that allows these individuals to survive into adulthood. However, the Fontan circulation, which diverts systemic venous blood directly to the pulmonary arteries without a subpulmonary ventricle, often leads to long-term complications, including hepatic dysfunction and cirrhosis because of chronic venous congestion. This unique vascular physiology predisposes Fontan patients to the development of end-stage liver disease (ESLD), significantly impacting their prognosis and quality of life.[1]

As a result, combined heart and liver transplantation (CHLT) has emerged as a potential therapeutic option for individuals with Fontan circulation complicated by ESLD. Although the concept of CHLT in Fontan patients holds promise, there remains a paucity of comprehensive evidence elucidating its efficacy, safety, and long-term outcomes.[2,3]

Received 2 September 2024. Revision received 9 January 2025.

Accepted 21 January 2025.

[1] Cardiovascular Diseases Department, Mayo Clinic, Rochester, MN.

[2] Medicine Department, Federal University of Health Sciences of Porto Alegre, Porto Alegre, Brazil.

[3] Internal Medicine Department, Mayo Clinic, Rochester, MN.

[4] Federal University of Pernambuco, Recife, Brazil.

[5] Medicine Department, Faculty of Higher Superior of the Amazon Reunida, Redenção, Brazil.

[6] Pediatric Cardiology Department, Mayo Clinic, Rochester, MN.

The authors declare no funding or conflicts of interest.

V.K.V., V.A., C.F.d.M. were involved in conception and design of the survey and statistical analysis. V.K.V., V.A., and E.B. were involved in data collection. V.K.V., I.F.F., and C.F.d.M. were involved in analysis and interpretation of the data. V.K.V., I.F.F., and E.B. were involved in writing of the article. R.K.A. and J.N.J. were involved in critical review of the article for content of significant intellectual importance.

Visual abstract is available online at doi.org/10.1097/TP.0000000000005400.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

Correspondence: Vanessa Karlinski Vizentin, MD, Department of Cardiovascular Diseases, Mayo Clinic, 200 1st SW, Rochester, MN 55905. (karlinskivizentin.vanessa@mayo.edu).

Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0041-1337/20/0000-00

DOI: 10.1097/TP.0000000000005400

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Fontan-associated liver disease (FALD), characterized by universal hepatic fibrosis with some progressing to cirrhosis, poses unique challenges in the context of transplantation. The presence of FALD may influence patient selection, perioperative management, and posttransplant outcomes. The technical aspects of CHLT in Fontan patients, including the surgical approach, organ allocation strategies, and immunosuppressive regimens, involve complex considerations that are highly dependent on the expertise, resources, and protocols of individual centers.[4,5]

This systematic review aimed to comprehensively evaluate the literature on CHLT in Fontan patients, focusing on patient characteristics, perioperative outcomes, posttransplant morbidity, and mortality. By systematically synthesizing data from available studies, we seek to elucidate the overall efficacy, safety profile, and prognostic factors associated with CHLT in this unique patient population.

MATERIALS AND METHODS

This systematic review with meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under protocol CRD42024552552. This study was designed and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guidelines.[6]

Study Eligibility

Inclusion in this meta-analysis was restricted to studies that met all the following eligibility criteria: (1) randomized control trials and observational studies; (2) patients with failing Fontan, any age; (3) studies reporting the CHLT procedure; (4) studies available for review in English; and (5) studies which reported any of the clinical outcomes of interest. Studies such as letters, editorials, expert opinions, case reports, and reviews; only abstract available; studies without usable data; and overlapping study populations were excluded from this analysis.

Search Strategy and Data Extraction

We systematically searched PubMed, Embase, and Cochrane Central Register of Controlled Trials from inception to January 2024 with the following search terms: "Fontan," "CHD," "congenital heart disease," "transplant," "transplantation," "liver," "CHLT," "heart-liver," "HLT," "HL." In addition, the references of included studies were evaluated for additional studies. Two authors independently extracted the data (V.K.V. and V.A.) following predefined search criteria and quality assessment. Disagreements were resolved by consensus. The baseline preprocedural characteristic information was recorded for each study.

Definition of Failing Fontan

For this review, failing Fontan was defined as clinical, laboratory, pathologic, and imaging findings of significant cardiac and/or liver function deterioration following the Fontan procedure. However, it is essential to note that there is no universally accepted consensus on the definition of failing Fontan, which may have introduced heterogeneity between studies. As a result, only studies with multimodal and extensive assessment of cardiac and liver function were considered acceptable for inclusion in the analysis.[7-9]

Endpoints

The primary efficacy endpoint was survival rate and secondary graft heart and liver rejection. The safety endpoints were postoperative complications: infection, renal, and neurologic events.

Quality Assessment

Two authors (I.F.F. and C.F.d.M.) independently evaluated the methodological quality of all included studies using the Cochrane Collaboration tool. We assessed the risk of bias in all studies using ROBINS-I (Risk of Bias in Nonrandomized Studies–of Interventions).[10] Disagreements were resolved by recruiting a third author to attain consensus (V.K.V.).

Data Analysis

This was a single-arm proportion meta-analysis. The statistical analysis was conducted using R version 4.3.2 (R Foundation for Statistical Computing). We conducted a proportional meta-analysis, pooling the data with the "meta" package functions for all endpoints. The arcsine transformation was applied along with the inverse method for binary endpoints, as recommended by Schwarzer et al.[11] Likewise, the inverse method was applied to continuous endpoints without transformation. Whenever available, we used mean and standard deviations to pool continuous data, and in the time it was missing, we estimated it through the Wan and Luo method.[12,13] Skewed data were used in the first moment, and then, through a sensibility leave-one-out analysis, we assessed its impact on each outcome to ensure proper results. Restricted maximum likelihood random-effects modeling was used for all analyses, as we assume that the data come from varied populations with different distributions. Cochran's Q test and I^2 statistics were used to evaluate heterogeneity; P values inferior to 0.10 and $I^2 > 50\%$ were considered significant for heterogeneity. The results were presented as pooled analysis in forest plots.

RESULTS

Study Selection and Baseline Characteristics

The initial search resulted in 1657 articles: 371 from PubMed, 1235 from Embase, and 51 from Cochrane Library, 398 duplicates were filtered out, and the remaining articles were reviewed through titles and abstracts. After applying the exclusion criteria, 56 studies were subjected to the full-text screening process, and an additional 52 studies were eliminated. A total of 4 articles[14-17] were identified for further analysis; the Preferred Reporting Items for Systematic Reviews and Meta-analyses flow chart is shown in Figure 1.

These 4 studies reported 67 patients, all of whom had previously undergone the Fontan procedure, followed up with heart failure, and subsequently underwent CHLT as a surgical approach.

The assessment of failing Fontan varied significantly across the included studies. In the study by Lewis et al,[14]

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

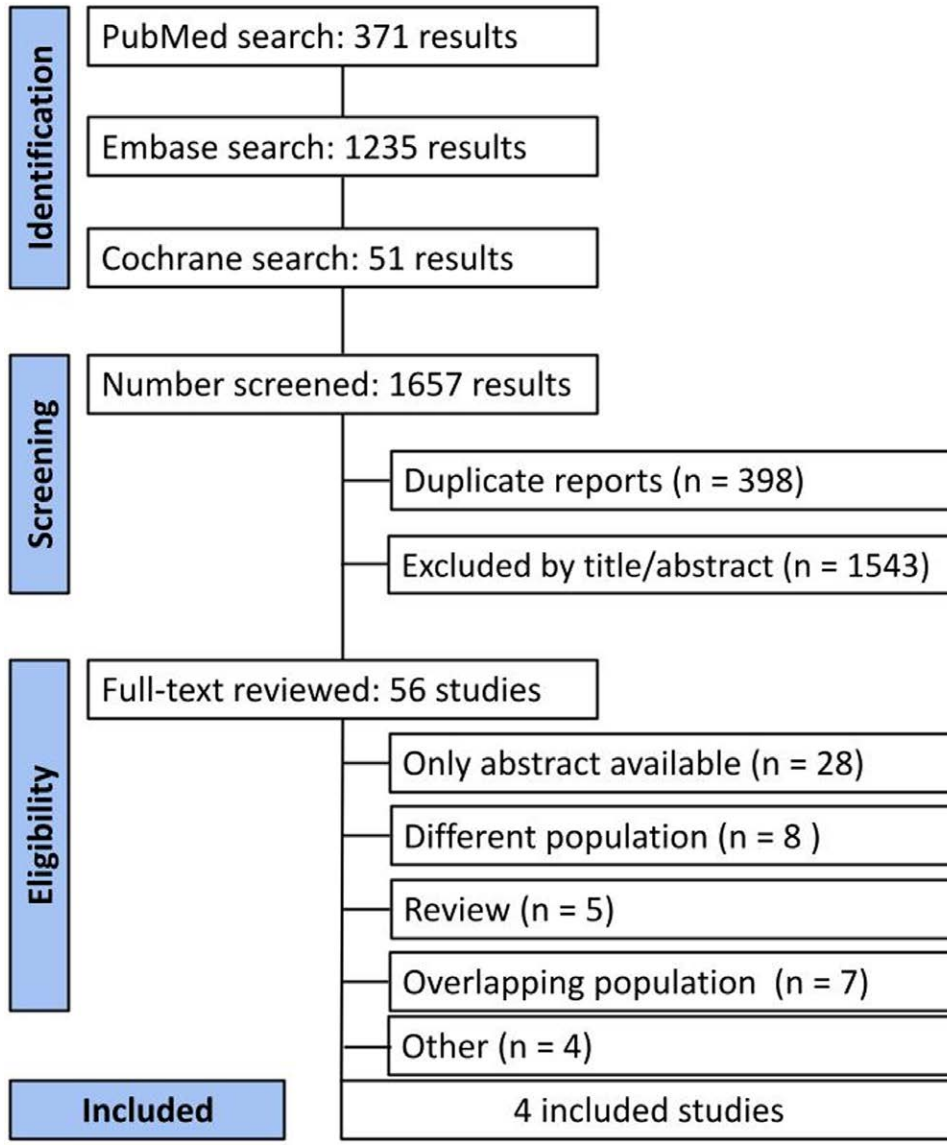

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram of study screening and selection.

there was no explicit definition for failing Fontan. Still, liver dysfunction was evaluated through clinical and diagnostic markers, such as ascites (≥2 paracentesis), splenomegaly, and esophageal varices. Imaging and pathology reports were used to evaluate liver morphology. A tentative calculation of FALD was made to quantify liver dysfunction objectively. D'souza et al[17] used a comprehensive approach that included separate heart and liver transplant candidacy evaluations, incorporating exercise testing, pulmonary function tests, hemodynamic assessment by cardiac catheterization, and hepatology evaluation from biopsies, metabolic panels, model for end-stage liver disease score calculation, and imaging to assess cardiac and hepatic morphology and function. In the studies by Wu et al[15] and Sganga et al,[16] patients were first evaluated for indications of heart transplantation, and both groups underwent formal liver transplant evaluations, which included a combination of imaging findings of cirrhosis and portal hypertension, pathology findings of fibrosis, and model for end-stage liver disease score calculation.

All included studies are retrospective cohorts performed in the United States. Table 1 presents other characteristics of the included studies and patients.

Pooled Analysis of All Studies

Survival Rate

All studies reported a 1-y survival rate, with pooled analysis showing a rate of 88.8% (95% confidence interval [CI], 70.9%-98.7%). The I^2 Statistic in the random-effects meta-analysis was 60%, indicating high heterogeneity between the pooled studies (Figure 2). Two studies also reported 5-y survival after CHLT transplant as 84% (Lewis et al) and 78% (Sganga et al). D'Souza et al reported a 100% survival rate in 4.6 y of follow-up of their cohort.

Postoperative Graft Rejection

Rejection assessment varied across the studies. Lewis et al did not provide specific data or clarify the grading

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

TABLE 1.

Baseline characteristics of included studies and patients

	Lewis et al[14]	Wu et al[15]	Sganga et al[16]	D'Souza et al[17]
	CHLT (n = 40)	CHLT (n = 11)	CHLT (n = 9)	CHLT (n = 7)
Type of study	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort
Country	United States	United States	United States	United States
Population	Adult Fontan≥16 y	Adult Fontan	All Fontan	Adult Fontan≥18 y
Age (y)	33 ± 7.7	37.0 (30.0–48.0)	19 (16–21)	36.8 (27.3–41.7)
Sex (male)	NA	7 (63.6%)	3 (33%)	4 (57%)
Time from Fontan completion	28 ± 5.7	NA	NA	22.9 (18.7–28.5)
Days on the waiting list	NA	80.0 (16.0–117.0)	131 d (109–149 d)	0.7 y (0.1–3.5 y).
MELD-XI score	8.6 ± 9.2	13.0 (9.4–15.4)	10 (9–11)	6.8 (0.6–18.5)
GI varices	14 (37%)	6 (54.6%)	6 (67%)	3 (42%)
Ascites	29 (74%)	9 (81.8%)	8 (89%)	5 (71%)
Splenomegaly	21 (75%)	8 (72.7%)	7 (78%)	NA
Serum creatinine	1.13 ± 0.7	1.2 (1.0–1.3)	0.82 (0.73–1.0)	NA
Bilirubin	1.46 ± 1	1.2 (1.0–2.2)	1.2 (0.9–1.3)	1.0 (0.3–3.9)
INR	NA	1.8 (1.3–2.9)	1.4 (1.3–1.5)	NA
Albumin	3.6 ± 0.9	3.6 (2.9–4.1)	4 (3.5–4.2)	3.0 (1.6–4.4)
Platelets	195 ± 93	198.0 (130.0–227.0)	118 (103–195)	193.0 (101.0–462.0)
Fibrosis grade≥3 on liver biopsy	NA	3 (27%)	3 (50%)	4 (57%)
VAD	NA	0 (0.0%)	0 (0%)	NA
Fontan pressure, mm Hg	17 ± 4.1	16 (14–20)	16 (12–28)	17 (14–18)
Diuretic				
Inotrope support	15 (38%) (≥2 inotropes)	NA	4 (44%)	4 (57%)
On anticoagulation	NA	7 (63.6%)	NA	6 (86%)
Hospitalized	NA	7 (63.6%)	4 (44%)	NA
UNOS status 1A/1B/2	NA	NA	3/0/6	NA/NA/5

Values are mean ± SD.

BMI, body mass index; CHLT, combined heart and liver transplant; GI, gastrointestinal; INR, international normalized ratio; MELD-XI, model for end-stage liver disease excluding international normalized ratio; NA, not available; UNOS, United Network for Organ Sharing; VAD, ventricular assistance device.

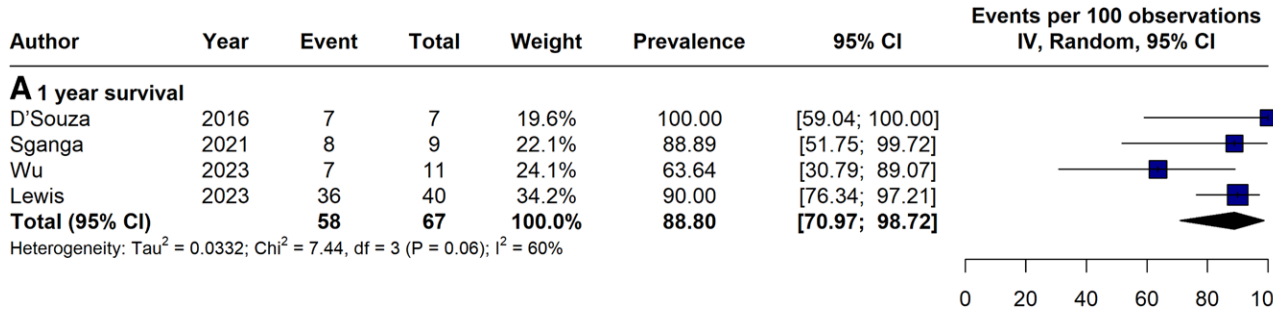

FIGURE 2. Survival proportion analysis. CI, confidence interval.

method for rejection. Wu et al, Sganga et al, and D'Souza et al performed surveillance biopsies and used the International Society for Heart and Lung Transplantation criteria to grade rejection.

Regarding heart graft rejection, none of the studies reported cases with a rejection severity of ≥2 (moderate or severe).[18] Wu et al and D'Souza et al reported mild cases of heart rejection, but none were greater than grade 1R. No graft loss was associated with these rejections. In the study by Sganga et al, no cases of heart rejection were reported in the CHLT cohort, whereas 12 cases of heart rejection were observed in the heart transplant (HT)-only cohort.

For liver graft rejection, as shown in Figure 3, the overall rate was 4.7% (95% CI, 0%-22.9%). Wu et al documented 3 cases of liver rejection, all managed with immunosuppressive therapy, and none resulted in graft loss. D'Souza et al reported 1 case of acute liver rejection, which was managed with steroids and did not lead to graft loss. Sganga et al observed 1 case of moderate acute cellular liver rejection, which did not result in graft loss.

Perioperative Data

Three studies reported perioperative and hospital data. All continuous data transformed followed a normal distribution except for D'Souza et al for cross-clamp time and length of hospitalization endpoints. Of these, the average length of hospital stay was 28.2 d (95% CI, 22.2-34.1), with low heterogeneity ($P = 0.20$, $I^2 = 37\%$; Figure 4). We

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

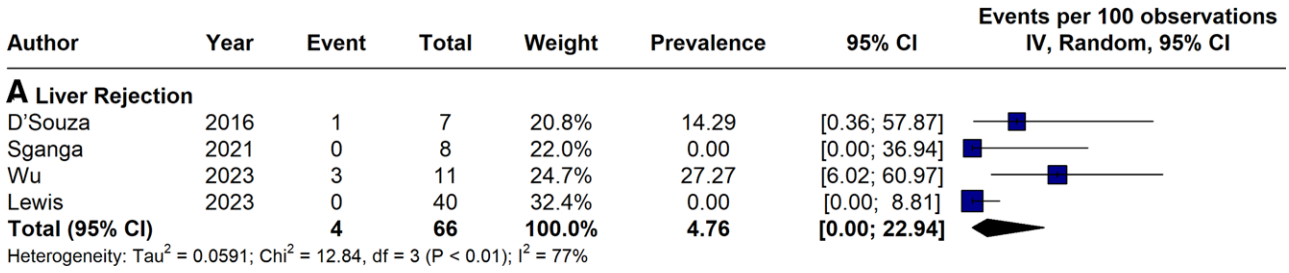

FIGURE 3. Liver graft rejection proportion analysis. CI, confidence interval.

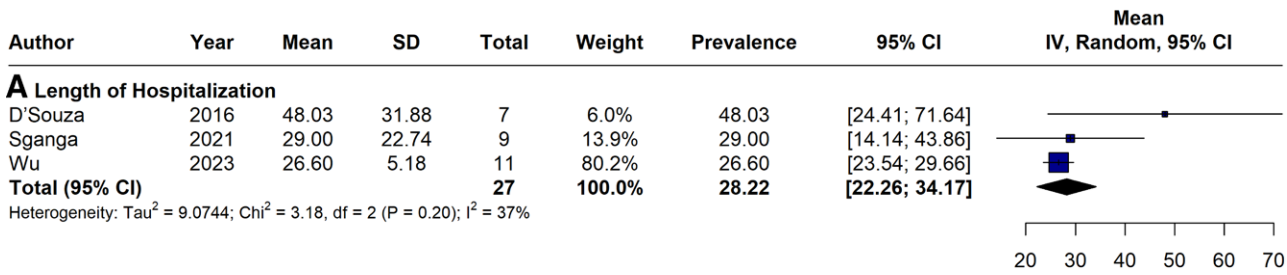

FIGURE 4. Length of hospitalization proportion analysis. CI, confidence interval.

also assessed the cross-clamp time and cardiopulmonary bypass time (CPB), which were 148.27 min (95% CI, 88.7-207.7; Figure 5A) and 235.93 min (95% CI, 193.6-278.2; Figure 5B), respectively. Both cross-clamp time and CPB had high heterogeneity between studies.

All studies provided further insights into the perioperative data. Lewis et al noted a mean allograft ischemic time of 237 min (not measures of dispersion). Sganga et al reported a median ischemic time of 293 min (255-336). D'Souza et al reported a median allograft ischemic time of 211 min (146-277). No patients undergoing transplant against a crossmatch. Wu et al performed all the transplants sequentially using a heart-first approach. All patients underwent general anesthesia and received epoprostenol after cardiac allograft implantation (before CBP separation), which was continued into the postoperative phase of care. All liver transplantations were performed using a caval-preserving "piggyback" technique.[19]

Immunosuppressive Regimen

The immunosuppressive regimens across the studies included induction therapy with either basiliximab or antithymocyte globulin (ATG), followed by maintenance therapy with tacrolimus, mycophenolate, and steroids. Specifically, Wu et al used basiliximab in 14 patients and ATG in 2 patients, whereas Sganga et al used methylprednisolone for induction along with either ATG or basiliximab, followed by mycophenolate mofetil, a calcineurin inhibitor (CNI), and steroids for maintenance. Lewis et al and D'Souza et al did not provide detailed information on their immunosuppressive regimens.

Postoperative Complications

Postoperative complications were reported by 3 studies.[15-17] The pooled incidence of renal outcomes is as follows: acute kidney injury (AKI) was reported with a pooled incidence of 75% (95% CI, 50.3%-93.1%; Figure 6A), with low heterogeneity ($P = 0.16$, $I^2 = 45\%$). The definition of AKI varied between studies; specifically, Wu et al and Sganga et al used the kidney disease: improving global outcomes criteria for AKI, whereas Lewis et al and D'Souza et al did not provide a clear definition for AKI. Temporary dialysis was required in 27.7% (95% CI, 9.4%-51.1%; Figure 6B), with low heterogeneity ($P = 0.21$, $I^2 = 37\%$).

The pooled neurologic event rate proportion was 7.5% (95% CI, 0.03%-26.4%; Figure 6C) with low heterogeneity ($P = 0.15$, $I^2 = 48\%$). The same 3 studies also reported rates of infection, with a proportion of 23.9% (95% CI, 3.1%-55.7%; Figure 6D), with high heterogeneity between studies ($P = 0.05$, $I^2 = 68\%$), and a rate for unplanned additional medical procedures with a proportion of 40.6% (95% CI, 23.2%-59.4%; Figure 6E) with no significant heterogeneity ($P = 0.85$, $I^2 = 0\%$).

Sensitivity Analysis

We performed a sensitivity analysis to explore the heterogeneity between studies ($I^2 > 50\%$). **Figures S1–S5** (**SDC**, http://links.lww.com/TP/D254; http://links.lww.com/TP/D255; http://links.lww.com/TP/D256; http://links.lww.com/TP/D257; http://links.lww.com/TP/D258) show the sensitivity analyses of the overall 1-y survival, liver rejection rate, cross-clamp time, CPB time, and infection rate, respectively.

Quality Assessment

Quality assessment of the included studies was performed with Cochrane's ROBINS-I tool for cohort studies.[10] All studies were classified as having a moderate risk of bias in the confounding domain, given their retrospective and nonrandomized nature. Only 1 study[14] was classified as low risk in the participant selection domain, given the use of appropriate analysis to mitigate selection bias, including propensity score matching, sensitivity, and

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

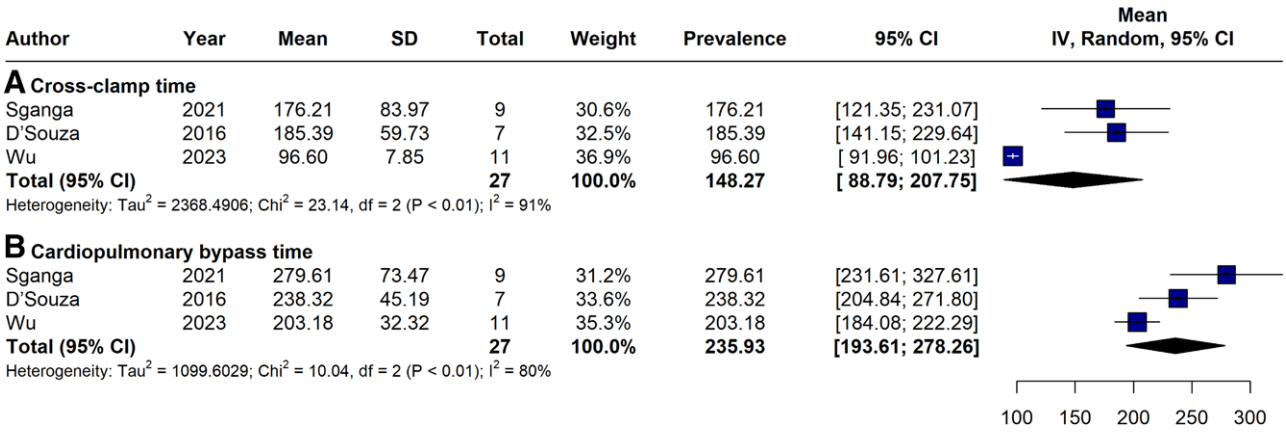

FIGURE 5. Perioperative proportion analysis. CI, confidence interval.

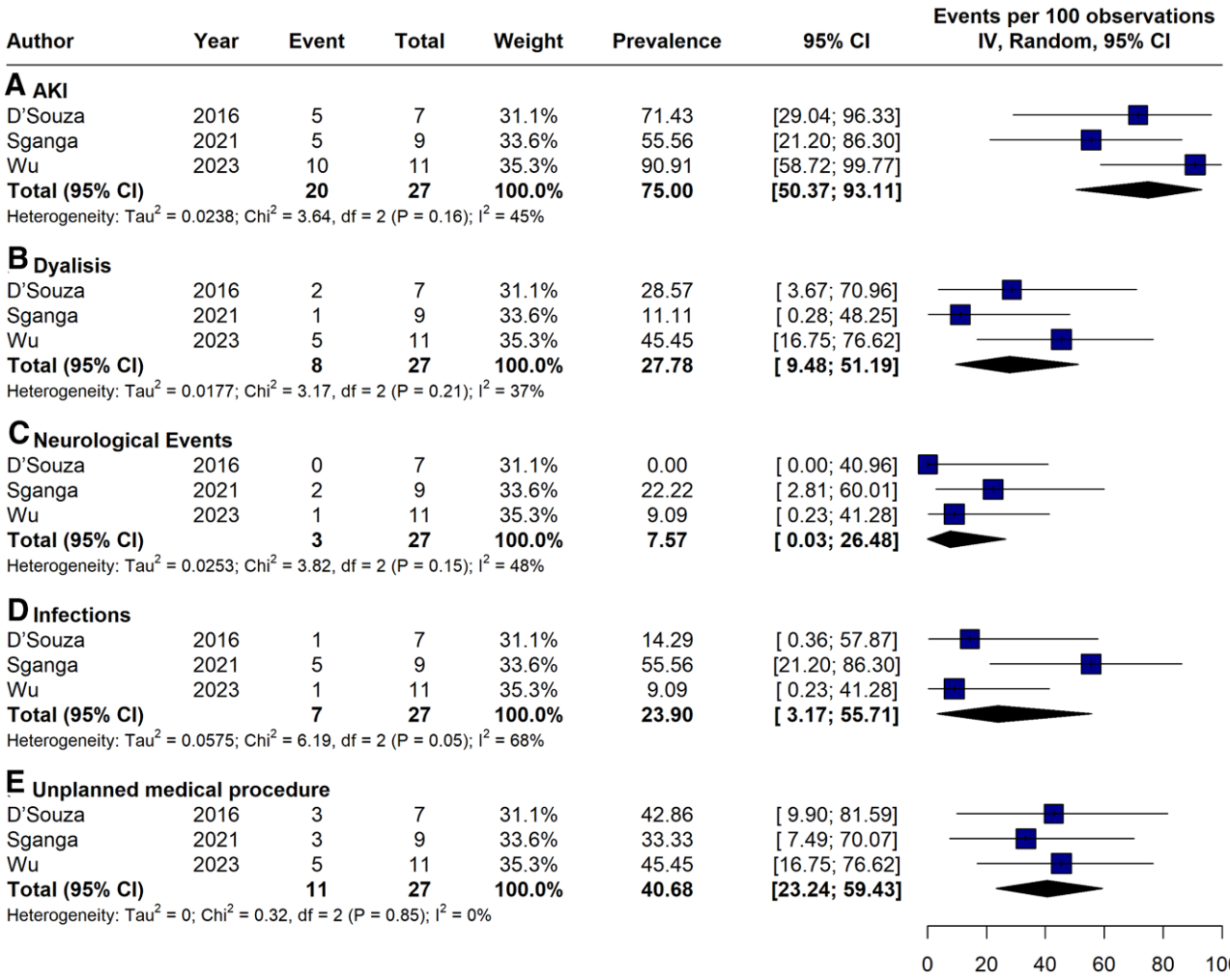

FIGURE 6. Postoperative complications proportion analysis. CI, confidence interval.

subgroup analysis. Overall, all studies were classified as having a moderate risk of bias (Table 2).

DISCUSSION

The Fontan procedure represents a significant advancement in managing congenital heart defects, offering individuals with single ventricle physiology a chance at prolonged survival. However, the unique physiology of the Fontan circulation predisposes patients to develop FALD, leading to ESLD and posing considerable challenges for long-term management. CHLT has emerged as a potential therapeutic approach offering the possibility of improved outcomes and quality of life. The complexities of FALD present unique challenges in transplantation, affecting patient selection, perioperative management,

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

TABLE 2.

Risk of bias among included studies according to Cochrane's ROBINS-I tool for cohort studies

Study	D1	D2	D3	D4	D5	D6	D7	Overall
D'Souza et al[17]	Moderate	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Sganga et al[16]	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Wu et al[15]	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Lewis et al[14]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate

Domains

D1: Bias because of confounding.
D2: Bias because of selection of participants.
D3: Bias in classification of interventions.
D4: Bias because of deviations from intended interventions.
D5: Bias because of missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported results.

and posttransplant outcomes. Addressing these challenges requires a thorough understanding of patient characteristics, perioperative outcomes, and posttransplant morbidity and mortality, which this systematic review and single-arm meta-analysis aimed to provide.[1-4]

The definition of failing Fontan remained inconsistent across centers and publications. None of the included studies provided explicit criteria or a singular definition of Fontan failure. Instead, they relied on comprehensive clinical evaluations, integrating various clinical, hemodynamic, and end-organ factors to identify eligible patients. These evaluations encompassed assessments of systemic venous congestion, hepatic dysfunction, and cardiac performance, among other parameters, rather than adhering to a standardized framework. This variability in patient selection could influence outcomes, as individuals with advanced liver dysfunction or systemic congestion may follow different posttransplant trajectories compared with those with predominantly cardiac failure.[7-9]

The studies' report of low rates of ventricular assistance device (VAD) and inotrope support before transplant is likely secondary to the complex hemodynamic factors in Fontan circulation. Fontan is a complex and multifactorial process with contributions from valvulopathy, systolic and/or diastolic dysfunction, chronic venous congestion, lymphatic dysfunction, and pulmonary hypertension.[20] Therefore, unlike other heart failure etiologies, patients with Fontan physiology undergoing circulatory support present unique challenges related to patient selection because causes of circulatory failure vary greatly, ranging from systemic-sided issues (ie, systolic dysfunction) to pulmonary concerns (ie, inefficient Fontan flow or increased transpulmonary gradient),[21,22] if it is the former, systemic VADs and inotropes may not be as beneficial as passive pulmonary blood flow, which may remain inadequate despite mechanical support. Unfortunately, most failing Fontan present with a combination of both, which complicates patient selection and may explain the inconsistent results associated with using VADs described in the literature.[21] Future research and strategies are needed to optimize bridging therapies for this high-risk population.

One-year post-CHLT survival rates were available in all included studies. The pooled analysis revealed a survival rate above 88%. Furthermore, 3 studies reported 5, or close, year survival rates of 100%, 84%, and 78%, shedding light on the longer-term outcomes following CHLT in Fontan patients.[14,16,17] Survival overall was comparable to other high-risk cohorts of adult heart transplant recipients.

The grading and severity of graft rejection are critical factors in determining long-term transplant outcomes and patient survival. In this study, 3 studies used the International Society for Heart and Lung Transplantation criteria for grading cardiac rejection.[18] The overall rate of heart graft rejection was low, with none of the studies reporting severe rejection (grade ≥ 2). Mild rejection (grade 1R) was observed in Wu et al and D'Souza et al, but no cases of severe rejection were noted, and no graft loss occurred because of heart rejection.

Liver graft rejection was reported in 4.76% of patients, with mild-to-moderate rejections being the most common. No severe liver rejection was observed, and none of the patients required liver retransplantation. These findings suggest that although liver rejection can occur in some Fontan patients, it is generally manageable with immunosuppressive adjustments and does not frequently lead to graft loss.[23]

A comparative analysis between the HT-only and CHLT groups provides key insights into the protective effect of the liver allograft on heart rejection and the characteristics influencing outcomes. In the study by Sganga et al, 12 cases of heart rejection were reported in the HT-only cohort, whereas no heart rejections were observed in the CHLT cohort. Similarly, in the study by Lewis et al, 4 deaths because of heart rejection occurred in the HT-only cohort, whereas no deaths were reported in the CHLT group. These observations support the hypothesis that a liver graft in CHLT may confer a protective effect against heart rejection through multifaceted immunological mechanisms. The liver allograft is thought to induce immune tolerance, mitigating T cell–mediated and antibody-mediated rejection in the cardiac allograft. Additionally, the liver can absorb and neutralize donor-specific antibodies implicated in antibody-mediated rejection.[24,25]

Beyond immunological benefits, Lewis et al identified distinct differences in patient profiles between the CHLT and HT-only groups. CHLT patients were typically older, had a longer interval between Fontan failure and transplant and demonstrated greater reliance on pulmonary vasodilators, diuretics, and inotropes, all markers of advanced disease. Despite these challenges, the survival outcomes for

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

carefully selected CHLT patients were superior to those of HT-only patients, reinforcing the necessity for robust patient selection criteria.

Complementary analyses by Lewis et al also highlighted the impact of preoperative factors on transplant outcomes. The additional article identified critical predictors of survival, such as the time from Fontan failure diagnosis to transplant evaluation, which significantly influenced survival at 1- and 5-y posttransplant. Other predictors of poor outcomes included veno-venous collaterals (increasing bleeding risk), lower extremity varicosities, New York Heart Association functional class IV, and mean arterial pressure <65 mm Hg, all reflecting advanced systemic disease.[26]

The immunosuppressive regimen typically includes a combination of CNIs, antimetabolites, and corticosteroids to reduce the risk of rejection. Tacrolimus, a commonly used CNI, is preferred because of its effectiveness in preventing acute cellular rejection and its better side effect profile compared with cyclosporine. Mycophenolate mofetil is often used in combination with tacrolimus to inhibit lymphocyte proliferation and reduce the incidence of rejection. Corticosteroids are administered perioperatively and tapered over time to mitigate inflammation and prevent acute rejection episodes. Additionally, induction therapy with agents like basiliximab or ATG is sometimes used in the early posttransplant period, particularly for patients who are highly sensitized or at higher risk of rejection. Future studies should assess new immunosuppressive regimens that consider the benefits of the liver allograft and explore the potential for reducing infection rates with lower pharmacologic interventions.[5,27,28]

Renal complications are a significant concern in Fontan patients undergoing CHLT. The pathophysiology involves multiple factors, including chronic elevation of central venous pressure inherent to Fontan physiology, perioperative hemodynamic instability, and exposure to nephrotoxic medications such as CNIs. AKI emerged as a prevalent complication, with a pooled incidence of 71.61%. The high incidence of low heterogeneity between studies highlights the importance of renal function assessment and early intervention in preventing further renal deterioration in Fontan patients undergoing CHLT. The extensive nature of CHLT, often requiring prolonged cardiopulmonary bypass, further contributes to renal injury through inflammatory responses and potential ischemia–reperfusion damage.[29,30]

A subset of these patients also required renal replacement therapy. The high incidence of dialysis, exceeding 30%, underscores the severe impact of perioperative renal complications on patient outcomes. Addressing these renal challenges necessitates thorough preoperative assessment, intraoperative renal-protective strategies, and vigilant postoperative monitoring to optimize outcomes.[31,32] Although specific long-term renal outcomes post-CHLT in Fontan patients are not extensively documented, the existing literature suggests that these patients are at significant risk for both acute and chronic renal complications. Continuous monitoring and management of renal function are crucial in optimizing long-term outcomes for this patient population.[33]

Despite the systematic approach and comprehensive analysis, several limitations merit consideration. First, the limited number of studies meeting inclusion criteria underscores the rarity of CHLT in Fontan patients. Heterogeneity across studies, particularly in endpoints, reporting, and patient characteristics poses challenges in data synthesis. Additionally, short follow-up durations may fail to capture long-term outcomes. Selection bias also impacts CHLT outcomes, as recipients often have more advanced disease and variability in referral timing and center expertise further complicates comparisons. Finally, the lack of consistent comparison strategies across studies limits the ability to draw robust conclusions about CHLT versus alternative treatment modalities like HT alone.

CONCLUSIONS

In summary, the systematic review and single-arm meta-analysis results provide valuable insights into the efficacy, safety, and perioperative outcomes of CHLT in Fontan patients. Although survival rates appear promising, the presence of graft rejection and postoperative complications underscores the complexities and challenges associated with transplantation in this unique patient population. The rate of renal complications is particularly notable and requires further evaluation. Future research endeavors should address comparative approaches, optimize perioperative management strategies, and conduct long-term follow-up studies to further refine the clinical approach to CHLT in Fontan patients.

ACKNOWLEDGMENTS

The authors thankfully acknowledge the Meta-Analysis Academy for its methodological support.

REFERENCES

1. Corno AF, Findley TO, Salazar JD. Narrative review of single ventricle: where are we after 40 years? *Transl Pediatr*. 2023;12:221–244.
2. McCormick AD, Schumacher KR. Transplantation of the failing Fontan. *Transl Pediatr*. 2019;8:290–301.
3. Kamsheh AM, O'Connor MJ, Rossano JW. Management of circulatory failure after Fontan surgery. *Front Pediatr*. 2022;10:1020984.
4. Emamaullee J, Zaidi AN, Schiano T, et al. Fontan-associated liver disease: screening, management, and transplant considerations. *Circulation*. 2020;142:591–604.
5. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e698–e800.
6. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev*. 2021;10:89.
7. Bhatt AB, Foster E, Kuehl K, et al; American Heart Association Council on Clinical Cardiology. Congenital heart disease in the older adult: a scientific statement from the American Heart Association. *Circulation*. 2015;131:1884–1931.
8. Rodriguez FH, Book WM. Management of the adult Fontan patient. *Heart*. 2020;106:105–110.
9. Hebson CL, McCabe NM, Elder RW, et al. Hemodynamic phenotype of the failing Fontan in an adult population. *Am J Cardiol*. 2013;112:1943–1947.
10. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Bmj*. 2016;355:i4919.
11. Schwarzer G, Chemaitelly H, Abu-Raddad LJ, et al. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. *Res Synth Meth*. 2019;10:476–483.
12. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

13. Luo D, Wan X, Liu J, et al. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res*. 2018;27:1785–1805.
14. Lewis MJ, Reardon LC, Aboulhosn J, et al. Clinical outcomes of adult fontan-associated liver disease and combined heart-liver transplantation. *J Am Coll Cardiol*. 2023;81:2149–2160.
15. Wu WK, Siegrist KK, Ziogas IA, et al. Perioperative characteristics and outcomes of fontan versus non-Fontan patients undergoing combined heart-liver transplantation: a retrospective cohort study. *J Cardiothorac Vasc Anesth*. 2024;38:745–754.
16. Sganga D, Hollander SA, Vaikunth S, et al. Comparison of combined heart–liver vs heart-only transplantation in pediatric and young adult Fontan recipients. *J heart lung transplant*. 2021;40:298–306.
17. D'Souza BA, Fuller S, Gleason LP, et al. Single-center outcomes of combined heart and liver transplantation in the failing Fontan. *Clin Transplant*. 2017;31.
18. Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J Heart Lung Transplant*. 2005;24:1710–1720.
19. Levi DM, Pararas N, Tzakis AG, et al. Liver transplantation with preservation of the inferior vena cava: lessons learned through 2,000 cases. *J Am Coll Surg*. 2012;214:691–698. Discussion 698.
20. Bedzra EKS, Adachi I, Peng DM, et al; Society of Thoracic Surgeons Fontan VAD Group. Systemic ventricular assist device support of the Fontan circulation yields promising outcomes: an analysis of The Society of Thoracic Surgeons Pedimacs and Intermacs Databases. *J Thorac Cardiovasc Surg*. 2022;164:353–364.
21. Villa CR, Alsaied T, Morales DLS. Ventricular assist device therapy and Fontan: a story of supply and demand. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2020;23:62–68.
22. Bernhardt AM, Copeland H, Deswal A, et al; Chairs. The International Society for Heart and Lung Transplantation/Heart Failure Society of America guideline on acute mechanical circulatory support. *J Heart Lung Transplant*. 2023;42:e1–e64.
23. Sánchez-Fueyo A, Strom TB. Immunologic basis of graft rejection and tolerance following transplantation of liver or other solid organs. *Gastroenterology*. 2011;140:51–64.
24. Wong TW, Gandhi MJ, Daly RC, et al. Liver allograft provides immunoprotection for the cardiac allograft in combined heart-liver transplantation. *Am J Transplant*. 2016;16:3522–3531.
25. Daly RC, Rosenbaum AN, Dearani JA, et al. Heart-after-liver transplantation attenuates rejection of cardiac allografts in sensitized patients. *J Am Coll Cardiol*. 2021;77:1331–1340.
26. Lewis MJ, Reardon LC, Aboulhosn J, et al. Morbidity and mortality in adult fontan patients after heart or combined heart-liver transplantation. *J Am Coll Cardiol*. 2023;81:2161–2171.
27. Nelson J, Alvey N, Bowman L, et al. Consensus recommendations for use of maintenance immunosuppression in solid organ transplantation: endorsed by the American College of Clinical Pharmacy, American Society of Transplantation, and the International Society for Heart and Lung Transplantation. *Pharmacotherapy*. 2022;42:599–633.
28. Reardon LC, DePasquale EC, Tarabay J, et al. Heart and heart-liver transplantation in adults with failing Fontan physiology. *Clin Transplant*. 2018;32:e13329.
29. Rathgeber SL, Lam C, Harris KC, et al. Hepatic and renal consequences of single-ventricle physiology palliated with the fontan operation. *Can J Cardiol*. 2022;38:1002–1011.
30. Niaz T, Stephens EH, Gleich SJ, et al. Acute kidney injury and renal replacement therapy after Fontan operation. *Am J Cardiol*. 2021;161:84–94.
31. Ivey-Miranda JB, Flores-Umanzor E, Farrero-Torres M, et al. Predictors of renal replacement therapy after heart transplantation and its impact on long-term survival. *Clin Transplant*. 2018;32:e13401.
32. Gale D, Al-Soufi S, MacDonald P, et al. Severe acute kidney injury postheart transplantation: analysis of risk factors. *Transplant Direct*. 2024;10:e1585.
33. Muraoka M, Nagata H, Yamamura K, et al. Long-Term renal involvement in association with Fontan circulation. *Pediatr Cardiol*. 2024;45:340–350.

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.